White Paper

Bringing Vaccines To The Population: COVID-19 Vaccines In 2021 And Beyond

Understanding COVID-19 vaccine development now and moving forward

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Introduction

As we look to 2021 and beyond, the COVID-19 pandemic remains an evolving international crisis. Never before has a vaccine been developed so rapidly, and tested at the same time as gathering fundamental virology, immunology and public health knowledge on a virus. The speed at which COVID-19 vaccines are being developed is unprecedented.

In the long-term, there is a hope and expectation of a pandemic slow down; but for life to become more open with a return to pre-COVID-19 'normal', a vaccine, or even multiple vaccines, is necessary. At the time of publication, there are at least 62 vaccines in clinical development or authorized for emergency use[1]. In China and Russia there are COVID-19 vaccines approved for use in certain populations within each country. The UK, EU and US amongst other countries, have approved novel mRNA vaccine by Pfizer-BioNtech and Moderna for emergency use; as well as the AstraZeneca/ University of Oxford in the UK. However, ensuring enough of a local, regional or global population is immune to the COVID-19 virus (SARS-CoV-2) either from vaccination or natural infection so transmission no longer occurs is no easy feat. It will require global collaboration on manufacturing, supply logistics, regional vaccination programs and more.

This report is a snapshot into understanding the fundamentals of SARS-CoV-2 immunity, the vaccine development journey so far, and where we hope to move forward.

Understanding immunity for SARS-CoV-2

A vaccine's primary goal is to mimic a natural infection, without causing illness, in order to create an immune response and immune system memory that will result in protection against infection and/ or development of illness should an individual be exposed to the true infection. With SARS-CoV-2, we are only beginning to understand the immune response and the variation between individuals. At this time, there are over 85,000 papers published on SARS-CoV-2, with ~5, 500 on COVID-19 vaccines[2]. But with different schools of thought across publications, there is limited information that can be stated with absolute authority.

For vaccine development, the response of the adaptive immune response is most crucial to understand as it involves the production of virus specific neutralizing antibodies and immune memory.

As primary defence, the innate immune response recognises the virus (attenuated virus, viral peptide/ proteins or viral vectors) triggering an inflammatory response and facilitating the adaptive immune response.

THE ADAPTIVE IMMUNE RESPONSE TO SARS-CoV-2

In short, SARS-CoV-2 infection elicits a specific adaptive immune response characterized by a strong T-cell activation and B-cell development (and the associated virus-specific antibody production).

Adaptive immune response is driven by two types of lymphocyte populations (white blood cells), namely T-cells (from the thymus) and B-cells (from the bone marrow). After SARS-CoV-2 is endocytosed and processed antigen-presenting cells (predominantly

dendritic cells) present virus derived peptides at their surface to T-cells. Antigen-specific T-Helper cells undergo clonal expansion and prime T-Cytotoxic cells to destroy SARS-CoV-2 infected host cells and trigger B-Cells to differentiate and secrete antibodies to neutralize the virus itself.

One of the features of SARS-CoV-2 virus molecular structure is the presence of Spike (S) trimer at its surface which includes a Receptor Binding Domain (RBD) that binds to Angiotensin Converting Enzyme 2 (ACE2) receptor on host cells to enter them. Either the RBD or other adjacent protein structures on the Spike can be bound by neutralizing antibodies and block the virus entry to host cells.

The antibody response is the most efficient at firstly clearing and secondly preventing infection via B-cell memory. However, there is not yet clear evidence whether the neutralizing antibody response against SARS-CoV-2 declines or is sustained over time and providing protective immunity. Levels of neutralizing antibodies can also be influenced by prolonged virus antigen availability. Better understanding of the immune response against natural SARS-CoV-2 infection can help the design and the development of better vaccines to generate a long-lasting protection to subsequent infection.

