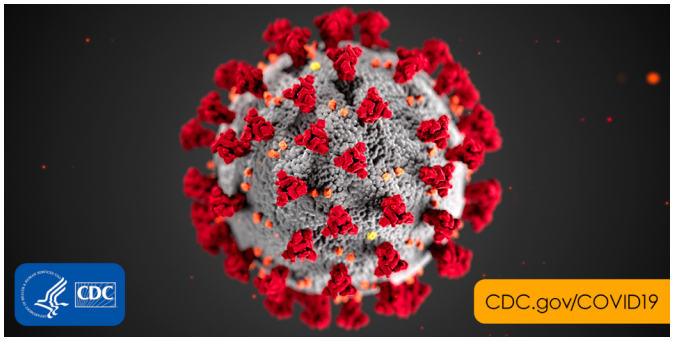
The Challenge of Rapidly Developing COVID-19 Vaccines

October 22, 2020



James H. Conway, MD FAAP

Professor of Pediatrics - Division of Infectious Disease

University of Wisconsin-Madison - School of Medicine and Public Health

Associate Director – UW-Madison Global Health Institute

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The NEW ENGLAND JOURNAL of MEDICINE

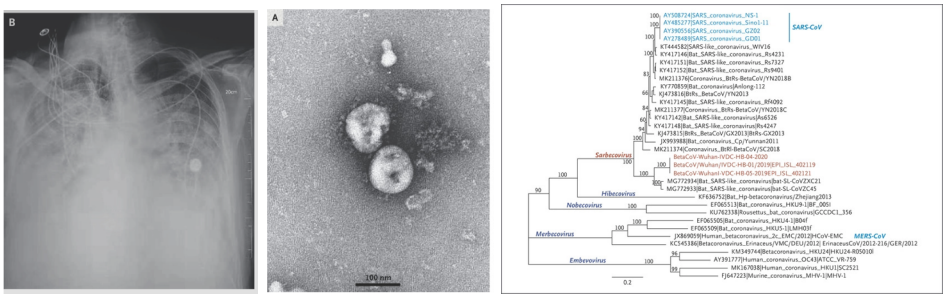
ORIGINAL ARTICLE BRIEF REPORT

A Novel Coronavirus from Patients with Pneumonia in China, 2019

Na Zhu, Ph.D., Dingyu Zhang, M.D., Wenling Wang, Ph.D., Xinwang Li, M.D., Bo Yang, M.S., Jingdong Song, Ph.D., Xiang Zhao, Ph.D., Baoying Huang, Ph.D., Weifeng Shi, Ph.D., Roujian Lu, M.D., Peihua Niu, Ph.D., Faxian Zhan, Ph.D., Xuejun Ma, Ph.D., Dayan Wang, Ph.D., Wenbo Xu, M.D., Guizhen Wu, M.D., George F. Gao, D.Phil., and Wenjie Tan, M.D., Ph.D. et al., for the China Novel Coronavirus Investigating and Research Team

January 24, 2020
DOI: 10.1056/NEJMoa2001017

1/24/2020 initial clinical description, virus isolation, and sequence analysis
(China first released sequence 1/12/2020)



2

WHO statement on novel coronavirus in Thailand

1/13/2020: First case outside of China

13 January 2020 | News release

1/30/2020: WHO declares COVID-19 a Public Health Emergency of International Concern

World Health Organization

WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020

11 March 2020

Good afternoon.

In the past two weeks, the number of cases of COVID-19 outside China has increased 13-fold, and the number of affected countries has tripled.

There are now more than 118,000 cases in 114 countries, and 4,291 people have lost their lives.

Thousands more are fighting for their lives in hospitals.

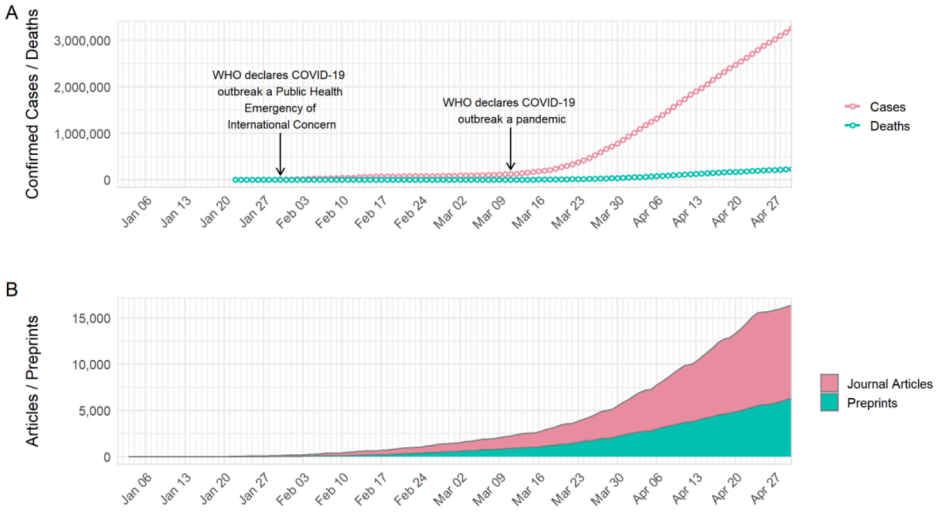
3/11/2020: WHO declares COVID-19 a Pandemic

3

Preprinting a pandemic: the role of preprints in the COVID-19 pandemic

Nicholas Fraser, Liam Brierley, Gautam Dey, Jessica K Polka, Máté Pálfy, Jonathon Alexis Coates

doi: https://doi.org/10.1101/2020.05.22.111294



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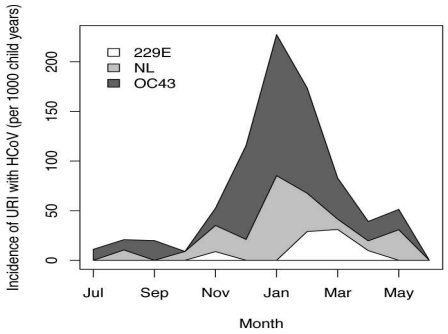
What do we know about Coronaviruses & immunity following infection?



