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Building a coronavirus vaccine portfolio: which governments made the right move?

Analysis and comparison of a panel of vaccine portfolios

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Abstract

In the current pandemic context, where an unprecedented mass of information is circulating in the media, it seemed relevant to analyze the composition of vaccine portfolios built by different countries to fight against the coronavirus. In this article, we explain that governments have an interest in having a balanced portfolio to mitigate risks related to clinical results, delays in production and delivery of doses, being major issues for the good deployment of vaccination campaigns.

From the review of the state of the art on the main vaccines developed to prevent Covid-19, we highlight two technologies that appear to be the most promising in many regards: messenger RNA and inactivated virus.

A systematic approach to scientific, logistical, economic, and social criteria is used to score the vaccine portfolio of each country or set of countries. Results show that the United Kingdom clearly stands out from the pack, thanks to a diversified strategy, speed of execution in negotiations, and a high number of doses ordered per capita. The solidarity of European governments, which have entrusted the European Commission with responsibility for health via the EMA, and the speed with which manufacturers of all sizes have enabled an accelerated development by multiplying partnerships and working closely with regulatory agencies, appear to us to be positive signals that could give the pharmaceutical industry the rightful credit for resolving an unprecedented health crisis.

Understanding the vaccine technologies available to prevent Covid-19

What are the different vaccine technologies?

INACTIVATED VIRUS VACCINE

These vaccines contain the viruses that cause the targeted disease. This is an established approach used in many proven vaccines: influenza, chickenpox, hepatitis A, polio, measles-mumps-rubella. In these vaccines, the virus is inactivated by chemical treatment, thus losing its ability to replicate in the body. The advantage is that the vaccine contains a wide variety of antigens. A disadvantage is that accurate testing of the inactivation is essential to ensure batch safety. *Covid-19: vaccines developed by Sinopharm (CN), Sinovac (CN), Bharat Biotech (IN), Valneva/Dynavax (FR/US)…*

MESSENGER RNA VACCINE

This type of vaccine requires the production of a piece of genetic material that is essential for recognition by the immune system. The identity card of the virus (strand of messenger RNA or mRNA) is synthesized and then encapsulated to allow its migration to the cytoplasm of the target cells. Its translation by ribosomes generates copies of the key protein of the virus (so called spike). The viral proteins are then detected, triggering the immune response. This technology is already used for veterinary vaccines but is new for humans: no human vaccine on the market has yet used this technique. *Covid-19: vaccines developed by Moderna (US), BioNTech/Pfizer (DE/US), CureVac (DE), Sanofi/Translate Bio (FR/US)…*

VIRAL VECTOR VACCINE

Widely used in gene therapy, these vaccines contain viral vectors different from those that cause the targeted disease. For example, the DNA of an adenovirus has been genetically modified to produce the spike proteins of Sars-CoV-2 in the body. These viral vectors are weakened so that they do not cause deleterious infection. There are two types: those that retain the ability to replicate in the cells of the vaccinated organism and those that have lost the ability to replicate because of the inactivation of certain key genes. *Covid-19: vaccines developed by Oxford/AstraZeneca (UK/SE), Johnson&Johnson/Janssen (US), Gamaleya (RU), CanSino (CN)…*

PROTEIN VACCINE

These vaccines contain only protein particles of the virus, which are injected into the body and recognized as an antigen. Many proven vaccines use this technology: influenza, hepatitis B, pertussis, papillomavirus. These non-infectious particles mimic the spike protein or a subunit of it: the cell receptor binding domain. Often, the immune response they provoke is mild, hence the addition of adjuvants consisting of immunostimulatory molecules to improve vaccine efficacy. *Covid-19: vaccines developed by Sanofi/GSK (FR/UK), Novavax (US), Medicago/GSK (CA/UK)…*

Spotlight on a promising technology: mRNA vaccine

The health crisis highlights the unique advantages of mRNA technology over more traditional vaccines. In addition to its efficacy and excellent safety profile, its main strength is its ability to accelerate development. It takes only a few weeks to select an mRNA-based vaccine candidate. Once the virus genome is known, it is possible to identify the proteins of interest, the DNA sequences that code for them, and to produce the corresponding mRNA. This makes it easier to produce on a large scale or to update it to cover new variants compared to more traditional vaccines.

