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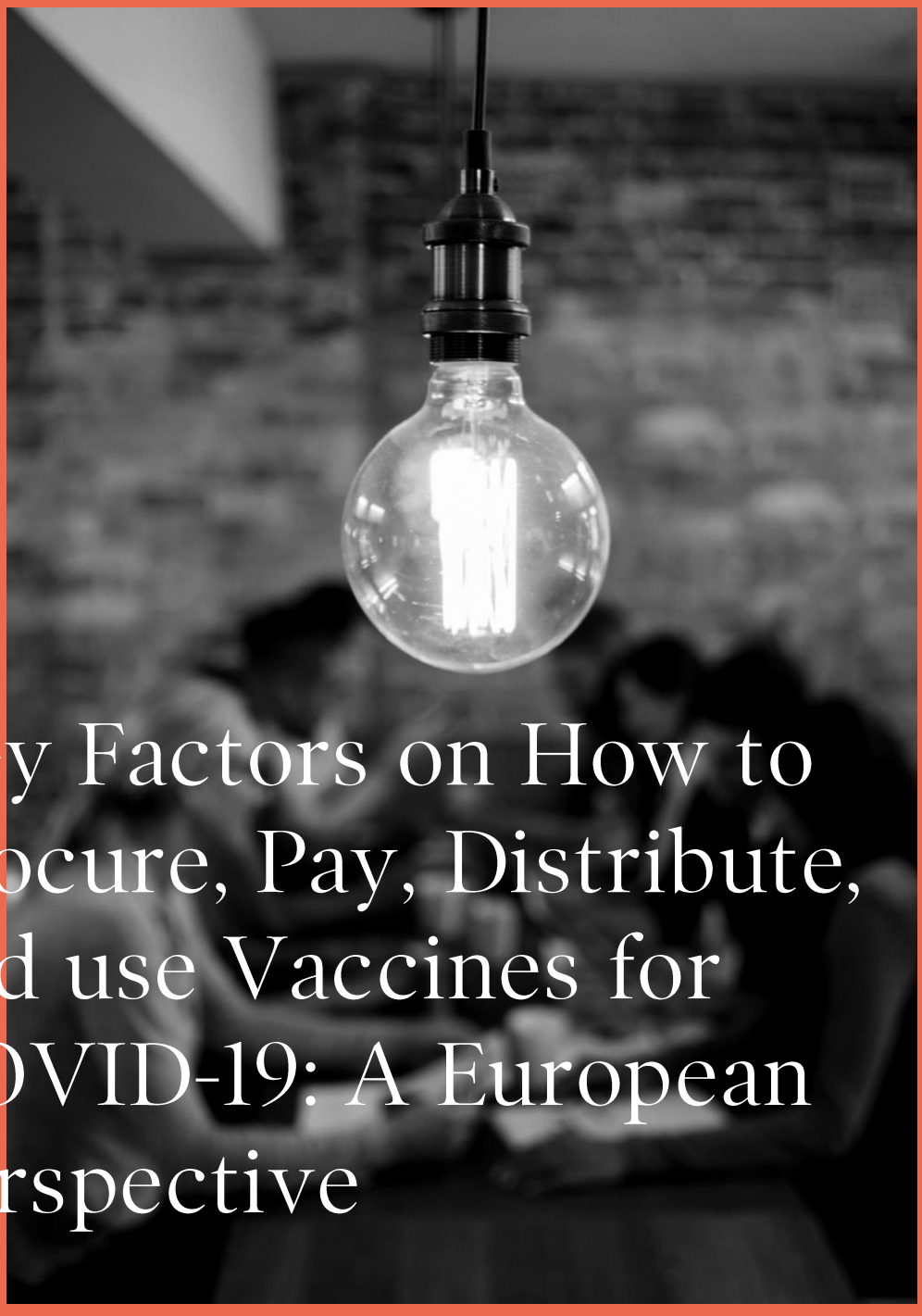

Key Factors on How to Procure, Pay, Distribute, and use Vaccines for COVID-19: A European Perspective

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Table of Contents

Executive Summary ..... **v**

1 Background **6**

1.1 Health and economic impacts and prioritisation of access to vaccines 8

2 Project portfolio and timeline **11**

2.1 What types of technology are expected, and what are the pros and cons of each one? 13

2.2 Project portfolio management 15

3 Licensing, efficiency thresholds and use of banding system **18**

3.1 Efficacy thresholds 18

4 Procurement of vaccines and their price **23**

5 Vaccine delivery issues **30**

6 Vaccination programmes and prioritisation strategy in MS **33**

7 Education and public awareness **39**

References **46**

Index of Abbreviations **50**

Executive Summary

This work is the English translation of the report '*Factores clave sobre como adquirir, pagar, distribuir y utilizar las vacunas para la COVID-19. Una Perspectiva Europea*', commissioned by the European Parliamentary group RENEW Europe, finished in November 2020. It discusses the need to prioritise vaccines vis-à-vis the impact of the COVID-19 pandemic on the health systems and gross domestic product of Europe.

We present the Phase III vaccines pipeline (as of November 2020) and the vaccines' technical differences, pros, and cons. The report introduces a vaccine classification system based on efficacy thresholds (or guardrails) and quality bands according to predefined Target Product Profiles (TPP) and the concept of advanced purchase agreements to incentivise vaccines' production in the pipeline ex-ante regulatory approval.

We establish that European-level coordination on contracting requires sending the right signals to developers on both volume contracting and pricing. In other words, to incentivise development, quality and investment in production capacity, contracts need to include pricing as part of a reward system. There is also a need to incorporate extended value-added elements into definitions of TPP levels and contracting processes, including pricing.

This report outlines essential potential criteria for distributing doses between the European Member States and highlights the need to inform the population for achieving the desired levels of vaccine uptake.

1 Background

Expectations for the arrival of an effective vaccine to help end the shock created by the COVID-19 pandemic have grown exponentially in recent weeks. The second wave of COVID-19 has demonstrated that the world will not overcome the pandemic until effective therapies and/or vaccines are developed and distributed efficiently. Living through this pandemic without effective therapeutic solutions has led to colossal health and economic losses, with a corresponding negative socio-cultural impact. Science has pledged to provide solutions within 6 to 12 months. However, the arrival of solutions has lead to political challenges that must be addressed.

The epidemiological situation that most European countries are experiencing during the second wave has led to further partial or total closures and travel restrictions, similar to those during the first wave between March and July, 2020. To date, France and Austria have re-imposed nationwide closures (as of November 24, 2020); Germany has closed bars and restaurants and imposed other restrictions; Spain has activated a state of alarm to allow regional governments to impose restrictions and closures, sectors of the economy have already been shut down, travel to different regions banned, and home visits are prohibited; the UK has introduced tighter restrictions on mobility and socialising, and either partially or entirely closed sectors of the economy. Other countries are likely to follow.

The main objective of these policies – i.e., non-pharmaceutical interventions (NPIs), implemented at different levels in different countries and regions – is to cut or reduce transmission of the virus, curb infection rates, reduce mortality, and relieve health systems of the excess burden of care due to COVID-19 patients. The aim is to minimise the healthcare impact by reducing hospitalisations due to COVID-19 and allowing patients with other pathologies to receive treatment, thus minimising avoidable mortality. Figure 1 shows the epidemiological evolution leading to the second wave in the European Union (EU), based on a seven-day moving average of new cases per million.

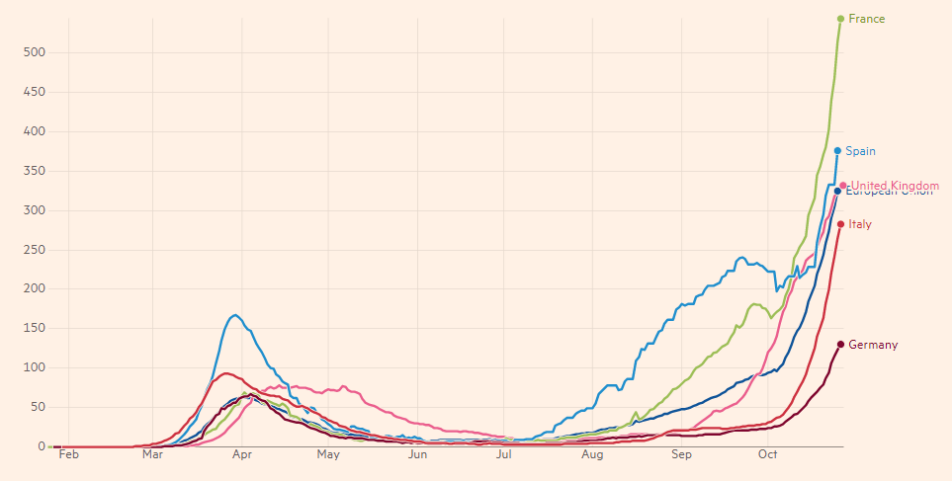

FIGURE 1: NEWLY CONFIRMED CASES OF COVID-19 IN THE EUROPEAN UNION, UK, FRANCE, SPAIN, GERMANY AND ITALY

Note: Seven-day moving average of new cases per million.
Source: Financial Times analysis of data from the European Centre for Disease Prevention and Control, the COVID monitoring project, the UK Government Coronavirus dashboard and the Spanish Ministry of Health.

Figure 2 shows the evolution of new deaths attributed to COVID-19 in the EU and EU5 countries, based on the seven-day moving average of recent deaths per million.

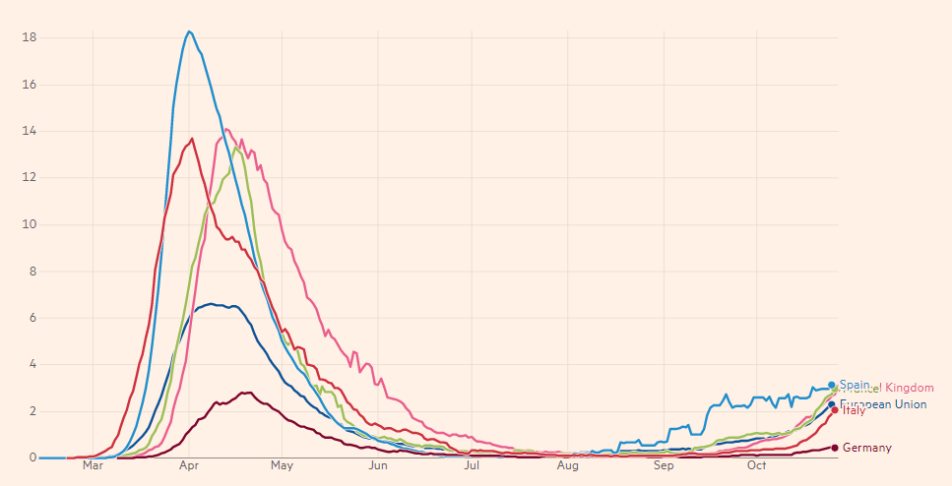

FIGURE 2: NEW DEATHS ATTRIBUTED TO COVID-19 IN THE EUROPEAN UNION, UK, FRANCE, SPAIN, GERMANY AND ITALY

Note: Seven-day moving average of new deaths per million.
Source: Financial Times analysis of data from the European Centre for Disease Prevention and Control, the COVID monitoring project, the UK Government Coronavirus dashboard and the Spanish Ministry of Health.

The first wave resulted in harsh NPIs in the form of complete national shutdowns in almost all countries, involving the halting of economic activity in most sectors, the prohibition of mass gatherings and/or public events, the closure of schools and universities, the recommendation of teleworking where possible, and the introduction of limitations on the provision of health services to patients with other pathologies, such as patients opting for elective surgery. The economic consequences of these measures have been widely discussed by different organisations such as the Organisation for Economic Co-operation and Development (OECD), the International Monetary Fund (IMF) or the European Commission (EC) (OECD, 2020; IMF, 2020; EC, 2020a). Estimates by these organisations suggest that the European gross domestic product (GDP) will decrease between 5% and 15% in 2020. Figure 3 shows the OECD's forecast of projected real GDP growth in 2020 given a COVID-19 "two-wave" scenario.

The economic recession and health crisis are expected to lead to additional indirect negative health impacts and accentuate inequalities, especially for the most socio-economically vulnerable (Blundell et al. 2020; van Dorn, Cooney and Sabin 2020; Marmot and Allen 2020; Patel et al. 2020; Burström and Tao 2020).

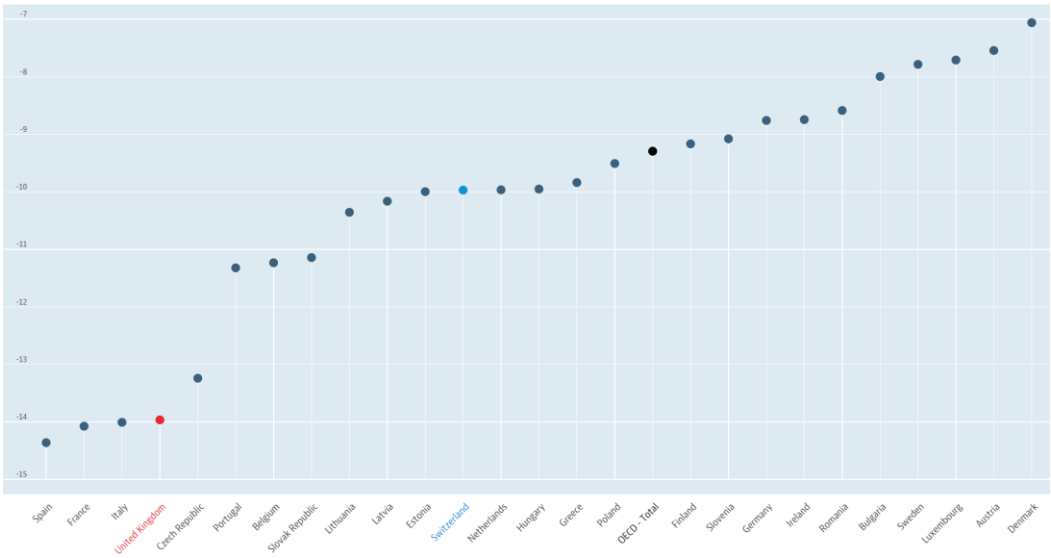

FIGURE 3: REAL GDP FORECAST FOR EU-27, UK AND SWITZERLAND
Note: Double-impact scenario (2 waves), Annual growth rate (%), 2020
Source: OECD Economic Outlook: Statistics and Projections

1.1 Health and economic impacts and prioritisation of access to vaccines

The importance of indirect effects of COVID-19 indicates the need to prioritise when deciding which sub-populations should be vaccinated and/or treated first, once new therapies and/or vaccines are approved.

