COVID-19 Vaccine Predictions: Using Mathematical Modelling and Expert Opinions to Estimate Timelines and Probabilities of Success of COVID-19 Vaccines

Anthony McDonnell, Robert Van Exan, Steve Lloyd, Laura Subramanian, Kalipso Chalkidou, Adrian La Porta, Jiabin Li, Eddine Maiza, David Reader, Julie Rosenberg, Jack Scannell, Vaughan Thomas, Rebecca Weintraub, and Prashant Yadav

Abstract

We collected publicly available information, interviewed experts, and used our diverse range of expertise to analyse and model the COVID-19 vaccine portfolio. There is significant uncertainty surrounding the development, approval and manufacturing of COVID-19 vaccines. We find that the chances of developing a safe and efficacious vaccine are high but it will not occur in the immediate future, and it is unlikely to be the silver bullet that resolves the pandemic and returns our world to normal. Using inputs generated from expert interviews, our modelling suggests that there is a 50 percent chance that by the end of April 2021 there will be a vaccine safe and efficacious enough to win approval from a stringent regulator; by the end of 2021, this rises to 85 percent. Inputs more optimistic or pessimistic than those we gained through expert interviews lead to very different results.

We also modelled how long it would take to manufacture COVID-19 vaccines once they are approved. Our modelling suggests that it will probably take more than a year to produce enough vaccines to inoculate the world's 50 million medical staff, and that it could be September 2023 before we have enough doses for the whole world. It is not clear that these early vaccines will be efficacious enough to end the COVID-19 crisis. The vast majority of experts we spoke with predict that first-generation vaccines will not be effective enough to end the pandemic on their own, and that it will take longer to develop vaccines that fully prevent infection. This means that the world must be prepared to commit to other public health measures to control the spread of the virus for years, and should invest in a wider, more diversified portfolio of vaccines through better international collaboration and market incentives, as well as focus on diagnostics and treatments. All this while carefully managing the collateral damage from the ongoing policy response.

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Preface

This paper draws together numerous data sources to estimate timelines and probabilities of developing, approving and manufacturing a COVID-19 vaccine. It does this in the context of significant uncertainty through applying well-established methods for combining the limited data we have on past successes and the current state of affairs with expert judgement. To the latter, we provided each of our experts with past data of success for each stage as our baseline estimates and asked them to update these with their subjective knowledge. We then fed this information into a model which runs thousands of simulations of potential futures to provide us with our probabilities of success. This is work in progress: the data are scarce, the experts few and the stakes high. But this is precisely why this work is so important.

Three broad observations and related policy recommendations warrant highlighting here.

1. **A vaccine for COVID-19 will take time to develop, and early vaccines are unlikely to be 100 percent effective or manufactured in large enough numbers for the whole of the world's population in a short time period. Governments and health agencies should plan for a long process dealing with COVID-19 and minimize collateral damage from health and economic shock of the COVID-19 response.**

Our analysis confirms our earlier position that getting to a vaccine is not a linear process. Our analysis suggests that we will get to one or more vaccines, but it will take time and the first vaccines to reach the market are probably not going to be 100 percent effective in protecting everyone from contracting the virus or from experiencing severe symptoms. This means the race to get to a vaccine will be a lengthy one.

During this period, other approaches—such as diagnostics and better treatments—must be pursued. At the same time, disruptions will continue and the policy response must consider the collateral damage of the virus—and the measures taken to tackle—it on human capital and livelihoods. CGD will continue to work on monitoring and estimating the health and economic effects of the outbreak and the reaction to it by governments around the world.

2. **Portfolio diversification is critical and can be encouraged (or stifled) depending on the financial incentives provided by high-income-country payers. We can do better through a performance-linked advance market commitment and more effective international cooperation.**

A diversified portfolio is of the essence. There still is time to improve on diversification and hence on our chances to get to a successful vaccine sooner, despite the fragmented and nationalistic approach to development most countries have adopted. Given our estimates on time to success, we can and should be encouraging the development of a marketplace for new entrants to come in to create a more diverse portfolio in parallel to existing deals tying governments to specific products (not yet developed) or specific manufacturing platforms. Through market creation linked to performance, national payers can act now to encourage the diversification needed to maximise the chances of succeeding sooner and for more people. CGD will continue to work with payers, development partners, multinational development banks and industry towards better

ways for underwriting future commitments linked to product performance, so that risk is shared between developers and payers and more middle-income countries as well as private investors engage in financing and shaping development.

We should also revisit the importance of international cooperation going beyond national borders. This is not to deny the tradeoffs inherent in choices between vaccinating a wealthy country's whole population versus exporting doses to other nations (rich or poor) in need after a country's key populations have been vaccinated. But in the medium term, collaboration outweighs the short-term gains of nationalistic tendencies and competition.

3. **Our tool is a work in progress. It is not meant to provide answers with certainty but rather to help us understand the uncertainty and time horizons, and to provide input in further modelling and assessments of procurement, pricing, and roll out globally and regionally.**

Our tool is a public good created thanks to large numbers of colleagues volunteering their time and expertise from diverse backgrounds. It remains a work in progress. We would like for it to be improved on (and for this we are making the code available) and updated as new information becomes available. It does not seek to offer definitive answers but rather, given the significant uncertainty, get us some way towards a better understanding of the multiple factors driving R&D in the current circumstances.

In addition to helping policymakers with future planning and emphasizing the importance of portfolio diversification, we hope this tool will also provide input in early health technology assessments of vaccines and in scenario analysis to inform procurement and pricing negotiations as well as distribution planning, in countries around the world.

The most important takeaways from this work are not the probabilities of success and manufacturing scale up for the different vaccine candidates, which are inevitably uncertain and will change as new data become available. Instead, the most important takeaways are about the importance of portfolio diversification, (self-interested) global cooperation, and maturity of policy response to deal with a threat that will not go away in the next few months but that is (and will be) taking a dramatic toll on people's livelihoods apart from the direct impacts of the virus.

Kalipso Chalkidou

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Executive Summary

Given the devastating health and economic consequences of the COVID-19 pandemic, global interest in a vaccine is intense. Vaccine candidate development for COVID-19 is progressing faster than for any other pathogen in history, with unprecedented levels of global collaboration and investment. However, independent projections of when an effective vaccine might be fully approved and available are scarce. Most forecasts come from governments or the companies running the vaccine trials—all parties with strong incentives to show they are making progress.

Because no one can know ahead of time whether vaccine research and development (R&D) will be successful, the best projections are both (a) probabilistic, and (b) based on pooling opinions from many experts with diverse interests. This paper seeks to inform decision-making by public and private sector decision-makers as well as by individuals by making such projections. It projects probabilistically how long it will take before COVID-19 vaccines are likely to receive full approval from a stringent regulator (as defined by the World Health Organization) and how long it will take before sufficient quantities of vaccine can be manufactured to immunize healthcare workers, then those over 65, then younger individuals with co-morbidities, and finally the wider population.

We believe that formal models of the COVID-19 pipeline can improve vaccine portfolio management, vaccine deployment, and policy development around the availability, or not, of COVID-19 vaccines. However, the models are just that: models. They may fail to capture important features of the world. They may also make the wrong assumptions about the features they do capture. We therefore encourage readers and researchers to help us improve the tools and the assumptions over time, so that important decisions are made with the best available data and the best available synthesis of the data.

Data Collection

The data for the study come from several sources. One is a master data file compiled from information on COVID-19 vaccine candidates in the public domain and data from the London School of Hygiene and Tropical Medicine. It includes information on the funding of each vaccine, provided by Policy Cures Research and through extensive online searches.

In addition to the master data file, we solicited the views of vaccine experts and manufacturers about how COVID-19 clinical trials and manufacturing are likely to unfold. For the R&D model, we conducted structured one-hour interviews with 16 experts on the probability of success (PoS) of each COVID-19 vaccine technology platform (i.e., inactivated, live attenuated, protein subunit, RNA, DNA vaccines, etc.) at each clinical trial phase (phase 1, phase 2, phase 3); how it might vary by company type and level of external funding; and other considerations about COVID-19 vaccines,

including efficacy (i.e., percentage reduction in risk of infection[1]) and duration of immunity. Respondents' estimates for each vaccine platform depended primarily on their predictions of safety and efficacy performance in large-scale phase 3 clinical trials. This is a smaller number of experts than we would have liked to have interviewed; so again, we highlight here this is work in progress and can and should be improved, especially as more information becomes available to update the model's inputs.

For the manufacturing scale-up and capacity models, we used results from the Coalition for Epidemic Preparedness Innovations (CEPI), which surveyed 113 drug substance and product manufacturers about their estimated available capacity for the fourth quarter of 2020 and all of 2021. We also conducted our own detailed analysis of the manufacturing requirements and techniques for each platform.

Modelling Methodology

We used the data inputs to develop three models, on R&D, manufacturing scale up, and manufacturing capacity.

The R&D model predicts when a COVID-19 vaccine might be fully approved (defined as granting of Market Authorization, or Market Authorization with conditions, by a stringent regulator—excluding any form of Emergency Use Authorization). It includes inputs from the master data file as well as the PoS estimates by the vaccine experts interviewed.

The latter includes experts' predictions for what the COVID-19 vaccine portfolio might look like, including the estimated PoS and timelines for each clinical trial phase (PoS higher than normal for phases 1 and 2, lower than normal for phase 3); the PoS for vaccine candidate platforms; and variations on the PoS by company type and funding level (highest PoS for experienced pharmaceutical company with substantial external funding; low PoS for small biotech firms or academic institutions unless they are either acquired by, or partner with, a larger firm). The R&D model assigns every vaccine candidate a PoS based on its stage of development, funding level and platform, and creates best-, most likely and worst-case timelines for completion of each phase. It then uses Monte Carlo simulations to project which vaccine platforms are likely to be successful and when.

The manufacturing scale-up model calculates the timelines for preparing factories and other infrastructure needed to manufacture approved COVID-19 vaccines. The inputs for this model are based on a detailed analysis of the stages of scale-up into manufacturing for each vaccine platform: process development; design and construction

[1] There are a variety of ways of measuring the efficacy of a vaccine. Here we take efficacy to mean the percentage reduction in the risk of infection, which we assume is the same for both symptomatic and asymptomatic infection, for severe infection, for death from infection, and for the ability to transmit the infection to others.

(including adapting existing facilities); and quality assurance/regulatory activities. Probabilistic ranges of time are assigned to each stage.

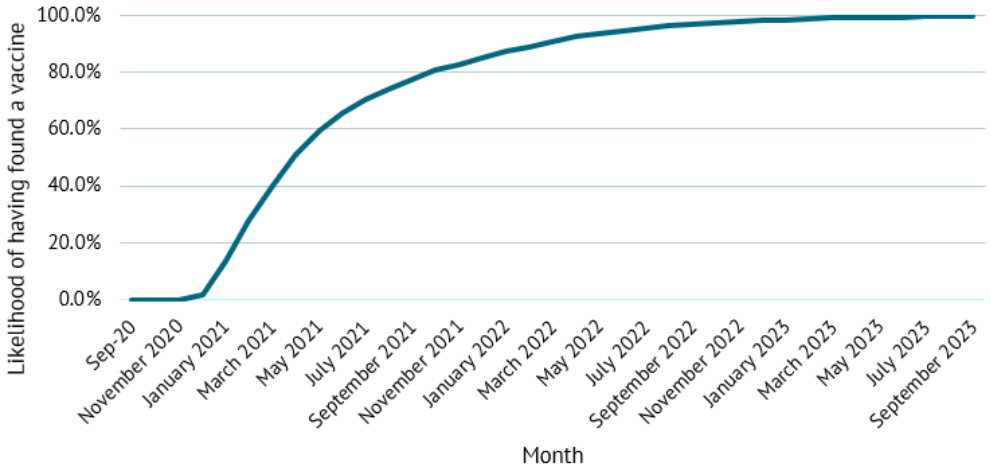
The manufacturing capacity model projects how long it will take to manufacture enough COVID-19 vaccine doses to meet the needs of priority target populations identified by the World Health Organization (first healthcare workers, then people over 65, then younger people with comorbidities) and the population at large. This model uses results from the R&D and manufacturing models, alongside estimates of global manufacturing capacity from the CEPI, to assign successful vaccines to the available capacity.

We do not, in this set of analyses, try to estimate how much the vaccines will cost and how they can be financed, or how long it will take to distribute and administer the doses to each of the groups and what the best (in terms of lives saved or economic damage prevented) allocation scenarios may be. Further, we do not consider vaccine hesitancy, which will determine vaccine uptake.

Results

Based on the information from the experts interviewed, the model projects the probability that a stringent regulator approves at least one vaccine is less than 2% in 2020, 50% by the end of April 2021, 85% by the end of 2021, and 98% by the end of 2022. Based on the Operation Warp Speed and CEPI portfolios as of September 2020, the model predicts a 78% chance that at least one of the Operation Warp Speed–funded vaccines will succeed and a 67% chance that at least one of the CEPI–funded vaccines will succeed.

Figure ES.1. Projected probability that at least one COVID-19 vaccine is approved, October 2020–September 2023



The model predicts a less than a 1% probability that no vaccine is approved from the current global portfolio, based on the inputs we derived from expert interviews. If, however, we use the more pessimistic inputs from experts, this rises to almost 20%**.** Importantly, the experts did not expect that first-generation vaccines will reduce

individuals' infection risk enough to engender herd immunity and bring the pandemic to an end. Other public health measures will have to continue. Our experts believed that later vaccines will probably be more efficacious than earlier ones and that we will likely not get a vaccine that does everything we need it to. Instead there could be trade-offs between thermostability, better efficacy in the elderly and duration of immunity. To do well on all fronts, we need to aim not just for approving one vaccine quickly, but for multiple vaccines, again highlighting the importance of portfolio diversification.

Our analyses also suggest that manufacturing enough doses will take time. The manufacturing scale-up and capacity models indicate that it will be late 2021 to early 2022 before the world will produce enough COVID-19 vaccine doses for healthcare workers (WHO priority group 1). Sufficient doses for at-risk/vulnerable groups (WHO priority groups 2 and 3) are projected to arrive about two to three months later. The model indicates that it will be at least 35 months from now (September 2023) before there are enough doses to vaccinate the entire global population.

Discussion and Recommendations

Given that it is unlikely we will get a fully effective vaccine developed, licensed and manufactured at scale to serve the needs of the whole world's population in the next twelve months or so, the world must plan to use the other public health measures in our arsenal for managing the outbreak and returning societies to near normality. These include continued investment in non-pharmacological measures such as social distancing, expansion of testing and contact tracing, and pushing for innovations in diagnostics and treatment which could be available sooner than vaccines. Our results highlight the importance of investing in or creating the marketplace for what are likely to be more effective second-generation vaccines (some of which may be in early clinical development now and others yet to be identified and enter development) as these will likely be crucial in eventually ending the pandemic.

The results also indicate the desirability of continuing to invest in a diverse portfolio of COVID-19 vaccines, as researchers do not yet know enough about the SARS-CoV-2 virus to make accurate predictions about which platforms will succeed. Diversification would also make manufacturing enough vaccine doses easier, as multiple approved vaccine products mean that companies could share the burden of producing billions of doses to meet global need. Further, diversification across borders and international cooperation would help ensure equitable vaccine allocation and distribution across countries and risk groups, in the event that specific vaccines are more or less effective for specific populations or initially available in limited quantities.

Operation Warp Speed and CEPI are well positioned in diversification of their vaccine portfolios from a technology standpoint, but there is room for improvement—for example, Operation Warp Speed could invest in inactivated vaccines which could play an important role ensuring sufficient production of vaccine doses given extensive current manufacturing capacity. Indeed, diversification makes sense from a manufacturing perspective—a global portfolio is more robust, risk resilient and efficient in ending the pandemic.

Next Steps

There is a clear need for a global conversation about the probabilities of developing a COVID-19 vaccine (or vaccines) and the likely timeline for manufacturing enough vaccine to substantially mitigate, and perhaps eventually end, the pandemic. This study aims to inform this discussion in a wider forum and to make the risks to vaccine development and manufacturing as clear as possible.

Our models focus on the likelihood and timelines of getting COVID-19 vaccines approved and doses produced. Separate efforts, some ongoing, are needed to plan for optimal vaccine distribution and uptake— key considerations in containing the pandemic. Health systems are not used to running global vaccine programmes for adults, and some of the leading vaccine candidates have challenging storage requirements (i.e., need to be stored in -80 Celsius) which will affect the world's ability to get vaccine doses to the people who need them.

Introduction

Given the devastating health and economic consequences of the COVID-19 pandemic, global interest in a vaccine is intense. Vaccine candidate development for COVID-19 is progressing faster than for any other pathogen in history, with unprecedented levels of global collaboration and investment. Scientific projections of when an effective vaccine might be approved and available are scarce, however, with most information coming from governments and the pharmaceutical industry, both of which have strong incentives to show they are making progress.

Because no one can know ahead of time whether vaccine research and development (R&D) will be successful, the best projections are probabilistic. The goal of this paper is to inform decision-making—by public and private sector decision-makers as well as individuals—by making such projections based on expert predictions.

The paper projects probabilistically how long it will take before COVID-19 vaccines are likely to be approved by a stringent regulator (as defined by the WHO)[2] and how long it will take before sufficient quantities can be manufactured. These projections are based on models that reflect information about the COVID-19 vaccine candidates from publicly available sources and the views of 16 vaccine experts interviewed for this study about various aspects of R&D.

This paper is organized as follows. The first section describes the methodology used to obtain inputs for the R&D and manufacturing models, both objective inputs from publicly available data sources and subjective inputs from interviews with vaccine experts. The second section describes the R&D and manufacturing models. The third section presents results from the expert interviews, followed by results from the R&D and manufacturing models. The fourth section presents policy implications of these results and sets out recommendations. The final section identifies next steps in the research agenda.

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2 The World Health Organization defines a "stringent regulator" as a regulatory authority that is (a) a member of the International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use, a group that includes the European Union, the US Food and Drug Administration, and the Ministry of Health, Labour and Welfare of Japan also represented by the Pharmaceuticals and Medical Devices Agency (as before October 23, 2015); (b) an ICH observer, a group that includes the European Free Trade Association, as represented by Swissmedic, and Health Canada (as before October 23, 2015); or (c) a regulatory authority associated with an ICH member through a legally binding mutual recognition agreement, a group that includes Australia, Iceland, Liechtenstein and Norway (as before 23 October 2015).
https://www.who.int/medicines/regulation/sras/en/#:~:text=The%20concept%20of%20a%20stringent,international%20regulatory%20and%20procurement%20community

Methodology

Collection of Objective Inputs

Objective inputs were collated from publicly available sources. Information on COVID-19 vaccine candidates available in the public domain was collated and used to compile a master data file. The London School of Hygiene and Tropical Medicine (*COVID-19 Vaccine Tracker*, 2020) generously shared the data behind its model with us in June; we updated it regularly, most recently on September 2, 2020.

The LSHTM vaccine tracker[3] is based on the latest pooled information from the WHO's COVID-19 vaccine landscape, the Milken Institute's vaccine tracker[4] and clinicaltrials.gov (a database of privately and publicly funded clinical studies conducted around the world). The master data file contains information on each vaccine candidate, including the vaccine name; platform; sponsoring company/institution; type of company/institution; country; development phase; and clinical trial start and end dates.

We conducted a detailed web search of each candidate and its sponsor company/institution to identify currently licensed human vaccine products; product pipelines; manufacturing facilities and capacity; and strategic partnerships with other entities relating to financing, manufacturing and other technical components, such as adjuvants, stabilizers and delivery technologies. We also read relevant media releases on each candidate.

We collected financial information on each sponsor company/institution in order to classify their size, as we anticipated this might influence likelihood of success. For pharmaceutical companies, we ascertained the company's annual revenues and then broke companies into three groups: large pharma (more than $10 billion in annual revenue), medium pharma ($50 million–$10 billion in annual revenue) and small biotech (less than $50 million in annual revenue).[5]

We also used information from Policy Cures Research (*COVID-19 R&D Tracker – Policy Cures Research*, 2020)[6] on external funding of vaccine candidates and information from on advanced purchase agreements (Callaway, 2020) to further classify vaccine candidates by

3 https://vac-lshtm.shinyapps.io/ncov_vaccine_landscape/

4 https://covid-19tracker.milkeninstitute.org/

5 British American Tobacco and SK Biosciences were treated as medium pharma even though their revenues met the criteria for large pharma, because pharmaceuticals are only a subset of these companies' activities. For 29 of the 153 commercial candidates, it was not possible to ascertain the annual revenue of the company. Where information was available, these candidates were assessed based on market capitalization, with companies with capitalization of more than $250 million classified as medium. All of the companies in North America and Western Europe for which revenue information was not available appear to be very small. Four Chinese, two Russian and one Korean company for which revenues were not available were classified as medium pharma. Academic and state-run institutes without a commercial arm or commercial partner were treated as small biotech firms.

6 https://www.policycuresresearch.org/covid-19-r-d-tracker

external funding level, another factor we anticipated might influence success. Vaccine candidates that had received more than $400 million of external funding or more than 100 million pre-orders were classed as having received "large external funding." Vaccines that received $50–$400 million grants or 10–100 million pre-orders were classified as having received "some external funding" (table 1).

