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mRNA VACCINES: A LUCKY SHOT?

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MRNA technology has proved in the context of the COVID-19 pandemic its breakthrough value as a basis for vaccines. There has been rapid development of highly safe, effective and robust mRNA vaccines, and these can be delivered at large scale. Yet the technology is the result of a long process of accumulation of innovation and capacity. It was a bumpy process that could easily have turned out differently. The mRNA vaccines story suggests that a vibrant vaccine ecosystem cannot be taken for granted in terms of delivering the breakthroughs needed for global pandemic preparedness and response. This paper examines the background of mRNA technology development to understand better how public vaccine research and development policy can be improved to generate the full global social benefits from breakthrough novel vaccine technologies, like mRNA.

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1 mRNA technology: a game changer

The development, testing and approval of several vaccines in less than one year has been one of the great achievements in society's battle with COVID-19. MRNA-based vaccines in particular were developed rapidly and have proved safe and highly effective, also against mutations of the virus. And being synthetic, their production technology has proved more robust than classic biological vaccine production technologies. The achievement is remarkable because messenger ribonucleic acid (mRNA) is a novel technology for production of human vaccines and human drugs more generally. Beyond the current pandemic, mRNA technology is seen as game changer for future development and production of vaccines against infectious diseases in general. Furthermore, mRNA has the potential to transform many other areas of medicine beyond infectious diseases, including cancer and rare diseases.

We look at the ways in which mRNA technology is a game changer for drug making and vaccines in particular. We ask whether its stellar performance in the COVID-19 pandemic was to be expected/in the making, or if the world was lucky this time. What can be expected of the technology in future? Will the bio-medical innovation ecosystem deliver the full social returns from breakthroughs like mRNA? Can we trust our public policy innovation system to support a novel technology like mRNA so its social returns are maximised? What lessons for pandemic preparedness and response need to be learned?

2 mRNA technology: a disruptive new breakthrough for vaccines

Vaccine technology has progressed from the classic use of whole inactivated and attenuated viruses to the use of subunits that only contain pathogen components that can trigger an immune response. Key milestones have included the development of viral-vector vaccines[1], and protein-based vaccines[2]. These vaccines are typically combined with different protein carriers (adjuvants) to improve immune response. These three technologies (inactivated viruses, viral vectors and protein-based) were the incumbent technologies for developing vaccines before the COVID-19 pandemic.

MRNA technologies introduce a new approach to vaccines. Rather than putting weakened or inactivated viruses, or components of them, into our bodies, *synthetic* mRNA based vaccines teach our cells how to make a protein – or even just a piece of a protein – that triggers an immune response. In essence, it uses our body as a drug factory. From the genetic sequence of a pathogen, a potential antigen-

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1 Viral vector vaccines use a modified version of a different virus to the target virus. Inside the shell of the modified virus, there is material from the target virus.

2 Protein subunit vaccines include harmless pieces (proteins) of the target virus instead of the entire germ.

encoding segment is identified. Its corresponding RNA is synthesised[3]. Synthesising may involve modifying the components of RNA and adding adjuvants to improve stability and efficacy and reduce toxicity. The synthesised sequence is packaged into an RNA carrier (typically lipid nanoparticles, LNP) to be deliverable into the body. Once in the body, cells receive instructions to make copies of the protein, while destroying the genetic material from the vaccine. The human body recognises that the protein should not be there and builds T-lymphocytes and B-lymphocytes that remember how to fight the target virus when infected in the future.

Two major types of mRNA technology are being developed: non-replicating mRNA and self-amplifying RNA. Non-replicating mRNA-based vaccines encode the antigen of interest, whereas self-amplifying RNAs encode not only the antigen but also the viral replication machinery. Self-replicating vaccine candidates also include instructions for the RNA to copy itself, allowing the production of new viral particles in the cells they infect, which then go on to infect new cells that will also make the vaccine antigen. They are more complicated to synthesise, but they can enable strong immune responses at lower vaccine doses[4].

Although mRNA technology can be applied to many areas, including cancer immunology, vaccines are an obvious application since the technology needs to produce only a small amount of protein for the vaccine to work.

From the genetic sequence of a pathogen, mRNA developers can quickly pull out a potential antigen-encoding segment. In the case of the coronavirus, its spike protein is the typical target. Unlike attenuated or inactivated vaccines, mRNA is precise in that it will only express a specific antigen, inducing a directed immune response using the innate immune system.

The ability of mRNA vaccine developers to design antigens *in silico* allows for much faster testing of vaccine candidates, compared to the conventional technologies. Developers can avoid complex and time-consuming cell culture production and fermentation-based manufacturing of target pathogens or antigens.

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[3] RNA acts as a messenger between DNA and ribosomes to make proteins. Rather than synthesising the RNA genetic material from the pathogen, an alternative approach is to use its DNA (DNA technology).

[4] For more technical details on the mRNA and other vaccine technologies, see for example Pardi *et al* (2018) and the *New York Times* Coronavirus Vaccine Tracker (https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html).

In addition, multiple mRNAs encoded for different viral proteins can be included in a single vaccine, allowing for the production of vaccines with instructions for multiple antigens, which are much harder to create with conventional vaccines.

The mRNA vaccine platform is also advantageous in terms of manufacturing[5]. MRNA is produced in a cell-free system and uses no animal-derived raw materials. Cell-derived impurities or contaminations, commonly found in other platforms, are thus absent, making the manufacturing of these molecules easier, faster and safer. Since a change in the encoded antigen does not affect the mRNA backbone physical-chemical characteristics, production can be standardised and scaled-up. MRNA can rapidly manufacture at scale vaccines against multiple targets, with minimal adaptation of processes and formulation.

3 Researching mRNA for drug development: a long and bumpy road

MRNA technology did not come out of the blue. A decade or more of research by many scientists helped inform the development of SARS-CoV-2 vaccines using the technology (see also eg Dolgin, 2021).

The discovery of mRNA was reported in *Nature* in May 1961. The path to synthesising of mRNA in a test tube was made possible in 1984 when Paul Krieg and Doug Melton, scientists at Harvard, showed that functional mRNA can be produced *in vitro*. When subsequently it was discovered by a team at the Salk Institute in California that cells can create proteins from mRNA delivered to them, the possibilities of using mRNA as a drug opened up. Scientists realised that this system could potentially be used to turn human bodies into medicine-making factories and treat a variety of diseases, ranging from infection, to cancer and rare diseases. A further step was taken when liposomes were used to package synthetic mRNA for delivery into cells.

Yet there remained critical problems. *In-vitro* transcribed mRNA could be destroyed by the body's immune response or it could cause serious side effects. No one knew how to make mRNA safe and effective in animals, let alone, humans.

In the 1990s and much of the 2000s, conventional wisdom among scientists and interested companies was that mRNA was too tricky and risky, and also lacking economic potential, especially for applications for infectious diseases. Resources could better be spent elsewhere.

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5 For more technical details on producing mRNA vaccines, see Sousa Rosa *et al* (2021).

With more prospects for greater economic returns were the cancer immunology mRNA applications. Following a successful trial on mice with a synthetic mRNA cancer vaccine, a spin-off from Duke University in the United States, Merix Bioscience (now called CoImmune), started in 1995 clinical studies on humans, but failed.

Meanwhile, Katalin Karikó, a Hungarian junior biochemist set out to find a way to make synthetic mRNA applicable to treat human diseases, with a special interest in cerebral diseases and strokes. While at the University of Pennsylvania, she tried unsuccessfully for years to obtain research funding, but her research was considered too risky, as she could not show preliminary findings. Her inability to support her research on grants resulted in her being taken off her faculty position at Penn. In 1995 she had to accept a non-faculty position, without prospect of advancing.

In 1997, she met at the school's photocopier, Drew Weissman, an immunologist, who shared her interest in developing a synthetic mRNA vaccine, specifically against HIV. Weissman could support their early-stage joint work partly on one of his existing NIH grants, which had no direct connection to mRNA research. Their breakthrough occurred when they discovered that when they replaced one of mRNA's four chemical building blocks, a nucleoside called uridine, with a slightly modified nucleoside called pseudouridine, it could enter into cells without alerting the RNA sensors. Their research was published in *Immunity* in 2005, after being rejected by several leading journals[6]. Though their breakthrough article is now extensively cited, and both researchers are highly recognised and the recipients of numerous prestigious prizes, in the first years after publication, they received only a few citations, as the scientific community remained sceptical about the mRNA approach. Karikó continued to have problems obtaining funding for her research. Weissman was more successful though he also had a number of funding bids turned down. Nevertheless, a few scientists picked up on their findings. A team led by Derrick Rossi, a stem-cell biologist, used the pseudouridine mRNA approach of Karikó and Weissman to successfully transform skin cells. In 2010, Rossi co-founded Moderna. Ingmar Hoerr, with a PhD on mRNA vaccines from the University of Tübingen, after some early successes with mouse data, founded CureVac together with his supervisors in 2000. Ugur Sahin and his wife Ozlem Tureci, at the University of Mainz in Germany, also began studying mRNA technologies in the late 1990s for application in cancer drugs. They started BioNTech in 2007.

The University of Pennsylvania filed and obtained patents on the Karikó and Weissman invention then granted exclusive patent rights to Cellscript, a small company in Madison, US, that produced lab

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6 Gina Kolata, 'Kati Kariko Helped Shield the World from the Coronavirus', *New York Times*, 8 April 2021, https://www.nytimes.com/2021/04/08/health/coronavirus-mrna-kariko.html.

reagents. Karikó and Weissman started their own company, RNARx. RNARx did not manage to secure a licensing agreement with Cellscript and ceased operations in 2013. Cellscript licensed non-exclusively to BioNTech and Moderna, collecting handsome licensing fees. CureVac did not use the stabilisation-through-pseudouridine approach and therefore did not license the University of Pennsylvania patent. In 2013, Karikó became senior vice president at BioNTech.

