COVID-19 Vaccines and Therapeutics Expert Predictions

Juan Cambeiro,[1,*] Tamay Besiroglu,[1,2] Dan Sluder,[1] and Thomas McAndrew[3,†]

[1] *Metaculus*

[2] *Faculty of Economics, University of Cambridge, Cambridge, United Kingdom*

[3] *Department of Biostatistics and Epidemiology, School of Public Health and Health Sciences, University of Massachusetts—Amherst, Amherst, Massachusetts, United States of America*

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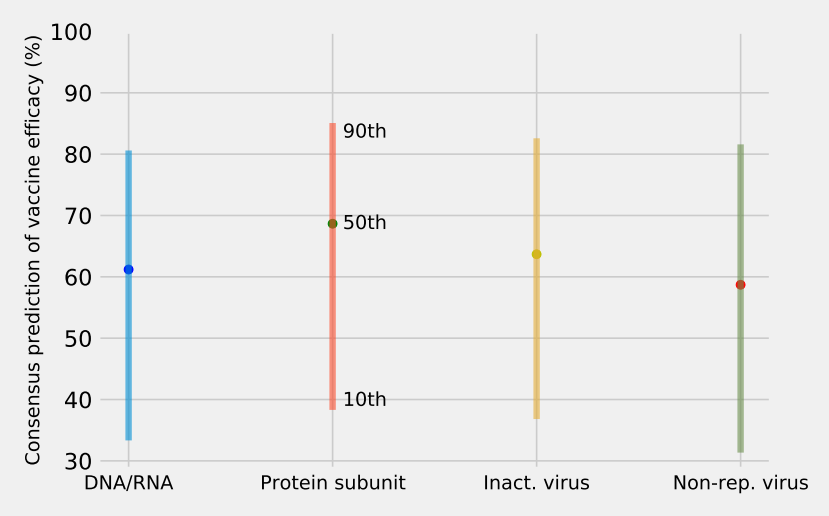
AGGREGATE EFFICACY PREDICTIONS SUGGEST A CHANGE IN THE VACCINE LANDSCAPE

We organised a forecasting session with subject matter experts and trained forecasters, and solicited predictions about the efficacy of the first approved SARS-CoV-2 vaccine for 4 different vaccine platforms. Experts predicted the most efficacious vaccine will use a protein sub-unit platform, though the gain in efficacy over the other three platforms was marginal (Fig.).

Platforms in order from the most to least effective median prediction assigned by the consensus was: protein sub-unit (median = 69%), inactivated virus (median = 64%), DNA/RNA (median = 62%), and non-replicating viral vector (median = 59%). Though the median predictions show the protein sub-unit platform was predicted to be most effective, the 80% consensus prediction intervals were similar across the 4 platforms (Fig).



Among consensus predictions on all platforms, the median efficacy was predicted to be above 50%. The lower 80% prediction interval (10th percentile) for all vaccine platforms was above 30%—a lower bound suggested in FDA guidance documents for vaccine treatments of SARS-CoV-2 [1].

A potential drawback to a lower efficacy vaccine, however, is that it will require treating a larger proportion of susceptible individuals to establish herd immunity [2]. In addition, expert consensus predicted a vaccine candidate will be approved by the FDA or EU one month sooner compared to last month's forecasting session. Expert consensus predicts an approved vaccine with lower efficacy on a shorter timeline. This is a signal experts may think regulatory agencies are willing to accept a vaccine with lower efficacy if it can be approved within months—an exchange of efficacy for speed.

With respect to therapeutics, experts predict that both an antiviral and monoclonal antibody/antibody cocktail are likely to demonstrate a significant survival benefit in Spring 2021.