The rapid emergence of this technology, which is still little known to the general public, has raised questions. Although no mRNA vaccine intended for humans has been marketed until now, these vaccines have been used in veterinary medicine for about ten years and,[1] for human medicine, have been tested on large clinical cohorts without giving any pharmacological warning (Zika, influenza, cytomegalovirus...). Today, real-world population data, especially in pioneer countries such as Israel, are very encouraging: they confirm the clinical results obtained in phase III for severe forms, and even indicate the possibility of disrupting the transmission chains related to asymptomatic forms.[2,3]

Logistical constraints will have to be adjusted in the near future: since mRNA is particularly fragile, its preservation at -80°C requires a specific delivery circuit and storage, which is difficult to set up in primary care or in low-income countries. To overcome these challenges, one might consider improving the formulation or even freeze-drying the doses to facilitate storage (as powder). Nevertheless, the major limitation of this technology is it requires cells to produce a single viral protein. In addition to the well-known S-spike protein, Sars-CoV-2 also has a nucleocapsid or N-protein, a membrane or M-protein and an envelope or E-protein. It may then be possible to develop mRNA vaccines that induce cells to produce some or all of these proteins to improve immune coverage in the event of a major spike mutation.

A proven technology for over a century: inactivated virus vaccine

While mRNA technology was particularly emphasized in the media during the health crisis, other vaccines use a technology that has been well proven for over a century. It consists of directly inoculating the virus itself, which has been rendered harmless: this is the use of an inactivated virus. Several candidate vaccines are in the game: three Chinese vaccines (one from Sinovac, two from Sinopharm), an Indian vaccine (Bharat Biotech), and a French-Austrian vaccine (Valneva).

The advantages of inactivated virus vaccines are multiple:

- The inactivation approach enables the immune system to be exposed to all the epitope proteins of the whole virus. One promising example is the Chinese company Sinovac's vaccine, which has already been administered to hundreds of thousands of people in China and in countries such as Brazil. The company says it is also effective against the South African variant, although the results have not yet been published in a peer reviewed journal. Valneva

is the only western company to offer a whole inactivated virus vaccine. To stimulate the immune response, Valneva's vaccine uses the CpG adjuvant through a collaboration with the US company Dynavax.[4,5]

- As the industrial know-how has been mastered by many players for decades, technology transfers could be rapidly implemented on a large scale to considerably increase global production capacities, including in developing countries. Moreover, the simplicity of storage conditions for an inactivated virus greatly facilitates delivery logistics (positive cold).[6]
- Finally, to address the emergence of new resistant variants, the robustness of this technology makes it straightforward to produce multivalent vaccines, i.e. combining several virus strains in a single injection, as is already the case for the winter flu vaccine. If Covid-19 persists on a seasonal basis, an important element will be the ease of producing updates for these multivalent vaccines

Analysis of building a vaccine portfolio against Covid-19

Today, building a portfolio involves high-risk negotiations since pre-orders come prior to final clinical results and large-scale industrial proofs of concept. Some governments have based their approach on price (European Commission), while others have not hesitated to pay a higher price in exchange for priority delivery or have agreed to share their population-level data (Israel). To be on the safe side, some countries have built a balanced portfolio, mixing highly mastered technologies with more innovative ones. Finally, the location of industrial production facilities has also been an important factor for governments when signing pre-orders.

To determine the best portfolio strategies, we analyzed the approaches of several countries based on two factors. The first one is relative to the technologies in each portfolio. The second factor, independent of the technologies, assesses each vaccine strategy. A country's combined score is the product of these two factors. Thus, each country or group of countries is assigned a score that is higher according to the relevance of its portfolio and the feasibility of its vaccine strategy.

The analysis is limited to countries where enough data are available, particularly the number of doses secured by governments.[7] Due to a lack of openness from some countries (e.g., not disclosing the number of doses produced locally), the study focuses on the following selection: United Kingdom, European Commission, United States, Japan, Israel, Canada, and Australia.

CRITERIA OF ANALYSIS

Each of the two factors described above is derived from the scoring of selected criteria (see appendices). Tables 1 and 2 represent criteria scores used for calculating the factor associated with the technologies that make up the portfolios, and the factor related to the vaccine strategy.

The darkest color indicates the highest score 1 2 3 4

Criteria per technology	Weighting of the criteria	Viral vector	mRNA	Inactivated virus	Protein
Efficacy	*4*				
Population subgroups	*1*				
Safety	*3*				
Logistic	*2*				
Price	*1*				
Ease of manufacturing	*1*				
Production capacity	*3*				
Speed to market	*2*				
Adaptation to variants	*3*				
Seasonality	*3*				

Table 1: Rating of vaccine technologies, details of criteria

Criteria per country	UK	EC	US	JP	CA	AU	IL
Speed / reactivity							
Industrial independence							
Risk diversification							

Table 2: Rating of vaccine strategy readiness, details of criteria

VACCINE PORTFOLIO SCORES

A country vaccine portfolio score is based on the multiplication of two factors:

- "Technology" factor, calculated via the evaluation of its underlying technologies in proportion to the number of doses per technology.
- "Strategy" factor, determined by the speed of negotiations, responsiveness of regulatory agencies, industrial sovereignty in dose production, and diversification of the portfolio vaccines to minimize risk.