In 2012, the US Defense Advanced Research Projects Agency (DARPA) began funding groups at Novartis, Pfizer, AstraZeneca, Sanofi Pasteur and elsewhere to work on RNA-encoded vaccines and therapeutics. None of the big-name firms however stuck with the technology.

The subsequent development of the mRNA-based technology for human medical applications was conducted by BioNTech, Moderna, CureVac and other small biotech companies. Potential applications beyond infectious diseases included rare diseases but particularly cancer was a major target area.

By the end of 2019, at the start of the COVID-19 pandemic, only a dozen clinical trial candidates had gone into people. About one third of these were abandoned after initial testing. Only one, from Moderna for a herpes virus, had progressed to a larger, follow-on study. None of the mRNA-based human drug projects had reached the market.

4 Developing mRNA COVID vaccines: a blockbuster

The fast and successful development of the mRNA COVID-19 vaccine should be considered as the outcome of a long and bumpy process of accumulation of innovation and capacity over time, which had reached sufficient maturity at a key moment when researchers could mobilise the technology they had been developing for many years to fight the novel coronavirus.

Already in January 2020, within four days of receiving the SARS-CoV-2 genome sequence, Moderna finalised the sequence for its mRNA vaccine, and was able to start in March 2020 clinical trials with humans. BioNTech started clinical trials in May 2020, joint with Pfizer. By December 2020, the Moderna and BioNTech/Pfizer vaccines had been approved for emergency use, meaning the time between the outbreak of the pandemic and the first approvals was only one year. Oxford/AstraZeneca, using the incumbent viral vector (VV) technology, obtained approval almost at the same time as BioNTech/Pfizer and Moderna in the United Kingdom and the EU, though at time of writing approval is still pending in the US. The VV vaccine from Johnson & Johnson obtained US emergency authorisation at the end of February 2021.

Not only were mRNA-based COVID-19 vaccines developed rapidly, clinical trials showed them to be very safe and with very high efficacy rates, much higher than normal for vaccines, beating expectations. The two approved mRNA vaccines proved highly effective also against mutations of the original coronavirus, including the Delta variant.

A third mRNA vaccine from Germany's CureVac had disappointing Phase 3 clinical trial results (CT3), with efficacy levels below 50 percent, a threshold for approval. CureVac choose not to use the modifications used by Moderna and BioNTech. These modifications, using the patented pseudouridine, help to avoid immune-defence reactions but also turned out to boost antibody response. CureVac went for the alternative self-replicating mRNA approach, with which it could reduce the dose for its vaccine (12 micrograms, compared to, eg, 100mg for Moderna). This different mRNA path chosen by CureVac may have resulted in its vaccine being insufficiently immunogenic. It is a reminder that mRNA technology is still early stage, with many unknowns, and is highly risky. CureVac abandoned its mRNA vaccine project in October 2021[7]. In collaboration with GlaxoSmithKline, CureVac is now working on another COVID-19 vaccine, this time using unmodified mRNA.

Beyond these three mRNA COVID-19 vaccine projects, more than 20 projects are in CT1 and/or CT2 using mRNA technologies to develop coronavirus vaccines, and there are more than 30 preclinical projects (ie about 20 percent of all coronavirus vaccine projects)[8]. US Arcturius Therapeutics, joint with Duke-NUS@Singapore, is in CT3 with a self-replicating mRNA vaccine candidate.

Failures are not uncommon, reflecting the high-risk nature of vaccine development. An early CT1 mRNA vaccine failure was from Imperial College London. France's Sanofi, joint with US based TranslateBio, abandoned its mRNA project in CT1/2 at the end of September 2021. Surprisingly for a new technology, but a testament to its game-changing potential, mRNA projects have not had worse failure rates for COVID-19 vaccines compared to incumbent vaccine technologies.

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7 See Zuzanna Szymanska and Ludwig Burger, 'CureVac drops COVID-19 vaccine, pins hope on next-generation shots', *Reuters*, 12 October 2021, https://www.reuters.com/business/healthcare-pharmaceuticals/curevac-withdraw-first-generation-covid-19-vaccine-candidate-2021-10-12/.

8 Source: own calculations based on WHO.

5 Producing mRNA COVID-19 vaccines: performance beyond expectations

The mRNA-based COVID-19 vaccines have also performed beyond expectations in terms of production, taking into account that this is also a new and different technology for the existing vaccine producers.

As mRNA is synthetic compared to incumbent biological vaccine technologies, existing vaccine production technology needed to be retooled or new production capacity built. Existing production capacity is either in facilities directly owned by major developers or by independent specialised companies contracting with developers, or acquiring licenses from developers to produce. Swiss Lonza and Celonic are large contract manufacturers for drugs. India's Serum Institute was the largest contract producer of vaccines pre-COVID-19, and is the major supplier of vaccines for low-income countries.

The synthetic mRNA vaccines can be produced more robustly at scale than other vaccines, which must rely on biological processes to produce inactivated viruses. Both AstraZeneca and Johnson & Johnson have faced problems in the manufacturing of their VV vaccines. A weakness of the mRNA vaccines compared to other vaccines is their need to be stored at very low temperatures. VV vaccines only need to be refrigerated rather than frozen.

In the third quarter of 2021, mRNA vaccines represent somewhat less than half of all production capacity for World Health Organisation (WHO) approved vaccines[9]. This is quite impressive for a new production technology and shows the advantages of mRNA technology for producing vaccines. Most of the current production capacity is in the US and Europe. The Serum Institute at time of writing does not produce mRNA vaccines. Both BioNTech and Moderna have announced plans to build production capacity also in other parts of the world[10]. Compared to Moderna, BioNTech/Pfizer has the largest production share with somewhat more than one third of all production capacity of WHO-approved vaccines. Most of its production is in-house in Pfizer's US and Belgian plants.

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9 Source: own calculations based on Airfinity (Q4 2021).

10 See Stephanie Nolen, 'Here's Why Developing Countries Can Make mRNA Covid Vaccines', *New York Times*, 22 October 2021, https://www.nytimes.com/interactive/2021/10/22/science/developing-country-covid-vaccines.html.

6 Supplying mRNA COVID vaccines

Being fast, safe, effective, robust against variants and stable in terms of their production at large scale, compared to alternatives, mRNA vaccines have become the major vaccines in use to deal with the pandemic.

Beyond the two mRNA vaccines from BioNTech/Pfizer and Moderna, the US has also approved the Johnson & Johnson VV vaccine, but not the AstraZeneca vaccine. Figure 1 shows that the two approved mRNA vaccines from Pfizer/BioNTech and Moderna represented in the second quarter of 2021 more than two thirds of all US supply agreements for approved vaccines.

Beyond the two mRNA vaccines, the EU has approved both the AstraZeneca and the Johnson & Johnson VV vaccines. The two mRNA vaccines represented about half of vaccines to be supplied to the EU (second quarter 2021). Although initially AstraZeneca was set to be the leading supplier of vaccines to the EU, the company's failure to guarantee production and certain safety concerns caused them to lose their leading supply position in the EU to BioNTech/Pfizer. By the third quarter of 2021, the two mRNA technology vaccines represented 85 percent of the EU's supply agreements, similarly to the US[11]. All booster vaccinations in the US and the EU are currently mRNA vaccines only.

Outside the major markets of the US and EU, mRNA vaccines take smaller shares of supply agreements. The WHO has approved, in addition to the two mRNA vaccines, the AstraZeneca vaccine and its Indian Serum Institute sister Covishield, the Johnson & Johnson vaccine and the Chinese Sinovac and Sinopharm (both inactivated viruses)[12]. WHO-approved vaccines can be distributed through COVAX, the initiative to distribute COVID-19 vaccines worldwide. Within the COVAX supply agreements, AstraZeneca and the one-dose Johnson & Johnson are currently the leading vaccines. Manufacturing bottlenecks have hindered both AstraZeneca and Johnson & Johnson from providing COVAX with the promised vaccines. Meanwhile, the supply of mRNA vaccines globally is set to increase, with promised donations from the US and EU and plans to increase production capacity for the rest of the world[13].

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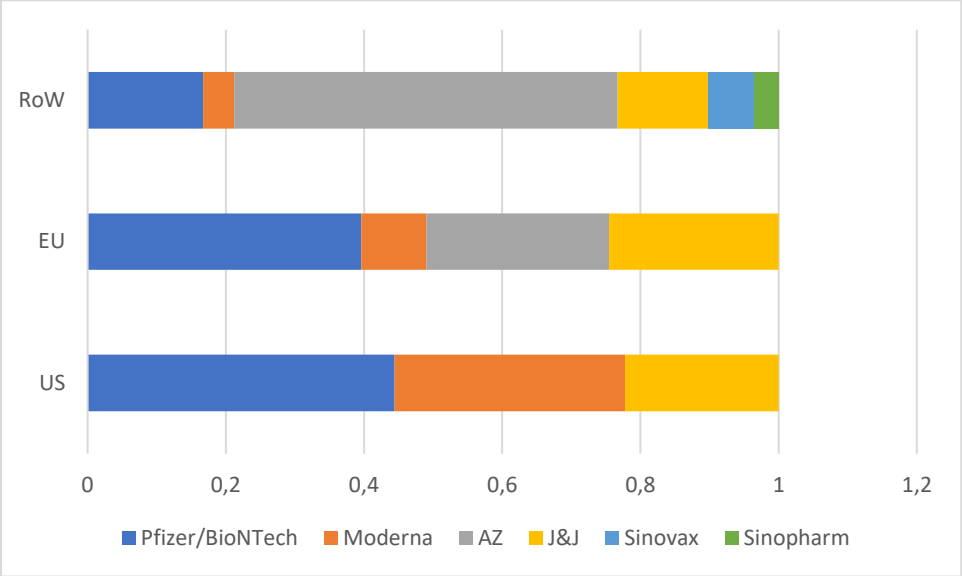
11 Source: own calculations based on Unicef. See https://www.unicef.org/supply/covid-19-vaccine-market-dashboard.

