

Immune response in natural infection

What is the proxy for protection?

How to speed up without compromising safety

Current COVID vaccine landscape

Most advanced vaccine candidates

What to expect looking at natural history non-COVID CoV

Science 2020;370:763

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**Coronavirus infection\***

The virus uses its surface spike protein to lock onto ACE2 receptors on the surface of human cells. Once inside, these cells translate the virus's RNA to produce more viruses.

1. Virus enters the body
2. Virus enters a cell
3. Virus fuses with vesicle and its RNA is released
4. Virus assembly
5. Virus release

**Immune response\***

Specialized 'antigen-presenting cells' engulf the virus and display portions of it to activate T-helper cells. T-helper cells enable other immune responses: B cells make antibodies that can block the virus from infecting cells, as well as mark the virus for destruction. Cytotoxic T cells identify and destroy virus-infected cells.

Long-lived memory B- and T-cells that recognize the virus can patrol the body for months or years, providing immunity

Spike protein locks onto ACE2 and pulls the virus into the cell

B-cells will make antibodies that can block virus from entry into cells

Natural infection induces mucosal sIgA and systemic IgG

Cytotoxic T-cells destroy virus-infected cells

Long-lived memory B- and T-cells patrol the body providing immunity upon re-exposure

Nature 2020; 580:576

sIgA (IgG)

SARS-CoV-2 infects ACE2-expressing nasal epithelial cells in the upper respiratory tract.

Presymptomatic/asymptomatic

IgG

Virus infects ACE2-expressing type II alveolar epithelial cells and patients exhibit **pneumonitis**.

Day 1

Symptomatic Early phase

**Severe disease** involves disruption of the epithelial-endothelial barrier, complement deposition, and hyperinflammation.

Days 7 to 10

Late phase

Science 2020;369:510

Virus neutralising antibodies (VNA) are currently the best proxy for protection

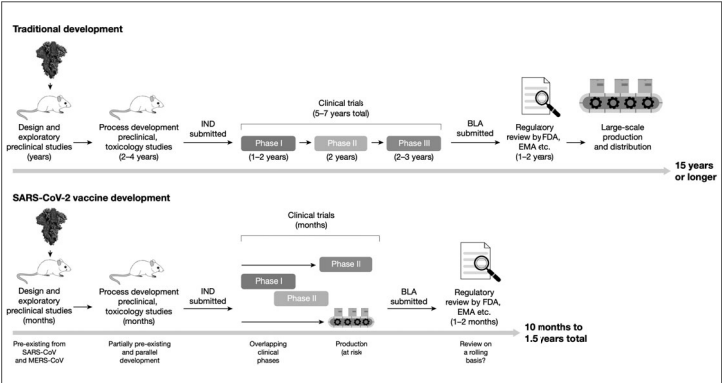
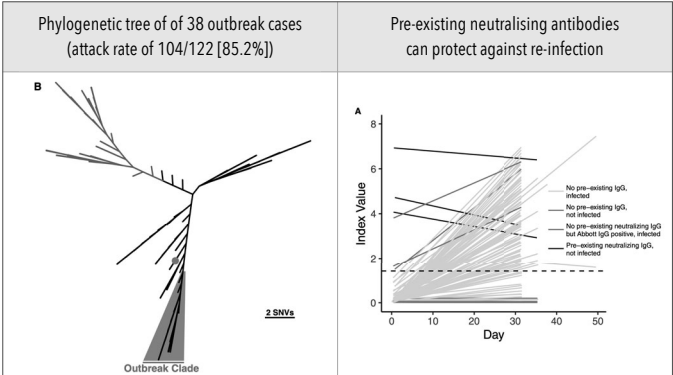
Protect against common-cold HCoV

Protect non-human primates against reinfection

Correlate of protection in NHP (purified IgG transfer and CD8-cell depletion experiments )\*

Observational study outbreak fishing trailer 'American Dream'