INNATE IMMUNITY

Also known as natural immunity or non-specific immune response, driven by monocytes, macrophages, dendritic cells, NK-cells. This is the first line of defence, sensing of danger signals from foreign cells or infectious agent (such as SARS-CoV-2) produce signals to drive initiation of adaptive response

ADAPTIVE IMMUNITY

Also known as acquired immunity, responds to specific infection through antigen-specific effector cells and generates memory to enable rapid response to subsequent infection

- **B-cells:** secrete antibodies IgA, IgM and IgG to neutralize an infection (important for vaccine immunity to SARS-CoV-2)
- **T-cells:** T-helper cells produce inflammatory cytokines and can provide direct help to B cells during antibody maturation towards high affinity neutralizing antibodies. T-cytotoxic (Killer) cells destroy virus infected host cells
- It is important to note, that severe disease is characterized by an unregulated inflammatory response or a cytokine storm, where tissue damage is mediated by host immune response rather than the virus

Several questions remain unanswered

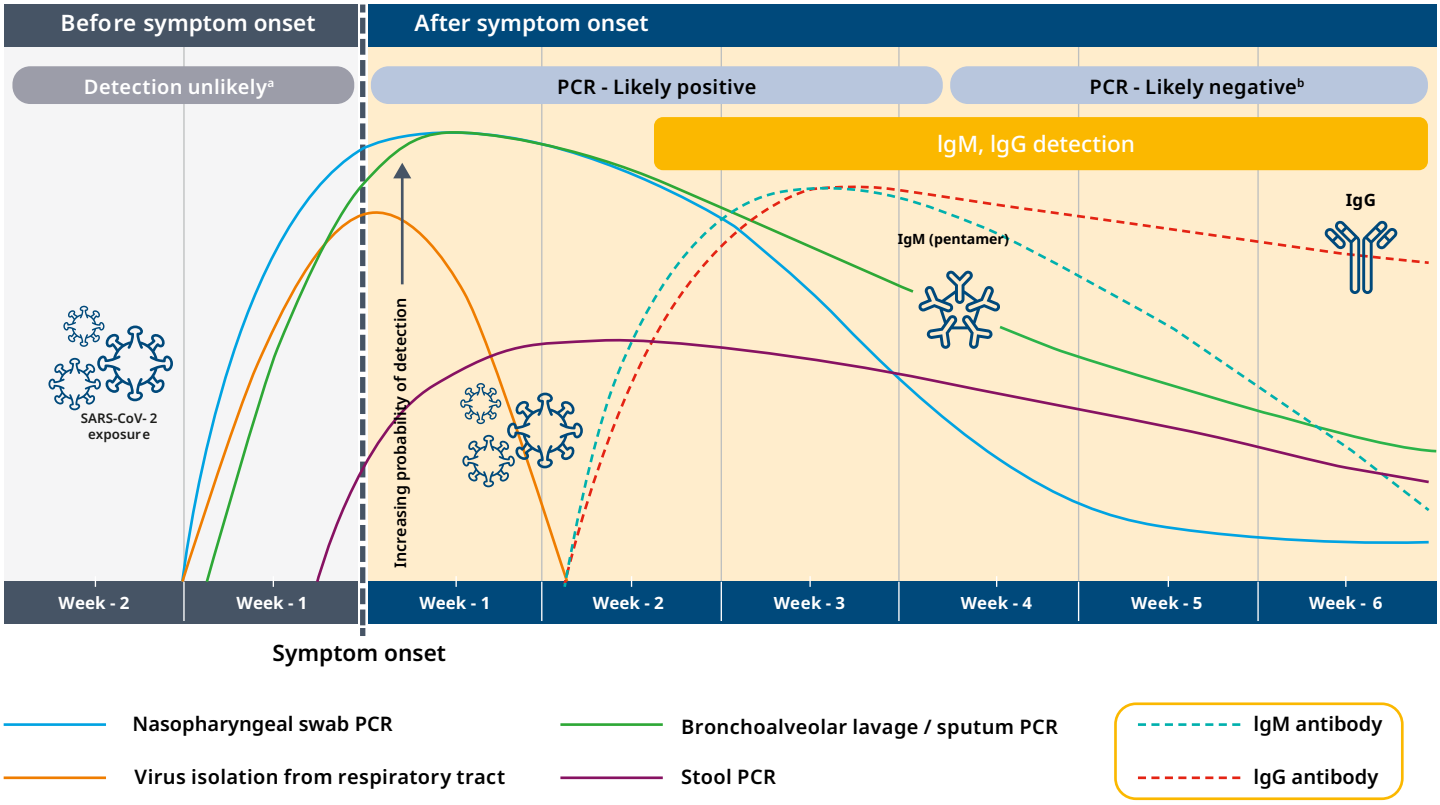
Will protective antibodies generated through natural infection persist over 1 year in asymptomatic and symptomatic convalescent patients?

