From: Lauer, Michael (NIH/OD) [E] [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=90FE9CAE30C64CFBB67ABD568E882796-LAUERM]
Sent: 7/6/2020 10:00:52 PM
To: Allen-Gifford, Patrice (NIH/OD) [E] [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=67262490d6d441b48efec1aff0700250-allengiffor]
CC: Lauer, Michael (NIH/OD) [E] [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=90fe9cae30c64cfbb67abd568e882796-lauerm]
Subject: Re: fyi (sensitive)
Attachments: Suspension of Grant_Daszak letter June XX 2020_final clean RPC Comments clean[1].docx; Executive Committee Meeting tomorrow, July 7, from 11:00 AM to Noon via Zoom

Hi Patrice – I see it's on the agenda for tomorrow.

[redacted] (b) (5)

Does this make sense?

Thanks, Mike

From: "Allen-Gifford, Patrice (NIH/OD) [E]" [redacted] (b) (6)
Date: Monday, July 6, 2020 at 5:27 PM
To: "Lauer, Michael (NIH/OD) [E]" [redacted] (b) (6)
Subject: FW: fyi (sensitive)

Hi Mike,
Further to last week's Exec Comm conversation, I know you remember that NIH received many letters about this grant, and some may require a more substantive response than others. Bearing in mind that we are not ready to send the attached draft letter, after you the attached draft has been sent, I propose [redacted] (b) (5) I will appreciate your guidance.
Thank you,
Patrice

From: Doswell, Greta (NIH/OD) [E] [redacted] (b) (6)
Sent: Tuesday, June 30, 2020 8:53 AM
To: Allen-Gifford, Patrice (NIH/OD) [E] [redacted] (b) (6)
Subject: FW: fyi (sensitive)

From: Tabak, Lawrence (NIH/OD) [E] [redacted] (b) (6)
Sent: Monday, June 29, 2020 9:41 PM
To: Collins, Francis (NIH/OD) [E] [redacted] (b) (6)
Subject: fyi

Francis,
Bob has cleared this.
Larry

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Institute of Allergy
and Infectious Diseases
Bethesda, Maryland 20892

6 July 2020

Drs. Aleksei Chmura and Peter Daszak
EcoHealth Alliance, Inc.
460 W 34th St
Suite 1701
New York, NY 10001

Re: NIH Grant R01AI110964

Dear Drs. Chmura and Daszak:

In follow-up to my previous letter of April 24, 2020, I am writing to notify you that the National Institute of Allergy and Infectious Diseases (NIAID), an Institute within the National Institutes of Health (NIH), under the Department of Health and Human Services (HHS), has withdrawn its termination of grant R01AI110964, which supports the project *Understanding the Risk of Bat Coronavirus Emergence*. Accordingly, the grant is reinstated.

However, as you are aware, the NIH has received reports that the Wuhan Institute of Virology (WIV), a subrecipient of EcoHealth Alliance under R01AI110964, has been conducting research at its facilities in China that pose serious bio-safety concerns and, as a result, create health and welfare threats to the public in China and other countries, including the United States. Grant award R01AI110964 is subject to biosafety requirements set forth in the NIH Grants Policy Statement (e.g., NIH GPS, Section 4.1.24 "Public Health Security") and the Notice of Award (e.g., requiring that "Research funded under this grant must adhere to the [CDC/NIH Biosafety in Microbiological and Biomedical Laboratories (BMBL)]."). Moreover, NIH grant recipients are expected to provide safe working conditions for their employees and foster work environments conducive to high-quality research. NIH GPS, Section 4. The terms and conditions of the grant award flow down to subawards to subrecipients. 45 C.F.R. § 75.101.

As the grantee, EcoHealth Alliance was required to "monitor the activities of the subrecipient as necessary to ensure that the subaward is used for authorized purposes, in compliance with Federal statutes, regulations, and the terms and conditions of the subaward . . ." 45 C.F.R. § 75.352(d). We have concerns that WIV has not satisfied safety requirements under the award, and that EcoHealth Alliance has not satisfied its obligations to monitor the activities of its subrecipient to ensure compliance.

Moreover, as we have informed you through prior Notices of Award, this award is subject to the Transparency Act subaward and executive compensation reporting requirement of 2 C.F.R. Part

170. To date you have not reported any subawards in the Federal Subaward Reporting System.

Therefore, effective the date of this letter, July 6, 2020, NIH is suspending all activities related to R01AI110964, until such time as these concerns have been addressed to NIH's satisfaction. This suspension is taken in accordance with 45 C.F.R. § 75.371, Remedies for Noncompliance, which permits suspension of award activities in cases of non-compliance, and the NIH GPS, Section 8.5.2, which permits NIH to take immediate action to suspend a grant when necessary to protect the public health and welfare. This action is not appealable in accordance with 42 C.F.R. § 50.404 and the NIH GPS Section 8.7, Grant Appeals Procedures. However, EcoHealth Alliance has the opportunity to provide information and documentation demonstrating that WIV and EcoHealth Alliance have satisfied the above-mentioned requirements.

Specifically, to address the NIH's concerns, EcoHealth must provide the NIH with the following information and materials, which must be complete and accurate:

1. Provide an aliquot of the actual SARS-CoV-2 virus that WIV used to determine the viral sequence.
2. Explain the apparent disappearance of Huang Yanling, a scientist / technician who worked in the WIV lab but whose lab web presence has been deleted.
3. Provide the NIH with WIV's responses to the 2018 U.S. Department of State cables regarding safety concerns.
4. Disclose and explain out-of-ordinary restrictions on laboratory facilities, as suggested, for example, by diminished cell-phone traffic in October 2019, and the evidence that there may have been roadblocks surrounding the facility from October 14-19, 2019.
5. Explain why WIV failed to note that the RaTG13 virus, the bat-derived coronavirus in its collection with the greatest similarity to SARS-CoV-2, was actually isolated from an abandoned mine where three men died in 2012 with an illness remarkably similar to COVID-19, and explain why this was not followed up.
6. Additionally, EcoHealth Alliance must arrange for WIV to submit to an outside inspection team charged to review the lab facilities and lab records, with specific attention to addressing the question of whether WIV staff had SARS-CoV-2 in their possession prior to December 2019. The inspection team should be granted full access to review the processes and safety of procedures of all of the WIV field work (including but not limited to collection of animals and biospecimens in caves, abandoned man-made underground cavities, or outdoor sites). The inspection team could be organized by NIAID, or, if preferred, by the U.S. National Academy of Sciences.
7. Lastly, EcoHealth Alliance must ensure that all of its subawards are fully reported in the Federal Subaward Reporting System

During this period of suspension, NIH will continue to review the activities under this award, taking into consideration information provided by EcoHealth Alliance, to further asses compliance by EcoHealth Alliance and WIV, including compliance with other terms and conditions of award that may be implicated. Additionally, during the period of suspension, EcoHealth Alliance may not allow research under this project to be conducted. Further, no funds from grant R01AI110964 may be provided to or expended by EcoHealth Alliance or any subrecipients; all such charges are unallowable. It is EcoHealth Alliance's responsibility as the

recipient of this grant award to ensure that the terms of this suspension are communicated to and understood by all subrecipients. EcoHealth Alliance must provide adequate oversight to ensure compliance with the terms of the suspension. Any noncompliance of the terms of this suspension must be immediately reported to NIH. NIH has taken additional steps to restrict funding in the HHS Payment Management System in the amount of $369,819.56. EcoHealth Alliance will receive a revised Notice of Award from NIAID indicating the suspension of these research activities and funding restrictions as a specific condition of award.

Please note that this action does not preclude NIH from taking additional corrective or enforcement actions pursuant to 45 CFR Part 75, including, but not limited to, terminating the grant award. NIH may also take other remedies that may be legally available if NIH discovers other violations of terms and conditions of award on the part of EcoHealth Alliance or WIV.

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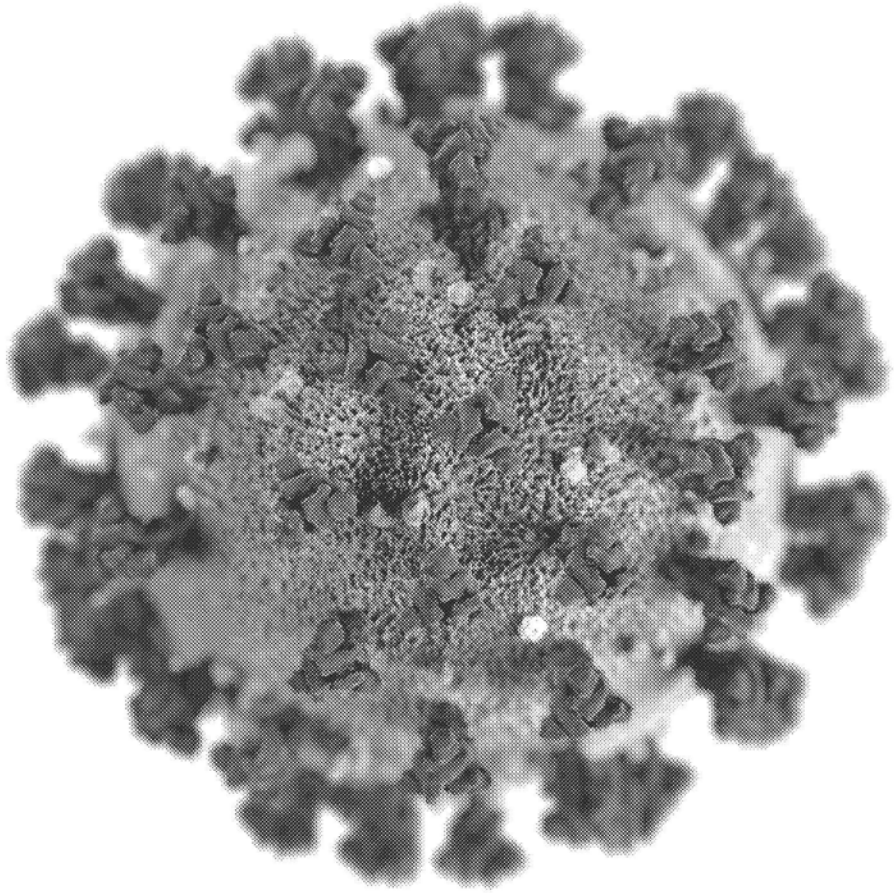
Sincerely,

Michael S Lauer, MD
NIH Deputy Director for Extramural Research
Email: (b) (6)

cc: Dr. Erik Stemmy
Ms. Emily Linde

COVID 19
CORONAVIRUS DISEASE

Overview of COVID-19 Disease



John T. Brooks MD – Chief Medical Officer
CDC, Division of HIV/AIDS Prevention
CDC, COVID-19 Response

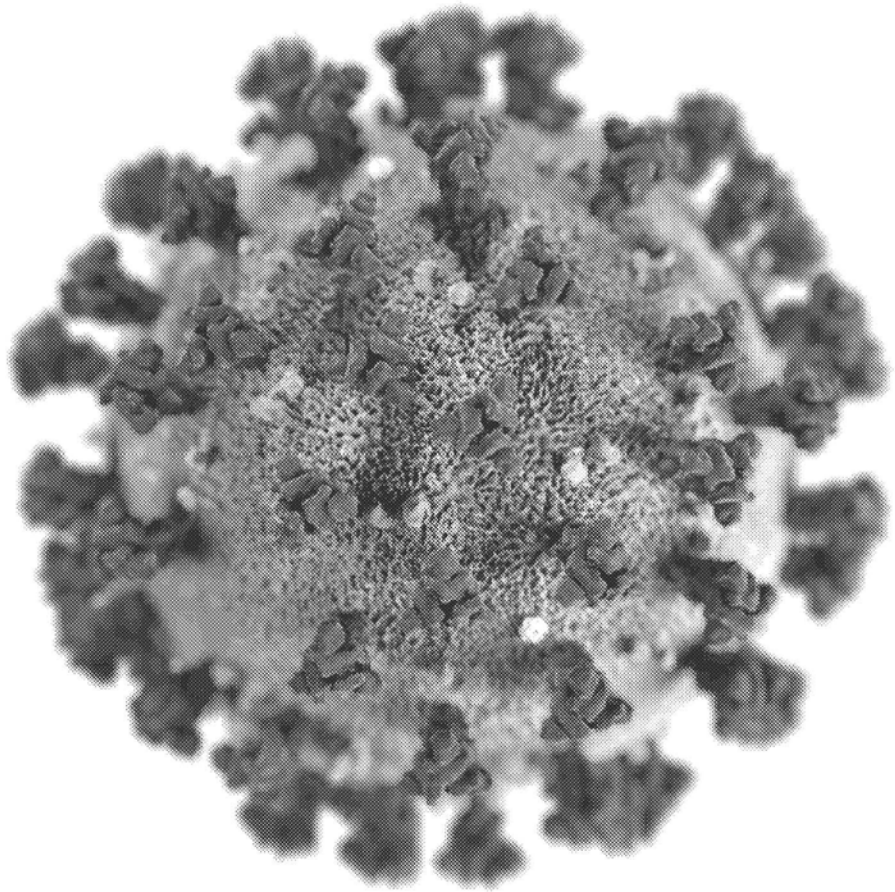
ACIP 2020 – June 24, 2020

For more information: **www.cdc.gov/COVID19**

Valid as of June 20, 2020

COVID 19
CORONAVIRUS DISEASE

Dr. Brooks has no relevant financial affiliations to disclose



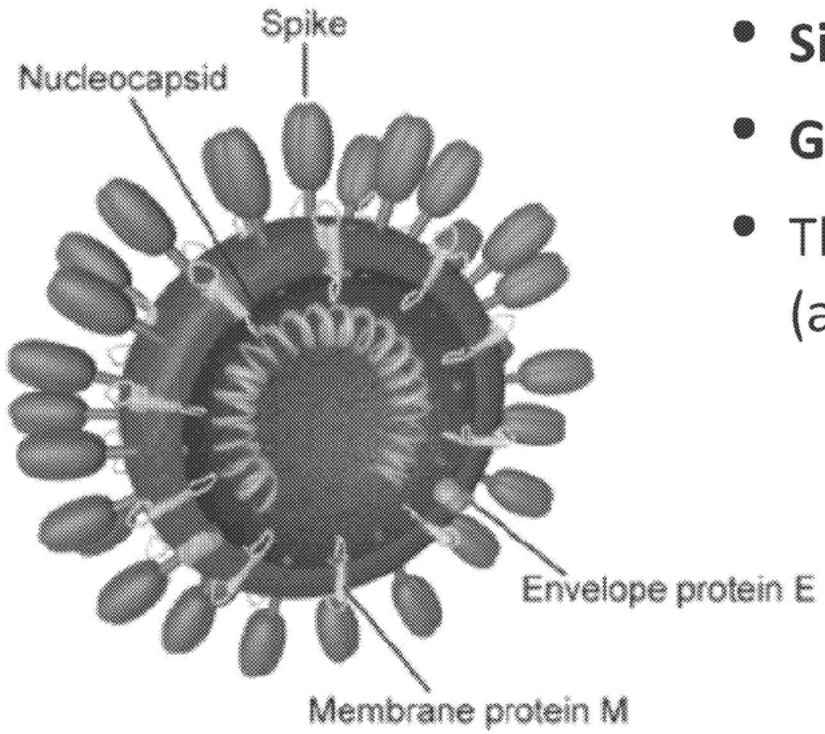
For more information: **www.cdc.gov/COVID19**

Valid as of June 20, 2020

COVID-19 Virology

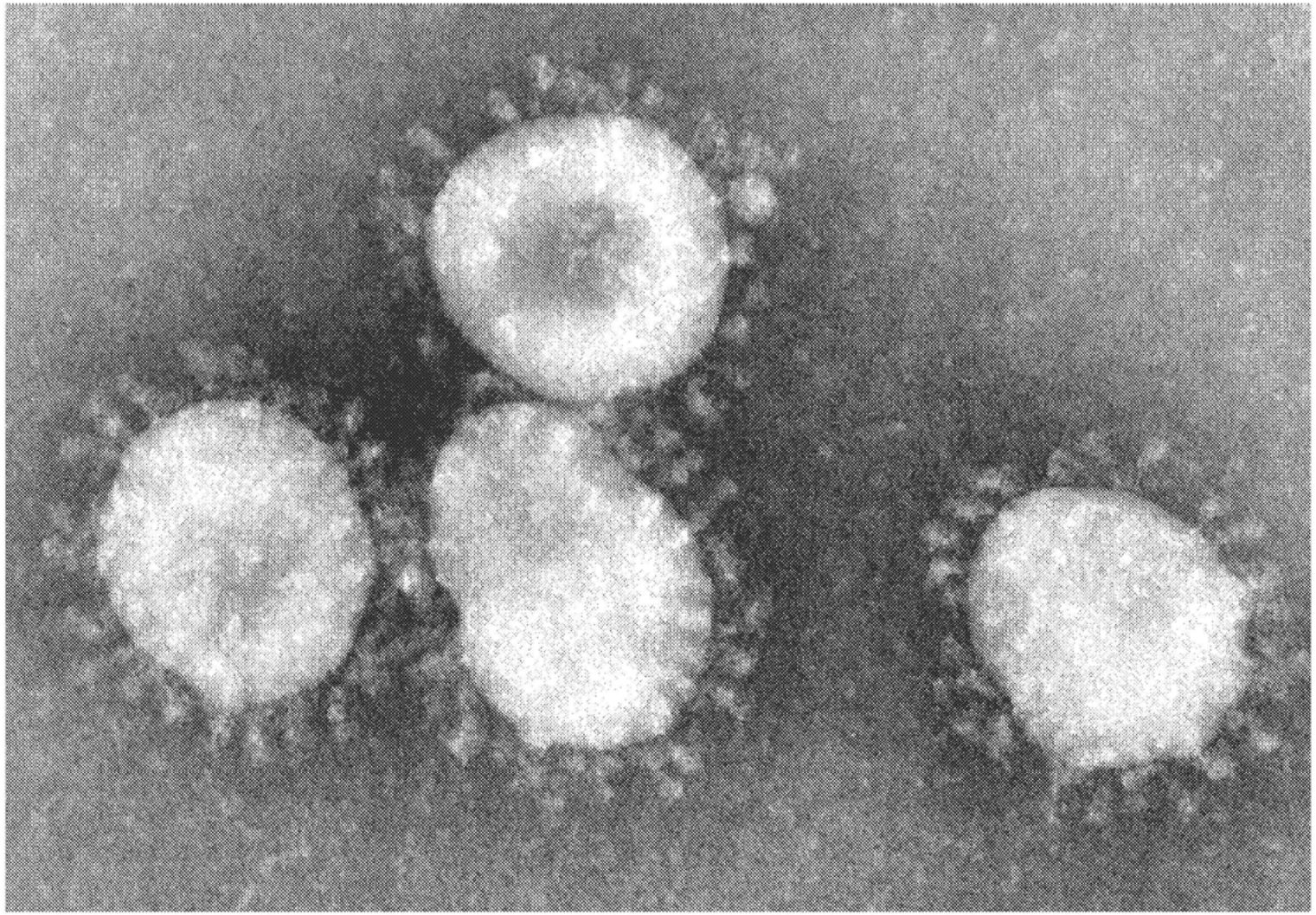
Valid as of June 20, 2020

Basic Structure of *Coronavirinae*



- **Single-stranded RNA viruses**
- **Genomes range from 25 to 32 kilobases**
- The coronaviral genome encodes **four major structural proteins** (all are required to produce a structurally complete viral particle)
  - Spike (S) protein: *binding*
  - Nucleocapsid (N) protein: *RNA synthesis*
  - Membrane (M) protein: *organization/assembly*
  - Envelope (E) protein: *organization/assembly*

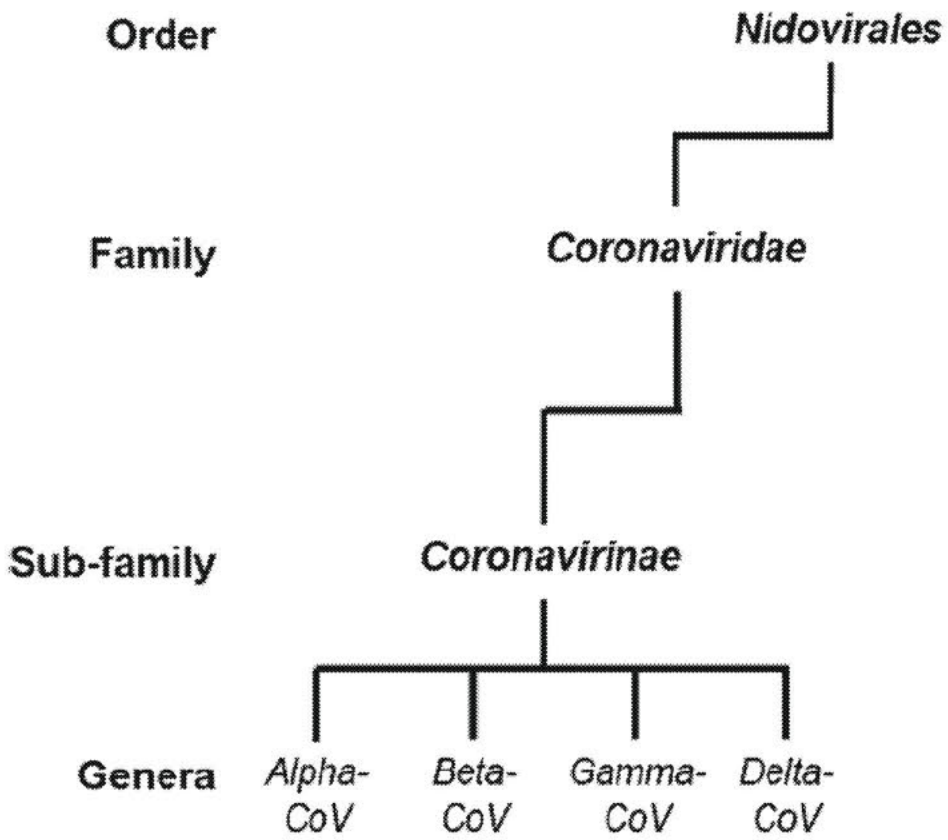
Electron Micrograph of Coronavirus Virions



Centers for Disease Control and Prevention's Public Health Image Library (PHIL), with identification number #4814.

Valid as of June 20, 2020

Coronaviridae/-virinae Belong to Order Nidovirales



Infect a wide variety of mammals and birds

- Alpha and beta: "mammals"
  - flying bats to beluga whales
- Gamma and delta: "birds"
  - sparrows to ostriches

Cause a variety of lethal diseases, with well-studied impact on the agricultural sector

- Illness is usually **respiratory or enteric**

Cong 2017, Viruses 9(182), doi:10.3390/v9070182

Seven Human Coronaviruses (HCoVs)

- **Common HCoVs (lower pathogenicity):**
  - HCoV-229E (alpha)
  - HCoV-NL63 (alpha)
  - HCoV-OC43 (beta)
  - HCoV-HKU1 (beta)
- **Other HCoVs (higher pathogenicity):**
  - SARS-CoV-1 (beta)
  - MERS-CoV (beta)
  - **SARS-CoV-2** (beta)

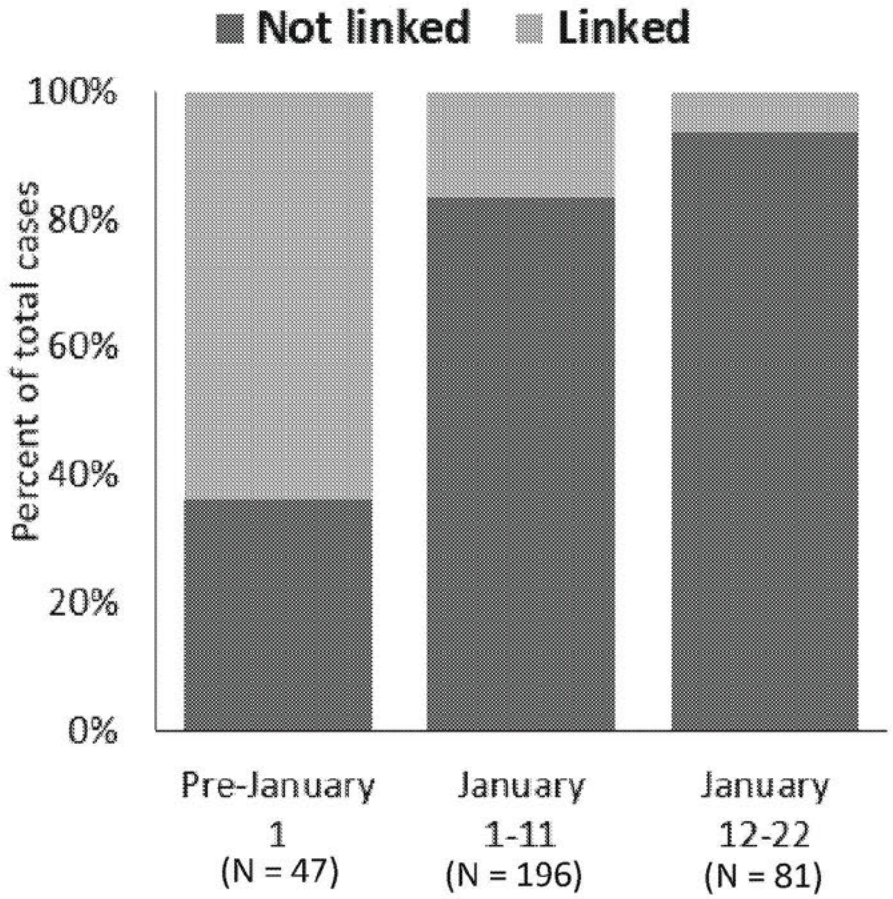
The illness COVID-19 is caused by SARS-CoV-2, which is more like SARS-CoV-1 than MERS-CoV

Song 2019, Viruses 11, 59; doi:10.3390/v11010059
https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it

COVID-19 Transmission

Valid as of June 20, 2020

Linkage of Early COVID-19 Cases* to Huanan Seafood Wholesale Market – Wuhan, China



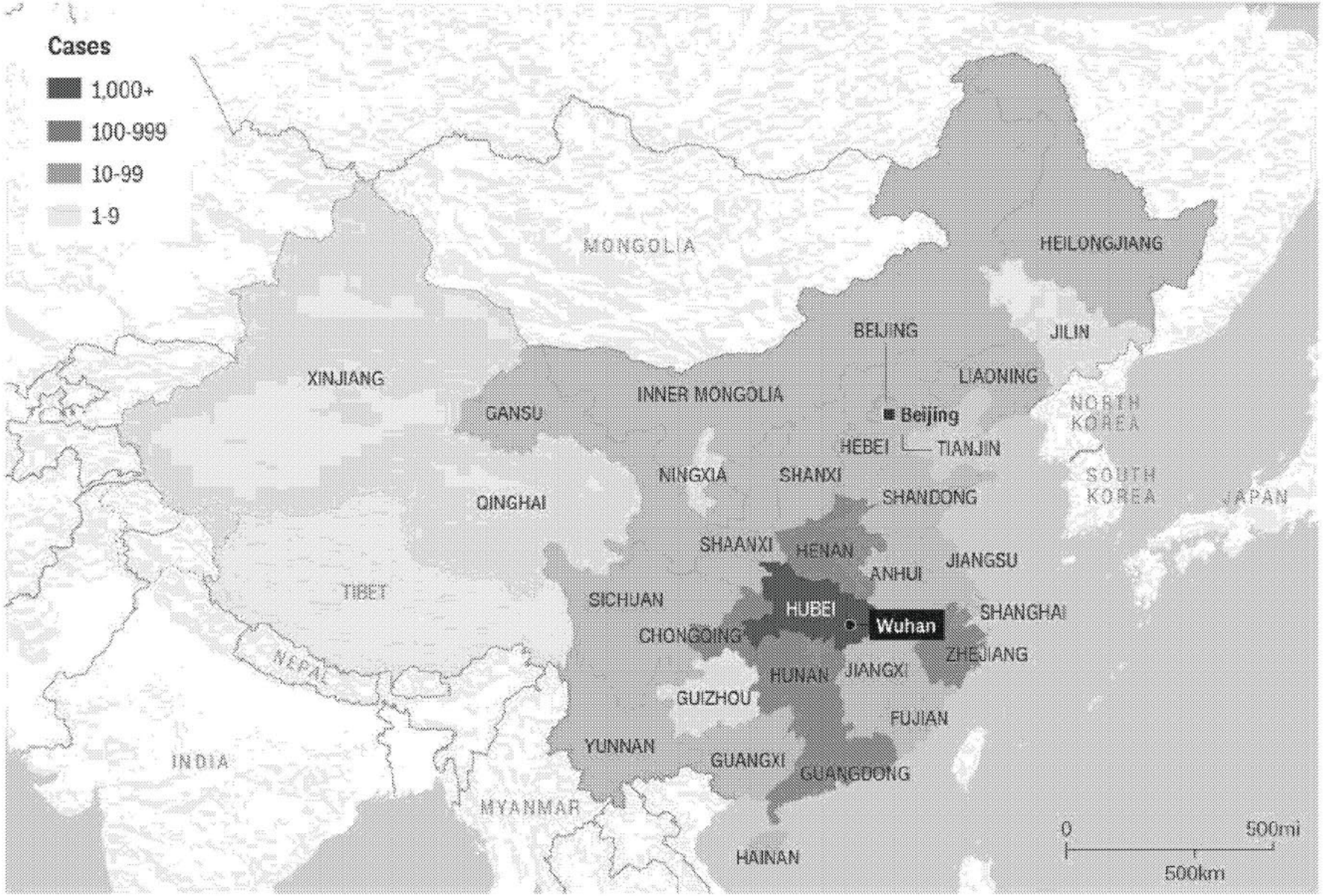
https://www.healthpolicy-watch.org/

Adapted from Li 2020, N Engl J Med; DOI: 10.1056/NEJMoa2001316.

* Total N=324 persons with complete exposure histories among 425 total cases

Valid as of June 20, 2020

Early Distribution of Cases: China as of 20-Jan-2020

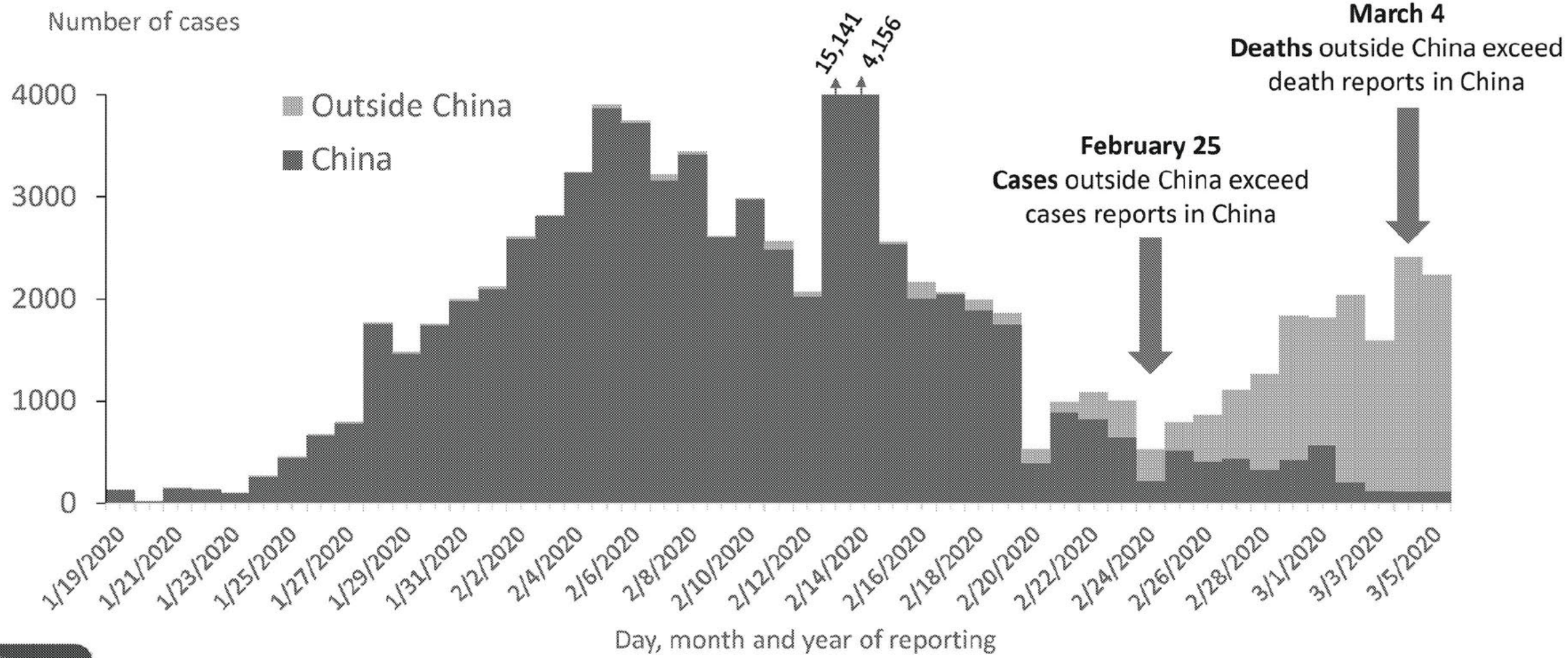


CNN Source: National Health Commission of the PRC. Data correct as of January 26, 08:30 P.M. CT
Graphic: Natalie Leung and Henrik Pettersson, CNN

CDC

Valid as of June 20, 2020

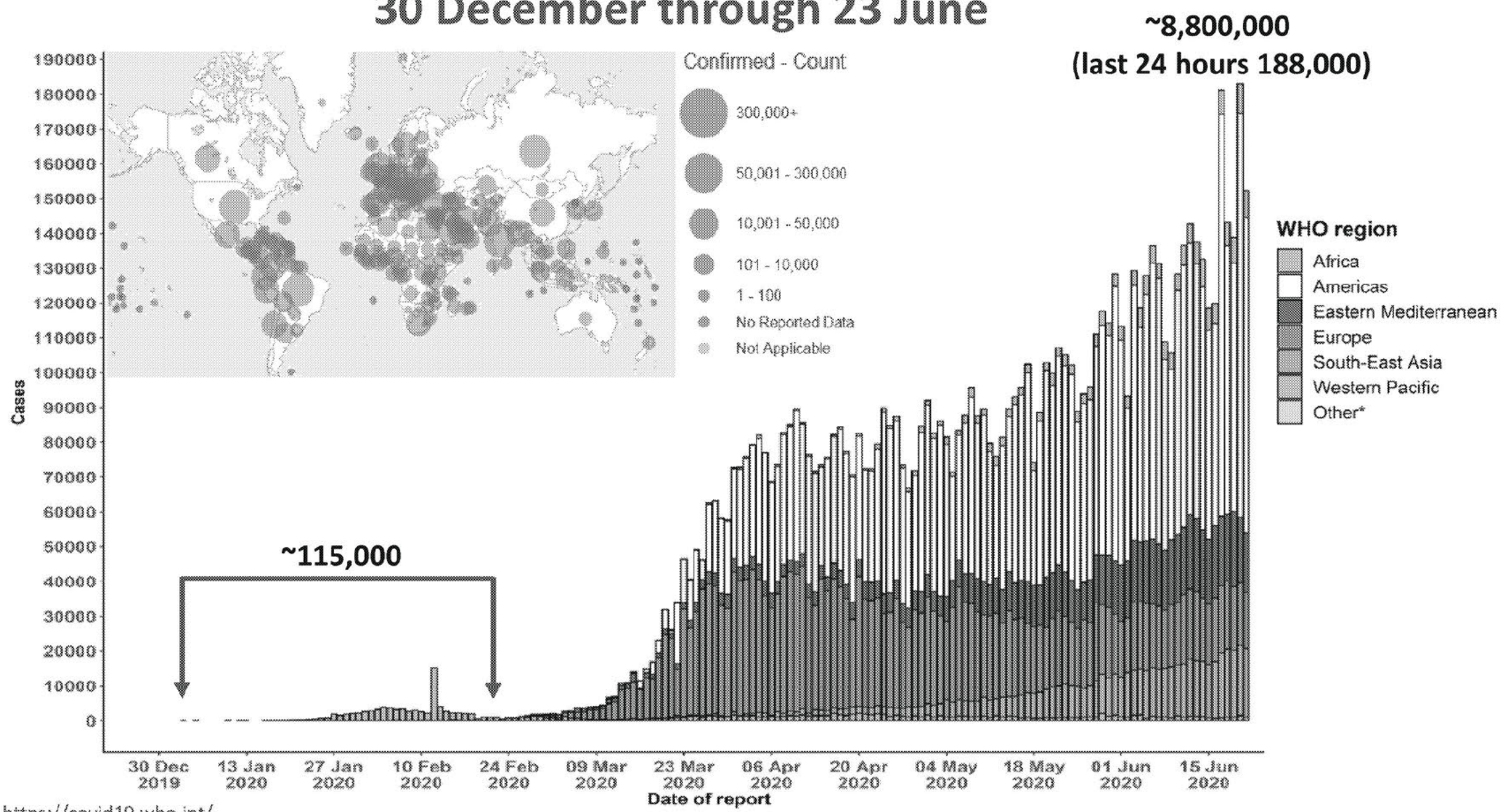
Distribution of COVID-19 cases in accordance with the applied case definitions in the affected countries, as of 05 March 2020



Courtesy of European CDC

Valid as of June 20, 2020

Number of confirmed COVID-19 cases, by date of report and WHO region, 30 December through 23 June



https://covid19.who.int/

Valid as of June 20, 2020

Transmission Dynamics of Pathogenic Human *Coronavirinae* (CoV)

	SARS-CoV-1	MERS-CoV	SARS-CoV-2
Incubation period, median (range)	4-6 days (up to 16)	4-6 days (range 2-14)	5 days (range 2-14)
Serial interval (days)	> Incubation (8)	> Incubation (12-14)	**< Incubation (4)**
Infectious before ill	No	No	**Yes**

SARS-CoV-2

- Peak infectiousness days before symptom onset (***pre-symptomatic***) and shortly thereafter
- A substantial fraction of infections, **estimated 30-35%, are *asymptomatic***

Lauer 2020, Ann Intern Med; doi:10.7326/M20-0504. Du 2020, Emerg Infect Dis; doi.org/10.3201/eid2606.200357.
Nichiura 2020, Int J Infect Dis; doi.org/10.3201/eid2606.200357. Lipsitch 2003, Science;300(5627):1966-70.
Park 2018, BMC Public Health; doi.org/10.1186/s12889-018-5484-8

SARS-CoV-2 in Human Samples and Transmission

Sample	Mode of transmission	Detected by PCR	Isolated by culture	Observed mode of transmission
Nasopharyngeal swab	RESPIRATORY	Yes	Yes	Yes
Oropharyngeal swab		Yes	Yes	Yes
Sputum		Yes	Yes	Yes
Stool	FECAL	Yes	Yes but likely rare	Not yet reported
Urine	URINARY	No	Not yet reported	Not yet reported
Blood/serum	TRANSFUSION	Not reliably	No	Not yet reported
Amniotic fluid	PERINATAL	No	Not yet reported	Not yet reported
Umbilical cord blood		No	Not yet reported	Not yet reported
Breast milk		Not reliably	No	Not yet reported
Cervicovaginal fluid		No	Not yet reported	Not yet reported
Semen	SEXUAL	Yes, but likely rare	Not yet reported	Not yet reported

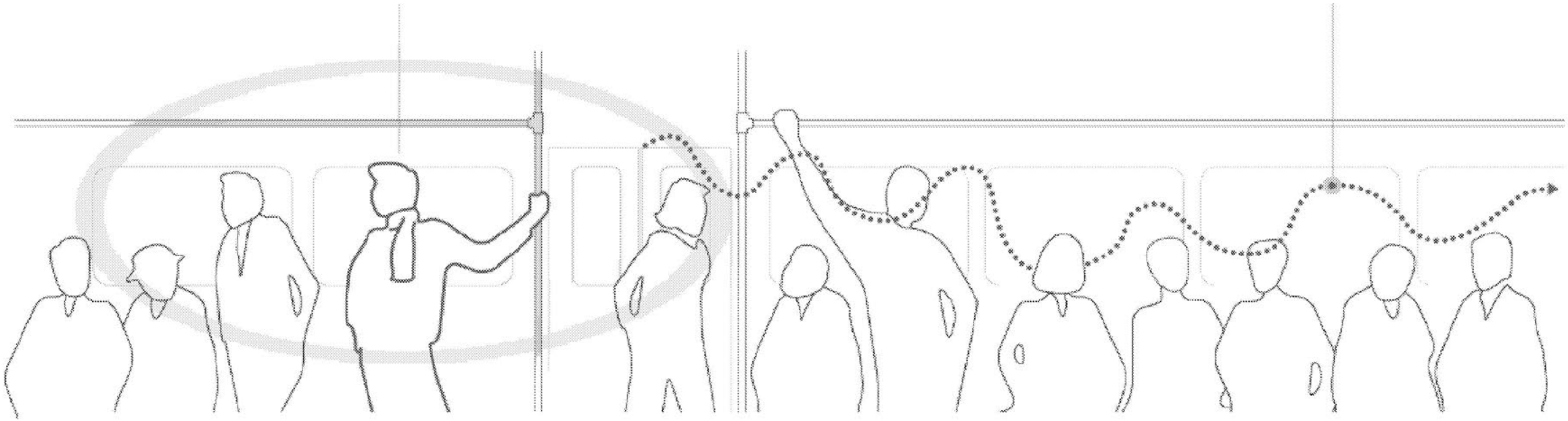
Zou 2020, N Engl J Med; DOI: 10.1056/NEJMc2001737. Pan 2020, Lancet Infect Dis; https://doi.org/10.1016/S1473-3099(20)30113-4. Zhang 2020; China CDC Weekly: http://weekly.chinacdc.cn/en/article/id/ffa97a96-db2a-4715-9dfb-ef662660e89d. Chen 2020; Lancet: https://doi.org/10.1016/ S0140-6736(20)30360-3. Zhu 2020, Transl Pedtr; http://dx.doi.org/10.21037/tp.2020.02.06. Li 2020, JAMA Network Open; doi:10.1001/jamanetworkopen.2020.8292. Yu 2020, Lancet Infect Dis; doi.org/10.1016/S1473-3099(20)30320-0. Chang 2020, Emerg Infect Dis; in press. Xiao 2020, Emerg Infect Dis; August 26(8). Xiao 2020, Gastroentrol; doi.org/10.1053/j.gastro.2020.02.055

Valid as of June 20, 2020

How Far Can SARS-CoV-2 Travel?

Respiratory droplets
About 6 feet (2 meters)

Airborne/aerosolized
Many meters



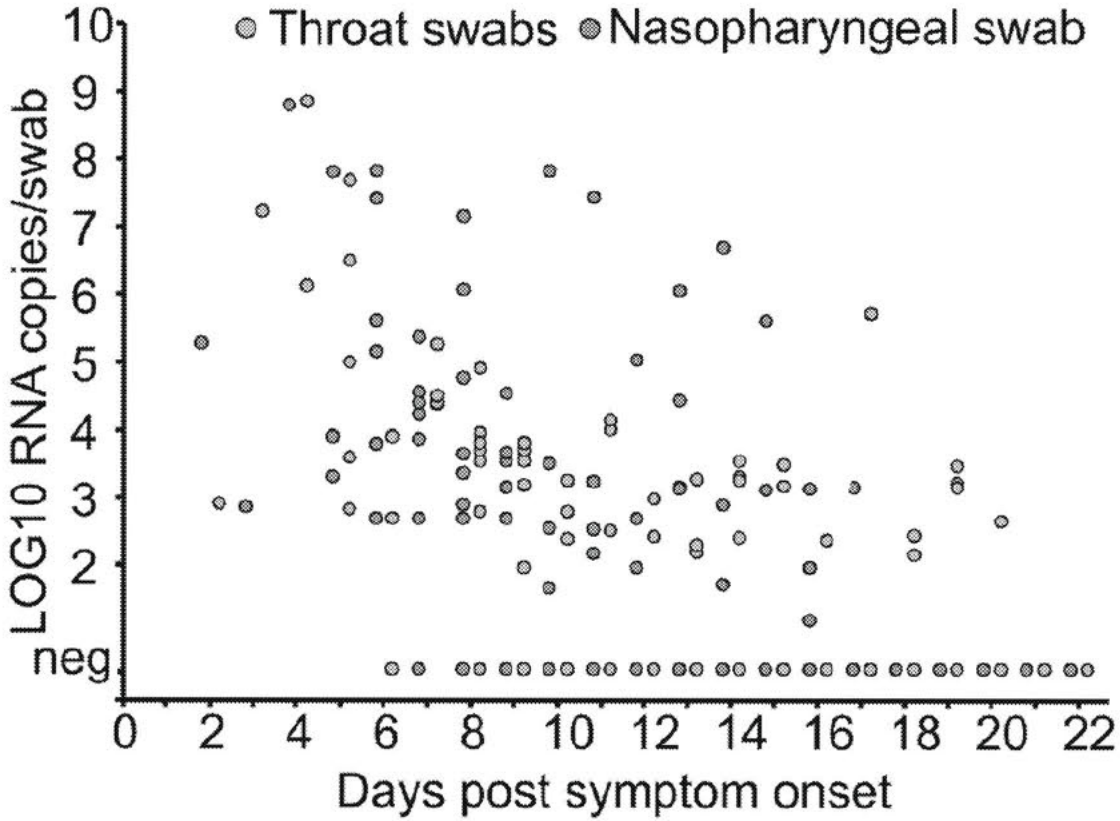
New York Times, January 31, 2020

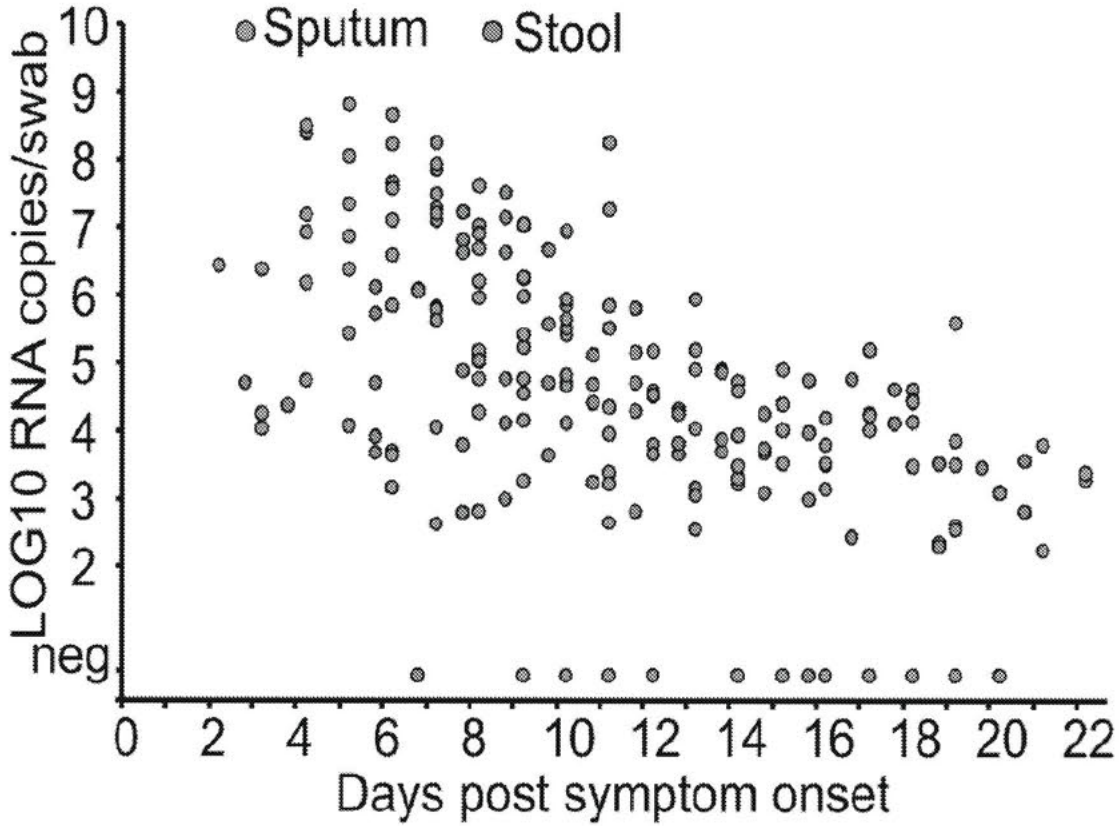
Valid as of June 20, 2020

COVID-19
Response to Infection

Valid as of June 20, 2020

Viral Burden Declines Steadily After Illness Onset

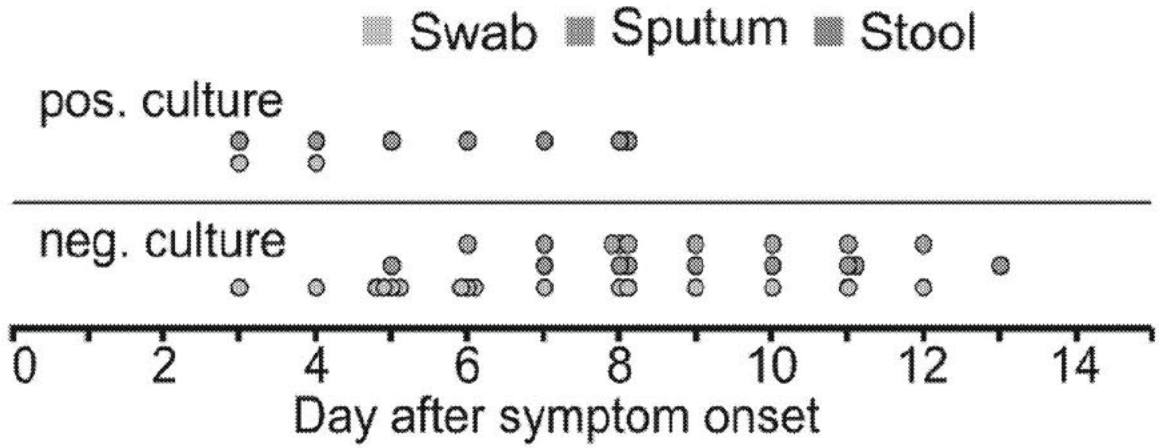




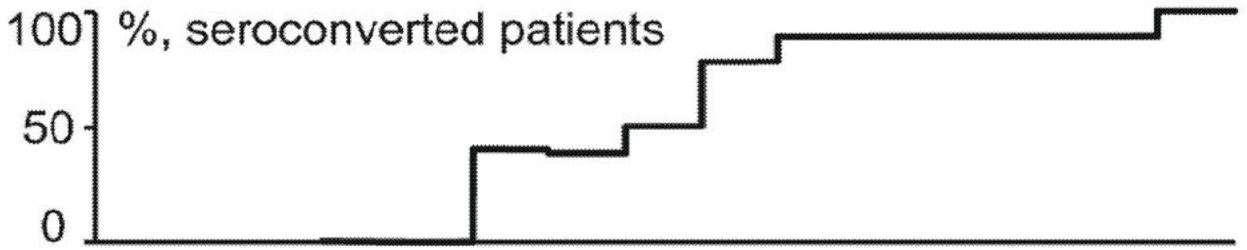
Wölfel 2020, Nature; doi.org/10.1038/s41586-020-2196-x.