Table 1. Number of vaccine candidates in each funding category

Category	Criteria	Number of candidates	Percent of portfolio
Large external funding	Received over 400 million USD in grant money or 100 million pre-orders	10	4
Some external funding	Received between 50-400 million USD in grant money or 10-100 million pre-orders	5	2
Large pharma	Annual revenue of over 10 billion USD. Not in receipt of external funding or pre-orders	8	3
Medium pharma	Annual revenue of 50 million-10 billion USD. Not in receipt of external funding or pre-orders	34	14
Small biotech/academic institution	Annual revenue of less than 10 million. Not in receipt of external funding or pre-orders	178	76

Note: Categories are mutually exclusive.

To calculate the global capacity for manufacturing vaccines, we collected information from the Coalition for Epidemic Preparedness Innovations (CEPI). In March 2020**,** CEPI sent a survey to all drug substance and drug product manufactures that were likely to have the capacity to manufacture vaccines asking them about their capacity in the fourth quarter of 2020 and all of 2021. A total of 113 manufactures responded (about one in three). These data served as a crucial input into our manufacturing capacity model. We also sent out our own survey to the firms or institutions behind all vaccine candidates. This yielded some useful information about manufacturing processes, but with only seven responses it was not sufficient to capture candidates' manufacturing capacity.

In appendix A we give high-level statistics from analysing the portfolio.

Collection of Subjective Inputs (Views of Vaccine Experts)

To select the key vaccine experts for interviews, we conducted a search of scientific papers on COVID-19 vaccines and contacted the authors. We also asked these experts to identify other high-level experts in their networks whose background, expertise and awareness of the COVID-19 vaccine candidate field would allow them to make informed projections about timelines and probabilities of success (a process known as *snowballing*). Interviewees included experts working in the vaccine industry, academia and regulatory agencies. Eighty experts were contacted as part of this process; 16 of them agreed to participate in one-hour interviews.[7] An overview of the type of people we interviewed is in appendix B.

Interviewers used a structured interview guide (given to the respondents in advance and shown in appendix D) to ask respondents about COVID-19 vaccine development, with most questions designed to elicit quantitative, closed-ended responses. Where possible, we tried to inform questions by giving the respondent historic information or examples (always at least two, so that they had a range), based on the theory that people give more accurate responses when asked to adjust numbers rather than generate new numbers themselves (Kahneman & Lovallo, 1993; Ville Satopää, 2020). Respondents were first asked about the relative difficulty of developing an approvable vaccine for COVID-19 versus other viral pathogens, where 1 was very easy and 10 very difficult. This question was used to sensitize them rather than to be used as a model input. Respondents were then asked to project the length of time required to complete individual trials (preclinical, phases 1–3, regulatory review) for leading COVID-19 vaccine candidates and the probability of moving from one trial phase to the next. They were given historic probabilities of success and timelines to inform their answer (Terry et al., 2018).

For each COVID-19 vaccine platform candidate (table 2), respondents were asked to give a quantitative assessment of the probability of success (PoS) (see appendix F for descriptions of each platform).[8] Because many of these platforms are very new, and funding levels and timeframes are unprecedented, it was initially unclear what reference estimates to use to inform responses. Historical success rates exist for vaccines in aggregate, but we are not aware of any good sources of how they change with vaccine platforms. Even if these aggregate rates did exist for some vaccine platforms, other platforms (such as RNA vaccines) are very new; historical data are therefore not available. We therefore took the following approach. For the first eight interviews, we asked respondents to rate each platform on a 1–10 scale, where 1 is most likely to succeed and 10 least likely to succeed. We then asked them to give a PoS for the riskiest and least risky platforms in phase 3. We used these figures to calculate an implied PoS for the other platforms by assuming that PoS changes linearly with platforms' rank

7 The literature suggests that 16 is sufficient number to capture divergent opinions (Dias et al., 2017).
8 The experts we interviewed also shared important qualitative information on the challenges of discovering and producing vaccines against COVID-19 that we have summarised in a blog.

between the highest and lowest PoS platforms.[9] We also asked candidates for non-platform-specific estimates for COVID-19 vaccines and used these figures to validate the platform numbers this methodology generated, by checking that the number given for the PoS of different candidates going through phase 3 matched the platform-specific numbers.

Table 2. How we categorised COVID-19 vaccine platforms

Platform	Number of candidates	Percentage of portfolio
Protein subunit	92	39.1
RNA	30	12.8
Non-replicating viral vector	29	12.3
DNA	20	8.5
Replicating viral vector	20	8.5
Inactivated	14	6
Other	6	2.6
Live attenuated	4	1.7
Unknown	20	8.5

Note: Vaccines for which we could not determine the platform were not included in the analysis.

After the first eight interviews were complete, we used the mean and range of estimates generated thus far to help subsequent interviewees calibrate their estimates. The reason for this change in approach is that we felt that in the long term it was best to collect

9 Formula is: PoSE = ((PoSB – PoSR)/(InputB – inputR)) * inputE. Where inputs are the numbers we collected for each platform, PoS is the probability of success, where E is the platform we are trying to estimate, B is the score for the platform ranked best and R the platform ranked riskiest or lowest.

information from experts in the same form that we are going to use in our modelling tool.

Two respondents (one from each group of eight) gave qualitative rather than quantitative assessments of the PoS. It was clear from these two responses which platforms these respondents thought most and least likely to succeed, as both gave very detailed responses. These were thus separately coded into scores by two researchers. Both researchers' scores were very similar; they were averaged. We then used the same adjustment technique to convert these into PoS, using the average inputs for riskiest and least risky platforms.

We asked respondents additional questions about the platforms:

- Is any platform significantly more or less likely to succeed?
- Would a scientific success or failure within a platform affect the PoS of other candidates that used the same technology platform?
- How is the organisations' funding category likely to affect the timelines and the PoS?

Finally, we asked respondents to estimate how many vaccine candidates from the current portfolio and in total might be approved and whether it would become easier or more difficult to approve more vaccines after the initial ones were approved. We also asked them to indicate whether and how vaccines might be used before full approval and to provide efficacy projections for leading vaccine candidates.

To check that respondents opinions had not changed between when our interviews took place and the time of publication, we emailed respondents on September 7 with the quantitative inputs (PoS per phase and PoS per platform) and asked if they wanted to update the figures, in the event that new information had become available or that our quantitative derivations did not capture their views.

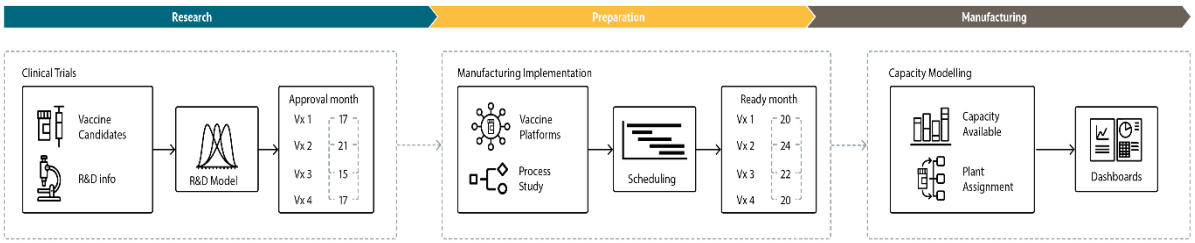
A separate qualitative process was used to generate subjective inputs for the manufacturing models. We spoke to experts at the Institution of Chemical Engineers, the International Society for Pharmaceutical Engineering, CEPI and the Clinton Health Access Initiative and conducted a broad literature review, using our own expertise in order to ascertain and estimates for different parts of the manufacturing process.

The Models

We developed three models. The R&D model was developed to predict probabilistically when COVID-19 vaccines would be approved by a stringent regulator. It includes both objective inputs on the global vaccine portfolio and subjective inputs on R&D PoS, etc., from the expert interviews. The manufacturing scale-up model projects the timelines for preparing factories and infrastructure for manufacturing. The manufacturing capacity model projects how long it will take before enough vaccine is manufactured to reach

medical staff, at-risk groups and the world's population (figure 1) given the constraints imposed by R&D and manufacturing scale up.

Figure 1. Overview of models



Modelling Research and Development Using Monte Carlo Simulations

Estimation of the probability of success in clinical trials has been studied in academic literature (Wong et al. 2019, Lo et al. 2020). Our paper builds on this work by using Monte Carlo simulation to estimate COVID-19 vaccine portfolio's probability of success.

Monte Carlo simulations are a kind of statistical model that apply a set of probabilistic rules (e.g., the odds of a coin toss coming out "heads" or the odds that a given COVID-19 vaccine candidate is successful in phase 3 trials) over and over again to the same starting conditions, to simulate a large number of future outcomes. The simulation could be something simple (e.g., tossing a coin 10 times) but is more often is aimed at understanding a complex relationship (e.g., the evolution of the global COVID-19 vaccine portfolio). By generating a large number of possible futures, each one consistent with what we now believe about the probabilities, one can get a quantitative sense of the kinds of outcomes that are more or less likely. How many times out of 30,000 simulations does one toss 9 or more consecutive heads with the coin? How many times out of 30,000 simulations is one or more COVID-19 vaccine approved before mid-2021? How many times out of 30,000 simulations are no COVID-19 vaccines approved in the next three years?

Monte Carlo simulations are often used for planning purposes and to understand and manage risk (e.g., what should we do now to make the bad outcomes less likely and the good outcomes more likely). They have rarely been used, however, to analyse R&D pipelines for planning and risk management.

Shnaydman and Scannell (Shnaydman & Scannell, 2020) introduced Monte Carlo simulations to the COVID-19 vaccine problem. They simulated the portfolio to illustrate how long it might take before the world had its first vaccine and to explore a range of strategies to minimize the risk of zero vaccine approvals within a given time period. They also argued for risk-mitigation from technical diversification, and how this was undermined by vaccine nationalism, (Scannell & Shnaydman, 2020)However, they did

not have access to vaccine experts to help finetune their modelling. CEPI is also using such simulations to optimize manufacturing capacity for COVID-19 vaccines.

In the R&D model, we use inputs collected on the vaccine's platform, funding and stage of development to project each vaccine's PoS and a range for the time it will take it complete each phase. In each run, the model then randomly decides whether a vaccine succeeds in a phase and precisely how long that phase takes. We collected information on what would happen to the timelines and PoS if a similar candidate succeeded or failed, as well as what would happen to all candidates when vaccines start to be approved. Midway through a run, the model adjusts a vaccine's PoS based on what is happening to other candidates. (For more detail on modelling R&D, see appendix C.)

Modelling Manufacturing

CGD and Ariadne Labs contracted the consulting firm Bryden Wood to model timelines for manufacturing COVID-19 vaccines. Working closely with the rest of the team, Bryden Wood built two models,[10] one to forecast the time it would take to scale up the manufacturing process, and a second to forecast the time it would take to manufacture sufficient doses of vaccine for various priority groups identified by the WHO (first healthcare workers, then those aged over 65, followed by other high-risk individuals, and then all others).

Modelling manufacturing scale-up

The transition from R&D to manufacturing is typically carried out by a large multifunctional team and includes process development activities, design and construction activities, and quality assurance/regulatory activities. Our manufacturing scale-up model is designed to estimate timelines between the completion of research and development and the start of the capacity model.

The model forecasts the time between full vaccine approval and the start of commercial manufacture. A drug substance that has been manufactured for early-stage clinical trials is usually produced at R&D scale (thousands or tens of thousands of doses). Once the drug is approved, manufacturing needs to be scaled up to commercial scale (millions or billions of doses). Under normal circumstances, this process takes several years.

We have broken the transition from R&D to manufacturing down and simplified it to form a series of steps for any vaccine. For each step, we assigned a probabilistic distribution of durations around a value based on experience. The distributions tend to be right skewed (meaning processes sometimes take a lot longer than planned but rarely take much less time than planned), because there are constraints that stop processes being completed more quickly than expected but many potential delays that are without constraints. Importantly for COVID-19 vaccines, we also considered the changes to

10 A copy of the Bryden Wood report is available at https://www.brydenwood.co.uk/projects/modelling-of-manufacturing-covid19-vaccines/s92100/.

normal practice. In particular, scale-up and preparation of manufacturing facilities will start before the vaccine has been approved (such manufacturing is known as "at risk").

Strict regulations to ensure that manufacturing processes and plants meet formal Good Manufacturing Practice[11] guidelines also add time to the transition from R&D to commercial manufacturing. Plant and equipment must be qualified to show that they are suitable for the intended use. All processes must be established to be safe and effective. Data on the product, process and plant must be submitted to regulators in every jurisdiction where the vaccine will be used. Requirements differ across jurisdictions. Regulators can ask for clarifications or improvements, sometimes requiring additional data to be generated or even modifications to plants or process. Intellectual property issues can arise when companies scale up manufacturing using contract manufacturing organisations. This is a particular risk for newer companies with newer manufacturing platforms as they may lack established process for dealing with intellectual property issues with suppliers of clinical material (this has already been a problem for two candidates). All these factors can cause delay.

In addition to the capacity to manufacture the drug product, scale-up requires sufficient quantities of auxiliary supplies, such as vials (or other primary containers), adjuvants, and, in some cases, single-use bioreactors.

Many factors, including the type of vaccine and the dosage form, affect how long each step takes. Through industry expert input, we developed a model to represent each stage of a vaccine's journey. The model incorporates three possibilities: capacity already exists at established manufacturing sites, existing manufacturing capacity requires modification, or build a new factory is required. The model includes all steps of "qualification"—validation and testing processes that ensure that equipment has been installed correctly and will perform as expected under real factory conditions. Individual timings are drawn from plausible ranges/distributions to account for the expected variability.

Modelling manufacturing capacity

To understand when enough vaccines might be produced for various WHO priority groups' needs, we used the CEPI data to build a picture of global manufacturing capacity. This included primary or drug substance capacity (manufacture of the active ingredient or drug substance, for instance inactivated virus or mRNA) and secondary or drug product capacity (manufacture of the dose form or drug product, for instance a packaged vial that contains the liquid solution for injection). We then modelled how different approved vaccines could be allocated to the available manufacturing capacity to predict the production rates and, from there, when the total number of doses produced could meet the WHO targets.

More specifically, each successful vaccine passes through the manufacturing scale-up model to determine a time for the start of primary and secondary manufacture. Vaccines

11 Good Manufacturing Practices are the practices required in order to conform to the guidelines recommended by agencies that regulate pharmaceuticals

are then allocated to platform-relevant available network capacity to project monthly and cumulative dose production. This level of detail may be important, given the possibility that different vaccines can be used for different populations, based on the level of immune response elicited. By comparing these production figures with the WHO targets, the time from the reference point to production milestones can be projected. Appendix G outlines the main assumptions used in the manufacturing model.

Given the pandemic emergency circumstances, and based on public reports and expert input, we assume that COVID-19 vaccine manufacturing scale-up and process development activities began March 1, 2020. We extend this assumption to all vaccine candidates in the manufacturing model. This assumption may be unfounded for less well-funded candidates, but the chances of these candidates reaching the manufacturing stage are already significantly reduced in the R&D model, so this assumption is unlikely to result in the overestimation of the overall timelines for vaccine availability.

Generating Model Inputs from the Expert Interviews

Factors affecting COVID-19 vaccine development

Most experts said that developing a COVID-19 vaccine with currently available knowledge and technology will be less difficult than developing the average vaccine—not as easy as developing vaccines against measles and smallpox but much easier than developing an HIV vaccine. Among the 11 experts who gave a rating, the mean and median ratings were 3.5 on a 1–10 scale (where 1 is the easiest possible pathogen and 10 is most difficult).

Experts noted several characteristics of COVID-19 that would likely help in the development of a vaccine:

- The novel coronavirus is similar to other respiratory viruses with which researchers have experience, such as SARS and MERS.
- The viral spike protein—against which many of the vaccines are targeted—is well understood (from respiratory syncytial virus [RVS], measles, mumps, HIV and influenza).
- The virus seems to have a relatively low mutation rate and relatively low genetic variability, which makes the evolution of vaccine resistance less likely and which tends to increase the time period over which any given vaccine will remain useful.
- Infected people appear to mount a protective immune response and to avoid rapid reinfection.
- Global transmission means that large-scale trials can be quickly conducted.

On the flip side, experts cautioned that other factors could hinder development of a vaccine:

- COVID-19 is a new respiratory virus that is not fully understood. Information about both the pathogen and immunity in natural infection is lacking.

- No coronavirus vaccine for humans has ever been produced, though numerous vaccines have been produced for coronavirus diseases in other mammals.

- We do not yet know the immunological correlates of protection. These are the response traits in individuals which predict whether or not they have become immune to infection.

- Natural infection may yield only short-duration immunity, suggesting that the vaccine will need to produce a large immunogenic response.

Likelihood of moving to and successfully completing phase 3 trials

According to the 16 vaccine experts, COVID-19 vaccine candidates currently in phase 1 and phase 2 have a higher PoS of reaching phase 3 than for past vaccines because of the urgent need to develop a vaccine, coupled with limited information on the characteristics of the immune response that is needed for good protection against infection. Therefore, as long as a vaccine candidate demonstrates a plausible antibody and/or cell-mediated immune response and reasonable tolerability with no major adverse effects, it likely moves on to phase 3. Several experts also noted that development is proceeding in an atypical two-step manner, with companies conducting either phases 1 and 2 simultaneously or conducting all three clinical phases simultaneously.

Many of the experts interviewed believed that the PoS in phase 3 would be lower than usual, because the candidates that they predicted would go through phase 1 and 2 more easily, would have their flaws exposed in phase 3. Rather than removing risk of failure from the overall R&D process, the risk of failure has simply been pushed to phase 3. Whilst the vast majority of respondents thought that phase 3 would have a lower success rate than is typical, three of the 11 respondents who commented thought the vaccine would be within the historic 60%–70% phase 3 success range (none thought it would be above 70%). These respondents recognised the reasons given for why COVID vaccines might find it more difficult in phase 3. However, they felt that this was offset by the relatively low efficacy hurdle required for the first-generation vaccines (i.e., a 50% reduction in risk or better), and because some data gathering might be pushed into phase 4 trials.[12]

12 Phase 4 trials are clinical trials that study the side effects caused over time by a new vaccine after it has been approved and is on the market. These trials look for side effects that were not detected in earlier trials; it may also study how well a new treatment works over a long period of time.

Table 3 presents respondents' forecasts of the PoS for each phase of clinical trials.

Table 3. Historical likelihood and expert forecasts of probability of success of well-funded COVID-19 candidates, by phase (percent)

Phase	*Historical development of simple vaccine*	*Historical development of complex vaccine*	*Experts' forecast for well-financed COVID-19 vaccine*
Preclinical	40	40	66 (n =5, ql =3)
Phase 1	70	50	78 (n = 8, ql = 4)
Phase 2	45	20	67 (n = 8, ql = 4)
Phase 3	70	60	46 (n = 8, ql = 3)
Approval	—	—	74 (n = 4, ql =0)
Overall: preclinical through Phase 3	9	2	16

Note: *n* is the number of quantitative responses; *ql* is the number of qualitative responses (respondents outlined whether they thought success rates would be higher or lower than the norm but did not give a figure).

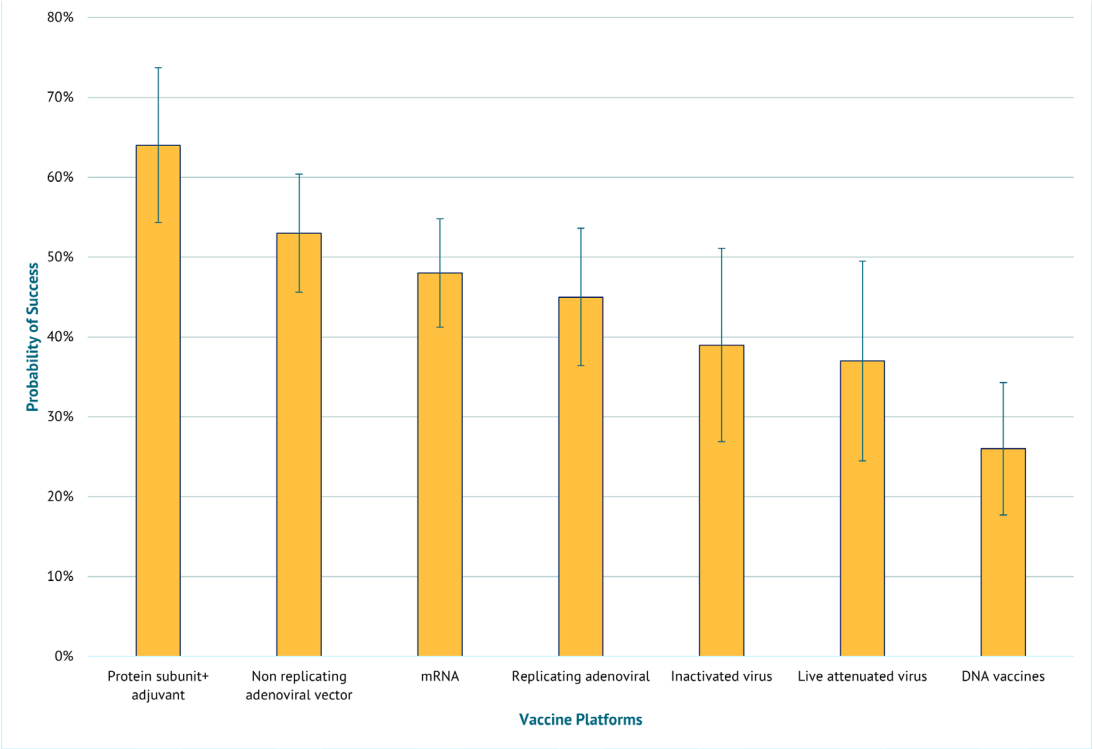
— Not available.