Can memory T- and B-cells confer protection?

Can vaccination be beneficial to previously infected people?

Will current vaccines protect against SARS-CoV-2 variants, such as the UK and South African variants?

Antibody Immune Response to SARS-CoV-2



Source: Adapted from Sethuramane et al. JAMA: https://jamanetwork.com/journals/jama/fullarticle/2765837

Where the SARS-CoV-2 vaccines are today

The development of SARS-CoV-2 vaccines are moving at 'warp speed' for vaccine development. Preliminary Phase III results released from Pfizer/BioNTech and Moderna for their mRNA vaccines are promising, and emergency authorization use (EUA) has been issued in the UK, US and EU in late 2020/early 2021, only 11-13 months since the SARS-CoV-2 virus genome was identified.

EXPEDITED CLINICAL TRIAL TIMELINES IN SARS-CoV-2 VACCINE DEVELOPMENT

The accelerated vaccine development timeline has been driven by several key factors:

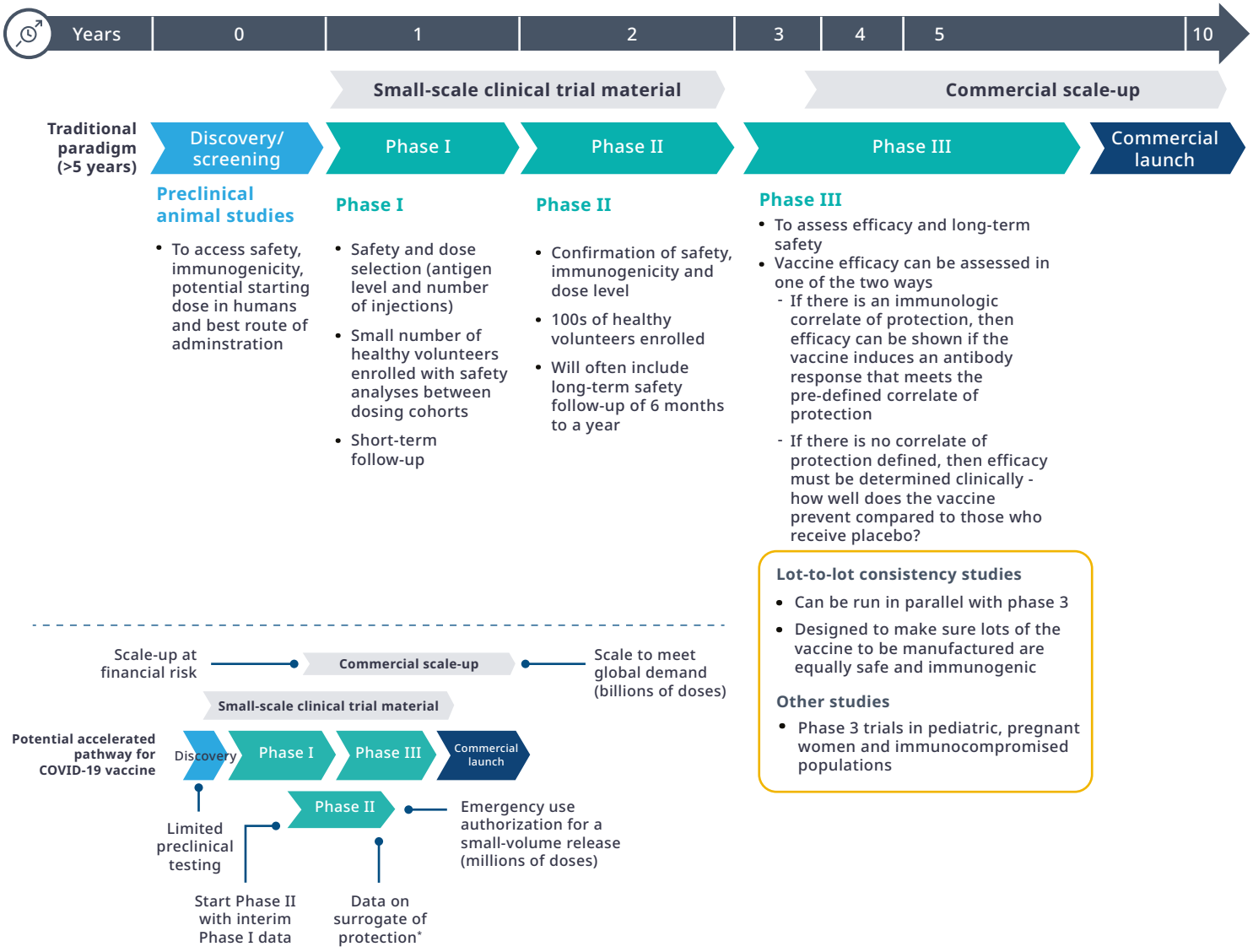
1. Global research effort has been pivoted to single focus on understanding SARS-CoV-2 and considerations for vaccine design
2. mRNA designs are the current front-runners in COVID-19 vaccine development, allowing an element of 'plug and play' of strategies used for SARS-CoV-1 (causing severe acute respiratory syndrome, SARS) targeting Spike (S) protein (conserved between the two coronaviruses). This has cut down the research time investment and allowed mRNA vaccine production to enter trials very quickly
3. Clinical trial phases have been combined into seamless trials, reducing the overall cost of vaccine development and speeding up timelines. Assuming the vaccine appears safe from preclinical and Phase I data, it can move forward into the next phase of development in a short period of time