- "The Pediatric Burden of Human Coronaviruses Evaluated for 20 Years". Tabot et al. PIDJ 2009
- Common coronaviruses (229E, NL63, OC43, HKU1) circulate annually
  - 5-15% of URI's each season
  - Reinfection is common

5

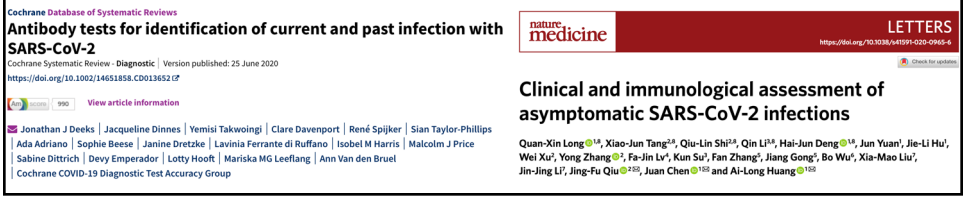
What do we know about Coronaviruses & immunity following infection?

- Found worldwide, winter/spring URIs
- Approximately 60% of children and 90% of adults >50 yo are seropositive
  - "Development of a nucleocapsid-based human coronavirus immunoassay and estimates of individuals exposed to coronavirus in a U.S. metropolitan population. Severance et al. *Clin Vaccine Immunol 2008*
- However mucosal immunity declines quickly
  - Only 8-31% have detectable secretory antibody
  - Reinfection is common
  - "Prevalence of Antibodies to Four Human Coronaviruses Is Lower in Nasal Secretions than in Serum" Gorse et al. *Clin Vaccine Immunol 2010.*

6

Some thoughts on COVID-19 immunity after wild-type infection

- The immunology and subsequent protection from repeat infection is still not understood
  - Reinfections now being documented
- In asymptomatic individuals, 40% are seronegative within 2-3 months vs. 12.9% in symptomatic pts.
- SARS & MERS IgG persist longer – up to 1 year
- A Cochrane review found that COVID-19 antibodies peak about 3 weeks after infection



Cochrane Database of Systematic Reviews

Antibody tests for identification of current and past infection with SARS-CoV-2

Cochrane Systematic Review - Diagnostic | Version published: 25 June 2020

https://doi.org/10.1002/14651858.CD013652

View article information

Jonathan J Deeks | Jacqueline Dinnes | Yemisi Takwoingi | Clare Davenport | René Spijker | Sian Taylor-Phillips | Ada Adriano | Sophie Beese | Janine Dretzke | Lavinia Ferrante di Ruffano | Isobel M Harris | Malcolm J Price | Sabine Dittrich | Devy Emperador | Lotty Hooft | Mariska MG Leeflang | Ann Van den Bruel | Cochrane COVID-19 Diagnostic Test Accuracy Group

nature medicine

LETTERS

https://doi.org/10.1038/s41591-020-0965-6

Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections

Quan-Xin Long[1,8], Xiao-Jun Tang[2,8], Qiu-Lin Shi[2,8], Qin Li[3,8], Hai-Jun Deng[1,8], Jun Yuan[1], Jie-Li Hu[1], Wei Xu[2], Yong Zhang[3], Fa-Jin Lv[4], Kun Su[3], Fan Zhang[5], Jiang Gong[5], Bo Wu[6], Xia-Mao Liu[7], Jin-Jing Li[7], Jing-Fu Qiu[2✉], Juan Chen[1✉] and Ai-Long Huang[1✉]

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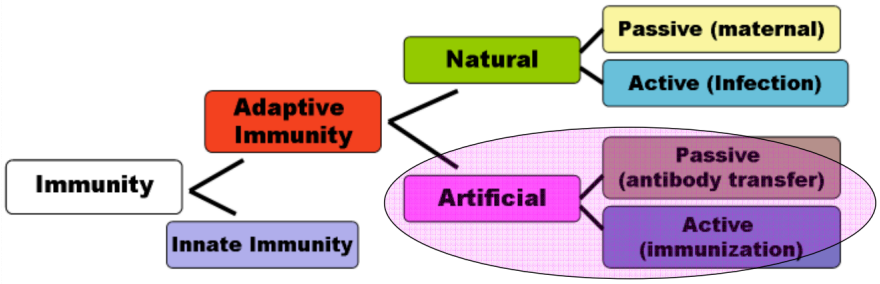
Ideal Vaccine Candidates

- EFFICACY: Produce immune protection that prevents infection
  - Long lasting & easily boosted
  - Prevents shedding & transmission to others
  - Activates both T-cells and B-cells
- SAFETY:
  - Does not cause enhanced immune response during infection
  - Minimal side effects after injection
  - No long term side effects