Demand-side factors: it is generally accepted that priority should be given to people with comorbidities who are most at risk, as well as the elderly, and health and social care workers, including nursing home staff (CDC, 2020; Anon, 2020; EC, 2020b). Carers of vulnerable people (i.e. those at high risk of severe COVID-19 or death due to age and/or comorbidity) essential workers, teachers, etc., should immediately follow.

However, these commonly accepted priorities do not inform how the first batches of vaccines should be allocated among the European Member States (MS) or regions within countries. Neither do they explain how other factors such as socio-economic inequalities, rates of marginalisation, economic disadvantage, household composition, and/or citizens' accessibility to health care should complement purely epidemiological and health data and criteria.

There is a proven correlation between economic marginality and disadvantage, and the risk of job loss (Blundell et al., 2020). Thus, protecting economically disadvantaged individuals after high-risk groups and their caregivers could be an optimal strategy to minimise health and economic impacts. Doing so would require an understanding of which regions or population areas within each country, and which countries, are most at risk due to socio-economic deprivation.

Other demand factors: The mental health impact associated with NPIs is one of the major indirect effects of this pandemic at the population level (Xiong et al., 2020). This is a crucial factor to consider as its effects are more likely to increase in the medium to long term, rather than in the short term. When planning for the efficient use of the relatively short first set of vaccines, it may be worth considering which countries or sectors of the population have been affected for longer and/or more intensely to NPI restrictions. These populations are more likely to suffer from mental health problems due to the pandemic – an indirect epidemic.

Supply factors: In addition to the demand factors discussed above, supply factors must be understood in shaping and establishing health and economic policy governing the procurement, distribution, and access to vaccines for COVID-19.

Science has responded with unprecedented speed to the challenge posed by the pandemic. There are currently eleven candidates in Phase III and more than 48 in clinical development, including Phase III candidates (WHO, 2020a). Assuming a 50% chance of success (according to Hay et al., 2014, for example) for the ten Phase III vaccine projects, five of the ten would be available for human use sometime next year. In a report published by the Center for Global Development, McDonnell et al. (2020) make a more pessimistic prediction, based on mathematical modelling, in estimating that there is only a 50% chance of having a safe and effective vaccine approved by the end of April 2021 (85% by the end of the year). Thus, given the importance and impact that the manufacture and distribution of the first approved vaccines' first doses, policymakers must choose an optimal strategy for regulating the licensing, pricing, distribution, and access urgently.

Therefore, we stress that supply-side factors will need to be taken into account in shaping the strategy at both national and European levels for each vaccine modality. These include the following:

- Expected clinical efficacy, i.e., not all vaccines will be equally effective
- Cost of production, transport, and storage
- The costs associated with the mode of administration, different modalities may be administered in different ways
- The timing of market entry, e.g., first entrants, second entrants, etc.
- A realistic scale of production

Making vaccines available *quickly* will be as crucial as providing *good* access. Unless the first vaccine is already of high quality – high level of effectiveness, and easy to store and administer - rapid access to the first available candidate will save lives. Still, if better options arrive later, resources should be available to invest in those successive, better options. It may well be that only the latest and best second candidates will meet the minimum requirements necessary to lift restrictions in order to ensure economic recovery and a significant reduction in the pandemic's social and health impacts.

Therefore, it is essential to establish a common EU strategy by creating procurement contracts and/or advance purchase commitments that provide the right incentives to the first generation of vaccine producers and the producers of the last and best products, should this be the case.

As explained in section 3, optimal contracts should ensure that second-generation vaccine manufacturers continue to invest in development even as first-generation vaccines are distributed. Also, they should ensure that producers can scale up manufacturing when their products, once approved, can be used on a large scale in the population and thus demonstrate their effectiveness in real-world use.

Answers to the questions of how to regulate vaccine prices and reward innovation, how to manage the vaccine portfolio and stockpile, and how to contract and share the risks associated with vaccine development are critical in trying to optimise the volume and quality of products used in the fight against the COVID-19 pandemic.

This report aims to provide some guidance to inform the policy debate in the search for a European strategy on procuring, paying for, distributing, and using new vaccines against COVID-19.

The report structure is as follows: in section 2, we will discuss pipeline management and candidate pipeline management. Section 3 considers licensing and candidate management with different properties. Section 4 suggests methods for vaccine procurement and pricing. Section 5 considers matters related to vaccine delivery to MS. Section 6 examines ways to allocate and distribute pre-contracted volumes across MS and regions. Finally, section 7 discusses elements related to education and public awareness of mass vaccination and population protection.

2 Project portfolio and timeline

To date (November 12, 2020), there are 48 vaccines in clinical evaluation, and a total of 211 if we add those in preclinical evaluation (WHO, 2020a). Eleven of the 48 projects in clinical development are already in Phase III, as shown in Table 1 below. There is no common estimate for the success rate of Phase III vaccines in the relevant scientific literature. In a recent study (Wong, Siah and Lo, 2019), the Phase III success rate (pre-approval) of the vaccines has been estimated at 85%. Previously, other studies estimated vaccine success rates from Phase III to approval to range from 50% (Hay et al., 2014) to 74.3% (Thomas et al., 2016). Taking the most pessimistic scenario, with the current pipeline, we will see around five candidates reach the market within the next year (this rises to seven or eight candidates if the most favourable success rates apply).

The diversity and volume of the project portfolio make the design of the procurement and distribution strategy and policy both vital and a complex puzzle to solve simultaneously.

Sponsor	Type	Platform	Phase III trials	Dose
University of Oxford/AstraZeneca	Chimpanzee adenovirus	Non-replicating viral vector	ISRCTN89951424 NCT04516746 NCT04540393 CTRI/2020/08/027170	2
Sinovac	SARS-COV-2 inactive	inactivated virus	NCT04456595 669/UN6.KEP/EC/2020 NCT04582344	2
Wuhan Institute of Biological Products/Sinopharm	SARS-COV-2 inactive	Inactivated virus	ChiCTR2000034780 ChiCTR2000039000	2
Beijing Institute of Biological Products/Sinopharm	SARS-COV-2 inactive	Inactivated virus	ChiCTR2000034780 NCT04560881	2
CanSino Biological Inc./Beijing Institute of Biotechnology	Vector: Adenovirus type 5	Non-replicating viral vector	NCT04526990 NCT04540419	1
Gamaleya Research Institute	Vector: Adenovirus type 5 and 26	Non-replicating viral vector	NCT04530396 NCT04564716	2
Janssen Pharmaceutical Companies	Vector: Adenovirus type 26	Non-replicating viral vector	NCT04505722	1
Novavax	Recombinant glycoprotein nanoparticles vaccine SARS CoV-2	Protein subunit	2020-004123-16	2
Moderna/NIAID	LNP-encapsulated mRNA	RNA	NCT04470427	2
BioNTech/Fosun Pharma/Pfizer	3 LNP-mRNAs	RNA	NCT04368728	2

TABLE 1: LIST OF VACCINE PROJECTS IN PHASE III CLINICAL DEVELOPMENT
Source: WHO, 2020a

An essential feature of the current pipeline is that it is large enough to ensure some degree of competition among the approved candidates, which will ensure that large-scale production and demand will be met. There are two basic concepts to consider in terms of vaccine options in the pipeline: 1. when marketing authorisations will be granted, and 2. when manufacturing capacities can be scaled up sufficiently to meet demand, or at least priority demand.

Generally, manufacturers expand production capacity after (and only after) obtaining a marketing authorisation or licence. The licence is granted by the competent regulator of the country or geographic area – e.g., the Food and Drug Administration (FDA) in the US and the European Medicines Agency (EMA) in the EU. Production is usually conditional on the restrictions on target populations imposed by the regulator to use the new vaccine or therapy. However, for obvious reasons, governments have had to incentivise producers of potentially successful vaccines to invest upfront in production despite the associated (but necessary) risk of over-investment by manufacturers during this pandemic.

Figure 4 shows the expected timeline for marketing authorisation and roll-out of the ten pioneer vaccines shown in Table 1. It shows that all of them expect approval and deployment between the fourth quarter of 2020 and the second quarter of 2021. The likelihood of their availability for use in Europe is mainly around the first and second quarter of 2021. Vaccine procurement and distribution plans in European MS rely on the assumption that broad access is provided around March-May 2021. Smaller quantities of vaccines produced by European or global manufacturers with a presence in Europe will be available in late 2020 or early 2021. In particular, the Oxford/AZ, Moderna/NIAID, and BioNTech/Pfizer candidates – for which the EMA has initiated the rolling review process – are likely to be the first ones available for use, provided their clinical development or regulatory review is not stopped for safety/efficacy reasons.

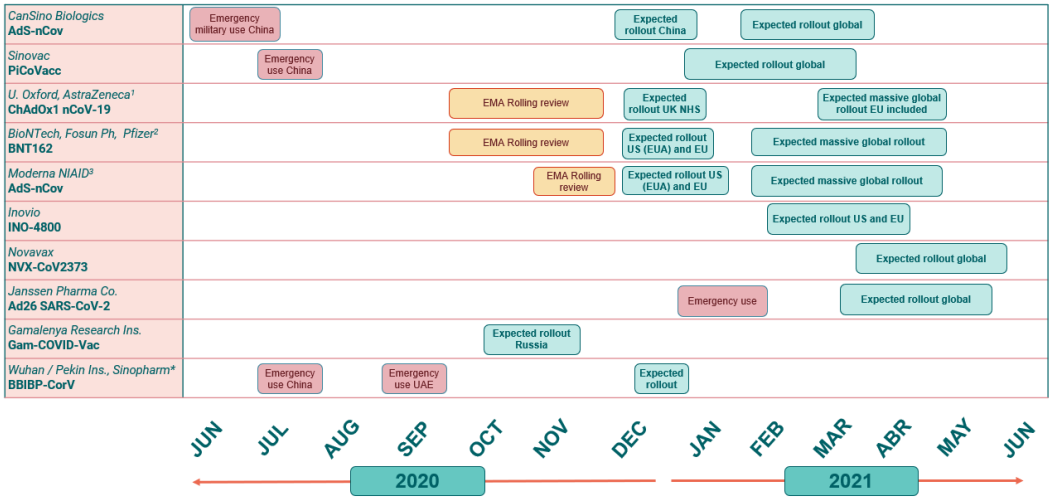

FIGURE 4: EXPECTED TIMING OF MARKETING AUTHORISATION AND LAUNCH OF COVID-19 VACCINE CANDIDATES IN PHASE III

Notes: 1 Oxford/AZ Vaccine has published preliminary Phase III results showing 90% efficacy with one dosing regimen and 62% efficacy with another viral vector-based vaccine. AstraZeneca's statement is available here: https://www.astrazeneca.com/content/astraz/media-centre/press-releases/2020/azd1222hlr.html. 2 BioNTech/Pfizer Vaccine has published preliminary Phase III results showing 95% efficacy of the BNT162 mRNA-based vaccine. Pfizer's statement is available here: https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-conclude-phase-3-study-covid-19-vaccine. 3 Moderna/NIAID Vaccine has released preliminary Phase III results showing 94.5% efficacy of the Ads-nCov mRNA-based vaccine. Moderna's statement is available here:: https://investors.modernatx.com/news-releases/news-release-details/modernas-covid-19-vaccine-candidate-meets-its-primary-efficacy. Continuous review: continuous real-time review as preclinical and clinical data becomes available: https://www.ema.europa.eu/en/news/ema-starts-second-rolling-review-covid-19-vaccine.

From the EC's perspective, the first stage of decision-making involves:

- **deciding on which vaccines to invest**
- **choosing which and how many producers to incentivise to expand production capacity before approval**
- **selecting how many doses to contract before marketing authorisation of the vaccine.**

From the project' pipelines point of view, these decisions raise many issues discussed in the following sections.

2.1 What types of technology are expected, and what are the pros and cons of each one?

The leading vaccine candidates can be classified into four different types: viral vector-based, genetic code-based, SARS-Cov-2-based, and recombinant protein-based. Viral vector-based vaccines for COVID-19 use a virus other than SARS-Cov-2 to serve as a carrier for the non-infectious material of SARS-Cov-2. The body's immune system responds to the non-infectious SARS-Cov-2 material by creating an immune response that protects against COVID-19. Candidates from Oxford/AZ, CanSino Biologics, Gamaleya Research Institute and Janssen Pharmaceutical Co. are of this type. The potency of the overall immunogenic response – the body's immune response to SARS-Cov-2 including the antibody response and T-cell response – associated with this type of vaccine depends on pre-existing immunity against the viral vector used as a carrier. The body can react against the carrier viral vector and mitigate the immune system's response to non-infectious SARS-Cov-2 material (Jeyanathan et al., 2020). This mainly affects the CanSino, Gamaleya and Janssen vaccines, which use non-replicating human adenovirus vectors. The CanSino vaccine candidate uses Ad5, Gamaleya Ad5 and Ad26, and Janssen Ad26 (see Table 1). The prevalence of Ad5 is high in blood and low in the respiratory tract, but the two vaccines in development that use Ad5 use the intramuscular (IM) administration route, making them more exposed to pre-existing carrier immunity. Thus, pre-existing cross-immunity could imply efficacy problems as it will react against the Ad5 carrier virus before allowing time for it to react against the non-infectious SARS-Cov-2 material.