Valid as of June 20, 2020

Ability to Culture Virus from Specimens Declines as Serologic Response to Infection Grows



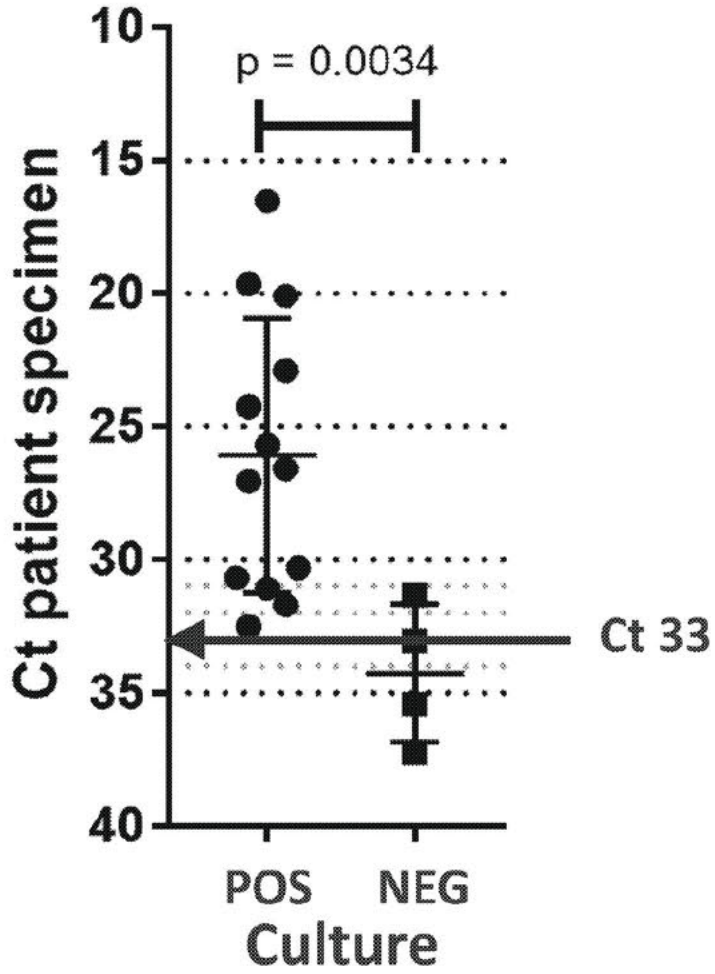
- After 8-10 days, replication-competent virus can no longer be recovered from respiratory tract specimens, in otherwise healthy persons with mild to moderate illness.
- In severely ill and immunocompromised persons, shedding of culturable virus may persist up to 20 days



- Within days after symptom onset, patients being to develop serologic response to infection that includes IgM, IgG, and IgA.
- IgG response includes neutralizing antibodies.

Wölfel 2020, Nature; doi.org/10.1038/s41586-020-2196-x. van Kampen 2020, medRxiv; doi.org/10.1101/2020.06.08.20125310

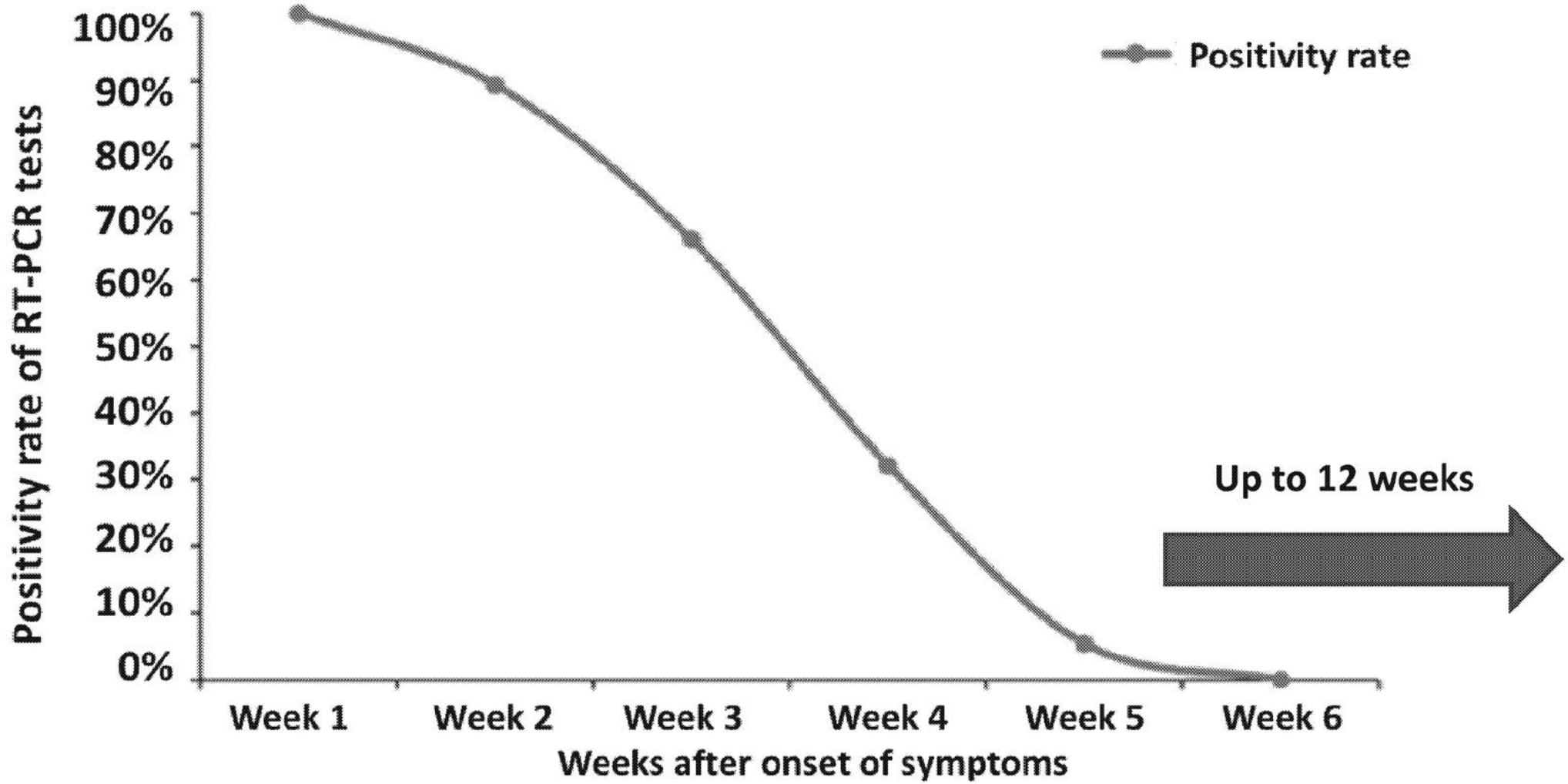
Ability to Culture Virus from Specimens Declines with Decreasing Viral Burden



CDC, unpublished data.

Valid as of June 20, 2020

PCR Can Remain Positive for Weeks After Recovery



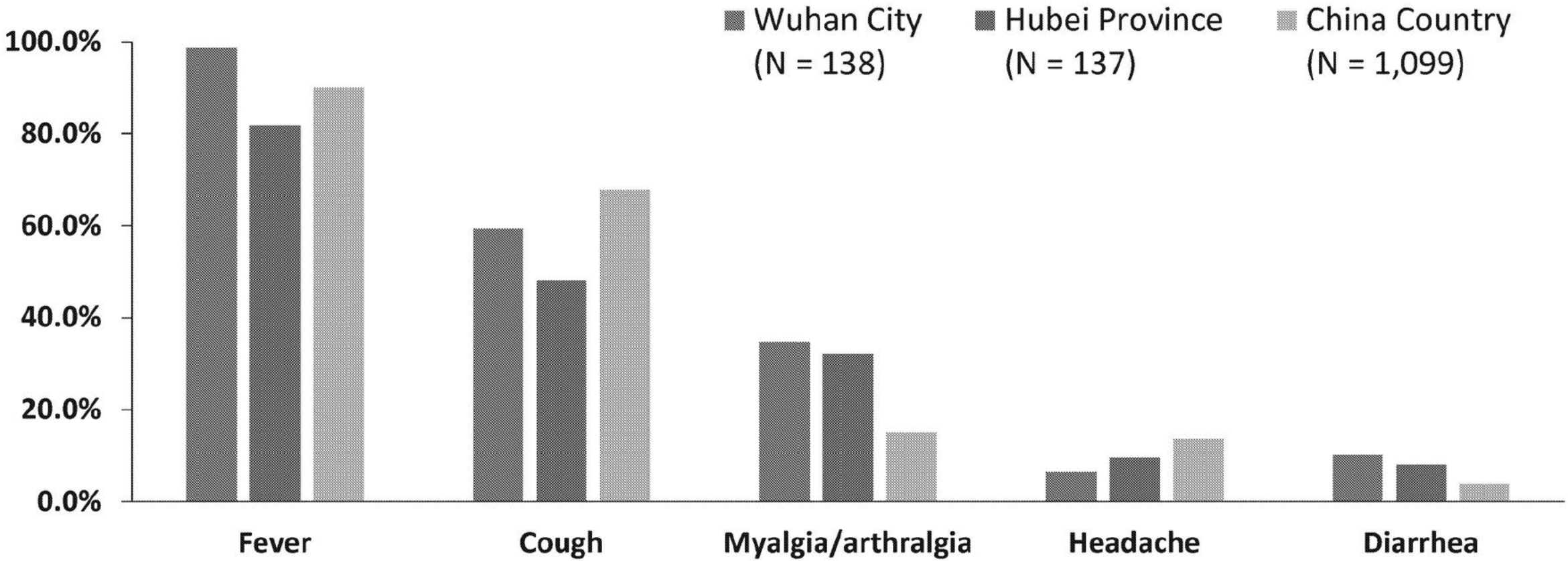
Xiao 2020, Clin Infect Dis; doi.org/10.1093/cid/ciaa460. Li 2020, J Med Virol; doi: 10.1002/jmv.25952.

Valid as of June 20, 2020

COVID-19
Clinical Epidemiology

Valid as of June 20, 2020

Signs/Symptoms of COVID-19



Liu 2020, Chinese Med J; DOI: 10.1097/CM9.0000000000000744. Wang 2020, JAMA; doi:10.1001/jama.2020.1585.
Guan 2020, N Engl J Med; DOI: 10.1056/NEJMoa2002032.

Valid as of June 20, 2020

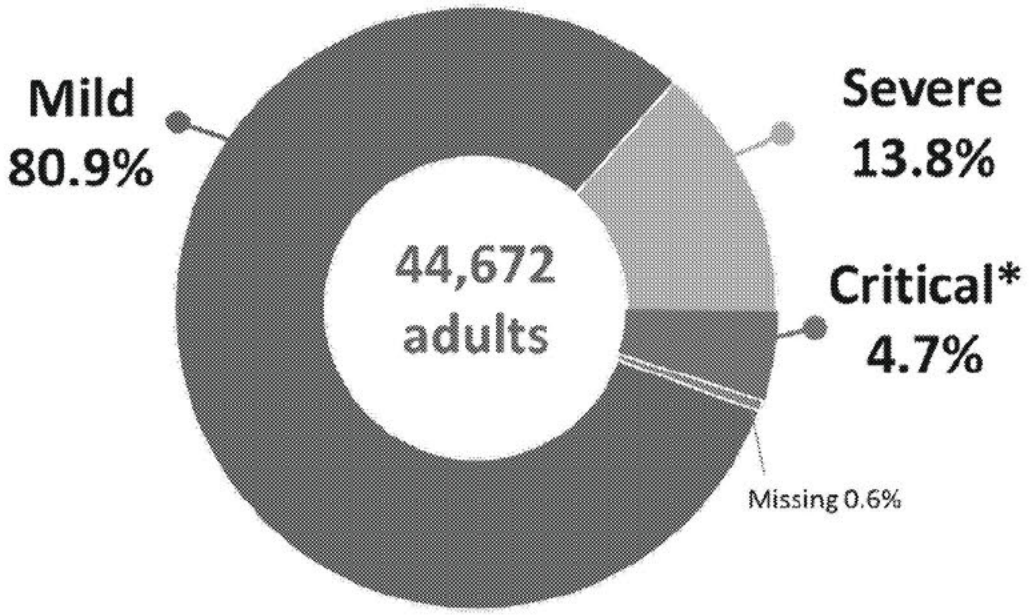
Signs/Symptoms of COVID-19

- No particular set of signs or symptoms can reliably discriminate COVID-19 from other respiratory viral illnesses such as influenza
  - Anosmia/dysgeusia
- Most people will recover spontaneously with supportive care
- Typical complications include pneumonia, respiratory failure, multiorgan system failure, and death

Liu 2020, Chinese Med J; DOI: 10.1097/CM9.0000000000000744. Wang 2020, JAMA; doi:10.1001/jama.2020.1585.
Guan 2020, N Engl J Med; DOI: 10.1056/NEJMoa2002032.

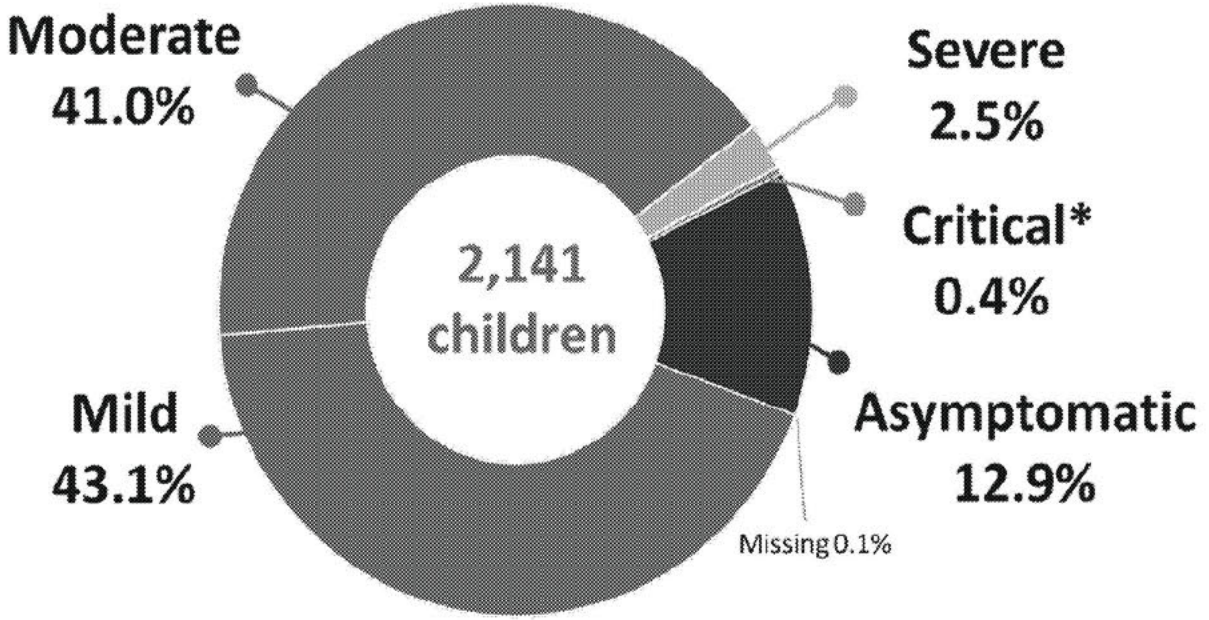
Illness Severity in Adults and Children with COVID-19, China

Severity of Illness, Adult COVID-19 (N = 44,672 confirmed cases)



* 1,023 (49%) deaths among 2,087 critically ill adults

Severity of Illness, Pediatric COVID-19 (N = 2,141 confirmed cases)



* 1 deaths among critically ill children

adapted from Zhang 2020, China CDC Weekly Report; 2(8):113-122 and Dong 2020, Pediatrics; doi 10.1542/peds.2020-0702.

Valid as of June 20, 2020

COVID-19 in High-Risk Groups

- **Comorbidity and advanced age increase risk for severe illness and death**
  - Cardiovascular disease, diabetes, chronic respiratory disease
- **Immunocompromised (medical, acquired) – emerging data reassuring**
  - For persons with HIV, risk likely greatest at low CD4 cell counts or not virally suppressed
  - No definitive evidence that cancer therapy worsens outcomes (incl. immnuosuppresives)

Zhang 2020, China CDC Weekly Report; 2(8):113-122 Rasmussen 2020; Am J Obstet Gynecol: https://doi.org/10.1016/j.ajog.2020.02.017
Lee 2020, Lancet; doi.org/10.1016/S0140-6736(20)31173-9

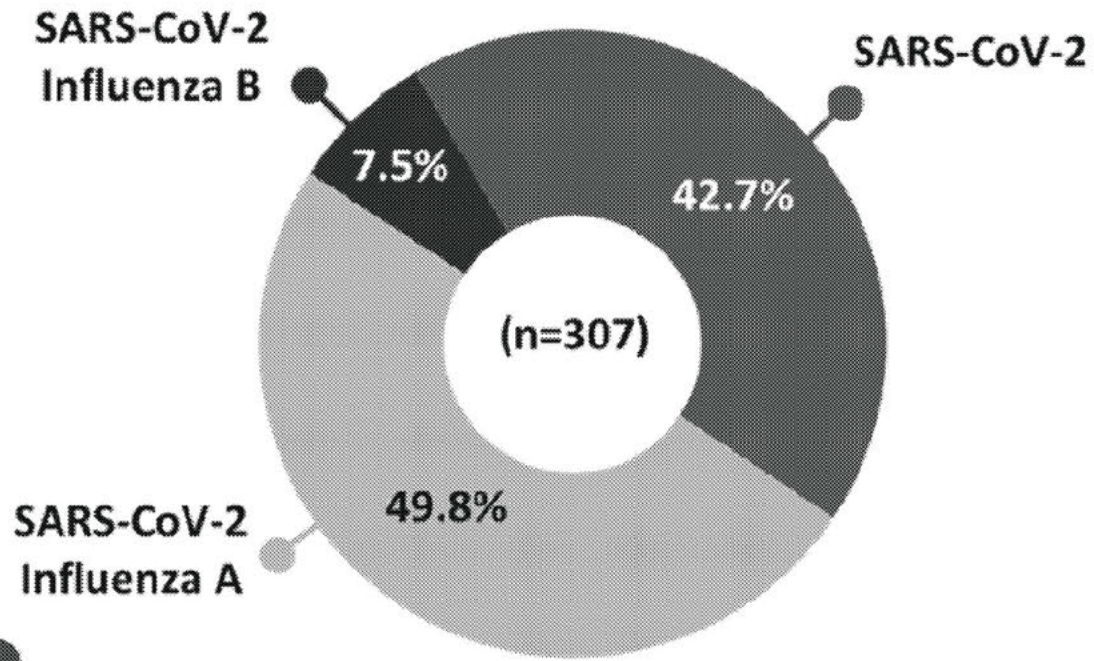
Unique Complications of COVID-19

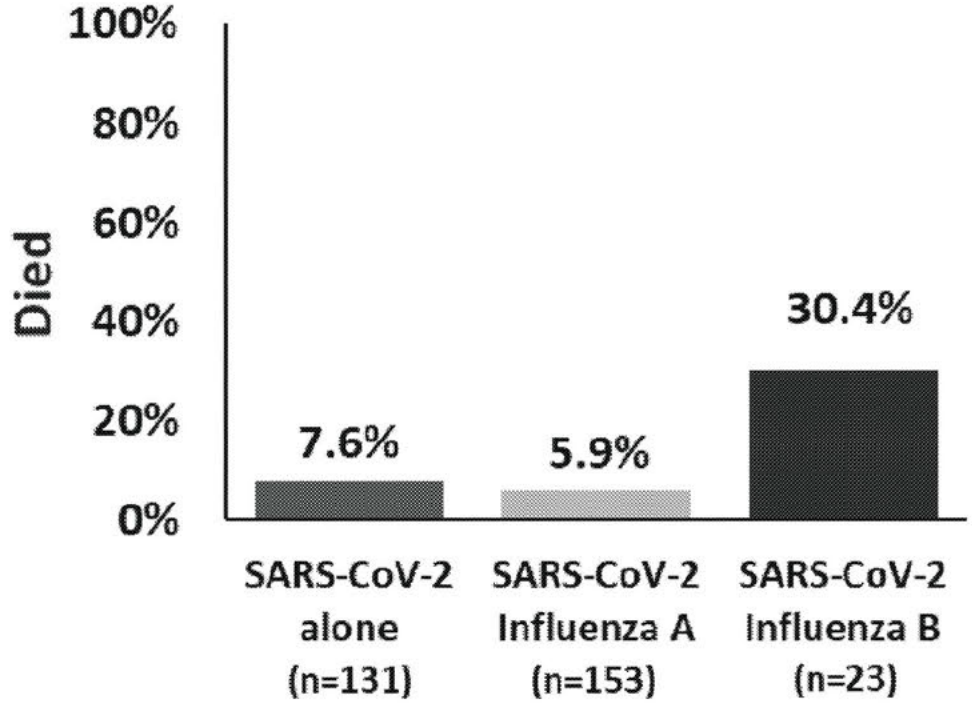
- **Diffuse endotheliitis**
  - Viral tropism for endothelial cells with inflammatory cell injury and death
- **Hypercoagulability**
  - Both local and embolic
  - ARDS complicated by thromboemboli (especially pulmonary embolism)
- **Peri- and post-infectious hyperimmune reaction**
  - Myocarditis (STEMI without coronary artery blockage)
  - Multiorgan inflammatory syndrome in children (MIS-C)

Varga 2020, Lancet; doi.org/10.1016/S0140-6736(20)30937-5. Fox 2020, Lancet Resp Med; doi.org/10.1016/S2213-2600(20)30243-5. Belot 2020, Euro Surveill;25(22):pii=2001010. Carsana 2020, Lancet Infect Dis; doi.org/10.1016/S1473-3099(20)30434-5. Riphagen 2020, Lancet; doi.org/10.1016/S0140-6736(20)31094-1 Lax 2020, Ann Intern Med; doi:10.7326/M20-2566. Verdoni 2020, Lancet; doi.org/10.1016/S0140-6736(20)31103-X

SARS-CoV-2 and Influenza Coinfection, Coinfection with Influenza B More Deadly

- Patients from a single hospital outbreak in Wuhan during Jan-Feb 2020
- Diagnoses made by assaying SARS-CoV-2 RNA and influenza IgM
- No significant differences in age (median 50's-60's), sex (M:F, 1:1), illness severity





Yue 2020, J Med Virol; doi:10.1002/jmv.26163.

Valid as of June 20, 2020

Valid as of June 20, 2020

Immune responses to SARS-CoV-2 infections

Natalie J. Thornburg, PhD

Respiratory virus immunology team lead

ACIP SARS-CoV-2 working group

June 24, 2020

Outline

1. What do we know about immunity to coronaviruses in general?
2. What do we know, so far about SARS-CoV-2 immunity?
3. How do we test for immune responses?
4. Updates on severity of disease vs. antibody response and antibody kinetics
5. Conclusions

Coronaviruses

- Common coronaviruses

229E

NL63

OC43

HKU1

- Uncommon coronaviruses

SARS-1

MERS

What do we know about protective immune responses in common CoV infections?

- In common CoV infections, protection is transient. Waning serum antibody contributes to susceptibility to reinfection.

- 229E Human challenge model (Callow et al, Epidemiol Infect., 1990)
  - 15 volunteers were inoculated with HCoV-229E.
  - 10 with lower antibody titers became infected; 8 developed colds.
  - On re-challenge a year later, 9 became re-infected (virus shedding) but none developed a cold

- Household respiratory virus infection study (Kiyuka et al, JID, 2018)
  - 2.5% NL63+
  - Most household subjects had one infection in 6 month study
  - Repeat infections with NL-63, OC43, and 229E detected in 21, 5.7, and 4.0% respectively; >90 days apart
  - A minority of repeat infections exhibiting higher viral titers on second infection (41% NL-63, 31% OC43, and 1% 229E)

Does SARS-CoV-2 immunity resemble common coronavirus immunity?

- Knowns
  - Most COVID-19 patients mount IgG and IgM responses to the virus
  - Many CoVID-19 patients mount neutralizing antibody responses
  - Magnitude of antibody response correlates to disease severity

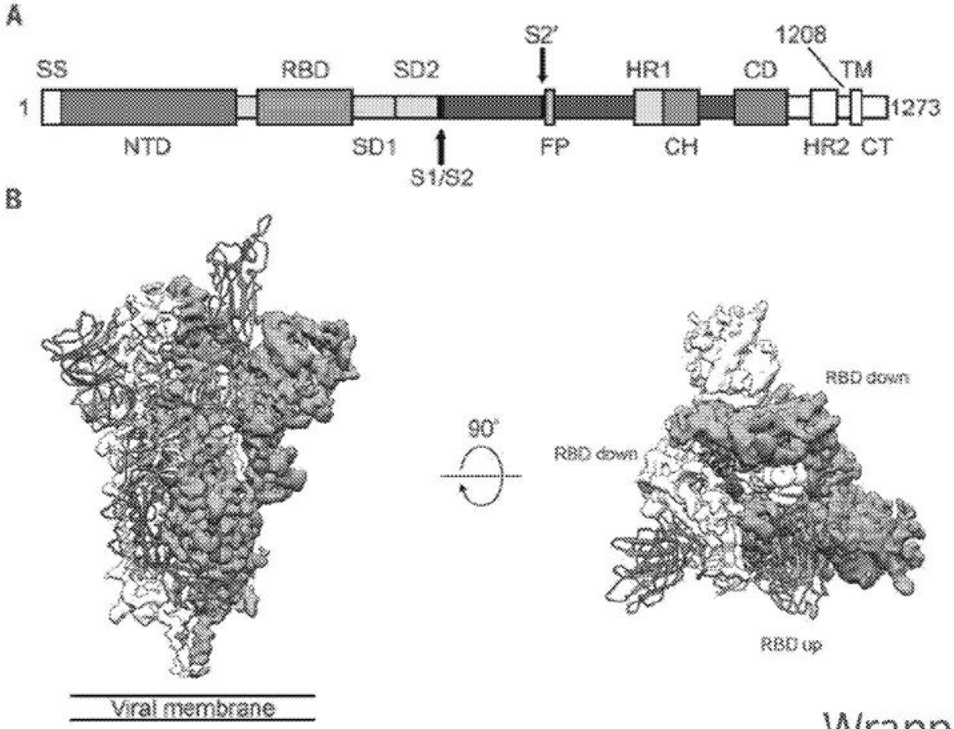
- Unknowns
  - Are COVID-19 patients susceptible to reinfection?
  - Are antibodies a correlate of immunity?
  - If so, what quality (Isotype, antigenic region, neutralizing)?
  - Is there a threshold of protection?
  - How long will serum antibodies last?

Assays to detect antibodies that bind SARS-CoV-2

- Antigens
  - Spike – Target for neutralizing antibodies
    - RBD
    - S1
    - Ectodomain (S2P)
  - Nucleocapsid – Abundant during viral replication

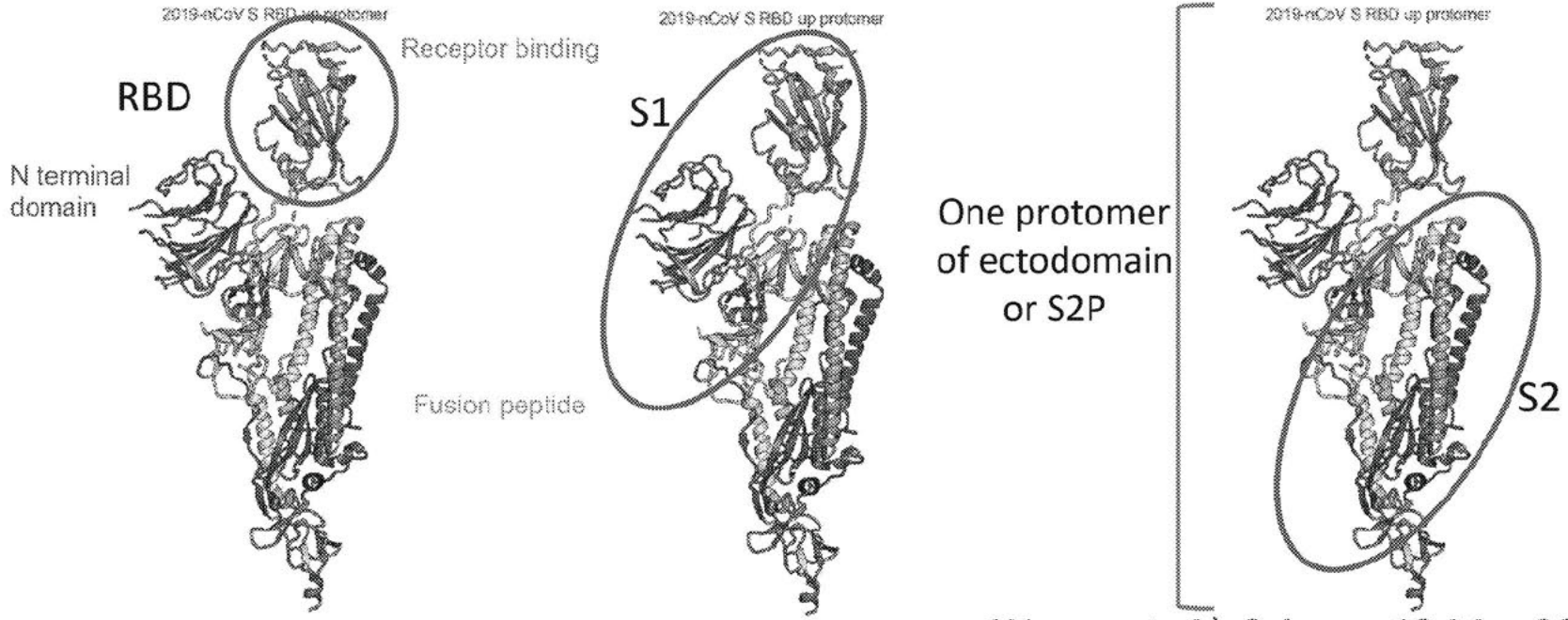
- Secondary antibodies
  - Pan Ig, IgG, IgM, IgA

Spike is highly glycosylated trimeric, class I fusion protein – metastable prefusion conformation



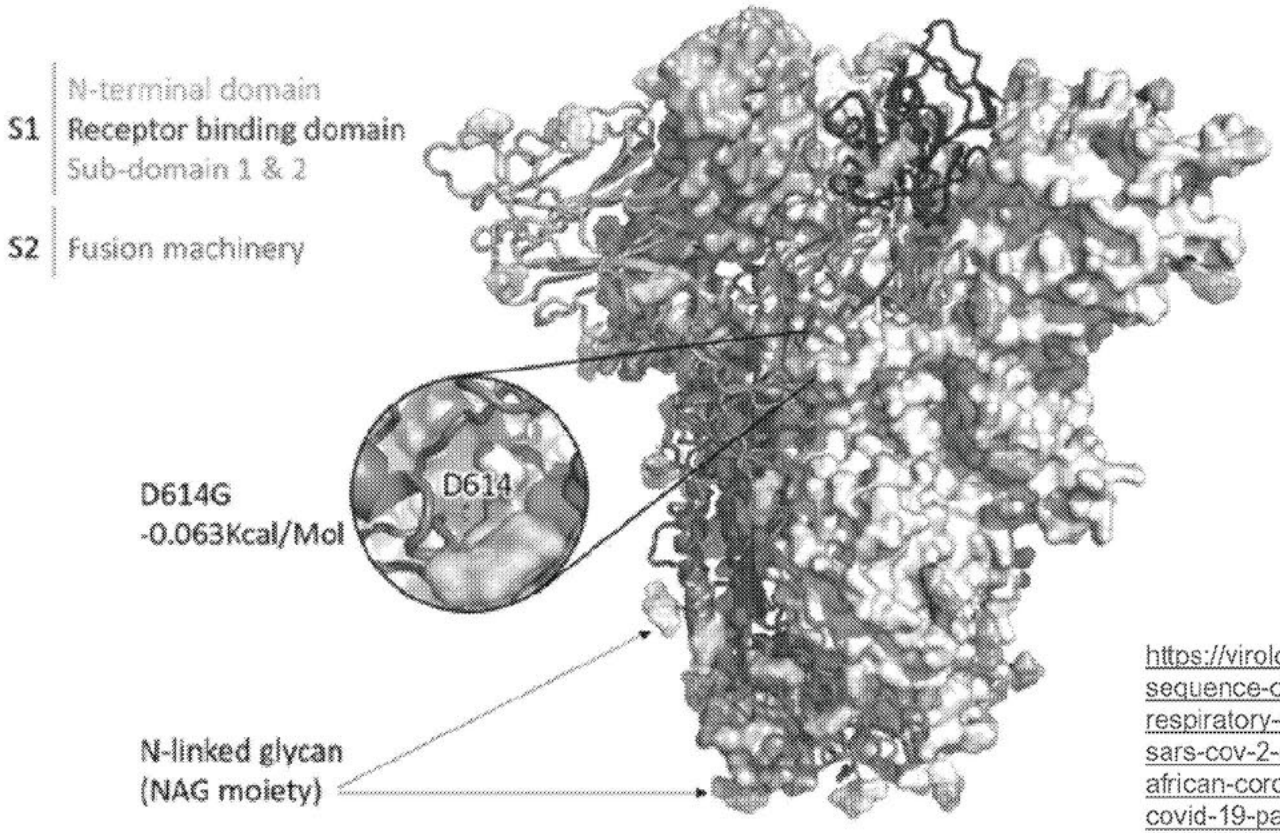
Wrapp et. Al, Science 13 Mar 2020

Three different forms of spikes used in most ELISAs: antibodies to all three might contribute to neutralization



Wrapp et. Al, Science 13 Mar 2020

Residue 614 is located at the S1 / S2 interface

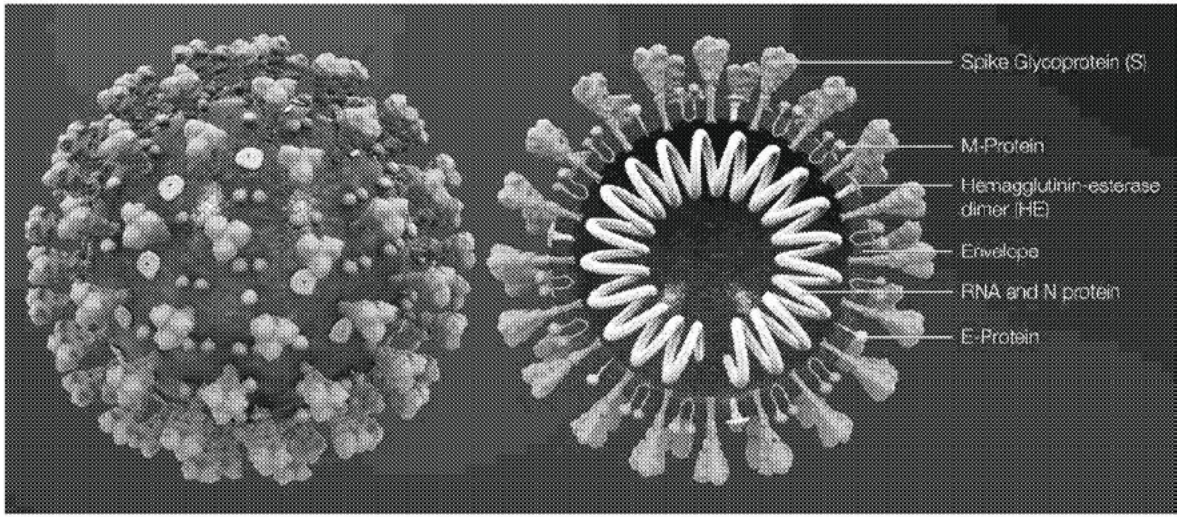


https://virological.org/t/whole-genome-sequence-of-the-severe-acute-respiratory-syndrome-coronavirus-2-sars-cov-2-obtained-from-a-south-african-coronavirus-disease-2019-covid-19-patient/452

Nucleocapsid protein ELISA

PROS

- Easy to produce large quantities of protein
- Abundantly expressed during early infection
- Used to identify immunity from natural infection vs. vaccine-induced immunity



CON

- Unlikely a target for neutralizing antibodies

ELISA and CMIA assays with FDA EUA authorization

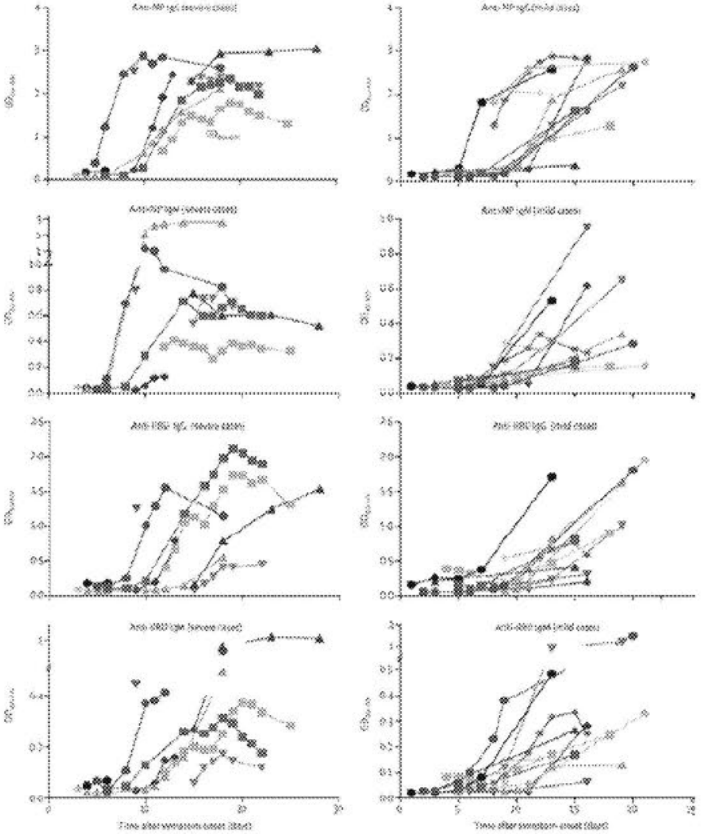
Manufacturer	Isotype	Antigen	% Positive Agreement (n)	Negative Agreement (%)
Euroimmune	IgG	S1	42.3-48.2; NCI panel 90 (597; 110)	98.6-100 (1756)
Roche Diagnostics	pan Ig	N	77 (209)	99.81 (5252)
Bio-Rad	pan Ig	N	92.2 (51)	99.60 (687)
Abbott Laboratories	IgG	N	95 (122)	95 (1070)
DiaSorin, Inc	IgG	S1/S2	72.5 (135)	99.3 (1090)
Ortho Clinical	IgG	S	87.5 (48)	100 (470)
Ortho Clinical	IgM, IgG	S	83 (36)	100 (400)
InBios	IgG	S	97.8(44)	99.0 (95)
Siemens	Pan Ig	S	100(47)	99.8 (1586)
Vibrant		S and N	98.1 (53)	98.6 (501)

Current as of 6/19/2020

Several different types of virus inhibition assays – with differing sensitivities, time to results, throughput, and need for containment lab

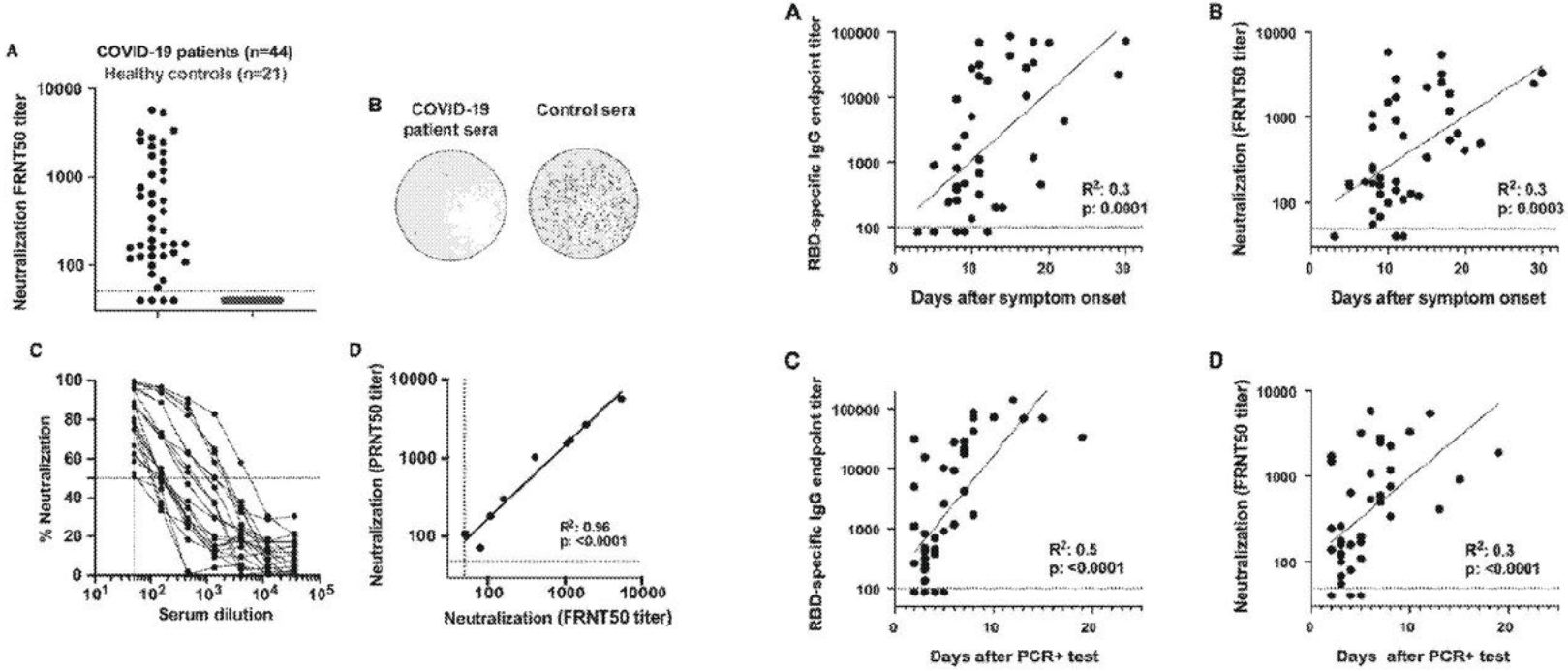
Assay
Plaque reduction neutralization titer
Clinical isolate microneutralization
Infectious clone reporter microneutralization
Focus reduction assay
Psuedovirus

More severe patients exhibit more robust and faster antibody responses



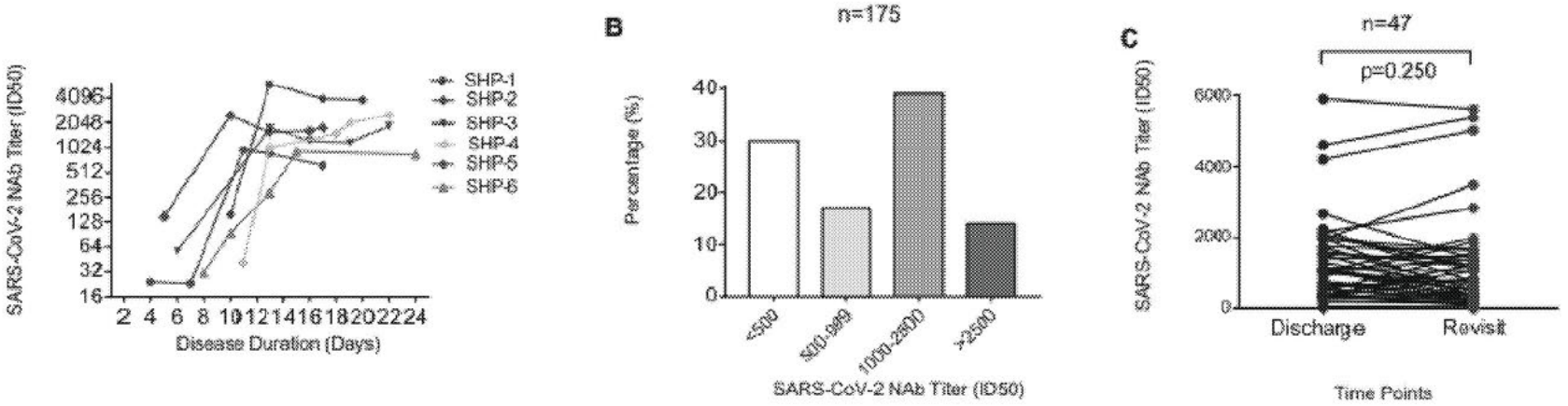
To et al. The Lancet. 20: 565-574

A majority of hospitalized COVID-19 patients develop neutralizing antibody responses



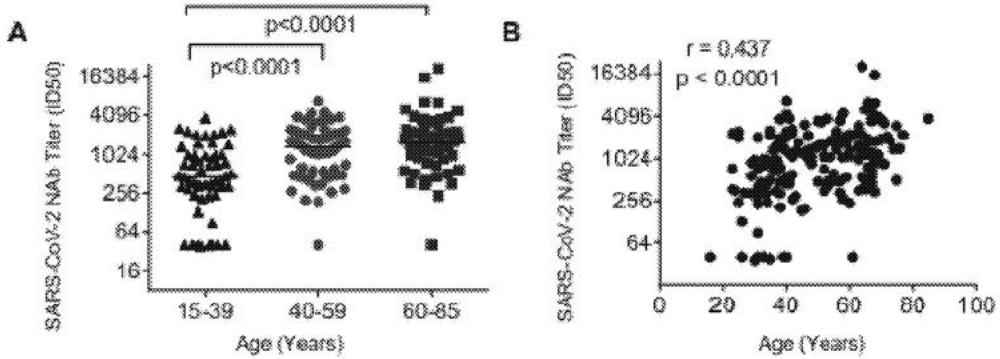
Suthar et al. Cell Reports Medicine. 2020 Jun 8

Thirty percent of patients with mild infection have low neutralizing antibody titers at hospital discharge



https://www.medrxiv.org/content/10.1101/2020.03.30.20047365v2.full.pdf+html

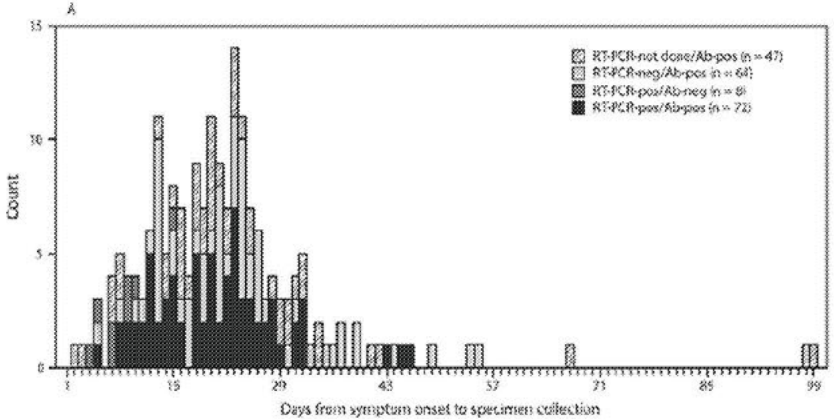
Older patients had higher neutralizing antibody titers

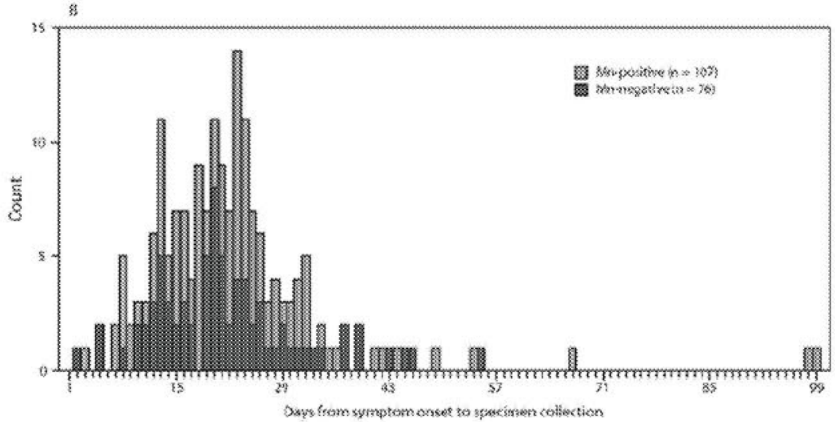


https://www.medrxiv.org/content/10.1101/2020.03.30.20047365v2.full.pdf+html

Most of what we know about SARS-CoV-2 immunology are from hospitalized patients. What about milder infections?

