

Clinical development of COVID-19 vaccines

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COVID-19 vaccine development is different

Many vaccines are being concurrently developed

- Increases the chance of a spurious result, regardless of whether studies test one vaccine or several

Need multiple vaccines

- We don't want weakly effective vaccines to interfere with evaluation of better vaccines

Specific safety concern

- “Enhanced disease” based on experience with RSV and other coronavirus vaccines

Need reliable data

- Very high deployment rates expected initially, so many people would be immunized before a mistake becomes apparent

Manufacturing

- If manufacturing resources are expended on the wrong vaccine, this will impact the ability to manufacture other vaccines

Vaccine development occurring in the middle of a pandemic

- High level of scrutiny and desire for rapid results

Statement of collaboration

We are scientists, physicians, funders and manufacturers who have come together as part of an international collaboration, coordinated by the World Health Organization (WHO), to help speed the availability of a vaccine against COVID-19. While a vaccine for general use takes time to develop, a vaccine may ultimately be instrumental in controlling this worldwide pandemic. In the interim, we applaud the implementation of community intervention measures that reduce spread of the virus and protect people, including vulnerable populations, and pledge to use the time gained by the widespread adoption of such measures to develop a vaccine as rapidly as possible. We will continue efforts to strengthen the unprecedented worldwide collaboration, cooperation and sharing of data already underway. We believe these efforts will help reduce inefficiencies and duplication of effort, and we will work tenaciously to increase the likelihood that one or more safe and effective vaccines will soon be made available to all.

Major areas of WHO focus

- Animal models*
- Assay development
- Clinical development, including human challenge studies**

*Nature. 2020 Oct;586(7830):509-515. doi: 10.1038/s41586-020-2787-6. Epub 2020 Sep 23.

**Clin Infect Dis. 2020 Aug 28:ciaa1290. doi: 10.1093/cid/ciaa1290.

Landscape

- >140 vaccines
- Technologies span:
 - RNA (mRNA, modified mRNA, self replicating)
 - DNA (including with electroporation)
 - Inactivated, adjuvanted
 - Live-attenuated
 - Vectored (replicating and non-replicating)
 - Subunit, adjuvanted
 - Virus-like particle
- 2 now deployed in the US under EUA (Pfizer, Moderna)
 - Others deployed elsewhere in the world under various regulatory mechanisms
 - Sinovac & Sinopharm (inactivated), AstraZeneca (Ad-vectored), Gamaleya, FBRI (Russia), Bharat Biotech
 - 8 more in phase 3 or phase 2/3 trials

Goals of COVID-19 vaccine clinical development

- Confidence
- Speed

The right vaccines, promptly

The desire to rapidly deploy the first vaccine should not keep us from finding the right vaccine

The right vaccine

Has sufficient efficacy

- Duration
- Efficacy against severe disease
- Effective in relevant subpopulations
- Precision around efficacy estimate supports rational decision-making about vaccine use

Is safe

- Sufficient duration of follow-up in a large enough population to support deployment in billions of people
- Doesn't cause enhanced disease

Is deployable

- Consistent manufacturing
- Stability, implementation, availability

Efficacy criteria

50% point estimate, 30% lower bound

This assures public health benefit, in addition:

- Likely greater impact on severe disease
- Viral vaccines that are effective against “all disease” have also prevented transmission
- This assures clinical trials of size adequate to assess other critical outcomes

Why is this important?

- Reduces risk of disinhibition
- Reduces risks associated with evaluating many vaccines
- Reduces the risk that the first vaccine stymies development of later, better vaccines
- Weakly effective vaccines are much less likely to induce herd immunity
- One chance to get this right
 - A weakly effective vaccine could do more harm than good
 - A weakly effective vaccine won't have sufficient public health impact to justify rushing it

Because statistical variability can affect the outcome of clinical trials, the lower bound of the **95% confidence interval provides substantial protection** regarding the true efficacy of a vaccine that would be deployed