8

Types of Immunity



- ACTIVE IMMUNITY:
  - B-lymphocytes – humoral immunity = produce antibodies
  - T-lymphocytes – cellular immunity = memory immunity, kill infected cells & viruses, direct traffic

- http://en.wikipedia.org/wiki/Immunological_memory

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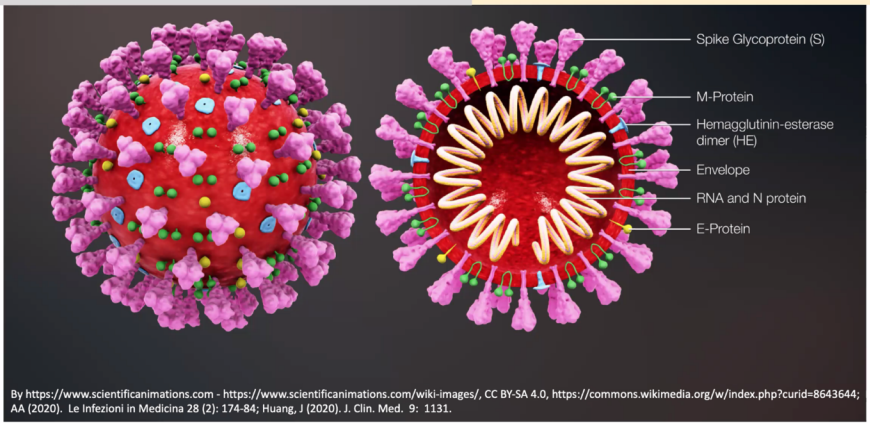
functional targets
- RNA-dependent RNA polymerase (RdRp)
- heterogeneous nuclear ribonucleoprotein A1 (hnRNP A1)
- glycogen synthase kinase 3 (GSK3)
- cysteine proteases

structural targets
- M protein
- Spike protein
- Envelope proteins



By https://www.scientificanimations.com - https://www.scientificanimations.com/wiki-images/, CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=8643644; AA (2020). Le Infezioni in Medicina 28 (2): 174-84; Huang, J (2020). J. Clin. Med. 9: 1131.

10

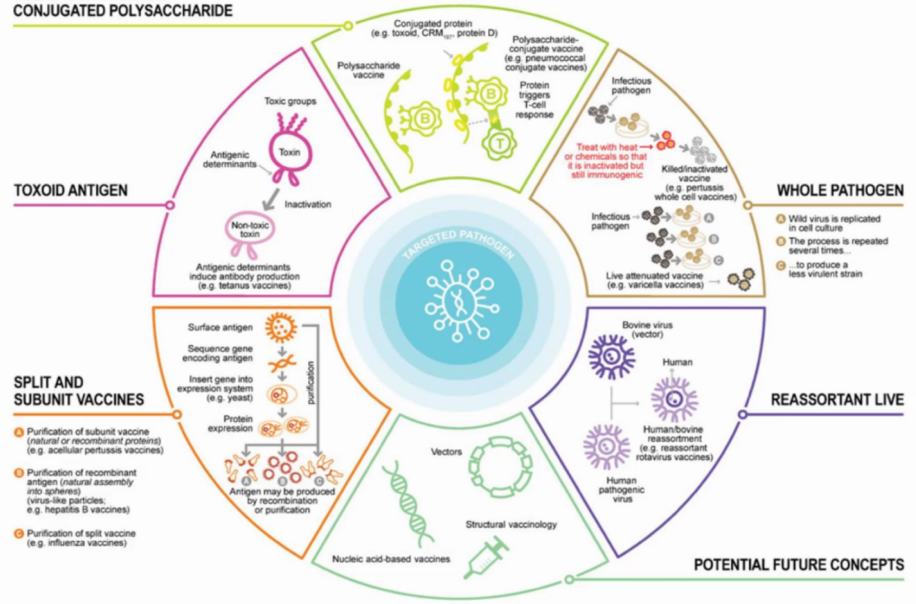


Figure 1. Different types of vaccines. Vaccines can be produced using different processes. Vaccines may contain live attenuated pathogens (usually viruses), inactivated whole pathogens, toxoids (an inactivated form of the toxin produced by bacteria that causes the disease), or parts of the pathogens (e.g. natural or recombinant proteins, polysaccharides, conjugated polysaccharide or virus-like particles).

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CHALLENGES to a COVID-19 vaccine

- Natural immunity to coronaviruses appears to be short-lived
  - serum neutralizing antibodies detection ≠ mucosal immunity
- Unclear surrogate marker of immunity
  - How do we assess vaccine efficacy?
  - Ethics of challenge trials?
- Best target antigen(s)?
- Anticipating progressive mutations?
- Optimal route of delivery?