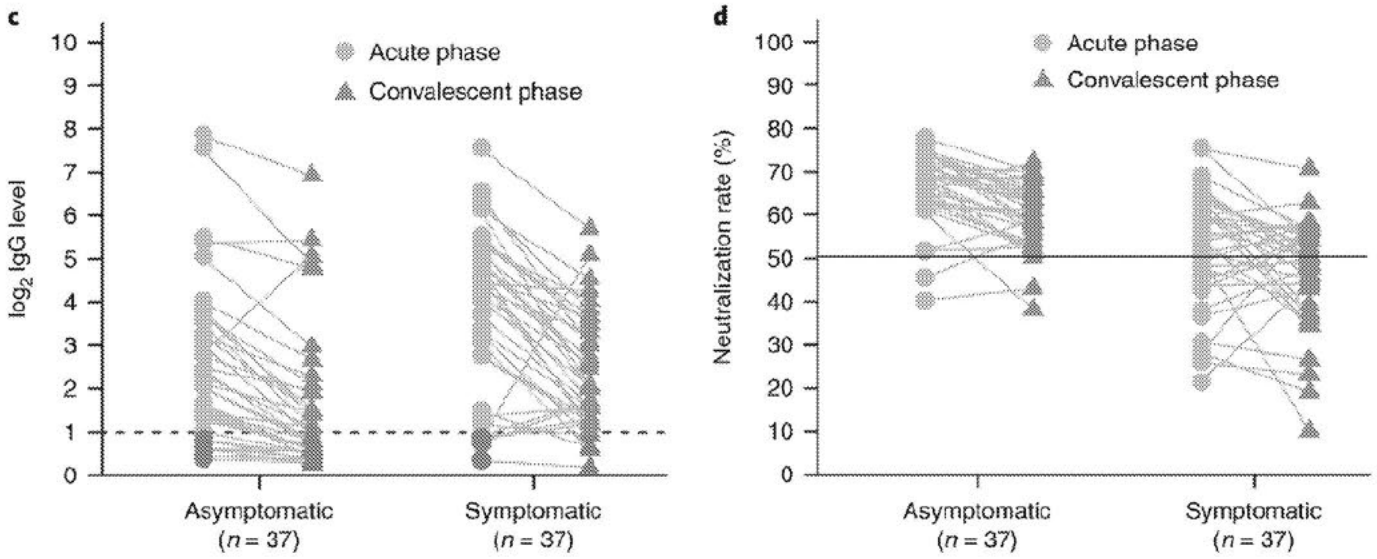
41% of antibody-positive USS TR sailors did not have detectable neutralization titers (IC100)





Payne et al. MMWR. 69: 714-721

Serum antibodies drop between acute phase and 8-weeks post discharge



Long et al. Nature Medicine. 18 JUN 2020

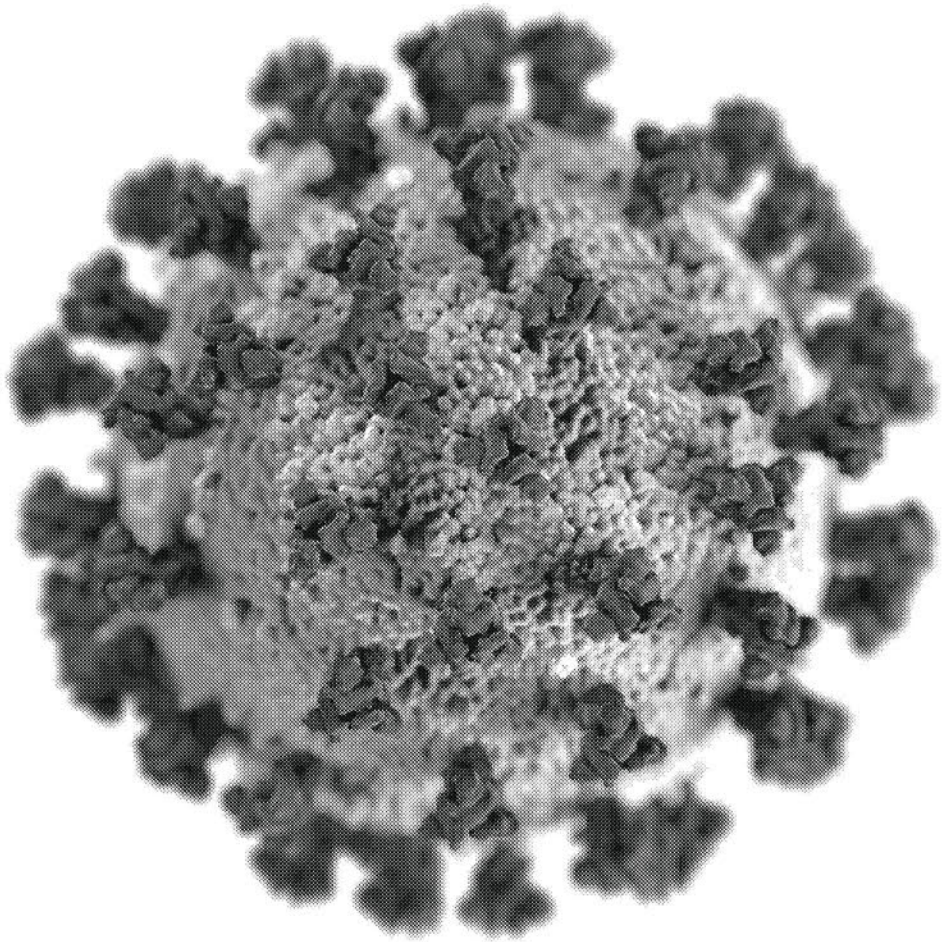
Conclusions

- Most SARS-CoV-2 patients mount serum antibody responses
- Even mild cases of SARS-CoV-2 can results in development of antibodies
- Magnitude of antibody response roughly correlates with severity (consistent with other coronavirus infections)
- A portion of individual with antibody responses may not develop serum neutralizing antibody responses
- By 8 weeks after discharge, a portion of patients have dropped bellow 50% inhibition neutralization threshold

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

CDC Coronavirus Disease 2019 Response

U.S. COVID-19 Epidemiology



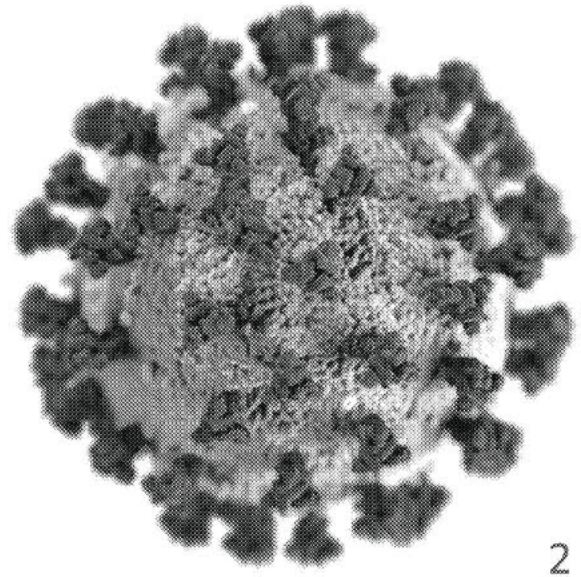
Sara Oliver MD, MSPH

ACIP Meeting
June 24, 2020

For more information: **www.cdc.gov/COVID19**

Outline

- Overview of U.S. COVID-19 Epidemiology
- Epidemiology among Healthcare Personnel
- Epidemiology among Long Term Care Facility (LTCF) Residents
- Epidemiology among Children
- Epidemiology among Pregnant Women
- Epidemiology among People in Congregate Settings
- Serology



Overview of U.S. COVID-19 Epidemiology

United States COVID-19 Cases by County

January 21 to June 23, 2020

USA

2,302,288

TOTAL CASES

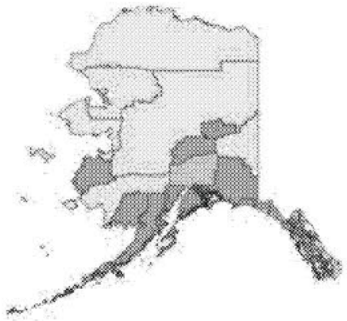
CDC | Updated: Jun 23 2020 12:15PM

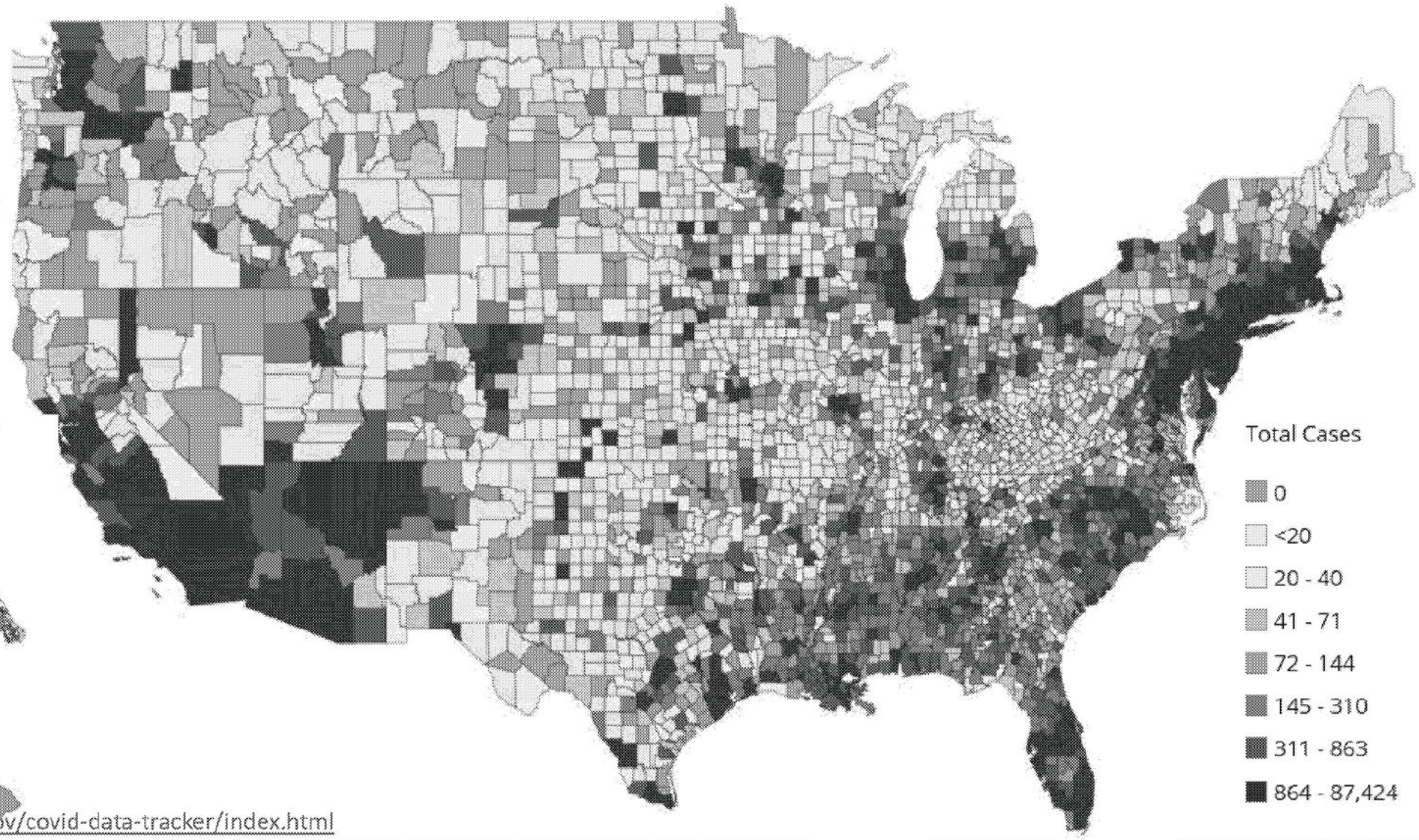
USA

120,333

TOTAL DEATHS

CDC | Updated: Jun 23 2020 12:15PM





https://www.cdc.gov/covid-data-tracker/index.html

Coronavirus Disease 2019 Case Surveillance — United States, January 22–May 30, 2020

- 1,761,503 aggregate U.S. cases of COVID-19 in this report
- Hospitalizations were **6** times higher among patients with reported underlying conditions than those without underlying conditions
- Deaths were **12** times higher among patients with underlying conditions

- Clinical outcomes varied by sex:

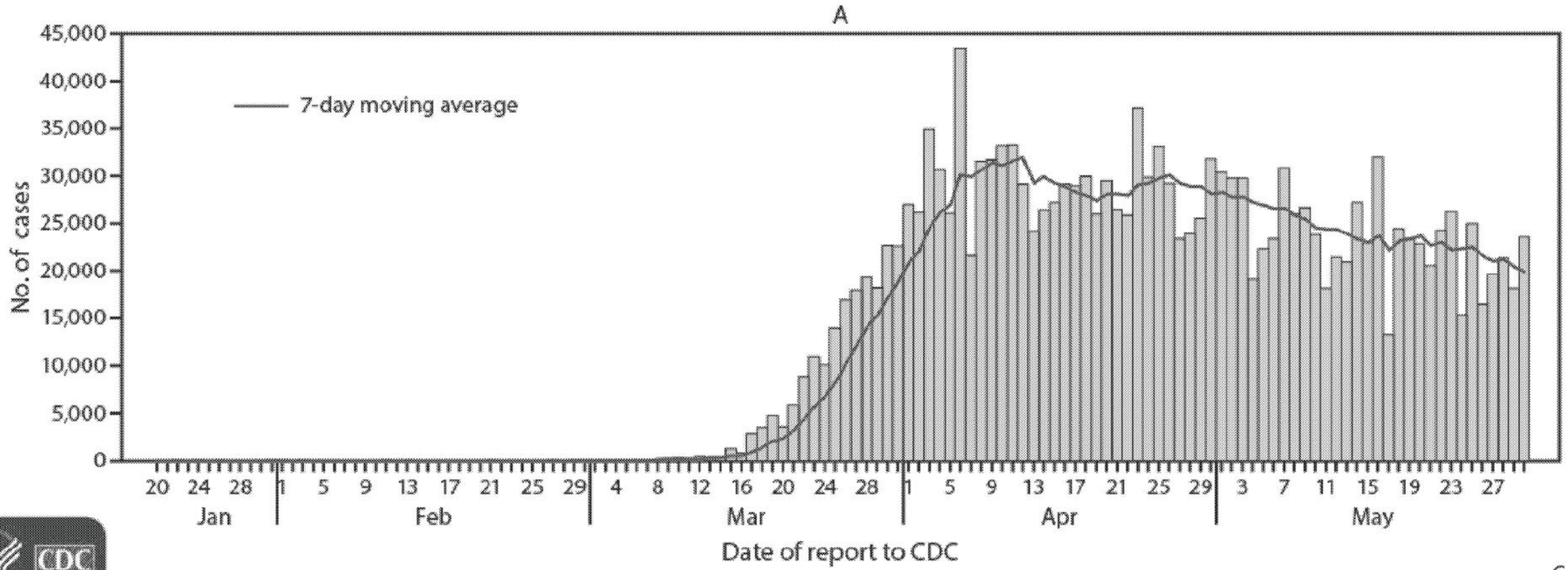
Males	**Females**
Hospitalized: **16**%	Hospitalized: **12**%
Admitted to the ICU: **3**%	Admitted to the ICU: **2**%
Died: **6**%	Died: **5**%

MMWR: Published June 15th
https://www.cdc.gov/mmwr/volumes/69/wr/mm6924e2.htm?s_cid=mm6924e2_w

ICU = Intensive Care Unit

Coronavirus Disease 2019 Case Surveillance — United States, January 22–May 30, 2020

FIGURE. Daily number of COVID-19 cases[*,†,§,¶] (A) and COVID-19–associated deaths[**] (B) reported to CDC — United States, January 22–May 30, 2020



https://www.cdc.gov/mmwr/volumes/69/wr/mm6924e2.htm?s_cid=mm6924e2_w

Coronavirus Disease 2019 Case Surveillance — United States, January 22–May 30, 2020

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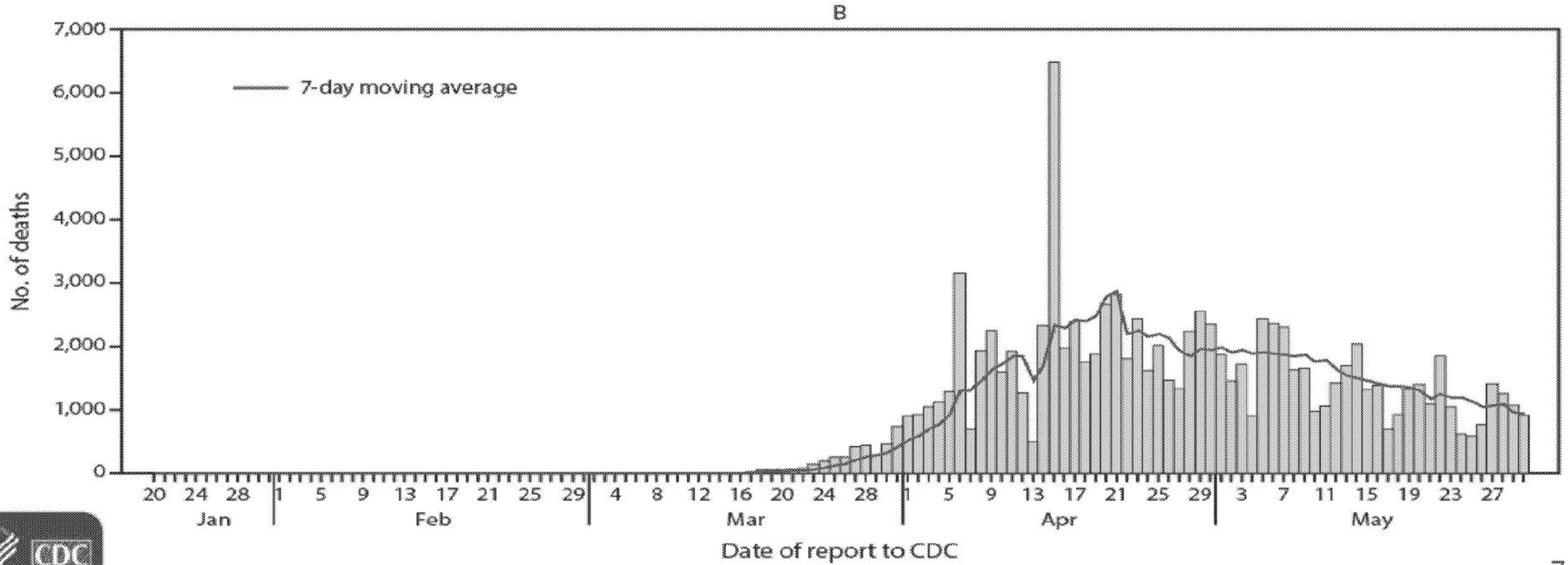
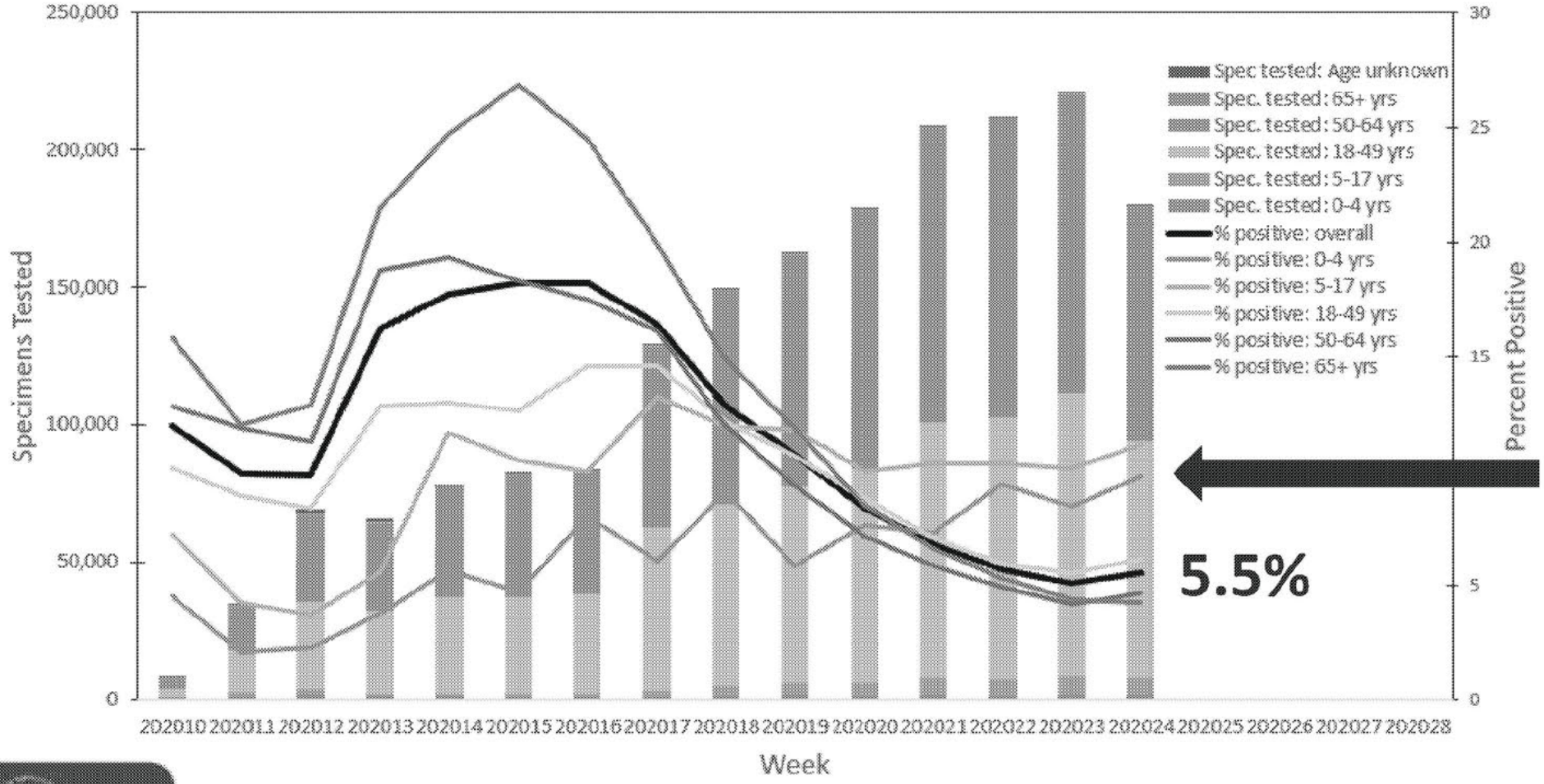


https://www.cdc.gov/mmwr/volumes/69/wr/mm6924e2.htm?s_cid=mm6924e2_w

Public Health Laboratories Reporting to CDC

March 1 to June 13, 2020

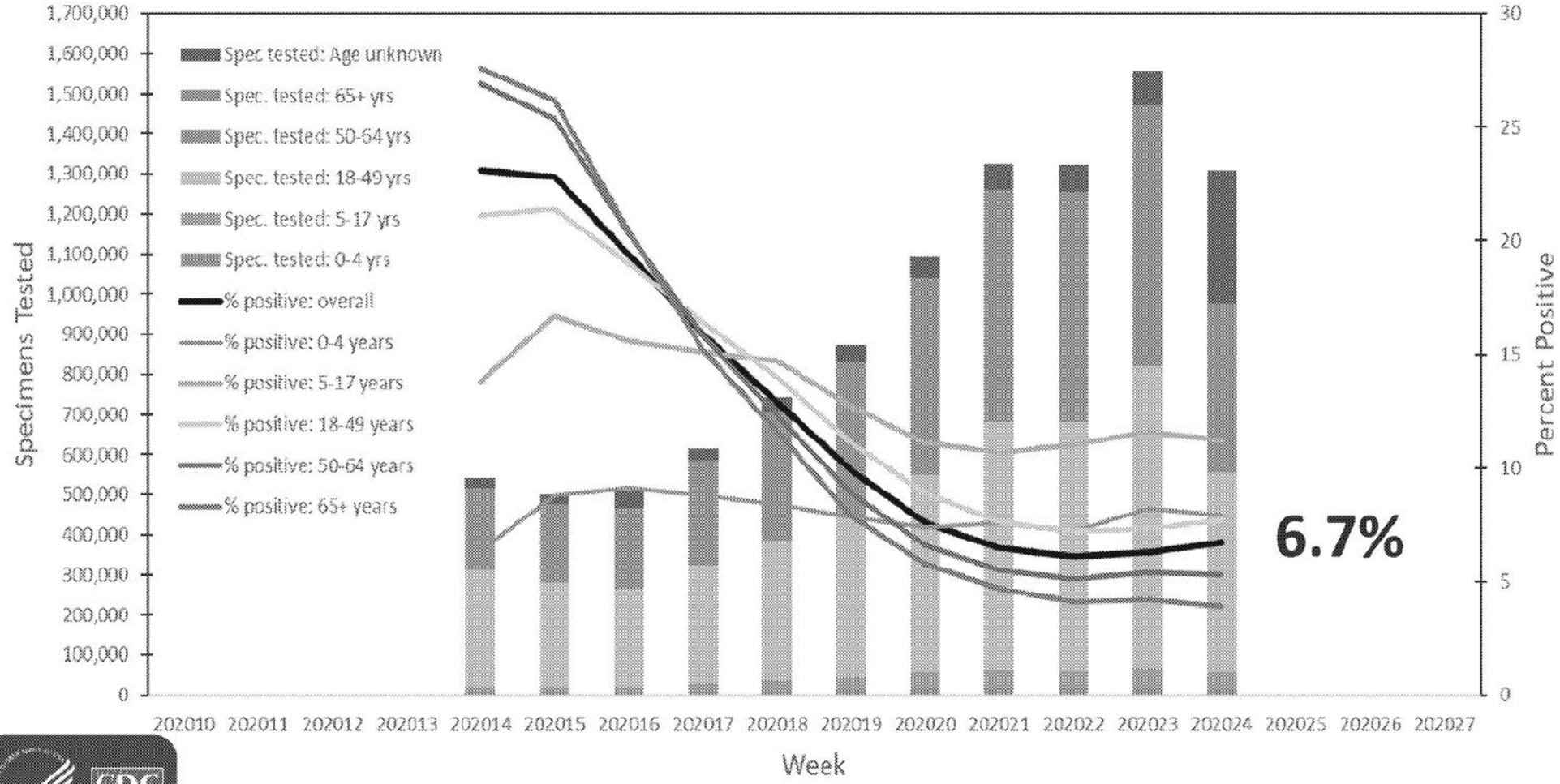


Percentage testing positive in children <18 years of age is **higher** than adult age groups

https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covidview/index.html

Commercial Laboratories Reporting to CDC

March 1 to June 13, 2020



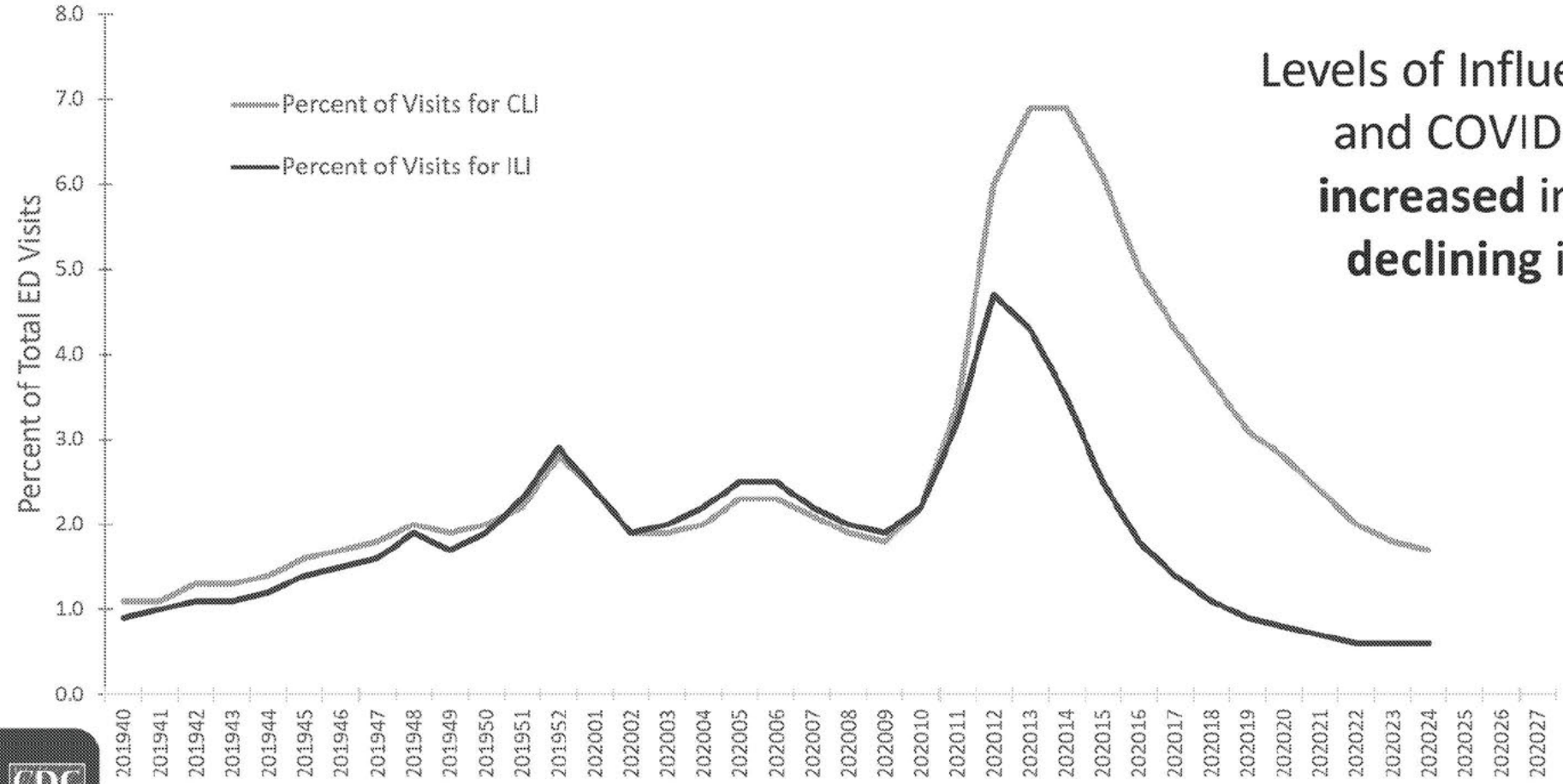
Percentage positive **low**, but **increasing** recently

https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covidview/index.html

Percent of Visits for ILI and CLI in Emergency Departments

National Syndromic Surveillance Program (NSSP)

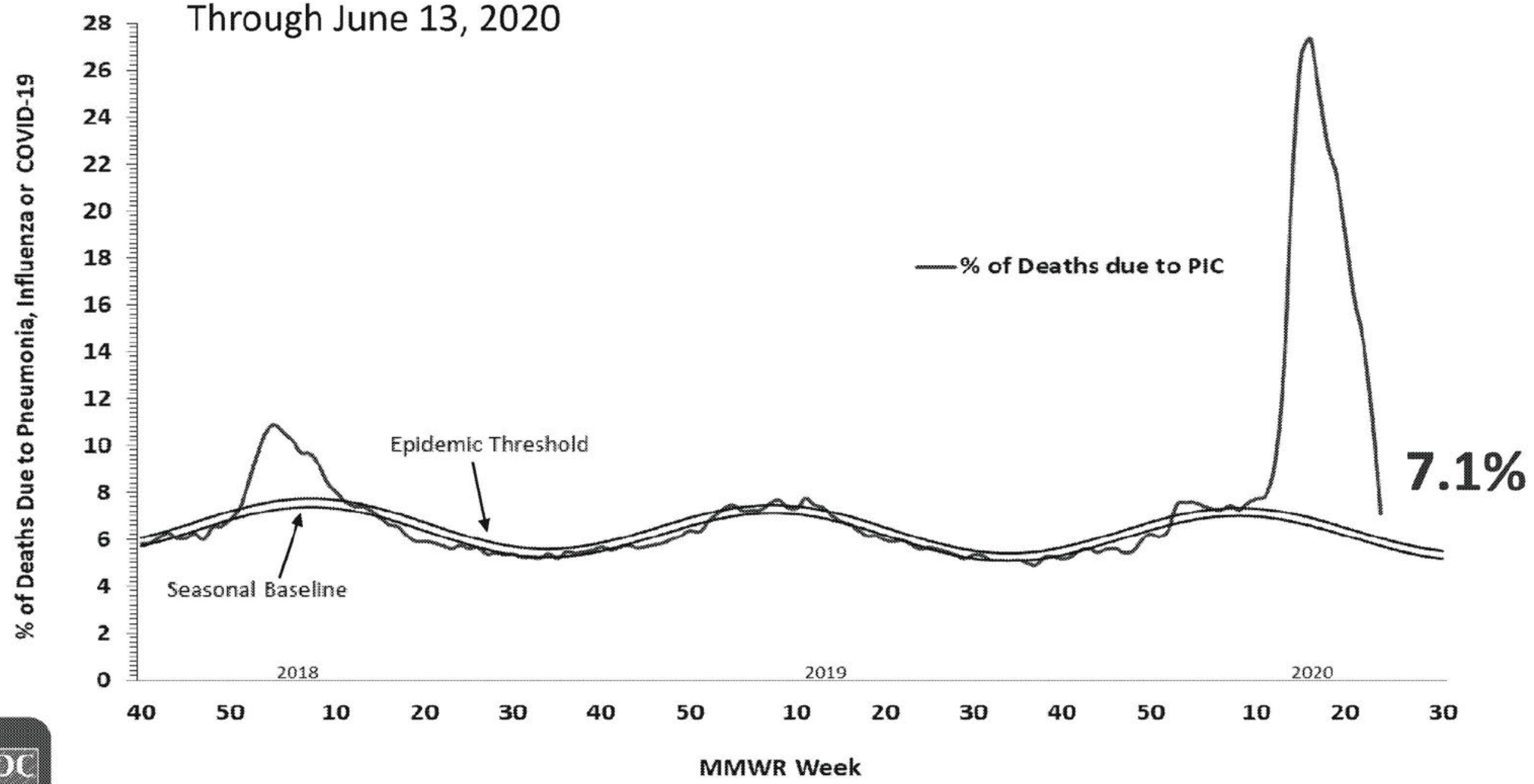
September 29,2019 to June 13, 2020



Levels of Influenza-like illness (ILI) and COVID-like illness (CLI) **increased** in late March, but **declining** in recent weeks

https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covidview/index.html

Pneumonia, Influenza and COVID-19 Mortality
NCHS Mortality Reporting System



https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covidview/index.html

NCHS = National Center for Health Statistics

COVID-NET:
Hospitalization Surveillance from 14 States

States participating in COVID-NET

Surveillance network collecting hospitalization data

- Catchment area ~10% of US population
- Patients must be a resident of the surveillance area and have a positive SARS-CoV-2 test within 14 days prior to or during hospitalization
- Charts reviewed by trained surveillance officers

MMWR April 17, 2020
https://www.cdc.gov/mmwr/volumes/69/wr/mm6915e3.htm

COVID-NET = COVID-19-Associated Hospitalization Surveillance Network

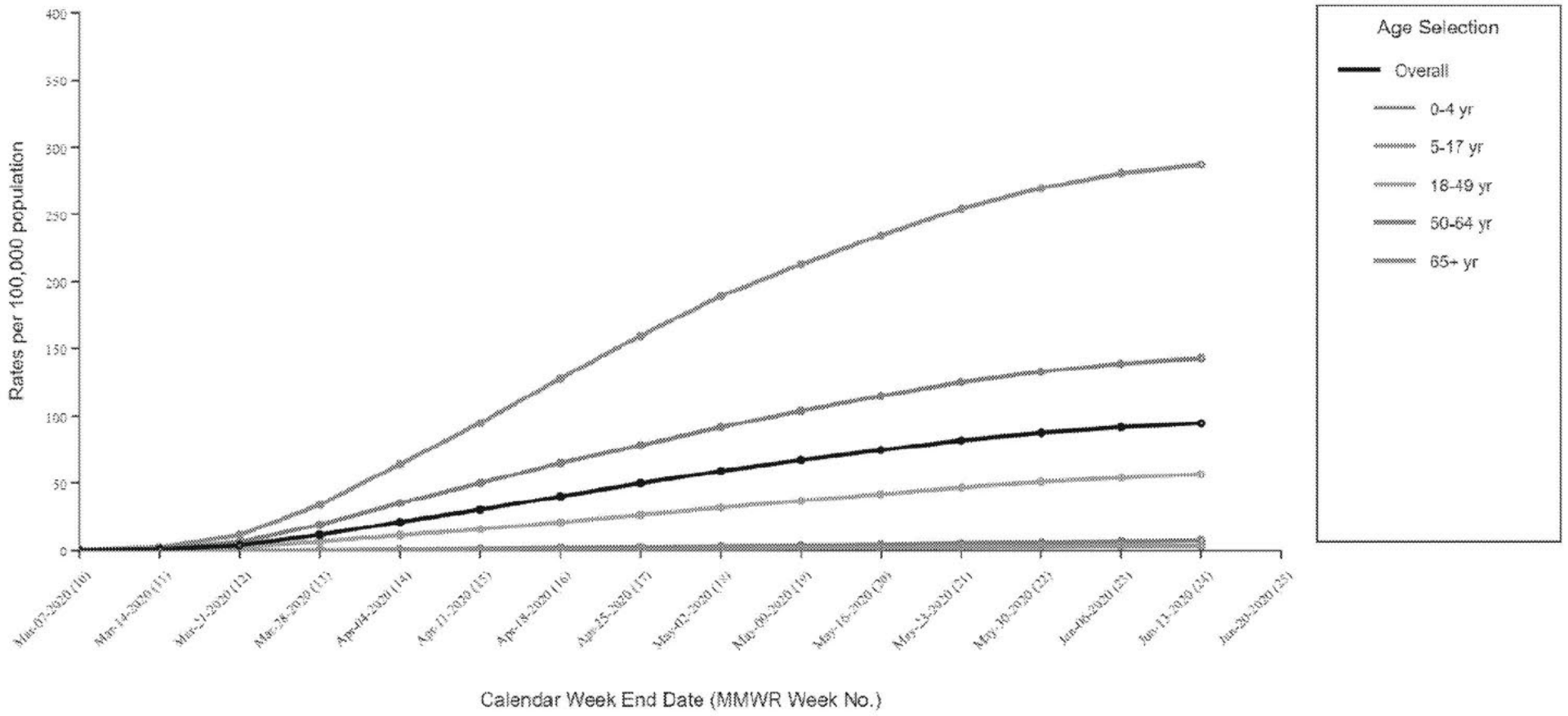
COVID-NET:
Hospitalization Surveillance from 14 States

March 1 to June 13, 2020

Overall:
94.5/100,000
population

Among adults ≥65
years of age:
287/100,000
population

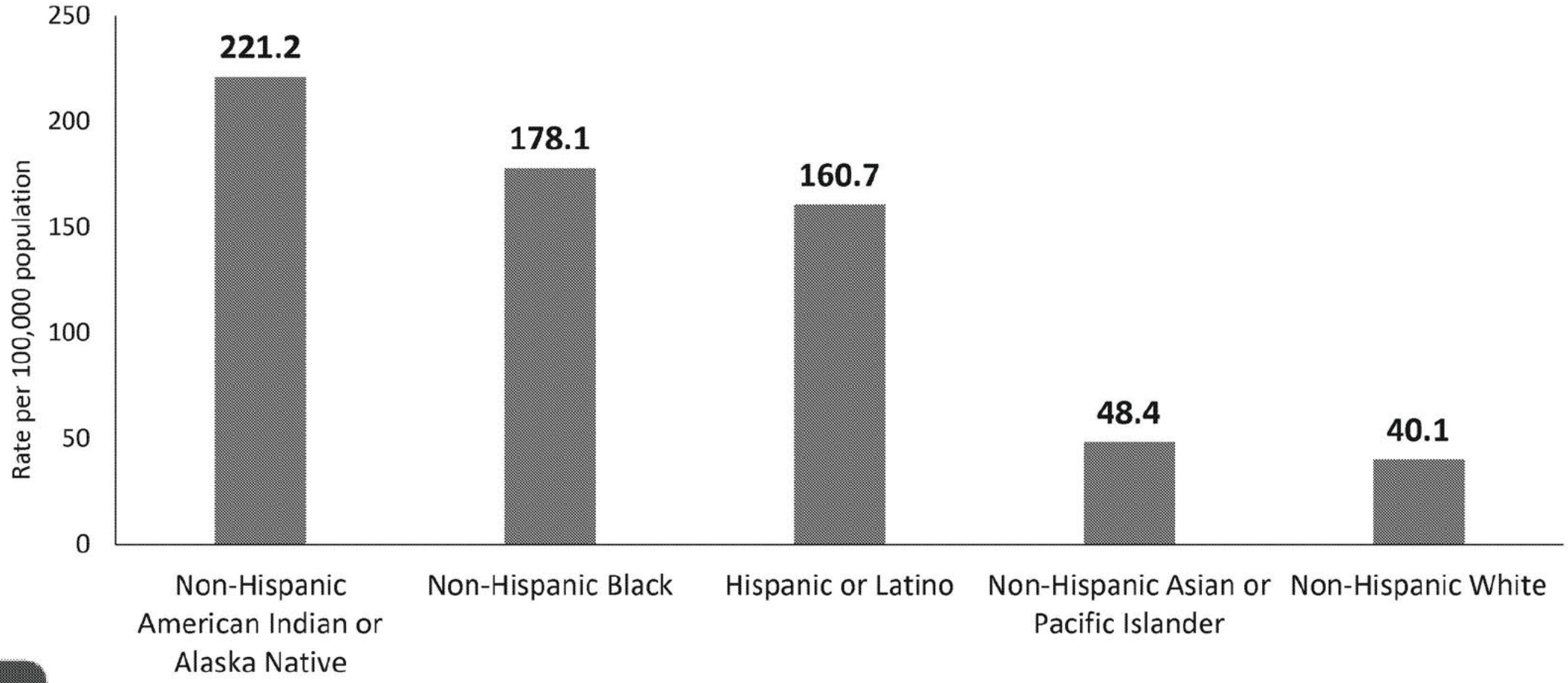
Cumulative Hospitalization Rate



https://gis.cdc.gov/grasp/COVIDNet/COVID19_5.html

COVID-NET:
Age-adjusted COVID-19-associated hospitalization rates, by race and ethnicity

March 1 to June 13, 2020



https://gis.cdc.gov/grasp/COVIDNet/COVID19_5.html

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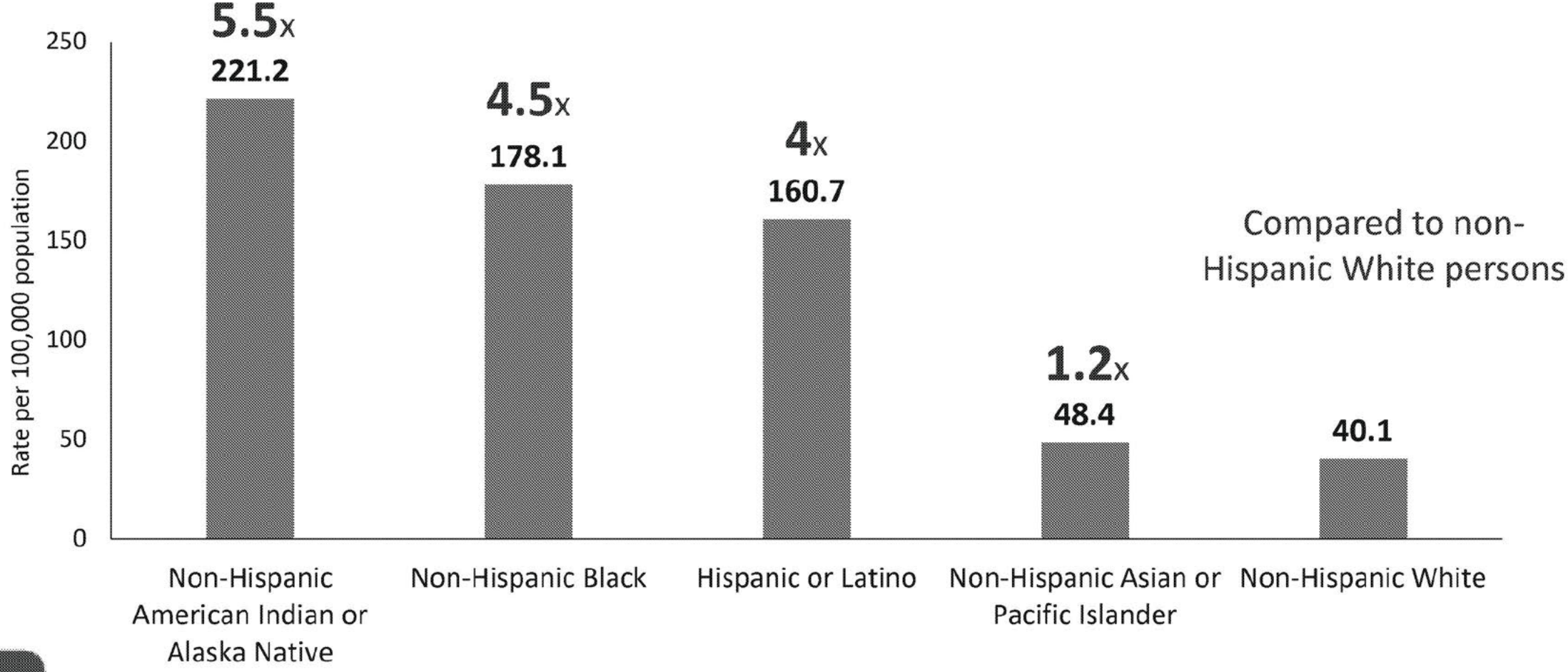
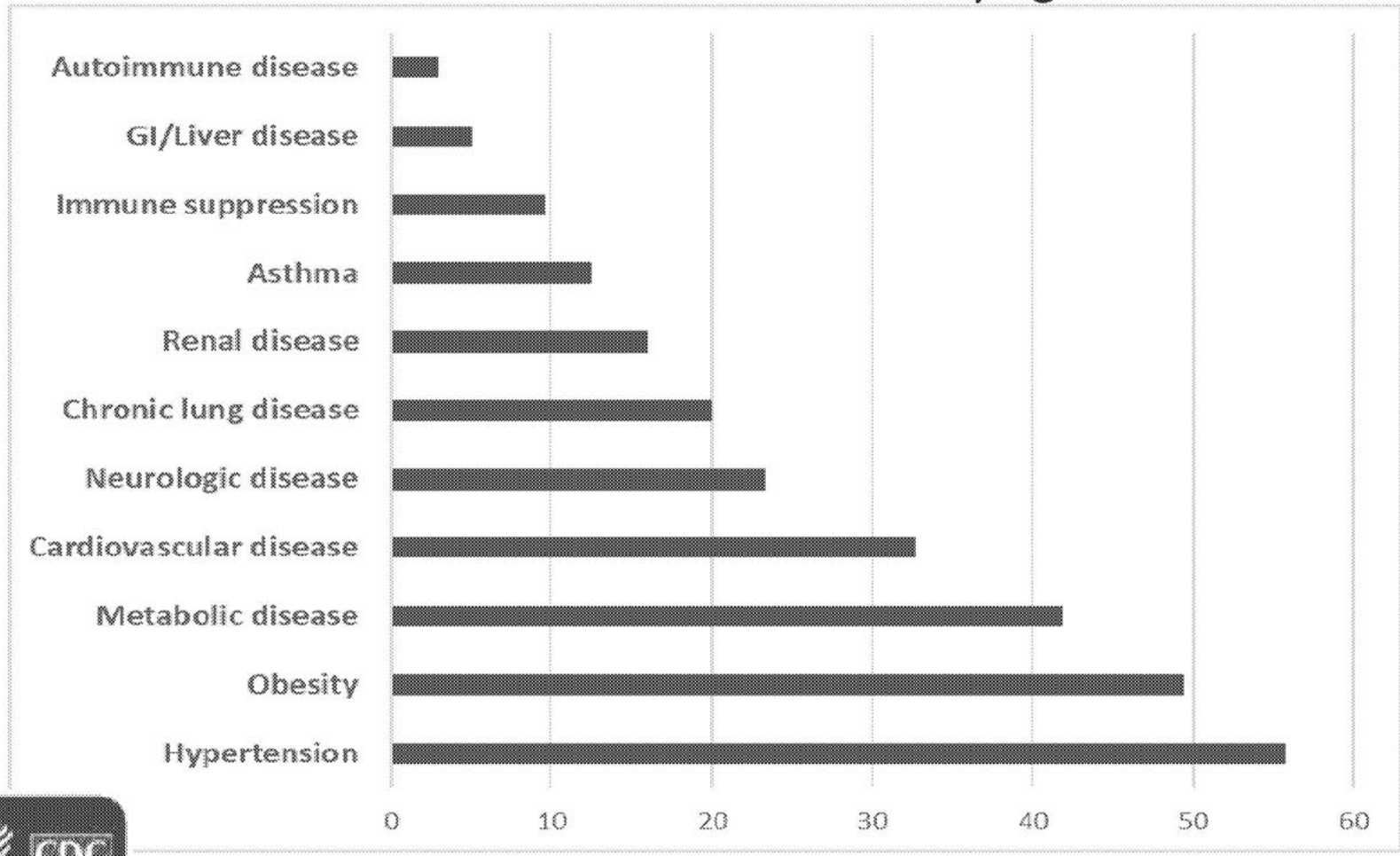


https://gis.cdc.gov/grasp/COVIDNet/COVID19_5.html

COVID-NET:
Hospitalization Surveillance from 14 States

March 1 to June 13, 2020

Underlying Medical Conditions Among **Adults**



91.2% of hospitalized adults reported an underlying condition

Hypertension: 56%
Obesity: 49%
Metabolic Disease (including Diabetes): 42%
Cardiovascular Disease: 33%

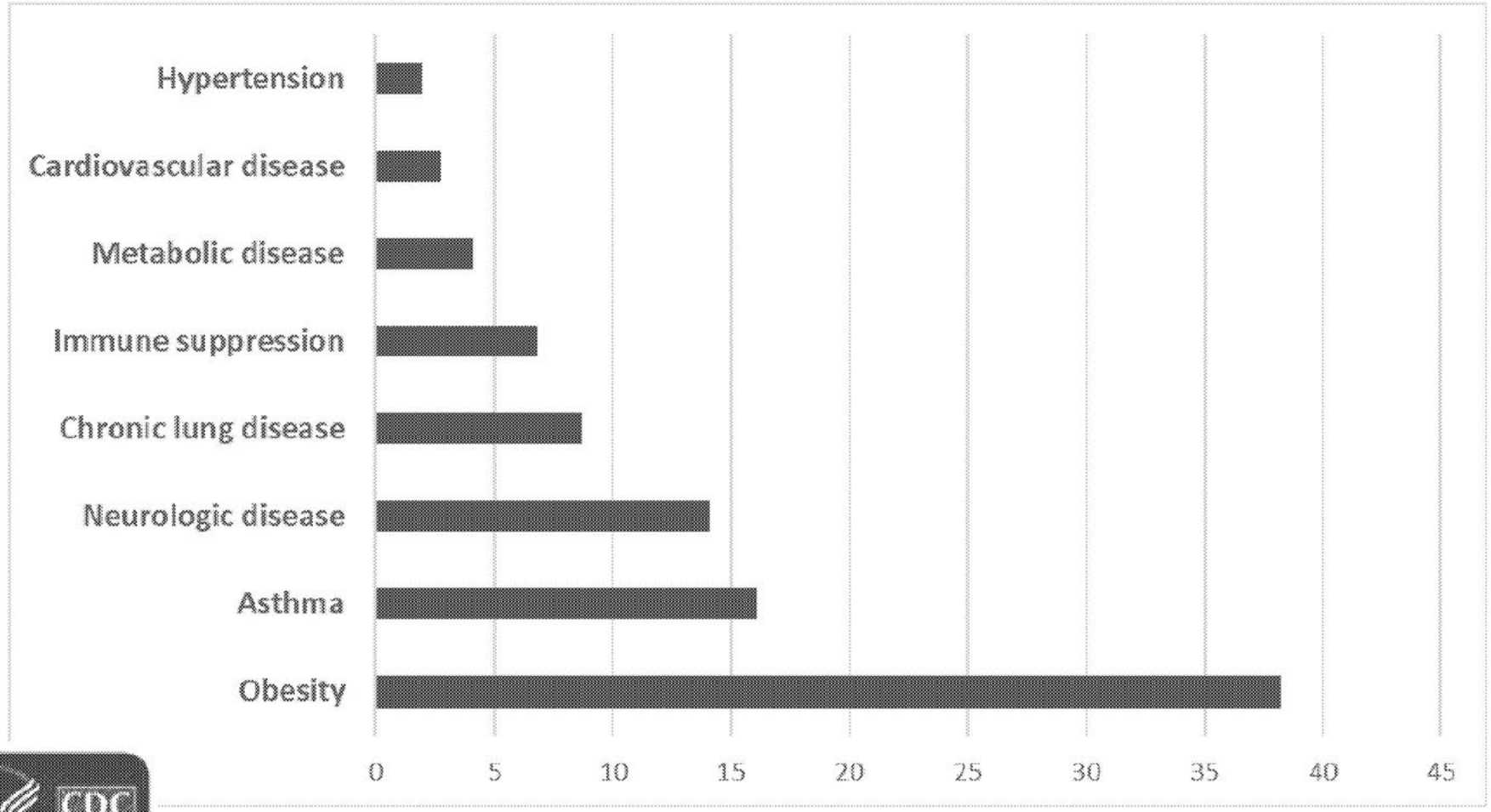
7,465 hospitalized adults with available information

https://gis.cdc.gov/grasp/COVIDNet/COVID19_5.html

COVID-NET:
Hospitalization Surveillance from 14 States

March 1 to June 13, 2020

Underlying Medical Conditions Among **Children** and **Adolescents**



53.3% of hospitalized children reported an underlying condition

Obesity: 38%
Asthma: 16%
Neurologic Disease: 14%

150 hospitalized children with available information

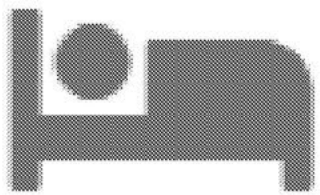
https://gis.cdc.gov/grasp/COVIDNet/COVID19_5.html

Risk Factors for Hospitalization

Characteristics Associated with Hospitalization Among Patients with COVID-19 — Metropolitan Atlanta, Georgia, March–April 2020

Early Release / June 17, 2020 / 69

- **220** hospitalized and **311** non-hospitalized COVID-19 patients from 6 metropolitan Atlanta hospitals/clinics
- Several factors independently associated with hospitalization, through adjusted Odds Ratios (aORs)*



Risk Factors	aOR
Age ≥65 years	3.4 (1.6-7.4)
Black race	3.2 (1.8-5.8)
Having diabetes mellitus	3.1 (1.7-5.9)
Lack of insurance	2.8 (1.1-7.3)
Male sex	2.4 (1.4-4.1)
Smoking	2.3 (1.2-4.5)
Obesity	1.9 (1.1-3.3)

*Adjusted for age, sex, race, obesity, past or current smoking, insurance status, and other underlying conditions

MMWR June 17, 2020 https://www.cdc.gov/mmwr/volumes/69/wr/mm6925e1.htm?s_cid=mm6925e1_w

COVID-19 Epidemiology among Healthcare Personnel

Healthcare Personnel (HCP)

Morbidity and Mortality Weekly Report

Characteristics of Health Care Personnel with COVID-19 — United States, February 12–April 9, 2020

CDC COVID-19 Response Team

315,531 COVID-19 cases reported to CDC → **49,370 (16%)** with information on HCP status → **9,282 (19%)** identified as a HCP

- Among 1,423 HCP patients who reported contact with a lab-confirmed COVID-19 patient in either healthcare, household or community settings, 780 (**55**%) reported having such contact only in **health care setting** within 14 days
- Most HCP not hospitalized
- Severe outcomes occurred across all age groups
  - **27** (of 4407: **0.6**%) deaths

MMWR April 17, 2020 https://www.cdc.gov/mmwr/volumes/69/wr/mm6915e6.htm?s_cid=mm6915e6_w

Healthcare Personnel (HCP)

- CDC reports and routinely updates cases and deaths among healthcare personnel on the CDC website

Cases & Deaths among Healthcare Personnel

As of June 23st

Data were collected from 1,952,346 people, but healthcare personnel status was only available for 424,304 (21.7%) people. For the 83,673 cases of COVID-19 among healthcare personnel, death status was only available for 53,902 (64.4%).

