Which policies for vaccine innovation and delivery in Europe ?[1]

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Abstract

This paper analyzes the subsequent steps of the covid vaccine experience in the European Union. It stresses the features of the US innovation ecosystem which were responsible for its success. It argues that the European Union did reasonably well in procuring vaccines and logistically organizing their delivery but that vaccine hesitancy proved to be a key constraint. The paper discusses European countries' vaccination strategies and their plusses and minusses. Finally, it draws some lessons for dealing with the tradeoff between drug and vaccine innovation and affordability, an issue whose importance is bound to grow with promising but costly scientific advances.

Keywords : vaccine innovation, covid-19, innovation ecosystem, vaccine hesitancy, drug prices, European health policy.

JEL numbers : I11, I18, L32, L65, O31.

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I. Introduction

This paper draws lessons from the covid vaccine experience for the European Union. In order to do so, it reviews the subsequent steps a successful vaccination campaign requires : (i) the development of safe and efficient vaccines ; (ii) sufficient high-quality-vaccine production capacity (ideally at 'socially acceptable' prices) ; and (iii) a vaccination strategy that is logistically effective and manages to convince the population to get vaccinated.

The emergence of new efficient vaccines in record time has been a great success of public and private international cooperation. However, credit should go here to the US 'Operation Warp Speed', and Europe should draw important lessons from this episode.

As for vaccination, it is fair to say that authorities in most EU countries have been up to the logistical job, but that vaccine hesitancy has been a key challenge. Different countries have performed quite differently, so lessons can be drawn about the various strategies, which should be informed by rigorous empirical studies. A general lesson though is the need for proper communication : in many countries, it was unfortunate that the 'right not to be vaccinated' was initially put forward assertively without questioning its potential inconsistency with the need to achieve herd immunity, which was simultaneously asserted.

Finally, the paper draws some lessons from this saga in terms of improving the tradeoff between innovation and affordability, a challenge which is growing with the emergence of new, costly therapies thanks to the progress of science. In particular, it suggests taking advantage of the new role the EU Commission has taken as representative of the 27 member states for price negotiations with pharmaceutical companies.

The paper focuses on Europe and therefore does not discuss the (very relevant) question of insufficient access to vaccines in lower-middle-income and especially low-income countries.[3] This is of course a key issue for which adequate levels of technology transfer, global production capacity and funding from rich countries is crucially needed.

[3] According to World Bank classification, low-income countries have a combined population of 665 million people (with the 10 largest being, in decreasing order of population : Ethiopia (118 million), DR Congo (92), Uganda (47), Sudan (44), Afghanistan (40), Mozambique (32), Yemen (30), Magagascar (28), North Korea (26) and Niger (25)) and lower-middle income countries a combined population of 3.33 billion (with the 10 largest being, in decreasing order of population : India (1.380), Indonesia (274), Pakistan (221), Nigeria (206), Bangladesh (165), Philippines (109), Egypt (102), Vietnam (97), Iran (84) and Tanzania (60)). Vaccination rates as of mid-January 2022 are very different across income groups, since the share of population having received at least one vaccine dose amounts to 9.5%, 53%, 79% and 78% for low-income, lower-middle-income, upper-middle-income and high-income countries respectively (and full vaccination rates are even more unequal (at 4.9%, 40%, 74% and 72% respectively), not to mention the inequality in terms of booster doses. This has not prevented official death tolls from being positively correlated with income across these groups since, as of mid-January 2022, low-income and lower-middle-income countries have suffered 363 and 659 deaths per million inhabitants respectively, against 910 and 1640 for upper middle-income and high-income countries respectively. Next to probable undercounting in poorer countries, the risk of potential future waves, possibly originating from new variants, and the fact that vaccinating the world is not very expensive for rich countries, are key reasons to significantly accelerate global vaccination.

II. Vaccine development, authorization and production[4]

The covid crisis and the question of vaccine development have been instructive in terms of what needs to improve in the EU. Indeed, while this crisis has revealed the weaknesses of the US social system compared to European social systems (Aghion et al. 2020b) and the mismanagement of the pandemic by the Trump administration (negligence in realizing the danger of the virus, pushing for excessively fast reopening of the economy, and resistance against mask wearing and generalised testing), nonetheless, together with Congress, the same administration has pursued a determined and aggressive strategy to ensure US leadership in covid vaccine R&D and to secure supplies of future vaccines to US citizens.

Although the European Commission took the lead in negotiating advance purchase agreements with vaccine manufacturers on behalf of the 27 member states and decided to provide loans to European biotechs engaged in vaccine development through the European Investment Bank, it has fallen short in matching the US effort to incentivize vaccine innovation – not only because of a lower level of financial investment, but also an inability to ensure coordination across member states as well as across the different funding schemes for research and innovation in healthcare (reflecting the more decentralized nature of R&D and health policies in Europe).

This is problematic because the best way to get one's economy back on track is to eliminate the virus. And, next to non-pharmaceutical measures (masks, social distancing, etc.), this means treatments and, first and foremost, vaccines.

General considerations

Regarding covid-19 vaccines, it is useful to distinguish two phases: *vaccine development*, and the *securing of vaccine supplies* once a vaccine has been found and authorized. Both are needed to bring vaccines to the patient (then one should still 'convince' people to get vaccinated).

Intuitively, contributing to vaccine development looks like a 'benevolent' action, since the whole world should benefit from the arrival of one, or several, covid vaccines. Instead, securing vaccine supplies in advance for one's citizens seems more 'selfish', especially if limited supply means denying vaccines to other countries' citizens. Nevertheless, advanced contracts for delivery will encourage private entities to energetically pursue vaccine development – the two are intertwined.[5]

More generally, when considering innovation for a 'global product', it is natural to wonder about the 'optimal' degree of competition and coordination to rapidly identify successful vaccines. In fact, we have observed an interesting mix of coordination and competition in the search for vaccines. Although political authorities in China were denying the upcoming disaster, Chinese scientists have been very open about their research results, which benefited the world research community. The first vaccines that became authorized could be rapidly developed because Chinese scientists published the genetic

[4] Partly based on Aghion et al. (2020a).

[5] See for example Levin et al. (2020) on 'advance market commitments' for new vaccines, as well as Veugelers (2021) more generally.

sequence of the virus as soon as it was deciphered. On the other hand, universities and private firms, large and small, have been competing aggressively to 'be the first' in the race for a vaccine, including in terms of raising funds from private and state sources.

From the perspective of world welfare, the cooperation/open science part is of course good. As for the competition on vaccine development, things are more subtle: on the one hand, more financial effort overall is a good idea to accelerate innovation for such a costly disease (just think of the cost of a lockdown). On the other hand, should we worry about money 'wasted' in funding more than 100 vaccine projects, including advance building of production facilities? As discussed by Bolton and Farrell (1990), in "times of war", speed is essential, and more coordination is preferable to "fine-tuning for the most efficient option" if such an optimal solution comes later. And indeed pandemics are war-like circumstances where speed is really crucial, much more so than is the case for 'regular vaccines' as in the case of malaria.

We can, however, safely conclude that speed has not been hampered in this case, given the rush we have observed. If anything, the risk to be worried about concerned that of 'cutting corners' in excessively fast approval of vaccines which might not be safe and effective enough. But that risk appears to have been dealt with pretty successfully at a time where more than 9 billion vaccine doses had already been administered by the end of 2021. Here authorization bodies (Food and Drug Administration in the US, European Medicines Agency in the EU, etc) have shown their ability to speed up the regulatory process without sacrificing on safety.