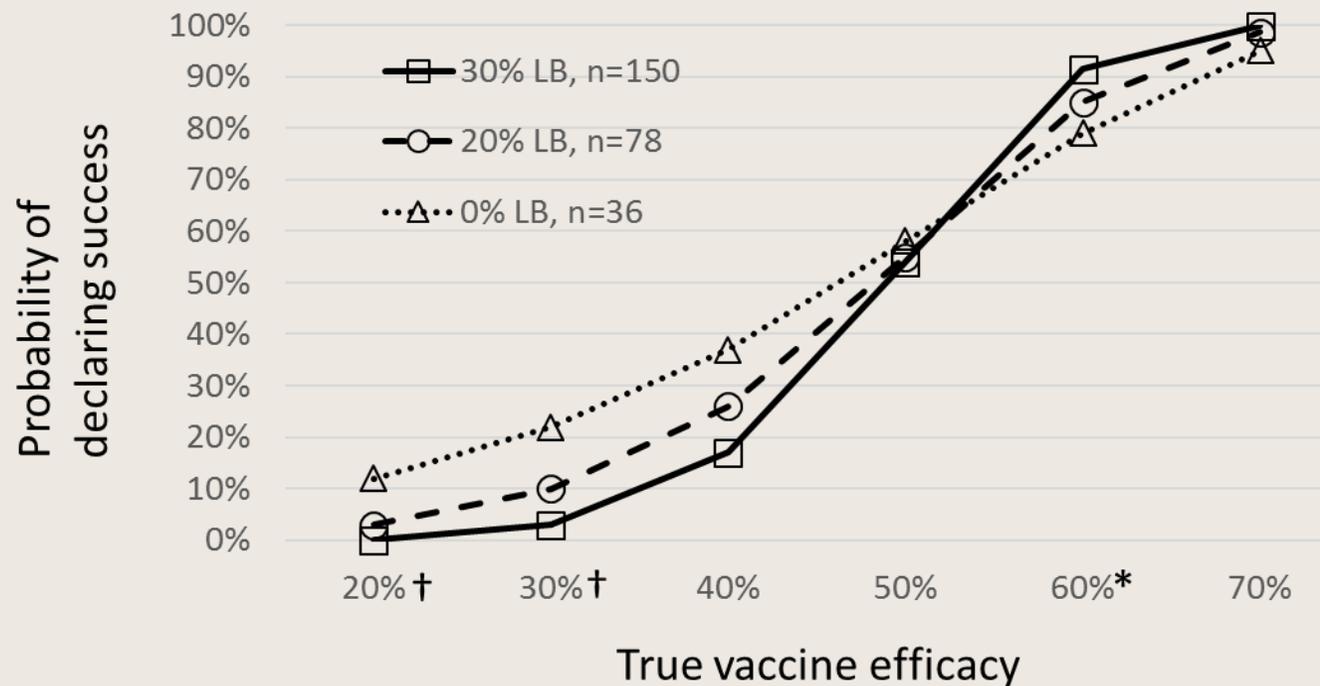
[https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(20\)31821-3/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31821-3/fulltext)

What if some vaccines have zero or low efficacy?⁹

Number of vaccines with presented true vaccine efficacy	Approximate likelihood of at least one positive result by true vaccine efficacy; 0% lower bound		
	0%	10%*	20%*
1	2.5%	6%	12%
3	7%	18%	32%
5	12%	27%	47%
10	22%	48%	72%
15	32%	62%	85%

*Calculated as likelihood of 24:12 or more favorable case split (with 95% lower bound of 1.3%) given true vaccine efficacy of 10% or 20%

Likelihood of declaring success for vaccines with varying efficacy, by 95% CI lower bound



*In a trial that requires a $\geq 50\%$ point estimate for success, a 30% lower bound is required in order to have a 90% chance of success if true vaccine efficacy is 60%

†A lower bound of 30% (with point estimate of 50%) greatly lowers the chance that a vaccine with only 20-30% efficacy will falsely be declared effective

Likelihood and timing of success by true vaccine efficacy

True efficacy	1 st interim 3.7 months*	2 nd interim 4.4 months	3 rd analysis 5 months
90%	97%	100%	100%
80%	54%	99.9%	100%
70%	15%	93%	99.7%
60%	3%	59%	90%

Once the trial is enrolled, the data come in quickly

*Time after 1st vaccination to accrue required number of cases for analysis

Two-dose regimen (1 month apart). Require 50% point estimate, 30% LB, and design with 90% power to detect a vaccine with true efficacy of 60%. 20,000 subjects in placebo and in vaccine group enrolling evenly over 3 months, 3% annual infection rate.

Time to study completion

Trial size	Lower bound	Time to final result*
20,000 per arm	30%	5 months
	20%	4 months
10,000 per arm	30%	7 months
	20%	5 months

*Time after 1st vaccination to accrue required number of cases for final analysis

Two-dose regimen (1 month apart). Require 50% point estimate, 30% LB, and design with 90% power to detect a vaccine with true efficacy of 60%. 20,000 subjects in placebo and in vaccine group enrolling evenly over 3 months, 3% annual infection rate.