CASES AMONG HCP	DEATHS AMONG HCP
83,673	464

https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/cases-in-us.html

Next Steps: Healthcare Personnel (HCP)

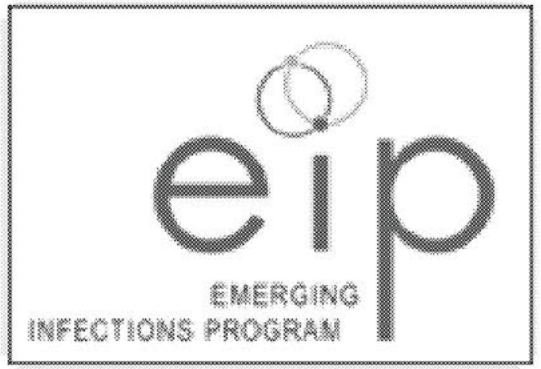
PROJECT COVERED

- Prospective cohort study of 1,600 HCP working in US Emergency Departments (ED)
  - Estimate attributable risk of occupational acquisition of COVID-19 infection for **emergency physicians and nurses**
  - Estimate attributable risk of occupational acquisition of COVID-19 infection related to **endotracheal intubation**
  - Identify **risk factors** associated with SARS-CoV-2 transmission during intubation
  - Determine the **prevalence** of symptomatic and asymptomatic COVID-19 infections occurring in ED HCPs
- Serial symptom questionnaires, SARS-CoV-2 serology (IgG) and self-collected nasal swabs (PCR) over a 12-week period

CDC

https://medicine.uiowa.edu/content/study-overview

Next Steps: Healthcare Personnel (HCP)



- Emerging Infections Program (EIP): network of 10 state health departments and local public health and academic partners

- EIP sites initiated projects on HCP COVID-19 case tracking
  - Surveillance for and interviews of HCP cases (10 EIP sites)
  - Comparison of HCP cases and HCP non-cases (5 EIP sites)

- As of 6/12, **1,044** cases reported among HCP from 9 sites, 425 interviews conducted

https://www.cdc.gov/ncezid/dpei/eip/index.html

Next Steps: Healthcare Personnel (HCP)

	AZ HEROES	RECOVER
	Collaboration between University of Arizona, CDC and NCI	CDC
Study Population	HCP, first responders, essential and frontline workers	HCP, first responders with direct contacts with patient and public with COVID-19
Study Design	Prospective longitudinal cohort	Cohort
Timeline	12 months	12 months
Specimen Collection	Repeat PCR and serology	Repeat PCR and serology
Objectives	Determine incidence of asymptomatic and symptomatic infection Estimate incidence of novel infection and repeat infection	Determine incidence of asymptomatic and symptomatic infection, with a focus on the clinical epidemiology and impact on missed work, presenteeism and functioning Immune response to SARS-CoV-2 infection

AZ HEROES: Arizona **H**ealthcare, **E**mergency **R**esponse and **O**ther **E**ssential Workers **S**urveillance Study
RECOVER: **R**esearch on the **E**pidemiology of **CO**VID-19 in **E**mergency **R**esponse and Healthcare Personnel

COVID-19 Epidemiology among Long Term Care Facility (LTCF) Residents

Long Term Care Facilities:
Skilled Nursing Facility, King County, Washington

- As of March 18th, **167** confirmed COVID-19 cases associated with the facility

101	50	16
residents	staff/HCP	visitors



- **86%** of tested residents were confirmed positive
- **34%** of residents died

MMWR March 27, 2020 https://www.cdc.gov/mmwr/volumes/69/wr/mm6912e1.htm?s_cid=mm6912e1_w
McMichael TM, et al. NEJM 2020

Long Term Care Facilities

- Reports suggest that once COVID-19 has been introduced into a long-term care facility, it has the potential to result in high attack rates among residents, staff members, and visitors.
- Many areas contribute to vulnerability of LTCFs:
  - Inadequate familiarity with PPE
  - Inadequate supplies of PPE
  - High prevalence of underlying conditions
  - Atypical presentations in elderly
  - Facilities share staff and patients

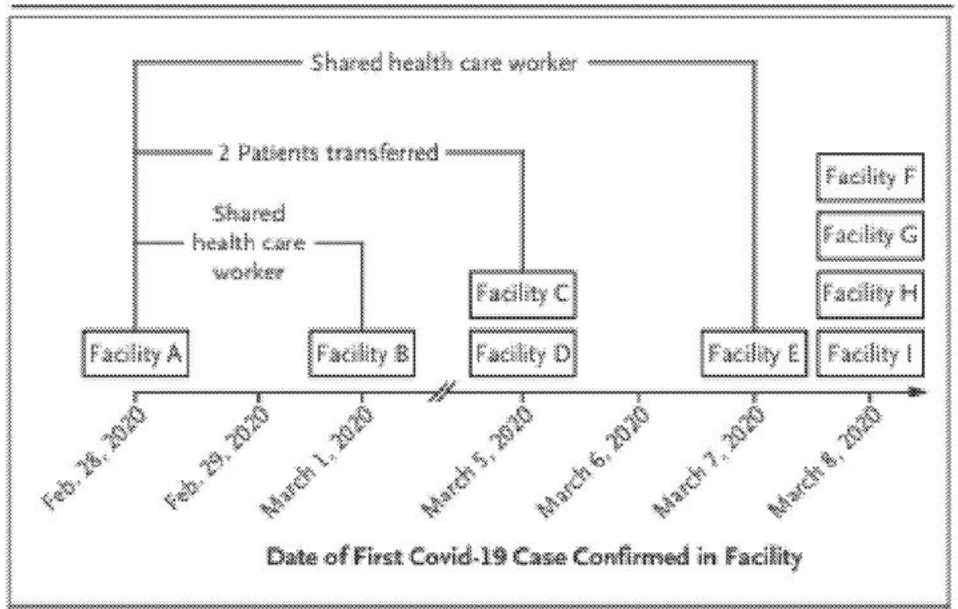


Figure 2. Timeline Showing Long-Term Care Facilities in King County with One or More Confirmed Cases of COVID-19.

McMichael TM, et al. NEJM 2020

Long Term Care Facilities

NHSN
NATIONAL HEALTHCARE SAFETY NETWORK

- As of the week ending June 7, almost 15,000 nursing homes are reporting COVID-19 in NHSN
  - These facilities reported over **107,000** confirmed COVID-19 cases, over 71,000 suspected cases and almost 30,000 deaths in residents
  - CMS began publicly reporting data from nursing homes on June 4, 2020
- CDC also tracks what states report publicly; these numbers include a broader range of LTCFs beyond nursing homes, such as assisted living facilities
- As of June 11, 2020, there were at least **245,605** cumulative confirmed or probable COVID-19 cases in residents and staff from 10,708 LTCFs across 51 U.S. states and territories based on state health department websites and other publicly available information

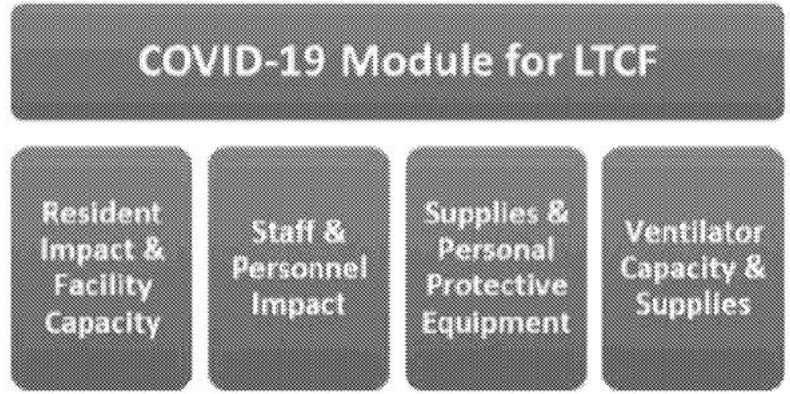
CDC

https://data.cms.gov/stories/s/COVID-19-Nursing-Home-Data/bkwz-xpvg/

Next Steps:
Long Term Care Facilities

NHSN
NATIONAL HEALTHCARE SAFETY NETWORK

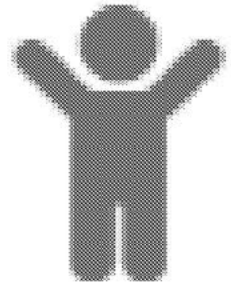
- Information collected through NHSN will be used to:
  - Strengthen COVID-19 surveillance locally and nationally
  - Monitor trends in infection rates
  - Help local, state, and federal health authorities get help to nursing homes faster



https://www.cdc.gov/nhsn/ltc/covid19/index.html

COVID-19
Epidemiology among Children

COVID-19: Infants and Children



- Children may have different or minimal symptoms
  - Abdominal pain or GI symptoms[1]
- May be more likely to be **asymptomatic**[1,2]

- Early in the outbreak in China, school-aged children had largest number of close contacts of any age[3]
- Efficiency of spread in schools by children is unknown. Existing data are reassuring, but limited[4-6]

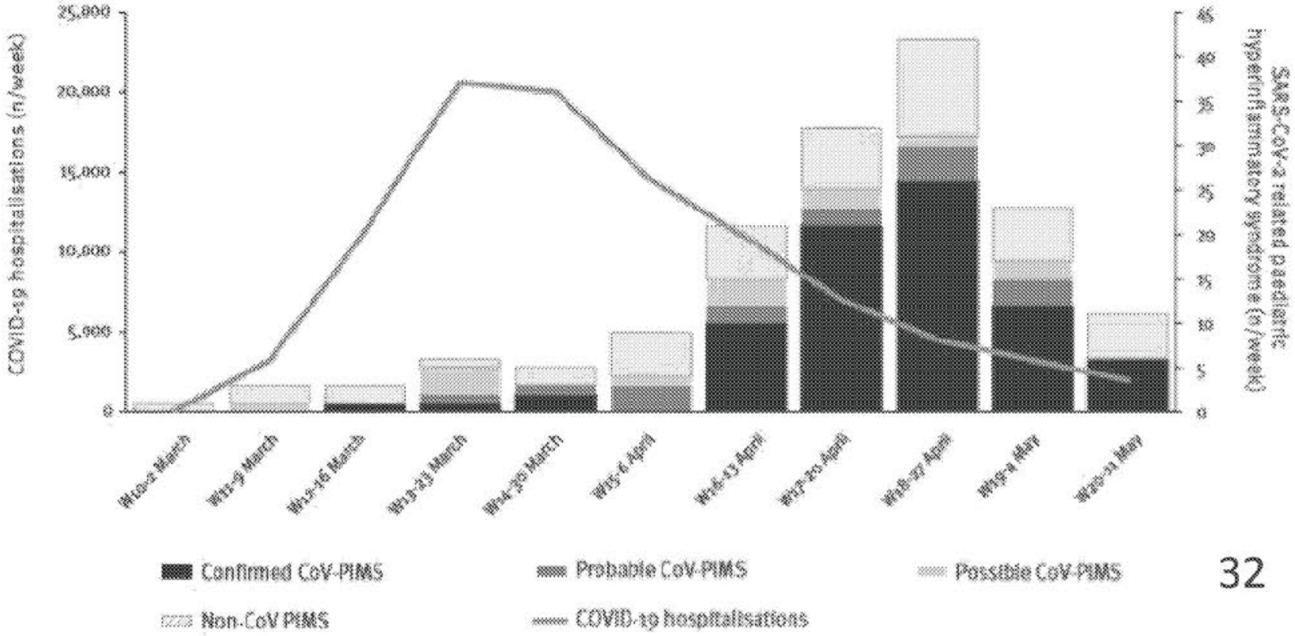
[1]MMWR April 10, 2020 https://www.cdc.gov/mmwr/volumes/69/wr/mm6914e4.htm?s_cid=mm6914e4_w
[2]Dong et al. Pediatrics. June 2020
[3]Zhang et al. Science April, 2020
[4]Heavey et al. Eurosurveillance May 2020
[5]Johansen et al. Eurosurveillance May 2020
[6]COVID-19 in schools- the experience in NSW April 2020 Report

Inflammatory Multisystem Syndrome in Europe

- Primarily described among children
- Initially called PIMS (Pediatric Inflammatory Multisystem Syndrome) in Europe
- Kawasaki-like disease and cardiac involvement

Epidemic curve peaked **4-5** weeks after peak of COVID-19 epidemic in France

Temporal distribution of COVID-19 hospitalisations and SARS-CoV2 hyperinflammatory paediatric cases, France, 2 March–17 May (n = 108)



Belot et al. Euro Surveill 2020

Inflammatory Multisystem Syndrome in Europe

- Pediatric Inflammatory Syndrome in England: March 23 to May 16
  - **58** children with fever and laboratory evidence of inflammation
  - SARS-CoV-2 PCR positive 15/58 (26%) children
  - SARS-CoV-2 IgG positive in 40/46 (87%) children

  → 45/58 (**78**%) had evidence of current or prior SARS-CoV-2 infection

  - All patients presented with persistent fever (3-19 days)
  - Abdominal pain n=31/58, **53**% Rash n=30/58, **52**%

29 (50%) children developed shock and myocardial dysfunction
8 (14%) children developed coronary artery dilation or aneurysm
2 (3%) children required extracorporeal membrane oxygenation (ECMO)

Whittaker et al. JAMA 2020

Multisystem Inflammatory Syndrome in Children (MIS-C)
Case definition among children aged <21 years

- Fever > 38.0°C

AND

- Laboratory evidence of inflammation

AND

- Evidence of clinically severe hospitalized illness with multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological)

AND

- One of the following:
  1. SARS-CoV-2 positive PCR test
  2. SARS-CoV-2 positive antibody test
  3. SARS-CoV-2 negative PCR and antibody tests but with identified COVID exposure within the four weeks prior to the onset of symptoms

*Details available at: https://emergency.cdc.gov/han/2020/han00432.asp

Multisystem Inflammatory Syndrome in Children (MIS-C)

The *Overcoming COVID-19* Study

- Coordinated by Boston Children's Hospital, funded by CDC
- **213** MIS-C cases enrolled at 53 participating health centers in 26 states
- Most were previously healthy and cardiovascular involvement was prominent

Key findings	
SARS-CoV2 PCR+ or antibody positive at admission	**73%**
Age, median (IQR)	**8.4** (3.6, 12.8)
<5 years	33%
5-21 years	67%
Previously healthy (except obesity)	73%
Male	63%
ICU	81%
Died	3%

81% cardiovascular involvement

50% with elevated troponin

38% with ejection fraction <55%

50% required vasopressor support

~9% had coronary aneurysms (z-score ≥2.5)
has long-term implications

Next Steps:
Multisystem Inflammatory Syndrome in Children (MIS-C)

- CDC MIS-C Surveillance
  - CDC recommends that healthcare providers report suspect cases of MIS-C to local, state or territorial health departments
  - Health departments then report cases the National Notifiable Diseases Surveillance System for case counts and case report forms are submitted using other MIS-C specific surveillance systems
- New Vaccine Surveillance Network
  - Seven US pediatric medical centers conducing active surveillance for acute respiratory and gastrointestinal illness
- COVID-NET
  - A population-based surveillance system collecting data on lab-confirmed SARS-CoV-2-associated hospitalizations among children

COVID-19
Epidemiology among Pregnant Women

Pregnancy and risk for severe respiratory viral illness

- Physiologic changes of pregnancy may increase the risk of severe illness [1]
  - Increased heart rate and oxygen consumption
  - Decreased lung capacity
  - Shift away from cell-mediated immunity
- Severe disease has been associated with other viral respiratory infections in pregnant women[1–4]

[1]Ramsey PS et al. Pneumonia in pregnancy. Obstet Gynecol Clin North Am 2001
[2]Galang RR et al. Severe Coronavirus Infections in Pregnancy: A Systematic Review [online ahead of print, 2020 Jun 16]. Obstet Gynecol. 2020
[3]Mertz D et al. Populations at risk for severe or complicated influenza illness: systematic review and meta-analysis. BMJ 2013
[4]Mosby LG et al. 2009 pandemic influenza A (H1N1) in pregnancy: a systematic review of the literature. Am J Obstet Gynecol 2011

Pregnant Women: New York City

- Prospective cohort study of pregnant women with lab-confirmed SARS-CoV-2 from March 13–April 12 at 5 NYC medical centers
- **241** women with positive SARS-CoV-2 test
  - 89% admitted for obstetric indications
- 148 (**61**%) asymptomatic at time of admission
  - **46** developed COVID-19 symptoms during hospitalization
- Body mass index (**BMI**) **≥30** associated with COVID-19 severity
    - Insurance type, age, race and ethnicity, and underlying medical conditions not associated with COVID-19 severity

Khoury R et al. Obstet Gynecol 2020

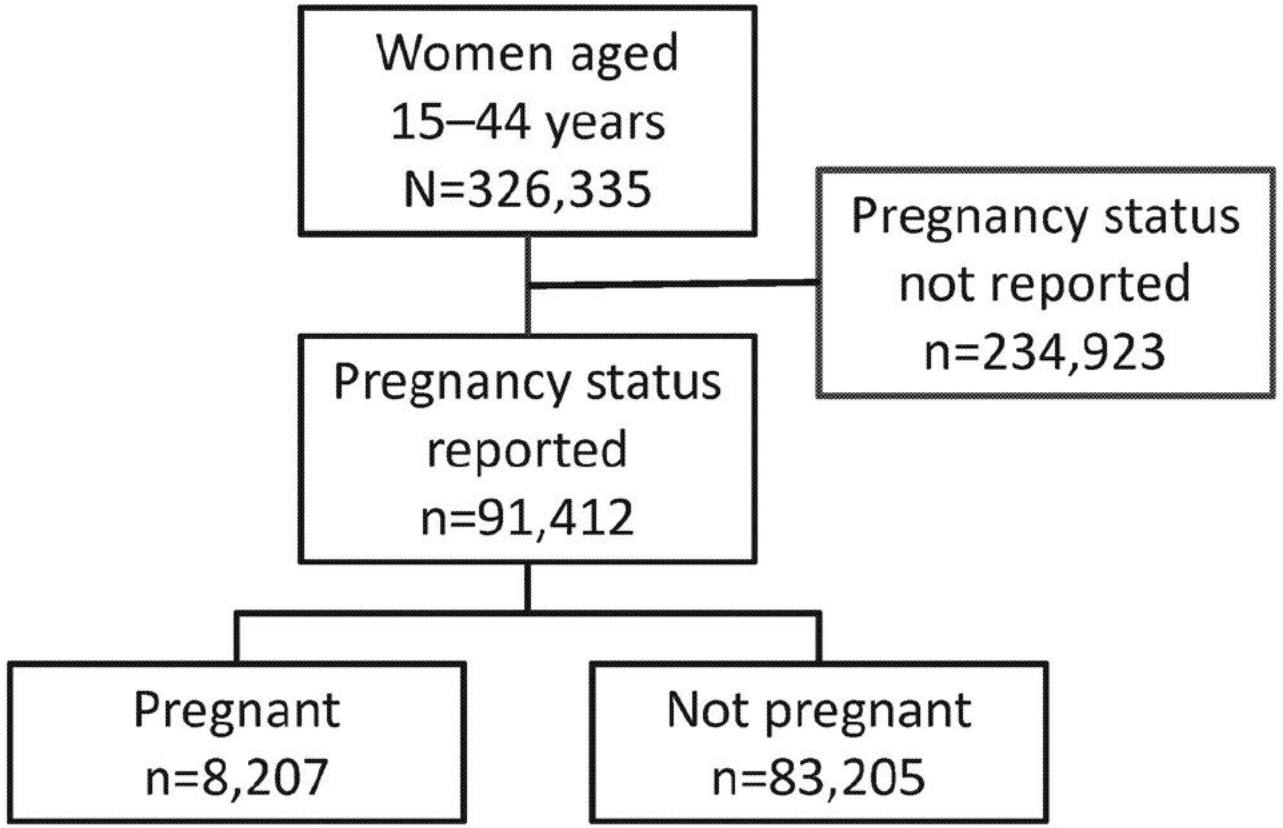
Pregnant Women: New York City

- 236/245 liveborn neonates with documented SARS-CoV-2 test results
  - 230 (**98**%) tested negative

- Preterm (<37 weeks gestation) birth rate in this cohort (**14.6**%) higher than in the general population (**10.2**%*)
  - Statistically significant linear trend between COVID-19 maternal severity and the risk of preterm birth

Khoury R et al. Obstet Gynecol 2020;
*Martin J et al. Births in the United States, 2018. National Center for Health Statistics

Women of reproductive age (WRA) with SARS-CoV-2 infection by pregnancy status — Jan 22–Jun 7



Inclusion Criteria

- Women aged 15-44 years
- Laboratory-confirmed SARS-CoV-2 infection
- 50 states, NYC, and DC
- Reported to CDC January 22–June 7, 2020 (data as of June 17, 2020)

Hospitalization, ICU admission, mechanical ventilation, and death among pregnant women and nonpregnant WRA with SARS-CoV-2 infection

Outcomes of Interest	No. (%)*		Crude RR (95% CI)	aRR (95% CI) †
	Pregnant women with COVID-19 (N = 8,207)	Nonpregnant women with COVID-19 (N = 83,205)		
Hospitalization§	2,587 (31.5)	4,840 (5.8)	**5.4 (5.2-5.7)**	**5.4 (5.1-5.6)**
ICU Admission	120 (1.5)	757 (0.9)	**1.6 (1.3-1.9)**	**1.5 (1.2-1.8)**
Mechanical Ventilation	42 (0.5)	225 (0.3)	**1.9 (1.4-2.6)**	**1.7 (1.2-2.4)**
Death	16 (0.2)	208 (0.2)	0.8 (0.5-1.3)	0.9 (0.5-1.5)

* Percentages calculated among total in pregnancy status group; those with missing data on outcomes were counted as not having the outcome.

† Adjusted for age as a continuous variable, dichotomous yes/no variable for presence of underlying conditions, and categorical race/ethnicity. Nonpregnant women are the referent group.

§ May include women admitted for obstetric care reasons who receive routine SARS-CoV-2 testing upon admission.

Hospitalization Bias

- Challenges in interpretation of **hospitalization** as an outcome, since data are not available to determine whether hospitalization was due to COVID-19 or pregnancy-related condition
- In an analysis of outcomes among pregnant versus non-pregnant women hospitalized with lab-confirmed COVID-19 from COVID-NET, the risk of ICU and mechanical ventilation was **lower** among pregnant compared to non-pregnant women, and there was no statistically significant difference in the risk of in-hospital death
  - Reason for admission is not specified; it is possible that non-pregnant women were predominately admitted for **medical illness**, whereas pregnant women admitted for medical illness or **labor/delivery**
  - Pregnant women admitted solely for labor/delivery are likely **healthier** than pregnant or non-pregnant women admitted for medical illness

Summary

- Largest U.S. cohort of pregnant women with lab confirmed SARS-CoV-2 infection
- More complete data are needed to fully understand the risk of severe illness due to SARS-CoV-2 infection in pregnant women and neonates
- Results suggest an increased relative risk of ICU admission and mechanical ventilation comparing pregnant women with nonpregnant women; however, the absolute risk of these clinical interventions is still very low in this population

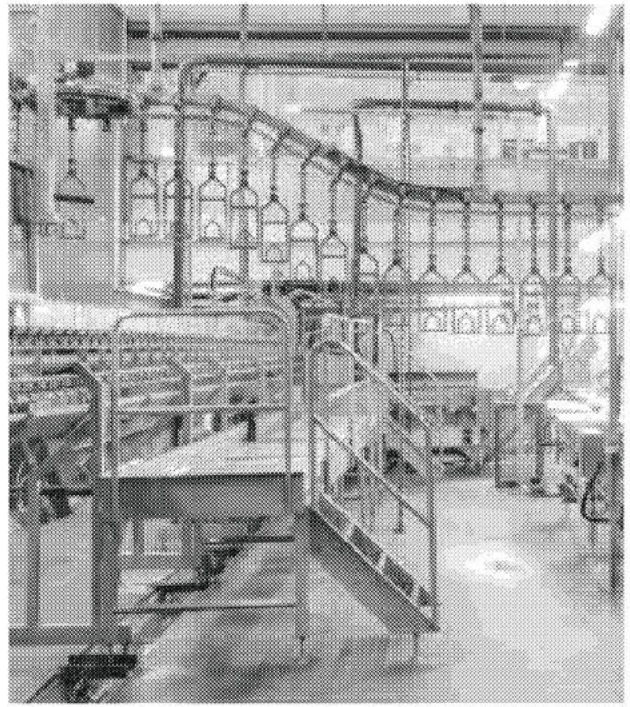
Next Steps: Pregnant Women

- Cohort studies, including retrospective electronic cohorts and prospective community cohorts
  - Assess incidence and seroprevalence of SARS-CoV-2 in pregnancy
  - Predictors for severity of disease
- Collecting surveillance data on pregnancy and neonatal outcomes
  - Surveillance for Emerging Threats to Mothers and Babies Network (SET-NET)
- Leveraging existing pregnancy surveillance systems
  - Pregnancy Risk Assessment and Monitoring System (PRAMS)
  - COVID-NET

COVID-19 Epidemiology among People in Congregate Settings

Congregate Settings:
Meat & Poultry Processing

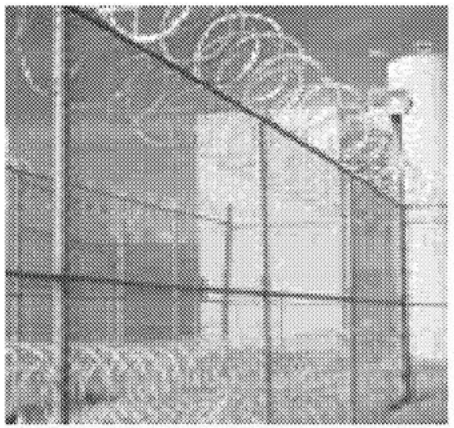
- 115 meat or poultry processing plants in 19 states reported COVID-19 cases to CDC in April 2020
- COVID-19 diagnosed in 4,913 (**~3**%) workers
  - By state, ranged from **0.6**% to **18.2**% of workers
- 20 COVID-19 related deaths reported



MMWR May 1, 2020 https://www.cdc.gov/mmwr/volumes/69/wr/mm6918e3.htm?s_cid=mm6918e3_x

Congregate Settings:
Correction & Detention Facilities

- **420** correctional/detention facilities with ≥1 COVID-19 case from 32 state and territorial health department jurisdictions
- COVID-19 diagnosed in **4,893** incarcerated persons and **2,778** staff
- 88 COVID-19 related deaths reported among incarcerated persons, 15 among staff



MMWR May 6, 2020 https://www.cdc.gov/mmwr/volumes/69/wr/mm6919e1.htm?s_cid=mm6919e1_e

Congregate Settings: Homeless Shelters

- 1,192 residents and 313 staff members tested in 19 homeless shelters in 4 U.S. cities from March 27–April 15
- Homelessness poses multiple challenges that can amplify spread of COVID-19

Shelters associated with a cluster

Seattle: **17%** positive

Boston: **36%** positive

San Francisco: **66%** positive

Shelters NOT associated with a cluster

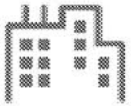
Seattle: **5%** positive

Atlanta: **4%** positive

MMWR April 22, 2020 https://www.cdc.gov/mmwr/volumes/69/wr/mm6917e1.htm?s_cid=mm6917e1_w

Serology

Seroprevalence Surveys



Large-scale geographic Seroprevalence Surveys: estimate the number of people previously infected with SARS-CoV-2 and not included in official case counts

- Including specimens from commercial laboratories and blood donations

Community-level Seroprevalence Surveys: cover smaller areas, with selection of participants systematically selected

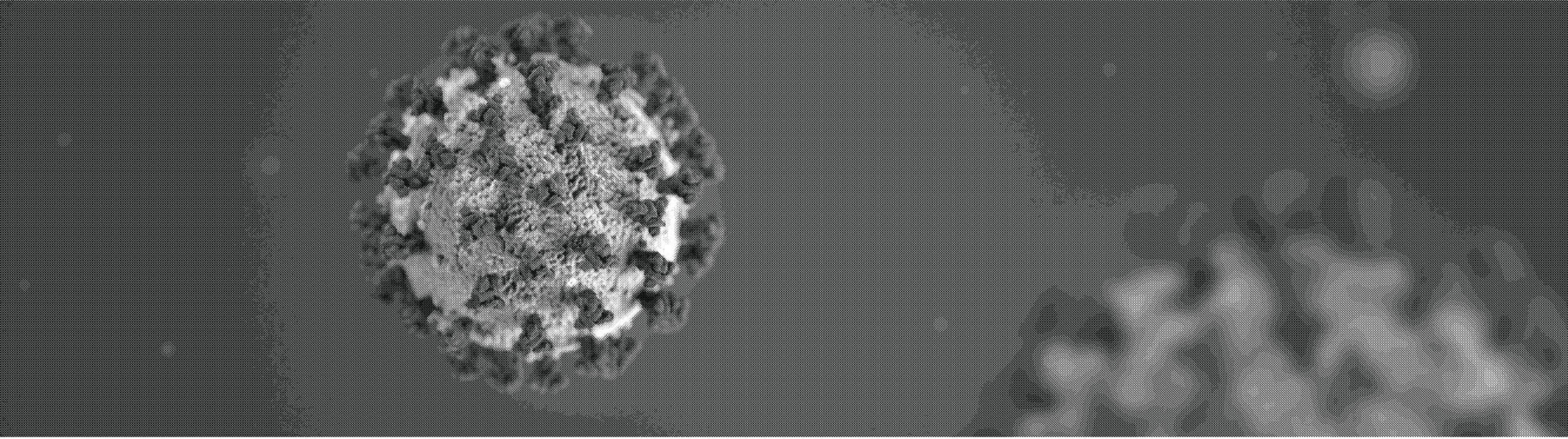
Special populations Seroprevalence Surveys: answer questions about specific populations, such as healthcare workers or pregnant women

Additional information:
https://www.cdc.gov/coronavirus/2019-ncov/covid-data/seroprevalence-types.html#special-populations-seroprevalence-surveys

Summary

Summary

- ~2 million cases of COVID-19 diagnosed in the United States through June
- Multiple sub-populations appear to have an increased risk, including older adults, healthcare workers, individuals at long term care facilities or other congregate settings, and those with underlying medical conditions
- Many projects are ongoing to better define characteristics of SARS-CoV-2 infections



For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

MIS-C Case Definitions

Table 1. Case Definitions for Emerging Inflammatory Condition During COVID-19 Pandemic From the World Health Organization, Royal College of Paediatrics and Child Health, and Centers for Disease Control and Prevention

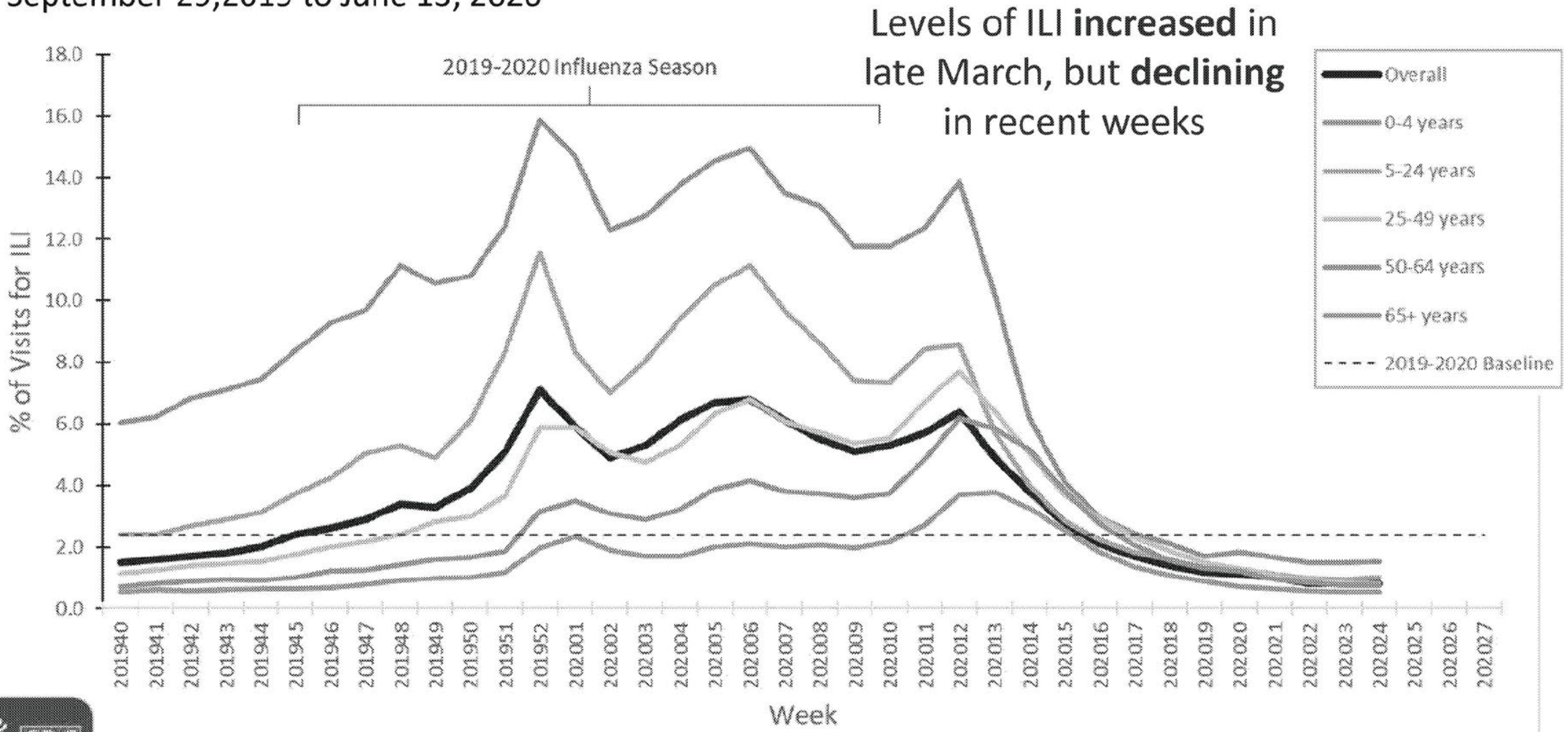
World Health Organization[8]	Royal College of Paediatrics and Child Health (United Kingdom)[7]	Centers for Disease Control and Prevention (United States)[9]
Children and adolescents 0-19 y of age with fever >3 d AND 2 of the following: 1. Rash or bilateral nonpurulent conjunctivitis or mucocutaneous inflammation signs (oral, hands, or feet) 2. Hypotension or shock 3. Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated troponin/NT-proBNP) 4. Evidence of coagulopathy (by PT, APTT, elevated D-dimers) 5. Acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain) AND Elevated markers of inflammation such as ESR, CRP, or procalcitonin. AND No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes. AND Evidence of COVID-19 (RT-PCR, antigen test, or serology positive), or likely contact with patients with COVID-19 Consider this syndrome in children with features of typical or atypical Kawasaki disease or toxic shock syndrome	A child presenting with persistent fever, inflammation (neutrophilia, elevated CRP, and lymphopenia) and evidence of single or multiorgan dysfunction (shock, cardiac, respiratory, kidney, gastrointestinal, or neurological disorder) with additional features (see listed in eAppendix in Supplement 2). This may include children fulfilling full or partial criteria for Kawasaki disease[a] Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus (waiting for results of these investigations should not delay seeking expert advice) SARS-CoV-2 PCR test results may be positive or negative	An individual aged <21 y presenting with fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multisystem (>2) organ involvement (cardiac, kidney, respiratory, hematologic, gastrointestinal, dermatologic, or neurological) Fever >38.0 °C for ≥24 h or report of subjective fever lasting ≥24 h Laboratory evidence including, but not limited to, ≥1 of the following: an elevated CRP level, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, lactic acid dehydrogenase, or IL-6; elevated neutrophils; reduced lymphocytes; and low albumin AND No alternative plausible diagnoses AND Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 wk prior to the onset of symptoms Additional comments Some individuals may fulfill full or partial criteria for Kawasaki disease but should be reported if they meet the case definition for MIS-C Consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection

Abbreviations: APTT, activated partial thromboplastin time; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; ECHO, echocardiography; ESR, erythrocyte sedimentation rate; MIS-C, multisystem inflammatory syndrome in children; NT-proBNP, N-terminal pro–B-type natriuretic peptide; PT, prothrombin time; RT-PCR, reverse transcriptase–polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a] Criteria for Kawasaki disease include persistent fever and 4 of 5 principal clinical features: erythema and cracking of lips, strawberry tongue, and/or erythema of oral and pharyngeal mucosa; bilateral bulbar conjunctival injection without exudate; rash (maculopapular, diffuse erythroderma); erythema and edema of the hands and feet and/or periungual desquamation; and cervical lymphadenopathy.

Percent of Visits for ILI reported to ILINet

September 29,2019 to June 13, 2020



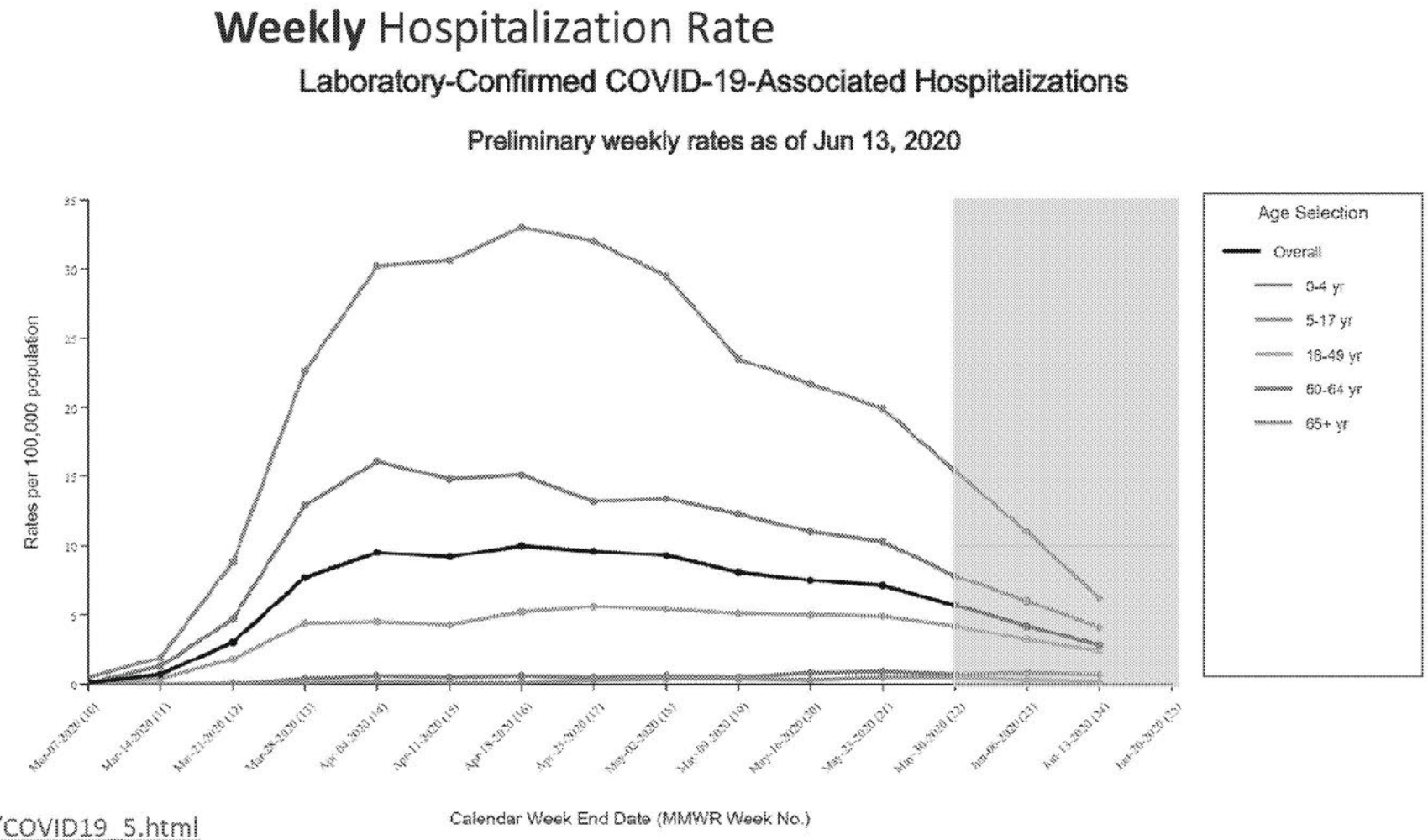
https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covidview/index.html

ILI = Influenza-like Illness

COVID-NET:
Hospitalization Surveillance from 14 States

March 7 to June 13, 2020

Weekly hospitalization rate demonstrates a slight decline in rates



https://gis.cdc.gov/grasp/COVIDNet/COVID19_5.html

Health Care Personnel (HCP)

PROJECT COVERED

- Serial symptom questionnaires, SARS-CoV-2 serology (IgG) and self-collected nasal swabs (PCR) over a 12-week period in 4 populations
  - Emergency physicians likely to be performing endotracheal intubations
  - Emergency physicians unlikely to be performing endotracheal intubations
  - Emergency department nurses
  - Emergency department non-clinical staff unlikely to have patient contact
- Study sites were selected to be high-volume academic emergency departments primarily from the following two national ED-based research networks:
  - EMERGEncy IDNet – This CDC-funded 12-site ED-based emerging infectious disease network was created for surveillance and research of emerging infectious diseases (PI: David Talan, MD); and
  - National Emergency Airway Registry (NEAR) – This 26-site network is the largest ED-based research network focused on a multicenter observational airway management studies (PI: Calvin Brown III, MD).

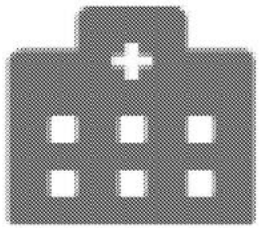
CDC

https://medicine.uiowa.edu/content/study-overview

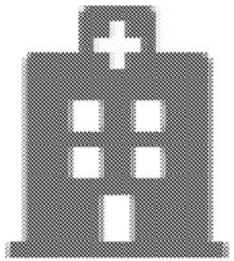
Health Care Personnel and Transmission

- First reported case of community transmission in U.S. in Solano County, CA

Patient with 4-day hospitalization at Hospital A



Due to clinical deterioration, patient transferred to Hospital B



Several days later, patient had COVID-19 test positive

<u>While at Hospital A</u>:
121 HCP exposed,
Three tested positive

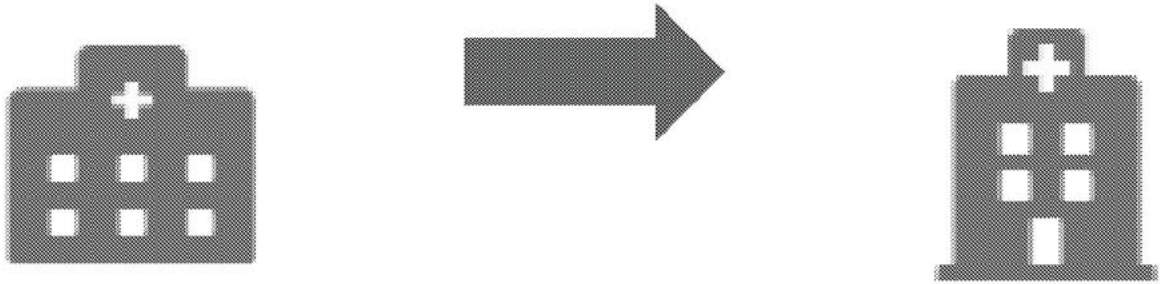
<u>While at Hospital B</u>:
146 HCP exposed,
None tested positive

MMWR April 17, 2020 https://www.cdc.gov/mmwr/volumes/69/wr/mm6915e5.htm?s_cid=mm6915e5_w

Health Care Personnel and Transmission

- First reported case of community transmission in U.S. in Solano County, CA

Multiple aerosol-generating procedures including BiPAP and intubation, with no PPE



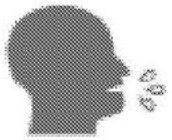
Patient remained on a closed system ventilator from arrival to receiving a positive test result

<u>While at Hospital A</u>:
121 HCP exposed,
Three tested positive

<u>While at Hospital B</u>:
146 HCP exposed,
None tested positive

MMWR April 17, 2020 https://www.cdc.gov/mmwr/volumes/69/wr/mm6915e5.htm?s_cid=mm6915e5_w

Health Care Personnel and Transmission



HCP with lab-confirmed COVID-19 associated with:

Performing physical examination

Exposure to the patient during nebulizer treatments

Longer duration exposure to the patient

Of the three HCP with lab-confirmed COVID:

One present for 3 hours while patient on BiPAP

One participated with BiPAP placement and intubation

One reported close contact with patient for 2 hours but not during aerosol generating procedures

MMWR April 17, 2020 https://www.cdc.gov/mmwr/volumes/69/wr/mm6915e5.htm?s_cid=mm6915e5_w

Pregnant Women

122,653 lab confirmed U.S. COVID-19 patients
Information on health conditions available for 7,162
February 12–March 28, 2020

4470 with no underlying conditions
311 (7%) with unknown status
305 (**7**%) hospitalized (not ICU)
99 (2%) hospitalized (ICU)
3755 (84%) not hospitalized

143 pregnant women
36 (35%) with unknown status
31 (**22**%) hospitalized (not ICU)
4 (3%) hospitalized (ICU)
72 (50%) not hospitalized

MMWR April 3, 2020 https://www.cdc.gov/mmwr/volumes/69/wr/mm6913e2.htm?s_cid=mm6913e2_w

Pregnant Women: Sweden

- Women aged 20-45 years in Intensive Care Registry from March 19-April 20
- Incidence of ICU admission with SARS-COV-2:
  - **14.4**/100,000 for pregnant/post-partum women
  - **2.5**/100,000 for non-pregnant women of same age

  ] Relative Risk: **5.39**
- Incidence of mechanical ventilation in ICU with SARS-CoV-2:
  - **7.4**/100,000 for pregnant/post-partum women
  - **1.8**/100,000 for non-pregnant women of same page

  ] Relative Risk: **4.00**

Collin, J et al. Acta Obstet Gynecol Scand 2020

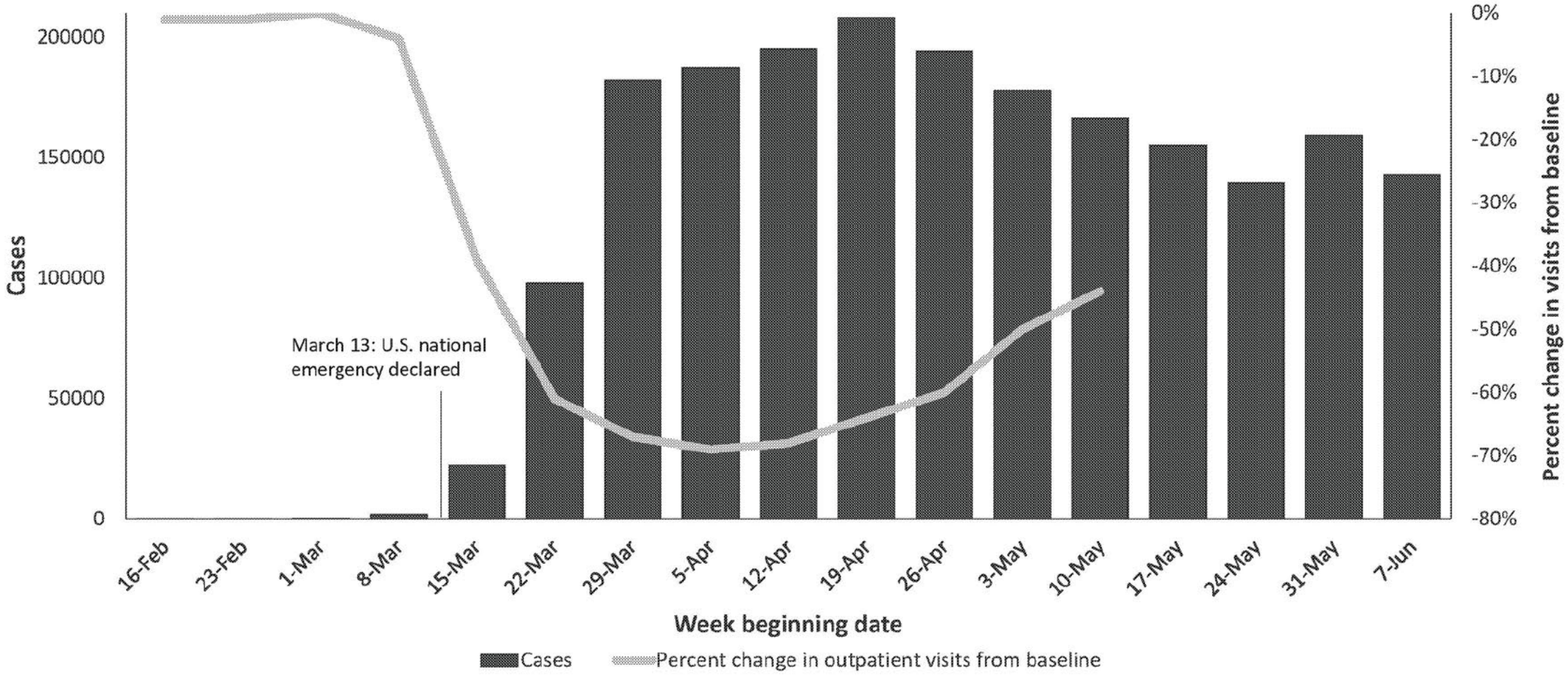
Maintaining and Strengthening Childhood Vaccination During the COVID-19 Pandemic

Melinda Wharton, MD, MPH
Director, Immunization Services Division

Advisory Committee on Immunization Practices
June 22, 2020

Substantial disruptions to outpatient medical care during COVID-19 pandemic

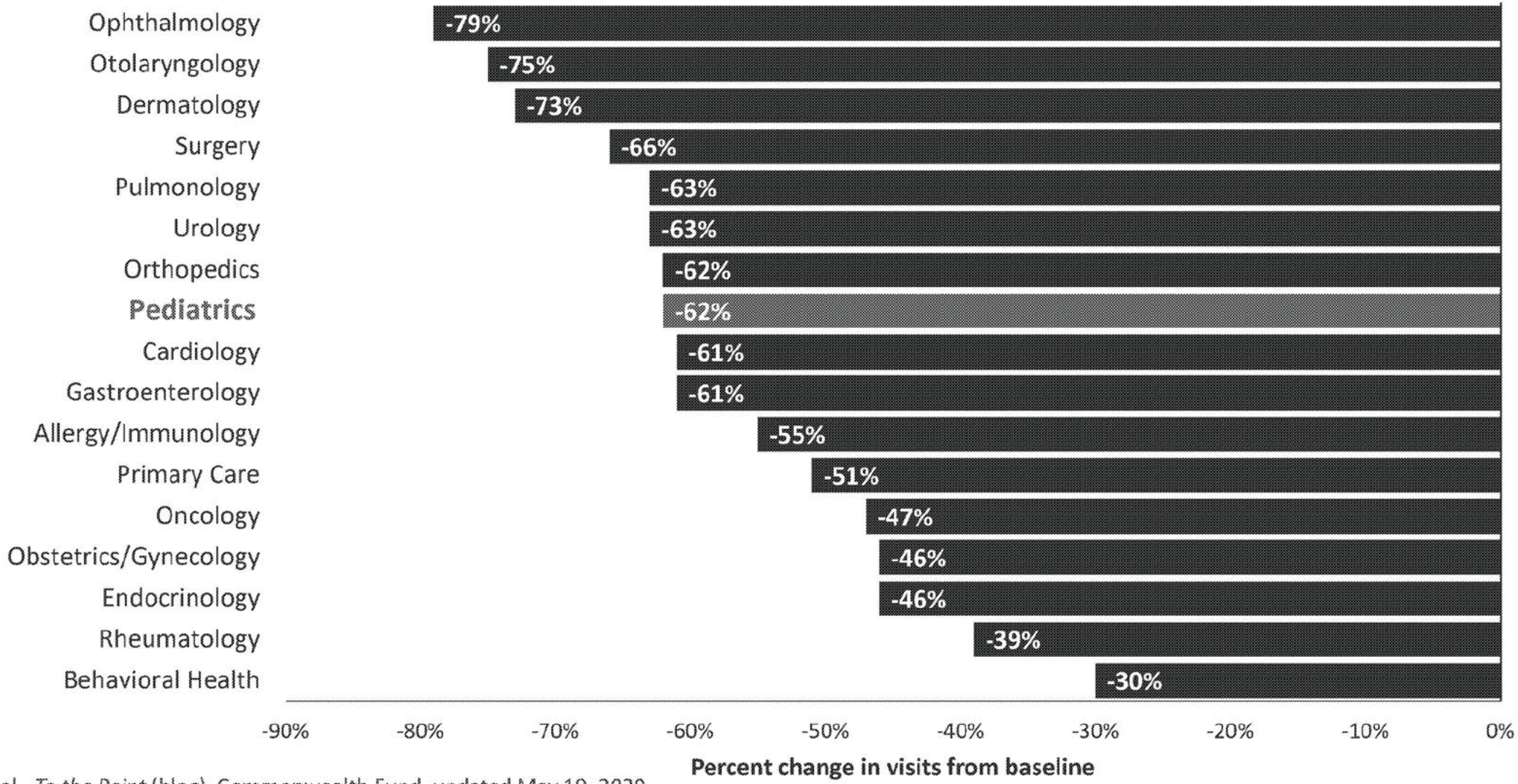
As number of COVID-19 cases increased and stay-at-home orders implemented, nearly 70% reduction in outpatient visits before starting to rebound



https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/cases-in-us.html; Ateev, M. et al., *To the Point* (blog), Commonwealth Fund, updated May 19, 2020.