The US versus the EU

As is well-known, the US is a clear leader in biotech innovation (see evidence summarized in Aghion et al., 2020a). Moreover, it set up an articulated US-centric covid strategy – Operation Warp Speed (OWS) – which built on an understanding of the complementarity between vaccine development and securing advanced supplies, thereby bringing together the negotiations with private entities on the two phases while relying on the combined expertise and financial weight of existing federal instruments, in particular the National Institutes of Health (NIH) and the Biomedical Advanced Research and Development Authority (BARDA). This gave the US a first-mover advantage.

Congress allocated almost $10 billion to OWS, of which more than $6.5 billion was allocated to BARDA and $3 billion for NIH research. In practice, during this pandemic, BARDA has provided funding to develop, among others, vaccines and treatments to fight Covid. By September 2020, BARDA had distributed more than $11 billion among more than 40 companies to fund the development of vaccines, diagnostic, therapeutics, rapidly deployable capabilities, and others (see Aghion et al., 2020a).[6]

[6] Operation Warp Speed also coordinates other initiatives such as the NIH's Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) public-private partnership (of which the European Medicines Agency is also a partner) and the NIH's Rapid Acceleration of Diagnostics (RADx) initiative.

The EU, instead, has pursued a less coherent strategy overall, and with fewer financial resources directly invested in candidate vaccines (European Commission 2020). Indeed, it looks more 'benevolent' than the US in terms of vaccine development, pushing for worldwide cooperation, but with much more limited funding commitment (see details in Aghion et al., 2020a). In fact, the EU made constant international cooperation efforts, as the Coronavirus Global Response exemplifies. By September 2020, this global action raised almost €16 billion from countries worldwide; the US did not contribute. The EU also contributes through the Coalition for Epidemic Preparedness Innovations (CEPI),[7] an innovative partnership between public, private, civil and philanthropic organisations. Additionally, the 'ACT-Accelerator' has one vaccine pillar, COVAX, of which CEPI is co-leader together with Gavi and WHO. However, in spite of these international cooperation efforts, the EU has been 'EU-centric' when trying to secure vaccine supplies for its member states and citizens. This does not sufficiently exploit the complementarity involved in the process, which adds to the problematic complexity of funding sources (within the European budget, EIB, member states, etc).

By September 2020, there were more than 130 candidate vaccines in preclinical evaluation and 30 candidate vaccines in clinical evaluation. Among these 30 candidates, 13 received support from BARDA, CEPI and/or the EU/EIB (see Table 1). Among these, three received support from both BARDA and CEPI (University of Oxford, Moderna and Novavax), one received support from both CEPI and the EIB (CureVac), and one from BARDA and EIB (BioNTech). BARDA provided consistently higher funding amounts.

And it is very striking that BARDA spent 8.69 billion dollars out of their 10.8 billion dollars on the five vaccines that have been approved, as of December 2021, by the European Medicines Agency (AstraZeneca, BioNTech-Pfizer, Moderna, Johnson & Johnson and Novavax). And obviously the funding did not go only to US companies (in fact the remaining 2.07 billion went to Sanofi, a French company).

It is also interesting that a very significant chunk of the funding went to biotech companies Moderna and Novavax, and even to BioNTech rather than its associate Pfizer, which benefited only indirectly. This confirms the importance of smaller firms in health innovation. This being said, the success of the BioNTech-Pfizer alliance shows the value of a close association with a big pharma company for scaling up the downward development and the production phases, even if Moderna's performance is quite impressive. And it is striking that, of the 'big four' pre-covid vaccine players, MSD, GSK, Sanofi and Pfizer, only the last one has emerged as a 'winner' of this race, thanks to its alliance with BioNTech.

All this is consistent with the desirability of putting limits to the power of mega incumbents whose strategic use of market power can even hamper or delay innovation, a problem documented in general by Covarrubias et al. (2019), and in the case of 'killer acquisitions' (purchases of smaller biotech firms by big pharma companies) by Cunningham et al. (2021).

[7] From a total of $1,280,588,290 for vaccine development for CEPI, the European Commission contributed with $109.2 million. The top contributors are the UK ($270 million), Norway ($213.5 million), Germany ($160.4 million), Saudi Arabia ($150 million) and Japan ($134 million), followed by the European Commission (source: The Covid-19 Health Funding Tracker from The Economist).

Coming back to OWS, as stressed by Slaoui (2020), who was appointed Chief Scientific Officer of OWS, there was a conscious decision to concentrate funding on three different technologies and two projects per technology (or 'dual sourcing') : BioNTech/Pfizer (Germany/US) and Moderna (US) for the mRNA technology, Johnson and Johnson (US) and Oxford/AstraZeneca (UK/Sweden) for the viral vector technology, and Novavax (US) and Sanofi/GSK (France/UK) for the protein subunit technology.

Table 1 Partnerships to develop vaccines against Covid-19: BARDA, CEPI and EU (through EIB)

Original company/institution	Partner(s)	Product Name	BARDA Award Amount ($)	CEPI funding ($)	EIB (€)	Status
University of Oxford (UK)	AstraZeneca, Iqvia	AZD1222	1,200,000,000	384,100,000		Phase II/Phase III
BioNTech (Germany)	Pfizer, Fosun	BNT162	1,950,000,000		100,000,000	Fast Track status by FDA
Clover Biopharmaceuticals (China)	GSK, Dynavax	SCB-2019		69,500,000		Phase I
CureVac (Germany)	GSK	mRNA vaccine		15,300,000	75,000,000	Phase I
Inovio Pharmaceuticals (USA)		INO-4800		22,500,000		Phase I/II
Institut Pasteur (France)	University of Pittsburgh, Merck&Co/MSD	PittCoVacc		5,000,000		Preclinical
Beth Israel Deaconess Medical Center (USA)	Janssen (J&J)	Ad26	1,457,887,081			Preclinical
Merck&Co/MSD (USA)	IAVI	rVSVΔG-CoV2	38,033,570			Preclinical
Moderna (USA)		mRNA-1273	2,479,894,979	1,000,000		Phase III
Novavax (USA)		NVX-CoV-2373	1,600,434,523	388,000,000		Phase I
Sanofi (France)	GSK	Recombinant SARS-CoV-2 Protein Vaccine Candidate	2,072,775,336			
University of Hong Kong		Influenza vector expressing RBD		620,000		Preclinical
University of Queensland (Australia)	CSL, GSK	Molecular clamp stabilized Spike protein with MF59 adjuvant		4,500,000		Phase I
Total			**10,799,025,489**	**885,400,000**	**175,000,000**	

Source: Aghion et al. (2020a) calculations based on BARDA, CEPI and Global Response Europe.

It is hard not to consider OWS as a success of 'industrial policy', bringing together, as stressed by Slaoui (2020) : (i) significant public money, (ii) competences from the whole 'ecosystem' : universities, BARDA, NIH, FDA, biotech companies, big pharma, and even the US Army, and (iii) a small unified decision structure to speed things up (as needed in pandemics), at arm's length from politics. Of course, there was quite some luck : the most successful technology, mRNA was available, thanks to years of research efforts (which had not benefited from the support they would have deserved : on this, see the detailed study by Veugelers, 2021). And the vaccines turned out to be even more successful in preventing severe forms of the disease than what could have been expected. But still, this episode has been a great success which other jurisdictions should definitely try and draw lessons from.