The prevalence of Ad26 is medium, so efficacy issues are also expected. Of the three candidates cited, the vaccine being developed by Gamaleya promises to be slightly superior to the other two because it combines the two vectors, reducing the likelihood of pre-existing anti vector immunity. The other candidate using a viral vector is the Oxford/AZ vaccine, which uses a chimpanzee adenovirus (ChAd). A vector against which pre-existing immunity is negligible, so strong immunogenicity is expected.

All candidates apart from CanSino and Janssen require two doses, which increases the cost. AstraZeneca, the pharmaceutical company developing the Oxford/AZ vaccine, which will ultimately become the marketing authorisation holder, has pledged to provide the vaccine on a not-for-profit basis (AZ, 2020a). It is also one of the three candidates that have made public preliminary results data from Phase III clinical trials so far (AZ, 2020b). According to the company's press release, the Oxford/AZ vaccine has met the final efficacy endpoint target with two dosing regimens. One of the two regimens uses a half dose followed by a full dose and has shown 90% efficacy. The second has shown a lower efficacy of 62% and uses two full doses. No case of infection in the vaccine group required hospitalisation or experienced severe symptoms. AstraZeneca has announced considerable progress in production capacity that would allow the manufacture and distribution of up to 3 billion doses by 2021 on a sequential basis, subject to marketing authorisation from the relevant regulators (e.g. EMA, FDA). The Oxford/AZ vaccine can be stored at temperatures of 2-8 degrees Celsius for at least six months, allowing it to be administered by means already available to healthcare systems.

Considering all the elements described above, the Oxford/AZ vaccine is the best candidate to be prioritised within this group.

Genetically coded vaccines provide genetic instructions that teach human cells to produce proteins of the selected virus to trigger an immune response against these proteins automatically. There are two classes within this group of vaccines: the single-stranded version of RNA or messenger RNA (mRNA) or gene-based DNA.

There are two mRNA gene-coding vaccine candidates in Phase III: Moderna/NIAID and Pfizer/BioNTech. The main advantage of this type of vaccine is that it solves the problem of pre-existing antivector immunity.

mRNA-based vaccines can be designed quickly and are straightforward to manufacture. Hence, they are expected to be inexpensive to produce. They produce a strong antibody response but require appropriate adjuvants to develop the T-cell response. Therefore, their overall immunogenicity depends on the choice of adjuvant and repeated vaccination is needed. Although inexpensive to produce, the need for multiple doses can increase the cost of a population immunisation programme, in addition to other complexities such as the need for frozen storage for transport and preservation. Freezing requirements can be problematic as, if storage conditions are not strictly adhered to, many doses may deteriorate and must be discarded, resulting in additional health and monetary costs.

Finally, there is currently no mRNA-based vaccine approved for human use. These so-called next-generation vaccines are likely to face higher regulatory hurdles. There are doubts about their long-term safety because there is a theoretical possibility that the DNA of the vaccines' genetic material (but not the RNA vaccines) could be integrated into the host DNA (Ng et al., 2020). However, decades of experience experimenting with this technology in developing other vaccines has accumulated an understanding of its safety and potential for baseline efficacy, which has been fundamental in developing the two COVID-19 vaccines.

So far, the Pfizer/BioNTech vaccine has released preliminary Phase III data, which shows 95% efficacy (Pfizer, 2020), making it the leading candidate in this group. The EMA has started evaluating the preclinical results obtained with the Pfizer/BioNtech vaccine through a rolling review procedure. The EMA has also granted Moderna/NIAID a rolling review (EMA, 2020a). As of November 24, Moderna/NIAID has published preliminary interim data from the Phase III trial of its vaccine, showing 94.5% efficacy (Moderna, 2020).

The Moderna/NIAID vaccine also offers an essential technological improvement compared to the Pfizer/BioNTech candidate: product stability and storage. The candidate developed by Moderna/NIAID can remain stable for 30 days stored at standard refrigerator temperatures of 2 to 8 degrees Celsius and up to 6 months at -20 degrees Celsius (Businesswire, 2020). This company has announced that an Emergency Use Authorisation (EUA) will be submitted to the FDA and other regulatory bodies (such as the EMA) in the coming weeks. They will also distribute 20 million doses by the end of 2020 and between 500 million and 1 billion doses during 2021. One of the greatest strengths, beyond its technical characteristics, is that the producer has manufacturing capacity in Spain and could increase investment in the country to supply the entire EU, which could help Spain, as it is one of the countries most affected by the pandemic. However, the development of this vaccine has received significant public funding from the US government (National Institutes of Health), and it is likely that much of the supply will be prioritised for use in the US. Therefore, on balance, signing an Advance Purchase Agreement (APA) complementary to the one already in place with Pfizer/BioNtech could be a good option for the EU.

Inactivated or weakened SARS-Cov-2 virus is used by the Sinovac and Sinopharm vaccines to induce an immune response in the inoculated host. The main advantage of this approach is that the inactivation process makes the vectors safer as they cannot replicate, even in immunosuppressed hosts (Krammer, 2020).

Unlike viral vector vaccines, inactivated SARS-Cov-2 vaccines optimise the amount of antigen delivered to the immune system. They induce a strong neutralising antibody response and a weaker T-cell response, which requires adjuvants. Overall, immunogenicity is weak and requires repeated vaccination (Jeyanathan et al., 2020). For obvious reasons, inactivated vaccines using SARS-Cov-2 are not affected by pre-existing antivector immunity. However, a concern with inactivated SARS-Cov-2 type vaccines is that they require manipulating vast quantities of infectious virus for their production (Amanat and Krammer, 2020). The latter imposes a clear constraint on the ability to scale up production, which is crucial for COVID-19 vaccines.

The two such vaccine projects already in Phase III are owned by Chinese companies Sinopharm and Sinovac. Both have been approved for emergency use in China. Sinopharm is a state-owned company in China, so if successful and effective, much of its production will be for priority use in China. This increases the likelihood of delays to access for other countries, including the EU. The same can be said of the Sinovac vaccine, although it is a private company. One suggestion could be to keep these two vaccines as secondary options and only consider them if their Phase III results are significantly better than more accessible options.

Finally, there is a recombinant protein-based candidate in Phase III developed by Novavax. Recombinant protein-based vaccines incorporate a virus protein or a protein that mimics the virus that triggers an immune response. This type of vaccine induces a strong neutralising antibody response, and as with inactivated virus-like vaccines, a weaker T-cell response, which is also dependent on adjuvants.

One of the main advantages of recombinant protein-based vaccines is that they do not require manipulating infectious viruses and are therefore considered safe to be used in immunocompromised individuals. Adjuvants can induce T-cell responses to enhance immunogenicity. There is accumulated experience with such vaccines (e.g. for influenza) and knowledge about producing them and their effectiveness and safety in the real world. The disadvantage is mainly the complexity of finding and making an optimal amount of protein antigens to elicit the desired immune response. Several boosters are needed if an insufficient immune response is to be achieved, which means higher costs for the system. Strategically, keeping Novavax on the EU radar may be an important value option, as it is the only vaccine in this class. Suppose Phase III trials show similar results to mRNA and viral vector types. In that case, it may be advisable to negotiate with Novavax an APA conditioning pre-specified volumes on the vaccine's potential efficacy.

2.2 Project portfolio management

Vaccine portfolio management is an essential policy strategy of vaccine management for COVID-19. For obvious reasons, the market for COVID-19 vaccines is subject to high global demand pressure, and supply problems are likely to arise due to limited production capacity in the short term. The development of new vaccines is a risky and unpredictable process. It is impossible to predict which candidate may fail or when it may fail. Typically, the risks associated with different types of vaccines are common to each of them. When designing vaccine procurement policies and distribution and vaccination plans, it is vital to follow a portfolio management approach to incentivise the development of different types of vaccines and expand production capacity for these options. This ensures that the risk of supply failure or shortages is well managed.

Other important factors in portfolio management (or diversification of options) include the likelihood that prices and costs may vary between alternatives (i.e., there may be single or multiple doses). Given that the total cost of protecting the entire population from COVID-19 has to be considered, setting the right incentives for the production and supply of large volumes can maximise the associated benefits in health, economic and social terms.

Also, different types of vaccines may work differently for different age groups. Therefore, alternative options will be needed to immunise the whole population (e.g., the elderly, key workers, economically vulnerable households, self-employed). Finally, logistics and storage require high-tech infrastructure in some cases. Vaccines using mRNA technology must be stored at sub-zero temperatures, the capacity of which can vary from country to country. Having options that cover the various types can help mitigate this problem wherever it arises.

SELECTION OF PROJECT PORTFOLIO

There appear to be two tiers of vaccines. In Tier 1 are Oxford/AZ (viral vector), Pfizer/BioNTech (mRNA) and Novavax (recombinant protein). As mentioned above, the Moderna/NIAID (mRNA) vaccine can be included in this group interchangeably with the Pfizer/BioNTech vaccine. The EC and EMA have made explicit their preference for these candidates at the first level, initiating rolling review processes for the two mRNA options and the viral vector option (EMA 2020 b,c,d).

AstraZeneca and Pfizer are large global pharmaceutical companies. Both firms have announced investments to expand production capacity and start production ahead of regulatory approval for their vaccines, which will allow them to produce 1.3 billion doses (Pfizer, 2020) and around 2 billion doses worldwide (AZ, 2020c; AZ, 2020d) by 2021.

Novavax also has ambitious goals. The company has announced agreements with other firms with larger production infrastructure to increase production capacity worldwide (Novavax, 2020), which is not surprising given its smaller size and the fact that it is more difficult to expand production capacity for this type of vaccine.

Tier 2 includes vaccines that are later in progression but use the same action mechanism as the three vaccines in Tier 1. These are Moderna/NIAID (mRNA) (if not included in Tier 1) and Janssen Pharm. (viral vector).

Recombinant protein-based vaccines that could be included in Tier 2 as an alternative to Novavax have not yet leapt Phase III clinical development and remain in Phase II or earlier. One option could be to focus on the GSK/Sanofi vaccine, still in Phase II but hoping to start Phase III in December. GSK/Sanofi has already signed an APA to supply 300 million doses to European countries in 2021 and expect to supply around 1 billion doses globally in the same year (Sanofi, 2020). This report has not reviewed the GSK/Sanofi vaccine in detail because we have focused on Phase III candidates. However, as both GSK and Sanofi are global pharmaceutical companies based in Europe, there may be a case for including them as an alternative to the Novavax vaccine, even if they are still in Phase II.

GLOBAL SUMMARY 1. Key points in pipeline decision-making and timing

- With promising preliminary Phase III results, Pfizer/BioNTech, Moderna/NIAID and Oxford/AZ vaccines are the candidates in a more advanced stage. They are in the best position to help address the health emergency first.
- Priority should be given to a vaccine procurement strategy that incentivises:
  i. Fluid discussions with these candidates to learn about the status of their projects.
  ii. Collaboration with the EMA to accelerate the regulatory review of these two candidates - already approved and underway.
  iii. Reaching agreements with these three manufacturers to secure the supply of certain pre-determined volumes - Pfizer/BioNTech and Oxford/AZ already have signed APAs, and Moderna/BioNTech is in the process.
- We favour a portfolio management approach to incentivise the development of a selected combination of candidates simultaneously. This will allow:
  i. Minimisation of risk of failure by having different candidates of each type.
  ii. Maximisation of the potential for rapid, large-scale delivery and cost savings through lower-priced or lower-cost-in-use options.
  iii. Maximisation of the chances of achieving herd immunity through vaccination in the shortest possible time.
- The portfolio management strategy could be based on the use of APAs to incentivise the selected candidates to ensure rapid development and investment in scaling up production capacity.
- We distinguish two levels of candidates that can guide the establishment of the strategy:
  i. Priority level: Oxford/AZ (viral vector), Pfizer/BioNTech (mRNA)/ Moderna/NIAID (mRNA) and Novavax (recombinant protein).
  ii. Alternative tier: Janssen Pharm. (viral vector), Moderna/NIAID (mRNA)/ Pfizer/BioNTech (mRNA) and GSK/Sanofi (recombinant protein).

3 Licensing, efficiency thresholds, and use of banding system

This section first examines the need to use efficacy thresholds to establish vaccine procurement and contracting strategies. We then discuss APAs and the need for a board of experts to oversee the processes and report to the EC.

3.1 Efficacy thresholds

Dealing with the consequences of the pandemic in European countries requires:

i. addressing the health emergency, i.e., save lives, and
ii. lifting NPIs (e.g., total or partial containment, travel restrictions), which negatively affect the economy and have indirect negative health impacts (e.g., mental health, neglecting other conditions).

Conditions on the level (threshold) of vaccine efficacy are justified. The threshold requirements will be different for vaccines at various stages, i.e. those at the marketing authorisation stage and those that have already been contracted and passed through the national procurement and distribution stages.

Let us illustrate the need to consider efficacy thresholds at each stage with an example: suppose a candidate shows an overall efficacy of 60% in Phase III, but when distributed to the population, its effectiveness decreases with age so that for the 70+ age group, it is only 30%. This vaccine would save younger lives and help address the health emergency, but not enough to lift NPIs. The health impact of COVID-19 would remain high, so the threat of health system collapse would not completely dissipate.