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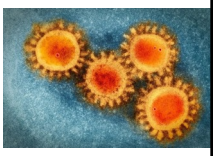
CHALLENGES to a COVID-19 vaccine



- Enhanced disease after vaccine?
  - Multisystem Inflammatory Syndrome-Coronavirus = MIS-C
- Durability of immunity? Need for boosters?
- Testing population vs. target population?
- Bypassing the usual progressive process for product development
- Mass manufacture & delivery
  - Many require ultra cold chain (-60 to -80F)
- Targeted & equitable distribution challenges

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Reasons for (modest) optimism

- An unprecedented GLOBAL effort to develop a vaccine!
  - Collaboration between companies
  - Widespread sharing of information including pre-prints
- MANY potential candidate vaccines & novel technologies
- LOTS of money being put into R & D
- National competition?
- Novel approaches to R & D – and production
- Prior efforts to develop MERS & SARS-CoV1

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http://vaxmap.org/

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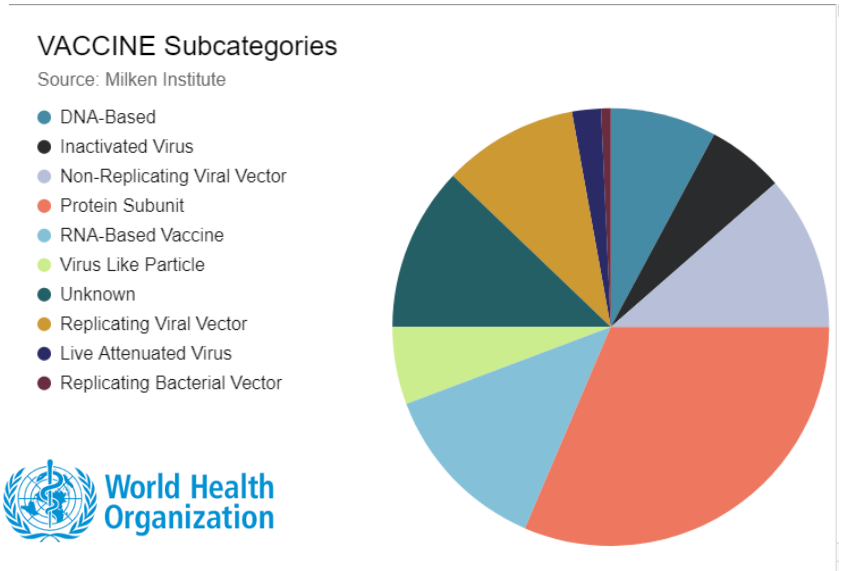
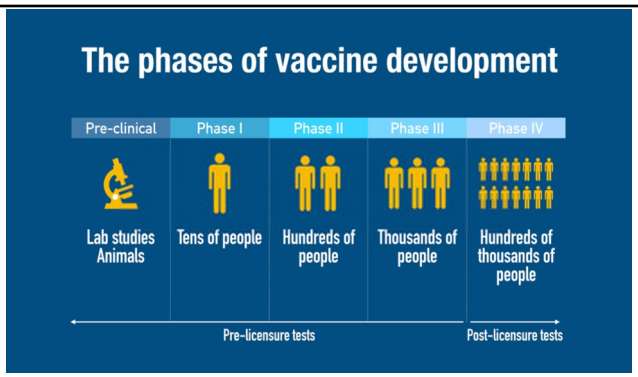
Currently 154 pre-clinical vaccine candidates registered



https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines

16



- 44 candidate vaccines in clinical trials:
  - 21 candidates in Phase 1 human trials
  - 13 candidates in Phase 1/2 or Phase 2 trials
  - 10 candidates in Phase 3 trials
- 1 vaccine licensed in Russia
- 1 vaccine approved for limited use in Chinese military

World Health Organization

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World Health Organization DRAFT landscape of COVID-19 candidate vaccines – 19 October 2020

COVID-19 Vaccine developer/manufacturer	Vaccine platform	Type of candidate vaccine	Number of doses	Timing of doses	Route of Administration	Clinical Stage			
						Phase 1	Phase 1/2	Phase 2	Phase 3
Sinovac	Inactivated	Inactivated	2	0, 14 days	IM		NCT04383574 NCT04352608 NCT04551547		NCT04456595 669/UN6.KEP/EC/2020
Wuhan Institute of Biological Products/Sinopharm	Inactivated	Inactivated	2	0,21 days	IM		ChiCTR2000031809 Interim Report		ChiCTR2000034780
Beijing Institute of Biological Products/Sinopharm	Inactivated	Inactivated	2	0,21 days	IM		ChiCTR2000032459		ChiCTR2000034780 NCT04560881
University of Oxford/AstraZeneca ★	Non-Replicating Viral Vector	ChAdOx1-S	1		IM		PACTR202006922165132 2020-001072-15 NCT04568031 Interim Report	2020-001228-32	ISRCTN89951424 NCT04516746 NCT04540393 CTRI/2020/08/027170
CanSino Biological Inc./Beijing Institute of Biotechnology	Non-Replicating Viral Vector	Adenovirus Type 5 Vector	1		IM	ChiCTR2000030906 NCT04568811 Study Report		ChiCTR2000031781 NCT04566770 Study Report	NCT04526990 NCT04540419
Gamaleya Research Institute	Non-Replicating Viral Vector	Adeno-based (rAd26-S+rAd5-S)	2	0,21 days	IM		NCT04436471 NCT04437875 Study Report		NCT04530396 NCT04564716
Janssen Pharmaceutical Companies ★	Non-Replicating Viral Vector	Ad26COVS1	2	0, 56 days	IM		NCT04436276		NCT04505722
Novavax ★	Protein Subunit	Full length recombinant SARS CoV-2 glycoprotein nanoparticle vaccine adjuvanted with Matrix M	2	0, 21 days	IM	NCT04283461 Interim Report Final Report	NCT04368988 Study Report	NCT04533399 (phase 2b)	2020-004123-16
Moderna/NIAID ★	RNA	LNP-encapsulated mRNA	2	0, 28 days	IM			NCT04405076	NCT04470427
BioNTech/Fosun Pharma/Pfizer ★	RNA	3 LNP-mRNAs	2	0, 28 days	IM		2020-001038-36 ChiCTR2000034825 NCT04537949 Study Report1 Study Report2		NCT04368728