Pediatrics among the hardest-hit specialties

62% reduction in pediatric outpatient visits by April 5th

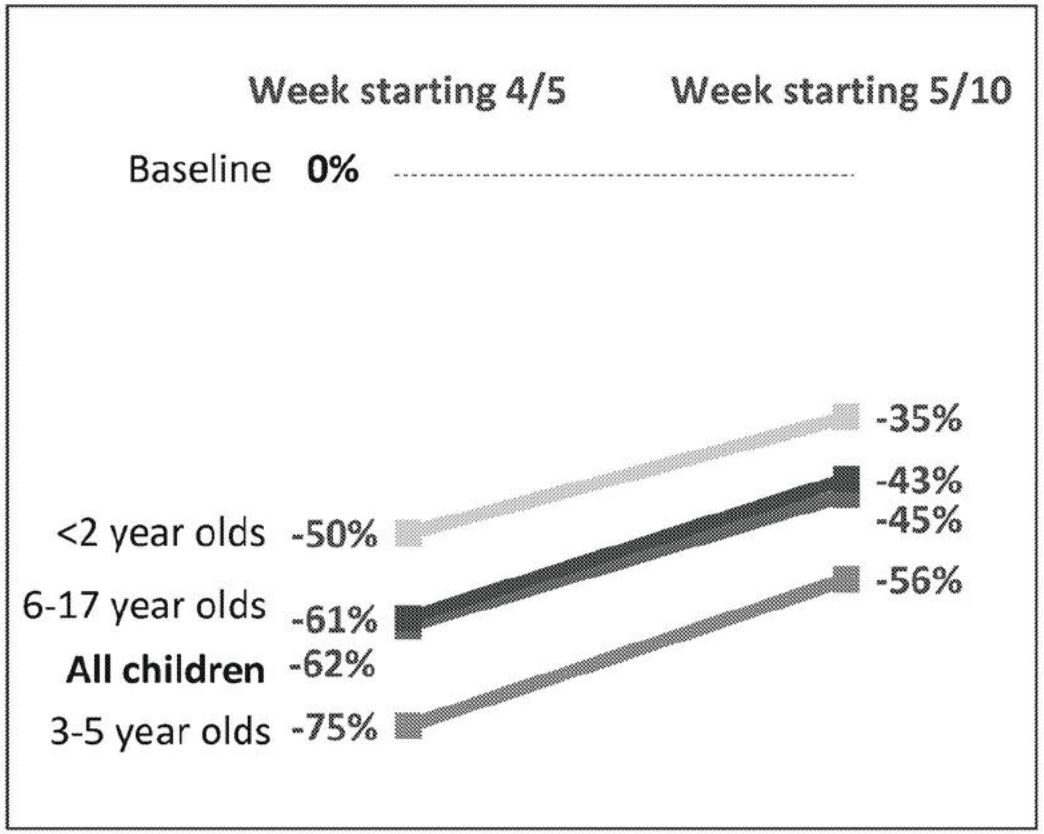


Ateev, M. et al., *To the Point* (blog), Commonwealth Fund, updated May 19, 2020.

Increases in outpatient visits across all pediatric age groups in May compared to April

- Pediatric outpatient healthcare utilization improved in May, but remains well below baseline

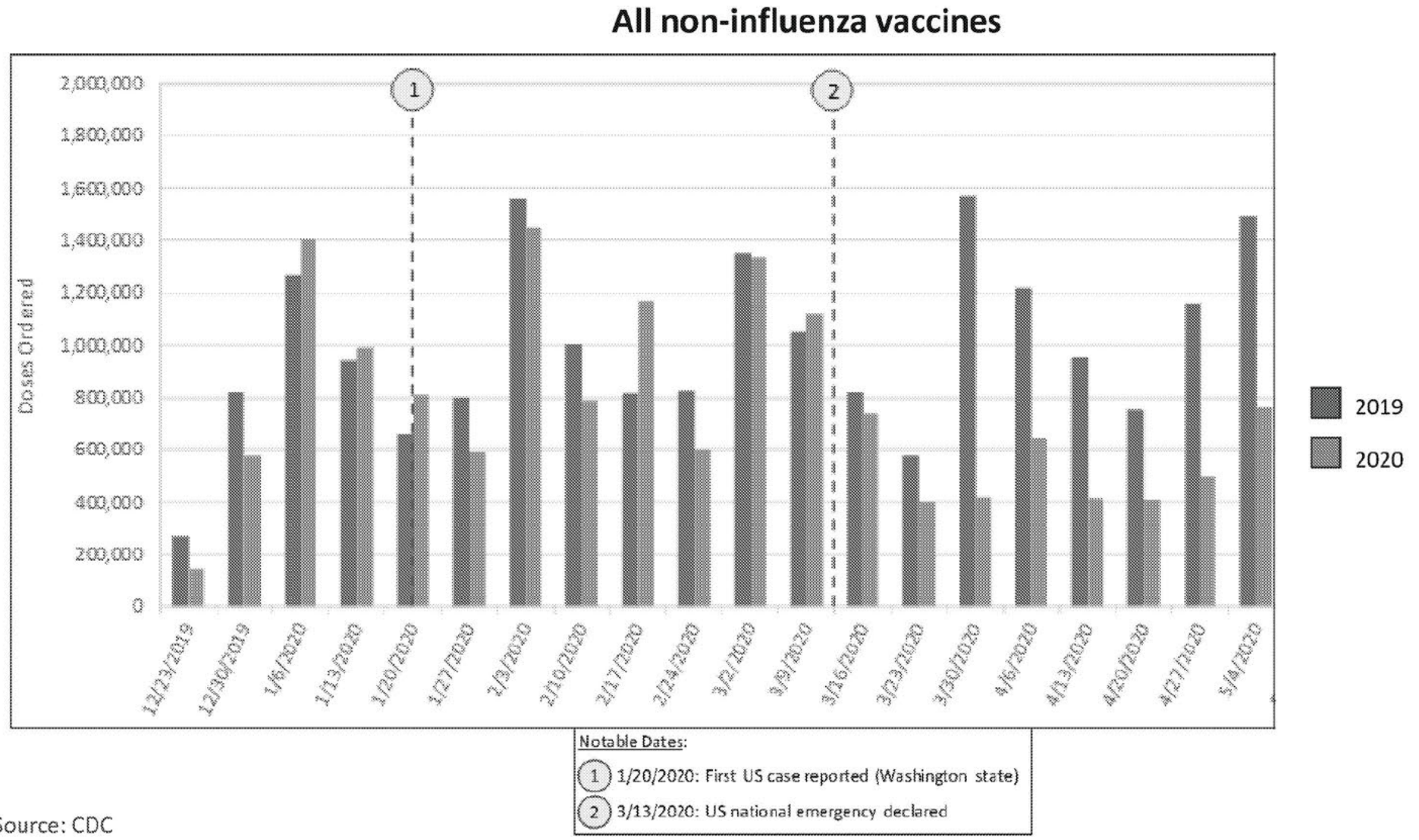
- By May 10, pediatric outpatient visits:
  - Highest in children <2 years
  - Lowest in 3-5 year olds



Ateev, M. et al., *To the Point* (blog), Commonwealth Fund, updated May 19, 2020.

COVID-19 pandemic and disruptions to routine childhood vaccination

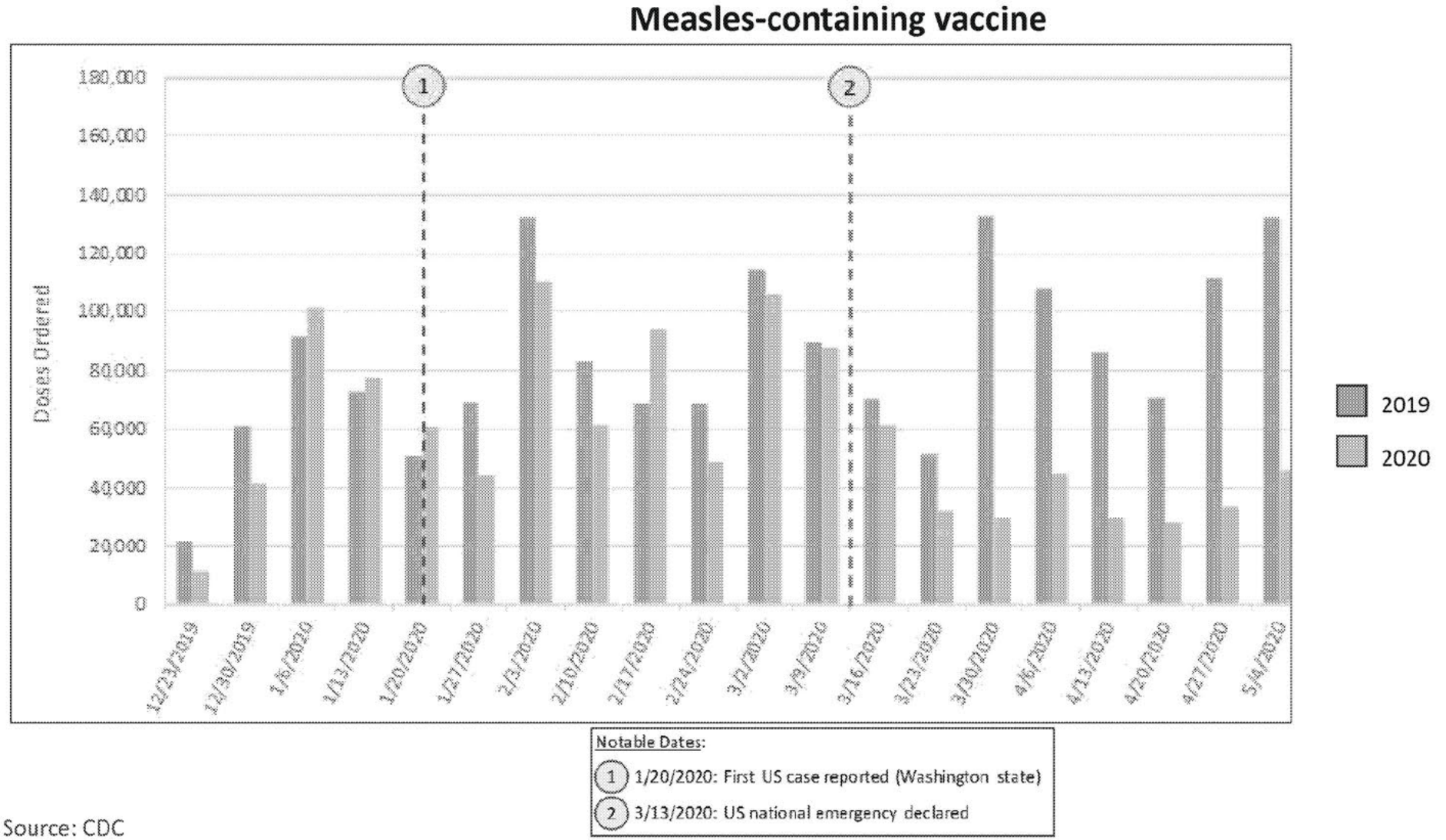
Weekly decreases in Vaccines for Children program provider orders for pediatric vaccines – United States, December 23, 2019-May 10, 2020



Source: CDC

COVID-19 pandemic and disruptions to routine childhood vaccination

Weekly decreases in Vaccines for Children program provider orders for pediatric vaccines – United States, December 23, 2019-May 10, 2020



Source: CDC

Primary care practices under stress

Economic struggles, reduced staffing, and low patient volume may all affect preventive care services

The Washington Post

Small medical practices struggle to survive amid coronavirus pandemic

Among a survey of primary care providers in early May

- **77%** report severe or close to severe stress
- **70%** report a >50% decrease in patient volume
- **40%** had laid off staff
- **40%** reporting absences due to illnesses/self-quarantine

Primary care collaborative survey, May 1-4, 2020 (n=773)

https://www.washingtonpost.com/health/small-doctor-practices-struggle-to-survive-amid-coronavirus-pandemic/2020/05/14/328984e6-9390-11ea-91d7-cf4423d47683_story.html
https://www.pcpcc.org/2020/05/06/primary-care-covid-19-week-8-survey

CDC activities with immunization programs and partners to support routine childhood vaccination

- **Monitor** vaccination service delivery to inform targeted interventions

- **Support**
  - Providers through the development of guidance and support materials
  - Catch-up vaccination through reminder/recall systems
  - Access to vaccines by identifying gaps in VFC provider network and increasing funding for VFC vaccine purchase and operations
  - Identification of policy interventions to support healthcare providers

- **Communicate**
  - Importance of vaccination to parents, providers, and partners
  - Information on VFC program to families

- **Plan** back-to-school vaccination activities during the summer and influenza vaccination in the fall

Supporting healthcare providers to deliver childhood vaccines

- Ensure providers are aware of available financial support through the Provider Relief Fund and how to apply for funding
  - As of June 9, now available to Medicaid and CHIP providers

- Promote catch-up vaccination through dissemination of information on best practices for reminder/recall, including refocusing of immunization program quality improvement activities

- Disseminate guidance on the safe delivery of vaccines during the COVID-19 pandemic

Provider relief fund portal: https://cares.linkhealth.com/#/
IQIP: https://www.cdc.gov/vaccines/programs/iqip/at-a-glance.html

CDC Interim Guidance for Immunization Services During COVID-19 Pandemic

- Vaccination is an essential medical service for all children and adolescents, ideally in the medical home
- Administer all due or overdue vaccines according to routine immunization schedule during the same visit
- Implement strategies to catch patients up on vaccines
  - Start with newborns, infants and children up to age 24 months, young children, and extending through adolescence
- Includes guidance for the safe delivery of vaccines (e.g., use of personal protective equipment, physical distancing)

https://www.cdc.gov/vaccines/pandemic-guidance/index.html

Communicating the importance of well-child and vaccination visits

- Encourage parents to return for well-child visits
- Use reminder/recall systems to help children get up to date as quickly as possible
- Discuss the safety protocols put in place to ensure patients can be safely vaccinated

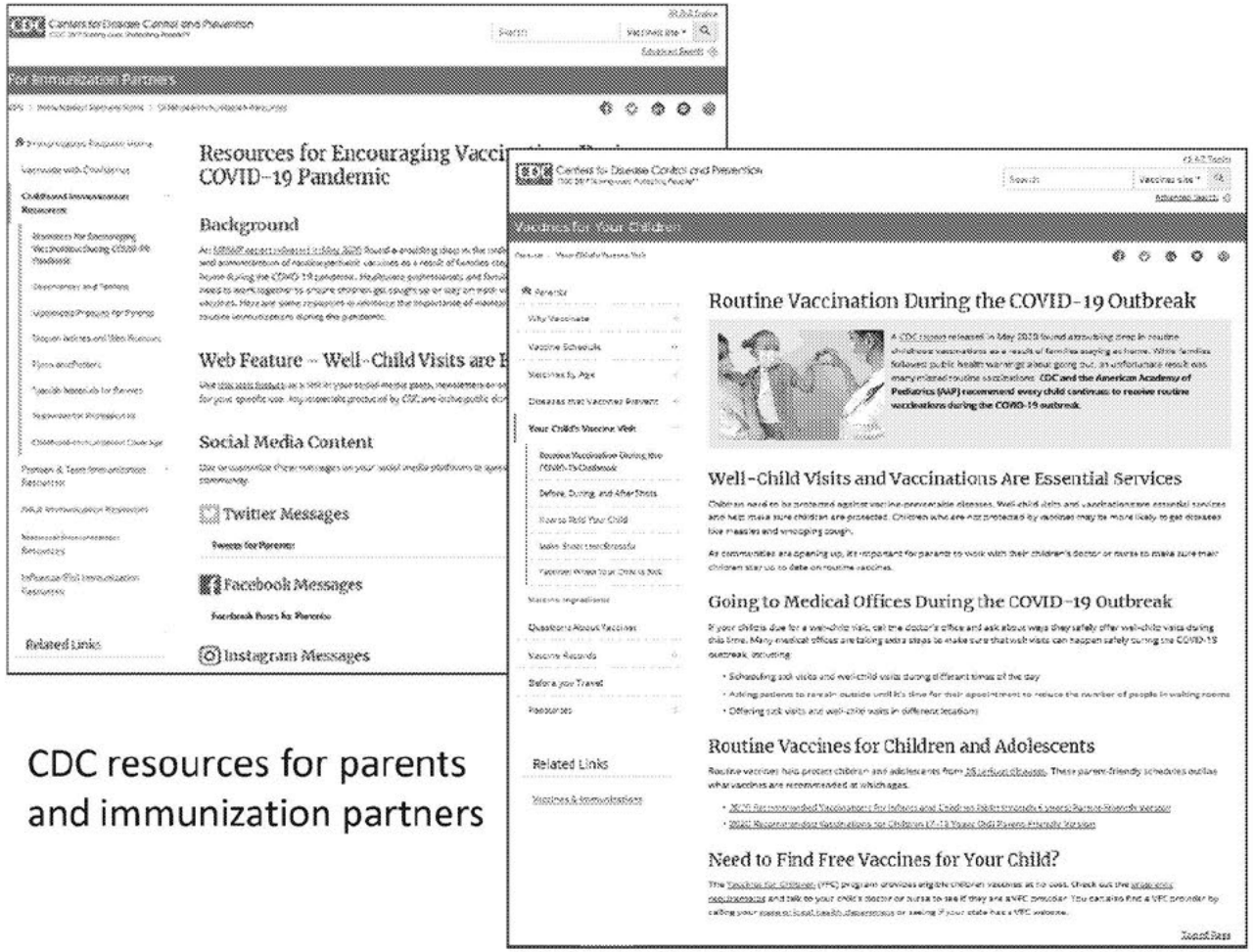
https://www.cdc.gov/vaccines/programs/vfc/index.html

Promoting awareness of Vaccines for Children (VFC) program among parents

- Prior to the pandemic, ~50% of U.S. children eligible to receive free vaccines through VFC
  - More may be eligible now due to recent loss insurance or increased economic hardship
- Parents of recently-eligible children may not be aware of VFC
- Partners and providers can help improve vaccine access by increasing awareness and enrollment in VFC program

https://www.cdc.gov/vaccines/programs/vfc/index.html

Resources for communicating with parents about routine vaccination during the COVID-19 pandemic



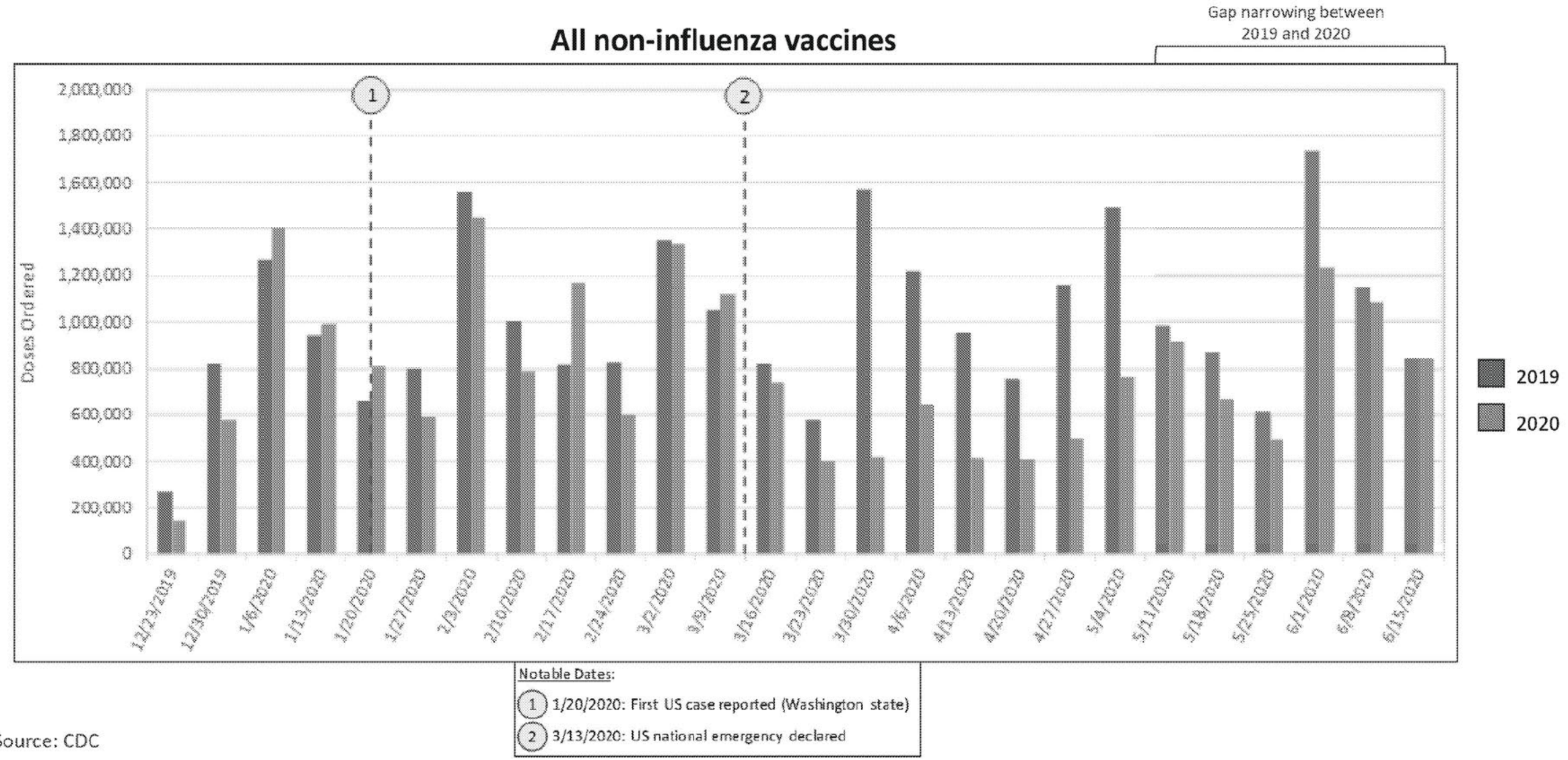
CDC resources for parents and immunization partners

AAP's #CallYourPediatrician campaign

https://www.cdc.gov/vaccines/parents/visit/vaccination-during-COVID-19.html; https://www.cdc.gov/vaccines/partners/childhood/stayingontrack.html
https://www.aap.org/en-us/about-the-aap/aap-press-room/campaigns/call-your-pediatrician/Pages/default.aspx

Signs of recovery in routine childhood vaccination

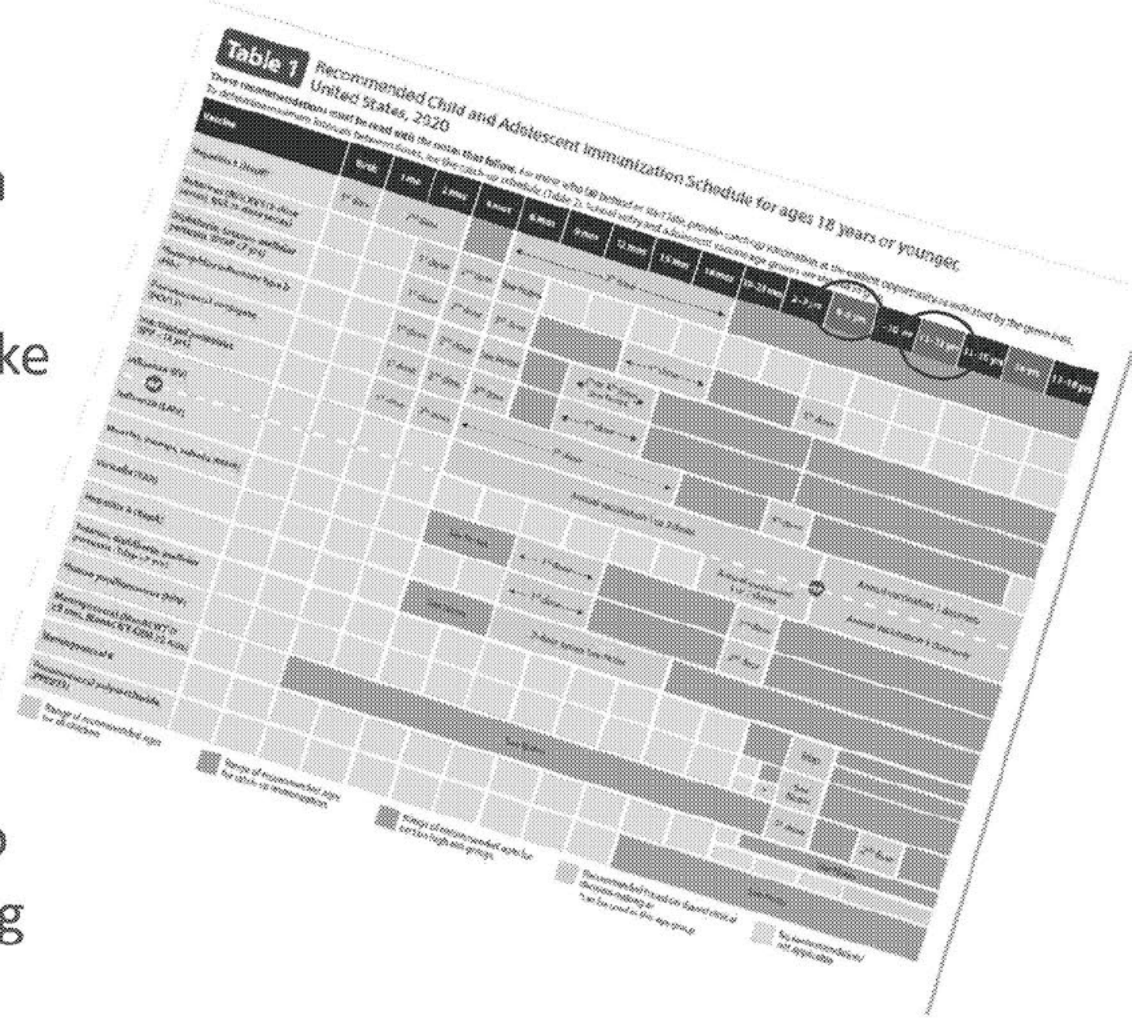
Weekly Vaccines for Children program provider orders for pediatric vaccines – United States, December 23, 2019-June 21, 2020



Source: CDC

School vaccination requirements provide a critical checkpoint for children's vaccination status

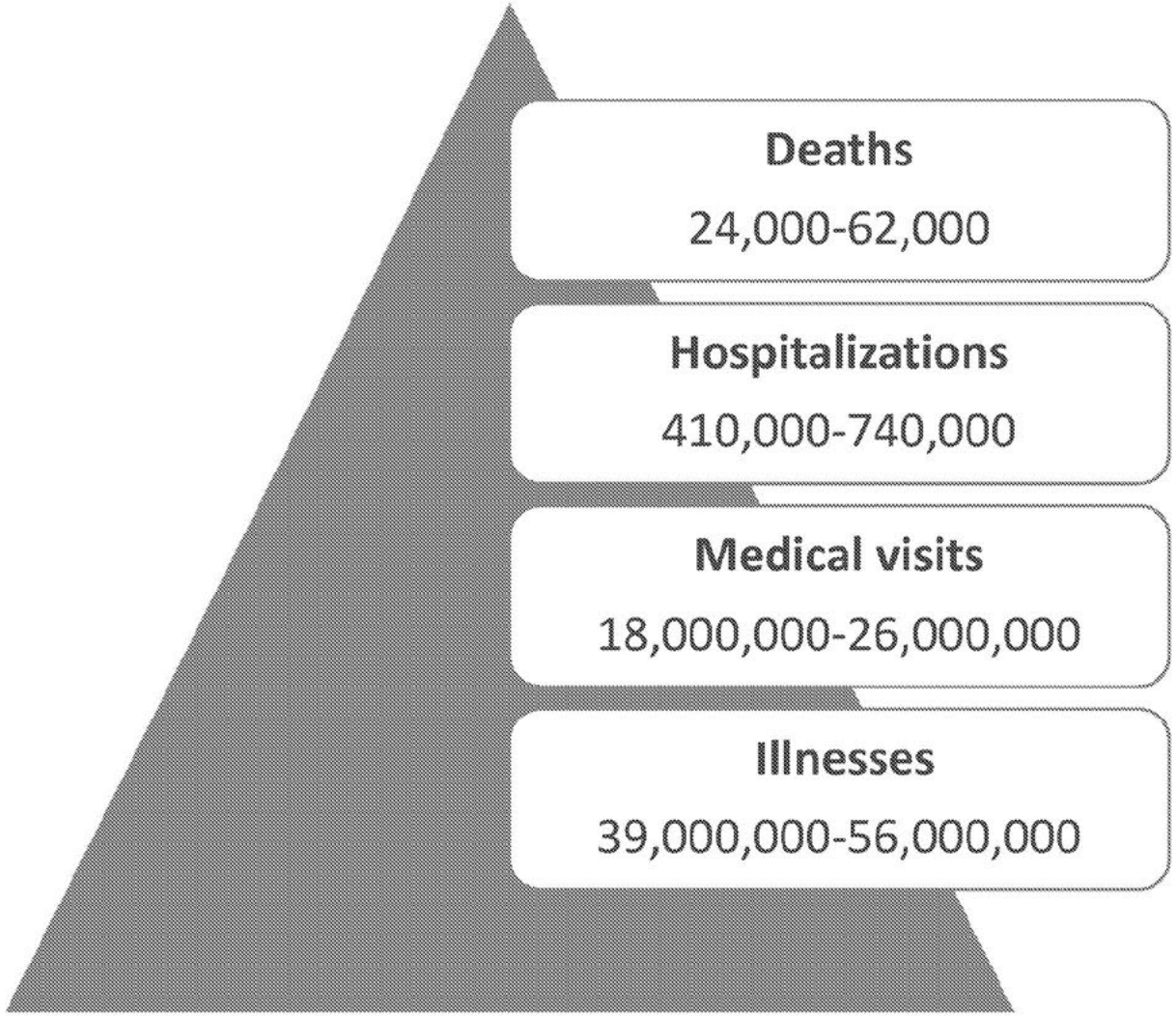
- Many children need to receive vaccines during the summer to stay up-to-date and comply with school vaccination requirements
- Important that back-to-school vaccine clinics take place this summer, to provide children an opportunity for vaccination
- If circumstances do not allow all children to receive needed vaccines, jurisdictions should consider extending provisional enrollment or grace periods to give children time to come into compliance without being penalized or resorting to an exemption



Influenza Vaccination, 2020-2021 Season

Summary of 2019-2020 influenza season

- Two consecutive waves
  - 1st wave predominantly influenza B/Victoria viruses
  - 2nd wave driven by influenza A (H1N1)
- Pediatric deaths reported to CDC for the 2019-2020 season: **185***



*As of June 13, 2020

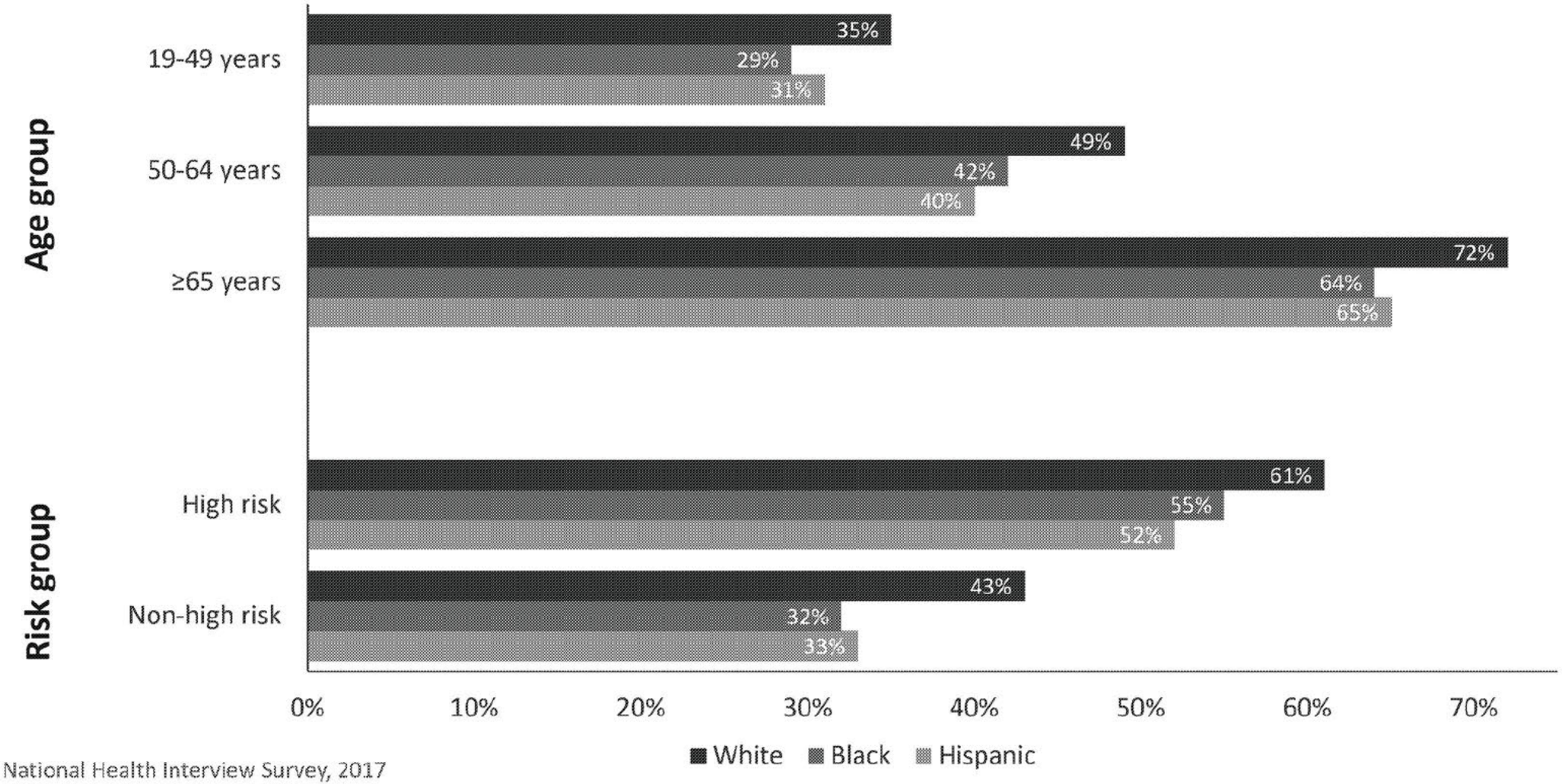
https://www.cdc.gov/flu/about/burden/preliminary-in-season-estimates.htm

Increasing seasonal influenza vaccine coverage to decrease healthcare utilization, 2020-2021

- We expect SARS-CoV-2 to continue to circulate in the fall
- Increasing influenza vaccine coverage will decrease stress on the healthcare system
  - Decrease doctor visits and hospitalizations
  - Decrease individuals needing diagnostic testing
- Focus on adults at higher risk from COVID-19
  - Staff and residents of long-term care facilities
  - Adults with underlying illnesses and African-Americans
  - Adults who are part of critical infrastructure

Racial and ethnic disparities in influenza coverage

Reducing existing disparities will be important to protect minority and at-risk populations for both influenza and future COVID-19 vaccines

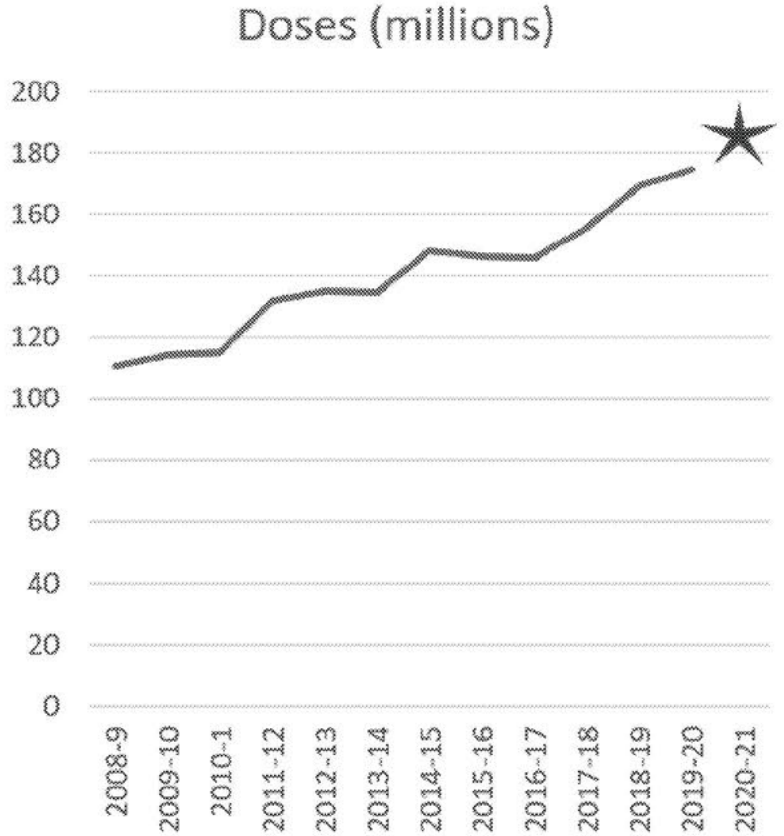


Source: National Health Interview Survey, 2017

Influenza vaccination planning for 2020-2021 season

- Maximize available vaccine supply
  - Expect >180M doses for U.S. market
- Operational considerations
  - Outreach to those at higher risk
  - Planning for potential need for social distancing
  - Extending influenza vaccination season (September through December or later)
- Enhancing communication
  - Align with COVID-19 messaging
  - Messaging for African-American and Hispanic communities

Influenza Vaccine Doses Distributed By Season, 2008-9 to 2019-20, and Projected, 2020-21

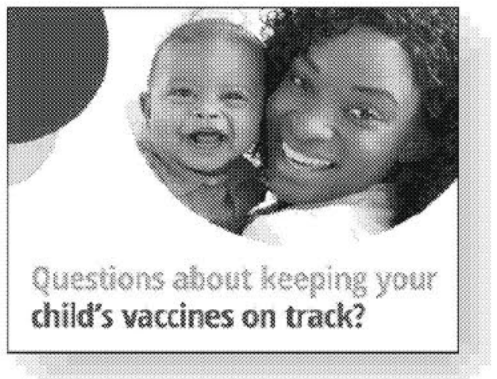


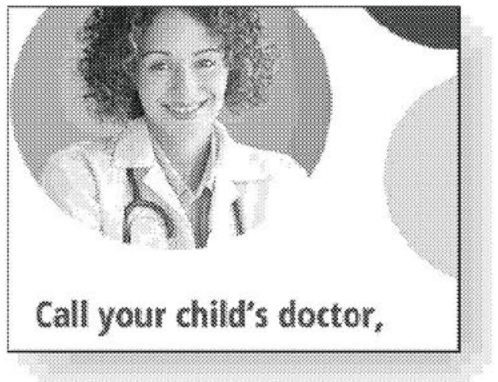
Supplemental Resources for Public Sector Influenza Vaccination for the 2020-2021 Influenza Season

- Two Components
  - Cooperative Agreement with 64 Immunization Program Awardees (2020-2021; $140 million)
  - Supplemental influenza vaccine doses (2020; 7.1 million doses)
- Funding to support operational costs associated with planning and implementation of expanded influenza vaccination program extending into December or later
- Supplemental vaccine doses to be allocated among the awardees
  - Strong recommendation for awardee partnerships with Community Health Centers (CHCs)
  - Facilitating connections with CHCs through CDC relationship with the National Association of Community Health Centers

Conclusions

- Substantial disruptions to routine childhood vaccination services have occurred during the COVID-19 pandemic, though signs of recovery are now being seen
- Catch up for childhood vaccination needs to be undertaken now so clinical capacity can be directed to back-to-school and influenza vaccination in the summer and fall
- Solutions to existing disparities in influenza vaccination should be sought and applied to COVID-19 vaccination
- Immunization programs, partners, and providers can help get childhood vaccination back on track by supporting catch-up vaccination efforts and communicating with parents about safe vaccination during the pandemic



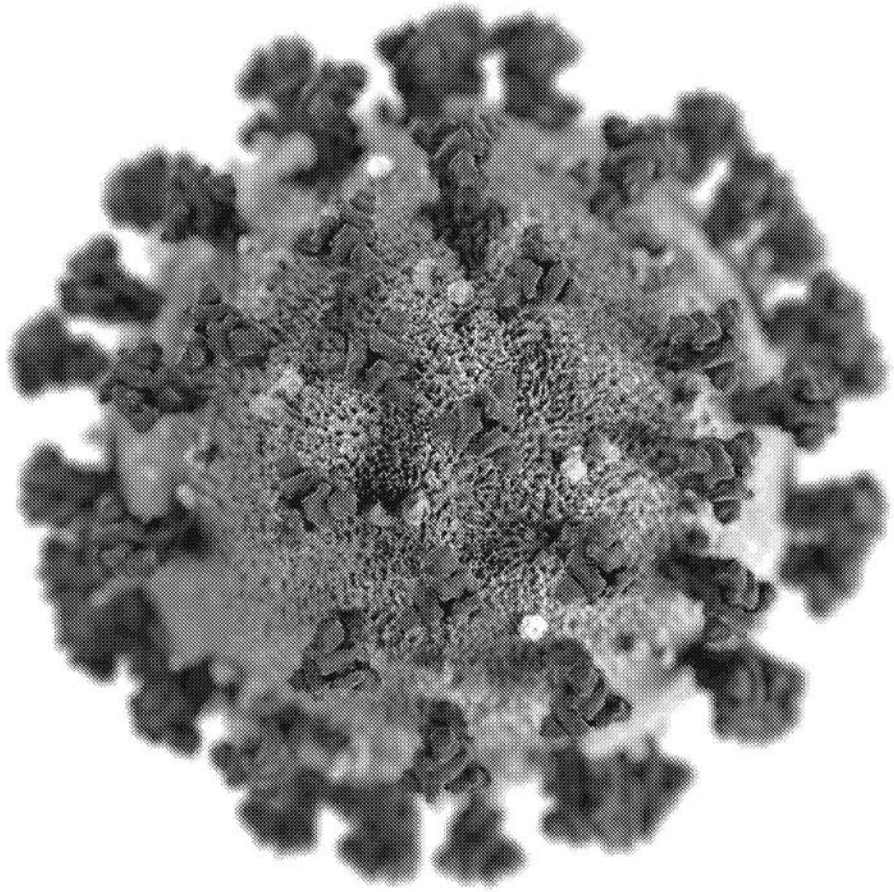


Thank you

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

COVID 19
CORONAVIRUS DISEASE

ACIP COVID-19 Vaccines Work Group



Dr. Beth Bell, Work Group Chair

June 24, 2020

COVID-19 vaccination in the United States

Need for equitable access to safe and effective vaccines and evidenbased vaccination policy

- Preparing for implementation of **safe and effective** COVID-19 vaccines is a critical next step to protect the public and reduce the impact of COVID-19 on society

- Increased risk of severe COVID-19 in vulnerable populations and racial/ethnic minority groups highlight the need for:
  - **Diverse representation** in clinical trials
  - **Equitable access** to vaccines, regardless of vaccination strategy or priority groups

- ACIP COVID-19 vaccines work group established to help inform **evidence-based approaches** to COVID-19 vaccination policy

ACIP COVID-19 Vaccines Work Group

- **Established**: April 2020

- **Role:** Collection, analysis, and preparation of information related to COVID-19 vaccines for presentation, discussion, deliberation, and vote by the ACIP, using an open and transparent process.

- **Membership:** 41 members, including ACIP voting members, liaisons, *ex-officios,* and expert consultants

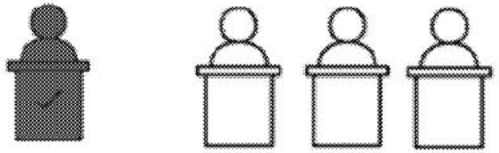
Expertise areas of COVID-19 Work Group members

- Epidemiology
- Vaccine safety
- Vaccinology
- Infectious diseases
- Immunology
- General medicine
- Geriatrics
- Pediatrics
- Obstetrics
- Immunocompromised hosts
- Vaccine administration/delivery
- Public health/surveillance
- Ethics
- Health equity
- Communications
- Emergency preparedness

COVID-19 Work Group composition

4 ACIP voting members

Chair



Beth Bell

Consultants

- Vaccinology
- Microbiology/Immunology
- Safety
- Ethics
- Health equity

Liaison representatives

AAFP · American Academy of Pediatrics · ACOG The American College of Obstetricians and Gynecologists · ACP · AGS Geriatrics Healthcare Professionals · AIM · AMA · ANA · APhA · astho · CSTE · IDSA · NACCHO

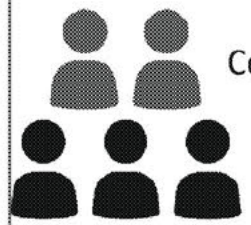
National Advisory Committee on Immunization

National Foundation for Infectious Diseases · National Medical Association · SHEA The Society for Healthcare Epidemiology of America

Ex-officio/government members

NIH · FDA · BARDA · CMS · Indian Health Service PHS · 1955

CDC participants



Co-leads: Kathleen Dooling
Sarah Mbaeyi

CDC experts

ACIP COVID-19 Work Group Terms of Reference

- **Policy topic under consideration:** Use of COVID-19 vaccines in the U.S. population.