For an integrated EU treatment and vaccine development strategy

Europe (especially if one adds to the EU the UK and Switzerland) is strong in health, with its universities, biotech companies, big pharma companies, and public money which is ample but scattered (the EU being rightly seen as 'a regulatory giant but a budgetary dwarf'). What is suboptimal is coordination.

Therefore the desirability of a renewed EU support strategy to the development and commercialisation of innovative technologies – which could be extended to other areas, for example, defence-related technologies, on the model of the Defense Advanced Research Projects Agency (DARPA) in the US, which, interestingly, has been instrumental in a number of non-defense innovations as well. This should not be a renewed industrial policy amounting to 'picking one winner' : as in the case of covid vaccines, the BARDA-DARPA model is one that mixes top-down and bottom-up, where government funds are devoted to financing competing teams that work on making new technologies become operational.[8] Once selected by the government, team leaders have full autonomy in deciding how to organise the research process and whom to involve in that process. The various teams will typically compete not only within Europe, but also with the US and more globally. So, this is about competition-friendly industrial policy, as advocated in Aghion et al. (2015).

Interestingly, by the end of 2020, the European Union has launched HERA, the Health Emergency Response and preparedness Authority, with explicit reference to BARDA and the US innovation ecosystem. It will be interesting to see to what extent it can boost European innovation in healthcare.

At this stage, let us just make three remarks. First, one key advantage of BARDA has been its flexibility, since speed is key in pandemics. This would plead for avoiding political constraints about 'juste retour', seven-year budgets, or (near) unanimity voting rules. Second, BARDA has taken a 'global view', so funding should not be exclusively restricted to EU entities ; despite Brexit, joining forces with Britain makes particular sense, given its (academic and industrial) expertise in the area (the same is true for defense). Third, the US success was not limited to BARDA : pooling more resources at the EU level to create an EU equivalent of the NIH is worth considering ; and the US has been able to use the leverage

[8] See Veugelers (2021) for a discussion of the various dimensions of this ecosystem.

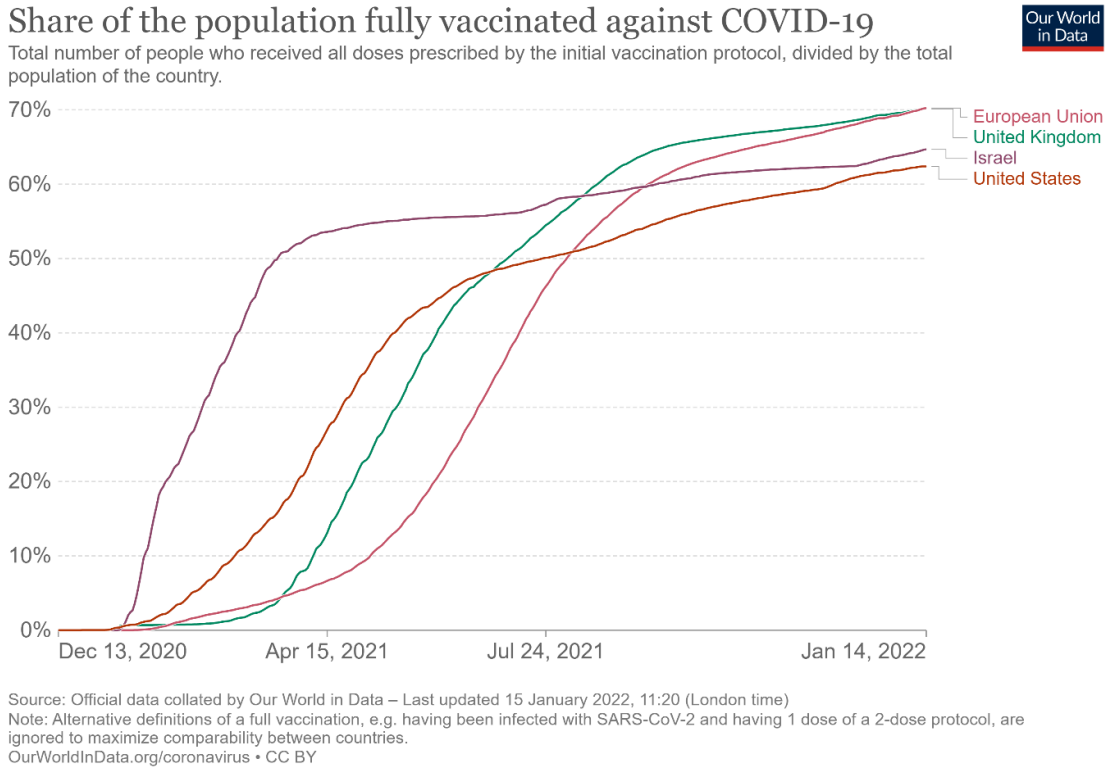
of the Defense Production Act to request private firm cooperation with OWS (not to mention the help of the US Army). It will be important the draw the full lessons of what made OWS such a success.

III. Securing supplies and setting up delivery systems[9]

Once vaccines exist, one should be able to secure vaccine doses. We focus here particularly on the EU, which centralized discussions with vaccine producers in order to obtain sufficient vaccine supplies at an appropriate price.

The EU Commission has been criticized in the first months of 2021 for insisting too much on low prices in their contractual negotiations with vaccine producers and not enough on speed of delivery, in a world where the opportunity cost of delaying the recovery was huge. This criticism is not unfair, and Figure 1 shows that countries like Israël, the UK and the US did get ahead of the EU in vaccination in the first half of 2021. This is particularly clear in the first quarter of 2021. In this respect, while the UK and the US benefited from their close links with respectively AstraZeneca and Pfizer and Moderna to accelerate purchases, Israël shows one does not have to be involved in R&D or production to be the first in terms of purchases : paying a high price is enough (they paid a multiple of what the EU paid for the same vaccine). Note however that Israël also allowed Pfizer/BioNTech to analyze in detail the impact of vaccination on the Israeli population, thereby contributing to global knowledge.

Figure 1



Anyway, after the first quarter of 2021, EU vaccination took off and, as seen below, many western EU countries are now ahead of the US, the UK and Israël in vaccination rates. And we should not forget