Multiplying these two factors gives the score for the country-specific vaccine portfolio. Table 3 shows the score for each factor (below 1) and the combined score (out of 5).

Country	"Technology" Factor	"Strategy" Factor	Combined Score
UK	0,698	0,917	3,20
US	0,691	0,833	2,88
EC	0,701	0,667	2,34
AU	0,678	0,667	2,26
CA	0,699	0,583	2,04
IL	0,697	0,583	2,03
JP	0,693	0,333	1,16

Table 3: "Technology" factor related to the technologies used, "strategy" factor related to each government vaccine strategies and combined score out of 5

PORTFOLIO ANALYSIS

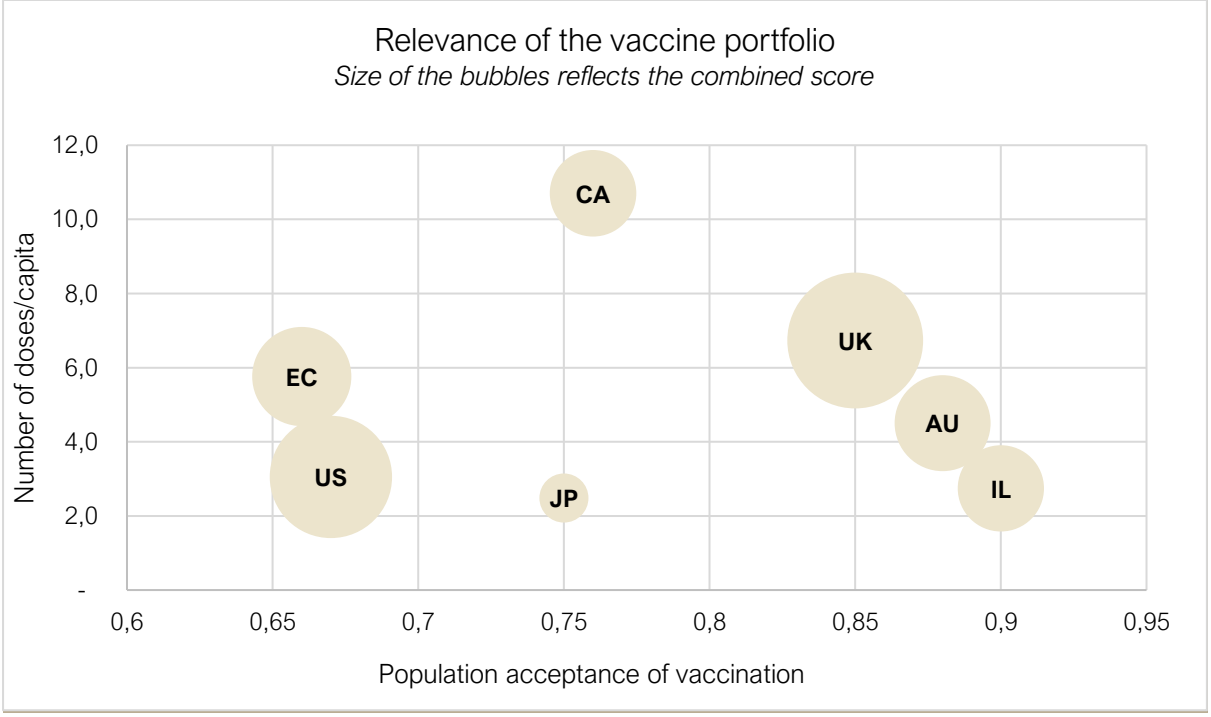

Figure 1: Positioning of countries according to their number of doses per capita (y axis) and vaccination acceptance (x axis)

To correctly interpret the combined score attributed to the countries vaccine portfolios, two elements should be considered: (i) the authors have made certain simplifying assumptions*, (ii) the rating criteria - of course open to criticism - aim at a certain degree of objectivity.

The United Kingdom scores highest, as a result of its diversified portfolio (including inactivated viruses), fast response to pre-orders, rapid approval by the health authorities (MHRA), and manufacturing sovereignty (notably AstraZeneca/Oxford's vaccine production site in Wales and

*No differentiation across vaccines of a given technology; inactivated virus technology is mainly used in the developing world thereby not addressed in this analysis; no protein vaccine has yet been approved against coronavirus by any regulatory agencies; and the emergence of new viral strains could disrupt efficacy assessed in the initial clinical trials.