12 See https://covid19.trackvaccines.org/agency/who/.

13 See for example *Reuters*, 'Moderna to supply 56.5 mln more doses of its COVID-19 shot to vaccine alliance GAVI', 29 October 2021, https://www.reuters.com/business/healthcare-pharmaceuticals/moderna-supply-565-million-more-doses-global-vaccine-alliance-gavi-2021-10-29/; and Michael Erman and Manas Mishra, 'Pfizer expects 2021, 2022 COVID-19 vaccine sales to total at least $65 bln', *Reuters*, 2 November 2021, https://www.reuters.com/business/healthcare-pharmaceuticals/pfizer-raises-covid-19-vaccine-sales-forecast-36-billion-2021-11-02/.

Figure 1: Shares of major COVID-19 vaccines in supply agreements, by region (doses)



Source: Airfinity as reported by the *Financial Times*. Note: Only WHO-approved vaccines are included: BioNTech/Pfizer, Moderna, AstraZeneca, Johnson & Johnson, Sinovac, Sinopharm, Covishield.

Prices of vaccines vary depending on product, time and region. Price differences reflect differences in costs of developing, producing and supplying vaccines, and also different company policies. Prices for the mRNA vaccines are in the range of $15-$40 per dose. This is higher than the VV vaccines from AstraZeneca and Johnson & Johnson, who committed to operate on a non-profit basis during the pandemic (with low prices of $3-$4 per dose for AstraZeneca and $10 for Johnson & Johnson). Projections for worldwide sales revenues for Pfizer/BioNTech vaccine in 2021 topped $26 billion[14], increasing to $33.5 billion as the vaccine is the lead vaccine for the EU and US booster programmes. For Moderna, which has been unable to scale up as quickly as BioNTech/Pfizer, sales projections for 2021 are smaller, yet still sizable: $19 billion. Estimates for the non-mRNA vaccines are much lower (Johnson & Johnson, $2.5 billion; AstraZeneca, $1.7 billion) (Statista, 2021).

7 The countries behind the mRNA COVID-19 vaccines

With both of the approved mRNA based vaccines originating in the EU or the US, the US and EU are the first movers and leaders in mRNA technology for vaccines. Also in the mRNA late-stage pipeline, the EU and the US dominate. Nevertheless, a few projects in the early phases of development originate from outside the EU and US. Japan, South Korea, Canada and India each have at least one mRNA project in early-stage clinical trials. China's approved vaccines are all based on the old inactivated virus

[14] Predictions in July 2021. Source: Statista.

technology. It is however also active on the mRNA technology. China's Academy of Military Medical Sciences, jointly with Suzhou Abogen BioSciences, has an mRNA-based vaccine in late development.

8 The firms behind the mRNA COVID-19 vaccines

8.1 Pre-COVID-19: small, young, academia-linked biotech

Pre-pandemic, the global vaccines market was highly concentrated, with four big vaccine producers, jointly representing about 90 percent of global vaccine revenues in 2019 (Statista, 2021). GSK was in 2019 the largest vaccine company, accounting for 24 percent of global vaccine revenues, closely followed by Merck (23.6 percent). Sanofi and Pfizer each had about one fifth of the market. Johnson & Johnson entered the vaccines market only recently. Novartis was previously one of the leading vaccine companies, but left the vaccines market in 2018 when it sold most of its vaccine business to GSK.

This high concentration reflects the importance of scale and big fixed investments in technology, production and distribution capacity. Clinical trial and commercialisation expertise, marketing and brand recognition, and deep pockets are other major advantages for big pharma.

With mRNA being a new, risky, disruptive technology for vaccine development (and drugs in general), it is unsurprising that new players, rather than the incumbent vaccine producers, were the first movers to develop this disruptive technology for infectious diseases.

Only a handful of young biotech firms were actively developing mRNA based drugs (section 3). Germany's CureVac, founded in 2000, is the 'oldest' of the young biotech firms working on mRNA vaccines. BioNTech, also German, was founded in 2008, the US's Moderna in 2010. Each had close ties to academia in their start-up phases, with lead academics as founders, employees or board members. The business models of all three companies were centred on mRNA technology for drug development. They were working on infectious diseases and also covering a wider set of applications, most notably cancer, and also rare diseases[15].

In the early 2000s, the four leading incumbent vaccine producers had the technology on their radar, but were not actively developing mRNA vaccine projects. Their development projects used the incumbent viral vector or protein-based technologies. A team at the Novartis research hub in Cambridge, Massachusetts was working in 2013 on RNA technology for vaccines. Novartis was at that

[15] There were also other mRNA start-ups, such as Translate Bio, a Massachusetts based company founded in 2011 and Arcturious Therapeutics, a California company founded in 2013, but these had a focus on therapeutics, not vaccines.

time a leading vaccine producer. The project however never got traction, and five years later Novartis sold its vaccines business to GSK. GlaxoSmithKline, which had acquired most of Novartis's vaccine assets, began evaluating an RNA-based rabies vaccine in 2019.

Pfizer entered in 2018 into a partnership with BioNTech to develop flu vaccines based on BioNTech's mRNA platform. Pfizer agreed to a $120 million upfront payment to BioNTech for research and an additional $305 million in potential payments. The agreement specified that after BioNTech had successfully completed its first clinical studies, Pfizer would be responsible for further clinical development and commercialisation. The deal thus exploited the comparative advantages of both parties. BioNTech would receive royalty payments based on worldwide sales in case of commercialisation.

Also Sanofi Pasteur, the global vaccines business unit of Sanofi, entered in 2018 into a cooperation and exclusive license agreement with Translate Bio to use their mRNA platform, which the company had been developing, most specifically for pulmonary diseases. Their cooperation was aimed at developing mRNA vaccines against infectious diseases, given Sanofi's interests.

That was more or less the full extent of clinical development for mRNA vaccines at the beginning of 2020. MRNA platforms were being developed by young companies, with the incumbent vaccine producers having the technology on their radar and some of them engaged in cooperative agreements with young mRNA biotech firms.

8.2 COVID-19: young biotech within the wider biopharma ecosystem

As soon as the genetic code of the coronavirus became public in January 2020, the young biotech firms that had been developing mRNA platforms were very quickly willing and able to use their mRNA platforms to develop coronavirus vaccines.

BioNTech identified several candidates for a COVID-19 vaccine, ready to start clinical trials. Building further on the collaboration it started in 2018 with Pfizer for influenza, it entered in March 2020 into a partnership with Pfizer to co-develop and co-commercialise coronavirus vaccine candidate BNT162, first for the US and Europe, to later scale up for global supply[16]. Similar to its 2018 agreement on mRNA flu vaccines, BioNTech received an upfront payment from Pfizer of $185 million. In addition, future milestone payments of up to $563 million were agreed. The deal gave Pfizer the right to use BioNTech

[16] The agreement excluded China, as BioNTech had already a license agreement with Fosun, granting the latter the right to manufacture and distribute in China.

COVID-19 vaccine patents. They agreed to split any possible revenues from a vaccine 50/50. Clinical trials started in May (with the BNT162b2 candidate Comirnaty). Successfully passing CT1/2 and CT3, BioNTech's was the first vaccine to be approved for emergency use in the US, UK and the EU, by the end of December 2020. It received full US Food and Drug Administration approval at the end of August 2021.

The partnership combined BioNTech's mRNA vaccine technology and expertise with Pfizer's financial resources, and its clinical development and regulatory expertise and vaccine production capacity. The initial production of the BNT162 vaccines at small scale for the initial clinical trials was done in BioNTech and Pfizer facilities. But for the larger-scale production of BNT162b2, Pfizer's production infrastructure in the US and Belgium was critical. BioNTech had only two production facilities for clinical trial production of its vaccines. BioNTech's production capacity was expanded when it acquired Novartis's facilities in Marburg, Germany. These facilities had to be mRNA refitted from their previous cancer immunotherapy application.

Moderna began developing a coronavirus vaccine on its mRNA platform in January 2020. The Moderna vaccine, Spikevax or mRNA-1273, delivered similar safety and efficacy results to Comirnaty, the Pfizer/BioNTech vaccine. Moderna's vaccine was authorised in the US only a week after Comirnaty. Unlike BioNTech, Moderna did not co-develop and co-commercialise with another (big) pharma-partner. It co-developed its vaccine with the US National Institute of Allergy and Infectious Diseases (NIAID) and could rely on US government support to finance its clinical trials. It also benefitted from advanced purchase agreements to bankroll its development and production, initially from the US, but also later from the EU and several other countries. Although it did not join with big pharma for its COVID-19 vaccine, Moderna engaged in several strategic research and licensing agreements, including with Merck and AstraZeneca. For the large-scale manufacturing of its COVID-19 vaccine, it entered into agreements with contract manufacturing firms. For instance, in May 2020 it signed a long-term agreement with Lonza, a Swiss multinational that provides development and manufacturing services to the biopharma sector. Lonza has major production facilities in Europe, the US and South Asia.