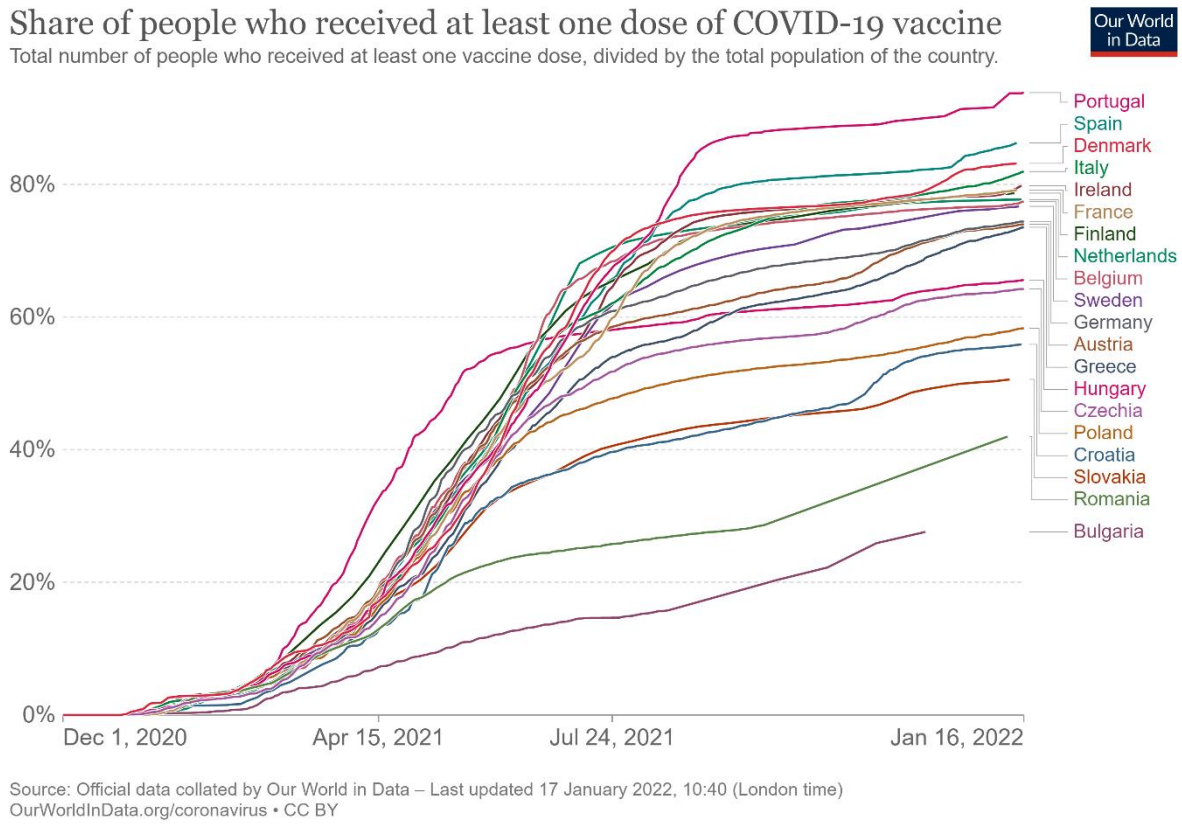
[9] Sections III and IV are partly based on Dewatripont (2021a,b).

the benefits of EU Commission intervention : it did favor equal treatment between member states while earlier a group of four countries (France, Italy, Germany and the Netherlands) had decided to join forces and bargain only for themselves. Thanks to the Commission, everyone agreed to go for centralized EU-wide bargaining. As stressed in section V, this can be a useful precedent for future price negotiations with pharma companies, in general but also for future versions of covid vaccines.

European Union

Figure 2 presents the 20 EU countries with a population above 4 million. It shows that, thanks to the EU Commission, vaccination rates went up with little variance across most member states in the first months of 2021.

Figure 2



We see indeed that :

- By the end of March, only two countries diverged significantly from the rest : Bulgaria on the low side, and this trend would continue, and Hungary on the high side, because of purchases of the Russian Sputnik vaccine, which is not yet approved by the EMA.
- During the course of May and June, other eastern-enlargement European countries started to lag the rest of the pack too : Romania, Slovakia, Poland, Czechia.

- Instead, the other countries stayed 'close together' until June, where divergence started to grow. By this time, vaccine hesitancy had become the key constraint, not vaccine availability or logistical challenges.

The bottom line is that pre-eastern-enlargement EU countries managed to set up vaccine delivery systems with broadly similar efficiency. Maybe this is because supply was a bit slow : it is not clear everybody would have been as efficient as Israël if they had had a similarly speedy supply.

IV. The challenge of vaccine hesitancy

The political economics of vaccination

The difficulty to address vaccine hesitancy became a much debated topic when one realized that achieved vaccination levels were deemed insufficient given new, more contagious, variants. Speed of required progress was stressed a lot, with talk of 'a race between vaccination and variants'.

Under these circumstances, significant tensions have been observed in a number of countries between the idea of 'free choice about vaccination' and increasingly coercive methods to induce/mandate vaccination. Interestingly, 'corona passes' documenting vaccination, recovery or a recent negative test had been quickly introduced as a condition for crossing borders in the EU as an international tourist without much controversy. The same was not true of their domestic use, which has generated strong opposition to a 'corona pass society' accused of being synonymous with discrimination and polarising private, 'invasive', enforcement. Nonetheless, a minority of countries moved quickly towards requiring a corona pass to access big events as well as cultural activities, fitness and sports clubs and hospitality venues (Israël, Denmark). As we will see below, many countries took (much) more time, but subsequently introduced a corona pass in one form or another[10].

The controversy about corona passes has been intensified significantly by the fact that authorities in most rich countries initially stated two things that were potentially contradictory: (1) vaccination should be a personal choice, and (2) we plan to reach 'herd immunity'. The latter is not an exact number, but early on it was commonly set at a vaccination rate of 70% of the total population, based on the original virus. It is now significantly higher, of the order of 90% with the delta variant (and even more with the omicron variant). The big challenge has then been: what if (1) and (2) are not compatible?

It would have been more astute to say: "With limited vaccine supply and high uncertainty early on about side-effects of these new vaccines, we shall start with volunteers, to whom we are grateful, and we shall fine-tune the strategy along the way while trying to accommodate legitimate vaccine fears as much as possible". It could be argued that stating (1) and (2) above, rather than this more cautious line, was maybe one of the most significant communication blunders in a crisis that has been rich in failures in this respect. Many such communication failures stem from a distaste for the unavoidable uncertainty the virus implies. People want 'perspectives', which leads authorities to promise a

[10] See Olui-Barton et al. (2022).

noncontingent 'return to pre-covid freedoms' that puts aside the intrinsic uncertainty about 'what the virus is up to', and also about 'what the population is up to' in terms of willingness to follow NPIs or be vaccinated. This feeds into pandering to ill-informed voters by political authorities ('we can trust the population about vaccination decisions and everything will be fine'), which is bound to disappoint and require 'flip-flopping'.

Statement (1) was moreover very surprising in a time of crisis when, for most of 2020, many individual rights had been constrained (thereby generating much inequality) in ways not seen since the end of World War II – the right to work, to be educated, to circulate, to meet in groups, and so on. All this was done in an increasingly 'sophisticated' way over time to better fine-tune 'proportionality' in balancing concerns over individual rights with public health concerns for each measure. Why did the 'right not to be vaccinated' have to be 'sanctified' so much instead of saying that the same cost-benefit analysis should be applied with vaccination too (as is done with some other vaccines in fact) ? The criticisms of corona passes mentioned above are valid, but they have to be weighed against the very high effectiveness of vaccines in terms of lives saved and their very low financial cost (less than €4 for two doses of the AstraZeneca vaccine, €24 for two doses of the Pfizer/BioNTech vaccine and €36 for two doses of the Moderna vaccine in the original contracts signed by the European Commission).[11]

This being said, while communication about the vaccination strategy has clearly suffered from insufficient caution, the gradual strategy followed in the first half of 2021 also had clear merits. Interestingly, the idea of a 'gradualist strategy' echoes a debate that took place more than 30 years ago over the transition from a centrally planned economic system to a market economy following the change of economic strategy in China after Mao's death and Deng Xiaoping's rise, and especially in the former Soviet Union and eastern European countries after the fall of the Berlin Wall. As argued then by Dewatripont and Roland (1992, 1995), in an uncertain environment it is advantageous, and at times unavoidable, to start first with 'more efficient and popular' policy measures, and thereby potentially build momentum for further reforms when earlier ones turn out to have positive effects.