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Current *most* proximal candidates

- **Moderna (mRNA-1273) - mRNA**
  - 100mcg – 2 doses, 28 days apart
  - 1:1 randomization, enrollment slower than expected
- **Pfizer/BioNTech (BNT162b2) - mRNA**
  - 30mcg – 2 doses, 21 days apart

- **Oxford/AstraZeneca (AZD1222)**
  - formerly ChAdOx1 nCoV-19
  - 2.5-5 x 10^{10} viral particles – 2 doses, 28 days apart
  - SAFETY & EFFICACY trial –
    - Enrolling 18-55yo subjects 2:1 randomization, 2 years
  - SUSAR (Suspected Unexpected Serious Adverse Reaction) reports – transverse myelitis, multiple sclerosis
  - All US trials currently suspended
  - FDA board of experts appointed for review

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Other potential candidates

- **Johnson & Johnson (Janssen)**
  - Non-replicating viral vector Ad26COVS1
  - Human adenovirus platform
  - 2 doses, 0 & 56 days
  - Studies currently on hold due to 'illness' in subjects
- **Novavax**
  - Protein subunit – SARS-CoV2 glycoprotein nanoparticle with adjuvant
  - 2 doses, 0 & 21 days
- **Sanofi Pasteur/GSK**
  - S protein produced in baculovirus
  - 2 doses, 0 & 21 days
- **Inovio/International Vaccine Institute**
  - DNA plasmid with electroporation
  - 2 doses, 0 & 28 days

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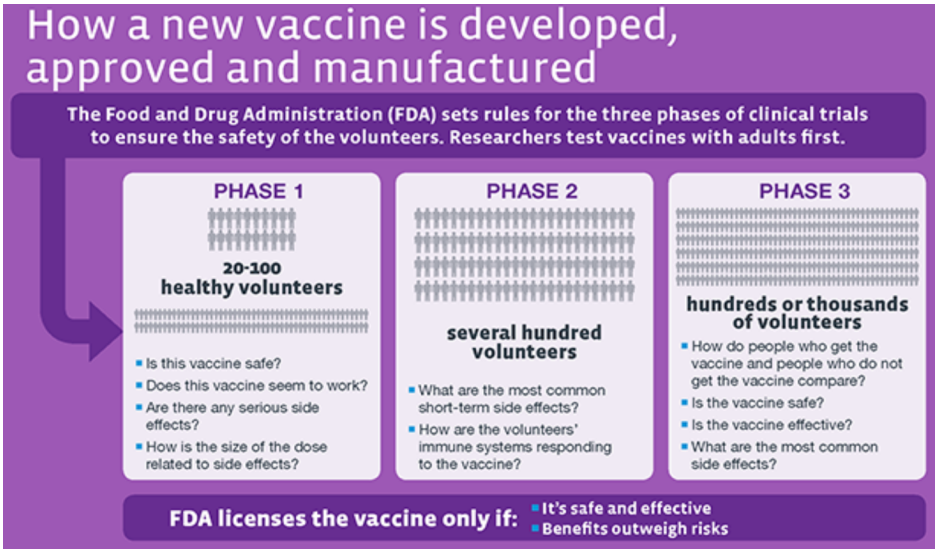

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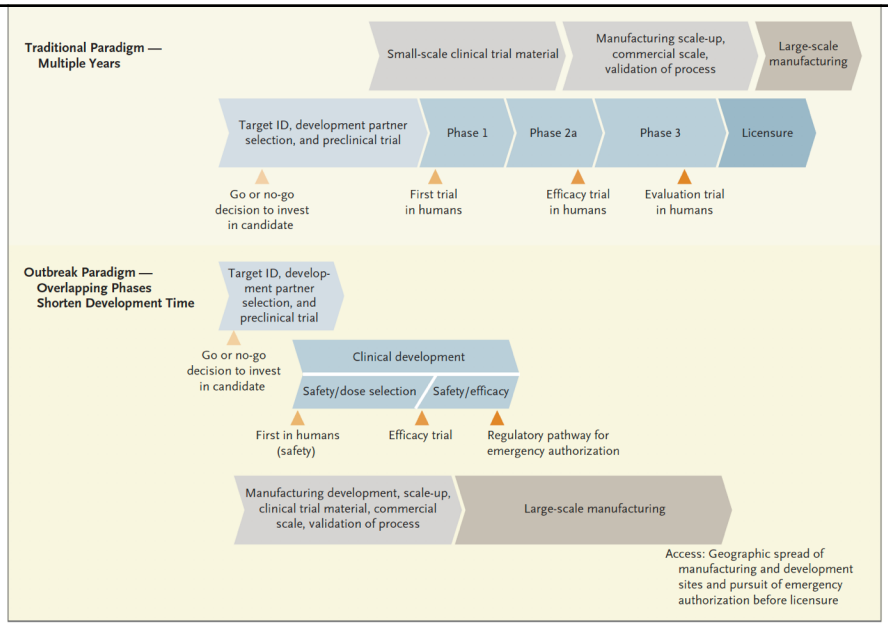

Difference between Traditional Vaccine Development and Development Using a Pandemic Paradigm.

Developing Covid-19 Vaccines at Pandemic Speed

Nicole Lurie, M.D., M.S.P.H., Melanie Saville, M.D., Richard Hatchett, M.D., and Jane Halton, A.O., P.S.M.