Curevac was also in a position to use its mRNA platform to quickly start developing a COVID-19 vaccine. Unlike BioNTech and Moderna, it chose to use an unmodified, self-replicating mRNA approach, which it hoped could reduce the dose for its vaccine, thus reducing costs. It also had simpler cold-chain requirements, facilitating storage and distribution. It started clinical trials in June 2020, somewhat later than BioNTech and Moderna. With good results on safety and efficacy from its CT1/2, it started in December 2020 the larger-scale CT3, supported by Bayer, a big pharma company. Reports about US President Trump's interest in paying CureVac to secure exclusive rights to a potential coronavirus

vaccine benefitted the company and helped secure funding from the German government and the EU[17]. Building on its initial clinical trial success, and an advance purchase agreement with the EU, CureVac also started to prepare for production at large scale, setting up a series of partnerships with big pharma companies including Bayer, GSK and Novartis[18], and with Swiss-based Celonic, a contract development and manufacturing organisation with production facilities in Germany and Switzerland.

In June 2021, however, CureVac reported disappointing CT3 results. The different mRNA path chosen by CureVac may have resulted in its vaccine being insufficiently immunogenic. In October 2021, CureVac abandoned its mRNA vaccine project. It started working on a new COVID-19 vaccine, this time using unmodified mRNA and in collaboration with GSK.

8.3 COVID-19: large incumbent vaccine firms within the wider biopharma ecosystem

With the exception of Pfizer, which partnered with BioNTech, the major incumbent vaccine developers, were late or unsuccessful movers in terms of COVID-19 vaccine development.

GSK joined forces with Sanofi to develop a COVID-19 vaccine based on Sanofi's protein-manufacturing platform, used for its seasonal flu vaccines, together with GSK's adjuvant platform. They received support from the US Biomedical Advanced Research and Development Authority (BARDA). After poor CT1/2 results, they had to reconfigure their vaccine. With an improved antigen formulation, they are at time of writing in CT3.

Alongside its joint project with GSK, Sanofi joined in June 2020 with TranslateBio to use the latter's mRNA platform to develop a COVID-19 vaccine. In September 2021, Sanofi fully acquired TranslateBio. At the end of September 2021, Sanofi announced it would drop its mRNA-based COVID-19 vaccine, because CT1/2 results were, although positive, not considered strong enough to compete with the mRNA vaccines already on the market.

Merck had two COVID-19 vaccine projects, both of which it abandoned in January 2021. One project used its measles virus vector platform, the other, in collaboration with IAVI, a non-profit US research organisation, used the Merck viral vector technology that was also used against the Ebola virus. It

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[17] See eg Reuters, 'Germany tries to stop US from luring away firm seeking coronavirus vaccine', 15 March 2020, https://www.reuters.com/article/health-coronavirus-germany-usa-idUSL8N2B8075.

[18] Novartis (March 2021 initial agreement for manufacturing of CureVac's COVID-19 vaccine candidate CVnCoV); Bayer (January 2021 collaboration and services agreement for the development and supply of CureVac's CVnCoV candidate); GlaxoSmithKline (July 2020 collaboration and license agreement to research, develop and commercialise CureVac's prophylactic and therapeutic non-replicating mRNA-based vaccines targeting infectious diseases).

worked on a therapeutic oral candidate to treat COVID-19, in partnership with US-based biotech company Ridgeback Bio. Merck entered a partnership to support the manufacturing and supply of Johnson & Johnson's viral vector COVID-19 vaccine.

Johnson & Johnson, which had only entered the vaccine market recently, developed a COVID-19 vaccine with the viral vector technology. More than two months after the first mRNA vaccines, Johnson & Johnson's coronavirus vaccine was approved for emergency use. Initially, the company struggled to manufacture its vaccines at the facilities of its US-based Emergent Solutions contractor. Concerns about rare blood-clot side effects also hampered the vaccine's initial roll-out. Its single dose was considered a comparative advantage, especially for supply to least-developed countries. But manufacturing problems have so far prevented the company from providing COVAX its promised doses of its vaccine.

AstraZeneca, another big pharma company, but not specialised in vaccines, entered into an agreement with Oxford University to co-develop and commercialise Oxford's COVID-19 vaccine, which uses the viral vector technology. Only days after the first mRNA vaccines in the US, it received approval for emergency use in the UK and in the EU. Its vaccine has a high efficacy, including against variants of the coronavirus, and has a low price and easier distribution, requiring refrigeration rather than freezing. But, like Johnson & Johnson's VV vaccine, its roll-out has been turbulent, with safety worries arising from rare blood-clot cases and manufacturing difficulties. Also clinical trial hiccups have prevented AstraZeneca from obtaining approval in the US. Supply shortfalls of the vaccine, particularly to least-developed countries via COVAX, worsened when India blocked the export of the vaccine from its licensee the Serum Institute, responsible for most of the AstraZeneca supply to least-developed countries. Confusing communication also undermined trust in the company, leading it to lose its leading position in EU vaccine supply agreements.

Coronavirus vaccines using the old inactivated-virus technology have been important in China and India[19]. They perform less well than mRNA and VV vaccines, and have limited approvals and use worldwide.

The drivers behind the breakthrough performance of mRNA vaccines were young US and EU biotech firms. But this happened within a wider biomedical ecosystem with many partners from academia, incumbent big pharma and biopharma services/production providers.

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[19] The French Valneva has an inactivated virus coronavirus vaccine in CT3.

9 mRNA COVID vaccines: a complex patent landscape

Vaccine technologies are typically well protected by patents. The patent landscape for the mRNA COVID-19 vaccines is a complex network.

Moderna, BioNTech and CureVac mRNA patents cover typically particular sequences of mRNA, such as the form of the spike protein synthesised.

The University of Pennsylvania holds more broad patents for mRNA technology, covering pseudouridine, which is used by both the Moderna and BioNTech modified mRNA vaccines. These patents, in line with the US Bayh-Dole Act, acknowledge US National Institutes of Health (NIH) grants, including the grant that had no direct connection to mRNA research (see section 3)[20]. The Act provides the US government with an array of retained rights in the work that it funds. Moderna and BioNTech licenses of the University of Pennsylvania patent contain a 'US government rights' clause, stating that they are *"expressly subject to all applicable United States government rights, including, any applicable requirement that products, which result from such intellectual property and are sold in the United States, must be substantially manufactured in the United States"*.

Patents cover not only the mRNA technology or vaccines directly, but also the lipid nanoparticles and the delivery system technology. Some early work on lipid nanoparticles was done by the University of British Columbia and Arbutus Biopharmaceuticals in 1998 and was patented. CureVac, Moderna and BioNTech all use these technologies and have access through arrangements and direct or indirect sublicenses. There are however legal entanglements related to the validity of these patents.

BioNTech and Moderna have each been somewhat active in seeking to invalidate competitor patents, with BioNTech filing oppositions against Moderna and CureVac patents, and Moderna filing opposition against a CureVac patent.

So far, no patent infringement lawsuits have been initiated by BioNTech, Moderna or CureVac. Undoubtedly companies do not want to be seen as hindering vaccination efforts in the full heat of the pandemic. The potential to invoke patent waivers might constrain companies from being too aggressive in exercising their IP rights.

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[20] The 1980 Bayh-Dole Act allows recipients of federal research funding the right to seek patents on inventions arising from that funding.

10 Public funding of mRNA COVID-19 vaccines

Public funding plays a substantial and critical role in vaccine development and production. Besides co-funding R&D projects, governments are the main purchasers of vaccines, and can support vaccine R&D projects if they commit to buying before approval, through advance purchase agreements, at guaranteed prices, improving the risk/reward trade-off for vaccine R&D projects.

10.1 Public funding of research

The development of mRNA vaccines relied on findings from basic research, mostly done in academia. The primary funder of basic research in biomedical sciences in the US is NIH. In the EU, beyond the science funding available at member-state level, there is the European Research Council (ERC) in the Excellent Science pillar of the EU's multi-annual Framework Programmes for Research (FP).

Franzoni *et al* (2021) discussed the bias against novel risky research in public science funding. In general, MRNA for vaccines and drug development, is a new high risk approach, and thus a victim of the risk bias in public science funding. Karikó and Weissmann's problems in getting their research funded by NIH and, for Karikó, not being supported by her university, illustrate the bumpy road for funding of early phases of research into mRNA. In the EU, CureVac won in 2014 a €2 million Horizon 2020 inducement prize for research into solving the vaccine 'cold chain' problem. Although the prize was not for its mRNA platform, CureVac won on the basis that its mRNA platform could produce vaccines stable at room temperature for long periods of time, thus not needing a 'cold chain'. ERC grants are relatively new instrument in the EU's FP, to fund high gain/high risk research. Sahin, the founder of BioNTech, received a €2.5 million ERC grant but only in 2018, and for his mRNA cancer immunology research at the University of Mainz.