4. Clinical trials (particularly Phase III) may be completed faster during an active pandemic since rate of infection is high (to assess a clinical endpoint for effectiveness) and existing population immunity is low

Typically, vaccine development can take ~10 years from Phase I and II stages, looking at initial safety and immunogenicity data, to Phase III looking at effectiveness of the vaccine, through to commercial launch. Though most recently the Ebola vaccine was approved with 5 to 6 years.

However, an immune correlate of protection (discussed further in "Understanding vaccine effectiveness") is often necessary to continue 'warp speed' vaccine development, in particular if the pandemic slows and there are few clinical cases. Without an immune correlate of protection, efficacy must be established through clinical endpoints – assessing for development of COVID-19 disease after vaccination – and this can slow down a vaccine's launch.

Typical vaccine development timeline



Adapted from BCG analysis; IQVIA expertise

** A surrogate of protection against COVID-19 is yet to be defined, at the time of writing there is no clear marker.*

Case study: Ebola vaccine developed in 5 years[3]

The Ebola vaccine is an example of a recent vaccine developed under expedited timelines.

The first phase 1 trial started in October 2014, releasing data by February 2015. However, the PREVAIL phase III trial (comparing 2 vaccines versus placebo) could not be completed due to waning of the outbreak and absence of clinical cases of Ebola disease.

The Guinea Ring trial (phase III) was the single efficacy licensing trial. 5837 subjects were enrolled between Apr 2015 to Jul 2015.

The first Ebola vaccine, rVSV-ZEBOV (tradename "Ervebo"), was approved by EU 11 Nov 2019 and FDA 19 Dec 2019.

SARS-CoV-2 Vaccine Effectiveness

An effective vaccine safely induces virus-neutralizing antibodies and then induction of memory B cells and T cells. Current vaccine designs have focused on the levels of virus-neutralizing antibodies produced.