So far, we know – from the press releases of three candidates assessed in this report as priority candidates – that Phase III efficacies are between 62% and 95%. The two mRNA vaccines have shown efficacies greater than 90%, and one viral vector vaccine has announced a 62% efficacy with double dosing of 90% with a half dose followed by a full dose. However, mRNA technology vaccines have much stricter storage conditions to preserve their stability – temperatures of -70 and -20 degrees Celsius. This makes them more costly and challenging to use on a mass scale. They may need to be considered for use in subpopulations if their effectiveness is greater than that of other candidates, provided there are no other less costly options requiring less investment in infrastructure and organisation of vaccination. In sum, it is vital to optimising the vaccination plan that the quality and characteristics of each new vaccine are appropriately considered.

The balance between vaccines' efficacy levels and the use of NPIs is crucial to understand why the best procurement policies should involve agreements that depend on vaccines' efficacy and quality, ex-ante and ex-post marketing. Efficacy may change with broader use in the real world, and contracts should be adjusted to incorporate the evidence as it becomes available.

Given the above, it would be advisable to have a policy based on quality and efficacy thresholds for the procurement and distribution of COVID-19 vaccines.

In the US, the FDA has effectively set a minimum efficacy level of 50%, and it is suggested that efficacy "[...] may be much more effective in preventing severe versus mild COVID-19, then developers should consider designing efficacy trials for formal hypothesis testing on a severe COVID-19 endpoint". (FDA, 2020).

The World Health Organisation (WHO) has established a target product profile (TPP)[1] for a COVID-19 vaccine (WHO, 2020b) that sets a 70% efficacy threshold among many other specified quality parameters (e.g., product stability and shelf life, duration of induced protection, dosing regimen).

The FDA's 50% threshold may be acceptable for the first vaccines on the market. This threshold may help to save lives but not to raise NPIs. Therefore, it would be advisable to leave the door open to accommodate better products in the future. The efficient contracted volume of a less effective candidate should not be too large to:

i. avoid discouraging the willingness of other options to enter the European market; and
ii. avoid overspending limited resources on sub-optimal uses.

The EU has announced that the EMA will not set a minimum efficacy level for contracted vaccines (Guarascio, 2020). The latter implies that the EU and the EC will rely on the EMA's case-by-case review. Details on what efficacy levels are considered acceptable have not yet been made explicit for COVID-19 related vaccines.

ADVANCE PURCHASE AGREEMENTS (APA)

The EU's proposal to ensure sufficient production and supply for its member states is based on the Emergency Support Instrument (ESI) (EC, 2020c), whereby:

i. there is a commitment to purchase a certain number of doses from the manufacturer at a given price once the EMA has granted marketing authorisation,
ii. the purchaser commits to finance part of the upfront costs incurred by the vaccine producers before the EMA grants the marketing authorisation.

This type of agreement addresses two major financial risks faced by companies: the risk of investing too much upfront in expanding production capacity, and the risk of not being reimbursed for too low a price and/or lower-than-expected demand.

The EU has decided to use APAs as a risk-sharing instrument, given the need to accelerate access to MS and their health systems. As noted above, final efficacy results are not known when APAs are negotiated. Therefore, examining scientific evidence in real-time during the late stages of experimental clinical development and the early stages of population use should be part of the APA between the producer and the EU.

The EU has set aside €2.7 billion to fund this scheme, and has so far made public the APAs with four applicants: Pfizer/BioNTech, Oxford/AZ, GSK/Sanofi and Janssen Pharm for a total of 1.2 billion doses (EC, 2020d), distributed as follows:

- Pfizer/BioNTech: 200 million doses – with the option of a further 100 million doses once efficacy/safety results are available.
- Oxford/AZ: 300 million doses – with an option for a further 100 million doses

[1] *According to the WHO, a Target Product Profile (TPP) defines the desired 'profile' or characteristics of a product that is targeted to treat (or vaccinate) a specific disease. TPPs define the intended use of that product, the target populations, and other desirable attributes of the product, including the safety and efficacy profile. The TPP can guide R&D in a particular therapeutic area, such as COVID-19 vaccines.*

- GSK/Sanofi: 300 million doses
- Janssen Pharmaceuticals: 200 million doses.

Based on the analysis in the previous section, negotiations with Novavax could be positive to securing an alternative recombinant protein candidate in the portfolio (besides GSK/Sanofi). Also, it would be desirable to negotiate an APA with Moderna/NIAID, something that has already been announced for the pipeline.

USE OF THRESHOLD-BASED SYSTEM

There is reason to believe that an EC/EMA Steering Committee (SC) could help ensure vaccine efficiency and procurement. The SC's responsibilities and obligations would have to be transparent and subject to scrutiny by the general public. In turn, the SC would be responsible and accountable to the EU and the EC.

Vaccine procurement contracts usually specify volumes, price and timing, but not the quality of the product (i.e., safety and efficacy). However, given that one of the characteristics of APA contracts is to share risk between seller and buyer, it would be critical to ensure quality. Otherwise, there could be perverse incentives leading to under-performance to make a profit. Thus, APAs should be linked to quality so that the reward and incentive would be an increasing function of the expected (and demonstrable) quality of the candidate.

Therefore, one of the SC's responsibilities would be to define the specific quality criteria that candidates must meet to be able to sell different volumes at given prices.

Advance market commitments (AMC) have already been implemented in the past by using TPPs to select the most promising eligible candidates. For instance, AMCs were used for the pneumococcal vaccine and the proposal made for a potential malaria vaccine for low-income countries (LICs) (Towse and Firth, 2020).

Taking all of the above into account, we suggest that SC could also be responsible for:

- Defining a European TPP (EMA TPP) as a basis for negotiations with producers (or explicitly acknowledged that the one specified by WHO is adopted).
- On this basis, the SC should:
    a. Specify the conditions under which qualities below the EMA TPP may be acceptable for limited or short-term emergency use – i.e. when the first-to-market vaccine does not comply with the EMA TPP but may still improve health.
    b. Continuously scrutinise the evidence on efficacy and safety as it becomes available, especially for Tier 1 candidates, for which it is essential to acquire informed expectations about efficacy and quality.
    c. Use informed expectations and the EMA TPP to negotiate agreements and sign contracts, including volumes, prices, and timelines.

Our suggestion is to use quality bands as a system of thresholds (guardrails) to inform APAs and frontloaded trading activity complementary to portfolio management.

In Table 2, we illustrate a possible approach to incorporating threshold bands. The APAs specify two components: a fixed amount and a variable term amount depending on the quality or band in which the candidate falls. The fixed amount corresponds to the minimum acceptable (MA) quality so that all candidates meet it. The variable term is the extra quantity of a product that would be contracted if its expected efficacy is higher than the MA and falls in a higher band. The higher the band, the higher the variable term.

In collaboration with the MS, the SC would first decide the efficient number of vaccine doses of Tier 1 above the minimum quality or efficacy to procure. Second, the SC would have to divide that quantity among Tier 1 candidates (and eventually into other tiers as they become available).

Our illustration starts as follows: Suppose that the required total quantity of vaccines with the minimum efficiency level is Q. Each candidate *i* has a quantity q_i, and there are five candidates (i.e. i=1,2,3,4,5). The same fixed quantity, *q*, will be acquired from each candidate, i.e., $q_1 = q_2 = \cdots = q_5 = q$. The sum of the number of vaccines procured from each candidate would be equal to the desired total quantity, i.e., $Q = q_1 + q_2 + q_3 + q_4 + q_5$.

Each candidate's quality (including efficacy) would place the product in a specific band, determining the variable term. This illustration defines the quality bands according to EMA and WHO thresholds, for example.

The proposed mechanism would add a quantity $t(v_{b1})$ above the fixed benchmark quantity, *q*, for candidates meeting the criteria in the first band, and a quantity $t(v_{b2})$ for candidates in the second band. Candidates' additional variable quantities will be granted until an efficient, overall quality-adjusted quantity Q* is reached for distribution in the EU Member States (MS).

Together with the SC and MS, the EC will determine the final quantity Q*, reflecting countries' needs.

Band	Fixed amount	Variable term
MA according to the WHO TPP	$\boldsymbol{q}$	$\mathbf{0}$
Between the WHO TPP and the EMA TPP	q	$t(v_{b1})$
Above the EMA TPP	$\boldsymbol{q}$	$\boldsymbol{t(v_{b2})}$

TABLE 2: PROPOSED QUALITY RAIL SYSTEM FOR APA PROCUREMENT

The quality levels define the threshold system. The threshold bands determine the pre-contracted quantities of each vaccine candidate. More variable term doses could be added to the fixed amount as quality/safety expectations (or eventually actual data) are updated. The informed expectations on product qualities can consider the expected level of efficacy/safety and other parameters such as storage instability, administration complexity, risk of transport, efficacy by age group, and disease severity. All of these are duly formulated and defined in the TPP. The SC will help the EC and MS develop informed product quality expectations through continuous data scrutiny.

GLOBAL SUMMARY 2. Licensing, efficacy thresholds and band system

- The EU might want to create a Steering Committee (SC) that oversees and applies a common strategy for the procurement and distribution of COVID-19 vaccines based on efficacy thresholds.
- The SC should define specific quality criteria that candidates must meet to supply different volumes at fixed prices. To do so, the SC will:
  i. determine a European Union Target Product Profile (EU TPP) or explicitly adopt the World Health Organisation TPP.
  ii. specify the circumstances under which a vaccine with an efficacy below the EU TPP may be acceptable for limited- or short-term emergency use, i.e., the first candidate on the market may not comply with the EU TPP but may help reduce the speed of contagion temporarily.
  iii. scrutinise and evaluate the evidence on the efficacy/safety of candidates as it becomes available to form informed expectations on their quality.
  iv. use these informed quality expectations to negotiate further volumes, prices and timeframes.
- Negotiations will be based on the guardrail system created by the EU TTP and other information.
- The European Commission, jointly with the SC and the MS, can then jointly decide the optimal quantity of vaccines to be contracted for each quality band, reflecting countries' needs.

4 Procurement of vaccines and their price

Vaccines have become the best hope for overcoming the global COVID-19 pandemic and returning to normal socio-economic functioning. Every day has been vital for the accelerated development of vaccines that are expected to save thousands of lives, prevent the overuse of health resources and mitigate the economic damage from the pandemic.

Scientific advancement has been unprecedented in the speed and effectiveness with which vaccines for COVID-19 have been developed. The accumulated knowledge in the field of vaccines and infectious diseases has helped create vaccines for COVID-19 in record time. However, the rapid response and promising success do not necessarily imply an easy path to ending the pandemic. Vaccine development is always a challenge, but the case of COVID-19 has proven to be particularly demanding.

Some problems may arise in the medium and/or long term after the vaccines have been licensed, for example:

Potential adverse selection: the first products to be developed ('winners') and introduced in the market may not necessarily be the best (game-changers). This underlines the importance of good portfolio management and strategic diversification. In the analysis by Shnaydman and Scannell (2020), they state that governments "should ideally support a portfolio of projects that balances, among other things, speed to market, vaccine platform risk, vaccine-specific risk, clinical trial capacity, regulatory capacity and manufacturing capacity". They also stress that "[...] a clear move towards diversity is necessary, even if some individual projects appear less attractive".

A second issue relates to the fact that expanding production capacity is particularly difficult and complex for most of these vaccines. The scale and speed at which the world needs to produce vaccines for COVID-19 are unprecedented. Shortages are a frequent problem for some vaccines already in use, and very few manufacturers have large-scale production capacity. Vaccine manufacturing is costly for several reasons, including variability of production processes, long lead times from approval to market introduction, and high costs – both fixed (i.e. facilities) and variable manufacturing costs (i.e. components, inputs) (Towse and Firth, 2020).

In order to speed up the manufacture and distribution of the first vaccines available in Europe, two necessary conditions have to be met:

i. appropriate incentives are in place to encourage producers to invest in increasing production capacity before approval; and
ii. manufacturing complexities and costs are understood and reflected in negotiated prices and volumes.

Third, demand is uncertain. The market is potentially large in the short term but uncertain in the medium to long term as some populations may achieve herd immunity at some point. Moreover, if a high-quality vaccine is found whose use will definitely allow restrictions to be lifted, demand for the vaccines that preceded it will decrease. Governments that initially seemed interested in vaccinating the entire population will probably realise that they have to act strategically and vaccinate certain key groups with the high-quality product and use the others for the remaining groups.

Another factor adding uncertainty in the vaccine market is discovering treatments and therapies that are better at fighting disease. Due to obvious budgetary constraints after a severe recession, governments may well consider a mixed option (i.e. vaccines and treatments).

Therefore, it is necessary to design contracts between the EU and vaccine manufacturers and procurement mechanisms that address and mitigate the negative impact of these issues.

Good portfolio management, linking contracted volumes to product quality through TPPs, and the use of threshold systems are mechanisms that could help address the issues of adverse selection, the need to increase production capacity, and demand uncertainty.

The combination of portfolio management and contracts where pre-contracted volume depends on quality ensures that quality improvement in vaccine development is promoted, and upfront investment in production capacity is encouraged through risk-sharing. The risk surrounding demand uncertainty is also addressed because a fixed volume is pre-contracted, and therefore part of the risk is transferred to the EU. Moreover, the intensity of the incentives increases with the expected quality of the candidate. The system of quality thresholds defines this relationship between incentive and quality. However, the risks are only shared, not completely eliminated. Products that are now in Phase III may end up partially or completely failing. Therefore, incentives and subsequent reward signals must be kept active for the potential emergence of better second-generation vaccines.

An optimal portfolio management strategy must incorporate price benchmarks, in addition to solely volume-specific agreements. As in the case of volumes, prices should also be linked to product value and quality in order to incentivise investment in both R&D and production capacity. This price-quality link becomes more relevant when targeting and incentivising second-generation vaccines.