In terms of high risk research funding, the US DARPA is frequently heralded for its successes in funding mission-oriented high-risk, high-reward research. Key to its success is attracting programme staff, who resemble more risk-taking, idea-driven entrepreneurs than administrators. Combined with high accountability and clear targets, programme directors have high individual discretion to design and select projects (Azoulay *et al*, 2019). DARPA recognised the high gain potential and was willing to take on the risk of supporting the development of mRNA for vaccines, already in its early research stages. Amy Jenkins, a programme director at DARPA, said, *"it was something that was much too risky for groups like the NIH to fund. There are scientific reasons why it may not work, but there are also*

scientific reasons why it may work, and that's absolutely the right place for DARPA to be investing"[21]. DARPA began funding groups developing RNA-encoded vaccines and therapeutics. All of the big pharma firms that received funding dropped out. Only CureVac and Moderna continued. DARPA funded CureVac and Moderna with contracts for developing their mRNA platforms for infectious diseases: $33 million for CureVac in 2011and $25 million for Moderna in 2013. In October 2020, DARPA provided Moderna with a grant for small-scale, rapid, mobile manufacturing of vaccines. Although the DARPA amounts were small in the total funding portfolio of these companies, they were nevertheless important as they covered early-stage and highly risky projects in the firms' portfolios in their early lives.

10.2 Public funding of development

For the relatively less-expensive, yet high risk, preclinical and early-stage CT1&2 development stages[22], public funding is typically still available. For vaccines, the US National Institute of Allergy and Infectious Diseases (NIAID), a division of NIH, acts as public funder in the US. Moderna received funding and co-partnered with NIAID for its COVID-19 vaccine. Public funding at the more expensive CT3 development stage is usually confined to much smaller shares of co-funding, in public private partnerships, if at all. In the US, this runs through the Biomedical Advanced Research and Development Authority (BARDA), which is a division, set up in 2007, of the Department of Health and Human Services, and NIAID.

The EU Framework Programme for research typically does not fund late-stage development. It has started more recently, though still on a small scale, to engage in public-private partnerships to co-fund development stages for specific (rare) diseases, through the Innovative Medicines Initiative (IMI). IMI, the EU's public-private partnership for funding early stage development of drugs, had no mRNA vaccine projects in its portfolio prior to the pandemic.

Loans from the European Investment Bank/European Investment Fund Group can cover later-stage development and production, through the European Fund for Strategic Investments (EFSI) and the InnovFin Infectious Diseases Finance Facility (IDFF). Pre-COVID-19 (in December 2019), BioNTech

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[21] Amy Jenkins, a programme manager in DARPA's Biological Technologies Office, interviewed by *BioCentury*. See Steve Usdin, 'DARPA's gambles might have created the best hopes for stopping COVID-19', *BioCentury*, 25 March 2020, https://www.biocentury.com/article/304691/darpa-s-gambles-might-have-created-the-best-hopes-for-stopping-covid-19.

[22] Aggregating success rates at the various stage leaves about an average 10 percent to 15 percent success rate for drug development overall. The highest dropouts occur in the early (pre-) clinical stage, the stage at which the development costs are still modest. While the early preclinical and Phase 1 stages require still modest budgets of on average €2.5 million, the most expensive stage, Phase 3, when testing for efficacy on a large scale, can run up budgets 100 times larger, up to €250 million. See for example Veugelers and Zachmann (2020).

received €50 million in venture debt financing for its personalised cancer immunotherapy programme. For its COVID-19 vaccine, it signed a €100 million euro loan agreement for the development and large-scale production of a portfolio of vaccines, including a vaccine candidate against SARS-CoV-2. Also, CureVac received in July 2020 a €75 million loan from the EIB.

A major new public-private funder dedicated to vaccine R&D at the global level is the Coalition for Epidemic Preparedness Innovations (CEPI), set up in 2017. CEPI supports a range of vaccine technology approaches for a range of infectious diseases. CEPI also invested in platform technologies that can be used for rapid vaccine development against unknown pathogens (Disease X). CEPI funds not only the research but also preclinical and early-stage clinical projects. CEPI operates not only as a funder, but also as a facilitator in an end-to-end approach, establishing partnerships for standardising clinical trials, as well as aiding manufacturing and distribution of vaccines. Its funding is a mix of public funding, with Norway, Germany and Japan the major country donors[23], and, on the private side, the Gates Foundation and the Wellcome Trust. Its advisory committee has executives from big pharma.

CEPI had several coronavirus-vaccine projects in its portfolio (Table 1). CEPI supported Moderna's mRNA-based coronavirus vaccines with $900,000. More substantial support was provided to CureVac. Most of CEPI's funding however went to the incumbent viral vector and protein technologies. Oxford was the major CEPI fund receiver for its VV coronavirus vaccine project. Although CEPI clearly helped to bridge the funding gap between vaccine research and early development, it still seemed constrained to allocate its limited budget to more risky, novel approaches.

Table 1: CEPI's portfolio of coronavirus vaccines 2020-2021

Company	Country	Technology	Current Status	Amount $m
Moderna	US	mRNA	Approved	0.9
CureVac	Germany	mRNA	Discontinued	15.3
AstraZeneca/Oxford	UK	Viral Vector	Approved	383
Inovio	US	DNA	CT2	22.5
Novavax	US	Protein	CT3	388
Clover	China	Protein	CT2/3	328
Biological E Ltd	India	Protein	CT1/2	5
SK Biosciences	S Korea	Protein	CT1/2	10 & 26.7
University of Hong Kong	HK	Viral Vector	Preclinical	0.6
VBI Vaccines	US	Viral Vector	Preclinical	33
Pasteur, Themis & University of Pittsburgh	FR/US	Measles Vector	Discontinued	4.9
University of Queensland	AUS	Protein	Discontinued	4.5

Source: https://cepi.net/wp-content/uploads/2020/12/Enabling-equitable-access-to-COVID19-vaccines-v4-18Mar2021.pdf.

[23] The EU also co-funds selected CEPI projects.

10.3 Public funding for commercialisation: advanced market commitments

Expected revenues provide the incentive for firms to invest and take the risks of engaging in vaccine R&D projects. North America and Europe are the critical markets for private incentives: representing less than one fifth of vaccine volumes, they represents about two third of vaccines revenues (Statista, 2021). Governments are the main purchasers of vaccines, and their willingness to buy vaccines, particularly before approval (advanced market commitments, AMCs) at guaranteed prices, critically affects the risk/reward trade-off for vaccine R&D projects and thus private investment incentives (eg Kremer *et al*, 2020).

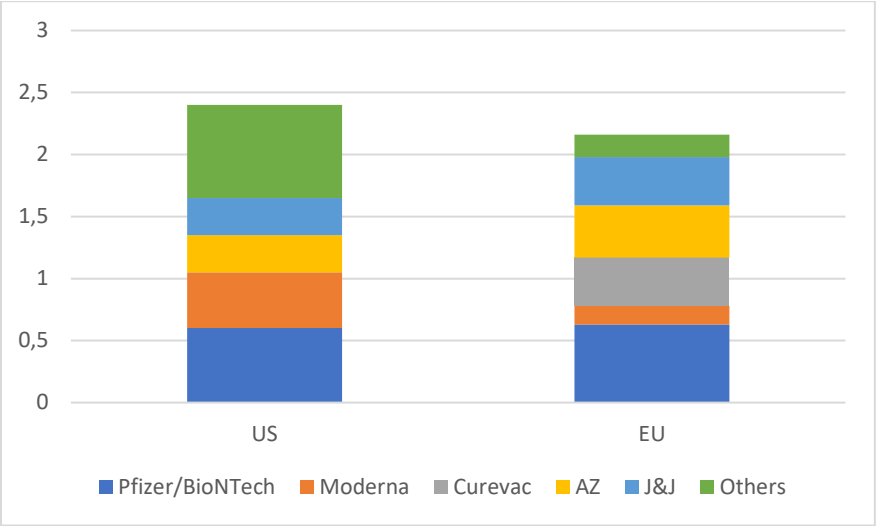
At the outbreak of the COVID-19 pandemic, the US government set up an interagency partnership between BARDA and the Department of Defense, known as Operation Warpspeed (OWS). To coordinate federal efforts to accelerate the development, acquisition and distribution of COVID-19 medical countermeasures. BARDA/OWS funds later-stage development, increases in manufacturing capacity and advance purchase contracts. With a total budget for vaccines committed up to August 2021 of about $28 billion, most of this budget (about 70 percent) went to advance agreements. BARDA/OWS at time of writing supports six vaccine candidates: Pfizer and Moderna with mRNA, Johnson & Johnson and AstraZeneca with VV, and Novavax and Sanofi/GSK with protein technology. Because of the success of the mRNA vaccine candidates in obtaining FDA clearance, it is not surprising that about 70 percent of the BARDA/OWS vaccine budget went to mRNA vaccines. Pfizer has received to date almost $10 billion, all of it via advance purchase arrangements. Moderna has received about $9.5billion, 15 percent of this for late stage CT and manufacturing capacity development.

Before the coronavirus pandemic, the EU did not engage in advance purchase agreements, which is an EU member-state competence. In response to the COVID-19 pandemic, the European Commission could use €2.15 billion from the Emergency Support Instrument, a special mechanism put in place by the EU, to coordinate negotiations for the advanced purchase of vaccines. The Commission signed seven advance purchase agreements with vaccine developers, including the Pfizer/BioNTech and Moderna mRNA vaccines, and also the CureVac mRNA vaccine. With a much smaller budget, the Commission managed to secure 2.16 billion doses (compared to 2.4 billion secured by the US). The EU had a larger share of lower-priced vaccines from AstraZeneca and Johnson & Johnson in its portfolio[24].