This approach is relevant for covid vaccination too ; the argument can be sketched as follows :

1. Assume a utilitarian government that wants to induce individuals to get vaccinated to reach a target X% of the population in order to keep a pandemic under control. It would like to achieve it as fast as possible (to best reduce the health risk) while concentrating as much as possible on those individuals for which the 'net utility' of vaccination – which depends positively on the individual health benefit of vaccination and negatively on its 'psychological cost' (fear, moral objections) – is highest.
2. The health benefit of vaccination is positively correlated with observables like age and co-morbidities. Therefore, within the population, the net utility of vaccination is also positively correlated with these observables.
3. Knowledge evolves over time about this health benefit, since one learns about : (i) the prevalence of negative side effects of the vaccines ; (ii) their effectiveness in terms of

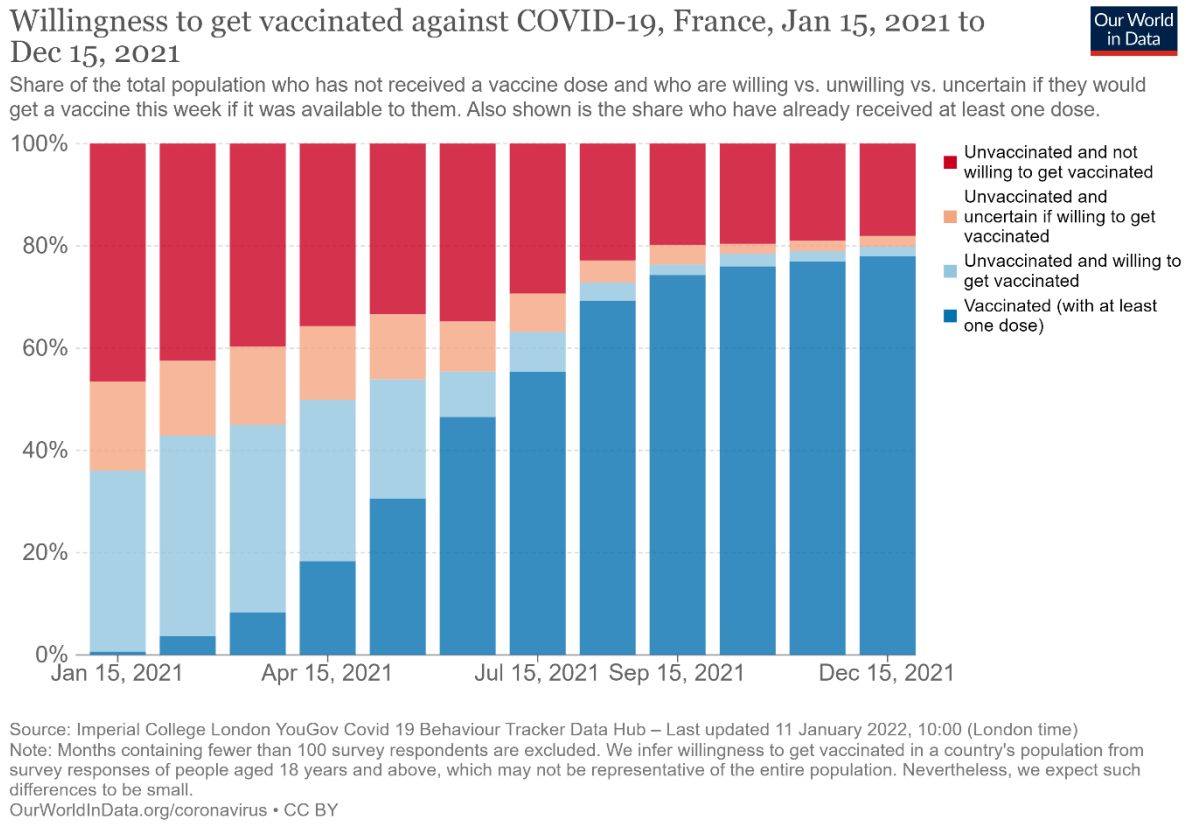
[11] Numbers contractually meant to be secret but disclosed in a tweet by the Belgian secretary of state for budget.

reduced contagion and reduced severity ; (iii) the contagiousness and severity of the new variants of the virus, and their impact on (i) and (ii).

4. The government is receiving vaccine doses gradually over time.

Because of 4, one cannot vaccinate everybody right away. It is therefore optimal to target first individuals belonging to groups most at risk and willing to be vaccinated. Note that these volunteers exert a positive externality on the rest of the population, by becoming less contagious but also by providing information about how risky and how effective the vaccine is (items (i) and (ii) of point 3 above). In the current case, the news has been good on these two fronts (on (ii) mostly in terms of protection against severe forms of the disease), and surveys run by psychologists have shown that the share of the total population willing to be vaccinated has risen during the first months of 2021 thanks to 'non-coercive' information provision (see for example Schmitz et al., 2022). This is also illustrated in Figure 3 for the case of France, a case we will return to later in this section : France started with 46.5% of its population unwilling to get vaccinated in mid-January and this had dropped to 33% by May. Note also the share of the population yet unvaccinated but willing to be was high in the initial months of 2021 : it stood at 23% in May, which indicates that vaccine supply was indeed still the key constraint at that point.

Figure 3



This strategy of vaccinating volunteers first, going from the most to the least vulnerable individuals, has thus created a virtuous circle and allowed to vaccinate initially hesitant people who have gradually volunteered to get vaccinated (seeing in particular that people who got vaccinated were safe and that the people who were getting seriously ill and possibly dying were mostly unvaccinated).

We can reach the first-best outcome in cases where the proportion of the population vaccinated willingly is sufficient to reach the vaccination target. This has however mostly not been the case, either because some countries did not manage to reach the initial 70% target, or because they did but it became insufficient due to new variants. This prompted many countries to move to more coercive strategies in the latter months of 2021, increasingly pressure to get vaccinated, with for example decisions to either :

- keep the corona pass options of recovery or a negative test as ways to retain the pass next to vaccination, but start to charge for the tests (many countries) ;
- turn the pass into a vaccination pass (e.g. France) ;
- generalize the pass to additional activities, in particular work (Italy, Luxembourg) ;
- make vaccination mandatory for some occupations (e.g. healthcare workers) and, more recently, for some age groups (50 in Italy, 60 in Greece) or even the whole adult population (Austria) ;
- start charging fines on the unvaccinated (Québec, Greece).

How can one explain such increasing toughness on the unvaccinated ? One element is linked to the fact that, with increasing vaccination, the unvaccinated become a dwindling minority, and there is growing impatience with them on the side of vaccinated people ('they have had time to think about it, they can see vaccines are safe, I did take the risk, why don't they ?'), and authorities react accordingly when balancing the interests of the whole population. This is a case of 'momentum without new information', that goes beyond Dewatripont-Roland (1992, 1995) : it just reflects the fact that, as shown in psychological surveys (see for example de Figueiredo et al. (2021),[12] a big majority of vaccinated individuals support extra constraints on the unvaccinated, given the positive externalities of vaccination through reduced contagiousness and hospital burden and therefore reduced strictness of non-pharmaceutical interventions which can also affect them.