Interestingly, they should send the signal that efforts in the search for quality improvement will be rewarded if a vaccine better than the existing approved ones is brought to the market. That is, any contract should incorporate elements of value-based pricing to indicate that there will always be room in the market for products that show significant improvements in the value offered.

In this proposal, we discuss two potentially valuable tools for a value-based pricing policy for COVID-19 vaccines: the first is the BRAVE narrative (Bell, Neri and Steuten, 2020), and the second is the Benefit Based Advanced Market Commitment (BBAMC) which is the anticipated market value commitment based on product benefit (Chalkidou et al., 2020).

Assessing the value of vaccines for COVID-19 is quantitatively and qualitatively challenging, given their multidimensional impact. Health Technology Assessment (HTA) agencies only consider benefits in terms of improved health, reduced health care costs and resource use (and enhanced quality of care), and sometimes (not always) short-term productivity gains for patients and their caregivers" (WHO, 2019).

However, vaccines can also generate substantial positive externalities (spillovers) that are not necessarily observed with other types of medical interventions (Mauskopf et al., 2018). Effective vaccines for COVID-19, as documented in Section 1 of this report, would generate colossal positive health, social and economic externalities beyond the direct impact of health benefits and health system resource savings. We have also discussed that the size of such externalities depends on the quality of the vaccine.

The BRAVE initiative developed by OHE (Bell, Neri and Steuten, 2020) addresses the question of the elements of vaccine value. Table 3 summarises from the BRAVE framework those most relevant to the case of COVID-19.

Element of value	Definition	TPP* level
Impact on life expectancy	Measurement of the impact on life expectancy and years of life lost.	MA
Impact on patients' quality of life	Impact on patients' quality of life due to improved physical, mental, emotional and social functioning.	MA
Burden of disease	Impact on the burden of disease for society (in terms of prevalence and severity of disease, estimated as the total amount of associated morbidity and mortality).	MA
Value for impact on other diseases	Impact on the cost and effectiveness of treatment of diseases, including the possibility of lifting INFs in the absence of vaccines for COVID-19.	MA
Value in terms of transmission	Impact on disease transmission patterns and associated morbidity and mortality.	WHO
Impact on caregivers' quality of life	Impact on caregivers' quality of life in terms of their physical, mental, emotional and social functioning. Affects parents of quarantined minors, nursing home caregivers and health care workers.	WHO
Social equity	Impact through equity enhancement. For example, COVID-19 vaccines may be particularly beneficial for socio-economically disadvantaged groups.	EMA
Patient productivity	Impact on the number of working days lost and productivity, both in terms of attendance at vaccinations and avoidance of illness and/or mortality. Particularly important are quarantines avoided with lower quality vaccines or the full restoration of the functioning of the economy and the workforce with high-quality vaccines.	EMA
Productivity of caregivers	Impact in terms of time spent and productivity of caregivers due to illness and travel, etc., as a result of the number of vaccinations required.	EMA
Offsetting costs within the health system	COVID-19 vaccines can also create value in the form of cost offsets by redefining the cost burden of COVID-19 patients and non-COVID-19 patients, for example.	EMA
Macroeconomic effects	Vaccines can have short-term macroeconomic effects, for example, by preventing pandemics and outbreaks of emerging diseases. They can also have long-term macroeconomic effects. The value of vaccines in this respect for COVID-19 is tangible and measurable.	EMA

TABLE 3: ELEMENTS OF EXTENDED VALUE OF COVID-19 VACCINES

*Notes: * Links the defined value element to the product quality as described in Table 2. The WHO level includes the MA elements, and the EMA level includes the MA and WHO elements.*

Therefore, it would be necessary to incorporate the elements of extended value-added into the definition of TPP levels. Candidates that can restore normality in the health system and the social and economic environment will be classified at the TPP of EMA or higher. Prices and financial incentives in contracts should reflect such extended added value in the form of positive externalities for society.

Linking the extended added value of vaccines, in development and approved, to price in a systematic and transparent way, would provide the right incentives for the industry to continue the search for better vaccines to tackle COVID-19 and prevent future outbreaks. Thus, private initiative efforts would also attract public investment in basic research, which will continue to provide the necessary impetus for innovation.

In the design of contracts, it must be borne in mind that the COVID-19 (SARS-Cov-2) virus may become endemic, thus making regular vaccinations necessary. Therefore, it is essential to have regulatory mechanisms in place to continue seeking effective solutions to deal with it.

A reasonable approach could be for the SC of the EC/EMA and the HTA agencies of the MS to work together to establish TPPs or quality bands that allow the different elements of extended value-added to be incorporated into pricing and contracting issues. They could do this through the European Network for Health Technology Assessment[2] (EUnetHTA).

The next step is to articulate how the extended value-added rule can be applied through TPPs and/or quality bands. To do this, we then describe the BBAMC mechanism and highlight the features that could be useful in shaping a value-based vaccine pricing system. We also examine the strategic objectives of including these criteria in the COVID-19 procurement space.

The BBAMC is a mechanism that:

i. uses extended value-added pricing to set the price of candidate vaccines and
ii. is designed to stimulate investment in R&D and production.

Partial or full funding of R&D as an incentive for the development of candidate vaccines does not solve the problem of adverse selection. That is, it incentivises the best candidates, the merely good ones and the mediocre ones equally. It is in everyone's interest to incentivise high-quality vaccines by rewarding them differently from mediocre ones. BBAMC rewards the benefit associated with a product increasingly with quality, but only upon their arrival on the market. Therefore, for high-quality products, arriving later is not a big problem as they know that they will be rewarded for their better quality. Thus, the BBAMC continues to stimulate investment in R&D and the search for better candidates. However, vaccine development efforts are greatly complicated by the need to ramp up production quickly, so there has to be a complementary incentive to promote investment in production capacity for companies.

The current EU proposal already finances part of the upfront costs faced by manufacturers through the ESI and the European vaccine strategy (EC, 2020cd). The risks are shared as the EU functions as an insurer, partially protecting manufacturers from the risk of over-investment if things do not go as expected with their candidates. The funds to support a manufacturer's effort by investing upfront in production capacity should also, as far as possible, be determined with the input of the EUnetHTA and the help of the EC/EMA MC. Still, the question remains on how to develop a measure of extended value-added for each vaccine. In the previous section, we discussed using threshold systems to assess the inherent quality of vaccines according to the TPPs.

The proposal is to refine the bands to be used by the EC/EMA to qualify and rank candidates and by EUnetHTA to assess extended added value and inform negotiations of contracted volumes and pricing decisions. Candidates who meet a higher TPP will be qualified for a higher reward – volume times price – and given priority in their use. It would be normal for countries with different payment systems and the capacity to charge different prices to allow equitable access and a fair level of reward for vaccines.

[2]*The European Network for Health Technology Assessment (EUnetHTA) is a network of health technology assessment agencies from a total of 29 European countries. Its primary objective is the development of reliable, up-to-date, transparent and transferable information between European countries for use in health technology assessment and the efficient use of health resources. For more information see: https://eunethta.eu/about-eunethta/*

The diagram in Figure 5 shows an adaptation of the BBAMC to the context of the current EU proposal, which is based on the use of FCAs and the financing of upfront investment to expand production capacity. In this example, the most desirable properties of the BBAMC, i.e. rewarding value and incentivising investment in R&D and expanding production capacity, are maintained.

Under the EU proposal, partnership agreements have already been signed with leading vaccine companies involving 1.2 billion doses from a diverse portfolio. The APAs specify payments and delivery conditions, including price, potential liabilities and requirements for production and use of production capacity (EC, 2020cd).

Prices have already been agreed with the pioneer companies. However, concerns remain about the need to reward and incentivise the development and large-scale manufacture of vaccines with improved quality that may come in a second round. A possible solution is to:

- continue to examine the pioneer candidates as their results become available
- adapt contracts with pioneer candidates according to demonstrated quality, i.e. decide on additional volume and financing of production capacity
- re-evaluate portfolio management as the actual quality of the pioneer candidates becomes known, and
- develop transparent compensation regulation:
    - based on extended value-added for second round products
    - providing that the best options will be taken (where there is room to do so) and priced in relation to their value.

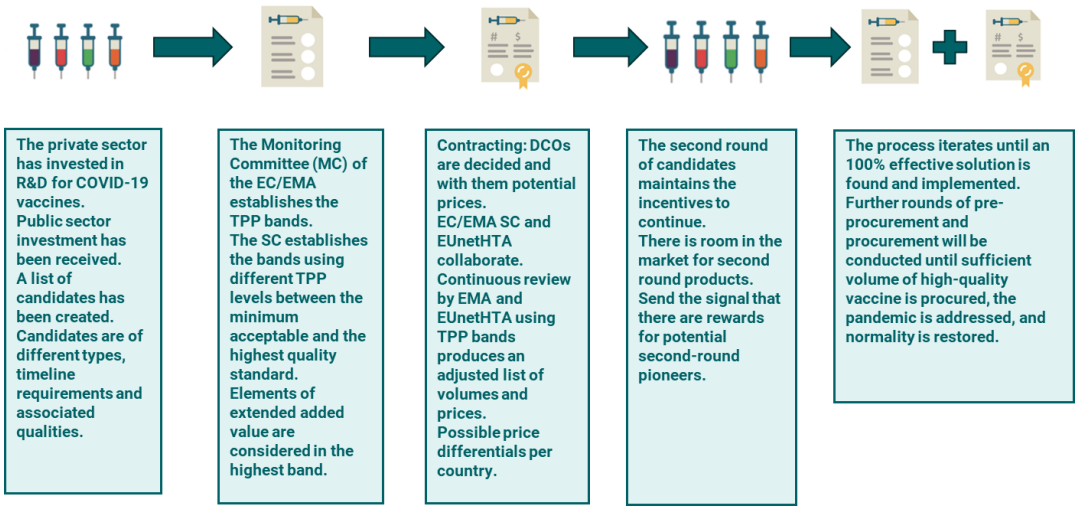

FIGURE 5: ADAPTATION OF THE BBAMC TO THE EU PROPOSAL USING APAS VIA THE IAE

Source: Authors' adaptation of the BBAMC EHO from https://www.cgdev.org/sites/default/files/BB-AMC-May-2020-ppt.pdf

Table 4 illustrates how prices could be set based on extended value-added and production rewards within a TPP tiered system. In the example below, the EC/EMA SC defines quality bands agreed upon by EUnetHTA to assess candidates' value and pricing issues. EUnetHTA could coordinate the value assessment processes of MS' HTA agencies.

Band	Quantity for APA - for pioneer vaccines	Prices of second-generation vaccines	Financing for increased production
MA to WHO TPP	q	p	R
WHO TPP to EMA TPP	$q + t(v_1)$	$p + k(v_1)$	$R + r(v_1)$
Over EMA TPP	$q + t(v_2)$	$p + k(v_2)$	$R + r(v_2)$

TABLE 4: VALUE-BASED PRICES OF COVID-19 VACCINES

The core element of the example is the quality bands. Once defined and made transparent by the EC/EMA SC, quality bands can be used for contracting too. Thus, contracts can specify quantities and prices, as well as increases in production capacity. The final price – based on the value-added of the vaccines and the amount of funding available to invest in scaling up production – will be determined according to the quality bands.

Higher quality means higher price rewards through premiums (k(v1), k(v2)) and, given that higher volumes will be contracted, higher financial support will be allocated to scaling up production capacity. The latter can also be made conditional on quality bands through premiums (r(v1), r(v2)).

The above illustration is only a description of the generic function of such a mechanism. In the following bullet points, we provide a more detailed explanation:

- **The core element of the example is the quality bands.** We assume that the leading companies are committed to supplying the EU with the volume of doses contracted through the APAs. For the agreed volumes, prices are fixed and not subject to further variations.
- **In some instances, the volumes agreed in the APAs may not be sufficient for an effective vaccination plan covering the entire EU population.** Some candidates may fail and/or real-world effectiveness may turn out to be lower than expected. In such cases, the lowest-value candidates will be eliminated from the second round of FCA negotiations. A value-based pricing approach could be used to contract the remaining or first-round survivors.
- **The leading candidates' real-world performance is uncertain,** as is the duration of effective immunisation. Say, for instance, that vaccines induce protection only for one year. Then, the second round of vaccination is likely to be needed in the medium term. It is important to note that products from the second round will be rewarded for their value to maintain enough incentives for innovators to continue pushing their second-generation projects forward. We recommend value-based pricing using bands.
- **Setting the price according to value will depend on evaluating the candidates by the evaluating agencies (HTAs) of the MS.** TPP bands will inform the value-based pricing and contracting guidelines of MS's HTAs through EUnetHTA. However, a joint EU / EC procurement strategy and contracting might also be an option. **Large-scale production capacity is an issue in the period of a pandemic emergency.** During the first round of negotiations (first approved vaccines), funding can be provided via direct grants or push funding. In the second round, priority should be given to re-using the manufacturing capacity funded in the first stage to increase manufacturing capacity for other, higher-quality candidates. First-round contracts should already incorporate this thinking by encouraging and/or enforcing manufacturers to subcontract facilities, for example. Any additional push funding should be exclusively targeted at filling the manufacturing gap that still results after using the existing manufacturing capacity generated in the first round.

GLOBAL SUMMARY 3. Pricing and procurement

European-level coordination in contracting requires sending the right signals to developers on both the price and volume required. Contracts need to include pricing as part of a reward system to incentivise the development of high-quality vaccines and investment in production capacity. Ideally, the definition of a TPP must incorporate extended value-added elements (Bell, Neri and Steuten, 2020).