[24] Negotiated prices are typically not publicly available, which makes it difficult to compare prices across vaccines and between the EU and the US. In December 2020, a list of prices the EU had paid for its vaccines leaked in the press (see eg Jillian Deutsch and Camille Gijs, 'Belgian secretary of state accidentally reveals EU vaccine prices', *Politico*, 17 December 2020, https://www.politico.eu/article/belgian-secretary-of-state-

The European Commission initially advance-purchased only moderate volumes of more expensive mRNA-based vaccines, but gradually, when their effectiveness, safety and reliability became clearer, newer agreements concentrated increasingly on the mRNA vaccines, at least the two successful ones. Its lower budget and later purchase of major shares of mRNA vaccines limit the impact of the EU supply agreements on the risk/reward balance of private investment in mRNA technology.

Figure 2: Share of mRNA vaccines in total advanced purchase agreements (doses)



Source: Bruegel based on Airfinity as reported in the *Financial Times*.

11 Private funding of mRNA vaccines

Although public funding of vaccine projects is important and substantial, the claim sometimes made – that the state funds most of the R&D for vaccines, justifying patent waivers[25] – ignores the substantial amounts spent and risk taking by private funders. While large incumbent firms have deep pockets, for new, young, small biotech firms, access to external financing is critical, especially for the later, more expensive development stages, which are typically not covered by public funding. But perhaps even more important is the substantial risk taking by non-public funders in the early stages of the mRNA technology, to 'correct' for the risk bias in public funding.

The funding stories of the young mRNA vaccine firms, BioNTech, Moderna and CureVac, show the importance of private funding, especially in the pre-pandemic, risky, early stages of development of the mRNA technology. Private venture capital, including corporate venture capital support from big

accidentally-reveals-eu-vaccine-prices/). In this list, the price per dose for BioNTech/Pfizer was more than six times higher than the AstraZeneca price, Moderna was nine times higher, and CureVac 5 times higher.

[25] See eg *The Economist*, 'Mariana Mazzucato, Jayati Ghosh and Els Torreele on waiving covid patents', 20 April 2021, available at https://www.economist.com/by-invitation/2021/04/20/mariana-mazzucato-jayati-ghosh-and-els-torreele-on-waiving-covid-patents.

pharma, and public equity financing, proved critical for these companies. Philanthropy was also an important early-stage financing source. The Gates Foundation funded early-stage research by BioNTech, Moderna and CureVac.

BIONTECH

For its early pre-COVID-19 research and development projects, BioNTech did not receive any sizeable public support. Its initial financing came from various private venture capital sources. The German Strüngmann brothers[26] were early investors in BioNTech, and are currently the majority shareholder. BioNTech's 2018 partnership with Pfizer also provided financing for the development of its mRNA platform. And right before the outbreak of the pandemic, BioNTech raised $150 million via its Nasdaq IPO. Although the amount may seem modest, it helped to secure further equity investments, including from China's Fosun and Singapore based Temasek. The Gates foundation provided equity investment for BioNTech's mRNA based HIV and tuberculosis vaccines.

Public funding for BioNTech pre-COVID-19 was limited. The ERC grant its founder Sahin received in 2018 was for his mRNA cancer research. The EIB provided a €50 million loan in December 2019 for its work on cancer treatments. Public funding became more substantial after the pandemic outbreak, most notably from the German government (BMBF, Bundesministerium für Bildung und Forschung) and EIB loans. Advance purchase agreements also brought in funding. Pfizer and BioNTech agreed to split 50-50 the revenues from their COVID-19 vaccine.

Table 2: BioNTech's financial portfolio (at May 2021)

BioNTech major investors			
European Commission-H2020	ERC-AdG Grant (U.Sahin) (Cancer mRNA)	2018	€2.5 million
Various	Venture Capital	July 2019	$325 million
Gates Foundation	Equity investment for preclinical mRNA based vaccines	Sept 2019	$55m (further expandable with $45 in grants)
IPO on Nasdaq Oct 2019; Money raised at IPO $150m			
EIB (EFSI)	Loan	Dec 2019	€50 millon
FOSUN (CN)	Equity investment (plus license to manufacture and distribute COVID-19 Vaccine in China)	March 2020	$135 million
Temasek (SN)	Post-IPO equity	June 2020	$250 million
Pfizer	Partnership for COVID-19 Vaccine	April 2020	$185m (of which

[26] The Strüngmann brothers' fund is based on the $7 billion they got when selling their generic drug-making company to Novartis (Forbes.com).

			$113m equity investment)
EIB	Grant/loan	June 2020	€100 million
BMBF	Grant	Sept 2020	€375 million

Source: Bruegel based on Crunchbase (consulted May 2021) and company websites.

MODERNA

Moderna received substantial public money in its early stage. The 2013 DARPA grant of up to $25 million for developing mRNA-based therapeutics was small but critical, because of its early stage. But, particularly in this early stage, Moderna also secured substantial venture capital funding from various sources. Baillie Gifford, a global investment company with headquarters in the UK, is the biggest single investor in Moderna. Unlike BioNTech, Moderna did not enter into an agreement with a big pharma company to develop its mRNA platform and commercialise its mRNA COVID-19 vaccine. Nevertheless, it benefitted from the deep pockets of big pharma through several corporate VC deals. Like BioNTech, it also went public with its December 2018 IPO on Nasdaq, raising $600 million. Since the outbreak of the pandemic it has received substantial public funding from DARPA and BARDA. It ran its clinical trials in collaboration with NIAID. Also the returns made on its advance purchase agreements with BARDA/OWS, and later, to a smaller extent, with the EU, filled the financial pockets of Moderna.

Table 3: Moderna's financial portfolio (up to May 2021)

MODERNA's major investors			
	VC funding	2013	$110 million
DARPA	Contract	2013	$25 million
Alexion Pharma	Corporate VC	2014	$25 million
Various (incl AZ)	Late stage VC	2015	$450 million
Gates Foundation	Grant (HIV)	2016	$20 million
AZ	Corporate VC	2016	$474 million
Various	Late stage VC	2018	$500 million
Merck	Late stage VC	2018	$125 million
IPO on Nasdaq on Dec 2018; Money raised at IPO $604m;			
BARDA	Grant for COVID-19 vaccine	2020	$483 million
BARDA	Grant for COVID-19 vaccine CT3	2020	$472 million
DARPA	Grant for small-scale rapid, mobile manufacturing	2020	$56 million

Source: Bruegel based on Crunchbase (consulted May 2021) and company websites.

CUREVAC

In its early years, CureVac had to rely on private venture capital, initially mostly small amounts from friends and family. The most important early venture capital funding came from German billionaire Dietmar Hopp, who co-founded SAP. The Gates Foundation and Baillie Gifford (which also invested in Moderna) also jumped in as early equity investors. CureVac went for an IPO somewhat later than BioNTech and Moderna, only after the pandemic broke out. It managed to raise somewhat more than $200 million. 2020 turned out to be a good year for CureVac to attract funding, particularly from German and EU public sources, following an apparent attempt by then US President Donald Trump to secure CureVac vaccine supplies. Equity investment from KfW, a German public development bank, grant funding from BMFB, debt financing from EIB and the advance purchase agreement with the European Commission filled its coffers. It remains to be seen how its financing will evolve given that it had to abandon its mRNA vaccine. Its next coronavirus vaccine is being developed jointly with GSK, which has also taken an equity stake in the company.

Table 4: CureVac's financial portfolio (up to May 2021)

CureVac's major investors			
Various	Venture capital	2010	€27 million
DARPA	Contract for collaboration with Sanofi & In-Cell-Art	2011	$33 million
Hopp (SAP co-founder)	Venture capital	2012	€80 million
European Commission (H2020)	Inducement prize	2014	€2 million
Gates Foundation	Equity investment	2015	$76 million
IPO on Nasdaq on Aug 2020; money raised at IPO $213m;			
KfW	Equity investment (23%)	2020	€300 million
EIB (EFSI)	Debt financing	2020	€75 million
Qatar Inv Auth	Equity investment	2020	$126 million
GSK	Equity investment (10%)	2020	$163 million
BMBF	Grant	2020	€250 million
Post-IPO equity follow-on in February 2021, raising $450 million			

Source: Bruegel based on Crunchbase (consulted May 2021) and company websites. Note: KfW: German state-owned development bank.

12 mRNA vaccines: an unfinished story

While the world remains focused on the rollout of COVID-19 vaccines, the roadmap for future vaccine technologies is and should already be on the horizon, in order to secure long-term pandemic preparedness and resilience. The vaccine technology roadmap will involve a portfolio of R&D and innovation projects, including:

- Incremental development projects, boosting and tweaking vaccines currently on the market, and development and trials of new vaccines for the current virus and its mutants (*1.2 vaccines)*.

- Research and development into the next generation of vaccines. These include universal vaccines that can offer preventive long-term effectiveness against a whole family of viruses *(2.1 vaccines)*.

Because of the high risks associated with projects, a portfolio approach will be needed, including multiple vaccines candidates and technologies[27]. Within this portfolio approach, mRNA technology should not be the sole technology, but given its unique advantages and stunning performance during the COVID-19 pandemic, it has earned a prominent place in the portfolio.

Yet, to develop the next generation of mRNA-based vaccines and drugs, mRNA technology, still in its infancy, needs further research and development (Rosa *et al* 2021). Further developments are needed to improve on longer-term efficacy and safety, and efficacy for targeted population segments (eg young children, patients with compromised immune systems). MRNA manufacturing processes still need to be standardised to improve scalability and cost-effectiveness. MRNA vaccine production processes need further improvements to deal with the cold-chain problem and/or to avoid the use of expensive and limited materials, while allowing for more distributed, local scale production (Rosa *et al*, 2021). Also needed are further improvements in the administration of mRNA-based vaccines on doses and on alternative modes of administering, such as pills rather than jabs.