At the same time, this also implies polarization, since the remaining unvaccinated individuals are those whom those psychological studies show to be most reluctant to get vaccinated. And as constraints faced by the unvaccinated become tougher and tougher, it is not surprising that concerns of discrimination lead to attempts to make vaccination mandatory, even if implementation challenges seem to lead many governments to prefer corona passes. On the other hand, it is surprising that not more has been done to use 'carrots' and not only 'sticks' to convince unvaccinated people, some of whom are poor, fragile and often 'disconnected' from society. Reaching more of these people, some of whom are not diehard opponents of vaccination, could allow to reach one's vaccination target while having to convince fewer such diehards.

Do corona passes work ?

We have already mentioned objections to corona passes in terms of discrimination and invasive enforcement. A key additional objection concerns the potential impact of these passes : what if

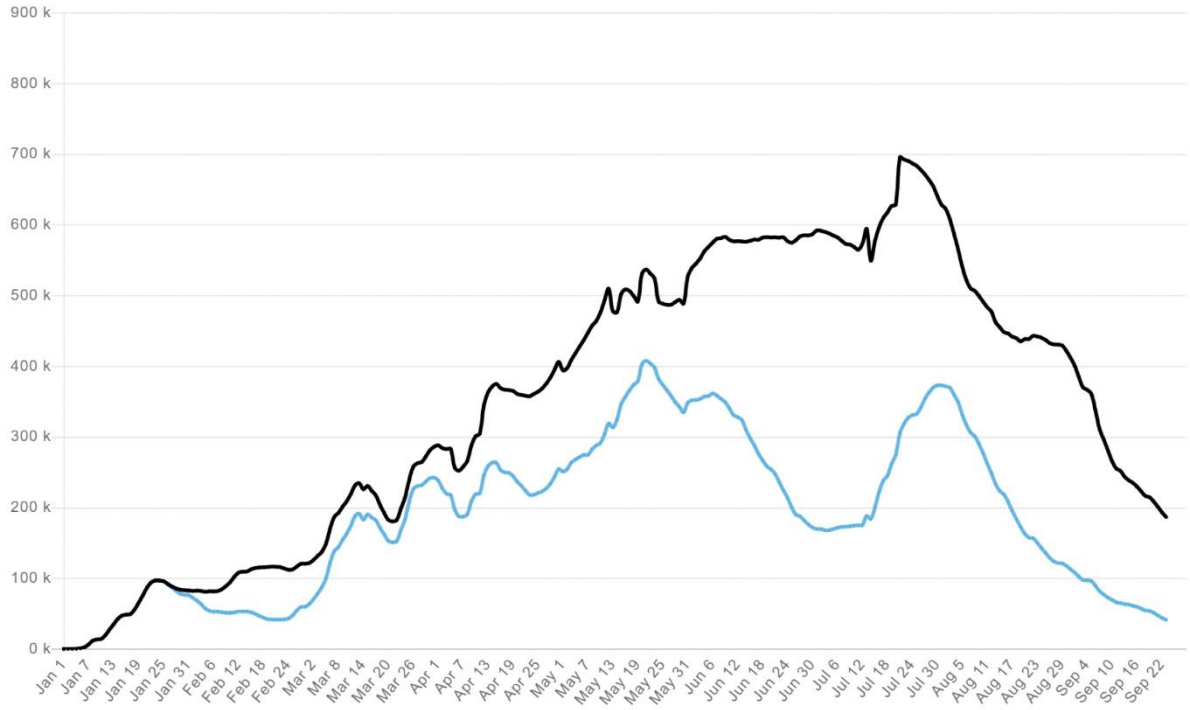
[12] See also the Belgian Motivation Barometer series (https://motivationbarometer.com/fr/) and the Belgian Corona Study (https://www.uantwerpen.be/nl/projecten/coronastudie/) organised by the Universities of Antwerp and Hasselt.

unvaccinated people refuse to get vaccinated, arguing that one has 'reneged' on their 'vaccination freedom', which could be expected from the evidence from psychological studies mentioned above ? In this case, not only could these passes be divisive, but there is also a risk that they could be counterproductive in terms of vaccination. At the same time, this survey evidence relates to hypothetical situations. How confident can we be that individual choices are going to be consistent with the answers from these surveys? It is interesting to quantitatively analyze actual experiences of corona passes as well as other measures to encourage vaccination.

In this respect, France is a potentially interesting case because the corona pass was announced solemnly on French TV by President Macron on 12 July with a well-defined timetable (it included a vaccination requirement for healthcare personnel, and a sanitary pass requirement in particular for cinemas and museums as of July 21 and hospitality venues as of 9 August) and with a clear goal (75% of the population with a first dose by early September).

The immediate impact of this announcement was a 'vaccination appointment rush', with almost one million appointments within 24 hours.[13] This response was stronger than even the supporters of the pass had hoped for. Figure 4 shows a significant rebound of daily first doses, which changed the vaccination dynamics for weeks (first doses is the appropriate indicator at a time when the binding constraint is vaccine hesitancy and the key hurdle is convincing people to get their first dose).

Figure 4 Total daily doses (black curve) and daily first doses (blue curve)



Source : Ministère français de la santé

[13] See https://www.liberation.fr/societe/sante/vaccination-tous-piques-de-doctolib-apres-les-annonces-de-macron-20210712_A7D33PZ4Y5HFPP6ZIW5TZLQZDA/

While this evolution is impressive, not everybody was convinced. Every Saturday last Summer after July 12, multiple demonstrations were organised across France against corona passes, with a peak of over 200,000 participants in total in subsequent weeks. On the other hand, more than 15 million French people have decided to get vaccinated between 12 July and December 31. And one thing which is clear is that no 'aggregate backlash' has taken place among the unvaccinated : as Figure 3 shows, France started 2021 with 35% of its population unwilling to get vaccinated in mid-June, but this number has been just below 20% since mid-September.

Moreover, France has risen spectacularly in the 'vaccination ranking' since 12 July. In a nutshell, at 54% of its total population having received a first dose at that date, France was only ahead of Greece among pre-Eastern enlargement EU countries. Two months later, its first-dose rate had risen to 74% and France was only behind Portugal, Spain, Denmark and Ireland. This being said, Portugal, from a higher base (62%), had grown by a spectacular 25% to reach top place at 87% (interestingly, it extended the corona pass to hotels and restaurant at roughly the same time as France). And Spain's growth equalled France's to reach 80%, while the attempt of the central government to introduce the corona pass was blocked by the Superior Court. In the next 4 months, the situation has been pretty 'stable', ranking-wise, but with stronger progress from countries with relatively low vaccination rates : while most countries rose by a further 4 to 8%, the two countries with the lowest vaccination rates in the region rose respectively by 12% (for Austria) and 14% (for Greece). And Italy rose by 9% and has been the only one to rise in the ranking, trailing only Portugal, Spain and Denmark by the end of 2021.

Interestingly, Italy, Austria and Greece have all 'tightened the screws' in the last four months of 2021, suggesting coercive measures do have an impact, as in France. On the other hand, countries such as Germany and Austria which introduced the corona pass a long time ago had not seen a very strong strong vaccination growth in the following weeks.

The above numbers are only suggestive. It would be interesting to better understand why the introduction of a corona pass seems to have had such a big impact in France but less so in some other countries.