The EC/EMA SC and MS healthcare agencies should collaborate through the EUnetHTA to define and develop procurement guidelines based on the EMA TPP bands. To do so, it is recommended that:

- An ongoing review of real-world evidence from the first round of vaccines is used to adjust portfolio management and contracts, with consideration for the potential unmet needs of the MS (i.e., additional volume might be required).
- The strategy should be transparent and make clear that:
    i. Lower-value candidates will be eliminated at the second round, and value-based procurement used after that.
    ii. Second-round vaccines that improve efficacy and/or the acquired immunisation duration compared to existing vaccines will be incentivised with value-based contracts.
    iii. Value-based pricing will depend on the evaluation of candidates by the MS HTAs coordinated by the EUnetHTA.
    iv. Manufacturing capacity created in the first round is to be used to produce second-round (and future) candidates. Large-scale production capacity is a problem in the short term: re-use of such capacity should be an option considered from the start to increase the production capacity of other potentially better second-wave candidates.

5 Vaccine delivery issues

To date, the EU APAs have secured a total of 1.2 billion vaccine doses, assuming all vaccine candidates progress successfully to marketing authorisation. The centralised procurement approach is strategically optimal given the challenges that MS face with other pandemic-related issues. Decentralised, country-level individual responses have contributed to increasing confusion about how to respond to the pandemic. Thus, we consider it reasonable to purchase and distribute at the EC level first.

The distribution of doses between MS requires a political strategy. The EC proposes that vaccines are allocated based on the size of the MS populations: "The allocation of access to vaccine doses between Member States would be made according to a population-based distribution key" (EC, 2020b).

If our interpretation of the proposal is correct, from the 300 million pre-contracted doses of Oxford/AZ vaccine, Spain would be allocated around 30 million doses – i.e., equivalent to the proportion (10%) of the population of Spain (47.3 million) relative to that of the EU-27 (447.7 million) (Eurostat, n.d.). This is in line with what the Spanish government has announced (El Pais, 2020).

Below, we highlight several potential challenges with relation to vaccine supplies and the allocation between MS:

- **Supplies will not arrive all at once:** Pre-contracted batches will be supplied by each manufacturer in waves. Therefore, by the time the first batch is delivered, a clear and transparent allocation rule should determine where to use these doses. It is crucial to allocate the new batches according to pre-established criteria of efficiency and solidarity. Likely, distributing them based solely on population shares will not be efficient. The EC might need to decide what MS should receive the first million doses manufactured by each developer. That decision should be subject to additional criteria.
- **Vaccines with different characteristics will arrive at separate times:** Vaccine candidates will tackle the disease to different extents. Classifying vaccines according to TPP-based bands means that vaccines under the same band could be used interchangeably, allowing for greater flexibility and efficiency. Additionally, vaccines in different bands could be used in different sub-populations to maximise their impact.
- **Storage infrastructure and vaccination capacity:** vaccines are complex biological products for which transport, storage, and use are subject to strict quality and safety conditions. For example, relevant details about product stability and storage of the two mRNA vaccines are available. They must be stored long-term at temperatures well below freezing, from -20 to -70 degrees Celsius, and they remain stable for shorter periods, i.e., between 5 and 30 days, in standard refrigerators. These requirements pose significant challenges to countries and their health systems. As such, it would not make sense to over-supply doses of such vaccines to countries that cannot use them in the timeframe required or that do not have the necessary long-term storage infrastructure. Any number of wasted units would be a considerable loss, and so the allocation of new supplies should take these factors into account for the sake of efficiency and solidarity.
- **Vaccination interruptions may occur due to safety concerns:** COVID-19 vaccines have been developed in record time. If all goes according to plan, they will be ready for mass vaccination in the second half of 2021, if not sooner. Although Phase III trials have used tens of thousands of volunteers, hundreds of millions will eventually need to be vaccinated. Reactions or adverse events are likely to arise, which will require pauses in vaccination

campaigns to conduct in-depth studies that will determine whether these events are related to the vaccine. In preparation for such exceptional situations, the EMA has established an unconventional pharmacovigilance procedure to safeguard human safety and public health (EMA, 2020e). This extraordinary procedure entails stricter conditions than usual. The combination of stricter pharmacovigilance and worldwide vaccine use makes it even more likely that interruptions in vaccination processes will occur. Therefore, it is essential to plan for allocating, relocating, or saving supply for later interventions to minimise the risk of unnecessary supply loss.

- **Vaccine candidates can fail:** we know that the process from Phase III to regulatory review is subject to a failure rate within the range of 50% to 75% (Wong, Siah and Lo, 2019; Thomas et al., 2016; Hay et al., 2014). If failures occur, the allocation strategy may need to be reviewed, along with the APA and the post-approval procurement strategy. If some MS have managed to secure more units from the successful options, reallocation of doses should be considered to reinforce MS solidarity and efficiency. MS should develop contingency plans to respond to potential failures.

The strategy for vaccine allocation should also consider pandemic and non-pandemic factors specific to each country, such as:

- **Epidemiological situation:** some MS might reach the peak of the second, third, or nth wave, while others are starting to lift restrictions with the arrival of the first batches of vaccines.
- **Country-specific health system stress levels:** Mortality indicators and loss of population health are linked to a countries' health systems' capacity and stress levels. We will see both direct mortality and health outcomes associated with COVID-19, and indirect outcomes, i.e., the lack of adequate treatment for patients with other conditions. The latter strongly correlates with the epidemiological situation, but some variability may occur due to different capacities of health systems and/or health coverage in different MS. Indicators reflecting the stress level of the health system should be considered when deciding who will be served first and to what extent. An agreement between MS and the EU would be required.
- **The severity of in-country restrictions:** if the population of a given MS is subject to containment measures that affect the normal functioning of public services, social relations, and the economy, it is also essential that these are considered for allocation purposes. Where countries in similar epidemiological and health care system stress situations face different levels of NPI measures, prioritising those with stricter restrictions in place will maximise the health and socio-economic benefit in the European aggregate. Benchmarking of NPI by MS should be considered, and contingency plans based on this information should be developed and agreed upon between MS and the EU.
- **Socio-economic factors:** the final element to be examined is how MS's socio-economic characteristics can play a role in priority setting. Countries with ageing populations, higher unemployment rates, greater inequality, higher population density and/or are more open and dependent on international relations (among others) could be considered for priority setting. Approach expected to be helpful to break ties when all other factors have failed to establish clear priorities.

It would not be defensible to weigh these factors more heavily than those discussed above. Still, the establishment of adjustments in the allocation rule should be debated and agreed upon, if possible, between MS and the EU.

Solidarity is also a fundamental component of the suggested strategy: "A truly European approach would avoid competition between Member States. It creates solidarity between all Member States, irrespective of their population size and purchasing power" (EC, 2020e).

It is essential to maintain the solidarity component as part of the allocation process. This would require a joint effort by the MS to ensure that their decisions prioritise solidarity over competition when conflicts of interest arise.

While we recognise that a population-based approach has many advantages (i.e., straightforward to apply and explain), taking into consideration additional criteria could make the distribution of doses more efficient. A comprehensive approach could improve the MS epidemiological situation, alleviate the stress on health systems, reduce the pandemic's socio-economic impact, and thus, maximise the health and economic outcomes of the EU as a whole. It would be advisable to balance the population-based approach with a more sophisticated approach to increase efficiency and solidarity.

However, the way by which all the additional factors discussed (e.g., epidemiological situation, health care system's stress, the severity of the restrictions, socio-economic factors) should shape the distribution policy will have to be decided after the first wave of the pandemic. Incorporating these factors in policymaking would be too complex and time-consuming while experiencing the present public health emergency. The criteria would need to be accepted, agreed upon, and included in the decision-making process by all MS between waves. To address the current health emergency, MS need a simple, easily implementable process to minimise response time, even if it is less effective. When time is critical, first-bests may be too costly vis-a-vis their benefits, and second-bests – such as using a population-based approach to distribution – might be a reasonable response.

GLOBAL SUMMARY 4. Issues with vaccine allocation and distribution among MS

For the allocation of vaccines between MS, the following factors should be considered:

- There might be other concerns besides the population of the different countries, i.e., the stress that the pandemic is exerting on the health systems, the resulting severity of restrictions, and their impact on the economy.
- Different vaccines will arrive simultaneously. Allocation of vaccines to countries and regions should be based on the principles of efficiency and solidarity.
- Vaccines may offer different value depending on the settings and circumstances in which they are administered.
- Storage infrastructure and vaccination capacity may vary by country and/or region. Allocation strategies should take this into account.
- Pauses in vaccination plans can occur if safety issues arise. MS should agree on a contingency plan to reallocate vaccine doses to minimise the risk of halting national or regional vaccination programmes.

6 Vaccination programmes and prioritisation strategy in MS

As discussed in this report, the EU's APAs-centralised procurement strategy has effectively addressed risk, generated appropriate incentives for manufacturers to scale up production capacity, and avoided the undesirable effects of MS competing for vaccine doses. Similarly, a coordinated vaccination strategy could help vaccinate effectively and in line with basic solidarity principles.

MS' vaccination strategies are not expected to differ by much. There is a significant agreement on how to prioritise subpopulations (WHO, 2020c; CDC, 2020; Anon, 2020; Anderson et al., 2020; Hassan-Smith, Hanif and Khunti, 2020; EC, 2020c; DHSC, 2020). Therefore, we anticipate that a general set of principles will characterise most vaccination plans.

Principles to be considered include:

- **Equity concern:** the obligation to consider and treat all persons with equal dignity, worth and value.
- **Mitigation of health inequalities:** the obligation to cover first and foremost those population groups most affected by the burden of co-morbidities or by conditions associated with an increased level of risk
- **Equity:** the obligation to prioritise assistance to population groups most affected by the pandemic
- **Transparency:** the obligation to apply full and clear guidelines in the vaccination schedule
- **Evidence-based:** vaccination plans must be based on the best available scientific evidence on disease transmission and its impact on society.

There is also joint agreement on the subpopulations that should be prioritised for vaccination (CDC, 2020; Anon, 2020; Hassan-Smith, Hanif and Khunti, 2020; Anderson et al., 2020):

- **People over 60 years of age:** those with elevated age-based risk of severe COVID-19 or death. Special attention is recommended for those living in residences or shared households with family members required to leave their home.
- **Vulnerable or high-risk population due to their health state:** those at high risk of severe COVID-19 or death due to co-morbidities or risk factors such as obesity, hypertension, asthma, heart conditions, pregnancy, diabetes, HIV/AIDS.
- **Health care and long-term care workers:** essential workers – those working in occupations that combat the effects of the pandemic – are at significant risk of being infected and of infecting vulnerable people.
- **Essential workers outside the health sector:** workers employed in sectors providing essential goods and services – including teachers, childcare providers, agricultural and food workers, transport workers, police officers, and emergency responders. Also, those workers who cannot maintain necessary physical distance – including factories, meat processing plants, and slaughterhouses.
- **Communities unable to maintain necessary physical distance:** such as those living in residences, prisons, refugee camps, and staff working in such communities or sites.

- **Vulnerable socio-economic groups and other groups at higher risk:** socially and economically disadvantaged communities, often characterised by increased population density, small living spaces shared by large families, employment and financial instability, and work in the informal economy. There is evidence that the deprived populations suffer chronic diseases more frequently and have worse prognoses than their less-deprived counterparts (Niessen et al., 2018; Mielck et al., 2014). This, together with comorbidities exacerbating the severity of COVID-19, means that COVID-19 might aggravate existing inequalities.
- **People in homeless shelters, group homes for people with disabilities**, e.g. mental illness, developmental and intellectual disabilities, and staff working in such settings.

Another point to bear in mind is that, although the high-priority sub-populations are well defined, there is no well-established plan for each of them in the short term if supplies are insufficient. For example, whether the strategy should minimise mortality per year or maximise average life-years gained (Anderson et al., 2020).

An example will help illustrate why these two principles may not coincide: imagine a country with a life expectancy of 84 years, an infection mortality rate of 25% for the >70 age group, and 10% for the 50-70 age group. For every 100 vaccines given to the older age group, 25 lives would be saved, and for every 100 provided to the younger age group, ten lives would be saved. However, the average years of life gained – estimated from the group midpoints (60 and 77) – would result in 240 years gained in the younger group and 175 years in the older group. The strategy of maximising average years of life saved requires precise calculations using demographic and epidemiological data. Public health authorities and policymakers should consider all of these alternatives when setting targets and priorities.

The prioritisation decision could also depend on the efficacy and effectiveness of each type of vaccine for different age groups. Suppose the first million doses have been significantly more effective for those aged 30-70 years than those over 70 years. In that case, a life-saving maximisation strategy could be to immunise the most vulnerable group first. In the short term, given the exponential increase in the fatality rate of infection with age, and assuming that the first vaccines are good enough for older age groups, it would be advisable to adopt a "life-saving" strategy. This would also help the health systems return to some semblance of normalcy, which will have large, positive spillover effects on health.

Expanding the capacity to vaccinate large proportions of the population in a short period of time is as important as prioritising use and setting targets. In England, for example, proposals to use football stadiums, town halls, and conference buildings are currently being discussed (The Guardian, 2020a). However, the locations and mode of administration will need to consider the type of storage conditions required for the type of vaccine used.

With minor differences, proposals by all MS are broadly in line with previous guidelines (Anon, 2020). The Spanish government has released its vaccination plan for the first half of 2021, aiming to vaccinate a substantial part of the population in the first half of the year (Ministerio de Sanidad, 2020). The German government has announced that hundreds of vaccination centres will be set up from December 2020. These are just a few examples of the many plans and declarations of intent that MS have published. The US Centers for Disease Control and Prevention (CDC) and the National Academies of Sciences, Engineering, and Medicine have also developed guidelines for the US on vaccinating different groups in various phases (CDC, 2020; Anon, 2020).

Figure 6 below shows an adapted version of the phased plans by the CDC and National Academies of Science, Engineering, and Medicine for the populations defined by the European Commission.