Valneva's vaccine production in Scotland). This last criterion is also emphasized in the objectives of the UK Vaccine Taskforce, which include support for the UK's industrial independence.[8]

The United States has the second highest score, which is explained by a massive funding of more than $10 billion to accelerate the development of vaccine candidates and the pace of portfolio building (Operation Warp Speed).[9,10] With this balanced portfolio, they are leveraging both adenovirus and mRNA technology and securing a significant number of doses from in-house US pharmaceutical companies.

The European Commission (EC) and Israel obtain similar scores, but with very distinct strategies: Europe has a more diversified portfolio and allows the production of several vaccines on its territory, whereas Israeli authorities have been more reactive and quicker in their negotiations. Although the number of doses per capita is lower in Israel, population needs are nonetheless covered; thanks to an exceptional responsiveness and a well-received campaign, the population is more prone to be vaccinated than in Europe, which contributes to the success of the vaccination rollout. With a higher expected number of doses per capita, the EU population is less likely to be vaccinated against Covid-19. The relevance of securing so many doses per capita in this context may be questioned, although the issue must be tempered: the European Union represents a group of countries, each with its own specificities.

To date, Australia has entered into 4 agreements for the supply of vaccines. Notably, Australia is the only country in the study that has not signed an agreement with Moderna, which drastically reduces its proportion of mRNA vaccines. Whilst Australia is diversifying the technologies in its portfolio, some would question the choice of relying on the Oxford/AstraZeneca vaccine for almost half of its supply, given its lower efficacy than Moderna and BioNTech/Pfizer vaccines. Its membership in the Commonwealth may be part of the answer. Despite the lack of agreements with some leading manufacturers, Australia remains well on track in the vaccine race since the country is able to produce some of its doses locally.

Canada is a special case, as it stands out for its number of doses per capita (> 10, the world record). It is also the only G7 country to receive doses through the COVAX.[11] While its portfolio is diverse, including 3 out of the 4 technologies, the government has been slow to negotiate, which reduces its score. However, Canada wants to increase domestic vaccine manufacturing and work closely with the EMA to speed up the approval process.[12]

Japan has the lowest score. The slow response of the authorities to the epidemic is above all political and can be explained by the priority given to the Olympic Games, giving the impression that the situation is under control, far from reality and favoring the spread of the virus.[13,14] In addition, regulatory requirements such as local clinical trials delay vaccine approval. To reach a sufficient production volume and guarantee supply, the use of external manufacturers (CDMO) and technology transfers will be necessary.

Conclusion and outlook

The construction of vaccine portfolios involves many criteria. Although scientific and economic criteria (clinical evidence, price per immunization, etc.) are the most pragmatic, geopolitical aspects (influence in the vaccine race, domestic production sites) and interests among governments interfere with the rational construction of portfolios. Unfortunately, the geographic distribution of doses is seemingly not based on practical calculations, but rather on diplomatic preferences often known as "vaccine diplomacy".[15] This reveals existing geopolitical divisions. Should not states put aside their national interests and join forces in a global fight against the pandemic? This would imply several actions:

- Removing dose ordering barriers for low-income countries; the WHO COVAX initiative is a step in this direction but needs to be scaled up.
- Encouraging technology transfers while maintaining patent protection to ensure that innovation is not hindered; collaborations have been set up to mass-produce doses, such as the agreements concluded by Sanofi with Janssen and Pfizer or those between Novartis, Bayer and CureVac.[16]
- Freeing up regulatory constraints; an example could be the EMA and FDA evaluation of the clinical outcomes from the Russian vaccine.
- Overcoming cultural biases; the fear of Chinese vaccines is not based on scientific evidence but results from a technical and historical mistrust that is no longer relevant nowadays.[17]

In addition, the Covid-19 crisis has given the pharmaceutical industry the opportunity to restore its public image, often affected by health scandals. The race for vaccines has favored the emergence of unprecedented partnerships between major pharmaceutical groups (e.g. Sanofi-GSK alliance) while highlighting the remarkable innovation engines of biotech companies (e.g. Moderna, BioNTech, CureVac, Novavax, Valneva...).