In this respect, the study which is 'closest' to the above pattern of significant but differentiated impact of corona passes across countries is the recent study by Olui-Barton et al. (2022). The authors use 'innovation diffusion models' and estimate that the introduction of corona passes by France, Italy and Germany led to respective increases of 13.0, 10.7 and 6.2 percentage point increases in vaccination rates in these countries by the end of 2021, taking as control groups countries that did not introduce corona passes. It is interesting to observe that, from a difference-in-difference perspective, the above numbers roughly parallel the evolution of vaccination performance during this period, since between July 12 and December 31, 2021, France increased its vaccination rate by 25% (79 – 54), Italy by 20% (80 – 60), Germany by 15% (74 – 69), and Belgium (a country that has a strong weight in the 'synthetic' control group, due to its similar vaccination dynamics to these three countries before mid-July) by only 11%. This confirms the strong impact of corona passes on vaccination.[14]

[14] The paper also estimates the benefits of this policy in terms of health and economic outcomes.

Two other studies also look at France, Italy and Germany (and some other countries or regions) with difference-in-difference methods. First, Mills and Rüttenauer (2022) look at a 60-day window and find increases in vaccination rates of 13 and 6.7 percentage points respectively for France and Italy, but no significant effet for Germany. Second, Karaivanov et al. (2021) find increases in vaccination rates of 6, 10 and 4.3 percentage points respectively for France, Italy and Germany over a 3-4 months window. Finally, François et al. (2021) look at France and find a 7.5 percentage point increase over three weeks.

While the studies have their differences, they clearly point to a significant impact of corona passes on vaccination, with reasonably consistent differences of outcomes across countries. Next to these studies, research would also be useful to understand how Spain managed to reach such a high vaccination rate with less coercion. And Portugal is interesting too : its stratospheric vaccination rate cannot just be the result of coercion, but must have to do with its 'vaccination culture'. Interestingly, this is a country where the 'right not to be vaccinated' never came up in public debate and where the antivaxx movement is very discreet.[15] Looking at these questions would call for a multidisciplinary analysis.

Let us end this section with a note of caution. The analysis here has focused on 2021, and therefore the alpha and delta variant. In Europe, the first months of 2022 have seen the arrival of omicron, which has been a true game changer : less lethal but much more contagious, it has led to many more infections, even for people who had already been vaccinated. This has raised immunity by infection and has reduced the vaccination momentum as well as coercive measures to foster vaccination. Hopefully, this could lead to a transition towards a flu-like endemic coronavirus. Waning immunity from vaccines and infections over time and potential new variants mean however that one should remain very vigilant for potential waves after the Summer of 2022.

V. Insufficient public leverage on the innovation/affordability tradeoff of new drugs

This section builds on the covid vaccine experience to draw a couple of lessons on the innovation/affordability tradeoff. While in pandemic times, the issue of vaccine prices can be second-order, for rich countries at least, given the opportunity cost of delay in terms of lockdowns and reduced growth, this experience is nonetheless instructive for 'quiet times', where affordability is a much more significant concern.

Excessive prices ?

As said earlier, in its negotiations with covid vaccine producers, the EU Commission was criticized in the first half of 2021 for having excessively insisted on low vaccine prices (instead of speed of delivery). This being said, since acquiring booster shots and improved vaccines will still be needed in the future,

[15] According to a private conversation with Portuguese scientists in an informal binational epidemic-management meeting.

containing prices will be a concern. In this respect, the words of Frank D'Amelio, the Chief Financial Officer of Pfizer are not very reassuring, to say the least : " In short, D'Amelio explained that Pfizer expects its COVID vaccine margins to improve. Under one pandemic supply deal, Pfizer is charging the U.S. $19.50 per dose, D'Amelio said, which is 'not a normal price like we typically get for a vaccine—$150, $175 per dose. So, pandemic pricing.' " (Sagonowsky, 2021). Next to massively boosting world supply and ensuring affordable access to current covid vaccines for poor countries, it is therefore important not to forget the need to avoid rents above competitive rates of returns for future versions of covid vaccines to be purchased by rich countries.

Now, while Pfizer, BioNTech and Moderna are making good money[16], typical discussions about innovation in pharma in general pits critics that complain about high prices and returns against an industry that stresses the high cost and riskiness of innovation. Obviously, as economists we would naturally assume that, for private private R&D to take place, especially from the ex-ante less 'commercially attractive' areas of 'neglected' diseases (rare diseases, several infectious diseases, complex diseases like Alzheimer, where industry is seen not be active enough) requires the researcher/innovator to anticipate the (discounted) net benefit (*B – C)* of innovation to exceed (*B – C)**, the net benefit of other potential uses of innovator's resources. Policy can act in particular on the gross benefit *B* (which is the result of price negotiations with funders after authorization) and also on the cost *C*.[17]

On the other hand, there is no reason, for either (*B – C)* or *(B – C)*,* to be above competitive returns. However, evidence indicates that, while biotech firms earn on average a (*B – C)* which is higher than (risk-adjusted) market-consistent rates of return (having in fact a higher risk more than compensating their ex-post high return), big pharmaceutical companies have for decades earned annual risk-adjusted rates of return that are 3% in excess of the market (see Thakor et al. 2015).

This is partly linked to the lobbying power of big pharma companies, especially in the US where prices have been quite high since George W. Bush got Congress to prevent Medicare from negotiating drug prices (see Danzon (2018); and also Case and Deaton (2020) more generally). This adds to the problem of the general weakness of competition today, which has led big firms in many sectors to earn pretty high returns recently, even leading to adverse macroeconomic consequences (see e.g. De Loecker and Eeckhout (2020), Philippon (2019) and Aghion et al. (2021)). In this respect, one should make sure that the new emphasis on 'industrial policy' be competition-friendly, as stressed by Aghion et al. (2015) and as successfully managed by OWS.

[16] With market caps on January 14 at $308 billion for Pfizer (up 42% since end 2019), $47 billion for BioNTech (up 510%) and $83 billion for Moderna (up 1158%). Instead, the other 3 big vaccine producers GSK, Sanofi and MSD saw their market caps evolve by -1%, +3% and -11% respectively. Of course, this is only a rough comparison.

[17] Note that neglected diseases have a number of specificities as far as this inequality is concerned : (i) *B* will typically be low when the potential market is small, either in terms of number of cases (e.g. rare diseases), or of low 'ability to pay' (diseases affecting poor countries); (ii) on the other hand, since low patient numbers reduce the threat to public budgets, higher prices per patient can at times be obtained, which raises *B*; (iii) as for *C,* it can be higher when the disease is pretty complex (e.g. Alzheimer); (iv) on the other hand, some neglected diseases can benefit from a fair amount of public funding, which lowers *C*, and finally (v) authorization on the basis of lower sample sizes for RCTs, typical for rare diseases, lowers *C* again.

The question of high prices has become an even bigger issue at a time when accelerating scientific progress opens up new opportunities, for example with gene therapies (and mRNA could provide another boost to this trend), which are both very promising and financially challenging. For example, Fischer et al. (2019) report: (i) three cases of treatments approved by the FDA and/or EMA in 2018-2019 costing between $373.000 and $850.000 per patient, for diseases affecting 1.000 to more than 2.000 patients in Europe and the US, (ii) one treatment costing $2.100.000 (Zolgensma, by Novartis), concerning more than 1.500 patients, and (iii) another one costing €1.580.000 (Zynteglo, by Bluebird), concerning more than 10.000 patients. Since this increasing trend is going to persist, it is important to find ways to keep public health budgets under control while ensuring that useful innovation can flourish.