The race for the next generation of mRNA vaccines and drugs is already underway. Projects are continuing to optimise coronavirus vaccines. The omicron variant has pushed the 1.2 vaccine agenda into high gear. Both BioNTech and Moderna are set to develop in a matter of weeks new versions of the vaccines and to standardize production to speed up the production of new versions.

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[27] See Veugelers and Zachmann (2020) for a proposal on how to design and finance a portfolio of vaccine candidates.

With its characteristics as a platform plug-and-play technology, companies are also trying to apply the current state of mRNA technology to other infectious diseases. Several mRNA vaccines against flu and HIV are in the clinical trial pipeline. Projects targeting drugs for rare diseases and particularly cancer are also being developed on mRNA platforms.

In these race for next generation drugs, BioNTech, Pfizer and Moderna can ride on their COVID-19 success, which has brought them added know-how, experience and financial resources. BioNTech is returning to its initial focus on personalised cancer treatments. Pfizer is applying its mRNA experience to its seasonal flu vaccine work. Moderna is going for broader vaccines for respiratory viruses, combining flu and coronavirus. Moderna is also researching, supported by a DARPA grant, small-scale rapid mobile manufacturing of mRNA vaccines. CureVac is jointly developing with Tesla RNA microfactories, portable automated printers, which would allow the distributed production of RNA vaccines.

Now that mRNA has proved a viable commercial platform, other young biotech companies and big pharma are getting more convinced that the mRNA technology will be highly valuable in the future of biomedical technology. Sanofi plan to invest €400 million a year to develop mRNA vaccines. The French pharmaceutical group announced in the third quarter of 2021 that it will open a *"dedicated vaccine mRNA center of excellence"*, spanning research and development, and manufacturing at sites in the US and France. The group aims to have at least six mRNA vaccine *"clinical candidates"* by 2025[28].

Several of the giants have aligned with the young, small mRNA market players for an array of mRNA collaborations. Examples include BioNTech's collaborations with Pfizer, Genentech and Sanofi; CureVac with Novartis, GlaxoSmithKline and Bayer; Moderna with Merck and AstraZeneca. Big pharma is also carving out positions in the mRNA market by scouting for acquisitions of small young mRNA companies. Some collaborative agreements, such as Pfizer/BioNTech and GSK/CureVac may expand into an acquisition. Early young pioneers now possess more leverage when forging deals with big pharma and other collaborators, and have deeper and more diversified financial resources. But, in particular, their experience and technological know-how, protected through their patent portfolios, and their deeper own and more diversified external financial resources are important bargaining chips when entering into agreements with other players.

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[28] Source: company website: https://www.sanofi.com/en/media-room/press-releases/2021/2021-06-29-10-00-40-2254458.

13 The roadmap for a public vaccine R&D policy

Given its high potential value for future pandemic response, how will mRNA development projects take off? Can the private biomedical ecosystem be relied on to deliver the next mRNA breakthroughs? Is there a risk that the ecosystem will favour the current winners, reducing the incentives for new or catch-up players to work on mRNA technology? Can we trust the private mRNA scene to deliver the socially optimal roadmap? What is the role for public support? How and how much public funding should be made available? How long will the interest last once the pandemic subsides? Will society want to risk supporting new next-generation vaccines?

With COVID-19, mRNA technology has shown its breakthrough value for vaccines. It could easily have been different. There is no way to know what would have happened if, for instance, Karikó's early funding applications had not been turned down, or if the leading vaccine producers had jumped onto mRNA technology already early on. Perhaps the mRNA technology might already have reached a stage of maturity that would have allowed the production and supply of many more mRNA COVID-19 vaccines at global scale, much sooner than the current target of end of 2022. There is also no way to know what would have happened if for instance the casual meeting at the photocopy machine would not have happened, if the mRNA technology had not been on DARPA's radar, if the Strüngmann brothers had not invested in a small start-up with a risky technology, or if Pfizer had not entered into a partnership with a start-up working with a disruptive technology. The mRNA story does show, however, that designer mRNA research and development, now considered a breakthrough and promise of future medicine, was difficult. The mRNA story should be learned from to improve and prepare better to respond to future pandemics. The cost of not responding as well as possible is too high.

The roadmap cannot be purely private or public. A holistic public R&D policy approach is needed along the whole value chain, from the generation of new ideas for vaccines to the last mile of administrating vaccines, leveraging and partnering with the private biomedical ecosystem. The corporate sector is pivotal because of its unique research and development competences, and its complementary production and commercialisation skills and assets to bring new solutions to market. The public sector plays a role as financer of R&D projects through grants, subsidies or tax credits. It also impacts the ecosystem by being the major procurer of vaccines and the designer of clinical trial and market-access regulation. Last but not least, through its horizontal innovation, competition and regulatory policy powers, it shapes the environment in which the private biomedical ecosystem can develop.

13.1 Leveraging the private biomedical ecosystem

For new disruptive breakthrough technologies, like mRNA, competences and incentives to deploy them often do not reside in incumbent players. The mRNA COVID-19 vaccine story is a strong testimony of the power of private individuals in the biomedical ecosystem, particularly the importance of stubborn scientists, new entrepreneurs and risk-capital providers, to deliver the breakthroughs from new technologies. The private vaccine ecosystem needs to be sufficiently contestable, incentivising these new players with their risky breakthrough ideas.

This requires clear intellectual property regimes allowing to capture value from new ideas. It also requires well-developed and competitive risk-capital markets to access deep financial resources, including for the later expensive development stages. Also important is access to complementary assets, which technology developers need in order to bring their vaccines and drugs to market. Dedicated biomedical services companies (such as Lonza, Celonic and ICON) can offer scale and specialisation advantages for these complementary assets (clinical trials, production). A well-developed market for biomedical services allows biomedical technology companies to contract highly-specialised clinical-trial expertise and production and distribution capacity at competitive prices, without the need to own themselves. In a contestable biomedical ecosystem, large incumbent firms are more challenged by new radical ideas that may destroy their incumbent positions. They will have greater incentives to further develop new risky technologies, either solo or in partnership with new innovators. When new players team up with incumbent big firms, it should be because of the latter's unique generic complementary competences they can jointly exploit, to speed up the bringing of new ideas to markets.

The mRNA story suggests improvements can be made to the current biomedical ecosystem, particularly by making it more contestable for new dedicated biotech enterprises. To get the most out of the private sector, public policy should ensure, with its horizontal innovation, competition and regulatory policy instruments, a deep, well-developed competitive and contestable biomedical corporate ecosystem along the whole vaccine value chain with well-connected vertically specialised players. The pre-pandemic wave of digital and green EU policy initiatives missed this ecosystem. It should be on their radar.

13.2 Publicly funding risky breakthroughs

The mRNA story shows the case for necessary improvements to public funding to address its risk bias, risking to potential breakthroughs with high social value being missed. To diversify risks, a portfolio of supported projects is needed across multiple vaccine technologies. Within this portfolio, risky novel approaches should take a prominent place (or at least should not be biased against) because of their higher social breakthrough value, even if their risk of failure is greater. Projects should cover the early risky research stages, with high externalities, but also their more expensive later phases of development and production and supply.

A risk-taking portfolio approach requires substantial budgets. Yet, finance should not be an issue as the social returns from vaccine R&I investment far outweighs the costs. Whatever amount is spent on R&I to address pandemics will be small compared with the costs to society in their absence (see G20 High-Level Independent Panel, 2021). Short term budget constraints can mean missing out on breakthrough projects.

Public funding for research and early-stage development

For early-stage research and development public funding, the mRNA story illustrates the importance of a DARPA-type approach to avoid the risk bias that hinders the more risky breakthroughs at early stage. There has been discussion about an EU-level structure modelled on DARPA (see eg Aghion *et al*, 2020). Germany has established the Federal Agency for Disruptive Innovation or SPRIN-D[29]. In the US, there has been discussion about expanding the DARPA model in the biomedical area (Collins *et al*, 2021).

It is important to stress that a DARPA-style approach requires more than just importing a label, to ensure its unique character as risk-taking public funder. It requires sufficient funding for such an agency, to allow it to make multiple bets. Equally important is to design it properly, and ensuring its key success factor: its autonomy and organisational flexibility, especially flexibility to recruit and accommodate the venture capital entrepreneur type of policy programmers and officers.

It is also important to stress that the DARPA model is not necessarily the appropriate model for all public funding of research and development. Azoulay *et al* (2019) identified *"DARPAble"* domains: mission-motivated research on nascent technologies within an inefficient innovation system. Missions must be clearly identifiable, associated with quantifiable goals and trackable metrics, so that policy officers can be given high levels of autonomy, together with clear mandates and accountability.

[29] See https://www.sprind.org/en/.

Azoulay *et al* (2019) argued that the DARPA model is not appropriate for funding basic research given that the 'mission' of basic research (progress in knowledge) is not clearly identifiable. It may nevertheless be inspirational for some specific scientific challenges for which goals can be clearly defined (like solving the human immune reaction to synthetic mRNA was in the 1980s). This still leaves as a challenge the addressing of the risk bias of science funding agencies – NIH in the US, ERC and national funding agencies in the EU, more generally. For more on how to avoid risk biases in public science funding, see Franzoni *et al* (2021).

A DARPA model may not be the silver bullet when there are structural inefficiencies in the larger innovation system, such as a lack of scale-up power for new innovators in the EU (see section 13.1). A DARPA on its own cannot compensate for this.