However, fighting the Covid-19 pandemic also raises multiple ethical challenges. For instance, the British government wishes to organize a *Human Challenge*, a clinical trial in which young healthy volunteers accept a direct inoculation of the virus to assess the effectiveness of vaccines. Although this initiative would accelerate clinical development, it nevertheless raises obvious questions of scientific relevance and, above all, of ethics. Similarly, administering a placebo to large cohorts of patients in Phase III clinical trials also brings up an ethical issue at a time when approved vaccines are available around the world.

Finally, while we have chosen to focus this study on vaccine portfolios, we have not forgotten the importance of developing an effective therapeutic arsenal to address the disease: many treatments are showing encouraging results.[18,19]

Appendices

Criteria per technology	Comment
Efficacy	This efficacy rate is based on the number of people who contract the disease among those vaccinated, compared to a group that received a placebo. This average efficacy rate varies between 50 and 94.5% depending on the technologies selected. Efficacy may also vary with new variants of the virus. According to the American Journal of Preventive Medicine, vaccine efficacy will need to be at least 60% to stop the current epidemic if 100% of the population is vaccinated. If vaccination coverage is limited to 75%, vaccine effectiveness will need to reach 80%.
Population subgroups	Certain categories of population may be excluded from vaccination (children, over 65 years old, pregnant women...) depending on the clinical results obtained.
Safety	Some technologies generate more significant side effects than others. The dosage of the vaccine evaluated in phase I clinical trials allows this criterion to be assessed.
Logistic	Delivery and storage conditions vary according to the technology. Some require being transported by cooled trucks and stored at -80°C, which implies complex logistics and storage in super freezers. Others are easier to store (positive cold and traditional refrigerator).
Price	The price per dose varies depending on the technology. The most innovative technologies often involve additional costs and heavy investments.
Ease of manufacturing	Manufacturing a vaccine consists of two main steps: the production of the active substance (antigen bulk) and the pharmaceutical production (fill/finish). Depending on the type of technology, production times differ. These two main production processes are not always carried out by the same players or on the same industrial sites. The speed of production (lead time) will depend on production capacity, the supply of raw materials, test reagents and any adjuvants.
Production capacity	The context leads to an accelerated development and an increase in dose production on an unprecedented scale. The major challenge of this race to mass production will depend on a successful coordination between all players involved: CDMO subcontractors, partnerships between manufacturers, technology transfers, guidelines from regulatory bodies, etc.
Speed to market	To get a vaccine to market, it must be licensed by the authorities responsible for the safety of pharmaceutical products. In the case of Covid-19, the development of vaccine candidates has never been so fast, thanks to considerable governments investments, major technological breakthroughs, accelerated administrative procedures, and unique alliances.
Adaptation to variants	Each time Sars-CoV-2 infects an organism, the virus can mutate. While most mutations are harmless, others are more potent. The effectiveness of vaccines is being questioned with the appearance of new, more virulent variants, such as the South African or Brazilian one, even if some pharmacos remain optimistic.
Seasonality	All other human coronaviruses have a seasonal pattern with attenuated transmission during summertime. The long-term effect of seasonality will depend essentially on the level of immunity conferred either by vaccines or by natural infection or cross-immunity with other coronaviruses.

Criteria per country	Comment
Speed / reactivity	The responsiveness of negotiations between manufacturers and governments for the elaboration of a portfolio is often for the purpose of priority delivery, early deployment of the vaccination campaign, and consequently better management of the health crisis.
Industrial independence	In a crisis where the defense of national interests takes primacy over multilateral cooperation, promoting industrial sovereignty leads - at least theoretically - to better control of vaccine supply.
Risk diversification	The balance of a portfolio corresponds to the diversity of vaccine technologies it contains. The more a country focuses on a single technology, the less attractive its portfolio will be, reflecting the high risk involved.
Acceptance of vaccination	Public acceptability is the percentage of the population willing to be vaccinated against Covid-19. The figures used here are from an Ipsos survey.[20]
Number of doses per capita	Clearly, the vaccine portfolio must match the population size of the country. Governments pre-order more doses than their population size to cover all their citizens (e.g. with a two-dose regimen) and to mitigate against possible clinical failure or delays in industrial supply of a particular vaccine.

Explanation of the rationale assumed for each criterion per technology/country

Country	Viral vector	mRNA	Inactivated virus	Protein	"Technology" factor
UK	130	107	100	120	**0,698**
UE	800	1465	0	300	**0,701**
CA	60	120	0	224	**0,699**
US	400	400	0	210	**0,691**
AU	53,8	10	0	51	**0,678**
IL	10	14	0	0	**0,697**
JP	144	170	0	0	**0,693**

Pre-orders by technology as of April 15, 2021, in million doses. Weighted "technology" factor

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