Moreover, not only is the equilibrium *(B – C)* 3% per year too high, but evidence points to an authorization bias against 'truly creative' innovation through an excessive reward of 'marginal' innovation'. Indeed, Fojo et al. (2014) look at US evidence on cancer therapies and stress the 'unintended effects' of expensive marginal therapies that earn higher risk-adjusted returns than more innovative ones, and are unsurprisingly pursued by for-profit pharma companies. This indicates a flaw in the authorization/pricing process for new therapies, since by making marginal innovation more lucrative, one raises the opportunity cost *(B – C)** of engaging in truly innovative research.

Improving the innovation/affordability tradeoff

Unsurprisingly, the covid vaccine experience has generated debates about the distribution of the rewards of innovation between private companies and the public sector.

Improving bargaining positions

A key innovation in the covid vaccine case has been the emergence of the European Commission as a negotiator on behalf of the 27 EU member states. This echoes efforts by groups of EU Member States to join forces in price negotiations with drug companies, with Belgium, the Netherlands, Austria, Ireland and Luxembourg being the first such group (see https://beneluxa.org/). More recent initiatives are the Valletta group regrouping southern European countries, the nordic pharmaceuticals forum and the Visegrad group.[18] The goal of such initiatives is to put these actors in a better position to require more transparency about R&D, manufacturing and distribution costs of the drug.

It is however thought that truly meaningful impact would require further coordination. The covid vaccine episode could be an opportunity to go more generally towards EU-wide coordination of negotiations with pharma companies, to limit their ability to put states in competition. Kyle (2007) documents big pharma strategies, showing in particular that new drugs are introduced earlier in jurisdictions that pay higher prices, which is in line with the priority given to Israel by Pfizer. One should therefore not draw the wrong lessons from the European covid negotiation : they constitute a precedent worth building upon in order to improve European member states bargaining power with pharma companies.

[18] See Bruce, F. (2021).

Bargaining moreover concerns both the number of states and the number firms. In this respect, one could wonder whether the EU Commission's decision to 'drop' AstraZeneca (and Johnson and Johnson) from future purchases takes sufficient account of the impact of competition between firms on negotiated price levels. It is understandable that authorities prefer to 'buy the best quality' for their citizens, but quality assessments are still evolving, along with the virus and its variants. Keeping one's options open could therefore be a valuable strategy, keeping in mind Frank D'Amelio's words.

Finally, this covid vaccine case is an extreme example of the asymmetric timing of the financial costs *C* and benefits *B* of health innovation : early stages of the process are heavily subsidized – in this case not only R&D but even production, given the urgency of vaccine development – but price negotiations, and especially renegotiations, happen later on and risk insufficiently rewarding earlier subsidies through price discounts. While it is unavoidable that such reward does not happen if subsidies do not lead to successful innovation, public authorities should really insist upfront on profit-sharing schemes in order to benefit from the upside of innovation.

Governance

In the pharma sector, currently, the later stages of innovation are implemented by the private sector, often by big pharma companies which typically buy biotech firms, which themselves built on publicly-funded research (universities, the NIH and BARDA in the US, etc). This innovation sequence is pretty 'natural', as argued by Aghion et al. (2008): academic researchers do 'value' academic freedom, which means they accept to work for lower wages in academia than they would in the private sector. Early on in the R&D process, this makes academia 'more competitive'. On the other hand, the 'cost' of academia is that academics may decide not to follow the most commercially profitable path. In a multi-stage R&D path where academic freedom lowers by a given percentage the probability of successfully reaching the next innovation stage, academia becomes costlier relative to private 'directed' research the closer one is to an authorized therapy. This endogenously rationalizes the observed innovation sequence of academic freedom followed by directed research, both actors having their own comparative advantage.

While this sequence is natural, achieving a fair distribution of the rewards of innovation has proved difficult in a system of large for-profit providers of new vaccines and therapies. The profit motive is a powerful drive whose rent-extraction costs are high, as detailed for example by Mazzucatto (2015, 2018), and information asymmetries and residual rights of control do allow producers to earn rents (as detailed for example by Laffont and Tirole (1993), Hart (1995) and Auriol et al. (2021)). One idea to limit these rents could be the introduction of 'common-good advocates' on the Board of pharma companies. Another could be to transform (part of) them into 'Benefit Corporations', as advocated by Fischer et al. (2019), so that 'shareholder value' stops being their overriding objective, an objective deriving now from their legal charter and, since the 1980s, increasingly put into practice (see for example Holmström and Kaplan, 2001).

Change could be enacted by leveraging companies' corporate social responsibility. Concretely, payers could incentivize companies involved in gene therapy to create *ad hoc* subsidiaries for these activities and organize them according to the Benefit Corporation concept (see Cummings, 2012) in order to subsequently obtain a B Corporation certification (https://bcorporation.net/). The Benefit Corporation declaration gives legal protection to companies to pursue social and environmental performance as

well as value for shareholders. The boards of Benefit Corporations are required to consider other stakeholders in addition to shareholders in their decision-making. The application to a B corporate certification further enhances accountability to social good, as the certification is done by an external third-party based on the company's verified performance on the B Impact Assessment, making the Benefit Corporation a certified B corporation.

By acquiring the status of certified B corporation, companies should be able to leverage the social impact of their pricing in their performance indicators, thus affording them the opportunity to bring their pricing down to a "market-consistent" level in order to enhance their social performance. Incentivizing large pharma companies to create subsidiaries with a B Corporation status for example for therapies for neglected diseases would follow the example of Unilever with Ben & Jerry.

Pushback is to be expected. But corporations themselves are increasingly recognizing the value to generate long-term value for all stakeholders instead of shareholders only and to shift their priorities from profit maximization to optimizing value creation, as demonstrated by the Business Roundtable 2019 Statement on the Purpose of a Corporation (see Business Roundtable 2019) of which several pharmaceutical companies are signatories to. The next step would be for payers to consider making reimbursement of gene therapy products conditional upon their commercialization by certified B Corporations. The greater objective should be a pricing policy that results from a credible alignment of industry, patients and payers' interests.

VI. Conclusion

This pandemic has been unique in its magnitude and should lead to a rethink of a number of institutional features in Europe. In particular, the US OWS success should call for a strengthening of the EU biotech innovation system, not only through a BARDA-like Health Emergency Response and preparedness Agency, but also a better coordinated EU health research budget like the NIH. More EU coordination could also arise thanks to the experience the Commission has acquired in its contractual negotiations with vaccine producers. The objective should be to improve the terms of the innovation/affordability tradeoff. Given the magnitude of public funds poured into health innovation systems, society at large could indeed obtain a higher share of successful innovation returns, without driving private actors away from the market.

The pandemic has also taught us a lot about how authorities are able/not able to elicit cooperation from the population, for non-pharmaceutical measures as well as vaccination campaigns. Given that individual rights have been curtailed to keep the pandemic under control in a way not seen since World War II, it is unsurprising that resistance has been significant at different times. Lessons have been learnt along the way however, in terms of the design of measures that optimize the sanitary benefit for a given economic or psychological cost. In this respect, it has been unfortunate that authorities in many countries were unable to properly place vaccination as one of several instruments that would need to be forcefully activated if the sanitary situation were to require it. Focusing at the start on the 'right not to be vaccinated' at a time where it was unclear whether this could be consistent with controlling the virus was a communication blunder which did not facilitate the situation. Countries did however manage to introduce instruments like corona passes which turned out to boost vaccination. Of course, new variants are already requiring strategic adaptations, whose calibration in a context of popular pandemic fatigue.

In any case, it will be necessary to properly draw the lessons of this pandemic to be better prepared for the next one, which could definitely happen.

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