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Operation Warp Speed (OWS)

Development

- Fourteen promising candidates chosen from the 100+ vaccine candidates currently in development
- Winnowed down to about 7 or 8 candidates, which are going through further testing in early stage small clinical trials.
- Large-scale randomized trials for the demonstration of safety and efficacy will proceed for three to five of the candidates.
- Current companies: J&J (Janssen), AstraZeneca-Oxford & Vaccitech, Pfizer-BioNTech, Moderna, Merck & AIVI, Vaxart, Inovio, Novavx, Sanofi & GSK

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Operation Warp Speed (OWS)

Allocation & Distribution

- Before the vaccines are approved, program intends to develop plans and infrastructure for distribution
- OWS also focused on expanding the supplies of materials and resources
  - Ex. cold-chain storage, glass vials, and other necessary materials for distribution.
- Advisory Committee on Immunization Practice & National Academy of Sciences have developed proposals for ethical allocation
- Each state will tasked with plan for distribution to health systems & public health providers

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DRAFT TABLE 1 Overview of Ongoing COVID-19 Vaccine Allocation Efforts *(To be updated as more information becomes available.)*

Effort	Leaders	Goals	Guiding Principles	Prioritized Groups
COVAX	WHO CEPI GAVI	• Provide a process mechanism for between-country coordination and allocation. • Offer advance purchase agreements to vaccine candidates meeting technical threshold criteria.	• Mitigate economic damage. • Accelerate availability of vaccine. • Ensure globally fair allocation and access for Low- and Middle- Income Countries.	Groups likely to be prioritized in first round of vaccination: 1. Health care system workers 2. Adults aged ≥65 years 3. Other high-risk adults with underlying conditions (e.g., hypertension, diabetes)
Guiding principles for immunization activities during the COVID-19 pandemic	WHO SAGE	• Provide a values framework for within-country prioritization and decision making about immunization services.	• Ensure continuity of routine immunization services during the COVID-19 pandemic (where feasible) to prevent outbreaks of vaccine-preventable diseases.	
Global Allocation Framework for COVID-19 Products	WHO	• Ensure equitable and fair allocation of COVID-19 products. • Issue policy recommendations to inform optimal use of scarce resources as more product-specific information becomes available.	• Reduce COVID-19 mortality and protect health systems to improve population well-being and reduce societal and economic impact. • Ensure flexibility to adapt to each new product, evolving epidemiology, and risk. • Use transparent criteria for allocating doses as they become available.	1. Health care workers 2. Adults aged≥65 years 3. Other high-risk adults
ACIP COVID-19 Vaccine Workgroup	ACIP	• Develop plan for allocation of vaccine in the United States	• Monitor effectiveness and safety in real time to revise recommendations based on the risk/benefit balance in different populations. • Ensure diversity in vaccine clinical trials to ensure that recommendations are based on safety and efficacy data across all populations who may benefit.	

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'Vaccine Nationalism': A New Dynamic in the Race to Quash Coronavirus

International pursuit for a shot is shifting into a contest of which world power can immunize its population first

Science Speaks: Global ID News

A PROJECT OF IDSA GLOBAL HEALTH

ABOUT SCISPEAKS SERIES LIVEBLOG ARCHIVES

COVID-19: China approves vaccine for use by military only without phase III study

BY GUEST WRITER ON JUNE 29, 2020.

By Daniel R. Lucey M.D., MPH, FIDSA

172 countries and multiple candidate vaccines engaged in COVID-19 vaccine Global Access Facility

World Health Organization

Gavi The Vaccine Alliance

NDTV CORONAVIRUS LIVE TV LATEST INDIA VIDEO WORLD

India's COVID-19 Vaccine Trial "Marks Beginning Of The End": Centre

Science Ministry's statement comes amid a row over a letter by the ICMR setting Augu Independence Day - as the target for releasing a novel coronavirus vaccine

All India | Reported by Arvind Gunasekar, Parimal Kumar, Edited by Chandrashekar Srinivasan | Updated: July 06, 2020 08:21 am IST

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POLITICS | HEALTH POLICY

FDA to Require Proof Virus Vaccine Is Effective Before Approving Its Use

Treatment would need to be at least 50% more effective than placebo in preventing disease

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Pharma pushback…

BIOPHARMA LEADERS UNITE TO STAND WITH SCIENCE

-- Nine CEOs sign historic pledge to continue to make the safety and well-being of vaccinated individuals the top priority in development of the first COVID-19 vaccines --

NEW YORK, September 8, 2020 — The CEOs of AstraZeneca (LSE/STO/NYSE: AZN), BioNTech (NASDAQ: BNTX), GlaxoSmithKline plc (LSE/NYSE: GSK), Johnson & Johnson (NYSE: JNJ), Merck (NYSE: MRK), known as MSD outside the United States and Canada, Moderna, Inc. (Nasdaq: MRNA), Novavax, Inc. (Nasdaq: NVAX), Pfizer Inc. (NYSE: PFE), and Sanofi (NASDAQ: SNY), today announced a historic pledge, outlining a united commitment to uphold the integrity of the scientific process as they work towards potential global regulatory filings and approvals of the first COVID-19 vaccines.

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AP | NORC at the UNIVERSITY of CHICAGO

Home › Projects+Programs › Expectations for a COVID-19 Vaccine

The Associated Press-NORC Center for Public Affairs Research

Expectations for a COVID-19 Vaccine

Most Americans expect a vaccine against COVID-19 to be available by some point in 2021, but only half say they will get vaccinated and many are unsure, according to the AP-NORC survey conducted in May 2020.