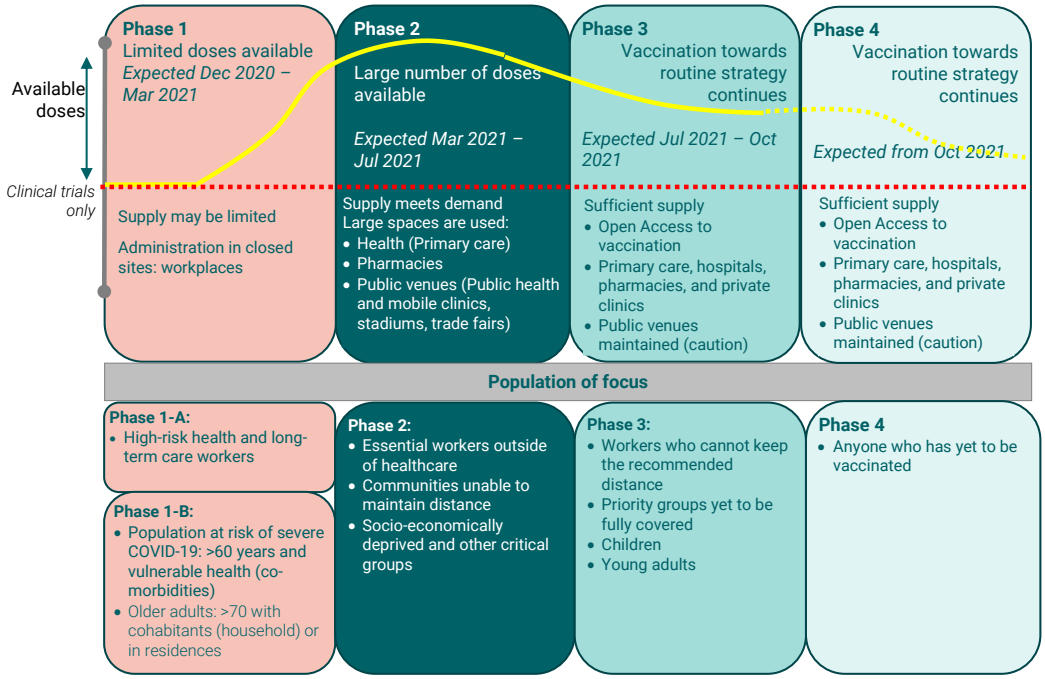

FIGURE 6: PHASE-BASED VACCINATION SCHEDULE
Source: Adapted from CDC, 2020; European Commission 2020b; Anon, 2020

The plan must consider who should be targeted first within each group in order to minimise mortality. In May 2020, the Nuffield Trust estimated that the COVID-19 mortality rate in the most deprived areas was double that of the most affluent (Nuffield Trust, 2020). Therefore, contrary to what has often been said in the media, COVID-19 does discriminate, and it does against the most socio-economically disadvantaged.

Policymakers have been quick to identify older people and people with co-morbidities as particularly vulnerable or at high risk, but the concept of vulnerability should be appropriately broadened to include those at high risk due to socio-economic factors. Socio-economically deprived populations often live in cramped, overcrowded accommodations, reside in high-density areas, have jobs that do not offer opportunities to work from home in unstable working conditions, and have co-morbidities such as diabetes and hypertension (Patel et al., 2020).

Therefore, giving additional priority within each priority group to populations at high risk due to socio-economic status would substantially improve the objective of minimising transmission and mortality while improving public health. Relevant government agencies in MS need to identify particularly socio-economically disadvantaged areas using objective indices[3].

[3] *An example of an index that can be used to assess the degree of economic and social deprivation of certain areas or communities proposed in Anon, 2020 is the CDC Social Vulnerability Index (SVI):* https://www.atsdr.cdc.gov/placeandhealth/svi/at-a-glance_svi.html

Through the EC, the EU has established a vaccination strategy (EC, 2020c). It advises on some actions that MS should undertake to carry out large-scale vaccination for their populations rapidly. Figure 6 also provides information on how vaccination facilities, infrastructure, and capacity should be used at each stage. In this aspect relevant to a vaccination plan, MS could take the following steps:

- **Ensure sufficient capacity of vaccination services to deliver COVID-19 vaccines:** this includes having a sufficiently skilled workforce and an adequate supply of protective equipment (October to November 2020 deadline). This requires estimating the number of citizens to be vaccinated based on vaccine availability and recruiting or redeploying health workers and other technical and non-technical staff, including providing job training programmes for those workers who can be reassigned.
- **Ensure easy access to vaccines for target populations in terms of both affordability and physical proximity (October-December 2020).** Again, estimates of the number of people targeted per cluster are needed. Estimates of the target number of clusters per area will inform the logistical decision on sites and each site's capacity to vaccinate.
- **Prepare the deployment of vaccines in the conditions required by the relevant vaccine:** transport and storage needs are different depending on the type of vaccine. This will require strict quality control and adequate transport and storage capacity. Any public centres or venues not needed for other public or private uses (trade fair venues, auditoriums, biological research centres etc.), should be adapted as vaccination centres. MS should establish public health committees and build sufficient capacity, taking into account the vaccine portfolio and always aligning with support from their governments and legislative institutions.

Eventually, policymakers will have to design a plan to lift all NPIs currently in place. Recently, when asked when we will be able to stop wearing protective masks, Dr Anthony S. Fauci – director of the U.S. National Institute of Allergy and Infectious Diseases (NIAID) – replied: "[…] we're going to have some degree of public health measures along with the vaccine for a considerable period of time. But we will start to approach normalcy – if an overwhelming majority of people take the vaccine - as we get into the third or fourth quarter [of 2021]" (NY Times, 2020).

Reaching herd immunity will depend on the real-world efficacy and safety of each type of vaccine and the duration of the vaccine response. For example, in a country like Spain, with 47 million inhabitants, if the threshold for herd immunity is set at 70%, about 32 million people would need to be immunised. Vaccines with 100% efficacy would allow 32 million to be vaccinated, but any vaccine with a lower efficacy rate would require a higher number of vaccines to reach herd immunity.

Knowing the real-world effectiveness by population group and the duration of immunity with the highest accuracy is crucial for designing and implementing an effective vaccination plan to minimise mortality and the pandemic's socio-economic impact. The design and implementation of an enhanced pharmacovigilance plan for COVID-19 vaccines is a prerequisite for planning the return to normality. This plan should be designed individually by each MS but coordinated by the EMA, as usual. The current situation will require faster processes and efficient systems for data collection, information sharing, and availability.

A pharmacovigilance plan aims to ensure that all new information gathered after marketing authorisation is reviewed promptly and that new information is shared with the public in a timely manner (Kelly, 2020). It involves monitoring vaccinated populations in the real world and following up those vaccinated in Phase III for long-term safety and efficacy.

The better the knowledge about how vaccines can help bring MS back to normal, the more successful, safe, quick, healthy and socio-economically beneficial the return will be. If better information on how vaccines perform in the real world allows policymakers to design better policies that can save more lives or return to normalcy sooner by lifting NPIs, any investment effort, even if large, will result in a positive return to society.

Pharmacovigilance evidence will inform decisions made by policymakers at different levels:

- **The extent to which vaccination is generating herd immunity:** produce estimates of the percentages of vaccines and the expected immunogenicity profiles, i.e. specific antibodies, T-cells. This information will provide an understanding of the actual percentage of people immunised, and therefore the percentage of people protected against infection.
- **The real-world efficacy of vaccines:** given the array of different APAs that the EC has signed with different vaccine companies, it is very likely that populations will be vaccinated with different products simultaneously. Mass use of various vaccines may help to understand in which sub-populations a given vaccine is more effective or causes fewer adverse reactions. A better understanding of this difference in efficacy in different population groups could contribute to the efficient use of available vaccines. It would also help to accelerate the elimination of NPIs as much as possible.
- **Mass vaccination of hundreds of millions of people will allow a better understanding of possible very- and ultra-rare adverse reactions (i.e. <1 per 100,000):** Mass vaccination implies that adverse reactions may occur, especially very rare ones that may have remained hidden in trials. In addition, reactions are likely to arise that need to be investigated concerning the vaccine and may affect vaccination schedules, e.g. by stalling and delaying them. Intensive monitoring can help minimise interruptions to vaccination and focus on using the safest vaccine options available as soon as they are known. This will make it easier to minimise the time to achieve herd immunity.
- **Research on long-term immunisation of vaccines:** It is crucial to know how long different vaccines protect from infection. Whether it is only months, or up to several years, will affect vaccine procurement, vaccination schedules, and ultimately, whether NPIs can be fully or only partially lifted. In addition, if there are significant differences in the long-term immunity induced by the different options, this would help in planning subsequent procurement and use of vaccines.

The knowledge generated should be rapidly shared and integrated into the public health institutions of each MS, which will be responsible for establishing a communication channel with policymakers, which in turn will have to design an optimal plan to return to normal socio-economic functioning.

GLOBAL SUMMARY 5: Vaccination programmes and prioritisation strategy in MS

- Vaccination plans should ensure that public health and social benefits are maximised, which is not always the case. A 'life saving' strategy may be good, but maximising the gain in aggregate expected life years should also be considered.
- A phased vaccination plan taking into account critical populations is recommended.
- COVID-19 has severely hit individuals of lower socioeconomic status. Therefore, there may be an argument to prioritise this group.
- Different logistic conditions will have to be considered, and investments by MS may be necessary.
- Access to the vaccination for vulnerable populations will have to be planned appropriately.
- Doses required to achieve herd immunity should be a consideration at any stage.
- A strong pharmacovigilance plan for COVID-19 vaccines must include a strict requirement to identify when herd immunity is achieved, react quickly in case of adverse effects, and learn about the duration of immunity associated with each vaccine.

7 Education and public awareness

Concerns about the safety and efficacy of vaccines among the population are not rare. The incredible speed with which vaccines for COVID-19 have been developed – one year to develop and approve what typically takes 4 to 7 years – can be seen as literally "unbelievable" by the general public.

The way governments have responded to the crisis has not made things any easier. Governments, and organisations such as the WHO, have struggled to respond to an unknown threat and its uncertain consequences. SARS-Cov-2 was a new virus, and COVID-19 a complex disease that science is still trying to understand and explain. We have witnessed conflicting policy responses from different world leaders, governmental U-turns, and political leaders discrediting science or the WHO (BBC, 2020; The Guardian, 2020b). We have even witnessed the WHO ignoring or being slow in accepting scientific findings, as in the case of aerosol transmission (NPR, 2020; WHO, 2020e).

Citizens are exhausted due to the high number of NPIs and the additional restrictions and uncertainty surrounding their daily lives. At the same time, while there is plenty of information available, most of the fundamental questions remain unanswered, e.g., how long does the natural immunity last? Will the immunity provided by vaccines be lifelong or just temporary? Will mutations of the virus bring new waves or drive the pandemic out of control again? Will citizens be fully locked down again? There is a conflict of interests between individual costs and benefits and the common good, which creates perverse incentives to behave selfishly, especially those who are less at risk of severe or even fatal outcomes from COVID-19. In this context, the public is more likely to develop views of denial, cynicism, or lack of trust. These beliefs are fuelling growing uncertainty about the potential efficacy of vaccines.

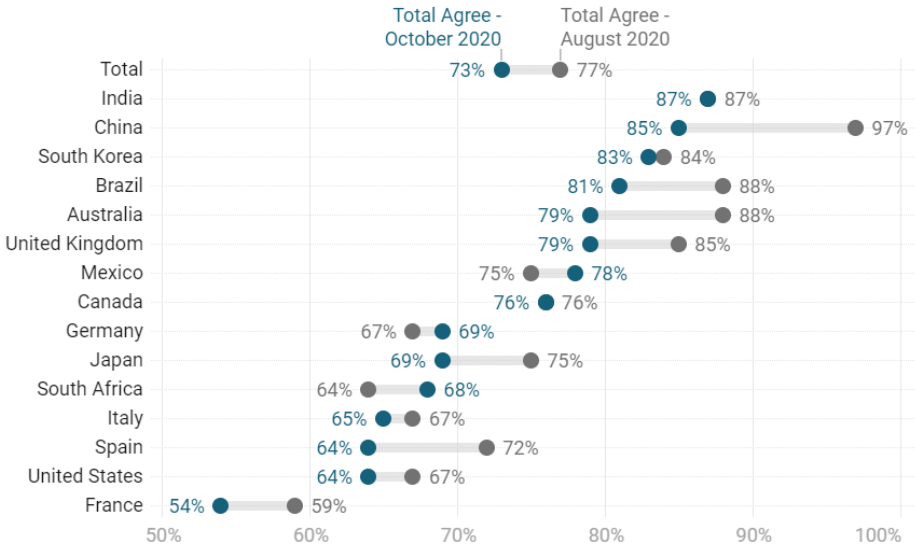

FIGURE 7: RATES OF AGREEMENT WITH "IF A VACCINE FOR COVID-19 WERE AVAILABLE, I WOULD GET IT"

Notes: 18,526 online adults aged 16-74 in 15 countries.
Source: Ipsos (2020)

Figure 7 shows how vaccine uncertainty has consistently increased across countries from August to October 2020. The graph shows the percentage of people agreeing with the statement "if there was a vaccine against COVID-19, I would get it" in August and October. The top two concerns globally cited by respondents are potential side effects (34%), and that clinical trials have moved too fast (33%) (Ipsos, 2020).

The growing hesitancy is a major concern because for vaccines to be effective as a public health intervention, it is crucial to vaccinate large proportions of the population to achieve herd immunity – in the case of measles, for example, 95% of the population must be vaccinated. In comparison, for polio, the threshold is about 80% (WHO, 2020d). This percentage increases as the effectiveness of the vaccine decreases and/or the transmission capacity of the virus increases. Therefore it is vitally important that, on a global level, citizens in all countries develop positive beliefs about the use of vaccines against COVID-19 so that a large percentage of the population is willing to be vaccinated.