* juan@metaculus.com
† mcandrew@umass.edu

FORECASTING SESSION DURATION, DEFINITION OF EXPERTS, AND LOGISTICS

From July 15th 2020 to July 25th 2020, predictions were made for 7 questions related to vaccine and therapeutic solutions to COVID-19. Two groups of experts were asked to participate: (i) subject matter experts (SMEs) and (ii) trained forecasters (TFs). SMEs were defined as those in the fields of molecular and cellular biology, microbiology, virology, biochemistry, and infectious disease. They have several years of experience in vaccine, antiviral, or biological research related to infectious disease, and are up-to-date with vaccine/antiviral research specifically focused on the novel coronavirus. TFs were defined as the top 1% out of a total pool of approximately 13,000 forecasters according to a Metaculus point system with track records spanning several years on the Metaculus forecasting platform.

A total of 15 experts (7 subject matter experts and 8 trained forecasters) participated and submitted 148 predictions for aggregation into a consensus distribution.

During the entire forecasting session, experts could submit multiple predictions for the same question and collaborate via a comment section underneath each question. Experts shared 6 comments with one another across all questions.

The consensus distribution for each question was hidden from experts from July 15th to July 20th. On July 20th the consensus distribution was revealed until the end of the forecasting session on July 25th. We hypothesize that predictions were revised by experts as they received new external information on vaccines and therapeutics or because of the differences between the expert's prediction and the ongoing consensus prediction.

SUMMARY OF PREDICTIONS

1. Experts assigned a median of May 2021 (80% CI: October 2020, June 2024) to when a SARS-CoV-2 vaccine candidate be approved for use in the United States or European Union. A probability of 5.6% was assigned to a date of July 2024 or later.

2. Experts assigned a median prediction of 61.5% (80% CI: 33.5%, 81%) to the efficacy of the first approved SARS-CoV-2 vaccine based on **a DNA or RNA platform**.

3. Experts assigned a median prediction of 69% (80% CI: 38.5%, 85%) to the efficacy of the first approved SARS-CoV-2 vaccine based on **a protein subunit platform**.

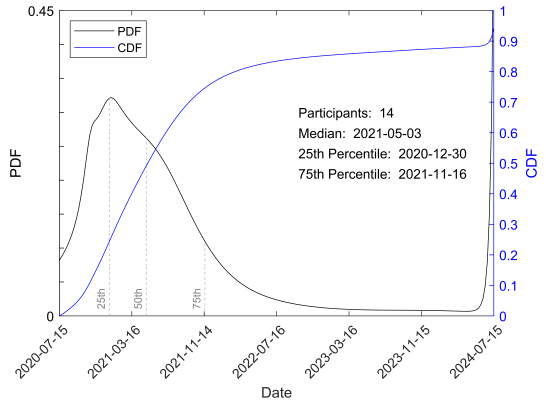
4. Experts assigned a median prediction of 64% (80% CI: 37%, 82.5%) to the efficacy of the first approved SARS-CoV-2 vaccine based on **an inactivated virus platform**.

5. Experts assigned a median prediction of 58.5% (80% CI: 32%, 81.5%) to the efficacy of the first approved SARS-CoV-2 vaccine based on **a non-replicating viral vector platform**.

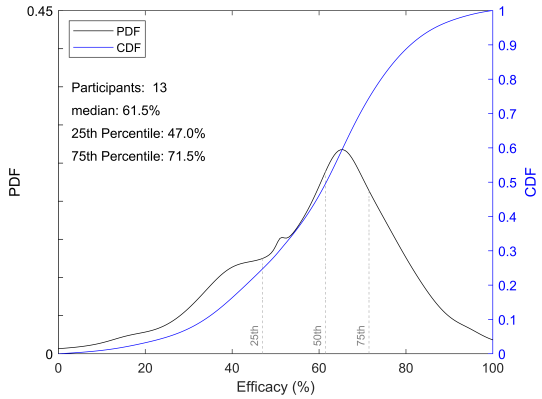
6. Experts assigned a median of May 2021 (80% CI: September 2020, July 2024) to when a SARS-CoV-2 antiviral shows a statistically significant survival benefit for the treatment group in an $n > 200$ RCT. A probability of 7.8% was assigned to a date of July 2024 or later.

7. Experts assigned a median of April 2021 (80% CI: October 2020, June 2024) to when a SARS-CoV-2 monoclonal antibody or antibody cocktail shows a statistically significant survival benefit for the treatment group in an $n > 200$ RCT. A probability of 5.7% was assigned to a date of July 2024 or later.