VACCINE DEVELOPMENT: THE BASICS

During vaccine development, different categories of data are collected, with two of the key immunologic data points being:

- The amount of antibodies that have been produced in response to the vaccine construct
- Level of T-cell responses

Neutralising antibodies prevent the virus from being able to attach to a target cell. Specifically, the antibodies bind to the RBD which is a key viral domain of the SARS-CoV-2 spike protein and preventing the virus from attaching to the ACE2 receptor. Therefore, a neutralizing antibody assays are a means of assessing vaccine immunogenicity. Phase 1 and 2 trials for all the advanced stage vaccines products demonstrated the stimulation of significant levels of neutralizing antibodies. For comparative purposes the concentrations of the neutralizing antibodies were compared to that found in convalescent patient sera (patients who have recovered from natural infection). In all cases the levels of neutralizing antibodies were equal to or greater than that in a natural infection, which was the justification to initiate phase 3 trials with the vaccines.

IMMUNOGENICITY
the ability to trigger an immune response, both in terms of magnitude and specificity

IMMUNE CORRELATE OF PROTECTION
measurement that correlates with the rate or level of a study clinical end point used to measure vaccine effectiveness in a defined population. Correlate of protection is adequate for efficacy analysis according FDA and EMA.

	FINDINGS
PFIZER RNA VACCINE	• IgG responses: 9.8 - 26.9 • fold Neut: 1.9 - 4.6 fold • T-cell: Th1 > Th 2 • Notes: NA
MODERNA RNA VACCINE	• IgG responses: 5.9 - 17 fold • Neut: 1 - 3.2 fold • T-cell: Th1 > Th 2 • Notes: NA
AZ CHAD VACCINE	• IgG responses: equivalent • Neut: equivalent • T-cell: Th1 • Notes: Boost raises response
NOVAVAX NANOPARTICLE PROTEIN VACCINE	• IgG responses: 5.7 - 7.6 fold • Neut: 3.4 - 4 fold • T-cell: Th1 • Notes: M1 matrix needed to drive response
J&J AD26 VACCINE	• IgG responses: equivalent • Neut: equivalent • T-cell: Th1 and CD8 • Notes: All data from single dose

Table I: Summary of Phase I and II study data

One of the key challenges facing SARS-CoV-2 vaccine development is comparing the induced neutralizing antibody response (for a vaccine, and between vaccines) response. Infectious wild-type virus assays can only be done in a high containment biological safety laboratory (category 3), which are limited throughout the world —and would limit Phase III trial progression. Other assays that could be used include pseudo viruses or viral like particle reporter viruses. The current lack of reference standards for the evaluation of magnitude of neutralizing antibody responses adds challenges for comparative evaluation of vaccines. To address this, the World Health Organization led a collaborative effort with labs around the globe, including Q^2 Solutions, to evaluate standardized panels and evaluations of binding assays and neutralization assays. These panels will aid in the assessment of the immune responses from the current and future trials.

While the primary desire is to license vaccines is based upon efficacy, the use of immunological surrogate correlates of protection may need to be deployed when the incidence of infection starts to drop in the population.

Vaccine effectiveness can be lower in the real population compared to a vaccine efficacy study. As data for SARS-CoV-2 vaccines emerges, there will be clarity on the induced antibody response, and the prolonged level of protection —to understand which, will require an immune correlate of protection.

THE SEARCH FOR AN IMMUNE CORRELATE OF PROTECTION

An immune correlate of protection enables vaccine developers to assess the anticipated efficacy of a vaccine based upon the induction of an immunological response such as neutralizing antibody, T-Cell response or combinations of multiple

immune-markers. Studies using an immune correlate are typically faster, than trials that follow clinical outcomes for those vaccinated with the real vaccine vs. the placebo arm. There is a long history of using immune correlates in vaccine development, for example with the seasonal influenza vaccines or in cases where exposing individuals to the virus would be unethical, such as with the anthrax vaccine.

Currently, there is no immune correlate for SARS-CoV-2 infection as it is a new virus and it will take time to understand at a population level. Vaccine clinical efficacy trials are the most traditional model of establishing an immune correlate of protection. This model is dependent on a high incidence of infection. High quality immunogenicity data from Phase III trials will help determine surrogate efficacy markers that correlate to protection. As the incidence of SARS-CoV-2 infection drops in the population there will be challenges in the utilization of efficacy data for vaccine licensure. In that scenario the use of immune correlates, if they can be established, will be critical.