Obtaining results quickly is not a good thing if it shortchanges other critical evaluations

Safety database

Efficacy in subpopulations

Efficacy vs. severe disease

Potential for enhanced disease

Duration of efficacy

Vaccines should be followed to ~150 endpoints and beyond, even if interim results suggest early efficacy

Early deployment of vaccines may interfere with getting all the needed data

Safety

The ability to evaluate vaccine safety depends on:

- **The number of participants** (e.g., for SAE evaluation)
- **Number of COVID-19 infections** (e.g., to evaluate potential for enhanced disease)
- **Length of follow-up** (where waning immunity may increase risk of enhanced disease)

Benefit-risk evaluations require clear assessment of risk

Vaccine hesitancy has already been raised as a concern; high vaccination rates required for maximum vaccine impact will require high public confidence in the vaccine

Could <2 months of clinical trial follow-up reasonably support vaccine deployment?

- Confidence in vaccine requires rigorous evaluation
- Initial deployment would be of vaccine that is still investigational, and this fact will need to be communicated
- Even after initial deployment, additional data collection will be important, including via blinded follow-up of trial participants
- Safety
 - Most vaccine-associated AEs are detected within 2 months
 - Collection of additional safety data will be important
- Efficacy
 - Considering importance of duration of effect, - beyond IgM and neutralizing peak
- Other vaccines have had longer follow-up

Conclusions (Reliability of results)

Reliable evaluation of COVID-19 vaccines is essential

- Studies must be able to exclude weakly effective vaccines
- The WHO criterion of 50% point estimate with 30% lower bound is the weakest criterion that achieves this
- “Reliability” also includes follow-up sufficient to address other data needs

Prompt evaluation of vaccines is also critically important

There is no need to sacrifice reliability for promptness

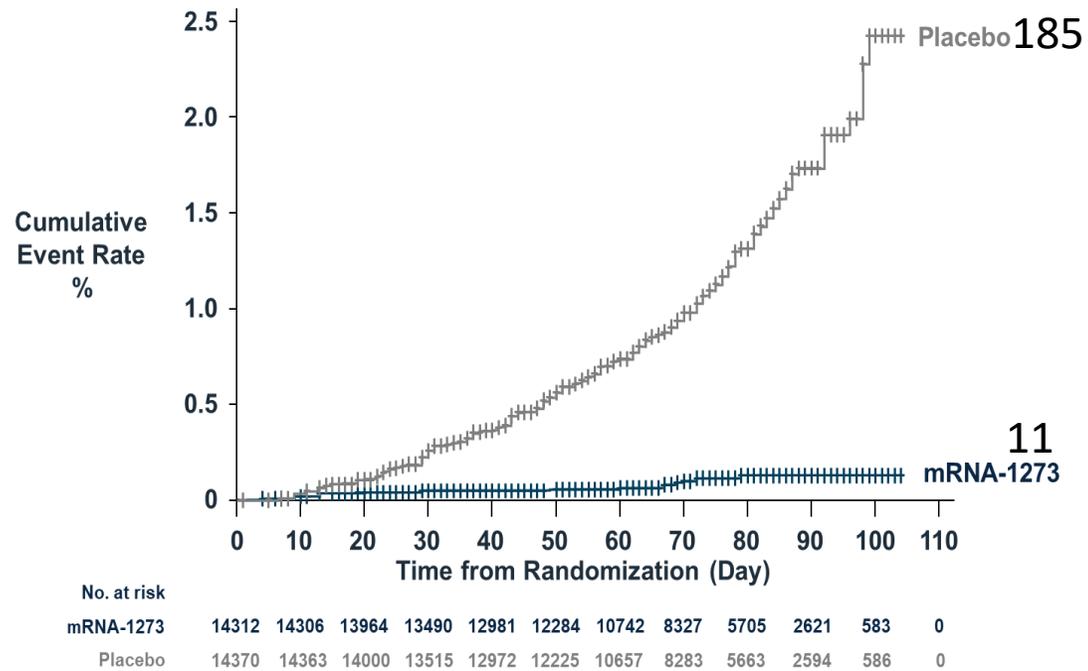
- Many factors can increase promptness of results

As compared with doing small, underpowered trials, the incremental cost of doing trials properly powered to demonstrate the needed results is very modest