HOW CAN WE FIGHT VACCINE HESITANCY AND REVERSE THE CURRENT TREND?

Campaigning is necessary for MS as an essential part of the vaccination programme. A clear, effective and transparent information campaign is a crucial element for the success of the COVID-19 vaccination programme. MS should develop a targeted communication strategy to ensure that the right messages about the benefits, risks, and importance of achieving high vaccination rates are conveyed to citizens and promote public confidence (EC, 2020e). Prioritised populations should be the first to be targeted by such campaigns, but success depends on effective communication and confidence-building across the population. To that end, MS should:

- Identify and share best practice guidelines on effective ways to address vaccine hesitancy
- Work with health professionals as trusted sources on vaccination issues
- Engage with key scientists and partners, i.e. EMA, academics, communicators, journalists, sociologists, to develop messages and their format.

Health authorities in each MS should consider setting up a Vaccine Communication Working Group for COVID-19, which will design, help implement, and monitor the impact of the information campaign.

Other primary objectives of the communication plan should be (CDC, 2020):

- **Educate the public** about the development, licensing, distribution and implementation of COVID-19 vaccines.
- **Ensure public confidence** in the approval/licensing process and the safety and efficacy of COVID-19 vaccines.
- **Help the public understand the differences between the EMA's "emergency authorisation procedure"**, which allows for rapid approval, and the EMA's standard authorisation (EMA, 2020f).
- **Ensure active, timely, accessible and effective public health and safety messaging** and outreach to key stakeholders and the public on COVID-19 vaccines.
- **Provide guidance** to local health departments, physicians and other hosts of COVID-19 vaccine delivery sites.
- **Track and monitor** public receptivity to COVID-19 vaccination messages.

Communication should be tailored to key audiences using appropriate media. Health workers are as crucial as vulnerable (or high-risk) populations or young people, but the messages and media used to reach each group need to be different to be effective.

Finally, another crucial aspect of the communication plan is its timing: it should start as early as possible before the end of 2020 and specifically target the groups intended to be first in the vaccination plan. A broader impact strategy should then be planned and implemented once the first target population has been successfully reached.

COMMUNICATING THE VACCINE APPROVAL PROCESS IN EUROPE: BUILDING PUBLIC CONFIDENCE

Most of the hesitancy is based on doubts about vaccine safety and adverse reactions and concern that clinical trials are moving too fast (Ipsos, 2020). The way by which companies in the race are releasing trial results to approve vaccines contributes to public doubts about the vaccine, rather than dispelling them. To Pfizer's first announcement of 90% efficacy in Phase III trials, Moderna responded with 94.5% a week later, and Pfizer countered with 95%. Focusing on these announcements damages rather than enhances confidence.

Mass media and social media releases should adapt press/radio/TV releases by focusing on the regulatory process and how the EMA assesses the evidence submitted by candidates once Phase III trials have been completed, rather than on the candidates' releases directly. The EMA website presents an excellent example of the kind of information needed to explain the general role of the EMA and its activities in safeguarding public health to the public while supporting companies in developing safe and effective vaccines for COVID-19 (EMA, 2020g).

The EMA has developed and implemented exceptional measures to maximise the transparency of its regulatory activities on COVID-19 treatments and vaccines - approved or under evaluation (EMA, 2020h). This is a correct strategy that should be followed by an action plan from MS to translate all information shared by the EMA to the general public in a digestible way. The COVID-19 Vaccine Communication Working Group of each MS should be responsible for taking this step.

The important points to explain to the public are:

- Why have the pharmaceutical industry and the EMA been able to speed up development and approval times for COVID-19 vaccines?
- How have development times been shortened while maintaining safety conditions?
- How have large numbers of volunteer participants in clinical trials helped better control efficacy and rare and rare adverse reactions?
- Explain and educate the public about the post-authorisation Phase IV drug monitoring plan. The efficacy and safety of vaccines in the real world will be closely monitored, and any potential adverse effects will be detected and investigated.

The different points can be easily explained and should be public knowledge. The EMA produces the material, but the channels between the EMA and the public and/or key stakeholders have to be built through the COVID-19 working groups.

MASS MEDIA AND SOCIAL MEDIA: DISPELLING DISINFORMATION

Clear messages and how they are communicated to target audiences may not be sufficient if the means are not adequate or if communication capacity is minimal.

A recent study by Johnson et al. (2020) shows that, although pro-vaccination groups outnumber anti-vaccination groups on social media, the latter's influence on groups with undefined positions is more powerful, so anti-vaccine views are increasingly trending. In other words, by being central and influential in social networks, anti-vaccine groups are reshaping the general public's opinion on vaccines.

The information campaign and communication strategy of MS must be designed and communicate their message effectively in social networks and mass media. These influence the mechanisms for taking up core positions and impact the views of undecided groups.

Raising the profile of health authorities and the scientific community on social media is very important because it indirectly informs other population groups (often adults and older people) who receive information through people active on social media (usually young people).

Some measures that would be advisable include:

- **Identifying key sources of information that influence opinions to i) dispel and challenge with evidence those who disseminate misinformation, and ii) raise visibility and promote those who disseminate evidence-based messages.**
- **Using traditional media to promote informative debates on the value of vaccines, i.e. print, radio, prime-time television and mass media.** Ideally, debates should include all points of view to allow the public to see first-hand how views that are not evidence-based do not hold up when subjected to serious debate.
- **Providing short reports and interviews on vaccines that discuss the scientific challenge to develop them**, the historical value they bring to society, the views of key researchers working on vaccines for COVID-19, etc. should be promoted in news, TV and radio programmes.

EDUCATION: THE VALUE OF VACCINES

It is important to communicate the broader value of vaccines to citizens who will receive the vaccine (Bell, Neri and Steuten, 2020). Having attempted to address concerns about safety and lack of confidence in the development and review of vaccines for COVID-19, it is crucial to convey a clear message about the value of vaccines:

- **Why vaccines will only work if a large percentage of the population is vaccinated,** promote a general education plan for the public on the effect of vaccines. Convey that getting vaccinated is an act of solidarity to protect others. It is not an individual treatment. It is a social response to a pandemic.
- **It is also imperative to show that in the context of the COVID-19 pandemic,** the value of vaccines goes far beyond the health and public health outcome dimension and provides enormous socio-economic benefits, as they promise to be the intervention that can enable the lifting of NPIs. Other valuable components such as the impact on caregivers' quality of life, social equity, the productivity of those potentially infected by COVID-19, the productivity of caregivers, cost offsets to the health system and macroeconomic effects need to be clearly shown to the public.
- **Use of historical examples of how vaccines have contributed to an enormous improvement in the quality of life of humanity.** Examples such as smallpox or polio have been eradicated, or measles which is now under control but could become a threat with the proliferation of anti-vaccine views. Media reports, news monographs, etc., should be used strategically to this end.

VOLUNTARY VS. MANDATORY

Voluntary vaccination must be the goal of policymakers. This will be a success in the face of growing anti-vaccine sentiment, so the campaign and communication strategy is crucial. Achieving the minimum percentage of vaccination required to achieve herd immunity through voluntary vaccination will be a success for science and the future of vaccines and immunisation programmes. The return on any investment made to achieve this with a communication plan is undoubtedly positive.

Compulsory vaccination will be heavily criticised and used against the acceptance of vaccines and science, now and in the future. It can be a double-edged sword because it effectively solves the problem in the short term but potentially creates a long-term problem by damaging the reputation and credibility of vaccines and pro-vaccination views.

However, there may be cases where individuals in some critical groups who refuse to be vaccinated may pose a serious public health problem. Examples include health care workers and long-term care social workers in residential care. These groups need to be the focus of an education and communication plan. This should be the priority approach. They should be informed about the whole EMA review process and the safety and efficacy profiles of vaccines. They should also be informed about the possible consequences of refusing to be vaccinated.

In addition to education and communication programmes, and in case these are not sufficient, incentives could be used as a second option. These may or may not be financial: for example, vaccine recipients could be entitled to employment benefits, i.e. holidays, flexible working hours, sponsored training, or rewarded with extra pay.

For the general population, the use of the pharmaceutical co-payment system could be an option. It could be evaluated as a tool to encourage voluntary vaccination, always as a secondary tool to the communication and information campaign. As any vaccination programme is likely to be phased, at the beginning of each phase, the authorities could establish a vaccination window during which the cost of the vaccine is fully reimbursed. After that, the co-payment rate could be progressively increased up to the full payment of the dose. But this would entail equity, ethical and legal concerns and would only be acceptable if adequate means are provided to ensure that the vulnerable and economically disadvantaged population has an equal opportunity to receive the vaccine during the full reimbursement window and in subsequent phases.

Social recognition is another alternative that can be used to encourage vaccination. The solidarity of those who volunteer for clinical trials should be acknowledged. They have put themselves at risk to demonstrate that vaccines are safe and effective. We are talking about tens of thousands of people who have made possible the rigorous assessment of the risk-benefit profile of the vaccine. It is thanks to them that we know approved vaccines are safe and ready for mass use. This component should be used to encourage commitment and solidarity from the general population in reciprocal response to them.

CONTINUED MONITORING OF PUBLIC RECEPTIVITY TO COVID-19 VACCINE MESSAGES

Another aspect of the communication strategy is implementing a continuous monitoring plan to assess the impact of the communication strategy. It is also essential to continuously check for any need to reform or redesign. The COVID-19 Vaccine Communication Working Group of each MS should include the following in its surveillance plan:

- Social media reporting: assess the impact of social media, generating reports based on metrics such as citations, views, mentions, number of 'likes', new or lost followers, etc.

- TV and radio audience: communication through traditional mass media should be monitored by examining audience rates, share and other relevant metrics.
- Ongoing surveys and polls of critical groups and the general population: the most relevant tool is to conduct regular surveys and polls to (i) see the general trend and (ii) determine where efforts need to be increased.

ONE MESSAGE, MANY WAYS OF EXPLAINING IT

When designing a vaccination campaign that fits today's needs, it is essential to consider the generational and educational differences between different segments of the population. Otherwise, there is a risk of using inaccessible vocabulary or overly traditional means of communication, and the message that should reach all citizens may fall by the wayside. It is important to emphasise generating understanding and engagement across all groups.

Against this background, managers of public health and communication must anticipate possible risks to prevent them. It is important, therefore, to start a public awareness campaign as soon as possible that takes into account the following elements:

- **It is likely that when a vaccine is implemented on a large scale, it will not work as well as hoped or promised. This does not mean that the vaccine is dangerous or may have unintended adverse effects. In this case, it is important to communicate that:**
    - There is no guarantee that the first vaccine will work with the expected success rates (e.g. 90%) and that this is the norm.
    - Indeed, the use of the vaccine will not be harmful to health and, although possible, it is improbable that new severe or severe adverse effects will occur.
    - To stress that: it has been possible to obtain results in record time thanks to four vital elements used at the same time as never before: 1. volunteers to take the vaccines, 2. public and private money, 3. scientific studies, 4; experience in the development of vaccines accumulated over decades in other diseases.

- **This must be communicated as soon as possible. Otherwise, it could happen that, for example, the vaccination campaign starts and the infection rate does not go down.**
    - In this scenario, if not made clear before the start of the campaign, scepticism could increase even more with arguments such as: "they made me get vaccinated for nothing, when another vaccine against COVID comes out I won't get it" and even "they put a chip in me".

Finally, young people bear a great responsibility in this context, as they are often the vehicle of information for their families, who rely on their opinions for information. There is a need to understand the most effective ways to generate impact using social media, usually under the slogan "by young people for young people", for example, using Instagram, TikTok, YouTube, and Twitter. Generating youth-targeted content is a key element of successful vaccination campaigns. Give a lot of visibility to exemplary actions undertaken by young people and much less to reprehensible actions (something that is failing miserably).

GLOBAL SUMMARY 6. Education and public awareness

- MS should develop a targeted public communication strategy to inform: risks and benefits, the importance of achieving high vaccination rates to reach herd immunity and healthcare system recovery, macroeconomic restoration, caregivers' and parents' wellbeing, etc.
- MS should consider creating a COVID-19 Vaccine Communication Working Group to design, help implement and monitor campaigns' impact.
- Communication of the vaccine approval process: EMA's proposal to increase vaccine transparency for COVID-19 vaccines should be used and complemented by the MS' action plan to educate the public about EMA's role in vaccine approval.
- It is key that the campaign understands and exploits social media and mass media communication tools to reach undecided groups.
- Having a robust, informative campaign is vital to avoid situations in which vaccination has to be made compulsory.
- The use of surveys, social media reports, and mass media impact assessments to evaluate the effectiveness of the communication strategy and react to emerging needs is essential.

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Index of Abbreviations

AMC	Advance Market Commitments
APA	Advance Purchase Agreement
BBMAC	Benefit Based Advanced Market Commitment
CDC	Centers for Disease Control and Prevention
ChAd	Chimpanzee Adenovirus
EC	European Commission
EMA	European Medicines Agency
ESI	Emergency Support Instruments
EU	European Union
EUA	Emergency Use Authorization
EUnetHTA	European Network for Health Technology Assessment
FDA	Food and Drug Administration
GDP	Gross Domestic Product
HTA	Health Technology Assessment
IM	Intramuscular
IMF	International Monetary Fund
LICs	Low-Income Countries
MA	Minimum Acceptable
MS	Member States
NIAID	National Institute of Allergy and Infectious Diseases (US)
NPI	Non-Pharmaceutical Interventions
OECD	Organisation for Economic Co-operation and Development
SC	Steering Committee
TPP	Target Product Profile
WHO	World Health Organisation

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