Historically, 8.8% of simple vaccines and 2.4% of complex vaccines that start preclinical research successfully complete a phase 3 trial. If one multiplies the phase-specific probability estimates from our experts, the implied probability of a candidate going from phase 1 to approval is around 16%. This difference is driven mostly by very different preclinical inputs. Respondents thought that a well-funded COVID-19 vaccine had a 66% chance of going through preclinical studies compared to a historical average of 40%. Our experts placed the likelihood of current phase 1 candidates completing phase 3 at 24% for COVID-19 vaccines compared to 22% for simple vaccines; this is consistent with their estimation that COVID-19 vaccine development is slightly easier than most viral pathogens. We also asked our experts for the probability that a vaccine is submitted for regulatory approval having completed phase 3 and gets approved, and this is included in our model.

Probability of success of specific vaccine platforms

Figure 2 shows the mean and 95% confidence intervals of PoS estimates for each vaccine platform in phase 3 trials. The mean probability of success for the seven platforms studied was 44%, and the mean probability of any well-funded COVID vaccine progressing through phase 3 was 46%. The similarities in these numbers gave us confidence in our approach. (See appendix F for the pro and cons of each vaccine platform.)

Figure 2. Projected probability of success of a phase 3 trial of the seven platforms for COVID-19 vaccine, according to interviewed experts



Note: Yellow bars show mean values. Blue lines show 95% confidence intervals

Most respondents indicated that several first-generation COVID-19 vaccines will probably be developed. There was consensus that candidates built on established vaccine platforms that have already brought products to market (particularly products based on protein subunits with adjuvants) are more likely to succeed than other technologies given, among other things, greater experience by firms and regulators. There was also consensus that more effective second-generation vaccines will eventually be approved and that newer technologies will have an important role in them.

According to the interviewees, the involvement of a pharmaceutical company or government funder with experience developing vaccines is critical to the expeditious development of a COVID-19 vaccine; substantial external funding of these companies increases the PoS (see appendix E). Where the main research organisation does not have this experience but has substantial amounts of external funding, these funders tend to be providing the required expertise. Funding increases the ability of companies to begin manufacturing large amounts of vaccine during clinical trials (before efficacy is proven) in order to create a stockpile ready to go upon licensure; it also accelerates the speed of clinical trials (by allowing companies to hire more experienced investigators and run more trial sites). External funding can also speed pharmaceutical research, although this, on its own, is not likely to improve the chances that a candidate vaccine will succeed.

Experts were virtually unanimous in predicting a low PoS for small biotech firms or academic institutions without substantial external support such as an acquisition by, or

partnership with, a larger pharmaceutical company. This is because the clinical and regulatory hurdles are so high. Experts highlighted that few small biotech firms or academic institutions have ever taken a vaccine to market on their own. We received 13 responses along the lines that these efforts were "a non-starter," "had no chance of success without funding," "can't do a phase 3," "won't pass phase 1." Candidates that received large funding, or create a partnership with a larger company, are not treated in this funding category for our model. The experts indicated that the difference between medium pharma and large pharma would be small for PoS but that large pharma could move more quickly.

Time needed to develop a COVID-19 vaccine

There was wide variation in experts' projections of how long it will take to complete each clinical trial phase (table 4). Many experts gave lower and upper bounds rather than a point projection. We used the mean response as the most likely scenario and the 20th and 80th percentiles they provided as the best- and worst-case scenarios, respectively.[13]

Table 4. Historical and expert projections of time needed to complete each phase of vaccine development

Item	Preclinical	Phase 1	Phase 2	Phase 3	Approval
*Historical vaccine development (**years**)*					
Simple vaccine	3.3	1.6	2.2	2.3	Not available
Complex vaccine	3.3	2	3.7	3.7	Not available
*Expert's forecast for COVID-19 vaccine development (**months**)*					
Most likely scenario	3	2	3	3	1
20th percentile	6	4	5	9	3
80th percentile	12	6	8	18	6

We also asked experts about platform timelines—were any likely to be faster or slower than the norm? We then adjusted them as outlined in the table below.

13 In order to capture the range of possibilities, where experts gave us a best and worst case scenario, we included both in the aggregation. Where one number was inputted, we included this twice so that all responses received equal weighting.

Table 5. Timelines for different platforms

	Experts who indicated faster	Responses that indicated slower	Our aggregation (model input)
Live attenuated virus	1 faster	3 said slower, another 3 said much slower	Much slower (twice standard timing)
Protein subunit+ adjuvant	2 faster, 1 fastest	2 slightly slower, 1 slower	Standard timing
Inactivated virus	2 faster, one "second fastest"	1 slower	Faster (75% of standard timing)
mRNA	1 faster, fastest	1 slower	Slightly faster (90% of standard timing)
Non-replicating adenoviral vector	1 faster	2 slower	Slightly slower (110% of standard timing)
Replicating adenoviral	none	2 slower	Slower (133% of standard timing)
DNA	1 faster	1 slower, 1 very slow	Slower (133% of standard timing)
Other vaccines	None	3 slower, 3 much slower	Much slower (twice standard timing)

Correlating failures

Our model is designed to update probabilities of success when other vaccines using the same technology platform succeed or fail (see Appendix C for details). This kind of correlated technical performance is a common feature of drug R&D. We therefore collected experts' views on the degree to which success or failure would make them more or less optimistic on the prospects of other vaccines with similar technology.

In practice, many experts struggled with this question, or only had comments on a handful of platforms. Where response rates were low, we aggregated the comments as medium correlation.

To put table 6 in concrete terms, it says that if one non-replicating adenoviral vector vaccine succeeds (or fails) then there is a relatively high likelihood that others will succeed (or fail). On the other hand, if one mRNA vaccine succeeds (or fails) it does not tell us much about the prospects of other mRNA vaccines.

Table 6. Risk correlations by platform

Platform	Responses on correlation of one vaccine candidate success/failure with PoS for other candidates in the same platform	Our aggregation
Live attenuated virus	High: 1 Medium: 1 Low: 1	Medium
Protein subunit+ adjuvant	High: 1 Medium: 1 Low: 1	Medium
Inactivated virus	High: 0 Medium 2 Low: 1	Medium
mRNA	High: 2 Medium: 1 Low: 4	Low
Non-replicating adenoviral vector	High: 5 Medium: 0 Low: 0	High
Replicating adenoviral[a]	High: 1 Medium: 0 Low: 0	High
DNA	High: 1 Medium 0 Low 0	Medium
Other vaccines	n.a.	None

Notes: n.a. Not applicable.

a. Three experts indicated this would be the same as non-replicating.

Efficacy of COVID-19 vaccines

There are a variety of ways of measuring the efficacy of a vaccine.[14] Here we take efficacy to mean the percentage reduction in the risk of infection, which we assume is the same for both symptomatic and asymptomatic infection, for severe infection, for death from infection, and for the ability to transmit the infection to others.

Experts gave a range of responses about COVID-19 vaccine efficacy. Of the 11 respondents who shared an opinion, most believed the first-generation vaccines would not be significantly above the US Food and Drug Administration's threshold of 50% efficacy; the mean projection was 61% (although some experts predicted that efficacy could be as high as 75%–80%). There was some discussion about differences in clinical trial endpoints but approval by a regulator would require clinically meaningful endpoints to support the conditions of use.

There was great uncertainty about the duration of immunity from a COVID-19 vaccine but some consensus that a two-dose vaccine could give several years of immunity against severe disease (two to five years was the most commonly mentioned duration). Experts indicated that boosters would likely be required, given the short duration of immunity from natural infection observed in other coronaviruses, like SARS and MERS. How often and how soon they would need to be administered is uncertain and will likely vary by vaccine.

Additional questions raised by experts

The experts suggested that some event could occur—such as a decline in the number of COVID-19 cases or a vaccine safety issue—that would slow all of the trials across the world at the same time. They also noted that the world might reach some kind of limit on how many phase 3 trials could be carried out and that future candidates would struggle to find sufficient trial sites.

Based on these comments, we added these two features to the model, but the decision to include them was made too late to include them in our survey. We assumed that on 30% of model runs something would happen that would slow down all phase 3 trials by 50%. We also assumed that if there were more than six trials in phase 3, all vaccines that reached phase 3 after this sixth candidate would run 50% more slowly. As with other model inputs, these assumptions can be adjusted by the user.

The experts we interviewed also shared important qualitative information on the challenges of discovering and producing vaccines against COVID-19 that we summarize here.

14 See, for example, the variety of efficacy endpoints in the Oxford / AstraZeneca phase III trial here: https://clinicaltrials.gov/ct2/show/NCT04516746. In this trial, the primary endpoint is "SARS-CoV-2 RT-PCR positive symptomatic illness"

Model Results

The Monte Carlo simulation produces a large number of alternative futures, each derived probabilistically from the starting conditions. The individual futures can be radically different from one another. However, the more simulations that are run, the more the distribution of alternative futures converges. We see good convergence with 30,000 simulations.

Defining Approval

We defined success from the R&D model as approval by a stringent regulator or clinical trial results that would be sufficient for approval by a stringent regulator.[15] Emergency use authorisations, granting access to vulnerable groups before full approval, were not classified as successes for the purposes of the model.

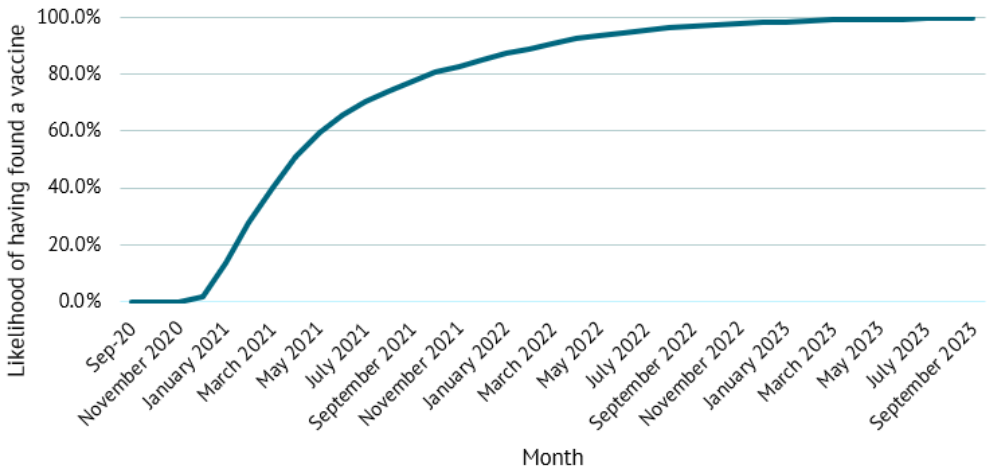
Some regulators are also likely to give a conditional approval, where the vaccine is licenced for full use but must undertake pharmacovigilance or further study in order to retain its licence. For example, a licence could be granted based six months of safety data, instead of the standard one year of safety data, but the one-year safety studies would still have to take place after licensure and retaining licensure would be conditional on this. Such conditional approval, when given by a stringent regulator, meets our definition of approval.

Results of the Research and Development Model

Based on the information provided by the experts interviewed, the model predicts that there is about a 1.7% chance that a vaccine will be approved by a stringent regulator in 2020. Beginning in early 2021, the odds of approval increase, with the chance of approval by January rising to 14%. The model projects the chance of vaccine approval at 50% by the end of April or early May 2021, 85% by the end of 2021, and 98% by the end of 2022 (figure 3).

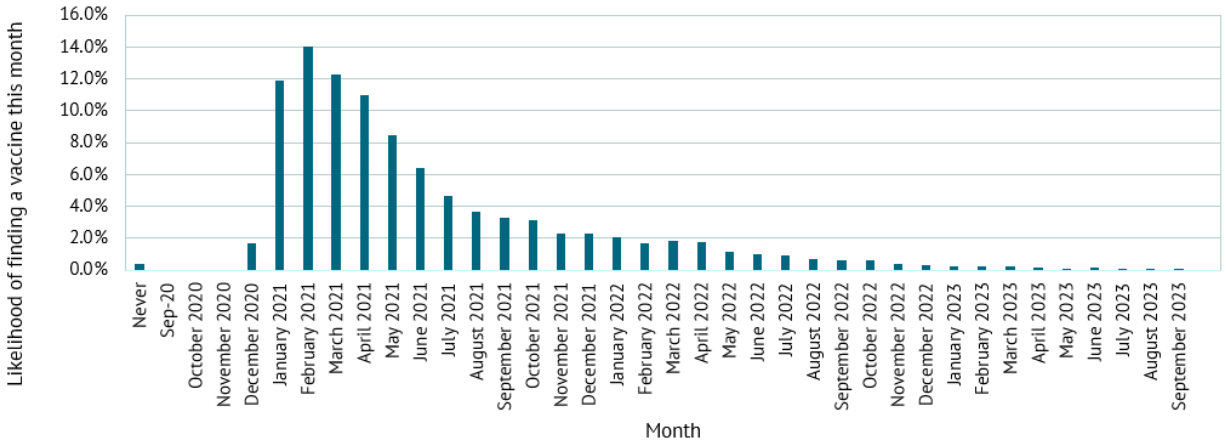
15 Candidates based in countries where the regulator is not deemed "stringent" by the WHO might never submit their vaccine for approval by such a regulator. We use "approval by a stringent regulator" as a benchmark for a safe and effective vaccine. A vaccine that can demonstrate that it would meet this criterion if it were submitted to such a regulator is viewed as successful.

Figure 3. Projected probability of at least one vaccine approval, October 2020–September 2023



Our model suggests that it is highly likely that the first vaccine will be approved between January and September 2021, with this happening in three out of every four runs, with there being a 50% chance that one is approved before the end of April. Only in 0.5% of simulations does no vaccine currently in the portfolio get approved.

Figure 4. Projected probability of first vaccine being approved, October 2020–September 2023



We analysed the PoS for two vaccine candidate portfolios: the US government's Operation Warp Speed and the vaccines supported by the CEPI, as of September 2020. The model predicts an almost 80% chance that at least one Operation Warp Speed[16]

16 Operation Warp Speed has announced partnerships with six companies to date: Moderna and Pfizer/BioNTech (both RNA vaccines); AstraZeneca/Oxford and Janssen (both replication-defective live-vector vaccines); and Novavax and Sanofi/GSK (both recombinant-subunit-adjuvanted protein vaccines).

candidate will be successful, and a 67% chance that at least one CEPI[17] candidate will succeed. These portfolio results are outlined in table 7, alongside success rates by vaccine.

Across our simulations, the protein subunit platform is the platform most likely to yield at least one approved vaccine, with approval in more than 85% of our runs. RNA vaccines are second. Non-replicating viral vector vaccines are third. Unsurprisingly, the average number of months until first success is higher for specific platforms than for the portfolio as a whole. This is because early, well-funded candidates will often fail, but one of the many other candidates early in development may succeed years later. This highlights the need to diversify both within vaccine platforms and across vaccine platforms.

Table 7. Probability of vaccine approvals, by platform, up to September 2023

Platform	At least 1	At least 2	At least 3	Successes per run	Number per success	Months to first success
Live-attenuated[18]	0.0%	0.0%	0.0%	0.00	0.00	0.0
Protein subunit	86.6%	62.0%	35.9%	2.10	2.42	20.9
Inactivated	54.7%	23.6%	8.3%	0.89	1.63	11.6
RNA	74.0%	37.6%	13.5%	1.29	1.75	12.8
Non-replicating viral vector	53.8%	26.7%	10.9%	0.95	1.76	14.6
Replicating viral vector	18.8%	2.5%	0.1%	0.21	1.14	27.9
DNA	7.1%	0.4%	0.0%	0.08	1.06	30.4

17 CEPI has established manufacturing agreements with AstraZeneca/Oxford, the University of Queensland/CSL, Clover Biopharmaceuticals, Novavax and SK Bioscience.
18 There are only four life attenuated vaccines in the portfolio, all at an early stage of development with low levels of funding. None succeeded in any runs of our model.

Other[19]	0.03%	0.0%	0.0%	0.003	1.00	33.0
CEPI Vaccines	67.0%	26.7%	6.0%	1.00	1.50	16.2
Operation Warp Speed Vaccines	78.6%	43.5%	16.6%	1.43	1.82	9.6
All platforms	99.6%	97.5%	92.4%	5.52	5.54	9

Vaccines that have similar underlying technology, that share a platform, are more likely to succeed or fail for the same reasons. It therefore makes sense for funders or governments to invest in candidates from multiple platforms in order to hedge their bets, if they have the resources to do so.

We have used our model to identify a portfolio that appears to maximise the chance of at least one vaccine approval while minimising the number of candidates in development. It is shown in table 8. In this approach, we find the vaccine candidate that is most likely to succeed and add it to the portfolio. We then look at all the runs of the simulation in which that candidate failed and find the candidate most likely to succeed in those remaining runs. The candidate is added to the portfolio and we then look for runs in which neither the first nor the second candidates succeeded. We repeat the process to find the 3rd, 4th, etc., portfolio members until we have identified six candidates.

This diversification strategy identifies a six-candidate portfolio with only a 14% chance of zero approvals (see the cumulative column in table 8), and a five-candidate portfolio with an 18% chance of zero approvals. This less risky than Operation Warp Speeds (21% chance of zero approvals from six candidates) and substantially less risk than CEPI (33% chance of zero approvals from five candidates).

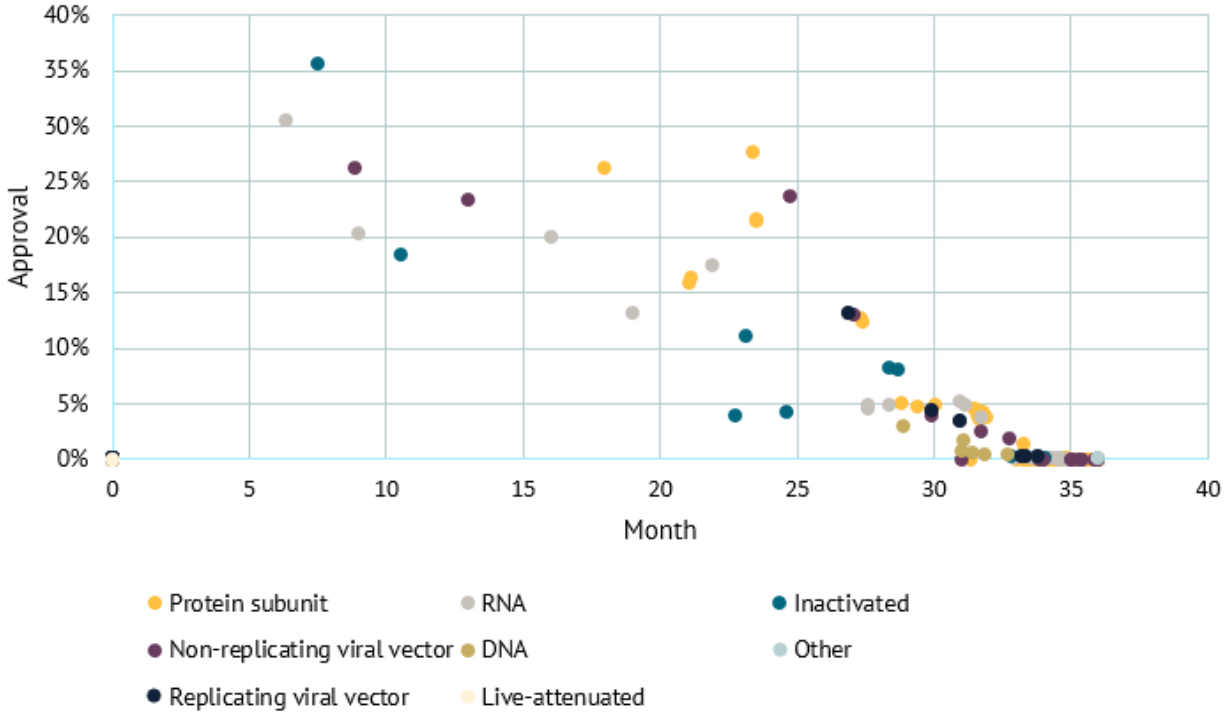
At first sight, it appears that Warp Speed has done a good job of technical diversification given political constraints and the need to minimize likely time to vaccine approval and deployment. However, our analysis also suggests that the US might have reduced risk to its population still further had Warp Speed been able to diversify by partnering with Chinese vaccine manufacturers. Similarly, the risk to the Chinese population could, in principle, be reduced by diversification, via deals with US and Western European vaccine producers. In short, vaccine nationalism undermines diversification and, as a consequence, puts people at risk.