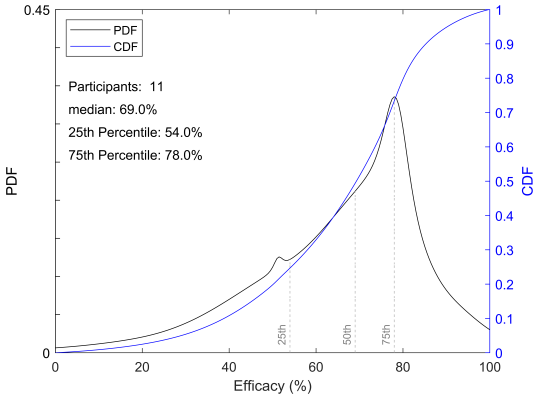
CONSENSUS PREDICTIONS



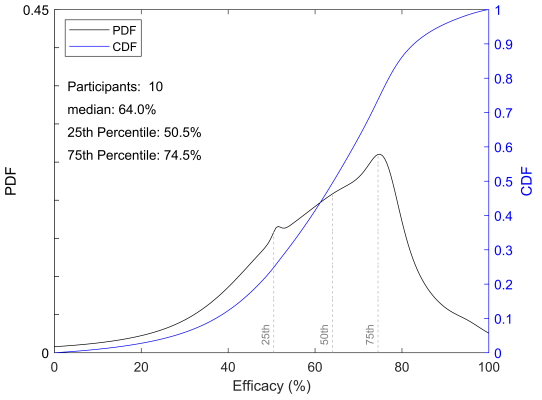
When will a SARS-CoV-2 vaccine candidate be approved for use in the United States or European Union?



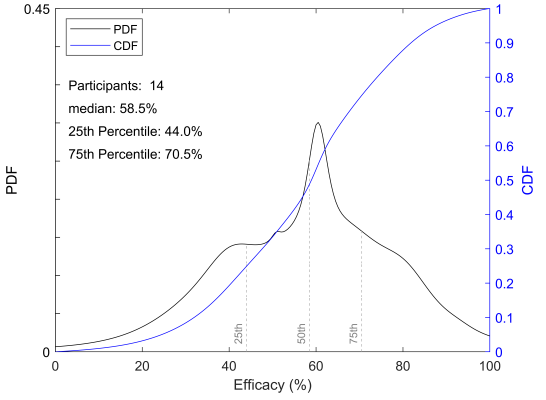
What will be the efficacy of the first US- or EU-approved SARS-CoV-2 vaccine based on a DNA or RNA platform?



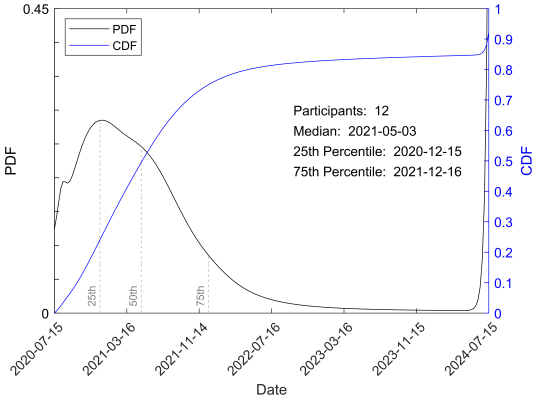
What will be the efficacy of the first US- or EU-approved SARS-CoV-2 vaccine based on a protein subunit platform?



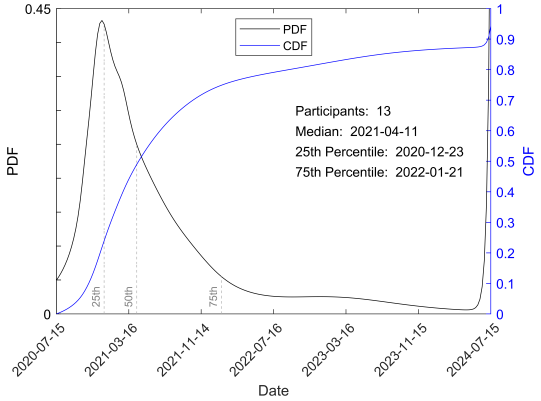
What will be the efficacy of the first US- or EU-approved SARS-CoV-2 vaccine based on an inactivated virus platform?