Other models for finding an immune correlate of protection, include animal models with challenge infections and population studies where there is an evaluation of the infection rates in high risk individuals in the population.

WHAT ELSE CAN IMPACT VACCINE EFFECTIVENESS?

In addition to establishing a standardized assay and finding an immune correlate to measure the magnitude and specificity of immune response, there are other unknown elements that could impact vaccine development and success. These may take months or years to fully understand.

Mechanism of infection
Though there is some understanding, the full mechanism of SARS-CoV-2 infection, and the subsequent immune response, remains unclear

Cross protection
Impact of pre-existing levels of specific or cross protective immunity from other common cold coronaviruses

Environmental factors
Impact of population health and susceptibility of transmission on efficacy of a vaccine

Infection rates and risk of re-exposure
Infection rates and risk of re-exposure whether this makes a difference to overall immunity for an individual or within a geographical area

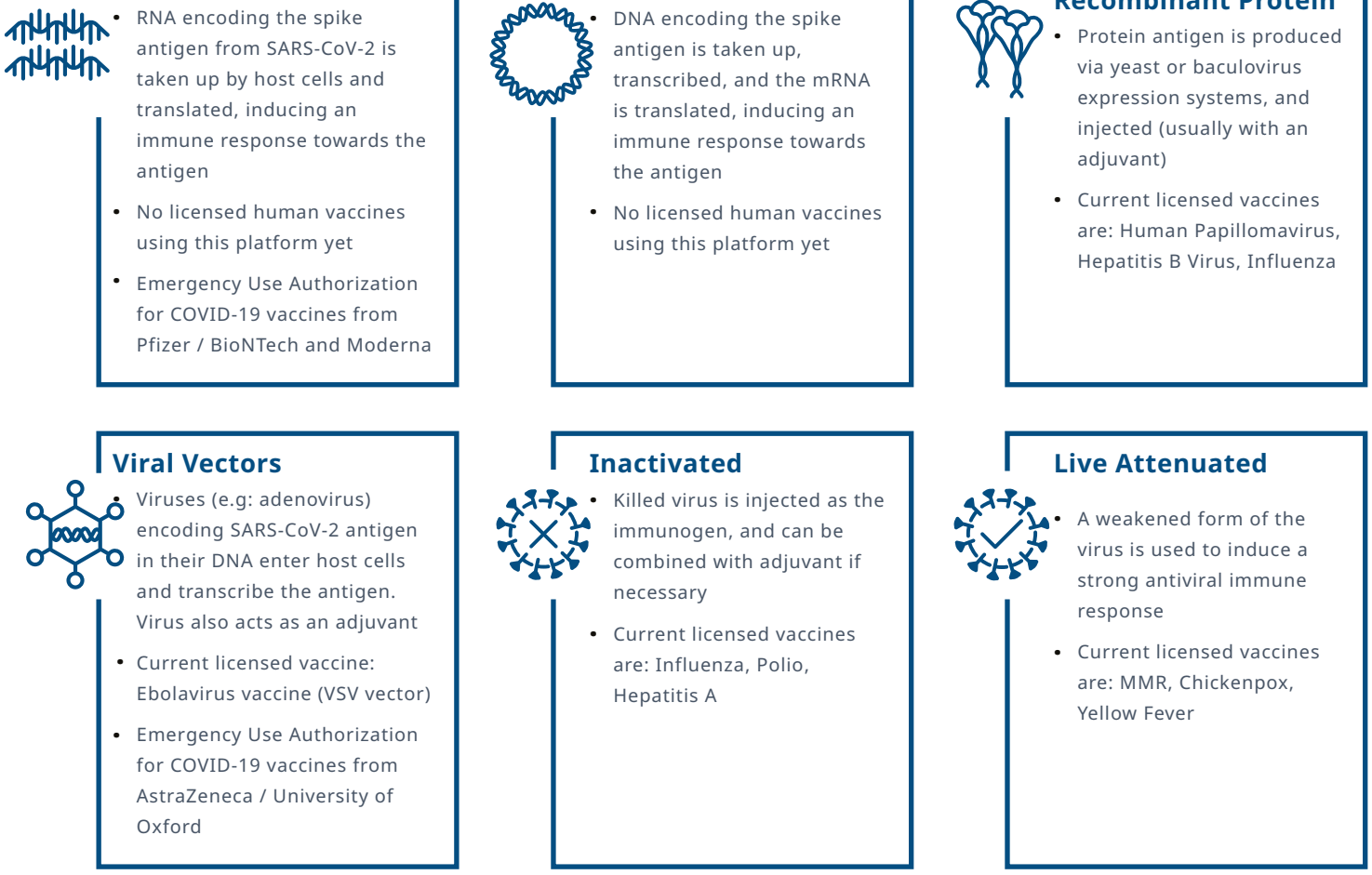
WHY IT'S IMPORTANT TO HAVE MULTIPLE VACCINES IN DEVELOPMENT?