19 The long R&D timelines for the "other" category mean there were no approvals within our simulation time window. Had we run the simulation beyond 2024, there would likely have been successes among the "other" vaccines.

Table 8. Building a low-risk vaccine portfolio

	Institutes	Platform	Funding	Country	Success Rate	Portfolio Contribution	Cumulative
1	Sinovac	Inactivated	Large external funding	China	35.0%	35.0%	35.0%
2	BioNTech/Fosun Pharma/Pfizer	RNA	Large external funding	Germany/ US	30.3%	19.6%	54.6%
3	Medicago Inc/Mitsubishi /GSK	Protein subunit	Large Pharma	Canada	27.4%	12.7%	67.3%
4	University of Oxford/AstraZeneca	Non-replicating viral vector	Large external funding	UK	26.3%	8.7%	76.0%
5	Novavax	Protein subunit	Large external funding	US	26.4%	6.0%	82.0%
6	Clover Biopharmaceuticals Inc/GSK/Dynavax	Protein subunit	Large Pharma	China/UK /US	22.0%	3.7%	85.7%

Figure 5. Probability of success against approval rate for every vaccine in the portfolio, colour coded by platform



Drugs from large pharma and/or with external funding are much more likely to yield approved drugs in our model. This is more driven by timing (we model out to September 2023) than by PoS. Vaccine candidates from medium pharma and biotech are much more likely to still be in pre-clinical development so are less likely to complete their clinical trials within the time horizon that we model.

Timing differences explain, for example, why BioNTech RNA vaccine was approved in 30% of vaccine runs and the Moderna RNA vaccine was approved in only 20%. They have the same funding category and the same platform, but BioNTech started its phase 3 trials three months before Moderna.

Table 9. Probability of vaccine approval by September 2023

Funding category	Average approval rate	Number of candidates	Proportion in pre-clinical
Large external funding	18.7%	10	40%
Some external funding	16.6%	5	40%
Large pharma	13.0%	8	38%
Medium Pharma	2.5%	34	88%
Small biotech/academia	0.3%	178	88%

Table 10. Probability of vaccine approval by September 2023, based on current phase of development

Phase	Number of candidates	Average number of success from the model	Number of small biotechs
Phase 3	1	35%	0
Phase 1, 2 and 3 simultaneously	6	15.7%	1
Phase 1 and 2 simultaneously	11	5.4%	8
Phase 1	21	8.6%	12
Pre-clinical	196	0.7%	157

Uncertainty

However, these outputs are all based on the inputs from our experts, which had a lot of variation, in order to understand how changes in variation impact the modelling outputs, we also looked at pessimistic and optimistic scenarios. For the pessimistic scenario we subtracted one standard deviation from the PoS inputs, and optimistic scenario we increased inputs by one standard deviation.

For timelines we already used the 20th and 80th percentile of estimates from experts as part of our standard assumption, which means we cannot also use them as optimistic and pessimistic scenarios, instead we multiplied (or divided) the inputs by 1.5 for the pessimistic (optimistic) scenario, table 11 outlines the standard, pessimistic and optimistic inputs for probability of success.

Table 11. Probability of success for optimistic, pessimistic, and standard scenarios

Input	Pessimistic scenario (percent)	Standard (percent)	Optimistic scenario (percent)
Pre-clinical: All platforms	44	66	88
Phase 1: All platforms	69	78	86
Phase 2: All platforms	54	67	80
Phase 3: Live attenuated	13	44	62
Phase 3: Protein subunit	43	65	85
Phase 3: Inactivated	14	43	64
Phase 3: RNA	33	47	64
Phase 3: Non-replicating adenoviral vector	36	50	71
Phase 3: Replicating adenoviral	27	44	62
Phase 3: DNA	10	26	33
Phase 3: Other	1	5	10
Regulatory approval: All platforms	74	60	88

In the pessimistic scenario, the chances of approving a vaccine from the current portfolio in the next three years is just over 80%, and the number of runs where two are approved falls just below 50%. Under these pessimistic assumptions, the median time to approval is April 2022. On average there are 1.7 vaccines approved in this timeframe. An operation Warp Speed vaccine is approved in almost 55% of the runs in this scenario and a CEPI vaccine is approved almost 50% of the time.

Using the optimistic inputs, at least five vaccines are approved in every run, with January 2021 being the month when a vaccine become more likely than not; in 90% of runs a

vaccine had been approved by the end of March 2021, and in 99% of runs one had been approved by the end of October 2021. There as an average of 18 vaccines approved in the next three years. The odds of a CEPI and Operation Warp Speed having an approval is both over 98%, and the odds of two vaccines from these portfolios are both about 90%.

In Appendix H contains a sensitivity analysis and highlights how timelines and probability for vaccine approval change given different inputs. It is also worth bearing in mind that some event that we have not modelled could shift the probabilities of success for all vaccines. This could include a mutation in the virus, or a breakthrough in treatment that could reduce demand for a new vaccine.

Results of the Manufacturing Model: Timeline for Vaccinating Target Groups

The manufacturing scale-up and capacity models project the length of time it would take to produce enough vaccine to vaccinate four target groups identified by the World Health Organization: health system workers (Target 1), adults over 65 (Target 2) and younger adults with co-morbidities (Target 3), the three groups the WHO has identified as the priority groups. We also project the timelines for reaching the rest of the population (Target 4) (WHO 2020). Target 4 is the upper bound for the number of vaccines the world needs. This approach assumes that target groups will be vaccinated in order of priority. In practice, distribution is unlikely to be optimal. We adopt the WHO assumptions that two vaccine doses will be needed and that 15% of vaccine production will be lost to wastage. The required number of vaccines doses are outlined in table 12.

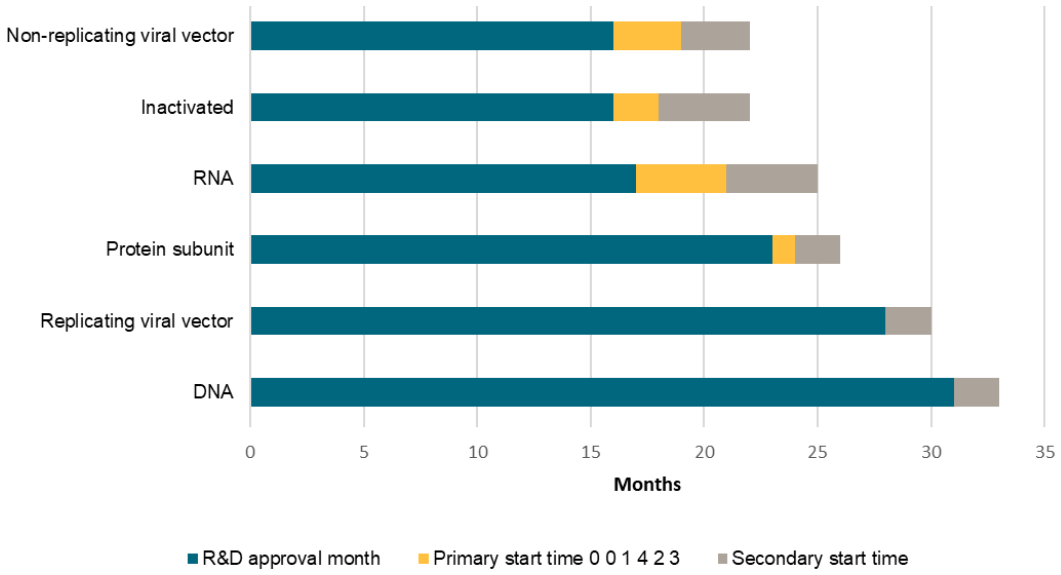
Table 12. Number of vaccine doses need to vaccinate target groups

Target group	*Number of doses required (million)*
1: Health system workers	115
2: Adults over 65	1,615
3: Adults with co-morbidities	4,265
4: Rest of world	18,000

Results of the Manufacturing Scale-Up Model

The results from the manufacturing scale-up model suggest that the time needed to get manufacturing ready will be very similar for all vaccines except DNA vaccines. When manufacturing starts is driven primarily by the outputs of the R&D model (figure 6).

Figure 6. Projected timelines for manufacturing COVID-19 vaccines, by platform



Results of the Manufacturing Capacity Model

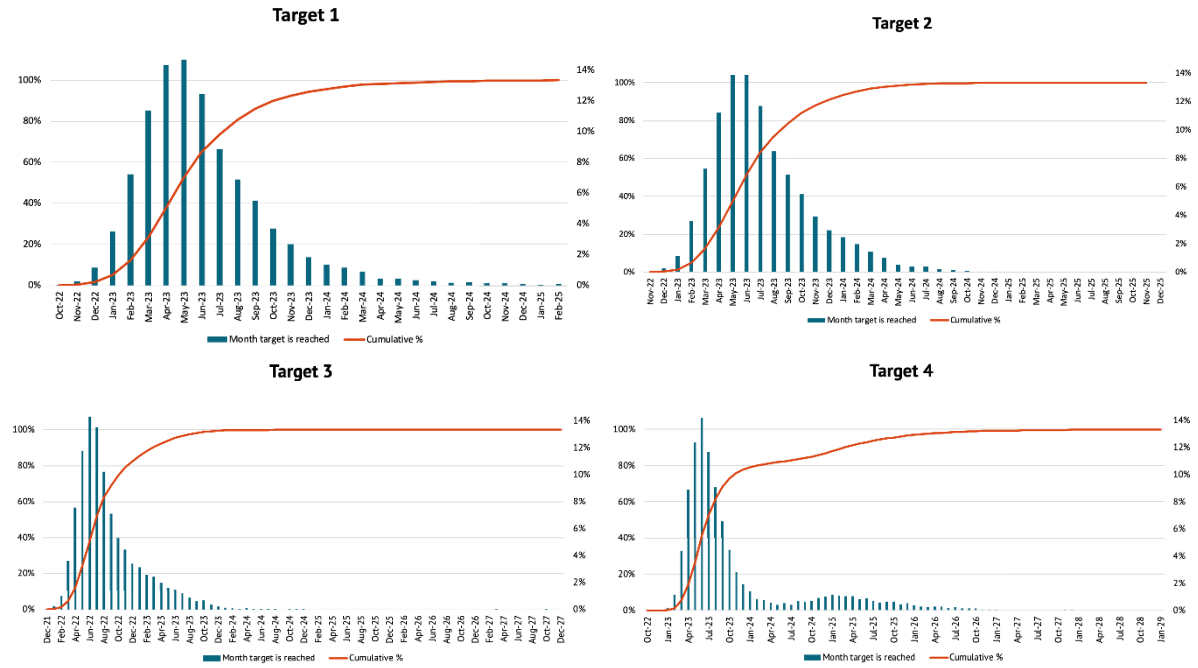
The outputs of this model are not probabilistic, as this model is a hybrid. The R&D model is probabilistic; however, the manufacturing models are deterministic rather than probabilistic, with the vast a majority of variables static. This means that the model runs should not be seen as probabilities for when enough vaccines should be produced. Instead the median case for the manufacturing model should be seen as the most likely timelines for when we will have enough doses of the vaccine, and any uncertainties will have come from changes in the R&D model.

According to the model, it will be at least December 2021 before the world is producing 115 million vaccine doses—the number needed to vaccinate the world's health care workers. It is possible that this could be accelerated in some countries if some form of emergency use authorization was implemented for this specific target group. But the world will still face the same manufacturing constraints.

Vaccinating target group 2 runs about six months behind target group 1. The model thus suggests that adults over 65 could be vaccinated by mid-2022. Vaccinating target group 3 (adults with co-morbidities) will take an average of another three months according to our models, thus becoming more likely than not in August 2022. The point that producing 18 billion doses becomes probable is not for 35 months (September 2023), which is what we would need to inoculate the entire world.

The model does not account for vaccine allocation strategies across countries, distribution issues, or vaccine hesitancy.

Figure 7. Vaccinating the population, by target group



These predictions are for the global population in each group. The time required to produce enough vaccine for a group within one country is likely to be different.

To understand the timelines generated by our model, we set the R&D approval times to zero and coded the model to calculate how long it would take to vaccinate the four target groups if only one vaccine was approved; we've broken this down depending on the platform for this vaccine. Because manufacturing capacity for DNA and RNA vaccines is limited, their development is slower than that of other candidates. Additional RNA capacity in particular, however, may already be under construction, shortening the time predicted. The time to produce the vaccine is longer if only one platform is used compared to if multiple platforms are used.

Figure 8. Time required to manufacture enough of one vaccine to meet targets, by platform

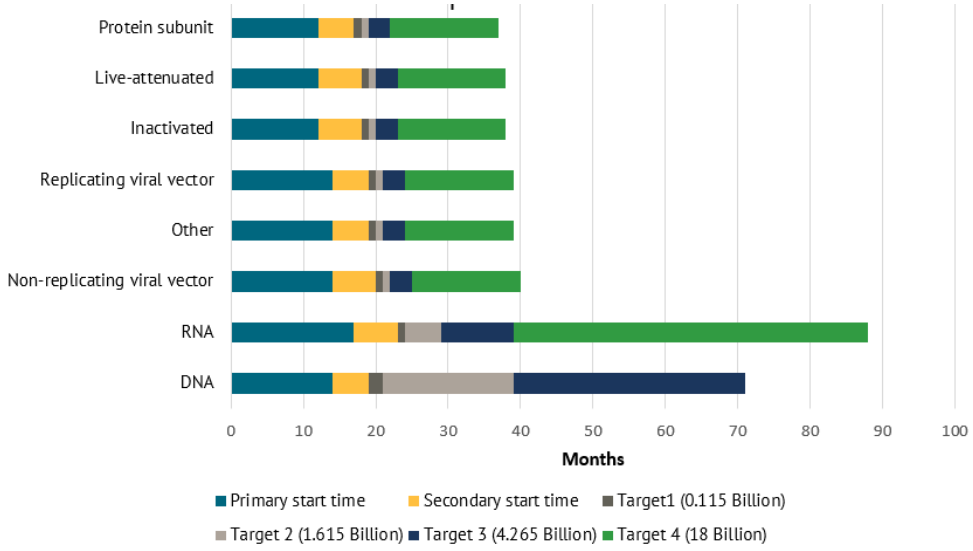
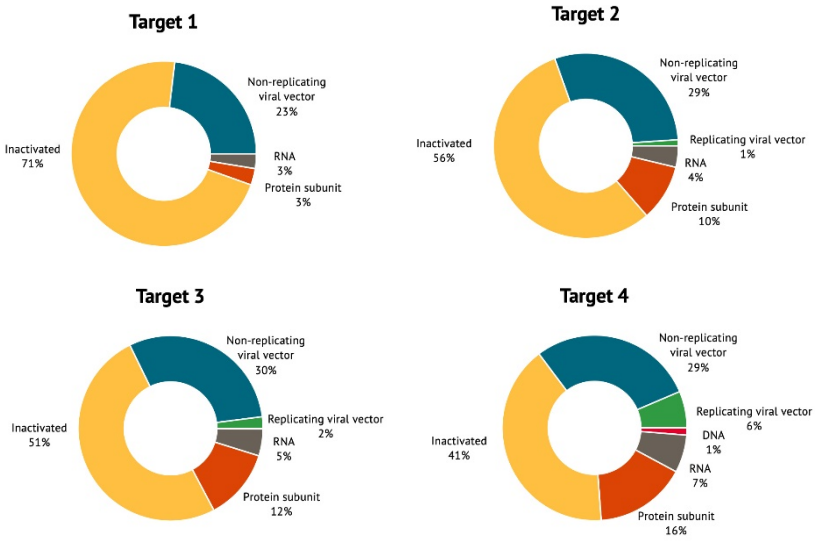


Figure 9 shows the proportion of each vaccine platform used to reach the four targets. This is an aggregate of all model simulations; most individual simulations will end up relying more heavily on one platform than indicated below.

Figure 9. Projected production of vaccines, by platform and target group



Among the possible worlds that we have simulated, we often see major contributions from RNA, protein subunit, viral vectors, and inactivated virus, but we very rarely see major contributions from DNA. In these future worlds, it might still be rare that RNA, protein, viral vector, and inactivated virus are all important at the same time. The high contribution of inactivated vaccines seems counterintuitive given that the expert informants gave this platform a relatively low probability of phase 3 success; however, this was offset by the vast manufacturing capacity for this platform type, particularly in

India. This means that the other types, including DNA, make very little contribution. This is either because they are unsuccessful in the R&D model or there is insufficient production capacity. To be clear, these graphs represent a hypothetical production scenario in which all the production capacity for all the platforms are used for optimal production. The actual production outcome is too complex to model and will likely be considerably different than this.

Recommendations

Global agencies and national governments should continue to invest in a wider, more diversified portfolio for COVID-19 vaccines

Most of the experts interviewed considered protein subunits the most promising platform. But too little is known about the virus to know which platforms will succeed. For this reason, we have argued that diversification of the COVID-19 vaccine portfolio is critical, so that when some vaccine candidates fail, others can be turned to.

Diversification will also make manufacturing sufficient quantities of the vaccine easier. Manufacturing and roll-out have never been conducted at the scale required for COVID-19, and have never been deployed for new technologies, such as RNA. Investing in multiple vaccine platforms will help mitigate potential feasibility issues with mass immunization for specific platforms (such as RNA cold storage requirements); while solutions to feasibility issues for one type of vaccine are being developed, other types of vaccines can be used. Diversification also helps enable equitable vaccine distribution across countries and risk groups, as some vaccine types may be available or accessible only in certain locations, or vaccine types might vary in efficacy/contraindications for specific at-risk populations. Ideally, multiple vaccines using multiple technologies will be approved, in order to optimize manufacturing capabilities and the chance of producing effective and safe vaccines.

Operation Warp Speed appears to be doing a good job of diversifying R&D risk in its vaccine candidate portfolio in the short term. The R&D model indicates that there is an almost four in five chance that at least one of the six vaccines backed by Operation Warp Speed will succeed. This PoS is considerably higher than the PoS of the CEPI portfolio (two in three chance) and close to the five in six chance for the ideal global portfolio, which includes a Chinese candidate that the US government would probably not be able to acquire. There is, nevertheless, a one in five chance that none of the Operation Warp Speed candidates will work. It may therefore make sense for Operation Warp Speed to consider backing more than six candidates in order to hedge its bets. The program should be flexible enough to add and remove candidates when new information comes to light.

More worrisome is the fact that Operation Warp Speed has not invested in any inactivated vaccines. Only one of the 172 candidates being developed outside of Asia is inactivated. Western governments appear reluctant to back a technology that will be slow

to produce results. However, inactivated vaccines could play an important role in producing enough vaccines to reach the entire world. It is short-sighted not to be investing in them. In addition, there is a need for further diversification of the Operation Warp Speed portfolio from a manufacturing perspective. Investing solely in US and European vaccine technologies goes against the US's own interests—the portfolio would benefit from investing in Chinese vaccines. This would also insulate America against domestic manufacturing problems, by diversifying this risk too. A global portfolio is more robust, risk resilient and efficient in ending the pandemic. With manufacturing capacity primarily concentrated in high-income countries, there is a considerable risk of other regions of the world being left behind in producing and accessing vaccines.

We must diversify; there still is time, we can and should be encouraging the development of a marketplace for new entrants to come in to create a more diverse portfolio. This links with CGD's work on market shaping and risk sharing.

During the wait for a COVID-19 vaccine, governments should invest in public health measures, diagnostics and treatment

Our R&D model is optimistic about getting a vaccine against COVID-19 approved. It is worth bearing in mind that there may be factors not included in the model that could affect its accuracy. While our experts believed the virus was unlikely to mutate due to the current limited genetic variation, a large mutation could undermine all of the vaccines in the portfolio. A breakthrough in treatments for COVID-19 could lead to a large drop in the demand for a vaccine and this too could reduce the chances that we get a vaccine approved quickly. However, there are so many candidates in the platform, trying to tackle this virus in different ways, that it seems highly likely that at least one will be successful in 2021, but probably not for another six months.

Even when first-generation COVID-19 vaccines become available for the general population, it is unlikely that they will be a silver bullet. Our expert informants' mean efficacy projection for first-generation vaccines disease prevention was 61%—too low to fully contain the virus. Even with high vaccine uptake, the number of cases could be large (albeit less severe). It is also not clear what proportion of the population these vaccines can protect. It is, therefore, likely that defeating COVID-19 will have to await second-generation vaccines, which will not be ready for many years—some may be in early clinical development now, and others have yet to be identified. These second-generation vaccines, which will likely be more effective and have better safety profiles, will be crucial in eventually ending the pandemic.

Given these findings, governments, industry, families and individuals should be preparing for a protracted period in which they use all the other public health measures in their arsenal to deal with COVID-19. Public health interventions, along with robust testing and contact tracing programs, will need to remain in place for some time. It also may make sense for governments to put more effort into finding rapid diagnostics or new treatments that allow society to return to normality whilst we wait for vaccines to be approved. For example, rapid daily tests could enable screening out of positive cases

before people enter workplaces or schools, thereby alleviating the need to quarantine large groups of close contacts in those venues.