\*McMahan et al. Nature 2020, 4 December



Continuous safety evaluation ensures vaccine safety	
Long-standing experience vaccine development	Rigorous pre-clinical and clinical testing
Cutter incident (1955) Inadequate inactivation polio vaccine virus	All batches are tested for safety
Vaccine associated enhanced respiratory disease Formaline inactivated RSV vaccine (1960) No neutralising antibodies	Understanding mechanisms of action vaccine and correlates of immune protection
Additional testing if serious event are detected pre- and post-licensure Rotavirus vaccine and intussusception (1998)	Rare severe adverse events trigger a safety pause to trial or use
	Continuing surveillance of potential vaccine-related adverse events post-licensure and post-marketing

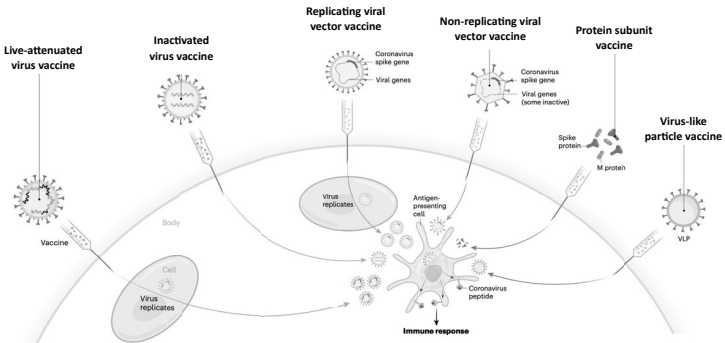
Science 2020, 17 November

Potential risks associated with vaccine development for COVID-19

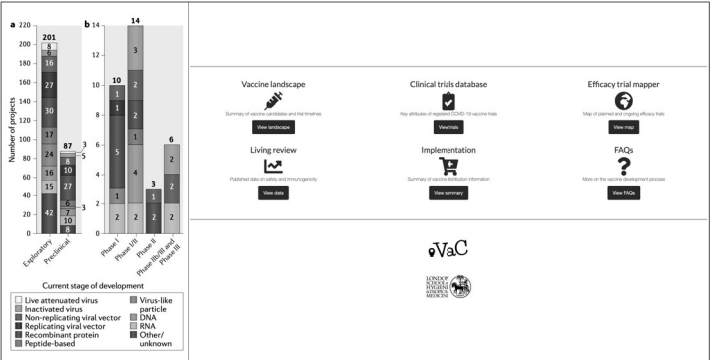
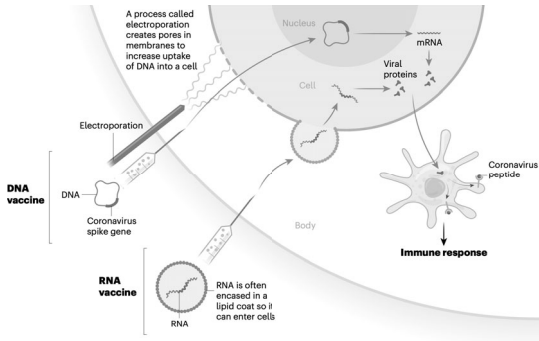
	Antibody-mediated		T cell-mediated
	ADE	VAERD	VAERD
Mechanism	Fc-mediated increase in viral entry	Immune complex formation and complement deposition	T <sub>H</sub> 2-biased immune response
Effectors	Macrophage activation and inflammatory cytokines	Complement activation and inflammatory cytokines	Allergic inflammation and T <sub>H</sub> 2 cytokines
Mitigation	Conformationally correct antigens and high-quality neutralizing antibody		T <sub>H</sub> 1-biasing immunization and CD8 <sup>+</sup> T cells