With a well-funded and well-designed DARPA model within a sufficiently developed broader biomedical innovation system, a more directed top-down targeted mission or prize approach can be implemented for risky vaccine breakthroughs. There could be a 'Mission for a universal vaccine' or a 'Produce your own vaccine' mission. These missions should not be about picking companies and technologies. Whichever firms and technologies are superior in delivering the desired missions should win, as CureVac's EU cold-chain prize winning example illustrated. If the mRNA technology wins, it should be because of its superior effectiveness for the desired missions, not because it is mRNA.

Publicly funding of later-stage development

Another weakness in the public funding system, highlighted by the mRNA story, is its reluctance to support the later development stages. These more expensive and closer-to-market stages require specific public funding instruments, involving bigger amounts of public support. This reluctance is notable in the EU (Aghion *et al*, 2020), where the scale and scope of the Framework Programme (FP) typically did not or has only recently included small-scale initiatives, like the Innovative Medicines Initiative. FP initiatives have also been poorly connected to each other and with EIB initiatives. A European BARDA could implement a larger set of public-policy instruments from the EU and EIF to support later development stages and to connect them with earlier and later-stage funded projects. This EU-BARDA should be sufficiently financially endowed and designed to allow risk taking, or to at least avoid bias against risky new approaches with high breakthrough social potential.

Pre-procuring vaccine supplies

As the public (health) sector is the main buyer of vaccines, smart procurement is an important instrument of public funding of R&D for vaccines, assuring *ex-ante* demand with favourable conditions. When building a portfolio of projects supported through advance market commitments, the objective should not only be seen short term to secure supply at the lowest prices possible, but also more longer term, as incentivising private investment[30]. To this end, the budget for advance market commitments should be sufficiently large and long-term. It should not be emergency funding, but committed *ex ante*, to be used in case of emergency. To manage risks, it should have a diversified portfolio of vaccines and within this portfolio it should avoid a bias against vaccines with new technologies. Advance market commitments with individual vaccines should include a sufficient upfront part with milestone upgrades.

13.3 Governing a holistic public policy approach

Activating funding is perhaps the easiest part of the job. More critical is how to use the funds, selecting portfolios of projects and partners, staying in co-pilot mode, incentivising and activating private partners in the selected projects, and deploying and connecting the whole arsenal of complementary health, regulatory and competition policy instruments. Managing public private partnerships along the whole vaccine value chain is a tall order policy agenda, particularly as pandemic preparedness requires taking a long-term perspective, while being agile and responsive to short-term shocks. This requires governance structures and initiatives in place *ex ante* with proper contingency plans for various scenarios *ex post*, and dynamic policy capabilities to adapt and learn in the face of rapidly changing conditions.

For this holistic vaccine R&D policy strategy to succeed, a strong governance structure is needed. In 2007, the US set up the Biomedical Advanced Research and Development Authority (BARDA) as the entity in the US administration responsible for coordinating, overseeing and investing in research and innovation, development and procurement of medical counter measures for threats including pandemics. Since its start, BARDA has supported the development of more than 100 vaccines and therapeutics and, together with its Operation Warp Speed (OWS), has played an effective role in the COVID-19 pandemic. Yet, better connecting the dots remains a challenge for BARDA. This holds particularly for coordinating and integrating clinical trial data and procedures across vaccines projects

[30] For a more elaborate discussion of how to use advance market commitments to stimulate research and innovation, see Kremer and Williams (2010) and Ahuja *et al* (2021).

and coordinating and integrating with health care data and services. BARDA should have Operation Warp Speed fully and permanently integrated *ex ante*, rather than only *ex post* in emergency. While the US should improve its BARDA/OWS governance, the EU, which announced in September 2021 plans to introduce a Health Emergency Preparedness and Response Authority (HERA), still needs to start.

13.4 Ensuring access to vaccine technology and intellectual property protection

Being a major co-funder of vaccine R&D projects, but especially as a pre-procurer through advanced purchase contracts, governments can and should be co-drivers in PPPs. This will not only ensure vaccine availability, but also availability at volume and prices that are globally socially optimal. To ensure private incentives for R&D investing at socially optimal values, vaccines, like other inventions, are protected by patents. Their holders have the right to exclude others from using their technology. Even if governments have the right to impose compulsory licensing in case of pandemics, activating this option *ex post* risks disincentivising future private investment.

To avoid this, conditions on vaccine patent rights and licensing of vaccine patents should only be imposed as part of a comprehensive policy package designed *ex ante*, combined with a public funding deal that can secure proper private incentives. Within such a package, governments can limit the duration and breadth of IP rights for supported vaccines. When providing public support to vaccine projects, governments can make public funding conditional on shorter IP protection periods being exerted by recipients of government funding, or can require the patents involved to be open access (compulsory licensing) or licensed under fair conditions. Imposing access conditions by limiting IPR rights should take into account that this may imply higher levels of public support to safeguard private incentives.

These conditions can be especially targeted to areas where there are the biggest gaps in access, such as for low-income countries. Public funding can be made conditional on any potentially successful vaccines being supplied in all countries at fair prices.

Designing such conditions should balance the social objective of broad and fair access to vaccine technology with the private incentives to develop such technologies. Differentiating conditions across high and low-income countries may help to attain such a balance.

Firms can always choose to opt out, ie not use the tied public funding. This tied public funding and opt-out may be particularly challenging for new young developers with risky projects, for which access to external funding is critical but for whom IP rights are the main asset. Given that small biotech

companies are the major tech developers of new risky breakthroughs, like mRNA, clear IP rights are especially important for them, so they can engage on a fair footing in agreements with other complementary asset holders. When designing conditions for public support and advanced purchase contracts, the incentives for these new young developers should be properly taken into account.

14 The roadmap for a global public vaccine R&D policy

With pandemic preparedness and responsiveness clearly a global challenge, a vaccine R&D roadmap with an eye toward good global outcomes is needed. There is already inherently bottom-up global cooperation in the academic and private R&D community (see OECD STI Outlook, 2021), but the current crisis has shown that it is national and regional public R&D entities in particular that are running behind in coordinating and collaborating globally.

For a global R&D policy strategy, it is necessary to have at least exchange of information and best practices. There should also be coordination of R&D projects, but also clinical trials and regulatory coordination, and finally pooled funding and joint programming. This will allow portfolios of R&D projects that are more efficient and effective which will reduce the global underinvestment problem and avoid short-term national biases.

There are several global institutions and initiatives, including the WHO, GAVI, COVAX and the Global Fund, but none are sufficiently funded and able to reach effectively across all parts of the R&D value chain. For R&D, there are no sufficiently powerful global governance platforms. Initiatives such as CEPI are still new and under-funded and under-governed.

A start could be made in tackling the global R&D governance problem by bringing together the BARDAs of all the major vaccine R&D-relevant countries/regions on a platform. The governance of this platform of BARDAs should ensure sharing, coordination and cooperation among partners. Such a global BARDAs platform could also provide funding for dedicated global R&I missions, such as a mission for vaccine variants tailored to poor countries, or to develop vaccine production technologies that can be produced in local hubs in the least-developed countries. It should also make it easier to connect and partner with other global initiatives along the value chain, for example with CEPI or with COVAX, to provide this initiative with a sufficient pipeline of vaccine supplies, or give third countries access to their funded technologies.

Such a global BARDAs platform with a selected coalition of the main R&D players can better share the risks and exploit the full potential of new, breakthrough technologies, mRNA as a global vaccines technology. This could be done without building a new global institution.

References

Aghion, P., S. Amaral-Garcia, M. Dewatripont and M. Goldman (2020) 'How to strengthen European industries' leadership in vaccine research and innovation', *VOXEU*, 1 September, available at https://voxeu.org/article/how-strengthen-european-industries-leadership-vaccine-research-and-innovation

Ahuja, A., S. Athey, A. Baker, E. Budish, J. Camilo Castillo, R. Glennerster … W. Wiecek (2021) 'Preparing for a Pandemic: accelerating vaccine availability', *BFI Working Paper*, 30 January, Becker Friedman Institute

Azoulay, P., E. Fuchs, A.P. Goldstein and M. Kearney (2019) 'Funding Breakthrough Research: Promises and Challenges of the "ARPA Model"', *Innovation Policy and the Economy* 19(1): 69–96

Collins, F.S., T.A. Schwetz, L.A. Tabak and E.S. Lander (2021) 'ARPA-H: Accelerating biomedical breakthroughs', *Science* 373(6551): 165-167

Dolgin, E. (2021) 'The tangled history of mRNA vaccines', *Nature*, 14 September

Franzoni, C., P. Stephan and R. Veugelers (2021) 'Funding Risky Research', *Working Paper* 28905, National Bureau of Economic Research

Kremer, M. and H. Williams (2010) 'Incentivizing innovation: Adding to the tool kit', *Innovation Policy and the Economy*, 10(1): 1-17

Kremer, M., J. Levin and C.M. Snyder (2020) 'Advance market commitments: insights from theory and experience', *AEA Papers and Proceedings* Vol. 110: 269-73, American Economic Association

Pardi, N., M.J. Hogan, F.W. Porter and D. Weissmann (2018) 'mRNA vaccines : a new era in vaccinology', *Nature Reviews Drug Discovery*, Vol. 17: 261–279

Sousa Rosa, S., D. Prazeres, A.M. Azevedo and M. Marques (2021) 'mRNA vaccines manufacturing: Challenges and bottlenecks', *Vaccine* 39(16): 2190–2200

Veugelers, R. and G. Zachmann (2020) 'Racing against COVID-19: a vaccines strategy for Europe', *Policy Contribution* 07/2020, Bruegel

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