- **Work Group activities:**
  - Review safety and immunogenicity data for COVID-19 vaccines
  - Review the epidemiology of COVID-19 disease and identify potential target populations for vaccination
  - Discuss potential vaccine prioritization plans in the event of insufficient early COVID-19 vaccine supply
  - Identify areas where additional data are needed to inform COVID-19 vaccine recommendations
  - Develop COVID-19 vaccine policy options that ACIP may consider for recommendation

- **Vaccine safety technical subgroup:** advises the main Work Group on the safety of COVID-19 vaccines, both during clinical development and post-licensure

Decision-making in the context of many unknowns and uncertainties

- Stand for the principles of evidence-based decision-making, equity, and transparency in the process
- Tension between the need to provide guidance and the limited available science base
- Strive to develop a robust understanding of what is known; make sure diverse voices are heard
- Make decisions based on the knowns at the time
- Recognize from the start that revisions will be needed as more information becomes available
- Advocate for implementation of the essential strategies and systems to ensure that pivotal data for decision-making get collected
- Promote a feedback loop to evaluate the impact of recommendations and commit to revising accordingly

Today's agenda

- **COVID-19 vaccine development**
  - Dr. Matthew Hepburn (Lead, Operation Warp Speed Vaccines)

- **Landscape of COVID-19 vaccines in development**
  - Dr. Kathy Neuzil (University of Maryland)

- **COVID-19 vaccine prioritization considerations**
  - Dr. Sarah Mbaeyi (CDC)

- **Work Group considerations and next steps**
  - Dr. Kathleen Dooling (CDC)

Work group members

ACIP members

- Beth Bell (chair)
- Grace Lee
- Jose Romero
- Keipp Talbot

Ex-officio/government members

- FDA: Doran Fink, Rachel Zhang
- NIH: Chris Roberts
- IHS: Thomas Weiser, Jillian Doss-Walker
- DOD: Eric Deussing
- CMS: Jeff Kelman
- BARDA: Christine Oshansky

CDC Co-leads

- Kathleen Dooling
- Sarah Mbaeyi

Liaisons

- AAFP: Jonathan Temte
- AAP: Sean O'Leary
- ACOG: Denise Jamieson (primary), Laura Riley (alternate)
- ACP: Jason Goldman
- AGS: Ken Schmader
- AIM: Rob Shechter (primary), Jane Zucker (alternate)
- AMA: Sandra Fryhofer
- ANA: Kendra McMillan (primary), Ruth Francis (alternate)
- APhA: Michael Hogue
- ASTHO: Marcus Plescia
- CSTE: Susan Lett
- IDSA: Jeff Duchin (primary), Carol Baker (alternate)

Liaisons, cont'd

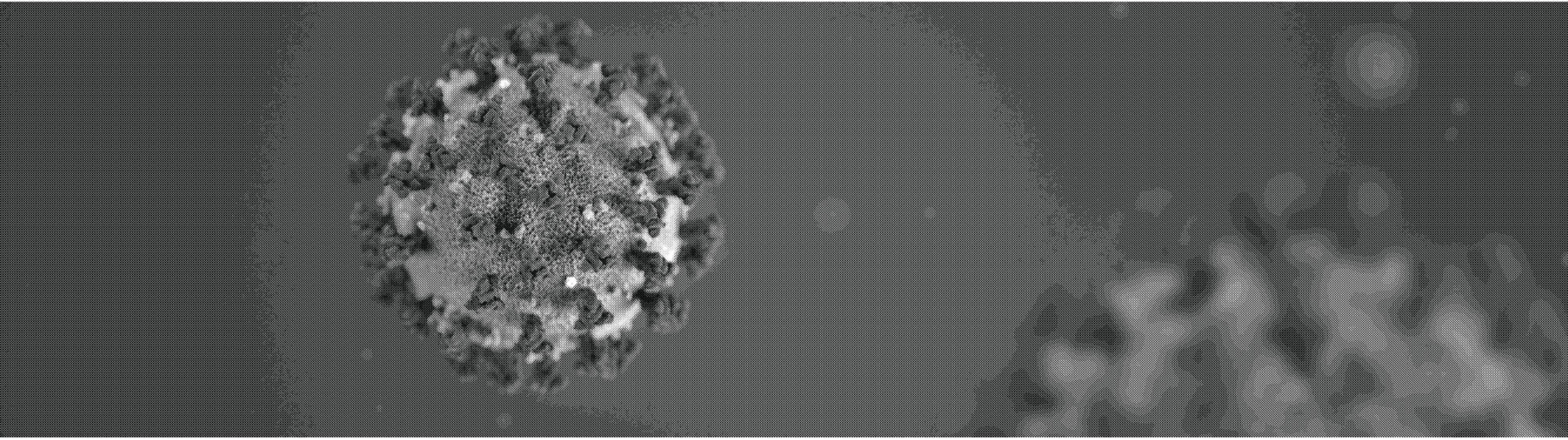
- NACCHO: Matt Zahn (primary), Jeff Duchin (alternate)
- NACI: Matthew Tunis (primary), Althea House (alternate)
- NFID: Bill Schaffner (primary), Marla Dalton (alternate)
- NMA: Oliver Brooks
- SHEA: David Weber

Consultants

- Ed Belongia (safety)
- Matthew Daley (safety)
- Kathy Kinlaw (ethics)
- Dayna Matthew (health equity)
- Kathleen Neuzil (vaccinology)
- Stanley Perlman (microbiology/immunology)

CDC participants

- Doug Campos-Outcalt
- Thomas Clark
- Amanda Cohn
- Jonathan Duffy
- Anthony Fiore
- Mark Freedman
- Sue Gerber
- Jack Gersten
- Sam Graitcer
- Lisa Grohskopf
- Rita Helfand
- Terri Hyde
- Tara Jatlaoui
- Cynthia Jorgensen
- Jessica MacNeil
- Rebecca Morgan
- Sara Oliver
- Anita Patel
- Stephanie Schrag
- Tom Shimabukuro
- Nathalie Thornburg
- Jennifer Verani
- Cindy Weinbaum
- Yon Yu
- Jane Zucker



For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

Thank you!

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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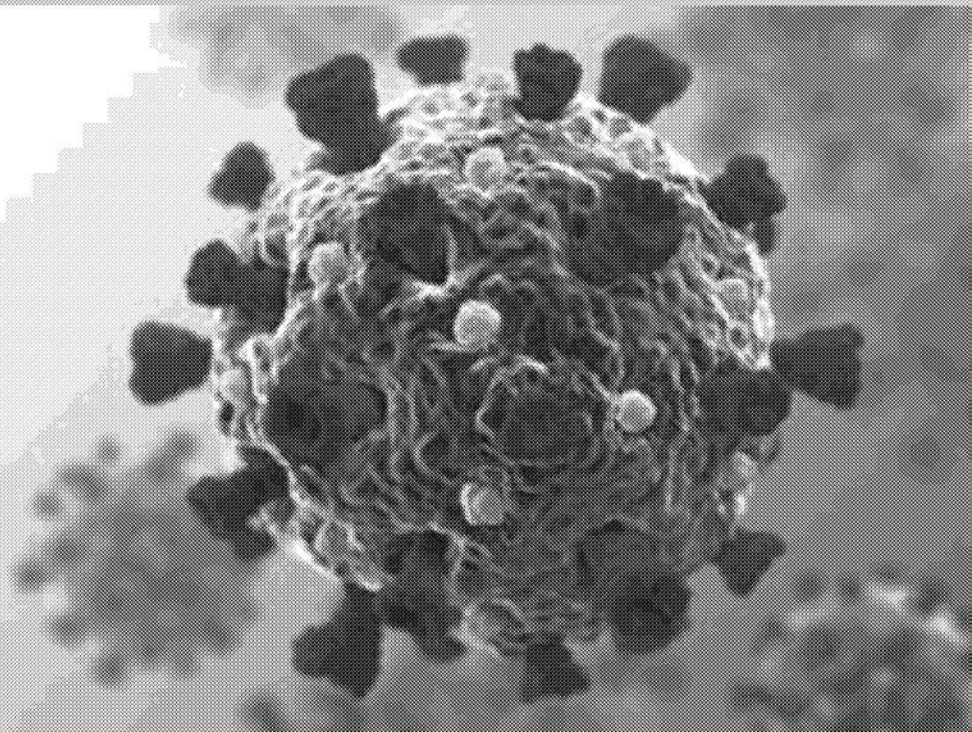
CENTER FOR VACCINE DEVELOPMENT AND GLOBAL HEALTH

CORONAVIRUS Vaccines

Kathleen Neuzil, MD, MPH

24 June 2020



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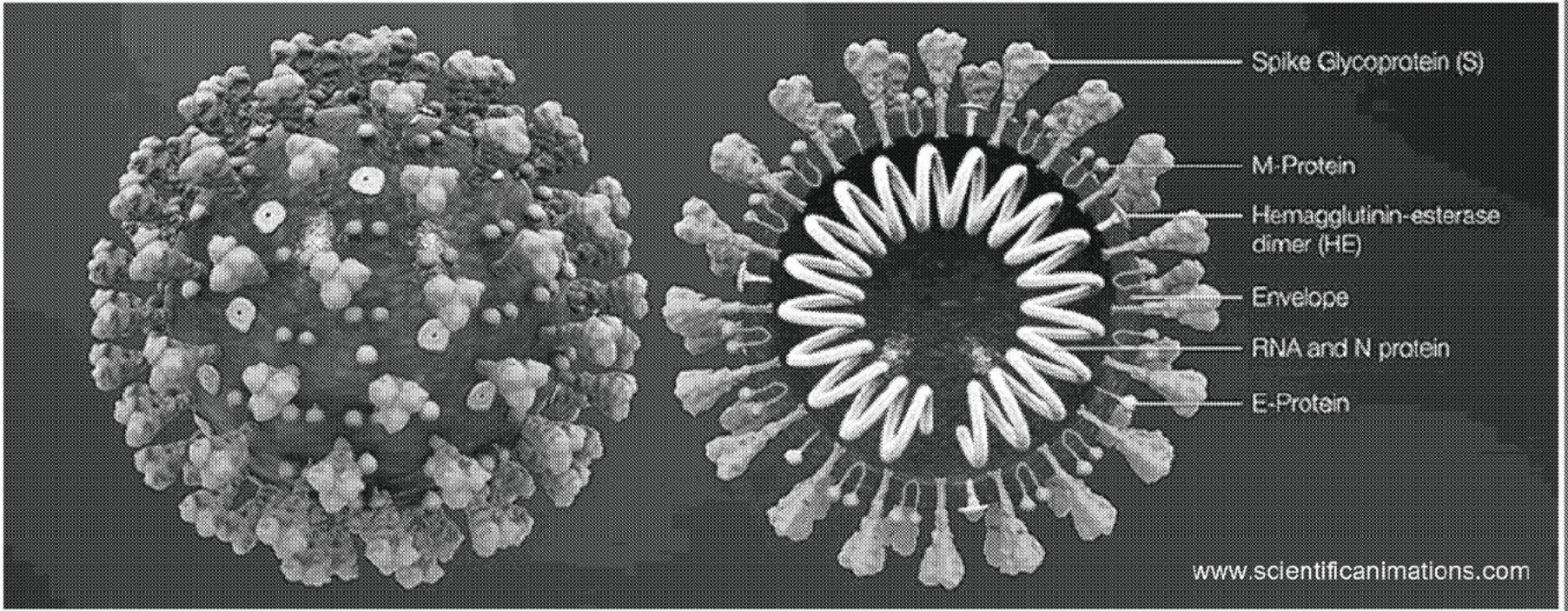
AND GLOBAL HEALTH

Outline

- Our Target: SARS-CoV-2
- The Complexity of Vaccine Development
- Vaccines for SARS-CoV-2
  - Vaccine platforms and attributes
  - Candidates in development
  - Upcoming trials

What do we know about the pathogen and immunity?

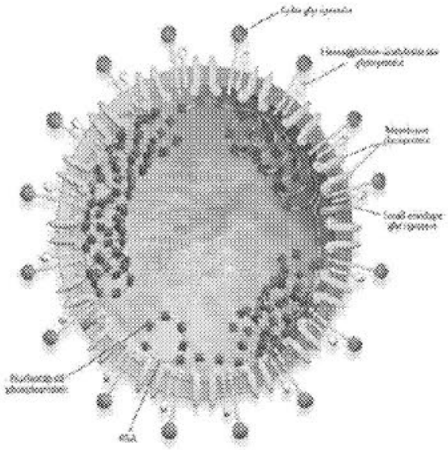


Single stranded, positive RNA with 4 major structural proteins:

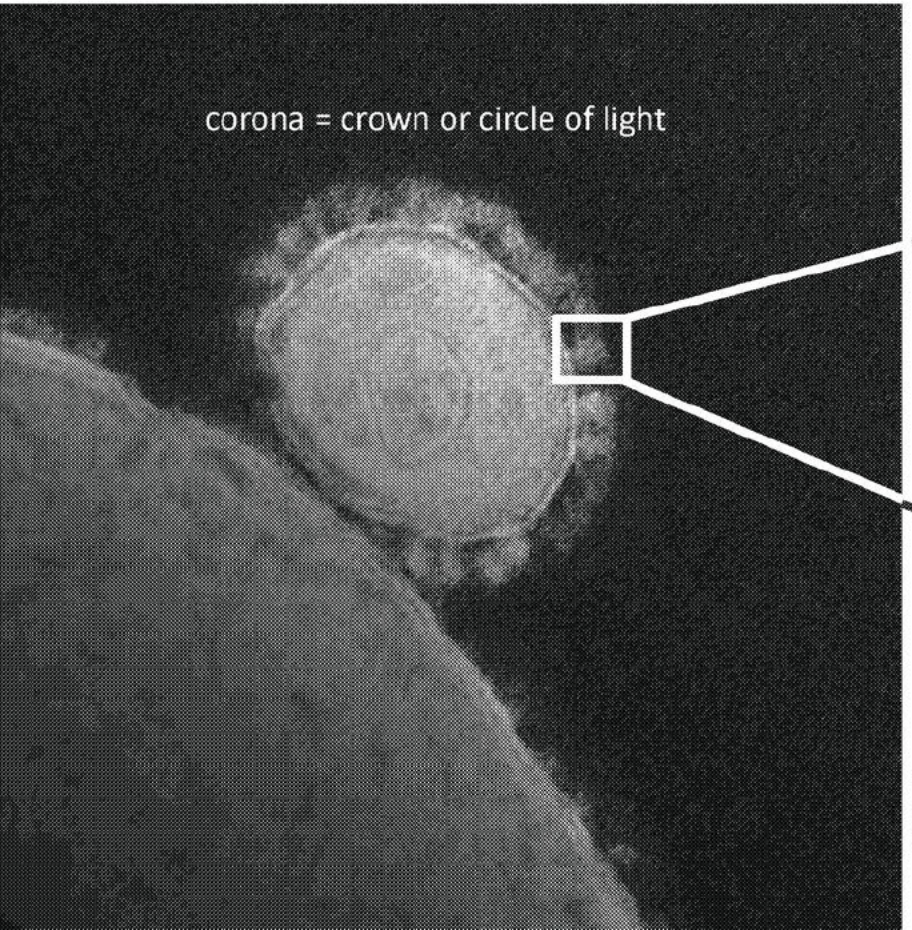
- Spike Protein (S) ⟶ Contains receptor binding domain
- M Protein
- Envelope (E) Protein
- Nucleocapsid (N) Protein

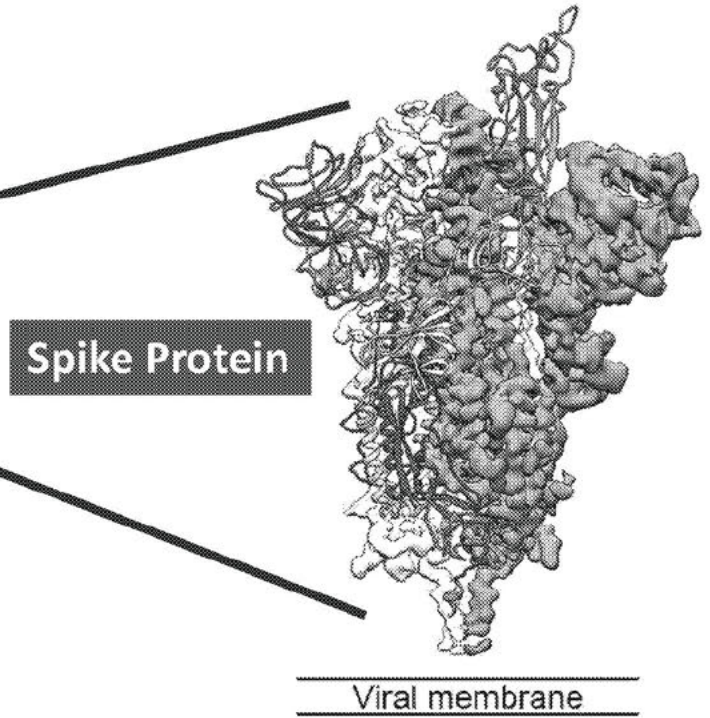
Vaccine Development Lessons from Other Coronaviruses

- Sequence comparison Spike S protein
  - MERS spike S protein 30% homologous
  - SARS Spike S protein is 80% homologous
- Good vaccine responses to several vaccine constructs in animals for SARS, MERS
- Phase 1 human trials in SARS, MERS
  - Broadly neutralizing antibodies
  - MERS development continues
  - SARS investments re-allocated



SARS-CoV-2 Spike Protein: Viral Entry

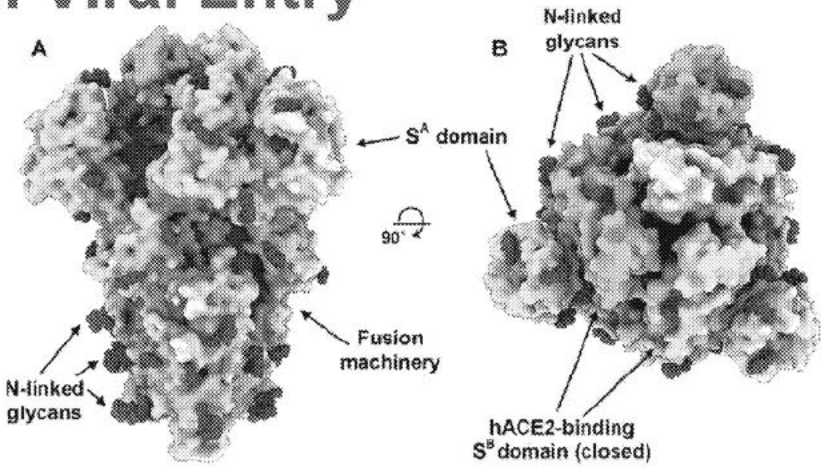


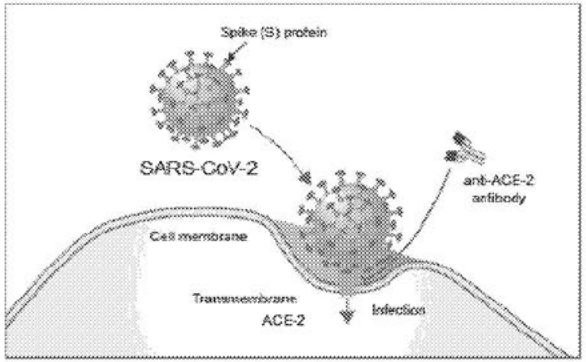


Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, Graham BS, McLellan JS. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. 2020 Feb 19:eabb2507. doi: 10.1126/science.abb2507.

SARS-CoV-2 Spike Protein: Viral Entry

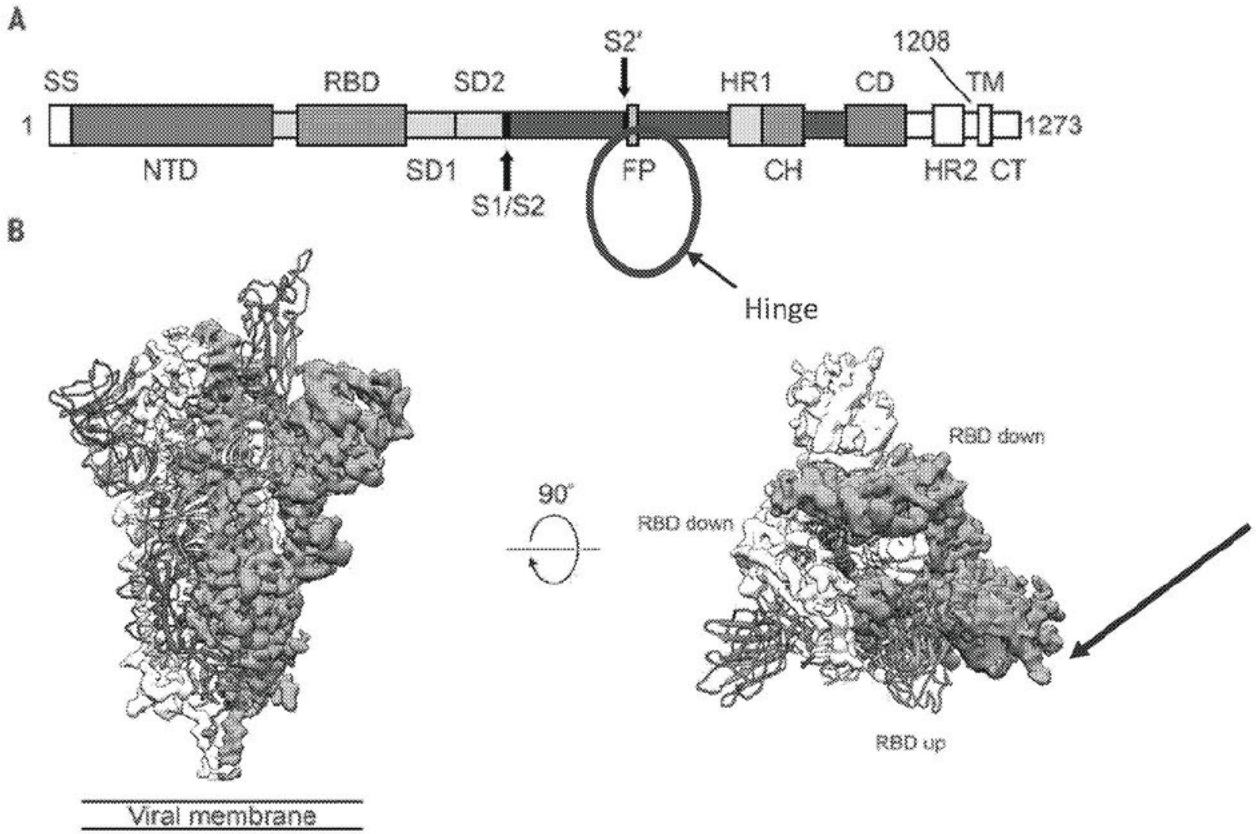
- Trimeric fusion protein
- Metastable prefusion conformation
- Undergoes substantial structural rearrangement to fuse the viral membrane with the host cell membrane
- Process triggered when S1 subunit binds to host cell receptor – S2 engages cell with fusion peptide
- Shedding of S1 subunit and transition of S2 subunit to stable postfusion conformation





bioRxiv https://doi.org/10.1101/2020.02.19.956581, Feb. 20, 2020

Conformationally Correct Protein

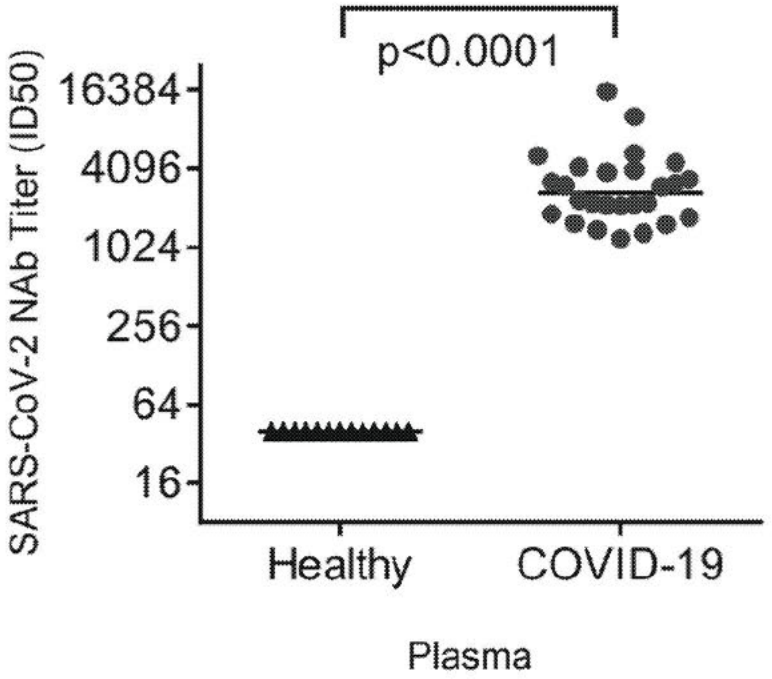


Receptor-binding domain of S1 undergoes hinge-like conformational movements that transiently hide or exposure determinants of receptor binding. Two stabilizing proline mutations effective for other betacoronaviruses applied to SARS-CoV-2.

Science 13 Mar 2020:Vol. 367, Issue 6483, pp. 1260-1263

What Do We Know About Immunity in Humans?

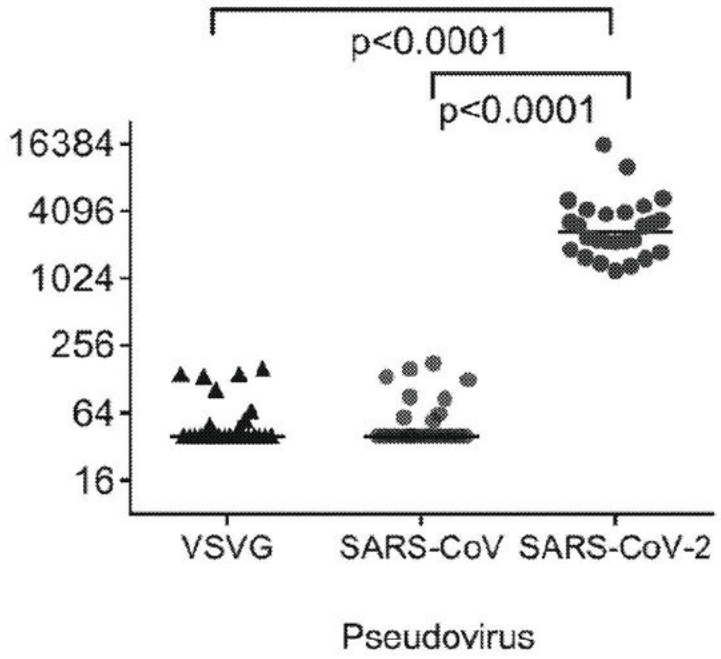
- Immune response post-infection to spike protein
- Neutralizing responses



medRxiv preprint doi: https://doi.org/10.1101/2020.03.30.20047365.

What Do We Know About Immunity in Humans?

- Immune response post-infection to spike protein
- Neutralizing responses
  - Don't cross-react with SARS virus
- Level of antibody needed to prevent re-infection?
- Duration of protection from natural immunity?
- Importance of T cell immunity?



medRxiv preprint doi: https://doi.org/10.1101/2020.03.30.20047365.

Does Infection with SARS-CoV-2 Protect Upon Re-Exposure?

Science

RESEARCH ARTICLES

Cite as: A. Chandrashekar *et al.*, *Science*
10.1126/science.abc4776 (2020).

SARS-CoV-2 infection protects against rechallenge in rhesus macaques

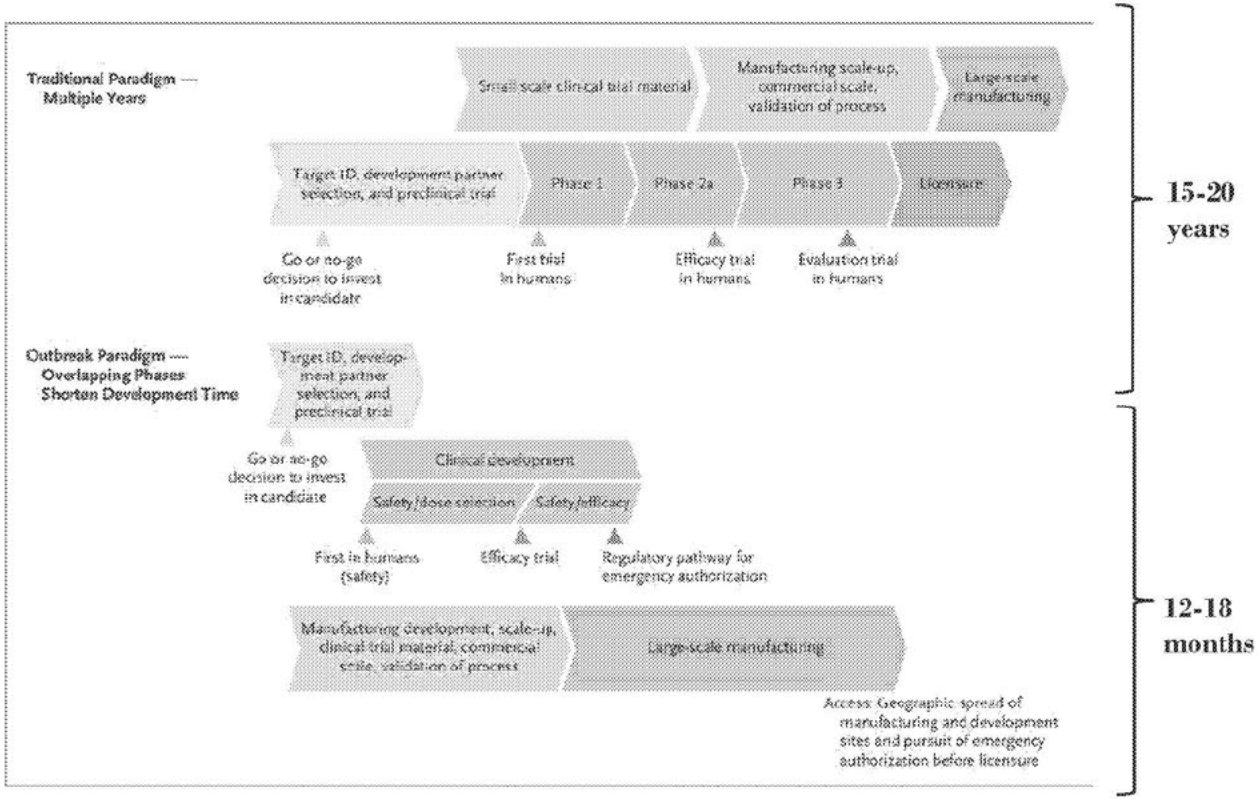
Abishek Chandrashekar[1]*, Jinyan Liu[1]*, Amanda J. Martinot[1,2]*, Katherine McMahan[1]*,

1 **Lack of Reinfection in Rhesus Macaques Infected with SARS-CoV-2**

2

3 Linlin Bao[†,1], Wei Deng[†,1], Hong Gao[†,1], Chong Xiao[†,1], Jiayi Liu[†,2], Jing Xue[†,1], Qi

Vaccine Development:
A Lengthy, Risky and Expensive Process

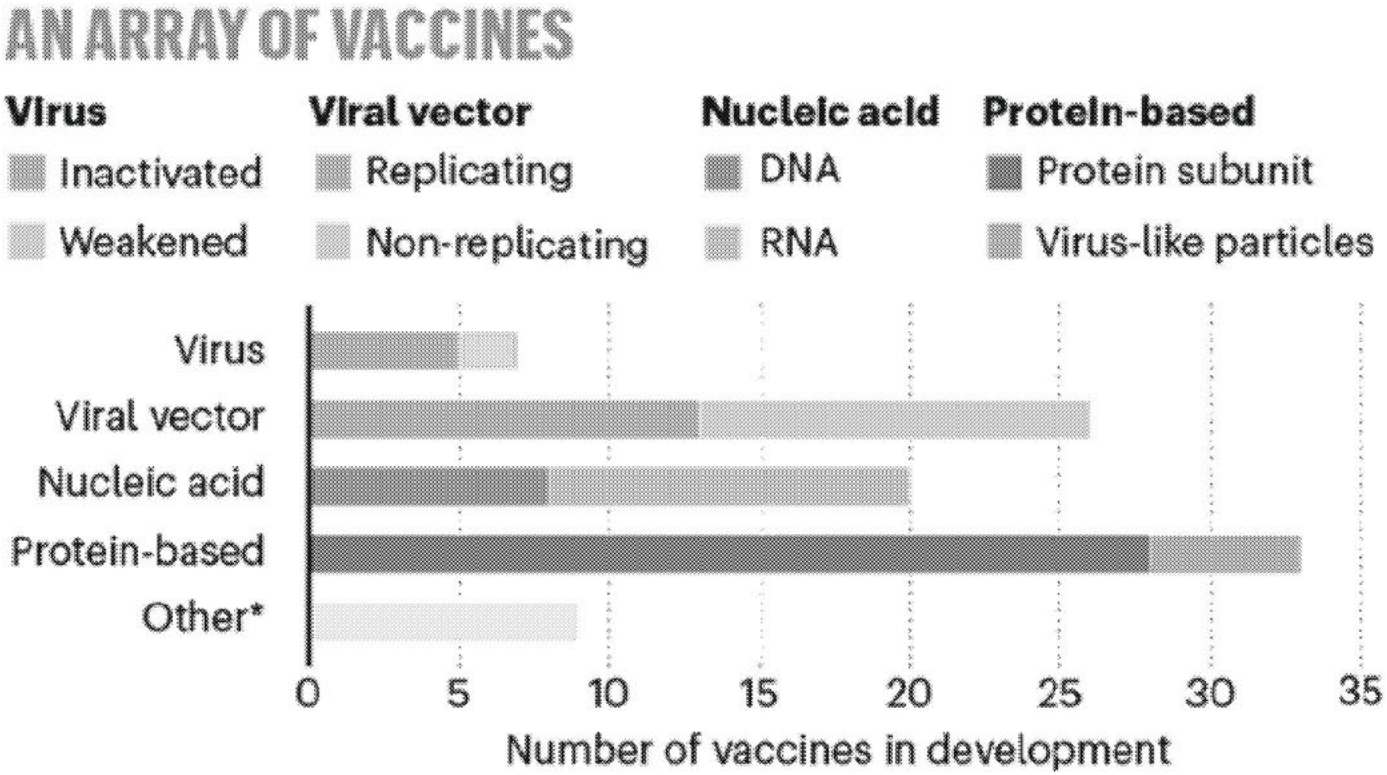


N Engl J Med 2020; 382:1969-1973 **DOI: 10.1056/NEJMp2005630**

Vaccine Platforms and Attributes

	Single Dose	Licensed Platform	Speed	Scale
DNA	No	No	Fast	Medium
RNA	No	No	Fast	Low to medium
Nonreplicating vector	Possibly	No	Medium	High
Replicating viral vector	Possibly	Yes	Medium	High
Protein subunit	No	Yes	Medium	High
Inactivated	No	Yes	Medium	Medium to high
Live attenuated	Yes	Yes	Slow	High

Vaccine Approach: Strategies

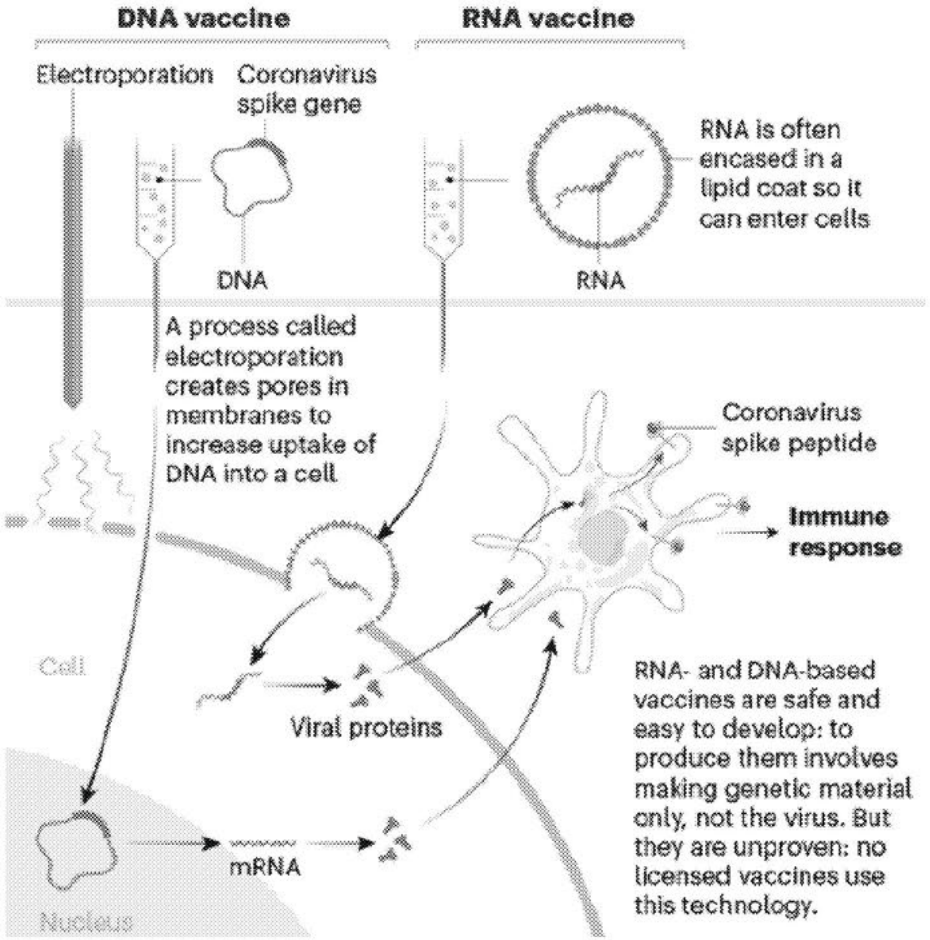


Nature **580**, 576-577 (2020)

COVID-19 Vaccine Candidates in Clinical Evaluation

Platform	Type	Developer	Phase	Same Platform
Non-replicating viral vector	ChAdOx1-S	Oxford/AZ	1/2	MERS, influenza, TB, Chik, Zika
Non-replicating viral vector	Ad Type 5	CanSino Biol Inc	2	Ebola
RNA	LNP-mRNA	Moderna/NIAID	2	Influenza, Zika, Chik
Inactivated	Inactivated +/- alum	Multiple Chinese developers	1/2	
Protein subunit	Recombinant GP nanoparticle/matrix M	Novavax	1/2	RSV; CCHF, HPV, VZV, Ebola
RNA	3 LNP-mRNAs	Pfizer/BioNTech	1/2	
DNA	DNA plasmid/electroporation	Inovio Pharm.	1	Multiple

Vaccine Approach: Nucleic Acid – DNA and RNA



Nature **580**, 576-577 (2020)

moderna

Moderna Announces Positive Interim Phase 1 Data for its mRNA Vaccine (mRNA-1273) Against Novel Coronavirus

May 18, 2020

After two doses all participants evaluated to date across the 25 µg and 100 µg dose cohorts seroconverted with binding antibody levels at or above levels seen in convalescent sera

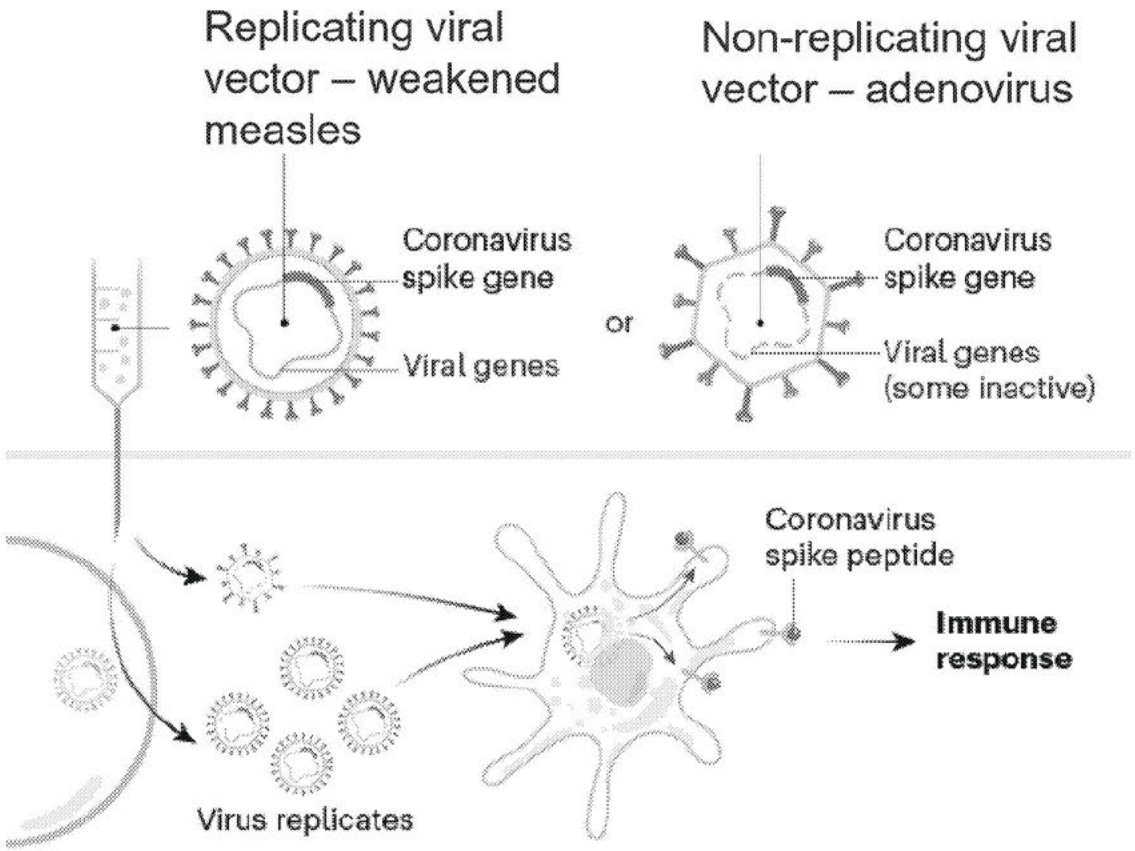
mRNA-1273 elicited neutralizing antibody titer levels in all eight initial participants across the 25 µg and 100 µg dose cohorts, reaching or exceeding neutralizing antibody titers generally seen in convalescent sera

mRNA-1273 was generally safe and well tolerated

mRNA-1273 provided full protection against viral replication in the lungs in a mouse challenge model

Anticipated dose for Phase 3 study between 25 µg and 100 µg; expected to start in July

Vaccine Approach: Viral Vectored Vaccine



[17] Nature **580**, 576-577 (2020)

Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomised, first-in-human trial

Feng-Cai Zhu, Yu-Hua Li*, Xu-Hua Guan, Li-Hua Hou, Wen-Juan Wang, Jing-Xin Li, Shi-Po Wu, Bu-Sen Wang, Zhao Wang, Lei Wang, Si-Yue Jia, Hu-Dachuan Jiang, Ling Wang, Tao Jiang, Yi Hu, Jin-Bo Gou, Sha-Bei Xu, Jun-Jie Xu, Xue-Wen Wang, Wei Wang, Wei Chen*

www.thelancet.com **Published online May 22, 2020 https://doi.org/10.1016/S0140-6736(20)31208-3**

Adverse Reactions to Ad5 Vectored COVID-19 Vaccine

	Low dose group (n=36)	Middle dose group (n=36)	High dose group (n=36)	Total (N=108)
All adverse reactions within 0–7 days				
Any	30 (83%)	30 (83%)	27 (75%)	87 (81%)
Grade 3	2 (6%)	2 (6%)	6 (17%)	10 (9%)
Injection site adverse reactions within 0–7 days				
Pain	17 (47%)	20 (56%)	21 (58%)	58 (54%)
Induration	2 (6%)	1 (3%)	1 (3%)	4 (4%)
Redness	2 (6%)	1 (3%)	1 (3%)	4 (4%)
Swelling	4 (11%)	4 (11%)	0	8 (7%)
Itch	2 (6%)	3 (8%)	0	5 (5%)
Muscular weakness	0	0	1 (3%)	1 (1%)
Systemic adverse reactions within 0–7 days				
Fever	15 (42%)	15 (42%)	20 (56%)	50 (46%)
Grade 3 fever	2 (6%)	2 (6%)	5 (14%)	9 (8%)
Headache	14 (39%)	11 (31%)	17 (47%)	42 (39%)
Fatigue	17 (47%)	14 (39%)	16 (44%)	47 (44%)

ELISA Antibody Responses to the RBD and Neutralizing Antibodies

	Day 14				Day 28			
	Low dose group (n=36)	Middle dose group (n=36)	High dose group (n=36)	p value	Low dose group (n=36)	Middle dose group (n=36)	High dose group (n=36)	p value
ELISA antibodies to the receptor binding domain								
GMT	76·5 (44·3–132·0)	91·2 (55·9–148·7)	132·6 (80·7–218·0)	0·29	615·8 (405·4–935·5)	806·0 (528·2–1229·9)	1445·8 (935·5–2234·5)	0·016
≥4-fold increase	16 (44%)	18 (50%)	22 (61%)	0·35	35 (97%)	34 (94%)	36 (100%)	0·77
Neutralising antibodies to live SARS-CoV-2								
GMT	8·2 (5·8–11·5)	9·6 (6·6–14·1)	12·7 (8·5–19·0)	0·24	14·5 (9·6–21·8)	16·2 (10·4–25·2)	34·0 (22·6–50·1)	0·0082
≥4-fold increase	10 (28%)	11 (31%)	15 (42%)	0·42	18 (50%)	18 (50%)	27 (75%)	0·046

- Dose-dependent antibody response
- High pre-existing Ad5 neutralizing antibody responses compromised neutralizing antibody post-vaccination, regardless of vaccine dose

Cite as: B. S. Graham *et al.*, *Science* 10.1126/science.abb8923 (2020).

Rapid COVID-19 vaccine development

By **Barney S. Graham**

Vaccine Research Center, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA. Email: bgraham@mail.nih.gov

Finding the fastest pathway to vaccine availability includes the avoidance of safety pitfalls

Potential risks associated with vaccine development for COVID-19

Antibodies that bind virus without neutralizing infectivity can cause disease through increased viral replication or formation of immune complexes that deposit in tissue and activate complement pathways associated with inflammation. T helper 2 cell (T_H2)–biased responses have also been associated with ineffective vaccines that lead to enhanced disease after subsequent infection. Antibody-dependent enhancement (ADE) of viral replication has occurred in viruses with innate macrophage tropism. Virus-antibody immune complexes and T_H2-biased responses can both occur in vaccine-associated enhanced respiratory disease (VAERD).