Governments should anticipate and plan ahead for manufacturing challenges. If our R&D model was optimistic about the probability of finding a vaccine, our manufacturing models were more cautious about how quickly that vaccine it can be manufactured. As many of our expert respondents told us, the world has never produced the quantity of vaccines needed to contain COVID-19 at the speed that societies are hoping to get them. It will likely take years before there are enough doses to treat low priority groups. This is a situation that could be made more challenging if we need to give people regular booster doses against COVID-19.

A second manufacturing challenge that does not get sufficient attention arises when the first-generation vaccines are less efficacious than second-generation candidates, which have used the knowledge garnered from the first to improve. We need to be careful about committing all spare manufacturing capacity to the first candidates. While many vaccine factories are fungible, switching production between candidates can be slow and complex. It therefore makes sense for governments to formulate plans to do this now.

Too often governments seem to treat the COVID-19 end point as the approval of a safe vaccine quicky, rather than taking more time to maximise efficacy.

We need to think about distribution

Our models focused on the likelihood and timelines of getting COVID-19 vaccines approved and doses produced. Future efforts are needed to plan for optimal vaccine distribution and uptake—key considerations in our ability to contain this pandemic. CGD's work on the importance of health technology assessment for governments and on understanding the net health benefit to COVID-19 policies is instructive.

But more work is needed in these areas so that governments are ready for pricing negotiations and coverage decisions to come.

Next Steps

This paper is intended to generate a discussion about reasonable timelines and probabilities of success for vaccines and to make the risks as clear as possible. We hope to build on this research, based partly on critiques from others. We therefore welcome questions and comments. If you have inputs on vaccine probabilities or ideas for how to improve this project, or you spot something that you do not think is right in our work, please let us know by emailing amcdonnell@cgdev.org.

Going forward, we will:

1. Launch a web version of our tool for others to test their assumptions
2. Build Monte Carlo simulations into the manufacturing model to track the timelines for manufacturing probabilistically
3. Host an event later this fall looking at what is required to scale up manufacturing of vaccines
4. Continue to collect updated inputs from experts on probabilities of success

This paper projects timelines for the *approval* and *manufacture* of COVID-19 vaccines, but there is a third crucial part of this process: the *rollout of vaccines* once they are manufactured. Health systems are not set up to run adult vaccination campaigns; hesitancy about the vaccine seems high; many of the leading candidates are highly temperature sensitive, which will create huge logistical problems; and there is concern that economic and political issues will disrupt the equitable distribution of vaccines. We hope to explore some of these issues in future work.

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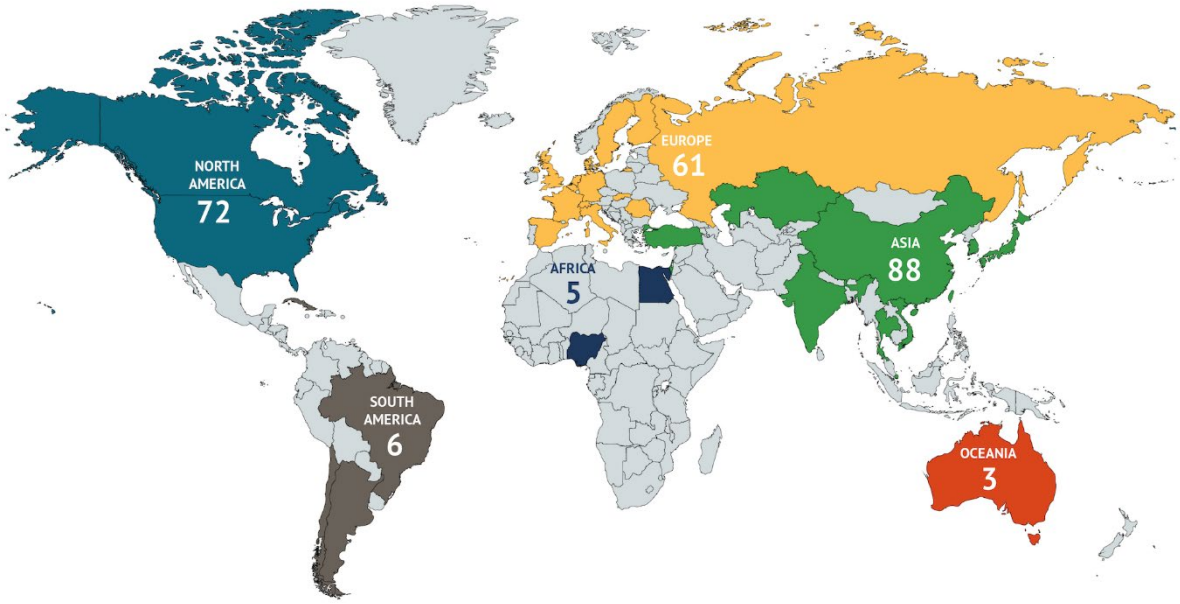
Appendix A. Entities Developing Candidate Vaccines

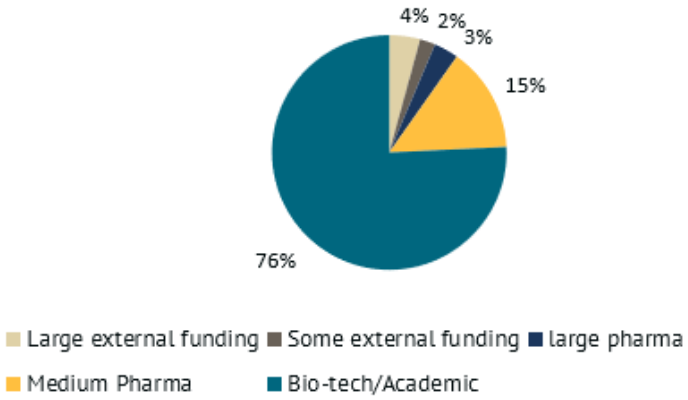
COVID-19 vaccines are in development on every continent. Ninety-five percent of the vaccines being developed (223 of the 235) are being developed in North America, Europe and Asia (figure A.1). Six countries—the United States, China, Canada, the United Kingdom, Russia and India—dominate vaccine development; each has at least 10 candidates. These six countries are working on about 60% of the world's vaccine candidates.

Figure A. 1. Number of COVID-19 vaccines being developed, by continent



Only 13 of the 235 vaccines are sponsored by large pharmaceutical companies that have a wide range of licensed human vaccine products (figure A.2). These companies have extensive experience in scientific and clinical vaccine development, regulatory submissions and production scale-up and are accustomed to meeting full-scale current Good Manufacturing Practice rules. They have the financial means and experience to support development.

Figure A. 2. Experience of institutions developing candidate vaccines



Another nine candidates have received external funding or pre-orders that suggest that they might behave like big pharma companies. Nine other institutions/companies are full-scale vaccine manufacturers but operate primarily as state suppliers. These companies are located in Asia or South America. They are comparable in size and experience to the large pharmaceutical companies.

Twenty-six other companies/institutions have produced at least one licensed vaccine but not a full range of vaccines. These companies have demonstrated success at bringing vaccines to market in a limited way.

Forty-nine vaccine candidates (21% of the total) are thus being developed by companies or institutions that have experience in developing human vaccines and bringing them through clinical development and regulatory approval to the market. They have experience marketing and distributing vaccines post approval and have good tracks record of effectiveness and safety.

Ninety-eight vaccines (42% of the total) are being developed by companies with human vaccines in their development pipeline. These companies have track records with the vaccine platform they are using and have demonstrated the scientific concept behind their candidate to some extent.

Some institutions did not provide details on their pipeline information online. These entities represented another 11% of the candidate portfolio. Most of them are located in Russia and China.

The remaining vaccine developers are mostly academic institutions or companies engaged in cancer or chronic disease therapeutics, small biotech production technologies or specialized vaccine delivery or stability technologies.

One hundred and two (102) developers (43% of the total) have or claim to have access to manufacturing facilities to produce a COVID-19 vaccine. All entities with licensed vaccine products have vaccine production facilities. Another 53 developers have either manufacturing capabilities or partnerships with Contract Manufacturing Organizations

(CMOs) capable of manufacturing their vaccine candidate. Only 18 candidate vaccines have specified their production capacity for COVID-19 vaccine. It is not clear whether the capacity is specifically for COVID-19 vaccine production or a projection of overall capacity.

Appendix B. Experts Interviewed

Our expert informants consisted of 16 experts from industry, academia and government/regulatory agencies.

Industry experts: Eight experts came from industry. These included individuals holding positions as chief executive officer, vice president for research & development, vice president for production development, and senior scientist at global multinational pharmaceutical companies with licensed vaccine products. In addition, our industry experts included several vaccine industry consultants who owned independent companies and who had decades of experience working in vaccine industry research, development, production or commercial operations.

Academic experts: Four experts came from academia. These included vaccinology researchers from academic institutions who were directly involved in vaccine research and development or who had expertise in aligned areas of vaccine research, such as infectious diseases, virology, immunology, etc.

Regulatory or government experts: The remaining four experts came from the public sector. These included experts with current or previous experience with the regulatory process through institutions such as the Centers for Disease Control and Prevention, the Federal Drug Agency, the Coalition for Epidemic Preparedness Initiatives, and others

Three of our sixteen experts were senior scientists engaged in the development of a leading COVID-19 vaccine candidate. Many of our experts hold vaccine-related patents. With one exception, each has 20–35 years' experience in vaccinology.

We used the information shared by our expert informants to assist in the design of our R&D model and to inform the model inputs. We are deeply grateful to all of them for sharing their time, knowledge and personal scientific opinions.

Appendix C. Modelling Research and Development

The model takes data on existing COVID-19 vaccines in various stages of clinical trials and expert opinions as to their likely success and predicts how many vaccines will get proper regulatory approval and on what timescales. The model uses Monte Carlo techniques to randomly decide an outcome given the input parameters and should be run a number of times (runs) to smooth out statistical fluctuations. The model currently consists of approximately 1,500 lines of Python. The source code is available here.

Inputs

There are two input files, both in JSON format. The first consists of all the vaccines listed on the Vaccines Page. The most important values are the institutes involved, the countries involved, the platform being used (inactivated vaccines, live attenuated vaccines, protein subunit, RNA and DNA), the estimated funding category (Large external funding, Some external funding, Large Pharma, Medium Pharma and Bio-tech/Academic), the start and end dates of the trial phases (Pre-Clinical, Phase I, Phase II, Phase III and Approval) if known and an arbitrary vaccine number for cross referencing. The vaccines file can be downloaded from here.

The second file consists of the values of all the parameters such as success rates at each phase, the timescales for each phase, factors that depend on the platform and funding category. The parameters file with default values can be made available on request

Initialisation

After reading the input files, the program checks whether all the paramaters are within specifications, e.g., that success rates are between 0 and 1. If any paramaters are outside the specifications, the run is aborted.

At the start of every try each vaccine is initialised. Each vaccine is allocated a Probability of Success (PoS) for each phase given in, P_i where $i = 0 \ldots 4$ is the phase. The PoS for Pre-Clinical, Phase I, Phase II and Approval these are the same whereas for Phase III it depends on which platform the vaccine is on. In addition, these PoS are multiplied by a factor that depends on the funding category the vaccine is in. If the factor is f then P_i is multiplied by the 5th root of this factor $\sqrt[5]{f}$. Since the overall PoS is given by $P = P_0 \times P_1 \times P_2 \times P_3 \times P_4$, this ensures that the overall PoS is multiplied by f. It is assumed that vaccines in the funding category Bio-tech/Academic will be bought out by Large Pharma if they succeed in Phase I and so in this case the square root of f is used since only two phases will be relevant. This feature can be switched off if required. The PoS values are stored for later use. Note that when multiplying a PoS by a factor the result is capped at 1 should it exceed 1.

Each vaccine is also allocated a start and end month for each phase. Firstly, all start and end dates in the input vaccines file are converted to months relative to the current month (= 0). Dates in the future are ignored by default (if not any end dates are used as 'best case' dates). Each vaccine is allocated a 'best case', a 'most likely' and a 'worst case' date for each phase based on the input parameter values given in for each phase

multiplied by factors that depend on the platform and the funding category . The start date of each phase that is not already known is set according to the overlap category for that funding category given in. The overlap categories are as follows (using the default values):

Almost simultaneous - the next phase starts 1 month after the start of the previous phase.

Mostly overlapped - the next phase starts 2 months after the start of the previous phase.

Phases I & II overlapped - Phase II starts 1 month after the start of Phase I, Phase III starts 1 month after the end of Phase II.

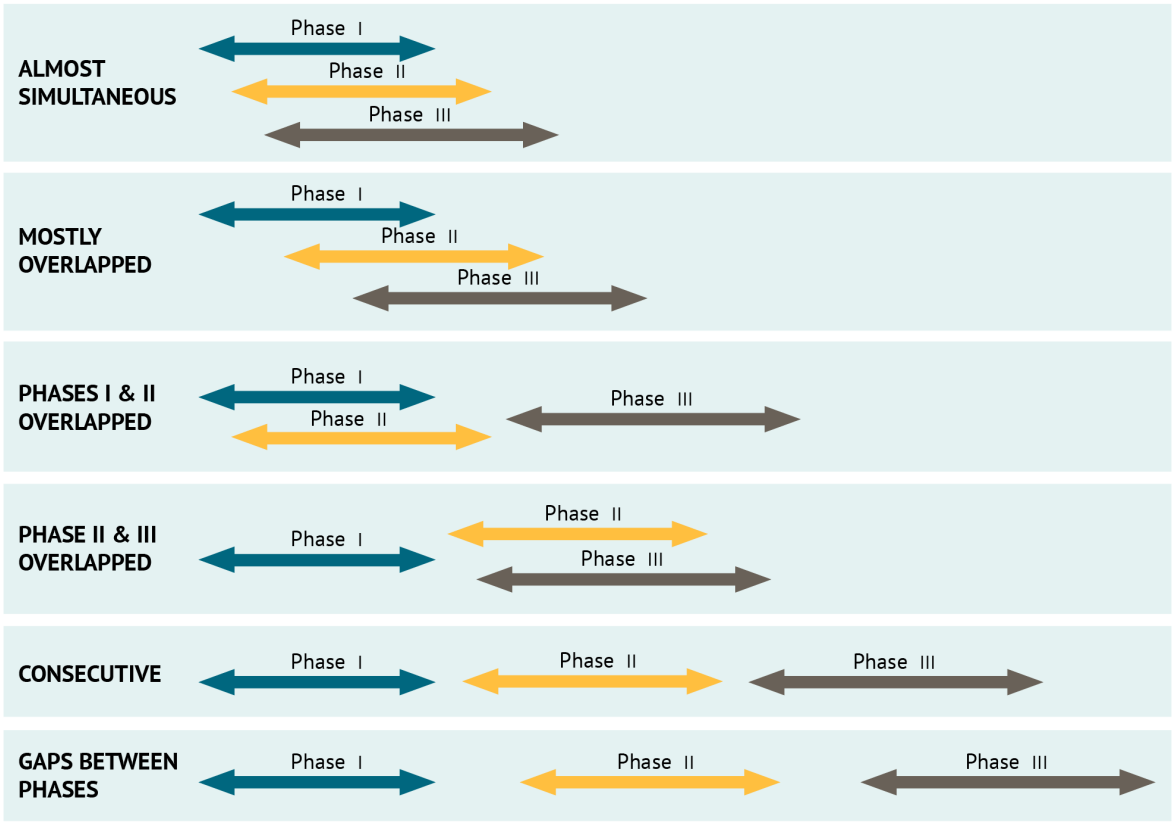
Phases II & III overlapped - Phase II starts 1 month after the end of Phase I, Phase III starts 1 month after the end of Phase II

Consecutive - each phase starts 1 month after the end of the previous phase.

Gaps between phases - each phase starts 6 months after the end of the previous phase.

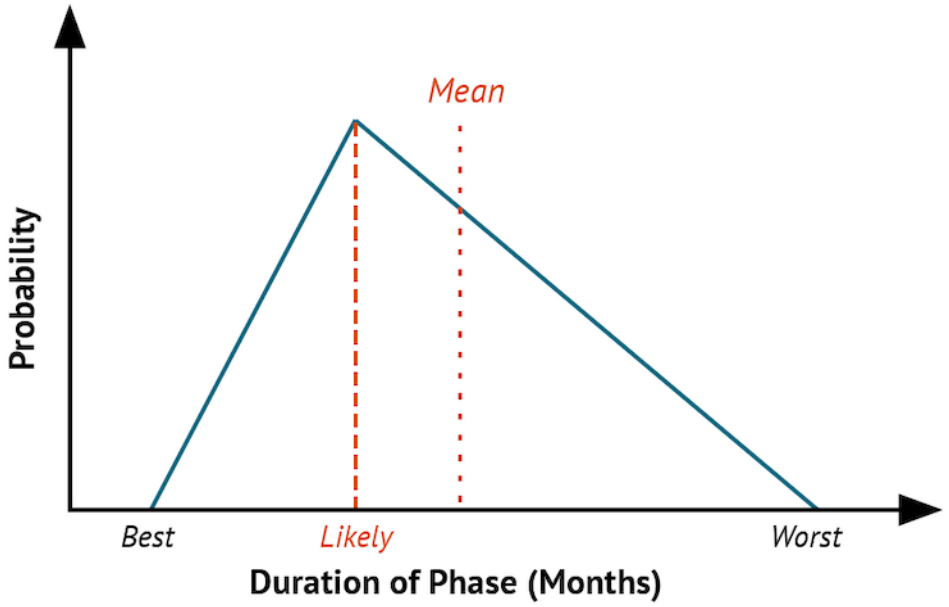
Phase I starts 1 month after the end of Pre-Clinical and Approval starts 1 month after the end of Phase III. These values are shown in of the detailed parameters. The overlap categories are illustrated in figure C.1.

Figure C. 1. Options for overlapping trails



Having set the start of each phase, the end of the phase is set by selecting a random phase length from a triangular distribution starting at the best case, peaking at the most likely case and ending at the worst case. Because in most cases the triangle is asymmetric the mean is to the right of the most likely value. This is illustrated in the figure below. In addition, a fraction of vaccines have their Phase III end dates delayed (see discussion below). Any end dates that come out before month 1 are set to month 1 as it assumed that otherwise these would be in the original vaccines file. The start and end months are stored for later use. Figure C.2 is a triangle distribution used to randomly select month lengths.

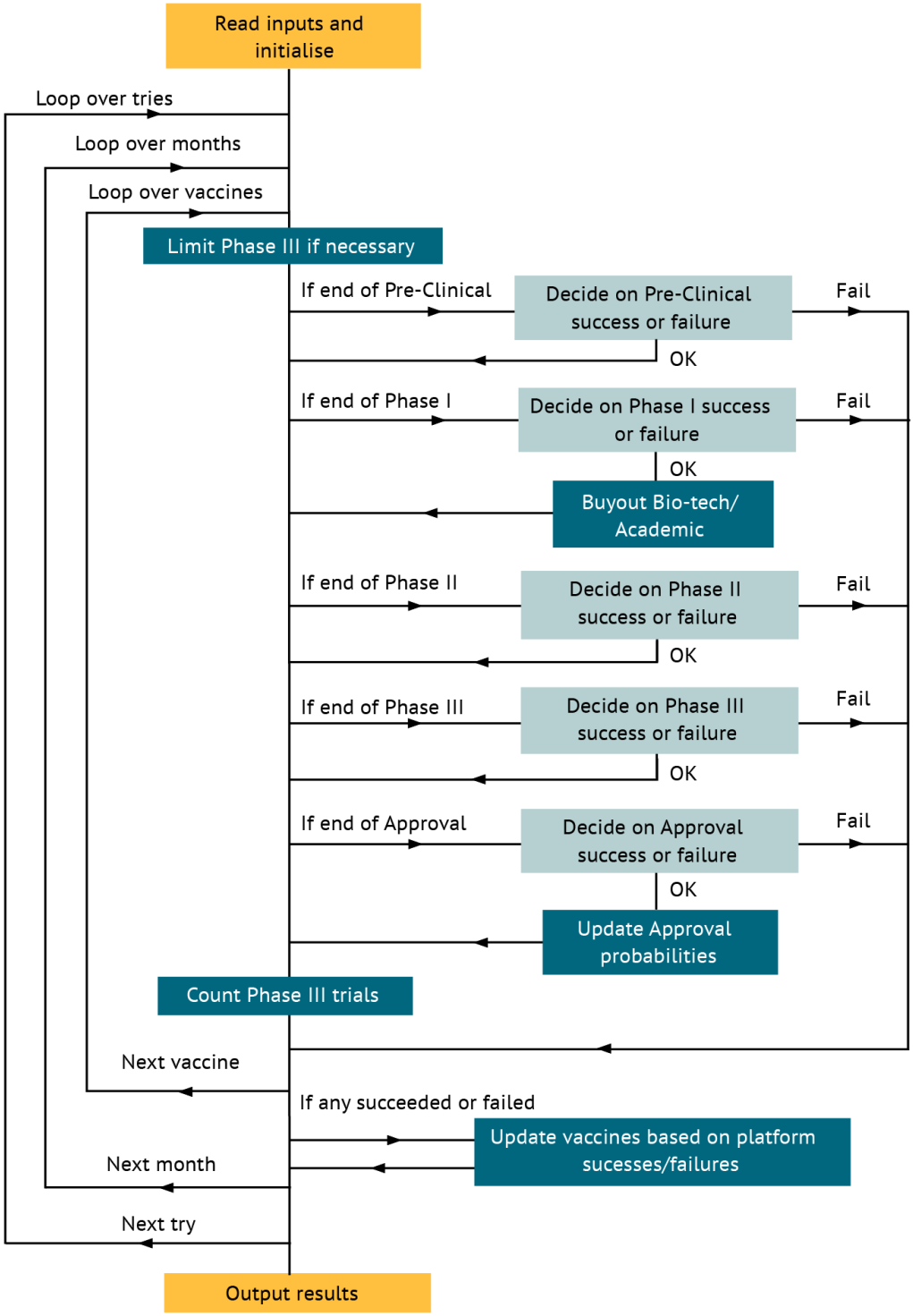
Figure C. 2. Triangle distribution for randomly selecting month lengths



Program Flow

The program proceeds as shown in the figure below. There is a main loop over tries then for each try the program loops over each month and for each month loops over each vaccine. To avoid any bias the order of the vaccines is randomised evert try. Each month each vaccine is tested to see if a phase ends that month. If so, a random number is used to decide whether the vaccine succeeds or fails dependent on its PoS for that phase. If it succeeds it continues for further months. If a vaccine succeeds the Approval Phase, this information is used to possibly inhibit further approvals as discussed below, and if a Bio-tech/Academic candidate succeeds at Phase I, this vaccine may be bought out as described below. If the vaccine fails, a second random number is used to decide whether the failure is technical or economic. All failures for well-funded vaccines are assumed to be technical whereas all failures for Bio-tech/Academic are assumed to economic. This information is used to calculate correlations as described below. Figure C.3 shows a flow chart for the model.