Science 2020;368:945

Protein-based vaccines	Gene-based vaccines
Inactivated whole virus	Live-attenuated virus vaccine
Virus like particle	Replicating recombinant vector virus (Measles vaccine virus strain)
Replication-incompetent vector virus (Adenovirus)	Nucleic acid (mRNA)
Spike protein	



Nature 2020; 580:576



Nature Rev Drug Discovery 2020;19:667

[https://vac-tshtm.shinyapps.io/ncov\\_vaccine\\_landscape/#](https://vac-tshtm.shinyapps.io/ncov_vaccine_landscape/#)

Table 1   Overview of NHP results									
Company (ref.)	Vaccine candidate (type)	Dose range (route)	Neut. titre after prime	Neut. titre after boost	T cell response	Challenge dose (route)	URT protection	LRT protection	Species
Sinovac <sup>34</sup>	PiCoVacc (inactivated virion + aluminium hydroxide)	3–6 µg (i.m.)	None <sup>a</sup>	1:10 range <sup>a</sup> after first boost; 1:50 range <sup>a</sup> after second boost	ND	10 <sup>6</sup> TCID <sub>50</sub> (i.t.)	Partial <sup>b</sup>	Partial (low dose) <sup>b</sup> Complete (high dose)	Rhesus macaques
Pfizer	mRNA-BNT162b2	30–100 µg (i.m.)	80–100	962–1,689 range	Yes	1.05 × 10 <sup>6</sup> PFU (i.n., i.t.)	Complete (2x)	Complete (2x)	Rhesus macaques
AstraZeneca <sup>49</sup>	ChAdOx1 nCoV-19 (non-replicating AdV)	2.4 × 10 <sup>10</sup> VP; 1 × or 2 × (i.m.)	1:5–1:40 range <sup>a</sup>	1:10–1:160 range <sup>a</sup>	Yes	2.6 × 10 <sup>6</sup> TCID <sub>50</sub> (i.t., oral, i.n., ocular)	Nons (1 ×) <sup>b</sup> Nons (2 ×) <sup>b</sup>	Partial (1 ×) <sup>b</sup> Complete (2 ×) <sup>b</sup>	Rhesus macaques
Janssen <sup>41</sup>	Ad26COV-S1 (non-replicating AdV)	1 × 10 <sup>10</sup> VP (i.m.)	1:100 range <sup>d</sup>	NA	Low	10 <sup>7</sup> TCID <sub>50</sub> (i.n., i.t.)	Complete in S.P.P group <sup>e</sup>	Complete in S.P.P group <sup>e</sup>	Rhesus macaques
Moderna <sup>37</sup>	mRNA-1273 (mRNA via LNPs)	2 × 10–100 µg (i.n.)	ND <sup>a</sup>	1:501–1:3,481 range <sup>a</sup>	Yes, CD4, T <sub>H1</sub>	7.6 × 10 <sup>5</sup> TCID <sub>50</sub> (i.n., i.t.)	Nons (10 µg) <sup>b</sup> Partial (100 µg) <sup>b</sup> Partial (100 µg) <sup>b</sup>	Partial (10 µg) <sup>b</sup> Complete (100 µg) <sup>b</sup>	Rhesus macaques
Novavax <sup>39</sup>	NVX CoV2373 (spike protein + Matrix-M)	2 × 1.5–25 µg	Not reported	17,920–23,040 range <sup>a</sup>	ND	10 <sup>6</sup> plaque-forming units (i.n., i.t.)	Partial (lowdose) <sup>b</sup> Complete (higher doses) <sup>b</sup>	Complete <sup>b</sup>	Cynomolgus macaques