Keeping trial results confidential

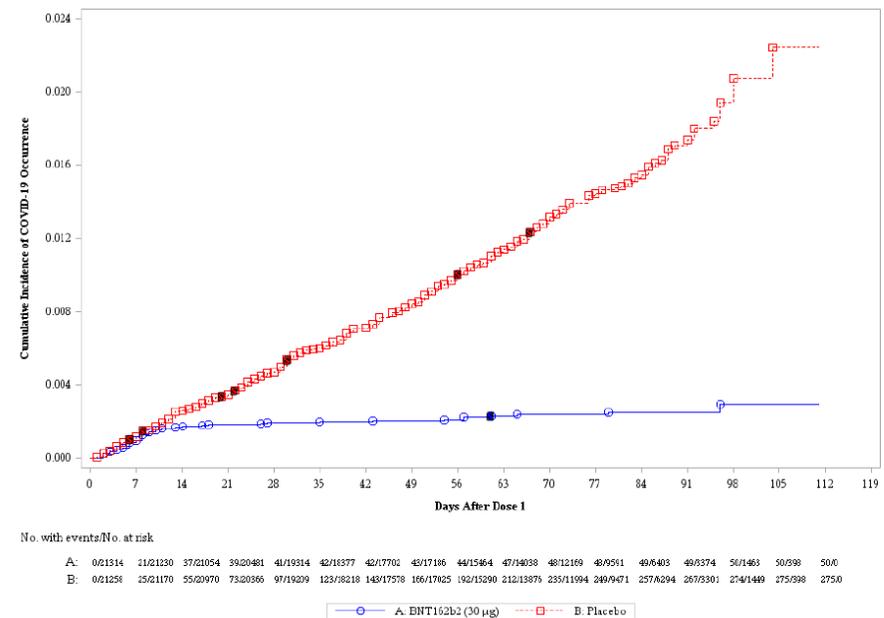
- Protections must be in place to assure that the same data are not used both to generate and confirm hypotheses
- Even pooled data (“blinded”) can provide important information, so certain trial modifications should not be permitted after data collection starts
- Predicting timing of analyses may have unintended consequences
 - If those dates elapse without announcement of results, may unintentionally provide information that will change behavior of investigators and trial participants

mRNA vaccines show high efficacy against COVID-19



Moderna

Figure 13 Cumulative Incidence Curves for the First COVID-19 Occurrence After Dose 1 – Dose 1 All-Available Efficacy Population



Pfizer

Adverse events

- Common Aes*
 - Injection site reactions
 - Fever
 - Headache
 - Muscle pain
 - Joint pain
 - Fatigue
- Questions
 - Immediate type hypersensitivity
 - Bell's palsy

*All less common after first dose and in older vaccine recipients

Other considerations

	Pfizer	Moderna
Ages eligible	>16	>18
Storage temperatures	-80°C - -60°C, or dry ice up to 5 days at 2-8°C, 6 hrs at RT after dilution	-25°C - -15°C up to 30 days at 2-8°C No dilution
Dose volume	0.3 ml	0.5 ml
Dose	30 µg x 2, 21 days apart	100 µg x 2, 1 month apart
Courses available 2020*	25 million	10 million
2021 Q1*		62.5 million
2021*	650 million	235 million (ordered)

* Based on public statements by manufacturers, 12/20

More vaccines are needed

- Even vaccines with lower efficacy may have an important role to play if they have other advantages, e.g., deployability, cost, # of doses, safety, duration of efficacy, etc.
- The most efficient way to evaluate these will be placebo-controlled trials
 - Non-inferiority trials can be contemplated, but have key limitations
 - Efficiency is around 1/3 relative to placebo, when they are feasible

What does responsible emergency deployment of a COVID-19 vaccine look like?

- Vaccine rapidly is delivered to those who need it
- Collection of additional placebo-controlled data, especially to support safety & longer term efficacy
 - Following well-accepted ethical principles that consider investigational nature of vaccine deployed under emergency authorizations, initial limited availability of vaccine, and public health recommendations regarding use of the vaccine
- When placebo-controlled studies can't be done, international collaboration on observational studies using many different systems will help to rapidly address safety signals, enhancing vaccine confidence and reducing risk of spurious signals

Conclusions

- World-wide collaboration has helped to bring us where we are, and is the logical path forward
- A lot has been accomplished, yet there is also still much to do
- The observed high efficacy of mRNA vaccines provides hope that we can soon bring life back to normal, either with the help of these vaccines or others that induce similar immune responses