What will be the efficacy of the first US- or EU-approved SARS-CoV-2 vaccine based on a non-replicating viral vector platform?



When will a SARS-CoV-2 antiviral show a statistically significant survival benefit for the treatment group in an $n > 200$ RCT?



When will a SARS-CoV-2 monoclonal antibody or antibody cocktail show a statistically significant survival benefit for the treatment group in an $n > 200$ RCT?

DETAILS ON EXPERT CONSENSUS DISTRIBUTIONS

The consensus distributions reported above include only the most recent predictions from each expert. The experts were allowed to update their predictions as many times as they wished. The consensus prediction assigned a probability to a value x of

$$f(x) = \frac{1}{E}\sum_{i=1}^{E} f_i(x)$$

where f is the consensus probability distribution, $f_i(x)$ is the most recent probability expert i assigned to the value x, and E is the number of experts .

RECORD OF QUESTIONS, QUESTION TYPE, AND RESOLUTION CRITERIA

1. When will a SARS-CoV-2 vaccine candidate be approved for use in the United States or European Union?

    - Available prediction range: [15 July 2020, 15 July 2024], where the upper bound was left open allowing experts to assign weight to a resolution of $>$ 15 July 2024.
    - Resolution Criteria: Resolution will be determined by the date of the first U.S. Food and Drug Administration (FDA) press release or European Medicines Agency (EMA) press release on the approval of a SARS-CoV-2 vaccine candidate. U.S. approval is defined as the date a vaccine candidate is licensed by the FDA as stated in a relevant press release. EU approval is defined as the date an EMA-recommended vaccine candidate is granted approval by the European Commission (EC) via marketing authorization as stated in a relevant press release. Approval under any other emergency procedures, such as under a FDA Emergency Use Authorization or EMA emergency procedure authorization, would not count for positive resolution.

2. What will be the efficacy of the first US- or EU- approved SARS-CoV-2 vaccine based on a DNA or RNA platform?

    - Available prediction range: Between 0% and 100% inclusive.
    - Resolution Criteria: Resolves as the median estimate of the absolute vaccine efficacy of the first SARS-CoV-2 vaccine based on a DNA or RNA platform. Approval in the US or EU should occur through the normal regulatory mechanisms and so the efficacy of any vaccine candidate approved on an emergency basis will not be considered for resolution. U.S. approval is defined as licensure by the FDA. EU approval is defined as when an EMA-recommended vaccine candidate is granted approval by the EC via marketing authorization. Approval under any emergency

procedures, such as under a FDA Emergency Use Authorization or EMA emergency procedure authorization, will not be considered.

3. What will be the efficacy of the first US- or EU- approved SARS-CoV-2 vaccine based on a protein subunit platform?

   - Available prediction range: Between 0% and 100% inclusive.
   - Resolution Criteria: Resolves as the median estimate of the absolute vaccine efficacy of the first SARS-CoV-2 vaccine based on a protein subunit platform. Approval in the US or EU should occur through the normal regulatory mechanisms and so the efficacy of any vaccine candidate approved on an emergency basis will not be considered for resolution. U.S. approval is defined as licensure by the FDA. EU approval is defined as when an EMA-recommended vaccine candidate is granted approval by the EC via marketing authorization. Approval under any emergency procedures, such as under a FDA Emergency Use Authorization or EMA emergency procedure authorization, will not be considered.