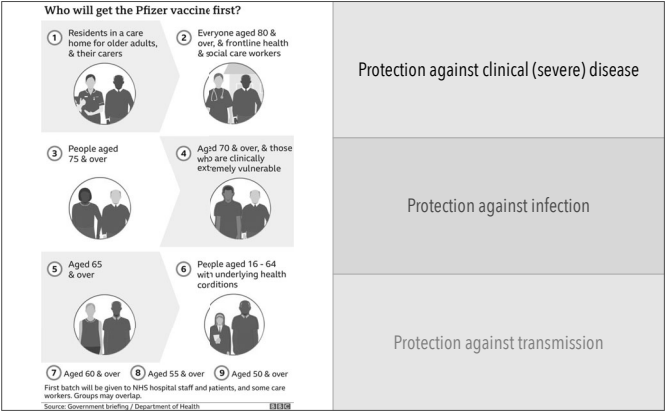
Nature 2020; 580:516 (modified results BioNTech added bioRxiv Sept 8, 2020)

BNT162b2 (Pfizer)	mRNA-1273 (Moderna)	NVX-CoV2373 (Novavax)	ChAdOx1 nCoV-19 (Astra Zeneca)	CoronaVac (SinoVac)
mRNA in lipid nanoparticles	mRNA in lipid nanoparticles	recombinant spike protein	Replication deficient vector	Inactivated whole virus
full-length spike protein with 2 stabilizing mutations	full-length spike protein with 2 stabilizing mutations	full-length spike protein with 2 stabilizing mutations	full-length wild-type version spike protein	
		saponin-containing Matrix-M		Al(OH) <sub>3</sub>
3-week prime-boost	4-week prime-boost	3-week prime-boost	4-week prime-boost	4-week prime-boost
Medium range VNA	Medium range VNA	High range VNA	Medium range VNA	Lower range VNA
70% fever	40% fever after booster dose	Malaise, fatigue, headache	Fatigue, headache, feverish	Excellent safety
Lower reactogenicity and immunogenicity in older people				Lower antibody titres in older persons

	BioNTech BNT162 (b1/s2)	Moderna mRNA-1273	Oxford ChAdOx1-S
Developer(s)	BioNTech, Fosun Pharma, Pfizer	Moderna, NIND	University of Oxford, AstraZeneca
Platform	RNA	RNA	Non-replicating viral vector
Dosing	2 doses, intramuscular	2 doses, intramuscular	2 doses, intramuscular
Description	Lipid nanoparticle-formulated mRNA encoding full-length spike (S) protein	Lipid nanoparticle-encapsulated mRNA encoding pre-fusion spike (S) protein	Simian adenovirus vector containing codon-optimised spike (S) protein
Efficacy data	Vaccine efficacy against COVID-19 reported to be 96% based on primary efficacy analysis of 170 confirmed cases (18 Nov 2020). These included 10 cases of severe COVID-19, 9 of which occurred in the placebo group.	Vaccine efficacy against COVID-19 reported to be 94.9% based on interim data from 95 cases (11 Nov 2020). These included 11 cases of severe COVID-19, all of which occurred in the placebo group.	Vaccine efficacy against COVID-19 reported to be 62% based on interim data from 131 cases (22 Nov 2020).
Storage requirements	Ultra-cold (–80°C to –60°C)	Refrigeration (2°C to 8°C) for up to 30 days or frozen (–10°C to –25°C) for long-term storage	Refrigeration (2°C to 8°C)
ONE Vaccine Access Test score	BioNTech and Pfizer given scores of 1.0 out of 10 and 0.8 out of 10, respectively	Moderna given score of 1.2 out of 10	AstraZeneca given score of 0.8 out of 10
Manufacture projections	50 million doses in 2020 and up to 1.3 billion doses in 2021 (20 Nov 2020)	500 million to 1 billion doses per year (22 Oct 2020)	3 billion doses in 2021 (22 Nov 2020)
Approval/consensus	Granted approval for emergency use in the UK (22 Dec 2020)	Not yet approved for widespread use	Not yet approved for widespread use

Vaccines undergoing phase II efficacy testing are included (see **Clinical trials** and **Trial mapper** tabs for further details). Information on storage requirements obtained from Poland et al (2020).