Figure C. 3. Flow chart for the model



Limiting Phase III Trials

In practice, Phase III trials may be slowed down if infection rates drop across the world. In addition, the overall number of trials might be limited, or they might be slowed down if too many Phase III trials take place simultaneously. At the end of each month the number of vaccines that have successfully passed Phase III is calculated. At the start of the next month if a vaccines is about to start Phase III if the number of already successful vaccines exceeds a limit (by default 6) then by default the end of the Phase III trial is delayed (in addition to the delay described above). There is also the option to prevent the vaccine entering Phase III until the total number drops below the limit. This is done by deferring the start of Phase III till the next month (which may happen several times). Any adjustments to Phase III are also applied to the start of Approval which will be similarly delayed.

Bio-tech/Academic Buyout

Some (by default 100%) Bio-tech/Academic vaccines that are successful at Phase I are randomly deemed to be bought out by Large Pharma organisations. In this case the funding category is changed, and the vaccine is re-initialised to update its PoS and timelines to reflect the new category. It then proceeds as if it were a Large Pharma candidate.

Limiting Approval

Once we have an adequate number of vaccines, it may become more difficult (or easier) for other candidates to be approved. Above some limit subsequent approvals will be less likely to succeed and the timeline will be longer. Each time a vaccine is successfully approved and the number of approved vaccines is above some limit (by default 3) all other vaccines have their Approval PoS and Approval phase length multiplied by some factor. These factors are cumulative so that it gets harder and harder to approve subsequent vaccines.

Correlations between Vaccines

It is likely that success or failure of one vaccine on a platform might impact other vaccines on the same platform i.e. a failure might indicate that this platform is inherently unsafe. Each time a vaccine succeeds or fails technically at Phase I, Phase II or Phase III the following procedure is enacted. Commercial failures are ignored. The number of successes, S, and technical failures, F, at that phase on that platform is used to calculate an aggregate $A = S \div (S + F)$. This aggregate is then compared to the *PoS, Pi,* for that platform and phase as described during initialisation above. A new PoS is then calculated as

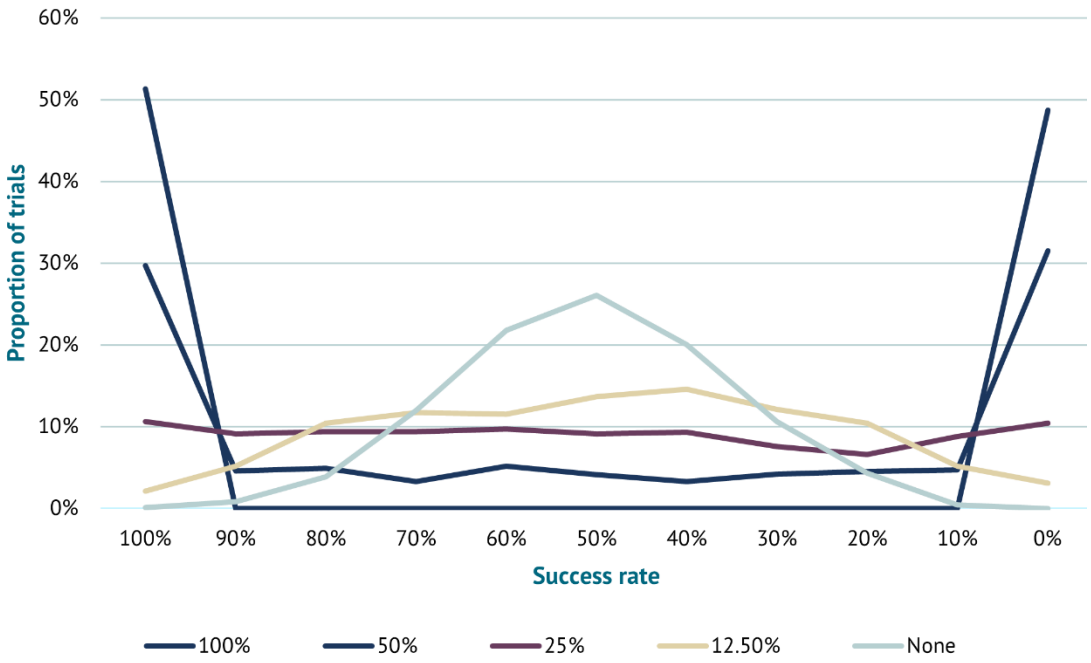
$$P'_i = ((A - P_i) \times C) + P_i.$$

This is a Bayesian type approach whereby the initial PoS, Pi is updated with new information based on A. The factor C is a correlation strength that depends on the platform (see Table 3 and Table b). The ratio $R = P'i \div Pi$ between the new and old PoS is then used to multiply the original PoS of all phases of all vaccines on the same

platform. There are then adjusted for the funding category as described in the initialisation. In this way if one vaccine on the platform succeed, the others are more likely to and likewise if one fails the others are more likely to fail. This introduces a correlation between vaccines on the same platform and drives a divergence of the overall PoS for that platform.

Figure C.4 is the output of a 1,000-run simulation that looks at the proportion of the first 10 vaccines in a platform that are successful when different adjustment rates are used. The adjustment is switched off for when the correlation is rated none; variation on this line is the randomisation inherent in Monte Carlo simulations. With 100% correlation you will see that all vaccines in a portfolio either succeed or fail. With no correlations each of the ten trial outputs in each run are grouped around the mean, and very view highish successful or highly unsuccess platform runs. With a 25% correlation, we found that any combination of successes and failures within a platform were about equally likely, when the input was 50% (other inputs would weight more strongly to either success or failure). 12.5% does have some very successful runs and complete flops, but here the majority of runs are near the mean. It is for this reason, that we used 25% correlation as our standard input. We then halved this to 12.5% for lowly correlated vaccine portfolios and increased it to 50% for highly correlated portfolios.

Figure C. 4. Changes in probability of success after funding adjustments



Outputs

Once all tries have been completed a number of files are created:

- An 'output' JSON file contains success rates, timelines and information about the average performance of each vaccine including their 'rank' according to this model.

- A summary JSON file containing the average of five 'benchmark' results - Months until >50% chance of a vaccine, Months until >90% chance of a vaccine, Months until >99% chance of a vaccine, Probability of at least one vaccine after 36 months and Number of vaccines approved after 36 months.

- A 'trials' CSV file suitable for use in Excel. This file has the format: Try number, Vaccine number, Phase I, Phase II, Phase III and Approval, where the phase columns contains the month at which the vaccine was successful. If it wasn't successful at any phase, the row is suppressed.

- We can share paper model outputs on request.

Appendix D. COVID-19 Vaccines Interview Guide

Questions (not all interviewees will necessarily be able to answer all questions).[20]

1. How difficult will it be to develop approvable COVID-19 vaccines versus vaccines for other viral pathogens? [1 = very easy, 10 = very difficult].

2. How long do you expect a vaccine trial to last for a well-funded or leading candidate?

	Pre-clinical	Phase 1	Phase 2	Phase 3	Regulatory review
WHO[21] estimate for simple & complex vaccines	3.3 years	1.6 & 2 years	2.2 & 3.7 years	2.3 and 3.5 years	Not given
Most likely scenario					
How might unforeseen events speed this up or slow it down?					

20 As discussed in the paper, there were some slight changes the questions during our interviews as the information in the public domain changed, we learnt what people were able to answer and what they were not. This exact version was used for the last 6 interviews.

21 This should have said Terry et al. 2018, as these are not WHO estimates

3. Different vaccine platforms[22]

Vaccine candidate/ platform	Probabilities of success thus far (mean, lowest and highest estimate)[23]	Probability of success (POS)	Significantly faster or slower?	POS change with one scientific success or failure?
Live attenuated virus Includes: Codagenics / Serum Inst				
Protein subunit+ adjuvant Includes: Sanofi/GSK				
Inactivated virus Includes: Wuhan/Beijing Institute /Sinopharm				
mRNA Includes: Moderna and BioNTech/Fosun Pharma/Pfizer- 3 LNP-mRNAs (4 candidates)				
Non-replicating adenoviral vector Includes: Johnson & Johnson, ChAdOx1-nCov19 and CanSino Ad5nCov				
Replicating adenoviral vector				
DNA vaccines				
New technology not listed above				

22 As discussed in the paper the first eight interviewees were asked to rank platforms out of 10, and then later given an opportunity to translate these into probabilities of success.

23 These estimates were updated for every interview based on our running tally. So there are no standard numbers we can share.

4. Some vaccines are much better funded than others. How would probabilities of success and timelines change for the following scenarios.

Funding type	Impact on Probability of success (multiplier)	Time to run an individual trial
Large external funding ($400m+)		
Some external funding ($50m-$400m)		
Involvement of a large pharma company (revenue +$10bn per year)		
Led by medium sized pharmaceutical company, that has experience taking things to market		
Led by biotech or academic institution with no experience taking things to market (including chances that candidate bought out)		

   a. If not answered, Do you think small candidates are still likely to be picked up by big pharma. What would need to happen for a pickup?

5. What probability do you expect for each phase? (this will be used to understand when vaccines fail in our model, overall probabilities of success will come from question 3.

	Pre-clinical	Phase 1	Phase 2	Phase 3	Regulatory review
WHO[24] estimate for simple & complex vaccines	40%	70% & 50%	45% & 20%	70 % & 60%	Not given
Your estimate for a COVID vaccine					

6. How many vaccine candidates do you think will be approved?

Generation	A few perfectly possible
First generation approvals	
Total approvals	

   a. Will it get more difficult to approve vaccines with time, if so when and how much more difficult.

   b. Do you anticipate the first vaccines to be used prior to full licensure, if yes how widely and when?

7. What efficacy would you expect we will get for a vaccine for candidates currently in the pipeline?

      a. Any sense of how long immunity might last

8. Do you have any views on individual candidates not captured above?

9. Anything else we should be thinking about?

24 This should have said Terry et al. 2018, as these are not WHO estimates

Appendix E. Importance of Funding to Vaccine Success

Table E.1. Experts' assessment of speed of vaccine development and probability of success, by type of developer

	Speed of vaccine development		Probability of success	
Developer	**Experts' assessment of effect on development**	**Quantitative model**	**Experts' assessment**	**Quantitative model**
Company with external funding of at least $400 million	• Substantially faster (3) • Faster (1) • Slightly faster (1) • No effect (1) (*n* = 6)	20% faster	• More likely to succeed (3) • Slightly more likely to succeed (3) • No effect (5) (*n* = 11)	Same
Company with external funding of $50–$400 million (n=66)	• No effect (5) • Faster (1) (*n* = 6)	Same	• No effect (7) (*n* = 7)	Same
Medium-size pharmaceutical company that has experience taking products to market	• Significantly slower (2) • Slower (2) • Slower (1) • No effect (4) (*n* = 9)	10% slower	• No effect (4) • Slightly more likely to fail (2) • More likely to fail (2) (*n* = 8)	5% lower

Small biotech company or academic institution with no experience taking products to market	• Much slower; will not go past phase 1 (n = 13)	Three times slower in preclinical and phase 1 trials (after which the model assumes if a candidate succeeds the vaccine has been bought out by a larger company or gained external funding. The candidates will thus progress at the timelines of large pharma after phase I.	• Cannot succeed on own; large companies could buy out four or five of these institutions	PoS through the end of phase 1 trials is 95% lower; model assumes that after phase I, candidates progress as if managed by a large pharma company

Note: All results are relative to large pharmaceutical companies that did not have external funding. Figures in parentheses show number of responses. Total number of responses in each row is less than 16 because not every respondent gave an estimate.

Appendix F. Background Information on Vaccines

Live Attenuated Virus

Live attenuated vaccines are capable of infecting the host and producing a strong immune response using a vaccine virus that has reduced virulence and is not pathogenic. These types of vaccines have been used for more than 200 years. Examples include vaccines for smallpox, yellow fever, polio (Sabin), measles, mumps, rubella, rotavirus and zoster.

Number of vaccines in development and distribution of funding

The portfolio includes four live attenuated virus vaccines (1.9% of all candidates) (Figure F.1). None of the candidates is well-funded.

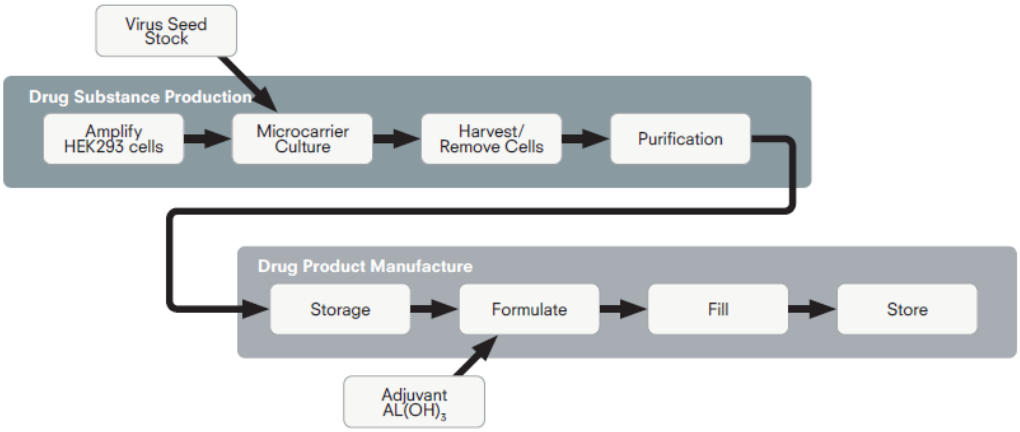
Our experts gave a well-funded candidate from this platform a 37% chance of passing through a phase 3 trial, with the 20th and 80th percentiles being 20% and 48% respectively. This is the second-worst ranking of any platform. Just one out of fourteen[25] interviewees ranked this as the best or joint-best platform, while three ranked it as the worst or joint worst. This saw the biggest fall in probability estimate between our interviews and follow up emails, having an original phase 3 success score of 44%. The reasons for their rankings are outlined below.

25 Fourteen interviews gave quantitative estimates for the probability of passing through phase III, whilst all sixteen gave qualitative evaluations

Table F.1. Positive and negative factors affecting development of a vaccine based on live attenuated virus

Positive attributes	Negative attributes
7 of 16 identified positive features Known technology - long history of success highly efficacious good immune response with long duration of immunity no adjuvant required may only need single dose examples, polio, measles, rotavirus	**11 or 16 identified issues** long time to develop attenuated strain long time for clinical evaluation of safety **safety issues** potential instability of attenuation (reversion to wild type) rare severe adverse events potential to cause vaccine associated disease outbreaks concerns with disease enhancement huge numbers needed to validate safety not suitable for immune compromised public acceptance issue potential for reintroduction of disease

Figure F.1. Production of drug substance and manufacture of drug product for a live attenuated vaccine



Live attenuated manufacturing

The manufacturing route is similar to inactivated live virus, but without the inactivation step as the virus is weakened. Lower biocontainment level is required than live wild virus. Often grown in cell lines on microcarriers, purification by gradient centrifugation followed by tangential flow filtration.

Manufacturing 100 million does in a year

For attenuated live vaccines, assume that a single 2000L bioreactor could produce 3.3M doses after purification. Running the reactor just 33 times would yield 100M doses

Comments on manufacturing

The existing MMR vaccine is an example of an attenuated live vaccine. However, one of the concerns with attenuated live vaccines is possible reversion to wild type.

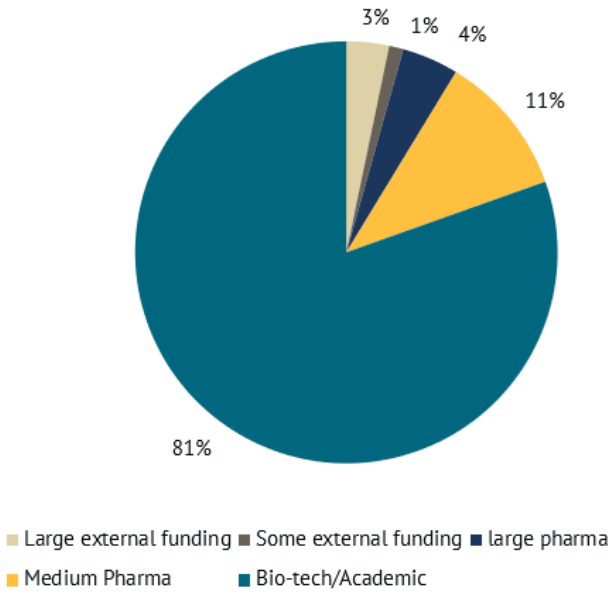
The microcarrier manufacturing route would allow adoption in many current bioreactor facilities.

Protein Subunit

Protein subunit vaccines consist of a broad range of technologies that produce an immune-stimulating viral protein antigen. This technology has a relatively long history of success in vaccines such as Hepatitis B, HPV, influenza and others. We include Virus Like Particle (VLP) vaccines in this platform as they are essentially a specific subclass of protein subunit technology.

There are 92 (44%) protein subunit vaccines in the portfolio including some very well-funded candidates, but the vast majority do not.

Figure F.2. Funding of and types of institutions working on protein subunit–based vaccine

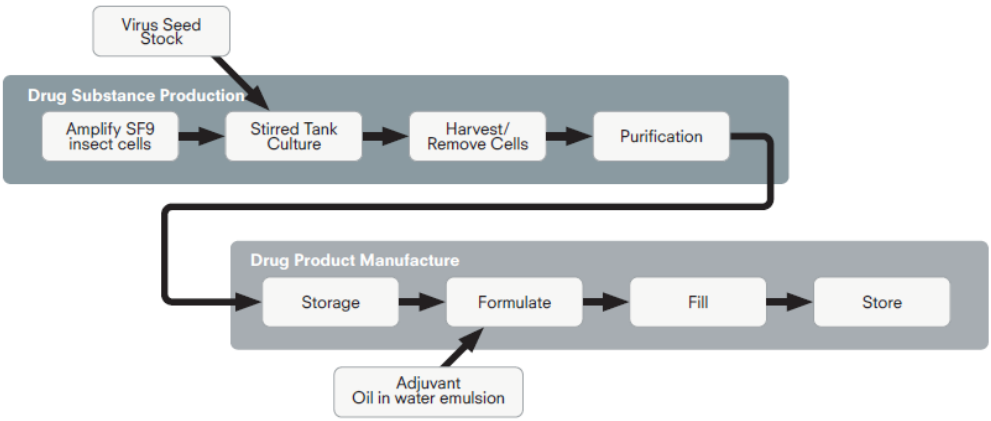


Our experts gave a well-funded candidate from this platform a 64% chance of passing through a phase 3 trial, with the 20th and 80th percentiles being 45% and 80% respectively. This is the best ranked candidate by some way. Ten of out of fourteen[26] interviews ranked this as the best or joint best platform while none ranked it as the worst or joint worst. The reasons for their rankings are outlined below.

Table F.2. Positive and negative factors affecting development of a vaccine based on protein subunit

Positive attributes	Negative attributes
11 of 16 identified positive features Known technology - standard methodology - easy to license safe and effective proven platform with long history - HPV, Hep B less likely to cause enhanced disease will be able to distinguish between infected vs vaccinated strong antibody response - potential booster for other COVID-19 vaccines relatively simple & well known manufacturing process most vaccine manufacturers have facilities and experience with the manufacturing process	**7 of 16 identified issues** effectiveness with corona viruses is unknown will need a good adjuvant may need booster doses T-cell response may be lower slower to develop will require two doses

Figure F.3 Production of drug substance and manufacture of drug product for a protein subunit vaccine



26 Fourteen interviews gave quantitative estimates for the probability of passing through phase III, whilst all sixteen gave qualitative evaluations

Protein subunit manufacturing of the protein subunit

The process has many similarities with the production of monoclonal antibodies. Host cells, typically SF9 insect cells, are expanded in bioreactors. They are then transfected with baculovirus, which encodes the expression of protein subunits. Purification involves a mixture of tangential flow filtration and chromatography.