First and foremost, having a number of vaccine formulations, with different viral targets, in development increases the likelihood of producing an effective vaccine. Phase III interim data from Pfizer and Moderna reported their vaccine effectiveness (VE) at between >94% and >95% efficacy respectively —well above the FDA approval threshold of 50% for a COVID-19 vaccine. The vaccine can target either the larger spike protein, or a specific part of it such as the receptor binding domain (RBD). Neutralizing antibodies can target the RBD and adjacent sites, blocking viral entry to the host cell.

However, vaccine effectiveness can vary between populations, age groups or the immunocompromised. As the vaccines are developed, different vaccines may be more suitable for a given group. In addition to VE, it is essential to maintain the variety of vaccine development to:

- Ease of manufacturing, storage and distribution capabilities (in particular, cold-chain logistics, which can increase overall cost significantly)
- Possibility of single injection versus two or more doses
- Ideally no adjuvant needed this can lead to immune problems
- Vaccine coverage for strain variants of SARS-CoV-2 if necessary
- Vaccines that induce prolonged immunity if after the current vaccine front runners fall short in this area after long term analysis
- Low cost we need vaccines that will be able to meet low income needs

Summary of vaccine platforms for COVID-19 vaccine candidates



Source: Adapted from Grigoryan L, Pulendran B. The immunology of SARS-CoV-2 infections and vaccines. Semin Immunol. Aug 2020

Long-term vaccine efficacy and safety

As vaccines are largely given to otherwise healthy individuals, the tolerance for adverse events is understandably low. Longitudinal data will inform dosage and treatment between populations. This is particularly relevant given age and sex factors can influence COVID-19 disease severity and outcome.

Within the industry, there is a significant and suitable amount of caution surrounding the safety of the vaccines in development. Pausing trials due to safety concerns is normal for any clinical trial, and naturally impacts timelines, but taken out of context can cause alarm. As learnings are taken from the past, for example the 1976 swine flu vaccine, the safety of any vaccine is paramount.

With vaccines receiving EUAs or being approved with limited data, post-authorization or post-market safety studies are expected looking forward. PMS studies will be used 2-3 years for:

- Long-term efficacy
- Design alteration following more fundamental research following the Phase III trials and vaccine rollout
- Efficacy between races e.g. Black, Indigenous and people of color (BIPOC)
- Efficacy in sub-groups such as paediatrics, pregnancy, immunocompromised populations, as well as between different age groups. This could also inform dosage in these groups
- Long-term safety, particularly for any adverse events not found in small trial cohorts (relative the general population)

Case study: Swine flu 1976 [4]

On February 4, 1976, a young soldier died of a new form of flu at Fort Dix, New Jersey, U.S. and the U.S. secretary of health, education and welfare, announced that an epidemic of the flu was due in the fall.

The Centers for Disease Control thought the flu was a new, deadly, genetically similar to the 1918 strain, and that 80% of the U.S. population needed to be vaccinated.

Eventually, this was found not to be the case but as a vaccine was expected there was a directive to deliver. October 1976, immunization began and within 10days ~40 million people had received swine flu immunizations.