[https://vac-lshtm.shinyapps.io/ncov\\_vaccine\\_landscape/](https://vac-lshtm.shinyapps.io/ncov_vaccine_landscape/)



'Because none of us is safe until all of us is safe'

ONE TAKE ACTION ABOUT ONE THE ISSUES BLOG

International

**Vaccine Access Test**

Are the actions of leaders in government and business ensuring that those who need a vaccine most, get a vaccine first?

The Vaccine Access Test answers this question.

For global distribution of COVID-19 vaccines will end the pandemic faster for everyone, saving lives and helping economies recover.

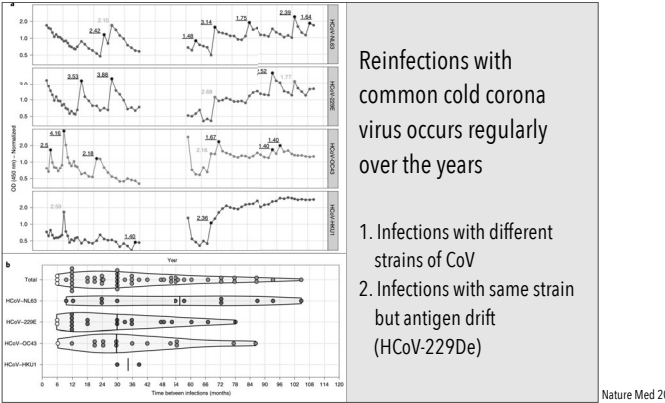
The science tells us that those most at risk of catching and spreading the virus, and those most vulnerable to it, must have access first, regardless of nationality or wealth.

We've consulted world-leading experts and our criteria based on what the science tells us counts as Progress. Here's what you measure:

- Supporting the COVID-19 Task Accelerator (ACT-A):** Launching the only mechanism positioned to deliver a coordinated global response.
- Multilateral Leadership:** Working with others to ensure everyone has access.
- Politeness:** Initiating and promoting policies that ensure everyone has access.
- Deals:** Agreeing deals that allocate doses to those most in need and ensure countries aren't a barrier to access.

We have scored 52 countries plus the EU and ALL the companies striking deals for promising vaccine candidates. Here's how they stack up.

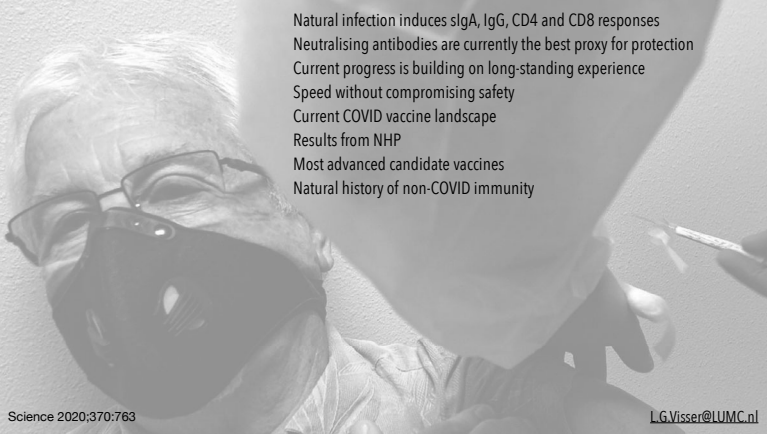
<https://www.one.org/international/vaccine-access-test/>



Reinfections with common cold corona virus occurs regularly over the years

1. Infections with different strains of CoV
2. Infections with same strain but antigen drift (HCoV-229De)

Nature Med 2020;26:1691



Natural infection induces sIgA, IgG, CD4 and CD8 responses  
Neutralising antibodies are currently the best proxy for protection  
Current progress is building on long-standing experience  
Speed without compromising safety  
Current COVID vaccine landscape  
Results from NHP  
Most advanced candidate vaccines  
Natural history of non-COVID immunity