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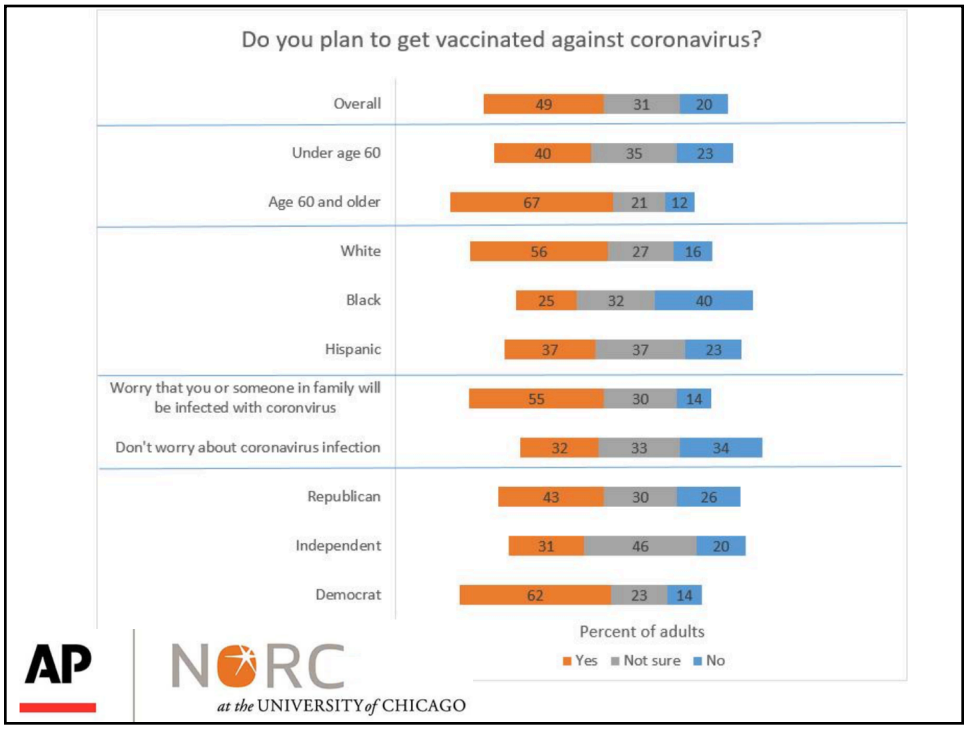
Do you plan to get vaccinated against coronavirus?
Overall
49
31
20
Under age 60
40
35
23
Age 60 and older
67
21
12
White
56
27
16
Black
25
32
40
Hispanic
37
37
23
Worry that you or someone in family will be infected with coronvirus
55
30
14
Don't worry about coronavirus infection
32
33
34
Republican
43
30
26
Independent
31
46
20
Democrat
62
23
14
Percent of adults
Yes
Not sure
No
AP
NORC
at the UNIVERSITY of CHICAGO

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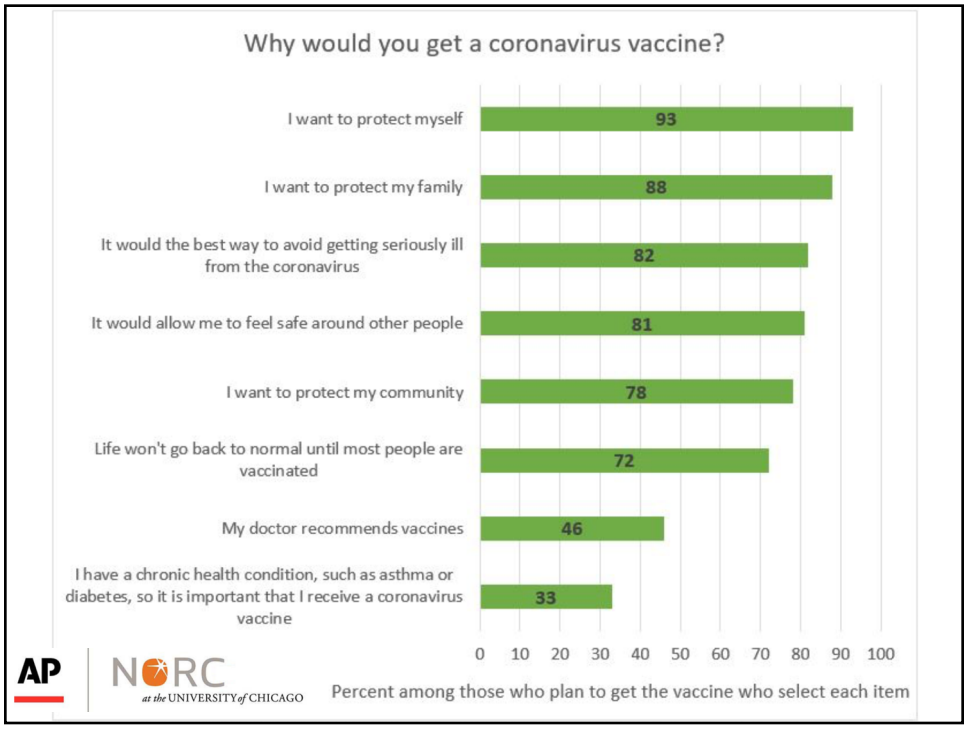
Why would you get a coronavirus vaccine?
I want to protect myself
93
I want to protect my family
88
It would the best way to avoid getting seriously ill from the coronavirus
82
It would allow me to feel safe around other people
81
I want to protect my community
78
Life won't go back to normal until most people are vaccinated
72
My doctor recommends vaccines
46
I have a chronic health condition, such as asthma or diabetes, so it is important that I receive a coronavirus vaccine
33
0 10 20 30 40 50 60 70 80 90 100
Percent among those who plan to get the vaccine who select each item
AP
NORC
at the UNIVERSITY of CHICAGO