	Antibody-mediated		T cell–mediated
	ADE	**VAERD**	**VAERD**
Mechanism	Fc-mediated increase in viral entry	Immune complex formation and complement deposition	T_H2-biased immune response
Effectors	Macrophage activation and inflammatory cytokines	Complement activation and inflammatory cytokines	Allergic inflammation and T_H2 cytokines
Mitigation	Conformationally correct antigens and high-quality neutralizing antibody		T_H1-biasing immunization and $CD8^+$ T cells

Summary

- Safe and effective vaccines that is accessible, affordable and globally available is needed for COVID-19
- Robust pipeline of promising candidates in clinical development
  - We need multiple wins
  - Many challenges – New disease, poorly understood immunity, uncertain trajectory of outbreak
  - Vaccine safety will be meticulously assessed
  - If enhanced disease occurs it will be carefully assessed and immune mechanisms investigated

Thank You

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Visit us online at www.medschool.umaryland.edu/cvd

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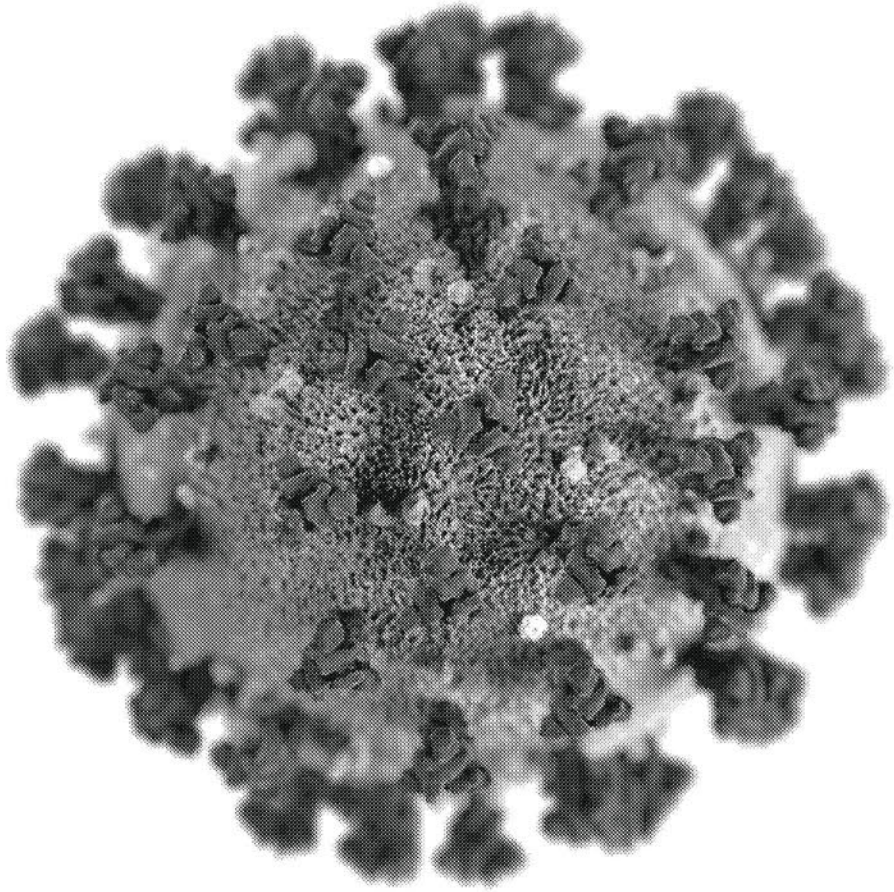
AND GLOBAL HEALTH

Considerations for COVID-19 Vaccine Prioritization



Sarah Mbaeyi, MD MPH

June 24, 2020

Identifying priority groups for COVID-19 vaccination

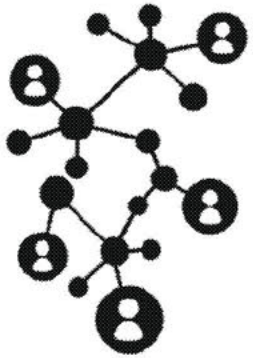
An essential roadmap for vaccine program planning and implementation

- Although the goal is to offer vaccine to the entire U.S. population, identifying priority groups for COVID-19 vaccination is essential to support vaccine planning
  - Necessary to begin planning prior to vaccine approval to avoid delays

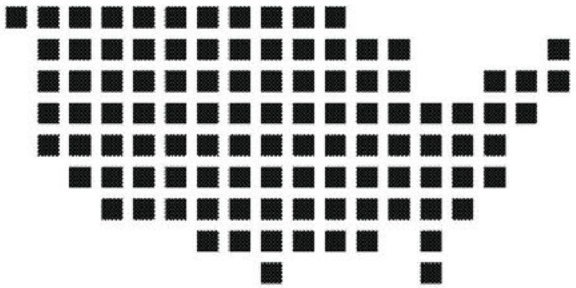
- Vaccine prioritization is challenging due to incomplete information on COVID-19 epidemiology and vaccines, including characteristics, timing, and number of doses

- **Identifying priority groups: essential to start now with the information available to date, with continuous reassessment as data become available**

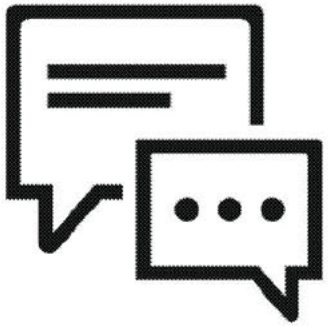
Importance of identifying COVID-19 vaccine priority groups for implementation planning



Strengthen vaccine distribution networks to reach target group



Develop state and local microplans for vaccine implementation



Create communications strategies to promote vaccination in priority groups

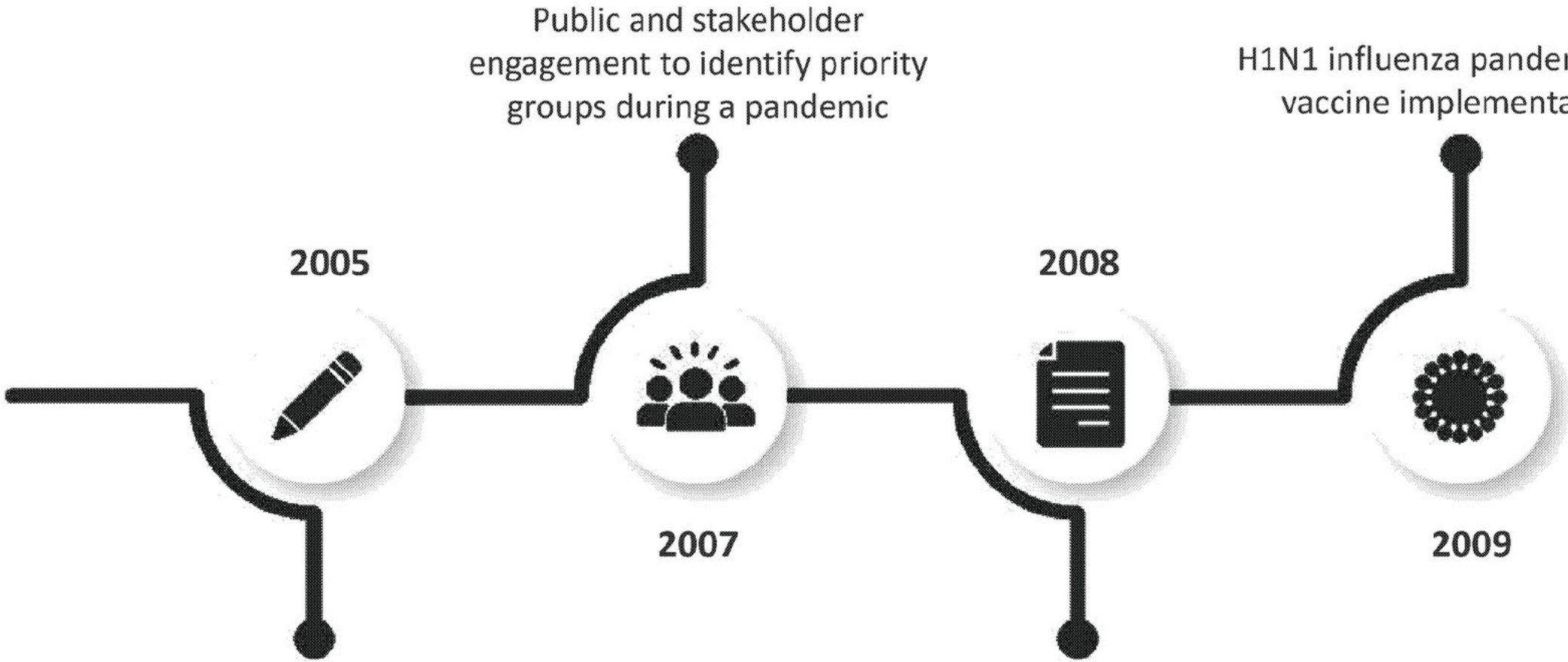
Plan evaluations to rapidly monitor vaccine safety, effectiveness, and coverage

Lessons learned from pandemic influenza vaccination

Framework for COVID-19 prioritization and implementation planning

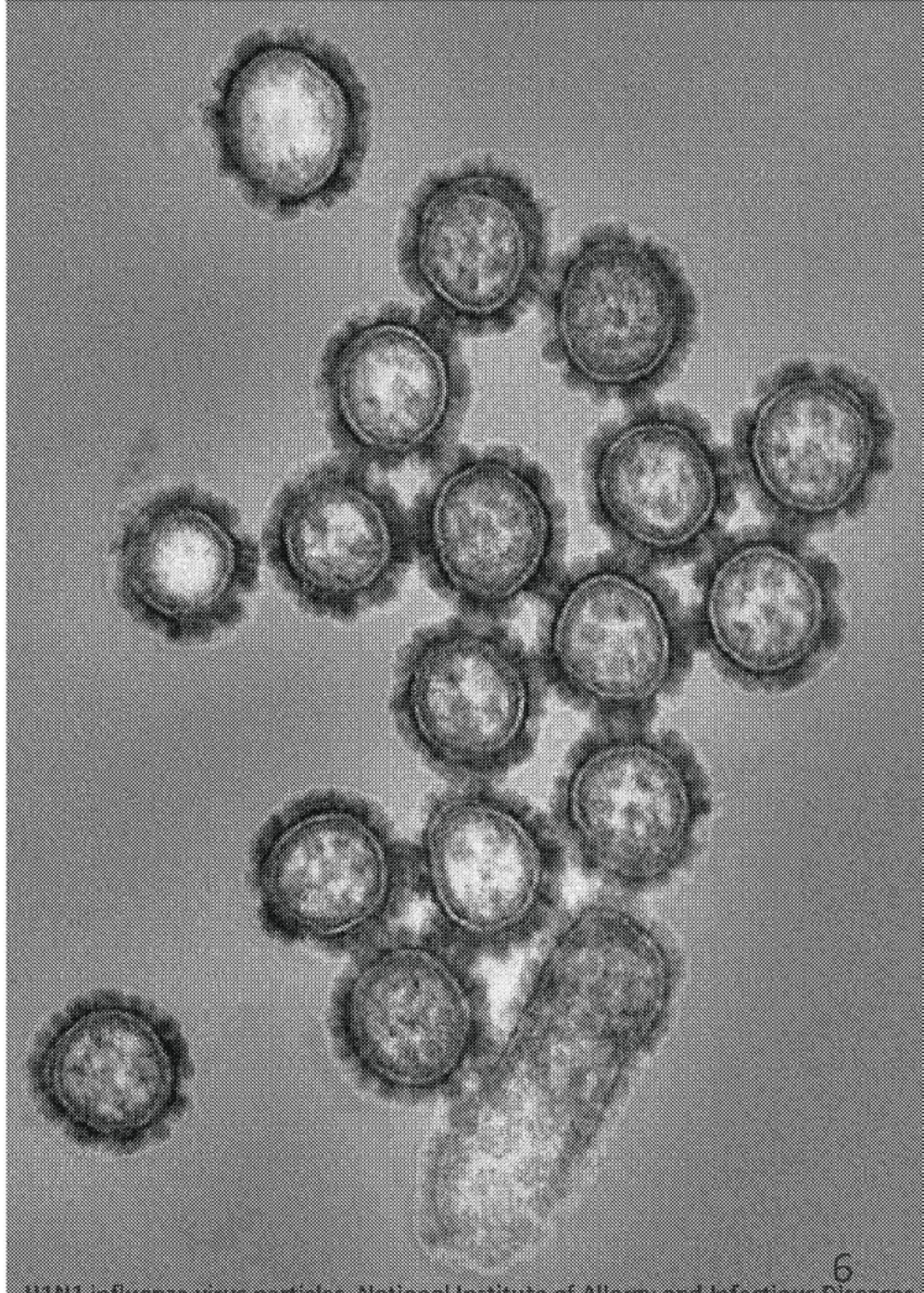
Pandemic influenza vaccine prioritization planning

Principles of pandemic vaccine planning to be adapted for COVID-19 vaccination



H1N1 influenza pandemic

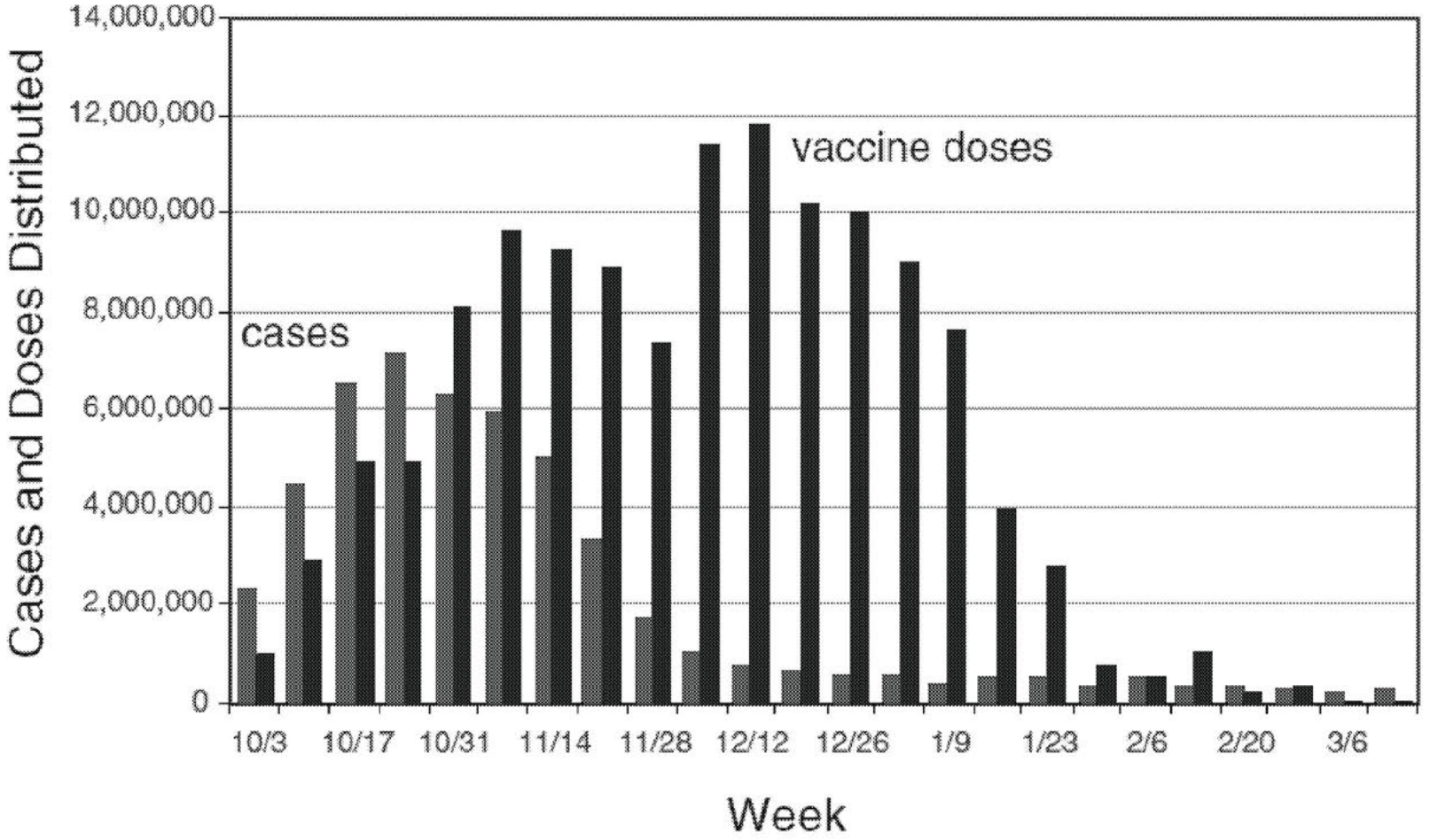
- Novel influenza A virus (H1N1) emerged in April 2009, leading to a global pandemic
- H1N1 vaccine became available in October 2009 during second wave of disease
- ACIP recommended priority groups for initial vaccination:
  - Persons at increased risk for severe disease
  - Healthcare personnel



H1N1 influenza virus particles. National Institute of Allergy and Infectious Diseases

H1N1 vaccine supply and demand

Estimated number of H1N1 cases and vaccine doses distributed – October 2009 to March 2010



High demand when supply limited and prioritized

Low demand when supply adequate

20% vaccine coverage by late January

Institute of Medicine. 2010. *The 2009 H1N1 influenza vaccination campaign: Summary of a workshop series.* Washington, DC: The National Academies Press; CDC. Interim Results: State-Specific Influenza A (H1N1) 2009 Monovalent Vaccination Coverage --- United States, October 2009--January 2010. MMWR. 59(12);363-368; Image credit: Reuters

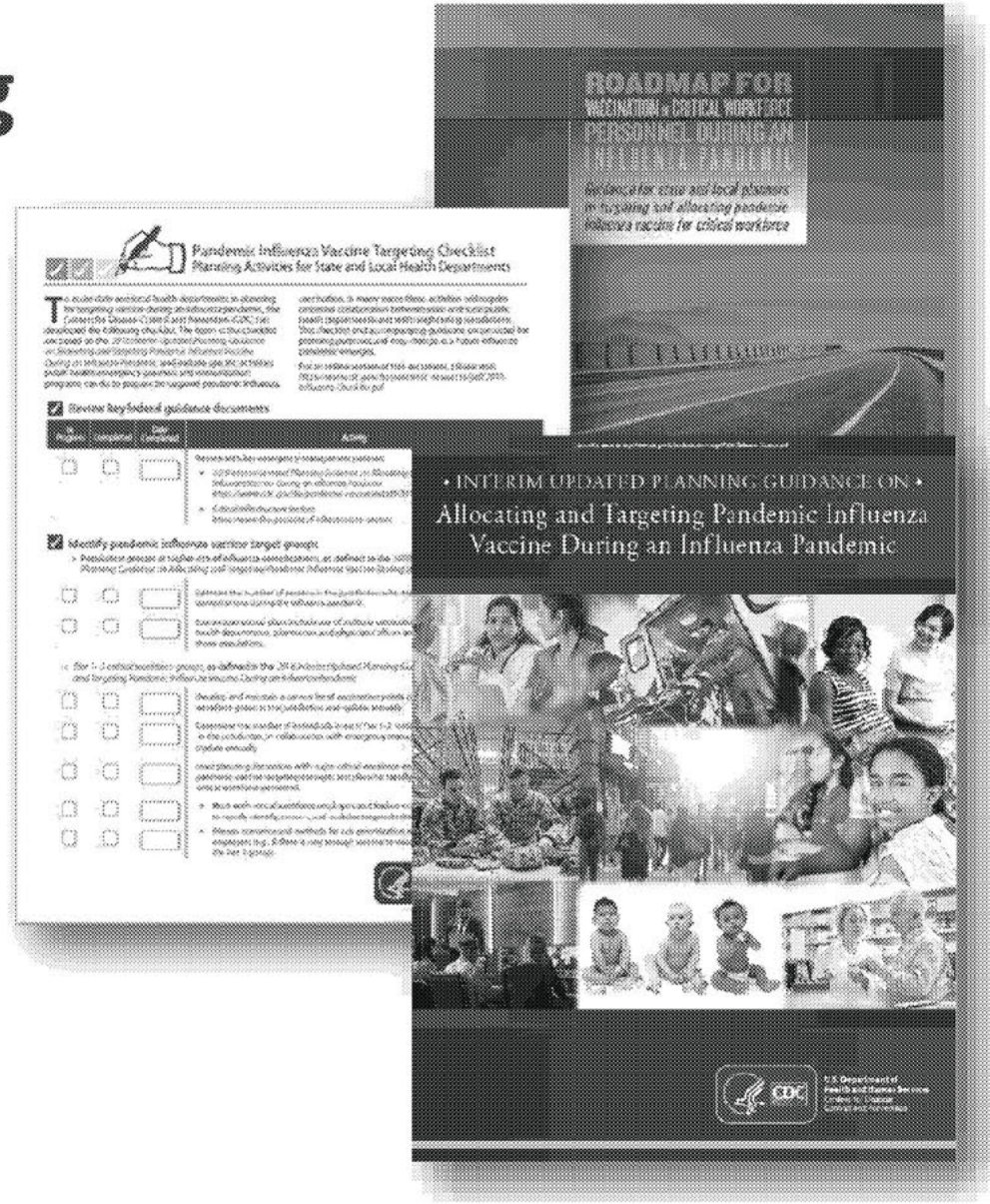
Lessons learned from H1N1 vaccine prioritization

- Overly optimistic vaccine supply projections
- Restrictive enforcement of priority groups can lead to vaccine surpluses
- Challenges in expanding vaccination outside of the priority groups to the general public
- Importance of population values
- Need for state and local flexibility in implementation
- **H1N1 experience: valuable lessons learned, though complexity of COVID-19 pandemic will lead to new challenges**

Institute of Medicine. 2010. *The 2009 H1N1 influenza vaccination campaign: Summary of a workshop series*. Washington, DC: The National Academies Press.

Guidance for allocating and targeting pandemic influenza vaccine

- Updated in 2018 based on lessons learned from H1N1 pandemic
- Occupational and high risk populations grouped into tiers for prioritization
- Provides framework for adaptation to COVID-19 vaccine prioritization



2018 guidance and associated support documents

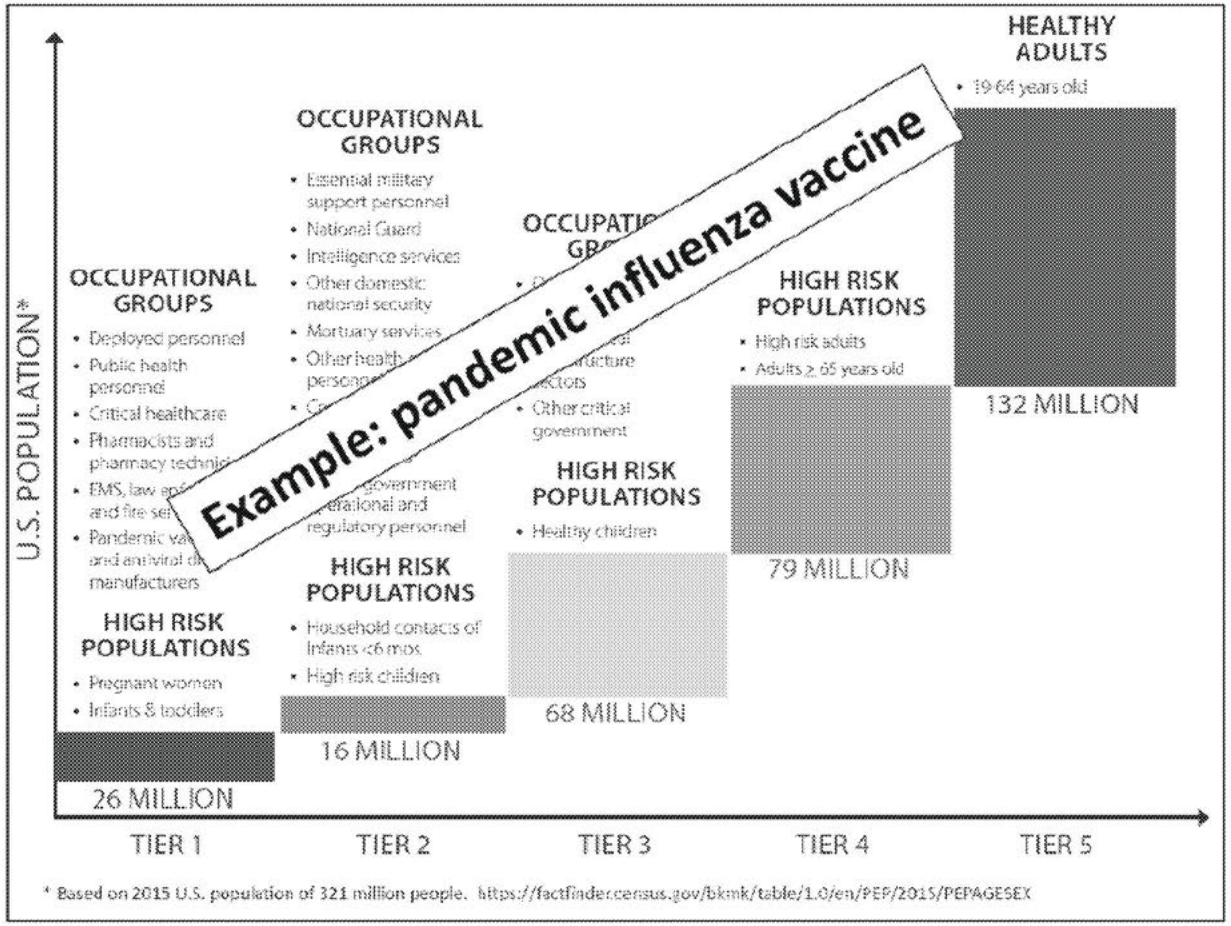
https://www.cdc.gov/flu/pandemic-resources/national-strategy/planning-guidance/index.html

Tiered approach to defining priority groups for vaccination

- Prioritization framework: roadmap for vaccine program planning

- Tiered priority groups to be adapted for COVID-19 based on:
  - Burden of disease and severity in risk groups
  - Impacts on society and critical infrastructure
  - Characteristics of vaccines
  - Number and timing of doses available

Allocating and targeting pandemic influenza vaccine during an influenza pandemic



https://www.cdc.gov/flu/pandemic-resources/national-strategy/planning-guidance/index.html

ACIP COVID-19 Vaccine Work Group

Considerations for identifying COVID-19 vaccine priority groups

Role of ACIP in identifying COVID-19 vaccine priority groups

- ACIP provides advice to the CDC director and HHS secretary on use of vaccines in the U.S. civilian population in a transparent, evidence-based process

- To help inform ACIP deliberations around use of COVID-19 vaccines, the work group is reviewing:
  - Epidemiology of COVID-19
  - Characteristics of vaccine candidates under development
  - Evidence-based vaccine recommendation, ethics, and equity frameworks

https://www.cdc.gov/vaccines/acip/committee/charter.html

Work Group Considerations: Objectives of the COVID-19 Vaccine Program

- Ensure safety and effectiveness of COVID-19 vaccines
- Reduce transmission, morbidity, and mortality in the population
- Help minimize disruption to society and economy, including maintaining healthcare capacity
- Ensure equity in vaccine allocation and distribution

Identifying vaccine priority groups: Current challenges and preliminary Work Group assumptions

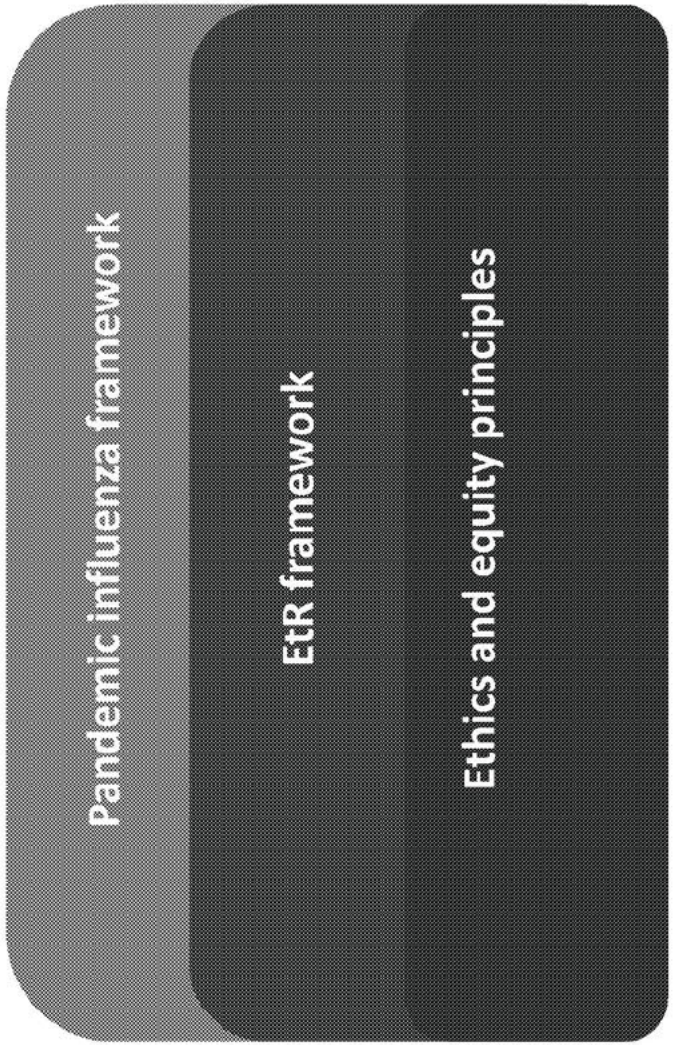
Challenges	Work Group assumptions for prioritization
Evolving understanding of COVID-19 epidemiology and immunology	• Prioritization should occur based on the information available to date and be continually refined based on data • A substantial proportion of the U.S. population, regardless of age, location, or occupation, remains susceptible to COVID-19.
Current absence of data on safety and efficacy of COVID-19 vaccines	• Vaccines will not be administered until safety and efficacy have been demonstrated. • Concerns for reduced efficacy in certain populations (e.g., older adults, immunocompromised individuals) should not preclude their inclusion as priority groups while data are pending.
Unknown timing and number of vaccine doses	• Number of initial doses may not be sufficient to vaccinate everyone in the priority groups, necessitating sub-prioritization. • Vaccine doses will become available in incremental quantities over several months.

Work Group Considerations: Process for identifying proposed priority groups for COVID-19 vaccination

Pandemic influenza framework for vaccine allocation	Principles of the Evidence to Recommendations (EtR) Framework	Ethics and equity principles
Criteria for prioritization		
• Burden of disease and severity • Pandemic severity and impacts on society • Vaccine supply	• Burden and severity of disease • Benefits and possible harms • Values of the target population • Acceptability to stakeholders • Feasibility of implementation	• Minimize death and serious disease • Preserve functioning of society • Reduce disproportionate burden on those with existing disparities Consideration should be give to: • Maximize benefits/minimize harms • Transparent, fair process • Just, fair stewardship of vaccines • Removing barriers to vaccination

https://www.cdc.gov/flu/pandemic-resources/national-strategy/planning-guidance/index.html; https://www.cdc.gov/vaccines/acip/recs/index.html

Work Group Considerations: Process for identifying proposed priority groups for COVID-19 vaccination

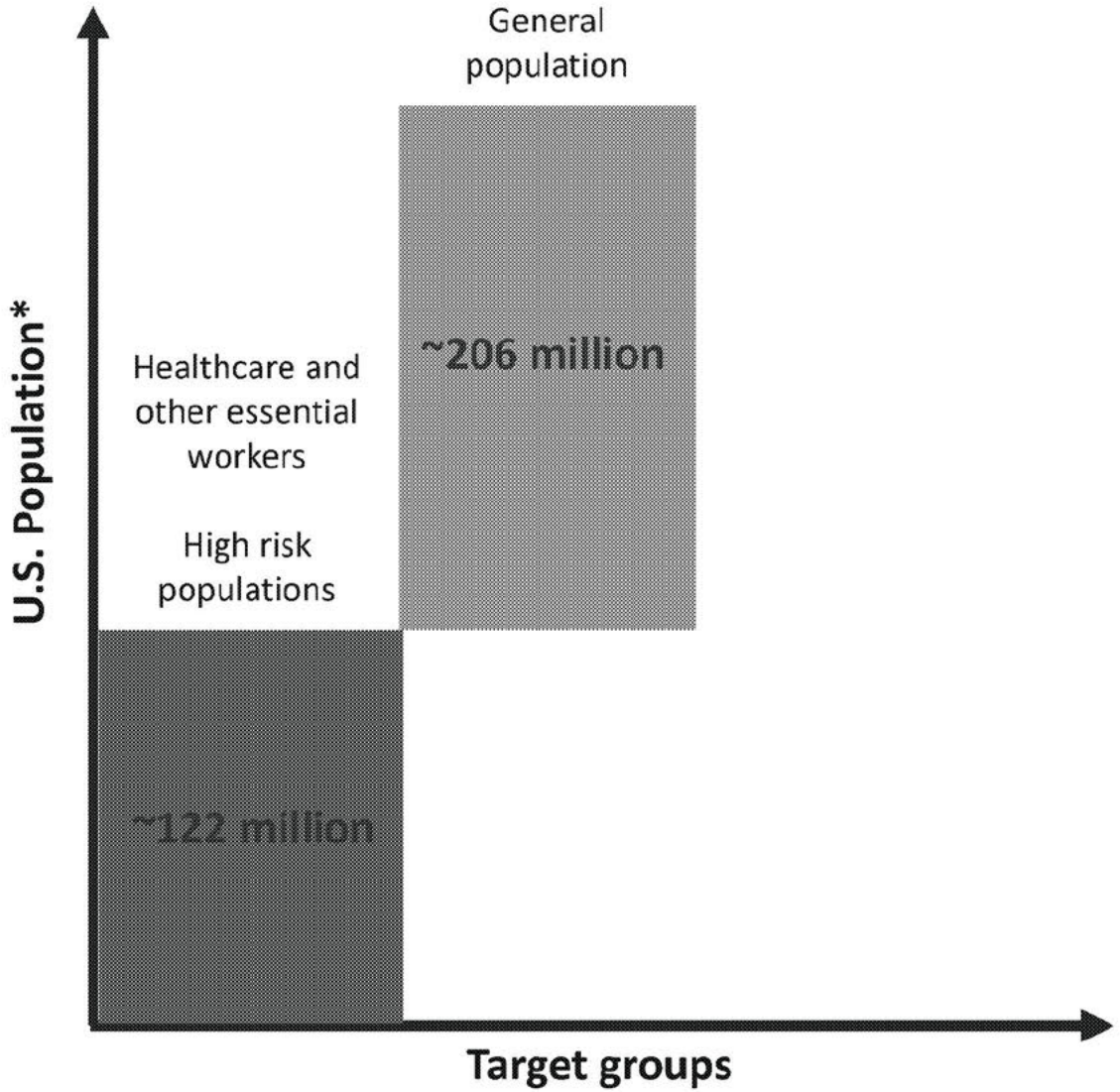


Proposed prioritization scheme:

- General approach for prioritization to help with operational planning for vaccine implementation
- Iterative process with priority groups to be refined as more information becomes available

https://www.cdc.gov/flu/pandemic-resources/national-strategy/planning-guidance/index.html; https://www.cdc.gov/vaccines/acip/recs/index.html

Work Group considerations: Highest priority given to healthcare/essential workers and high-risk populations, followed by general population

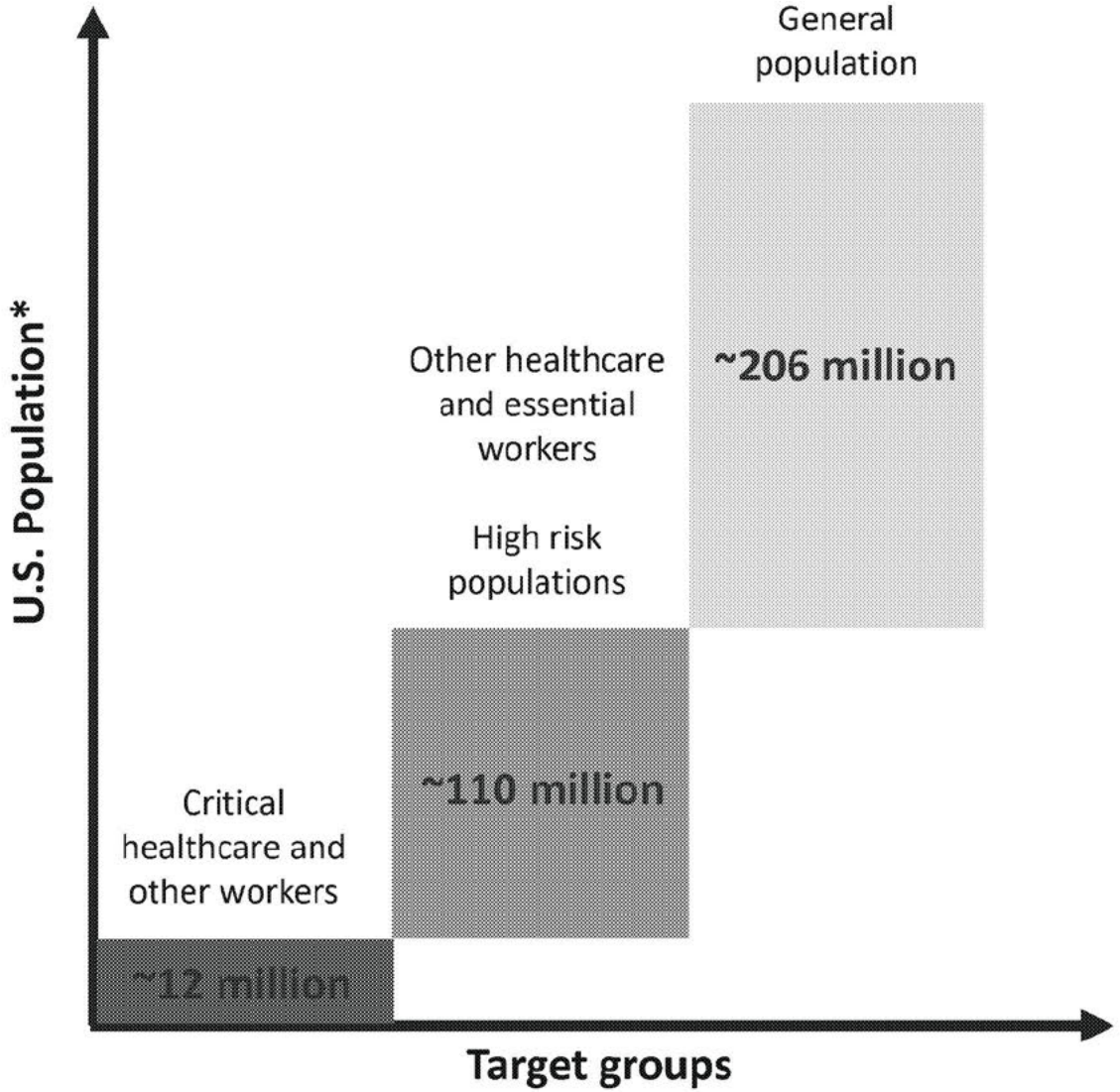


Proposed priority group includes (to be further refined):

- Healthcare personnel
- Essential workers
- Adults aged ≥65 years
- Long term care facility residents
- Persons with high-risk medical conditions

* Based on 2019 U.S. population of 328 million and information from Department of Defense, Department of Homeland Security, Department of Health and Human Services, and U.S. Census Bureau

Work Group considerations: Among target groups, subset of critical healthcare and other workers should receive initial doses

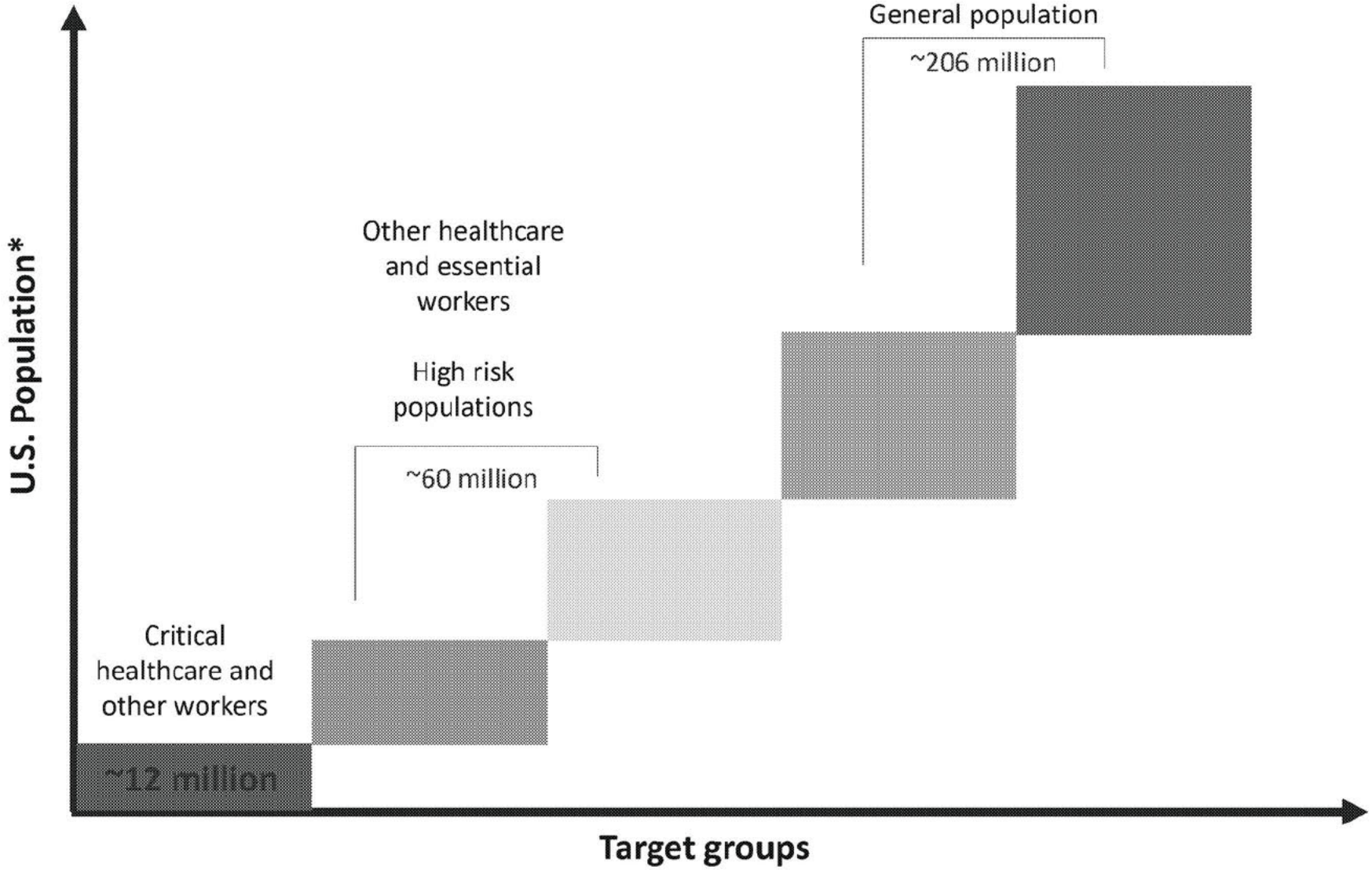


Highest priority target group includes:

- Highest risk medical, national security, and other essential workers
- Rationale: protect healthcare infrastructure and other critical societal functions

* Based on 2019 U.S. population of 328 million and information from Department of Defense, Department of Homeland Security, Department of Health and Human Services, and U.S. Census Bureau

Work Group considerations: Further tiering of target groups may be necessary based on vaccine supply and program planning



* Based on 2019 U.S. population of 328 million and information from Department of Defense, Department of Homeland Security, Department of Health and Human Services, and U.S. Census Bureau

Additional data to inform prioritization

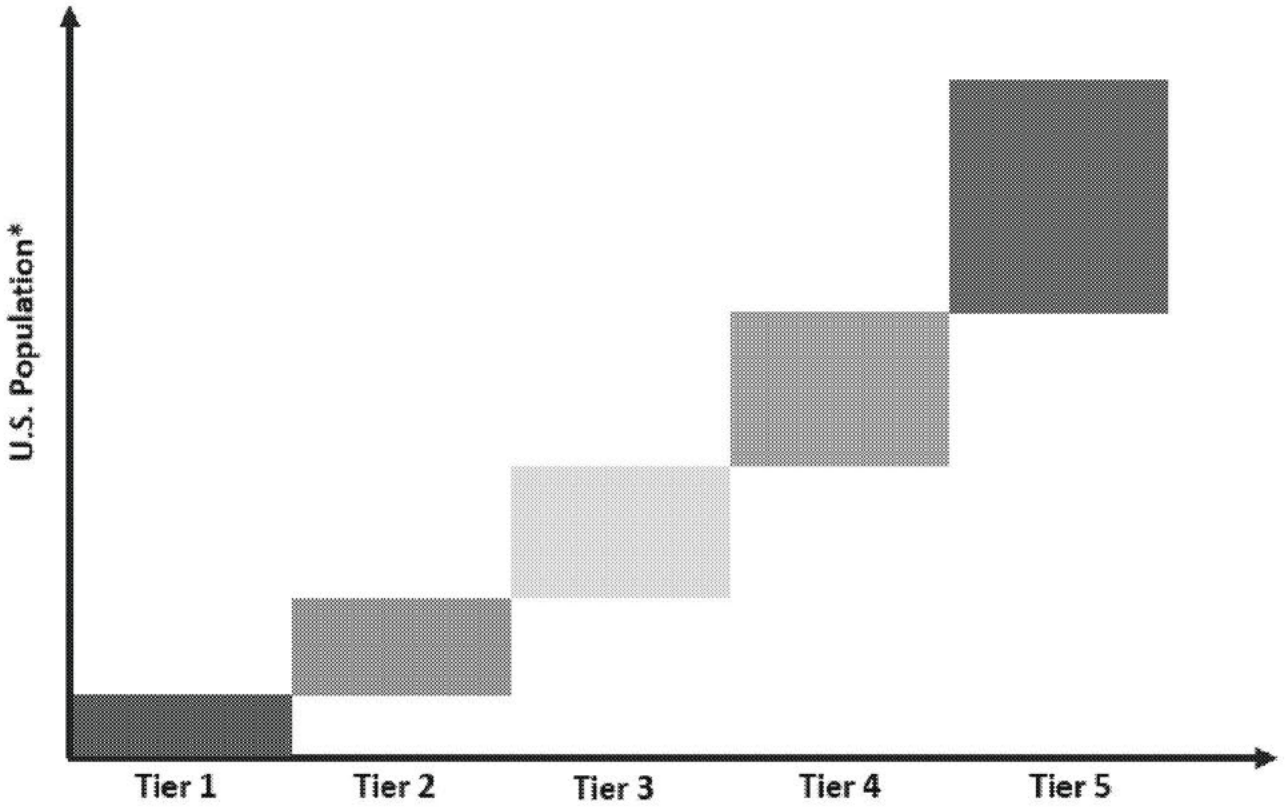
- Remaining information gaps in certain population subgroups:
  - Risk of disease and severe outcomes
  - Vaccine safety and efficacy
  - Transmission dynamics and level of population immunity

- Additional data to inform prioritization will be helpful, though may need to make decisions in the setting of unknowns for vaccine implementation planning

Summary

- Identifying priority groups for initial COVID-19 vaccination prior to approval of a vaccine is critical for implementation planning
- Lessons learned from the H1N1 influenza pandemic highlight importance of national guidance while allowing for state/local flexibility in implementation
- Work Group proposes priority groups for COVID-19 vaccination, including healthcare/ essential workers and persons at increased risk for severe disease
- Prioritization will need to be refined as more information becomes available.

Discussion: Key population groups where ACIP feedback needed to support vaccination program planning



Which tier for key populations?

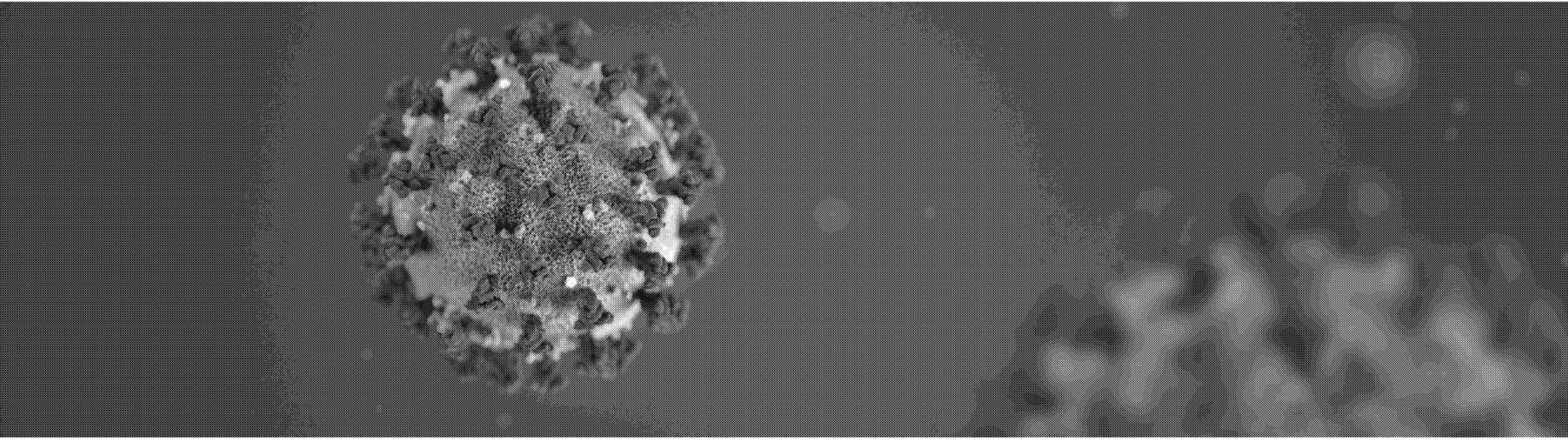
- Critical healthcare/other workers
- Long-term care facility residents
- Other congregate settings
- Children
- Pregnant women
- Racial/ethnic groups at high risk

Are there other data that ACIP would like to review?

Next steps

- Proposed priority groups to be further refined based on ACIP feedback

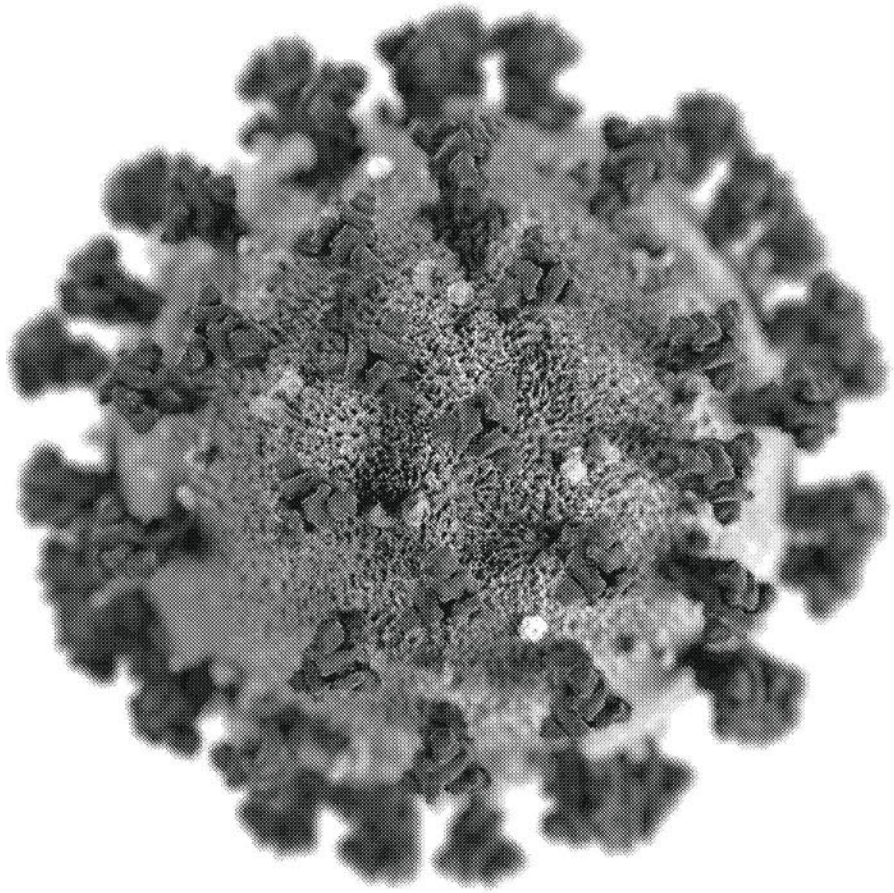
- Goal for next ACIP meeting: Completed prioritization framework



Thank you

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

ACIP COVID-19 Vaccines Work Group



Work Group Considerations and Next Steps

Kathleen Dooling, MD MPH

June 24, 2020

Work Group Considerations: Objectives of the COVID-19 Vaccine Program

- Ensure safety and effectiveness of COVID-19 vaccines
- Reduce transmission, morbidity, mortality of COVID-19 disease
- Help minimize disruption to society and economy, including maintaining healthcare capacity
- Ensure equity in vaccine allocation and distribution

Summary- COVID-19 Immune response

What we know

- Most people with SARS-CoV-2 develop antibodies, usually within 2 weeks
- Most people with SARS-CoV-2 mount neutralizing antibody responses

Key unknowns for vaccine policy

- What is the duration of immunity following SARS-CoV-2 infection?
- Will neutralizing antibodies protect against viral infection?
- Are there immunologic correlates of protection?

Summary- COVID-19 Epidemiology in the U.S.

What we know

- Multiple populations with evidence of high risk of COVID-19 disease or severity
- Occupation
  - healthcare, agricultural
- Individual characteristics
  - Older adults, underlying medical conditions
- Social determinants
  - Belonging to American Indian, Black or Hispanic race/ethnic groups
  - Long-term care, Correctional facilities, homeless

Key unknowns for vaccine policy

- Proportion of viral transmission contributed by children
- Risk of disease and severity in pregnant women
- Incidence of MIS-C*, and long term sequalae
- Current level of population immunity and heterogeneity by factors such as geography/occupation/race/ethnicity

MIS-C*- Multisystem inflammatory syndrome in children

Summary- Development of COVID-19 Vaccines

What we know

- Multiple platforms are being utilized to develop COVID-19 vaccines
- Multiple approaches increase the chances of developing safe and effective vaccines to meet national and global needs
- Vaccines must meet stringent safety standards in clinical trials. Otherwise, the vaccine will not be used in the population

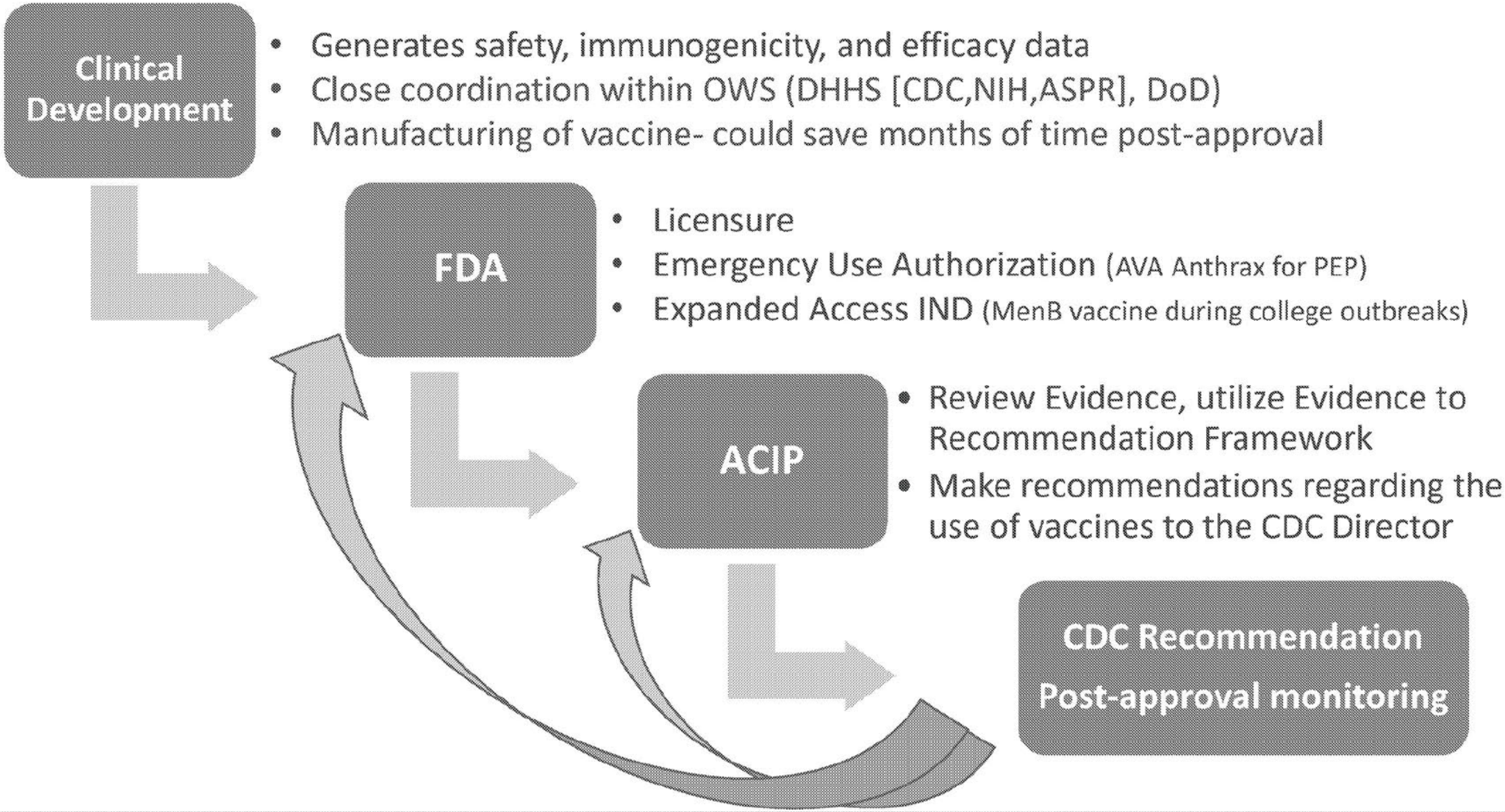
Key unknowns for vaccine policy

- Vaccine characteristics
  - # doses
  - Route of administration (SQ*/IM^/electroporation)
  - Storage temperature
- Vaccine performance
  - Immunogenicity and efficacy by age and risk groups
  - Interval from vaccination to protection
  - Vaccine effect on acquisition of infection and transmission
  - Adverse event profile by age and risk groups
  - FDA approved populations

SQ*- subcutaneous

IM^- Intramuscular

Path from clinical development to recommendation



Evidence to Recommendation Framework

PROBLEM

- Is the disease of public health importance?