4. What will be the efficacy of the first US- or EU- approved SARS-CoV-2 vaccine based on an inactivated virus platform?

   - Available prediction range: Between 0% and 100% inclusive.
   - Resolution Criteria: Resolves as the median estimate of the absolute vaccine efficacy of the first SARS-CoV-2 vaccine based on an inactivated virus platform. Approval in the US or EU should occur through the normal regulatory mechanisms and so the efficacy of any vaccine candidate approved on an emergency basis will not be considered for resolution. U.S. approval is defined as licensure by the FDA. EU approval is defined as when an EMA-recommended vaccine candidate is granted approval by the EC via marketing authorization. Approval under any emergency procedures, such as under a FDA Emergency Use Authorization or EMA emergency procedure authorization, will not be considered.

5. What will be the efficacy of the first US- or EU- approved SARS-CoV-2 vaccine based on a non-replicating viral vector platform?

   - Available prediction range: Between 0% and 100% inclusive.
   - Resolution Criteria: Resolves as the median estimate of the absolute vaccine efficacy of the first SARS-CoV-2 vaccine based on an inactivated virus platform. Approval in the US or EU should occur through the normal regulatory mechanisms and so the efficacy of any vaccine candidate approved on an emergency basis will not be considered for resolution. U.S. approval is defined as licensure by the FDA. EU approval is defined as when an EMA-recommended vaccine candidate is granted approval by the EC via marketing authorization. Approval under any emergency procedures, such as under a FDA Emergency Use Authorization or EMA emergency procedure authorization, will not be considered.

6. When will a SARS-CoV-2 antiviral show a statistically significant survival benefit for the treatment group in an $n > 200$ RCT?

   - Available prediction range: [15 July 2020, 15 July 2024], where the upper bound was left open allowing experts to assign weight to a resolution of $>$ 15 July 2024.
   - Resolution Criteria: Resolves as the date when the first peer-reviewed research article of a SARS-CoV-2 antiviral to enroll more than 200 patients publishes a statistically significant survival benefit for the treatment group. For our purposes, "statistically significant" means that the upper bound of the 95% confidence interval of the hazard ratio for death between treated and control patients is less than 1.0. Moreover, the results would have to be statistically significant for the entire treatment group when compared to the control group in order to resolve positively.

7. When will a SARS-CoV-2 monoclonal antibody or antibody cocktail show a statistically significant survival benefit for the treatment group in an $n > 200$ RCT?

   - Available prediction range: [15 July 2020, 15 July 2024], where the upper bound was left open allowing experts to assign weight to a resolution of $>$ 15 July 2024.

- Resolution Criteria: Resolves as the date when the first peer-reviewed research article of a SARS-CoV-2 monoclonal antibody or antibody cocktail to enroll more than 200 patients publishes a statistically significant survival benefit for the treatment group. For our purposes, "statistically significant" means that the upper bound of the 95% confidence interval of the hazard ratio for death between treated and control patients is less than 1.0. Moreover, the results would have to be statistically significant for the entire treatment group when compared to the control group in order to resolve positively.

PARTICIPATING EXPERTS

Subject-matter experts

Name	Affiliation
Andrew Azman	Johns Hopkins University
Rebecca Dutch	University of Kentucky College of Medicine
R. Kiplin Guy	University of Kentucky College of Pharmacy
Nelson Lee	University of Alberta, Canada
David J. Margraf	University of Minnesota
Jeff Morgan	Catholic University of America
Ulrich Strych	Baylor College of Medicine

Top Forecasters

Name	Affiliation
Shahar Avin	Centre for the Study of Existential Risk, University of Cambridge
Damon Cham	
Jack Chen	
Sylvain Chevalier	
James Clough	
Eli Lifland	
David Manheim	University of Haifa's Health and Risk Communication Research Center
Cory Schillinger	

[1] Center for Biologics Evaluation and Research. Development and Licensure of Vaccines to Prevent COVID-19, June 2020. Library Catalog: www.fda.gov Publisher: FDA.

[2] Sarah M Bartsch, Kelly J O'Shea, Marie C Ferguson, Maria Elena Bottazzi, Patrick T Wedlock, Ulrich Strych, James A McKinnell, Sheryl S Siegmund, Sarah N Cox, Peter J Hotez, et al. Vaccine efficacy needed for a covid-19 coronavirus vaccine to prevent or stop an epidemic as the sole intervention. *American Journal of Preventive Medicine*, 2020.