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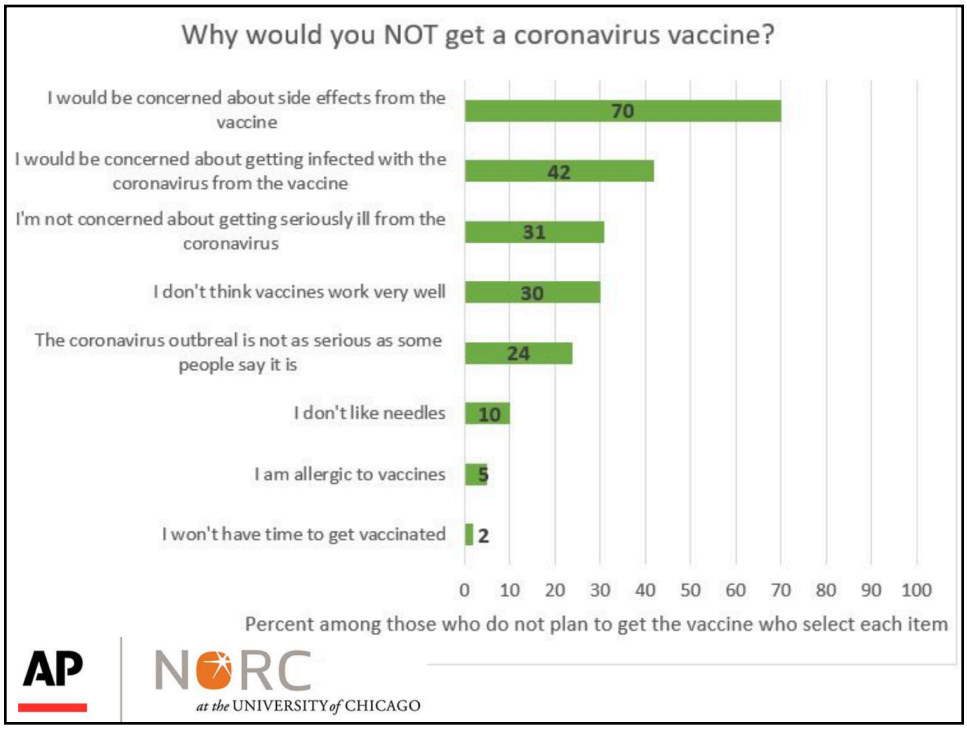

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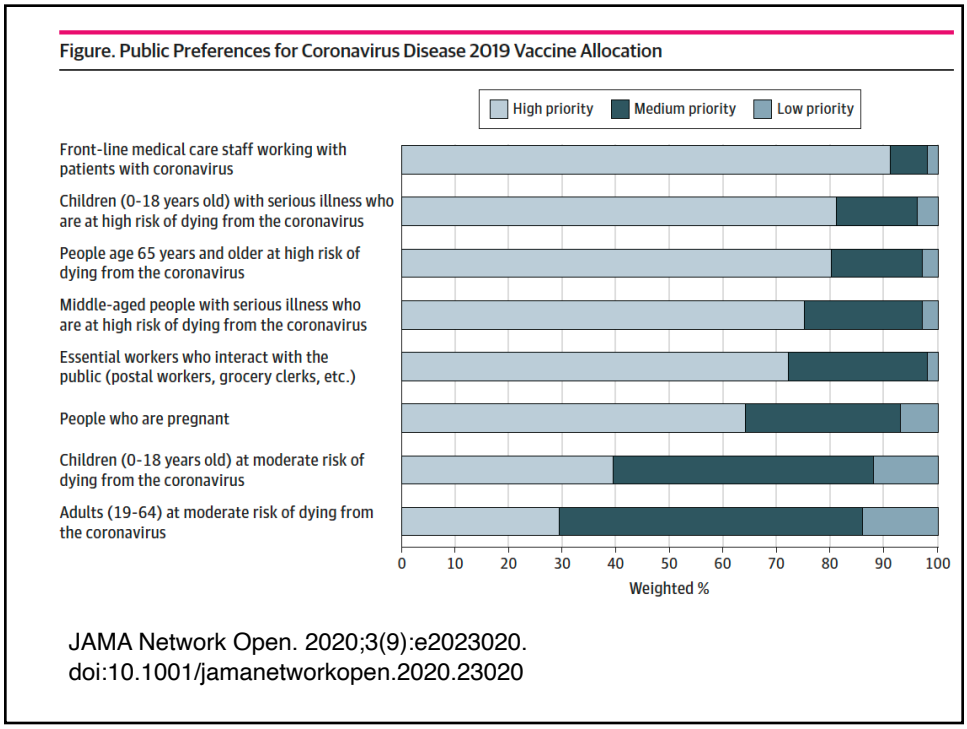

JAMA Network Open. 2020;3(9):e2023020.
doi:10.1001/jamanetworkopen.2020.23020

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