Manufacturing 100 million doses in a year

With a single dose in the order of 15 µg, a single 2000L bioreactor could produce 5M doses after purification. Running the reactor just 20 times would yield 100M doses.

Comments on manufacturing

Sanofi Flublok's vaccine is a protein subunit vaccine. We believe that manufacturing can be very productive and has been demonstrated at large scale.

The insect cell manufacturing route would allow adoption by many current bioreactor facilities. This technology could be easily scaled.

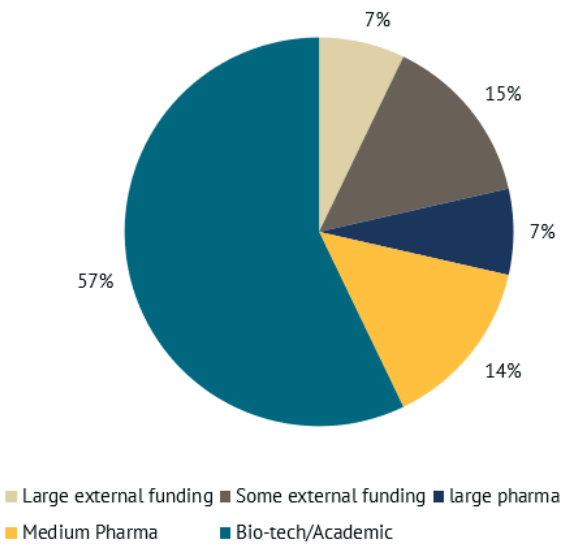
Inactivated Virus

Inactivated virus vaccines are made from isolated strains of the wild virus that are inactivated by chemical or heat treatment. This technology is tried and true, having been used in polio (Salk), influenza, rabies and Hepatitis A vaccines.

Number of vaccines in development and distribution of funding

The portfolio includes 14 inactivated virus vaccines (6.7% of all candidates). Twenty-two percent are well-funded.

Figure F.4. Funding of and types of institutions working on an inactivated virus vaccine

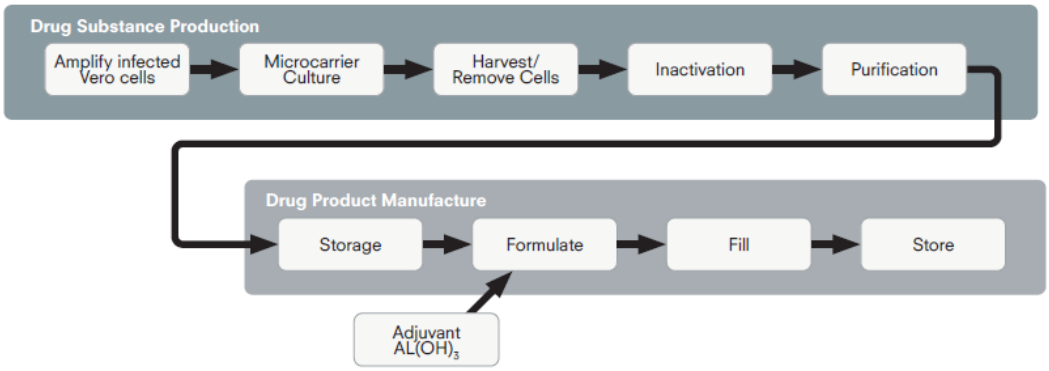


Our experts gave a well -funded candidate from this platform a 39% chance of passing through a phase 3 trial, with 20th and 80th percentiles of 20% and 60%, respectively. This platform is the fifth- highest rated. Two of 14 experts ranked it best or joint best; 1 ranked it as the worst.[27] This platform is one of three that saw a decline off more than 1 percentage point between our interviews and follow-up emails (the initial PoS was 43%). Table F.3 describes the positive and negative factors affecting this platform's PoS.

Table F.3. Positive and negative factors affecting development of a vaccine based on an inactivated virus

Positive attributes	Negative attributes
10 of 16 identified positive features	**11 of 16 identified issues**
Known technology	requires higher level biocontainment (level 3 production facility) for growth of live pathogenic virus
demonstrated protection for SARS/MERS in mouse challenge studies	validation of inactivation process is a regulatory challenge
no disease enhancement	concerns similar to concerns about respiratory syncytial virus vaccine in this application
good immune response	disease enhancement was an issue with inactivate dengue
broad immune response, not just spike protein	vaccine enhanced immune pathogenesis
does not require adjuvant	Long cycle time, long development time
long history (Hepatitis A, influenza, rabies)	could be stability issues
simple production	

Figure F.5. Production of drug substance and manufacture of drug product for an inactivated virus vaccine



Inactivated virus manufacturing

Often grown in Vero cell lines on microcarriers, inactivated virus vaccines involve live SARS-CoV2 viruses that require biocontainment facilities at containment level 2+ or 3[28]. The virus then needs to be inactivated by formalin and UV, before being purified and filtered.

Manufacturing 100 million doses in a year

A single 2000L bioreactor could produce 3.3M doses after purification. Running the reactor just 33 times would yield 100M doses.

Comments on manufacturing

Inactivated vaccines such as egg-based influenza vaccines have been used for decades. The use of microcarrier technology using Vero cell lines has increased productivity. These vaccines are effective, but their manufacture requires containment level 2+ or 3 facilities. Scale-up might require displacing other vaccines, as stainless steel rather than single-use technology would be safer.

RNA

RNA vaccines represent a very new technology that has been used to treat various forms of cancer and some other chronic diseases. No licensed infectious disease vaccines have been produced using this technology.

RNA that can produce a viral protein antigen is engineered and delivered into host cells, usually using a lipid nanoparticle delivery technology. Once in the host cells, the RNA can manufacture viral protein antigen to stimulate an immune response. The variation in candidates is related largely to the delivery technology used.

Number of vaccines in development and distribution of funding

The portfolio includes 30 RNA vaccines (14.4% of all candidates). Seventeen percent are well-funded.

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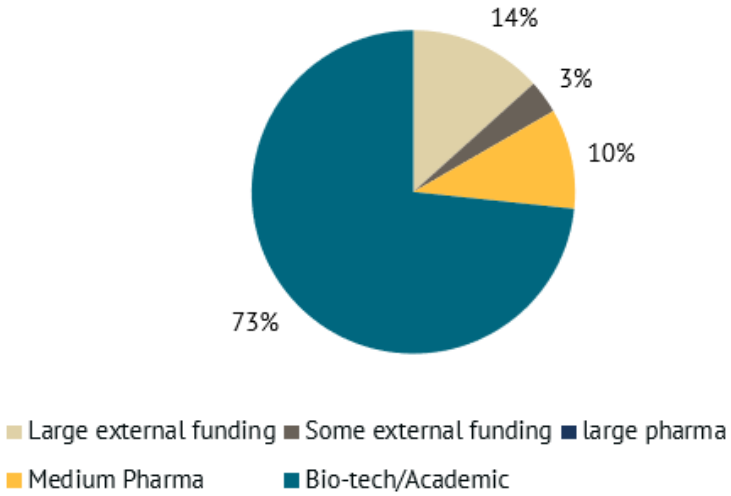
28 Products being researched or manufactured in labs, that are more dangerous to the general public have to be processed in higher rated containment labs, which have more safety procedures, to reduce the risk of contaminating the public. The highest rating on the system is 4, very few labs meet containment 3 or 4 criteria, needing to manufacture anything a lab of greater than containment 2 creates capacity issues and slows production.

Figure F.6. Funding of and types of institutions working on an RNA vaccine



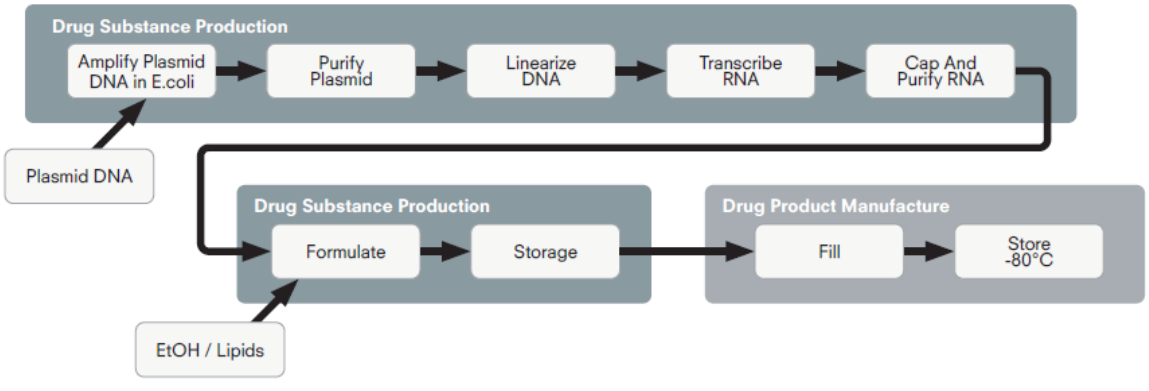
Our experts gave a well-funded candidate from this platform a 48% chance of passing through a phase 3 trial, with 20th and 80th percentiles of 35% and 63%, respectively. This platform is the third-highest ranking. Three of 14 experts ranked it as the best or joint best platform; 2 ranked it as the worst or joint worst.[29] Table F.4 describes the positive and negative factors affecting this platform's PoS.

29 Fourteen respondents provided quantitative estimates of the probability of passing through phase III; all 16 gave qualitative evaluations.

Table F.4. Positive and negative factors affecting development of an RNA-based vaccine

Positive attributes	Negative attributes
11 of 16 identified positive features.	**12 of 16 identified issues**
Theoretical potential	Experimental technology - no human vaccines have been developed with this technology
human use in experimental cancer vaccines	challenges with in process sterilization
Immunogenicity looks good	Moderna data difficult to interpret - rabies data was unimpressive.
neutralizing antibody production is acceptable	Lipid nanoparticle delivery systems vary with each vaccine
antigen is membrane bound - may produce better response	Some lipid nanoparticles are toxic - high doses are not tolerable
relatively well tolerated	serum neutralizing antibody is highly variable
rapid development and manufacturing	no CD-8 response
	highly unstable formulations - need -80C storage
	working on lyophilized product or stabilized to -20C
	large scale manufacturing unproven
	may require high dose - issues with tolerance
	several innate immune response sensors are activated by RNA
	needs adjuvant, needs two doses
	long term safety questions
	regulatory challenges especially with the production process and facilities

Figure F.7. Production of drug substance and manufacture of drug product for an RNA vaccine



Manufacturing RNA vaccines

This platform is characterised by low volume production, normally undertaken in small scale bioreactors. The labile product requires storage at –80°C.

Manufacturing 100 million doses in a year

With a single dose in the order of 50μg RNA, a single 250L bioreactor could produce 1 million doses after purification. Running the reactor 100 times would yield 100M doses.

Note that the dose for self-amplifying mRNA is in the order of 1μg, requiring a bioreactor volume 50x smaller to produce a similar number of doses.

Comments on manufacturing

RNA vaccines have attracted much attention. The rapid production method means that a successful RNA vaccine could be made available quickly. However, to date no licensed RNA vaccines are on the market.

Self-amplifying RNA has the advantage that smaller does being effective. Administration of the dose may require an electroporation device, adding to the already complex cold supply chain.

Non-Replicating and Replicating Viral Vector

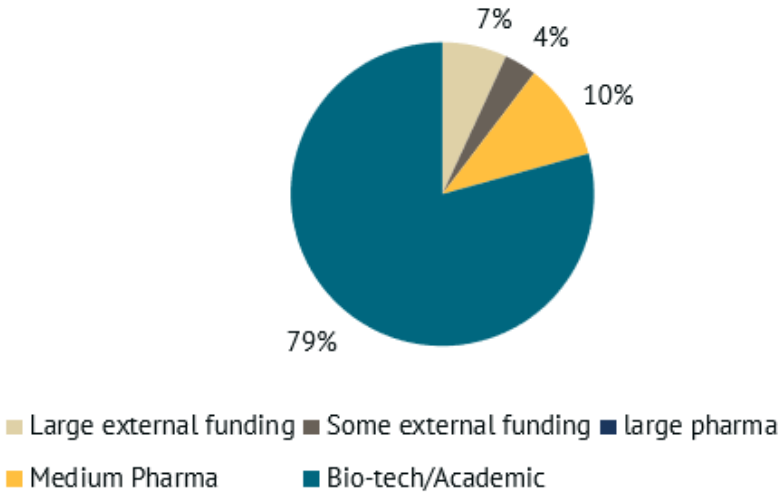
Non-replicating viral vector vaccines consist of a genetically modified virus vector (adenovirus, pox virus and alphaviruses have been used) that has insertion sites for certain genes from the target pathogen (usually the COVID-19 spike protein). Deletions in the viral genome render replication incompetent.

There is some experience with this technology in the gene therapy field. The technology has never been successfully used as an infectious disease vaccine for mass immunization programs in humans, however.

Number of vaccines in development and distribution of funding

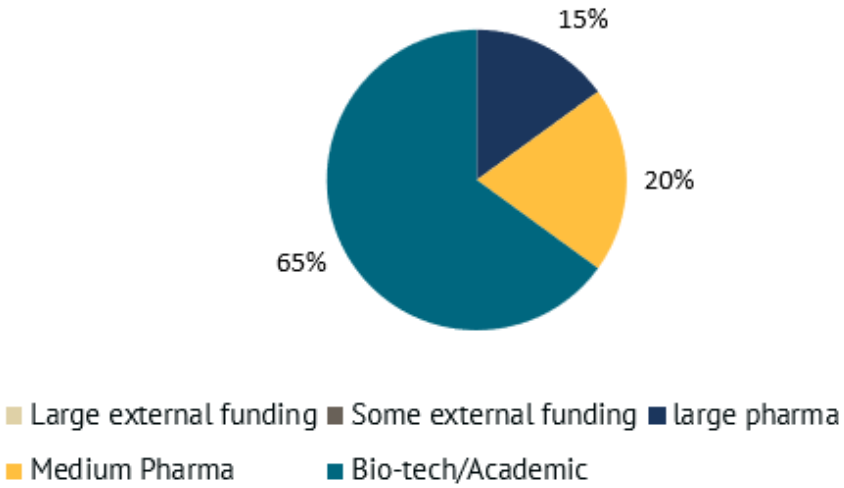
The portfolio includes 29 non-replicating viral vector vaccines (13.9% of all candidates) (figure F.8). Eleven percent are well-funded.

Figure F.8. Funding of and types of institutions working on a nonreplicating viral vector vaccine



Replicating viral vector vaccines are similar to non-replicating viral vector vaccines, except that they are able to replicate in the host. This feature makes them similar to live viral vaccines. The portfolio includes 20 of these vaccine (9.6% of all candidates). None of them is well-funded.

Figure F.9. Funding of and types of institutions working on a replicating viral vector vaccine



Our experts gave a well-funded candidate non-replicating viral vector vaccine a 53% chance of passing through a phase 3 trial, with 20th and 80th percentiles of 41% and 57%, respectively. This platform is the second-highest ranking. Two of the 14 experts ranked it as joint best platform; 1 ranked it as the joint worst.[30] This platform was the only one that saw an upwards shift in the PoS between the original interviews and follow-up emails of more than 1 percentage point (the original score was 50%). Table F.5 describes the positive and negative factors affecting this platform's PoS.

Table F.5. Positive and negative factors affecting development of a vaccine based on a non-replicating viral vector

Positive attributes	Negative attributes
12 of 16 identified positive features	**13 of 16 identified issues**
relatively easy, high-productivity manufacturing process	platform has been studied for decades without success
Ad26 vector used in phase III HIV trial demonstrated safety	Ad5 vector has challenges with pre-existing antibodies in population
In a pre-clinical study, Ad26 vector had good response in monkeys (J&J vaccine)	Ad5 vector (Cansino) has low neutralizing antibody even in highest dose
In a pre-clinical study, Chimp Ad vector was safe and had good response (Oxford)	Ad Chimp (Oxford) has low immune response
Ad5 is used in Cansino Ebola vaccine	Ad26 (J&J) immune response was not impressive; could be a problem if a booster dose is required
Good safety data based on pox vectors	generally low immune responses; platform needs two doses
considerable experience in vaccine development programs	reactogenic
platform better understood than RNA	Merck had problems with Ad5 vector in other vaccines
good approach for a pandemic response with the right vector	Merck Ad5 HIV vaccine had lingering safety concerns related disease enhancement caused by pre-exposure to Ad5
	concerns in general about quality of immune response and duration of immunity

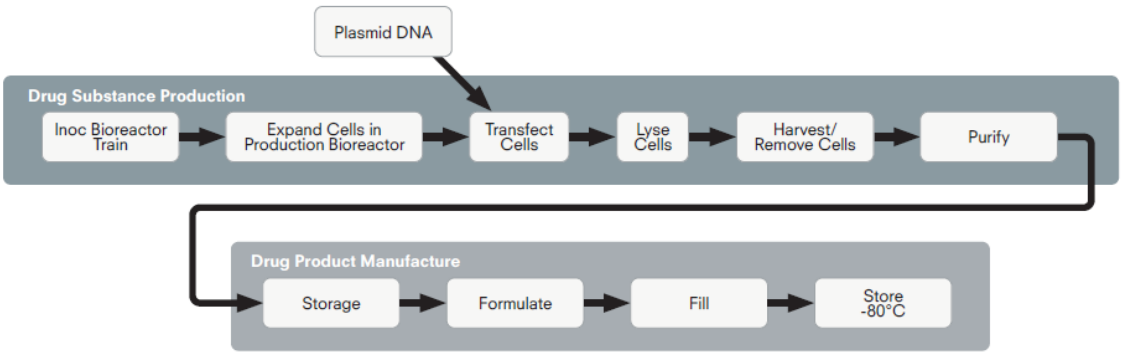
Our experts gave a well-funded replicating viral vector vaccine a 45% chance of passing through a phase 3 trial, with 20th and 80th percentiles of 28% and 54%, respectively. This platform is the fourth-highest ranking of the seven. One expert ranked it as the joint best platform; two ranked it as the joint worst. Table F.6 describes the positive and negative factors affecting this platform's PoS.

30 Fourteen respondents provided quantitative estimates of the probability of passing through phase III; all 16 gave qualitative evaluations.

Table F.6. Positive and negative factors affecting development of vaccine based on a replicating viral vector

Positive attributes	Negative attributes
5 of 16 identified positive features greater immunogenicity than non-replicating vector vaccines VAXART has developed military vaccines using Ad4 and Ad7 that have been approved. Given orally with good safety and immunogenicity Ebola vaccine developed with this platform is reasonably promising	**10 of 16 identified issues** greater safety issues than non-replicating viral vector vaccines no human vaccines for general use in public no experience in immunocompromised patients, people over 65 or children less experience than non-replicating viral vector vaccines manufacturing scalability is questionable risk of chromosomal integration quality of immune response is variable same issues with choice of vector as non-replicating viral vector vaccines attenuated measles vector is a concern in adults (pre-existing immunity to measles could undermine the effectiveness of a measles vector vaccine) hyper typic immune response; risk of enhanced disease (SARS/MERS)

Figure F.10. Production of drug substance and manufacture of drug product for replicating and non-replicating viral vaccines



Manufacturing replicating and non-replicating viral vaccines

The process has many similarities with the production of monoclonal antibodies. Host mammalian cells, typically HEK293T, are expanded in bioreactors. They are then transfected with plasmids, which encode the non-replicating virus. After sufficient virus

has been formed, the cells are lysed and the cell debris removed. Purification involves a mixture of tangential flow filtration and chromatography. The labile product requires storage at –80°C.

Manufacturing 100 million doses in a year

With a single dose in the order of 1e11 viral particles, a single 2000L bioreactor could produce 10M doses after purification. Running the reactor just 10 times would yield 100M doses.

Comments on manufacturing

Platform processes for other virtual vector vaccines, such as Ebola, suggest that viral vector vaccines for COVID-19 could be developed very rapidly. Viral vector production could be rapidly scaled using 2000L single-use bioreactor technology.

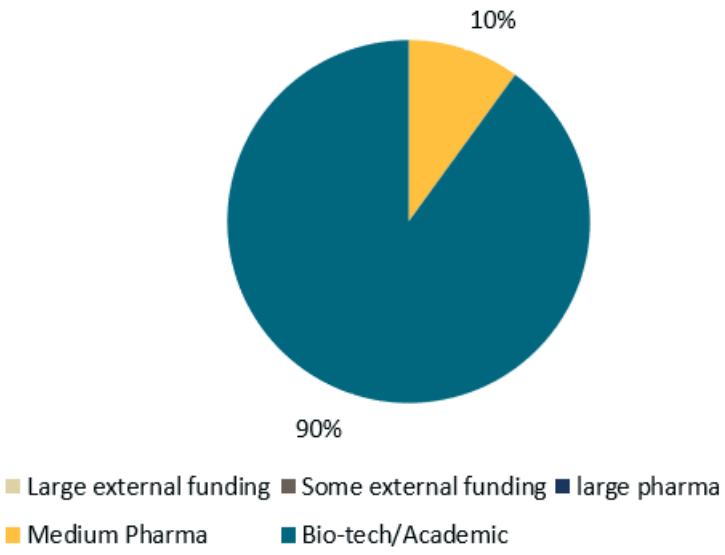
DNA

DNA vaccines have been in development for decades, but so far, no human vaccines using this technology have been licensed. This platform uses a short segment of DNA that codes for the desired protein antigen, which is introduced into the host's cells, where it uses the normal cellular apparatus to produce the antigen in vivo. Various methods have been used to introduce the DNA plasmid into host cells, including mechanical devices such as electroporation.