But the epidemic never occurred and cases were limited to Fort Dix. Unfortunately, some recipients of the vaccine developed Guillain-Barre syndrome, a rare neurological disorder. With intensified surveillance, it was established that the number of cases was in excess of the general population.

What happens next?

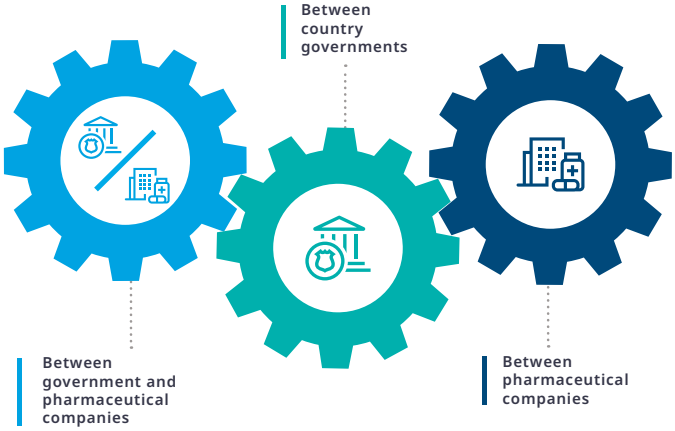
Emergency Use Authorization for the use of SARS-CoV-2 vaccines has been granted late 2020/early 2021, given:

- Threat agent can cause serious and life-threatening disease
- Based on totality of data, it is reasonable to believe that the product may be effective to prevent COVID-19
- The known and potential benefits outweigh the known and potential risks of the product
- There is no adequate, approved, and available alternative to the product

However, as mentioned in previous sections establishing an associated standardized assay and immune correlate is key to maintaining development momentum. Though there is high financial burden and effort in developing multiple vaccines, again as previously discussed, this should also be maintained.

In addition to the development of the vaccine itself, vaccine manufacturing capabilities will need to be increased and safely. Lot-to-lot studies, can be done in conjunction with Phase III to ensure there is safety and immunogenicity consistency with each lot as the primary lot that was used in Phase I, Phase II, Phase III development. There is a large financial expenditure committed in order to develop manufacturing capabilities for each vaccine candidate even before it has been validated for safety and efficacy.

Finally, distribution of the vaccine or multiple vaccines with two doses several weeks apart globally, during a pandemic, will require collaboration between government and pharmaceutical companies, between country governments, and between pharmaceutical companies. In particular, for the cold-chain supply logistics. No single company or single country has the capabilities to do it all.



In closing

Across the industry the progress shown is extremely encouraging and is a credit to the multiple stakeholders —research scientists, governments, pharmaceutical companies, clinical research organizations— who have risen to the challenges this pandemic has raised already. However, SARS-CoV-2 will not disappear even with a successful vaccine, and mask wearing and social distancing are measures that are likely to stay for the foreseeable future. However, a successful vaccine will help pave the way for society return to the 'new normal'.

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IQVIA hosted a webinar in November 2020 “Managing Development of COVID-19 Vaccines in 2021 and Beyond”, bringing together experts from IQVIA and Q^2 Solutions. The resulting discussion and knowledge from the speakers supported the development of this whitepaper.

Appendix

TABLE OF ABBREVIATIONS

ABBREVIATION	EXPLANATION
ACE2	Angiotensin Converting Enzyme 2
IgA, IgM and IgG	Immunoglobulin A, Immunoglobulin M, Immunoglobulin G
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
S	Spike trimer
RBD	Receptor Binding Domain

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IQVIA (NYSE:IQV) is a leading global provider of advanced analytics, technology solutions and clinical research services to the life sciences industry. Formed through the merger of IMS Health and Quintiles, IQVIA applies human data science —leveraging the analytic rigor and clarity of data science to the ever-expanding scope of human science — to enable companies to reimagine and develop new approaches to clinical development and commercialization, speed innovation and accelerate improvements in healthcare outcomes. Powered by the IQVIA CORE™, IQVIA delivers unique and actionable insights at the intersection of large-scale analytics, transformative technology and extensive domain expertise, as well as execution capabilities. With approximately 67,000 employees, IQVIA conducts operations in more than 100 countries.

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