Number of vaccines in development and distribution of funding

The portfolio includes 20 DNA vaccines (9.6% of all candidates). None is well-funded.

Figure F.11. Funding of and types of institutions working on a DNA vaccine



Our experts gave a well-funded candidate from this platform a 21% chance of passing through a phase 3 trial, with 20th and 80th percentiles of 11% and 26%, respectively. This platform is the lowest ranked. None of the 14 experts ranked it as the best or joint best; 12 ranked it as the worst or joint worst.[31] This platform was one of three that was downgraded between the in-depth interviews and the follow-up emails (the original PoS was 26%, 5 percentage points higher). Table F.7 describes the positive and negative factors affecting this platform's PoS.

Table F.7. Positive and negative factors affecting development of a DNA-based vaccine

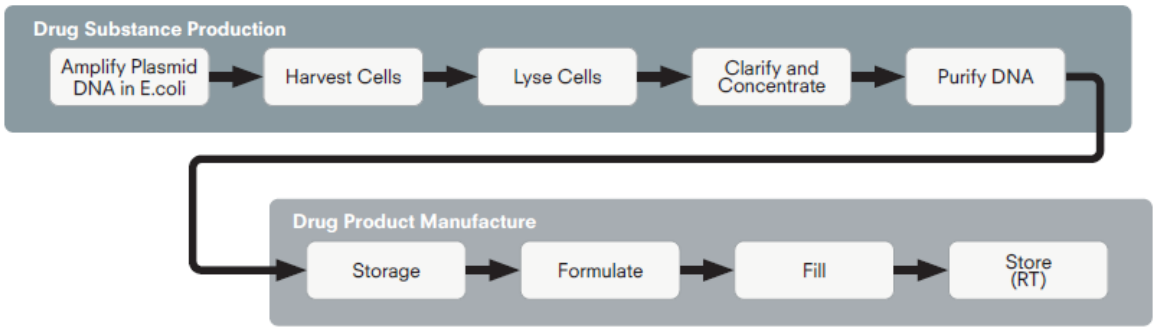
Positive attributes	Negative attributes
6 of 16 identified positive features	**13 of 16 identified issues.**
Innovio's electroporation delivery system may work better than other DNA candidates	Notoriously unsuccessful in humans
considerable experience with platform in vaccine development trials	requires breakthrough in delivery system and/or unapproved adjuvant technology
MERS candidate was highly immunogenic in monkeys	electroporation delivery system makes mass immunization difficult
immunogenic in small animal studies for COVID-19 vaccine	poor antibody response; even high doses tend to be ineffective
can protect in monkeys with electroporation delivery	safety issue related to DNA integration into host genome
good T-cell response	
veterinary DNA vaccines are effective	
can be used in immunocompromised subjects	
possible oral formulations	
rapid scalable manufacturing	

DNA manufacturing

This platform uses a short segment of DNA which codes for the desired protein antigen which is introduced into the host's cells where it can use the normal cellular apparatus to produce the antigen in vivo. Various methods have been used to introduce the DNA plasmid into the host cells including mechanical devices such as electroporation.

31 Fourteen respondents provided quantitative estimates of the probability of passing through phase III; all 16 gave qualitative evaluations.

Figure F.12. Production of drug substance and manufacture of drug product for a DNA vaccine



Manufacturing of the protein subunit

Characterised by low volume requirements for drug substance. Initial amplification of DNA in medium scale bioreactor. Purification involves a mixture of tangential flow filtration and chromatography. DNA formulations are stable at room temperature, a big advantage over RNA synthesis.

Manufacturing

With a single dose in the order of 1mg DNA, a single 5000L bioreactor could produce 1M doses after purification. Running the reactor 100 times would yield 100M doses

Comments on manufacturing

DNA vaccines were discovered decades ago. Although they raise antibodies in animal trials, they have generally been found to be ineffective, however.

The rapid production method means that a DNA vaccine could be available early. However, the PoS is lower than for other vaccine types.

Appendix G. Main Manufacturing Capacity Model Assumptions

Below we outline all the main assumptions used in the manufacturing capacity model.

Product and process

1. Drug substance (primary) plant capacities are characterised by bioreactor capacity; downstream processing capacity is assumed to be suitable and to match bioreactor capacity.

2. All products within a platform have the same DS (doses/litre bioreactor) productivity.

3. The same facility must be used for phase III trials and commercial manufacture.

4. Primary plants produce 25 batches a year.

5. All products are delivered as aseptic liquids.

6. Two doses are required per patient.

7. Fifteen percent of output is lost post-production.

8. Facilities exist but require modification (no new build).

9. Plant, microbial and yeast platforms are ignored.

Scheduling

1. Manufacturing activities are defined as all activities needed before a vaccine is approved for manufacture excluding research and development and clinical trials. Manufacturing activities include process development and scale-up and the transfer or technology.

2. Primary manufacturing activities always start at risk; they do not wait for positive clinical trial results.

3. Secondary manufacturing starts at risk, but dose form commercial manufacture waits for drug approval.

Supply chain

We presume no upstream supply chain restriction. Possible pinch points include restriction enzymes (RNA), single-use bioprocess materials, vials, syringes and adjuvants.

Allocation of products to plant capacity

1. Each country is treated as one block of capacity for each DS platform.

2. Each country is treated as one block of secondary capacity.

3. As a vaccine is approved, it takes all available DS capacity in the correct capacity class until a second vaccine is approved, at which point capacity is split evenly and so on.

4. No more than three vaccines within any platform are manufactured.

5. Vaccines are selected on a first-come-first served basis as they are approved by the R&D model.

6. Capacity of any type is allocated optimally; no allowance is made for national or commercial restrictions.

Appendix H. Sensitivity Analysis of the R&D Model

The analysis presented in this appendix reveals what happens when various inputs in the model are adjusted with all other factors else held constant.

Parameter: Phase PoS - Pre-Clinical

	Parameter value (default = 0.66)				
Item	0.2	0.5	0.75	0.9	1
Months until > 50% chance of a vaccine	9.0	10.0	10.0	10.0	10.0
Months until > 90% chance of a vaccine	20.0	20.0	22.0	22.0	21.0
Months until > 99% chance of a vaccine	33.0	36.0		34.0	32.0
Probability of at least one vaccine after 36 months (percent)	99.4	99.0	98.7	99.3	99.6
Number of vaccines approved after 36 months	4.1	4.1	4.1	4.2	4.3

Parameter: Phase PoS - Phase I

Parameter value (default 0.78)	0.2	0.5	0.75	0.9	1
Months until > 50% chance of a vaccine	13.0	12.0	10.0	9.0	9.0
Months until > 90% chance of a vaccine	29.0	25.0	22.0	20.0	18.0
Months until > 99% chance of a vaccine				32.0	32.0
Probability of at least one vaccine after 36 months (percent)	93.5	97.5	98.8	99.6	99.5
Number of vaccines approved after 36 months	2.5	3.2	4.0	4.5	4.7

Parameter: Phase PoS - Phase II

Parameter value (default 0.66)	0.2	0.5	0.75	0.9	1
Months until > 50% chance of a vaccine	11.0	11.0	10.0	9.0	10.0
Months until > 90% chance of a vaccine		25.0	20.0	18.0	18.0
Months until > 99% chance of a vaccine			33.0	29.0	27.0
Probability of at least one vaccine after 36 months (percent)	89.4	97.8	99.6	99.9	99.8
Number of vaccines approved after 36 months	2.1	3.3	4.5	5.0	5.2

Parameter: Phase PoS - Approval

Parameter value (default 0.74)	0.2	0.5	0.75	0.9	1
Months until > 50% chance of a vaccine	24.0	13.0	10.0	9.0	9.0

Months until > 90% chance of a vaccine		28.0	21.0	18.0	17.0
Months until > 99% chance of a vaccine			35.0	28.0	29.0
Probability of at least one vaccine after 36 months (percent)	70.9	96.2	99.2	99.9	99.7
Number of vaccines approved after 36 months	1.3	2.9	4.1	4.7	5.1

Parameter: Platform Phase III PoS - Live-attenuated

Parameter value (default 0.37)	0.2	0.5	0.75	0.9	1
Months until > 50% chance of a vaccine	10.0	10.0	10.0	10.0	10.0
Months until > 90% chance of a vaccine	21.0	22.0	21.0	21.0	22.0
Months until > 99% chance of a vaccine			33.0		34.0
Probability of at least one vaccine after 36 months (percent)	98.4	98.9	99.4	98.9	99.3
Number of vaccines approved after 36 months	4.0	4.1	4.1	4.1	4.1

Parameter: Platform Phase III PoS - Protein subunit

Parameter value (default 0.64)	0.2	0.5	0.75	0.9	1
Months until > 50% chance of a vaccine	10.0	10.0	10.0	10.0	10.0
Months until > 90% chance of a vaccine	25.0	22.0	21.0	21.0	20.0
Months until > 99% chance of a vaccine			32.0	32.0	29.0
Probability of at least one vaccine after 36 months (percent)	95.8	98.6	99.5	99.6	99.7
Number of vaccines approved after 36 months	3.1	3.7	4.3	4.5	4.7

Parameter: Platform Phase III PoS - Inactivated

Parameter value (default 0.39)	0.2	0.5	0.75	0.9	1
Months until > 50% chance of a vaccine	11.0	10.0	9.0	9.0	9.0
Months until > 90% chance of a vaccine	24.0	19.0	16.0	14.0	15.0
Months until > 99% chance of a vaccine		31.0	29.0	27.0	28.0
Probability of at least one vaccine after 36 months (percent)	98.8	99.5	99.7	99.7	99.8
Number of vaccines approved after 36 months	3.8	4.2	4.5	4.7	4.7

Parameter: Platform Phase III PoS - RNA

Parameter value (default 0.48)	0.2	0.5	0.75	0.9	1
Months until > 50% chance of a vaccine	11.0	10.0	9.0	9.0	9.0
Months until > 90% chance of a vaccine	24.0	20.0	16.0	16.0	16.0
Months until > 99% chance of a vaccine			28.0	28.0	26.0
Probability of at least one vaccine after 36 months (percent)	98.6	98.8	99.5	99.9	100.0
Number of vaccines approved after 36 months	3.6	4.0	4.5	4.7	4.9

Parameter: Platform Phase III PoS - Non-replicating viral vector

Parameter value (default 0.53)	0.2	0.5	0.75	0.9	1
Months until > 50% chance of a vaccine	10.0	10.0	10.0	10.0	10.0
Months until > 90% chance of a vaccine	24.0	22.0	20.0	18.0	19.0
Months until > 99% chance of a vaccine			35.0	30.0	30.0
Probability of at least one vaccine after 36 months (percent)	98.6	98.6	99.0	99.8	99.6
Number of vaccines approved after 36 months	3.7	4.0	4.3	4.3	4.4

Parameter: Platform Phase III PoS - Replicating viral vector

Parameter value (default 0.45)	0.2	0.5	0.75	0.9	1
Months until > 50% chance of a vaccine	10.0	10.0	10.0	10.0	10.0
Months until > 90% chance of a vaccine	21.0	22.0	21.0	21.0	20.0
Months until > 99% chance of a vaccine		36.0	35.0		32.0
Probability of at least one vaccine after 36 months (percent)	98.9	99.0	99.3	98.8	99.2
Number of vaccines approved after 36 months	3.9	4.1	4.1	4.2	4.2

Parameter: Platform Phase III PoS - DNA

Parameter value (default 0.21)	0.2	0.5	0.75	0.9	1
Months until > 50% chance of a vaccine	10.0	10.0	10.0	10.0	10.0
Months until > 90% chance of a vaccine	22.0	21.0	21.0	20.0	21.0

Months until > 99% chance of a vaccine	36.0		35.0	34.0	
Probability of at least one vaccine after 36 months (percent)	99.1	98.5	99.0	99.3	98.8
Number of vaccines approved after 36 months	4.0	4.2	4.1	4.1	4.1

Parameter: Platform Phase III PoS - Other

Parameter value (default 0.05)	0.2	0.5	0.75	0.9	1
Months until > 50% chance of a vaccine	10.0	10.0	10.0	10.0	10.0
Months until > 90% chance of a vaccine	22.0	22.0	22.0	21.0	22.0
Months until > 99% chance of a vaccine					36.0
Probability of at least one vaccine after 36 months (percent)	98.7	98.7	98.9	98.8	99.0
Number of vaccines approved after 36 months	4.0	4.0	4.0	4.1	4.0

Parameter: Platform Phase III PoS - Unknown

Parameter value (default 0.02)	0.2	0.5	0.75	0.9	1
Months until > 50% chance of a vaccine	10.0	10.0	10.0	10.0	10.0
Months until > 90% chance of a vaccine	21.0	21.0	21.0	22.0	21.0
Months until > 99% chance of a vaccine	34.0	35.0	31.0	33.0	34.0
Probability of at least one vaccine after 36 months (percent)	99.5	99.3	99.6	99.6	99.1
Number of vaccines approved after 36 months	4.0	4.1	4.1	4.0	4.1

Parameter: Best Case - Pre-Clinical

Parameter value (default 3)	1	2	3	4	5
Months until > 50% chance of a vaccine	10.0	10.0	10.0	10.0	10.0
Months until > 90% chance of a vaccine	22.0	21.0	21.0	22.0	22.0
Months until > 99% chance of a vaccine	34.0	36.0	36.0		34.0
Probability of at least one vaccine after 36 months (percent)	99.3	99.1	99.0	98.9	99.1
Number of vaccines approved after 36 months	4.1	4.0	4.1	4.0	4.1

Parameter: Most Likely - Pre-Clinical

Parameter value (default 6)	4	5	6	7	8	9	10	11
Months until > 50% chance of a vaccine	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0
Months until > 90% chance of a vaccine	22.0	21.0	21.0	21.0	21.0	21.0	21.0	20.0
Months until > 99% chance of a vaccine	34.0	33.0	32.0	36.0	36.0		35.0	36.0
Probability of at least one vaccine after 36 months (percent)	99.1	99.3	99.5	99.0	99.0	98.8	99.2	99.0
Number of vaccines approved after 36 months	4.1	4.1	4.0	4.1	4.1	4.1	4.0	4.0

Parameter: Worst Case - Pre-Clinical

Parameter value (default 12)	7	10	13	16	19	22
Months until > 50% chance of a vaccine	10.0	10.0	10.0	10.0	10.0	10.0
Months until > 90% chance of a vaccine	21.0	22.0	22.0	21.0	22.0	21.0
Months until > 99% chance of a vaccine	33.0	36.0				
Probability of at least one vaccine after 36 months (percent)	99.5	99.2	98.7	98.7	98.8	98.6
Number of vaccines approved after 36 months	4.1	4.1	4.0	4.1	3.9	3.9

Parameter: Best Case - Phase I

Parameter value (default 2)	1	2	3
Months until > 50% chance of a vaccine	10.0	10.0	10.0
Months until > 90% chance of a vaccine	22.0	22.0	21.0
Months until > 99% chance of a vaccine	36.0		
Probability of at least one vaccine after 36 months (percent)	99.2	98.9	98.9
Number of vaccines approved after 36 months	4.1	4.1	4.0

Parameter: Most Likely - Phase I

Parameter value (default 4)	3	4	5
Months until > 50% chance of a vaccine	10.0	10.0	10.0
Months until > 90% chance of a vaccine	21.0	21.0	21.0
Months until > 99% chance of a vaccine	34.0	34.0	35.0
Probability of at least one vaccine after 36 months (percent)	99.4	99.2	99.4
Number of vaccines approved after 36 months	4.1	4.1	4.0

Parameter: Worst Case - Phase I

Parameter value (default 6)	5	8	11
Months until > 50% chance of a vaccine	10.0	10.0	10.0
Months until > 90% chance of a vaccine	22.0	21.0	21.0
Months until > 99% chance of a vaccine	34.0	33.0	
Probability of at least one vaccine after 36 months (percent)	99.1	99.4	98.5
Number of vaccines approved after 36 months	4.1	4.0	3.9

Parameter: Best Case - Phase II

Parameter value (default 3)	1	2	3	4
Months until > 50% chance of a vaccine	10.0	10.0	10.0	10.0
Months until > 90% chance of a vaccine	20.0	20.0	21.0	21.0
Months until > 99% chance of a vaccine	36.0	33.0	32.0	
Probability of at least one vaccine after 36 months (percent)	99.0	99.7	99.7	98.9
Number of vaccines approved after 36 months	4.1	4.1	4.1	4.0

Parameter: Most Likely - Phase II

Parameter value (default 5):	4	5	6	7
Months until > 50% chance of a vaccine	10.0	10.0	10.0	10.0
Months until > 90% chance of a vaccine	21.0	22.0	21.0	22.0
Months until > 99% chance of a vaccine	34.0		32.0	
Probability of at least one vaccine after 36 months (percent)	99.2	98.8	99.4	98.6
Number of vaccines approved after 36 months	4.1	4.1	4.1	4.0

Parameter: Worst Case - Phase II

Parameter value (default 8):	6	9	12	15
Months until > 50% chance of a vaccine	10.0	10.0	10.0	10.0
Months until > 90% chance of a vaccine	21.0	21.0	20.0	22.0
Months until > 99% chance of a vaccine	36.0	35.0		
Probability of at least one vaccine after 36 months (percent)	99.0	99.1	98.8	98.7
Number of vaccines approved after 36 months	4.1	4.0	4.1	4.1

Parameter: Best Case - Phase III

Parameter value (default 3)	1	3	5	7
Months until > 50% chance of a vaccine	10.0	10.0	11.0	12.0
Months until > 90% chance of a vaccine	20.0	21.0	23.0	24.0
Months until > 99% chance of a vaccine	29.0	33.0	36.0	
Probability of at least one vaccine after 36 months (percent)	99.5	99.2	99.1	98.1
Number of vaccines approved after 36 months	4.3	4.2	3.8	3.6

Parameter: Most Likely - Phase III

Parameter value (default 9)	4	6	8	10	12	14	16
Months until > 50% chance of a vaccine	8.0	9.0	10.0	11.0	11.0	12.0	13.0
Months until > 90% chance of a vaccine	18.0	19.0	21.0	23.0	22.0	24.0	24.0
Months until > 99% chance of a vaccine	33.0	31.0	34.0	36.0			
Probability of at least one vaccine after 36 months (percent)	99.4	99.5	99.0	99.1	98.7	98.1	98.6
Number of vaccines approved after 36 months	4.5	4.4	4.1	3.9	3.8	3.6	3.5

Parameter: Worst Case - Phase III

Parameter value (default 18)	10	13	16	19	22	25	28	31	34
Months until > 50% chance of a vaccine	8.0	9.0	10.0	10.0	11.0	12.0	13.0	13.0	15.0
Months until > 90% chance of a vaccine	18.0	20.0	21.0	22.0	22.0	24.0	26.0	27.0	28.0
Months until > 99% chance of a vaccine	28.0	31.0	33.0	34.0					
Probability of at least one vaccine after 36 months (percent)	99.5	99.7	99.4	99.2	98.7	98.5	97.7	97.2	96.6
Number of vaccines approved after 36 months	4.7	4.5	4.2	4.0	3.7	3.6	3.4	3.2	3.1

Parameter: Best Case - Approval

Parameter value (default 1)	1	2
Months until > 50% chance of a vaccine	10.0	10.0
Months until > 90% chance of a vaccine	22.0	22.0
Months until > 99% chance of a vaccine	34.0	33.0

Probability of at least one vaccine after 36 months (percent)	99.0	99.5
Number of vaccines approved after 36 months	4.0	4.0

Parameter: Most Likely - Approval

Parameter value (default 3)	2	3	4	5
Months until > 50% chance of a vaccine	10.0	10.0	11.0	11.0
Months until > 90% chance of a vaccine	21.0	21.0	22.0	23.0
Months until > 99% chance of a vaccine	36.0	34.0	32.0	
Probability of at least one vaccine after 36 months (percent)	99.2	99.5	99.6	98.2
Number of vaccines approved after 36 months	4.2	4.0	4.0	3.9

Parameter: Worst Case - Approval

Parameter value (default 6)	4	7	10
Months until > 50% chance of a vaccine	10.0	10.0	11.0
Months until > 90% chance of a vaccine	20.0	20.0	23.0
Months until > 99% chance of a vaccine	35.0	35.0	
Probability of at least one vaccine after 36 months (percent)	99.1	99.0	98.8
Number of vaccines approved after 36 months	4.2	4.1	3.8