BENEFITS & HARMS

- How substantial are the expected benefits?
- Are there harms? How substantial?

Evidence to Recommendation Framework

VALUES

- Does the target population value the vaccination?

ACCEPTABILITY

- Is the vaccine program acceptable to key stakeholders?

FEASIBILITY

- Is the vaccine program feasible to implement?

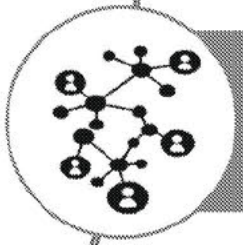
Guiding Principles for COVID-19 Vaccines

ACIP COVID-19 Vaccine Work Group: Proposed Guiding Principles

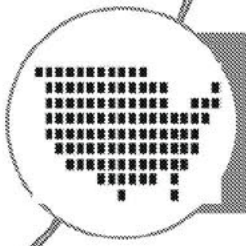
EQUITY

Safety is paramount. Vaccine safety standards will not be compromised in efforts to accelerate COVID-19 vaccine development

Inclusive clinical trials. Study participants should reflect groups at risk for COVID-19 to ensure safety and efficacy data are generalizable



Efficient Distribution. During a pandemic, efficient, expeditious and equitable distribution and administration of approved vaccine is critical



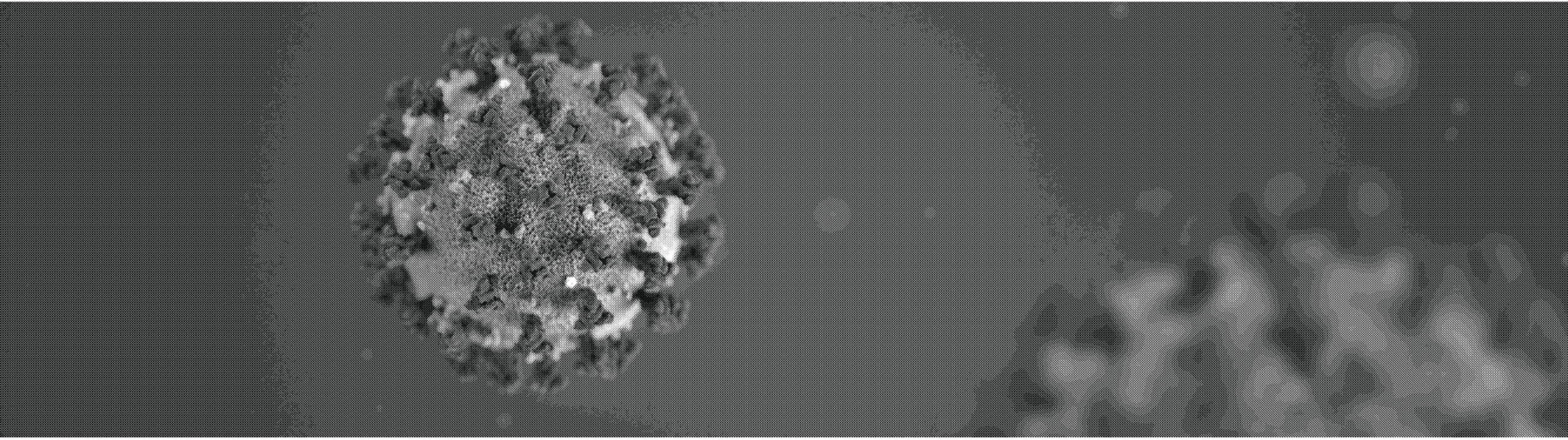
Flexibility. Within national guidelines, state and local jurisdictions should have flexibility to administer vaccine based on local epidemiology and demand

Next Steps for the Work Group

- Define the critical and important outcomes (benefits and risks for EtR)
- Review clinical trial data for candidate vaccines, as it becomes available
- Advance understanding of safety issues with each vaccine platform and safety studies in Phase III & IV
- Further refine Tier Groups for allocation of early vaccine, based on ACIP feedback
- Review proposed implementation strategies

Questions for ACIP

- Do you agree with the proposed guiding principles?
- Do you agree with the next steps?
- What topics would you like to see presented at the next ACIP meeting?



Thank you

For more information, contact CDC
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TTY: 1-888-232-6348 www.cdc.gov

Clinical Trials Results Reporting Extensions for Good Cause – NIH Process Options

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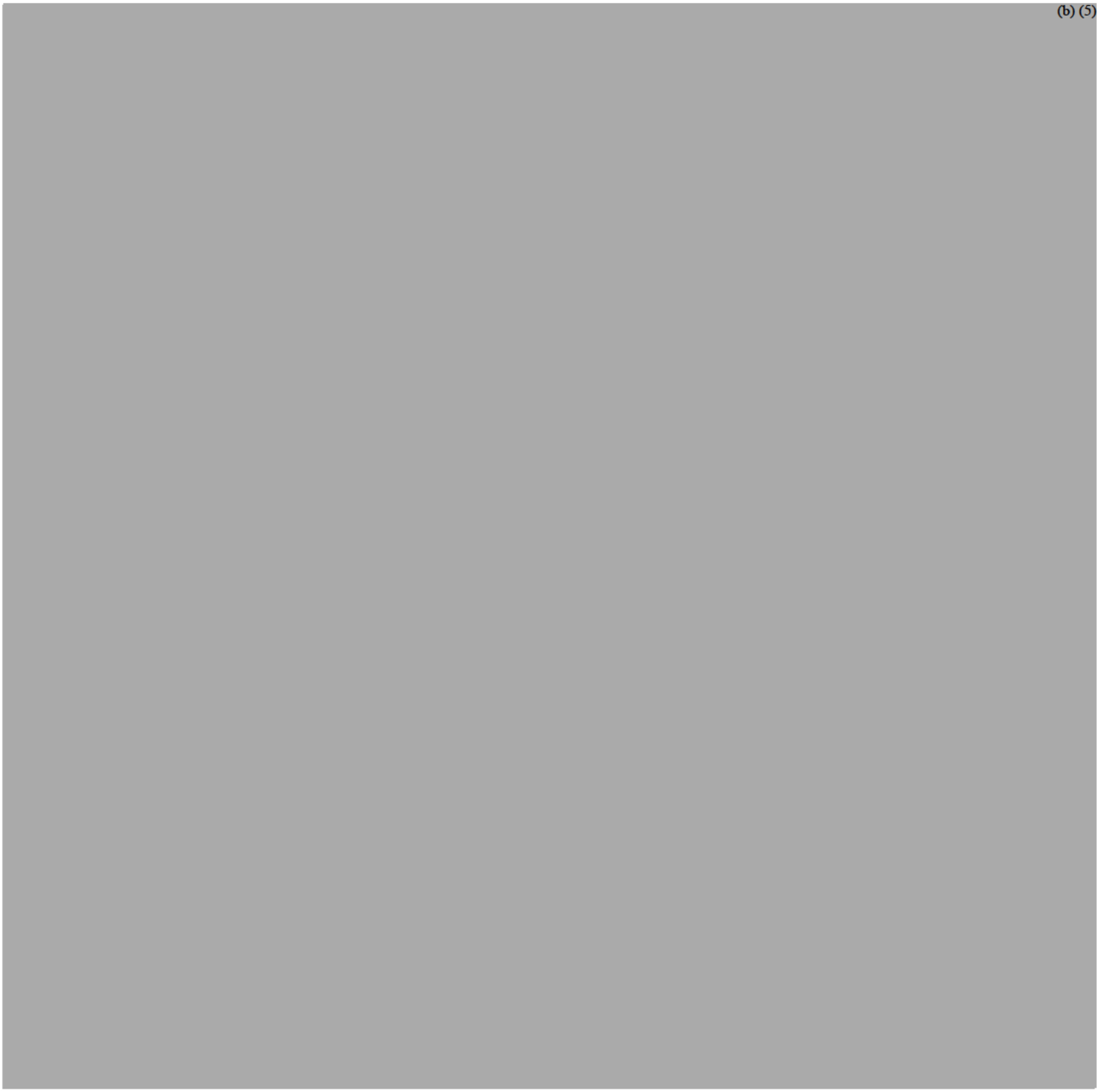

From:	Lohmann, Larry (NIH/OD) [E]
To:	McBride, Aidan (NIH/OD) [C]
Cc:	Higgins, Lauren (NIH/OD) [E]
Subject:	FW: 3.18.21 Letter to Director Collins from House Energy and Commerce Minority
Date:	Thursday, March 18, 2021 11:12:42 AM
Attachments:	2021.03.16 - NIH Letter on WIV.pdf US STATE DEPT CABLES in Appendix to GOP-Report-OriginsOfCOVID-19-Global-Pandemic-Including-Roles-of-CCPandWHO.09.20.20.pdf

Hi Aidan,

Thank you for checking on that other letter. Could you please enter this letter and the attachment in? It will likely have some additional information after I'm able to speak to HHS, but want to make sure it is in there.

Thanks,
Larry

From: "Clutterbuck, William" (b) (6)
Date: Thursday, March 18, 2021 at 9:38 AM
To: "Lohmann, Larry (NIH/OD) [E]" (b) (6)
Cc: "Slobodin, Alan" (b) (6)
Subject: 3.18.21 Letter to Director Collins from House Energy and Commerce Minority

Hello Larry,

Please see the attached letter to NIH Director Collins, regarding the origins of the COVID-19 pandemic.

This letter was signed by House Energy and Commerce Ranking Members McMorris Rodgers, Guthrie, and Griffith.

Attached to this email, you will find the 2018 U.S. Department of State cables mentioned in the letter.

Please respond to this email to confirm receipt.

Thank you,

William Clutterbuck
Staff Assistant
House Committee on Energy & Commerce
2322 Rayburn House Office Building
Tel: (b) (6) | (b) (6)

FRANK PALLONE, JR., NEW JERSEY
CHAIRMAN

CATHY McMORRIS RODGERS, WASHINGTON
RANKING MEMBER

ONE HUNDRED SEVENTEENTH CONGRESS

Congress of the United States

House of Representatives

COMMITTEE ON ENERGY AND COMMERCE

2125 RAYBURN HOUSE OFFICE BUILDING
WASHINGTON, DC 20515-6115
Majority (202) 225-2927
Minority (202) 225-3641

March 18, 2021

The Honorable Francis Collins, M.D., Ph.D.
Director
National Institutes of Health
9000 Rockville Pike
Bethesda, MD 20892

Dear Dr. Collins,

We write to request information, assistance, and needed-leadership from the National Institutes of Health (NIH) to advance an independent, scientific investigation into the origins of the COVID-19 pandemic.

The COVID-19 pandemic has been the worst public health crisis in the U.S. in about a hundred years. Over a year has passed since the deadly virus reached our shores and yet, the origin of the virus has yet to be determined. An independent, expert investigation of the origin of COVID-19 is of paramount importance to public health and biosecurity. As noted by Stanford Medical School Professor David Relman:

> A more complete understanding of the origins of COVID-19 clearly serves the interests of every person in every country on this planet. It will limit further recriminations and diminish the likelihood of conflict; it will lead to more effective responses to this pandemic, as well as efforts to anticipate and prevent the next one. It will also advance our discussions about risky science. And it will do something else: Delineating COVID-19's origin story will help elucidate the nature of our very precarious coexistence within the biosphere.[1]

Recently, the World Health Organization (WHO) attempted to investigate the origin of COVID-19. The WHO said that this investigative mission would be guided by the science, be

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[1] David A. Relman, *Opinion: To stop the next pandemic, we need to unravel the origins of COVID-19*, PNAS (Nov. 2020), *available at* https://www.pnas.org/content/117/47/29246.

"open-minded," and "not exclude[e] any hypothesis."[2] Unfortunately, China did not provide complete access or independence for the critical WHO mission. On February 13, 2021, National Security Advisor Jake Sullivan issued the following statement:

> We have deep concerns about the way in which the early findings of the COVID-19 investigation were communicated and questions about the process used to reach them. It is imperative that this report be independent, with expert findings free from intervention or alteration by the Chinese government. To better understand this pandemic and prepare for the next one, China must make available its data from the earliest days of the outbreak.[3]

Because of rising tensions between the U.S. and China, the WHO scrapped plans for an interim report.[4] An international group of science experts, including specialists in virology, microbiology, and zoology, asked for a new review.[5]

The NIH, as a premier scientific institution, must lead in order to foster a transparent, independent, and science-based investigation into the origin of the COVID-19 pandemic. Such an effort must meet the WHO's stated goals of an open-minded investigation that does not exclude any plausible hypothesis.[6] In addition, the NIH is well-positioned to gather and provide information through oversight of its grants and other federal awards. Thus, the NIH is in a unique position to investigate the possibility that the pandemic stemmed from a laboratory accident or leak, especially regarding the Wuhan Institute of Virology (WIV).

NIH raised concerns over a possible link between WIV and the COVID-19 outbreak during its review of federal awards to EcoHealth Alliance, a global environmental health nonprofit organization dedicated to protecting wildlife and public health from the emergence of disease. Of the $13.7 million in federal awards that NIH authorized for EcoHealth Alliance, 17

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[2] Smriti Mallapaty, *Where did COVID come from? WHO investigation begins but faces challenges*, NATURE (Nov. 11, 2020), *available at* https://www.nature.com/articles/d41586-020-03165-9.

[3] The White House, Statement of National Security Advisor Jake Sullivan (Feb. 13, 2021), *available at* https://www.whitehouse.gov/briefing-room/statements-releases/2021/02/13/statement-by-national-security-advisor-jake-sullivan/.

[4] Betsy McKay, Drew Hinshaw and Jeremy Page, *WHO Investigators to Scrap Plans for Interim Report on Probe of Covid-19 Origins*, THE WALL STREET JOURNAL (Mar. 4, 2021), *available at* https://www.wsj.com/articles/who-investigators-to-scrap-interim-report-on-probe-of-covid-19-origins-11614865067?mod=latest_headlines

[5] Jaime Metzl, et al, *Call for a Full and Unrestricted International Forensic Investigation into the Origins of COVID-19* (March 4, 2021), *available at* https://s.wsj.net/public/resources/documents/COVID%20OPEN%20LETTER%20FINAL%20030421%20(1).pdf. The co-organizer of the letter and a WHO advisor on human genome editing, Jaime Metzl, PhD, said there is an eighty-five percent chance the pandemic started with an accidental leak from the WIV or Wuhan CDC laboratory, *available at* https://jamiemetzl.com/origins-of-sars-cov-2/. ("I have no definitive way of proving this thesis but the evidence is, in my view, extremely convincing. If forced to place odds on the confidence of my hypothesis, I would say there's an 85% chance the pandemic started with an accidental leak from the Wuhan Institute of Virology or Wuhan CDC and a 15% chance it began in some other way (in fairness, here is an article making the case for a zoonotic jump "in the wild"). If China keeps preventing a full and unrestricted international forensic investigation into the origins of the pandemic, I believe it is fair to deny Beijing the benefit of the doubt.")

[6] Washington Post Editorial Board, *We're still missing the origin story of this pandemic. China is sitting on the answers*, THE WASHINGTON POST (Feb. 5, 2021), *available at* https://www.washingtonpost.com/opinions/2021/02/05/coronavirus-origins-mystery-china/?arc404=true.

projects sponsored by the National Institute of Allergy and Infectious Disease (NIAID) have provided over $7.9 million in federal awards for research of viral emergence from bats in Southeast Asia.[7] EcoHealth Alliance passed some of its funding to the WIV, and in 2020, NIH made efforts to obtain information from EcoHealth Alliance about WIV related to concerns about the origins of COVID-19. In April 2020, NIH wrote to EcoHealth Alliance and Columbia University about an NIH-funded project entitled, "Understanding the Risk of Bat Coronavirus Emergency:"

> It is our understanding that one of the sub-recipients of the grant funds is the Wuhan Institute of Virology ('WIV'). It is our understanding that WIV studies the interaction between corona viruses and bats. The scientific community believes that the coronavirus causing COVID-19 jumped from bats to humans likely in Wuhan where the COVID-19 pandemic began. There are now allegations that the current crisis was precipitated by the release from WIV of the coronavirus responsible for COVID-19. Given these concerns, we are pursuing suspension of WIV from participation in Federal programs. It is in the public interest that NIH ensure that a sub-recipient has taken all appropriate precautions to prevent the release of pathogens that it is studying. This suspension of the sub-recipient does not affect the remainder of your grant assuming that no grant funds are provided to WIV following receipt of this email during the period of suspension.[8]

In January 2021, the U.S. Department of State issued a fact sheet about the activity at the WIV.[9] Among other revelations, it reported the following:

- The U.S. government has reason to believe that several researchers inside the WIV became sick in autumn 2019, before the first identified case of the outbreak, with symptoms consistent with both COVID-19 and common seasonal illnesses. This raises questions about the credibility of WIV senior researcher Shi Zhengli's public claim that there was "zero infection" among the WIV's staff and students of SARS-CoV-2 or SARS-related viruses.[10]

- Starting in at least 2016, WIV researchers conducted experiments involving RaTG13, the bat coronavirus identified by the WIV in January 2020 as the closest sample to SARS-CoV-2 (96.2 percent similar).[11] There was no indication that this research was suspended at any time prior to the COVID-19 outbreak.

- The WIV has a published record of conducting "gain-of-function" research to engineer chimeric viruses.[12] But the WIV has not been transparent or consistent about its record of

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[7] NIH RePORTER, *Research Portfolio Online Reporting Tools* (queried Mar. 4, 2021), *available at* https://reporter.nih.gov/search/qlYUeI9DIk2JfWUdCcWxcA/projects/charts.
[8] Mark Moore, *NIH investigating Wuhan lab at center of coronavirus pandemic*, NEW YORK POST (Apr. 28, 2020), *available at* https://nypost.com/2020/04/28/nih-investigating-wuhan-lab-at-center-of-coronavirus-pandemic/.
[9] U.S. Department of State, *Fact Sheet: Activity at the Wuhan Institute of Virology*, Office of the Spokesperson (Jan. 15, 2021), *available at* https://2017-2021.state.gov/fact-sheet-activity-at-the-wuhan-institute-of-virology//index.html.
[10] *Id.*
[11] *Id.*
[12] *Id.*

studying viruses similar to the COVID-19 virus, including "RaTG13," which was sampled from a cave in Yunnan Province in 2013 after several miners died of SARS-like illness.[13]

- WHO investigators must have access to the records of the WIV's work on bat and other coronaviruses before the COVID-19 outbreak. As part of a thorough inquiry, they must have a full accounting of why the WIV altered and then removed online records of its work with RaTG13 and other viruses.[14]

- Despite the WIV presenting itself as a civilian institution, the U.S. has determined that the WIV has collaborated on projects with China's military.[15] The WIV has engaged in classified research, including laboratory animal experiments, on behalf of the Chinese military since at least 2017.[16]

- The U.S. and other donors who funded or collaborated on civilian research at the WIV have a right and obligation to determine whether any of our research funding was diverted to secret Chinese military projects at the WIV.[17]

Notably, the State Department's former lead investigator who oversaw the Task Force into the COVID-19 virus origin stated recently that he not only believes the virus escaped from the WIV, but that it may have been the result of research that the Chinese military, or People's Liberation Army, was doing on a bioweapon.[18]

Accordingly, it is imperative to determine not only where SARS-CoV-2 originated, but also how and if NIH's funding and research to projects at the WIV could have contributed to SARS CoV-2. To assist our requests and inquiry, please provide the following by April 19, 2021:

1. An assessment from a classified U.S. Defense Intelligence Agency (DIA) report included the possibility that the origins of SARS CoV-2 could have emerged accidentally from a laboratory in Wuhan, China due to unsafe laboratory practices.[19] The DIA report cited U.S. government and Chinese researchers who found "about 33 percent of the original 41 identified cases did not have direct exposure" to the market.[20] That, along with what is known of the WIV's work in past few years, raised reasonable suspicion that the

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[13] *Id.*
[14] *Id.*
[15] *Id.*
[16] *Id.*
[17] *Id.*

[18] Jennifer Griffin, Former top State Dept. investigator says COVID-19 outbreak may have resulted from bioweapons research accident, Fox News (March 13, 2021), *available at* https://www.foxnews.com/world/top-state-official-coronavirus-bioweapon-accident

[19] Fred Guterl, Naveed Jamali and Tom O'Connor, *The Controversial Experiments ad Wuhan Lab Suspected of Starting the Coronavirus Pandemic*, NEWSWEEK (Apr. 27, 2020), *available at* https://www.newsweek.com/controversial-wuhan-lab-experiments-that-may-have-started-coronavirus-pandemic-1500503.
[20] *Id.*

pandemic may have been caused by a lab error, not a wet market.[21] Further, a WHO inspector on the recent mission noted that "we know not all of those first 174 early COVID-19 cases visited the market, including the man diagnosed in December 2019 with the earliest onset date."[22] What information does the NIH have on the earliest COVID-19 cases?

2. According to an editorial on February 23, 2021, in *The Wall Street Journal* by former Secretary of State Mike Pompeo and Miles Yu, "[China's] army of scientists claim to have discovered almost 2,000 new viruses in a little over a decade."[23] How many of these discovered viruses does the NIH have information on and were any of these viruses discovered at the WIV?

3. According to *The Wall Street Journal* editorial mentioned in the previous question, some have alleged that the WIV's virus-carrying animals were sold as pets and may even show up at local wet markets.[24] Is the NIH aware of these allegations? If so, please provide any information the NIH has related to these allegations.

4. Please provide all information that NIH has about laboratory accidents and/or biosafety practices at the WIV since January 1, 2015.

5. Please provide all information that NIH has from NIH staff, grantees, sub-grantees, contractors, or subcontractors about communications and events at the WIV from August 2019 to the present.

6. Please provide all information that NIH has from NIH staff, grantees, sub-grantees, contractors, or subcontractors about their communications with China-based NIH, Chinese National Science Foundation, CDC, and China CDC about events at the WIV from August 2019 to the present.

State Department Cables

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[21] *Id.*

[22] Dominic Dwyer, I was the Australian doctor on the WHO's COVID-19 mission to China. Here's what we found about the origins of the coronavirus, THE CONVERSATION (Feb. 21, 2021), *available at*https://www.theguardian.com/commentisfree/2021/feb/22/i-was-on-the-whos-covid-mission-to-china-heres-what-we-found. *See also* Jeremy Page and Drew Hinshaw, *China Refuses to Give WHO Raw Data on Early Covid-19 Cases*, THE WALL STREET JOURNAL (Feb. 12, 2021), *available at* https://www.wsj.com/articles/china-refuses-to-give-who-raw-data-on-early-covid-19-cases-11613150580#:~:text=BEIJING%E2%80%94Chinese%20authorities%20refused%20to,over%20the%20lack%20of%20detail. ("Chinese authorities refused to provide World Health Organization investigators with raw, personalized data on early Covid-19 cases that could help them determine how and when the coronavirus first began to spread in China, according to WHO investigators who described heated exchanges over the lack of detail. The Chinese authorities turned down requests to provide such data on 174 cases of Covid-19 that they have identified from the early phase of the outbreak in the Chinese city of Wuhan in December 2019. Investigators are part of a WHO team that this week completed a monthlong mission in China aimed at determining the origins of the pandemic.")

[23] *Id.*

[24] Mike Pompeo and Miles Yu, *NIH Presses U.S. Nonprofit for Information on Wuhan Virology Lab,* THE WALL STREET JOURNAL (Feb. 23, 2021), available at https://www.wsj.com/articles/chinas-reckless-labs-put-the-world-at-risk-11614102828.

7. What information does NIH have about the WIV's responses to the 2018 U.S. Department of State cables (attached to this letter) regarding safety concerns?

8. The April 2018 cable from the U.S. Department of State stated that the WIV planned to invite University of Texas Medical Branch Galveston (UTMBG) researchers to do research in Wuhan's labs. Please provide any information NIH received that indicates whether the WIV invited UTMBG researchers, and whether UTMBG researchers conducted any research in Wuhan's labs.

    a. If there was such research, please provide information and any documents related to this research.

9. Why was it pertinent to the NIH investigation that the "nonprofit [EcoHealth Alliance] must provide the "WIV's responses to the 2018 Department of State cables regarding safety concerns"?[25]

    a. Did EcoHealth Alliance provide this information? If so, how did NIH use the information to further its investigation?

EcoHealth Alliance, Columbia University Health Sciences

10. Was the 2019 NIH federal award to EcoHealth Alliance reviewed and approved by the HHS Potential Pandemic Pathogen Care and Oversight (P3CO) committee?[26]

    a. If so, please provide the documentation with the committee's decision.

    b. Please also provide the names of the individuals who were members of the committee at the time.

11. Please provide all correspondence and communications between NIH and EcoHealth Alliance, since January 1, 2020, related to federal funding involving the WIV. The documentation should include, but not be limited to, correspondence between NIH and EcoHealth Alliance dated sometime in April 2020, on July 8, 2020, and sometime in August 2020.

12. In April 2020, NIH suspended a 2019 federal award to EcoHealth Alliance, in part, because NIH did not believe the work aligned with "program goals and agency priorities."[27] Please specify the work that was done by the EcoHealth Alliance that did

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[25] Meredith Wadman, *NIH imposes 'outrageous' conditions on resuming coronavirus grant targeted by Trump*, SCIENCEMAG (Aug. 19, 2020), *available at* https://www.sciencemag.org/news/2020/08/nih-imposes-outrageous-conditions-resuming-coronavirus-grant-targeted-trump.
[26] National Institutes of Health, *Notice Announcing the Removal of the Funding Pause for Gain-of-Function Research Project* (Dec. 19, 2017), *available at* https://grants.nih.gov/grants/guide/notice-files/NOT-OD-17-071.html.
[27] *Id.*

not align with the agency's program goals and priorities, and when that work was conducted.

a. Was an evaluation of EcoHealth Alliance's work and whether it aligned with the agency's program goals and priorities conducted by the NIH before the award was issued? If yes, please provide any related documentation. If not, why not?

13. In April 2020 correspondence with EcoHealth Alliance, NIH wrote that it "received reports that the Wuhan Institute of Virology…has been conducting research at its facilities in China that pose serious bio-safety concerns."[28] What are the sources for those reports to NIH and what were the specific allegations reported?

14. Why did the NIH request that EcoHealth Alliance provide a sample of the pandemic coronavirus that the WIV used to determine its genetic sequence for SARS CoV-2?[29]

a. Why is this information important to NIH's investigation?

b. Has NIH obtained the sample and if so, what evaluations have been done, and for what purpose?

c. If NIH has not yet obtained the sample, what are the planned studies and evaluations NIH will conduct with the sample when it is obtained?

15. What is the nature of NIH's concerns about purported restrictions at the WIV including "diminished cell-phone traffic in October 2019, and the evidence that there may have been roadblocks surrounding the facility from October 14-19, 2019[,]" about the WIV lab or virus origin?[30]

a. What is the basis of information to NIH about the purported restrictions at the WIV?

b. What are the other purported restrictions at the WIV in October 2019?

16. After terminating EcoHealth Alliance's 2019 project entitled "Understanding the Risk of Bat Coronavirus Emergence," the NIH later offered to reinstate the EcoHealth Alliance funding in July 2020 if EcoHealth Alliance agreed to meet certain conditions.[31]

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[28] Betsy McKay, *NIH Presses U.S. Nonprofit for Information on Wuhan Virology Lab*, THE WALL STREET JOURNAL (Aug. 19. 2020), *available at* https://www.wsj.com/articles/nih-presses-u-s-nonprofit-for-information-on-wuhan-virology-lab-11597829400.

[29] Meredith Wadman, *NIH imposes 'outrageous' conditions on resuming coronavirus grant targeted by Trump*, SCIENCEMAG (Aug. 19, 2020), *available at* https://www.sciencemag.org/news/2020/08/nih-imposes-outrageous-conditions-resuming-coronavirus-grant-targeted-trump.

[30] *Id.*

[31] Betsy McKay, *NIH Presses U.S. Nonprofit for Information on Wuhan Virology Lab*, THE WALL STREET JOURNAL (Aug. 19. 2020), *available at* https://www.wsj.com/articles/nih-presses-u-s-nonprofit-for-information-on-wuhan-virology-lab-11597829400.

a. Please provide all of the information presented to NIH from EcoHealth Alliance in response to NIH's conditions for reinstatement.

b. What actions did NIH take based upon the information received? How has the information been used in NIH's investigation?

c. One condition for the federal award reinstatement was for EcoHealth Alliance to arrange for an outside inspection of the WIV and its records, "with specific attention to addressing the question of whether WIV staff had SARS-CoV-2their possession prior to December 2019."[32] Why is it pertinent to the NIH's investigation if staff at WIV had SARS-CoV-2 in their possession prior to December 2019? What is the potential significance if the staff did have the virus in their possession prior to December 2019?

d. What information does NIH have that was used for the basis of requesting that the EcoHealth Alliance "must 'explain the apparent disappearance' of a scientist who worked in the Wuhan lab," and on social media was rumored to be "patient zero" of the pandemic?[33]

    i. What is the potential significance about the whereabouts of this scientist and the photo being removed from the website?

17. Please provide all correspondence and communications between NIH and Columbia University related to federal funding involving the WIV, including email correspondence in April 2020 between Dr. Michael Lauer, Deputy Director of extramural research, and Naomi Schrag of Columbia University.

    a. In an April 2020 email, Dr. Lauer advised Naomi Schrag of Columbia University that it would be helpful for NIH "to know about all China-based participants in this work since the Type 1 grant started in 2014 - who they were and how much money they received."[34] Why did NIH request that Columbia University provide information about all of the China-based participants?

        i. What is the pertinence of the timeframe starting in 2014 for the requested information?

        ii. Did Columbia University provide the NIH with the requested information about all of the China-based participants from all grantees since 2014? If so, please provide the information1. If not, why not?

Federal Funding Records

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[32] *Id.*
[33] *Id.*
[34] Meredith Wadman and Jon Cohen, *NIH's axing of bat coronavirus grant a 'horrible precedent' and might break rules, critics say*, SCIENCEMAG (Apr. 30, 2020), *available at* https://www.sciencemag.org/news/2020/04/nih-s-axing-bat-coronavirus-grant-horrible-precedent-and-might-break-rules-critics-say.

18. Please provide ledgers or any accounting for dispersion of all NIH federal funding awards that EcoHealth Alliance has sent to the WIV, including through contracts, grants, donations, cooperative agreements, staffing, or any other support or means. In addition, please provide the results and outcomes from the funding and support.[35]

19. What is the total amount of NIH federal funding per year from 2017 through 2021 that has directly or indirectly supported the WIV scientists or research through grant recipients, including to EcoHealth Alliance; Wildlife Trust, Inc.; Columbia University Health Sciences; Trustees of Columbia University; University of North Carolina Chapel Hill; Vanderbilt University; University of Virginia; and Oregon Health and Science University?[36]

20. According to a report in *The Washington Post* on April 14, 2020, the WIV issued a news release in English about the final visit from U.S. Embassy scientist diplomats in Beijing, which occurred on March 27, 2018.[37] Does the NIH have a copy of this news release? If so, please provide a copy.

21. For NIH award recipients that have provided support to the WIV since January 1, 2012, please provide annual reports, trip reports related to the WIV, documentation of any survey or field trips by the WIV, and interim data summaries from the WIV.

22. Please provide copies of all grantee annual reports, progress reports, projects, studies, and observations since 2014 where foreign sites for all Type 1 and Type 2 awards have been documented as involving the WIV.

23. Please provide copies of all grantee annual reports, progress reports, projects, studies, and observations since 2014 for NIH domestic grantee awards with a foreign component involving the WIV.

24. Please provide the name(s) of the NIH program manager(s) or officer(s) responsible for overseeing the grants to EcoHealth Alliance and time period(s) of responsibility.

25. Please provide the name(s) of the NIH Scientific Review Officers responsible for reviewing and approving any NIH financial awards to EcoHealth Alliance and any other funding recipients that supported the WIV.

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[35] Betsy McKay, *NIH Presses U.S. Nonprofit for Information on Wuhan Virology Lab*, THE WALL STREET JOURNAL (Aug. 19. 2020), *available at* https://www.wsj.com/articles/nih-presses-u-s-nonprofit-for-information-on-wuhan-virology-lab-11597829400.

[36] National Institutes of Health, Research Portfolio online Reporting Tools, NIH RePorter *available at* https://report.nih.gov/ (last accessed March 6, 2020).

[37] Josh Rogin, *Opinion: State Department cables warned of safety issues at Wuhan lab studying bat coronaviruses*, THE WASHINGTON POST (Apr. 14, 2020), *available at* https://www.washingtonpost.com/opinions/2020/04/14/state-department-cables-warned-safety-issues-wuhan-lab-studying-bat-coronaviruses/.

26. According to an editorial in *The Wall Street Journal*, the WIV housed tens of thousands of bat samples and laboratory animals in 2019.[38] Please provide any information the NIH has on the number of bat samples and animals at the WIV.

    a. Did any NIH scientists who are fluent in Mandarin review the Chinese scientific literature on the WIV research related to coronaviruses that is dated before February 1, 2020?

27. Does the NIH have the unpublished sequences of bat coronaviruses that were maintained in the WIV database before December 30, 2019, or before the database was removed from the internet?[39] Does NIH have the full sequences of the eight viruses sampled in the Yunnan province on an EcoHealth Alliance bat-virus sampling trip in 2015?

    a. Please provide NIH's analysis if the sequences have been analyzed.

    b. If NIH does not have the sequences, can NIH get this information from the EcoHealth Alliance or from other NIH-funded sources?

28. Please provide the original version of "Origin and cross-species transmission of bat coronaviruses in China" that was submitted to *Nature* by EcoHealth Alliance on October 6, 2019, published August 25, 2020, and funded in part by NIAID (award number R01AI110964).[40] If NIH does not have the October 6, 2019 report, can NIH obtain it from EcoHealth Alliance for this response? If so, please provide the report.

29. Have NIH, EcoHealth Alliance, or other NIH award recipient(s) been denied permission or access to results of any WIV research, which indirectly received financial support from NIH awards? If so, please provide the date(s), individuals involved, and circumstances of each denial.

We request that the NIH provide the requested documents and information in a coordinated response from all stakeholders and the appropriate divisions within NIH, including but not limited to subject matter experts from NIH's Division of Security and Emergency Response, the Office of Management Assessment, the Center for Scientific Review, the National Institute of Allergy and Infectious Diseases, and the Office of Extramural Research. After the requested information has been provided, we ask that the NIH provide a briefing to the Minority Committee staff to discuss the information that the NIH has related to the origins of SARS-CoV-2, including any potential links to the WIV. Finally, we request that you appoint an NIH working group representing an appropriate diversity of scientific disciplines to collect data and

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[38] Mike Pompeo and Miles Yu, *NIH Presses U.S. Nonprofit for Information on Wuhan Virology Lab*, THE WALL STREET JOURNAL (Feb. 23, 2021), *available at* https://www.wsj.com/articles/chinas-reckless-labs-put-the-world-at-risk-11614102828.

[39] Washington Post Editorial Board, *We're still missing the origin story of this pandemic. China is sitting on the answers*, THE WASHINGTON POST (Feb. 5, 2021), *available at* https://www.washingtonpost.com/opinions/2021/02/05/coronavirus-origins-mystery-china/?arc404=true.

[40] Latinne, A., Hu, B., Olival, K.J. et al,. *Origin and cross-species transmission of bat coronaviruses in China*, Nature (Aug. 25, 2020), *available at* https://www.nature.com/articles/s41467-020-17687-3#Ack1.

information related to COVID-19 origins (including the WIV), and that the NIH working group coordinate and consult with foreign scientific agencies involved in similar work.

Your assistance with this request is greatly appreciated. If you have any questions, please contact Alan Slobodin or Diane Cutler of the Minority Committee staff.

Sincerely,

Cathy McMorris Rodgers
Republican Leader
Committee on Energy and Commerce

Brett Guthrie
Republican Leader
Subcommittee on Health

H. Morgan Griffith
Republican Leader
Subcommittee on Oversight and Investigations

Attachment

Cc: The Honorable Frank Pallone, Chairman
The Honorable Diana DeGette, Chair, Subcommittee on Oversight and Investigations
The Honorable Anna Eshoo, Chair, Subcommittee on Health

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SBU

MRN:	18 BEIJING 138
Date/DTG:	Jan 19, 2018 / 190739Z JAN 18
From:	AMEMBASSY BEIJING
Action:	WASHDC, SECSTATE *ROUTINE*
E.O.:	13526
TAGS:	SHLH, ETRD, ECON, PGOV, CN
Captions:	SENSITIVE
Reference:	17 WUHAN 48
Subject:	China Opens First Bio Safety Level 4 Laboratory

1. (SBU) **Summary and Comment:** The Chinese Academy of Sciences (CAS) has recently established what is reportedly China's first Biosafety Level 4 (BSL-4) laboratory in Wuhan. This state-of-the-art facility is designed for prevention and control research on diseases that require the highest level of biosafety and biosecurity containment. Ultimately, scientists hope the lab will contribute to the development of new antiviral drugs and vaccines, but its current productivity is limited by a shortage of the highly trained technicians and investigators required to safely operate a BSL-4 laboratory and a lack of clarity in related Chinese government policies and guidelines. (b)(5)

(b)(5)

(b)(5) **End Summary and Comment.**

China Investing in Infectious Disease Control

2. (U) Between November 2002 and July 2003, China faced an outbreak of Severe Acute Respiratory Syndrome (SARS), which, according to the World Health Organization, resulting in 8,098 cases and leading to 774 deaths reported in 37 countries. A majority of cases occurred in China, where the fatality rate was 9.6%. This incident convinced China to prioritize international cooperation for infectious disease control. An aspect of this prioritization was China's work with the Jean Merieux BSL-4 Laboratory in Lyon, France, to build China's first high containment laboratory at Wuhan's Institute of Virology (WIV), an institute under the auspices of the Chinese Academy of Sciences (CAS). Construction took 11 years and $44 million USD, and construction on the facility was completed on January 31, 2015. Following

two years of effort, which is not unusual for such facilities, the WIV lab was accredited in February 2017 by the China National Accreditation Service for Conformity Assessment. It occupies four floors and consists of over 32,000 square feet. WIV leadership now considers the lab operational and ready for research on class-four pathogens (P4), among which are the most virulent viruses that pose a high risk of aerosolized person-to-person transmission.

Unclear Guidelines on Virus Access and a Lack of Trained Talent Impede Research

3. (SBU) In addition to accreditation, the lab must also receive permission from the National Health and Family Planning Commission (NHFPC) to initiate research on specific highly contagious pathogens. According to some WIV scientists, it is unclear how NHFPC determines what viruses can or cannot be studied in the new laboratory. To date, WIV has obtained permission for research on three viruses: Ebola virus, Nipah virus, and Xinjiang hemorrhagic fever virus (a strain of Crimean Congo hemorrhagic fever found in China's Xinjiang Province). Despite this permission, however, the Chinese government has not allowed the WIV to import Ebola viruses for study in the BSL-4 lab. Therefore, WIV scientists are frustrated and have pointed out that they won't be able to conduct research project with Ebola viruses at the new BSL-4 lab despite of the permission.

(b)(6)

(b)(6) Thus, while the BSL-4 lab is ostensibly fully accredited, its utilization is limited by lack of access to specific organisms and by opaque government review and approval processes. As long as this situation continues, Beijing's commitment to prioritizing infectious disease control - on the regional and international level, especially in relation to highly pathogenic viruses, remains in doubt.

(b)(6) noted that the new lab has a serious shortage of appropriately trained technicians and investigators needed to safely operate this high-containment laboratory. University of Texas Medical Branch in Galveston (UTMB), which has one of several well-established BSL-4 labs in the United States (supported by the National Institute of Allergy and Infectious Diseases (NIAID of NIH)), has scientific collaborations with WIV, which may help alleviate this talent gap over time. Reportedly, researchers from GTMB are helping train technicians who work in the WIV BSL-4 lab. Despite this, (b)(6) they would welcome more help from U.S. and international organizations as they establish "gold standard" operating procedures and training courses for the first time in China. As China is building more BSL-4 labs, including one in Harbin Veterinary Research Institute subordinated to the Chinese Academy of Agricultural Sciences (CAAS) for veterinary research use, (b)(6) the training for technicians and investigators working on dangerous pathogens will certainly be in demand.

Despite Limitations, WIV Researchers Produce SARS Discoveries

6. (SBU) The ability of WIV scientists to undertake productive research despite limitations on the use of the new BSL-4 facility is demonstrated by a recent publication on the origins of SARS. Over a five-year study, (b)(6) (and their research team) widely sampled bats in Yunnan province with funding support from NIAID/NIH, USAID, and several Chinese funding agencies. The study results were published in PLoS Pathogens online on Nov. 30, 2017 (1), and it demonstrated that a SARS-like coronaviruses isolated from horseshoe bats in a single cave contain all the building blocks of the pandemic SARS-coronavirus genome that caused the human outbreak. These results strongly suggest that the highly pathogenic SARS-coronavirus originated in this bat population. Most importantly, the researchers also showed that various SARS-like coronaviruses can interact with ACE2, the human receptor identified for SARS-coronavirus. This finding strongly suggests that SARS-like coronaviruses from bats can be transmitted to humans to cause SARS-like disease. From a public health perspective, this makes the continued surveillance of SARS-like coronaviruses in bats and study of the animal-human interface critical to future emerging coronavirus outbreak prediction and prevention. (b)(5) (b)(5) WIV scientists are allowed to study the SARS-like coronaviruses isolated from bats while they are precluded from studying human-disease causing SARS coronavirus in their new BSL-4 lab until permission for such work is granted by the NHFCP.

1. Hu B, Zeng L-P, Yang X-L, Ge X-Y, Zhang W, Li B, et al. (2017) Discovery of a rich gene pool of bat SARS-related coronaviruses provides new insights into the origin of SARS coronavirus. PLoS Pathog 13(11): e1006698. https://doi.org/10.1371/journal.ppat.1006698

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MRN:	18 WUHAN 38
Date/DTG:	Apr 19, 2018 / 190551Z APR 18
From:	AMCONSUL WUHAN
Action:	WASHDC, SECSTATE *ROUTINE*
E.O.:	13526
TAGS:	SHLH, PGOV, CN, PREL, TBIO, KGHI, CDC, EAID, KHIV, IN, JP, TW, TSPL, PINS, SENV
Captions:	SENSITIVE
Reference:	A) 18 BEIJING 138 B) 17 BEIJING 2458 C) 11 MUMBAI 630 D) 17 TOKYO 716 E) 13 SEOUL 790
Subject:	China Virus Institute Welcomes More U.S. Cooperation on Global Health Security

1. (SBU) **Summary with Comment:** China's Wuhan Institute of Virology, a global leader in virus research, is a key partner for the United States in protecting global health security. Its role as operator of the just-launched Biosafety Level 4 (or "P4") lab -- the first such lab in China -- opens up even more opportunities for expert exchange, especially in light of the lab's shortage of trained staff (Ref A). (b)(5)

(b)(5)

(b)(5) **End Summary with Comment.**

2. (U) Wuhan Institute of Virology researchers and staff gave an overview of the lab and current cooperation with the United States to visiting Environment, Science, Technology and Health Counsellor Rick Switzer and Consulate Wuhan Consul General Jamie Fouss in late March. In the last year, the institute has also hosted visits from the National Institutes of Health (NIH), National Science Foundation, and experts from the University of Texas Medical Branch in Galveston. The institute reports to the Chinese Academy of Sciences in Beijing.

P4 Lab is Open and Transparent, Officials Emphasize

3. (SBU) The Wuhan P4 lab, referring to labs with the highest level of safety precautions, became fully operational and began working with live viruses early this year. Institute officials said they believed it is the only operational P4 lab in Asia aside from a U.S. Centers for Disease

Control (CDC)-supported facility in Pune, India (Ref C). China plans to stand up a second P4 lab in Harbin. Institute officials said Japan's biosafety labs are "old" and lack cutting-edge equipment, so they consider Japan's labs to be "P3 Plus" (*Note*: the Japanese government says it has one P4-level lab in the Tokyo suburbs, though its activities are limited, and Japan is building a new P4 lab in Nagasaki, see Ref D. Taiwan operates at least one P4 lab. South Korea was close to opening a P4 lab as of last year, see Ref E. *End.Note.*) Wuhan's lab is located about 20 miles from the city center in Zhengdian district, and the institute plans to gradually consolidate its other training, classroom and lab facilities at that location.

4. (U) Officials described the lab as a "regional node" in the global biosafety system and said it would play an emergency response role in an epidemic or pandemic. The lab's English brochure highlighted a national security role, saying that it "is an effective measure to improve China's availability in safeguarding national bio-safety if [a] possible biological warfare or terrorist attack happens."

5. (SBU) Institute officials said there would be "limited availability" for international and domestic scientists who had gone through the necessary approval process to do research at the lab. They stressed that the lab aimed to be a "worldwide, open platform" for virology. They said they welcomed U.S. Centers for Disease Control (CDC) experts, noting that the Chinese Academy of Sciences was not strong on human disease expertise, having only focused on it in the last 15 years, after the SARS outbreak. A Wuhan-based French consulate official who works on science and technology cooperation with China also emphasized that the lab, which was initiated in 2004 as a France-China joint project, was meant to be "open and transparent" to the global scientific community. "The intent was to set up a lab to international standards, and open to international research," he said. French experts have provided guidance and biosafety training to the lab, which will continue, the French official said. Institute officials said that France provided the lab's design and much of its technology, but that it is entirely China-funded and has been completely China-run since a "handover" ceremony in 2016.

6. (U) In addition to French assistance, experts from the NIH-supported P4 lab at the University of Texas Medical Branch in Galveston have trained Wuhan lab technicians in lab management and maintenance, institute officials said. The Wuhan institute plans to invite scientists from the Galveston lab to do research in Wuhan's lab. One Wuhan Institute of Virology researcher trained for two years at the Galveston lab, and the institute also sent one scientist to U.S. CDC headquarters in Atlanta for six months' work on influenza.

NIH-Supported Research Revises SARS Origin Story

7. (U) NIH was a major funder, along with the Natural Science Foundation of China (NSFC), of SARS research by the Wuhan Institute of Virology's [redacted] This lends weight to the theory that SARS originated in bat populations before jumping first to civet cats (likely via bat feces) and then to humans. [redacted]

(b)(6)
(b)(6) team has provided support in statistical modeling to assess the risk of more coronaaviruses like SARS crossing over to human populations.

Ready to Help with the Global Virome Project

8. (U) Institute officials expressed strong interest in the Global Virome Project (GVP), and said Chinese funding for the project would likely come from Chinese Academy of Sciences funding already earmarked for One Belt, One Road-related initiatives. The GVP aims to launch this year as an international collaborative effort to identify within ten years virtually all of the planet's viruses that have pandemic or epidemic potential and the ability to jump to humans. "We hope China will be one of the leading countries to initiate the Global Virome Project," one Wuhan Institute of Virology official said. China attended a GVP unveiling meeting in January in Thailand and is waiting for more details on the initiative. The officials said that the Chinese government funds projects similar to GVP to investigate the background of viruses and bacteria. This essentially constituted China's own Virome Project, officials said, but they noted the program currently has no official name.

9. (SBU) The Wuhan Institute of Virology's (b)(6) is the (b)(6) (b)(6) (b)(6) which is designed to show "proof of concept" and be a forerunner to the Global Virome Project. (b)(6) with the EcoHealth Alliance (a New York City-based NGO that is working with the University of California, Davis to manage the (b)(6) recently planned to visit Wuhan to meet with (b)(6) (b)(6) noted that China has expressed interest in building the GVP database, which would put China in a leadership position. Other countries have confidence in China's ability to build such a database, but are skeptical on whether China could remain transparent as a "gatekeeper" for this information. (b)(6) said (b)(6) expressed frustration with the slow progress so far in launching GVP, noting that the effort lacked funding sources, needed to hire a CEO, and would have to boost its profile at G7, G20 and other high-level international meetings.

U.S.-China Workshop Explores Research Partnerships

10. (U) The Institute also has ongoing collaboration with the U.S. National Science Foundation, including a just-concluded workshop in Shenzhen, involving about 40 scientists from the United States and China, on the topic of the "Ecology and Evolution of Infectious Diseases." Co-sponsored by the Natural Science Foundation of China (NSFC), (b)(6)
(b)(6)
(b)(6) The workshop explored opportunities for U.S.-China research cooperation in areas like using "big data" to predict emerging infectious diseases, climate change's effect on vector-borne diseases, and pathogen transmission between wildlife, domestic animals and humans.

11. (SBU) Some workshop participants also expressed skepticism about the Global Virome Project's (GVP) approach, saying that gaining a predictive understanding of viruses with pandemic potential would require going beyond the GVP's strategy of sample collection, to take an "ecological" approach that considers the virome beyond vertebrate systems to identify

mechanisms driving pathogen evolution. A follow-on workshop will be held in June at the University of Berkeley. NSF and NSFC hope to jointly announce a funding call for collaborative projects later this year.

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Cleared By:
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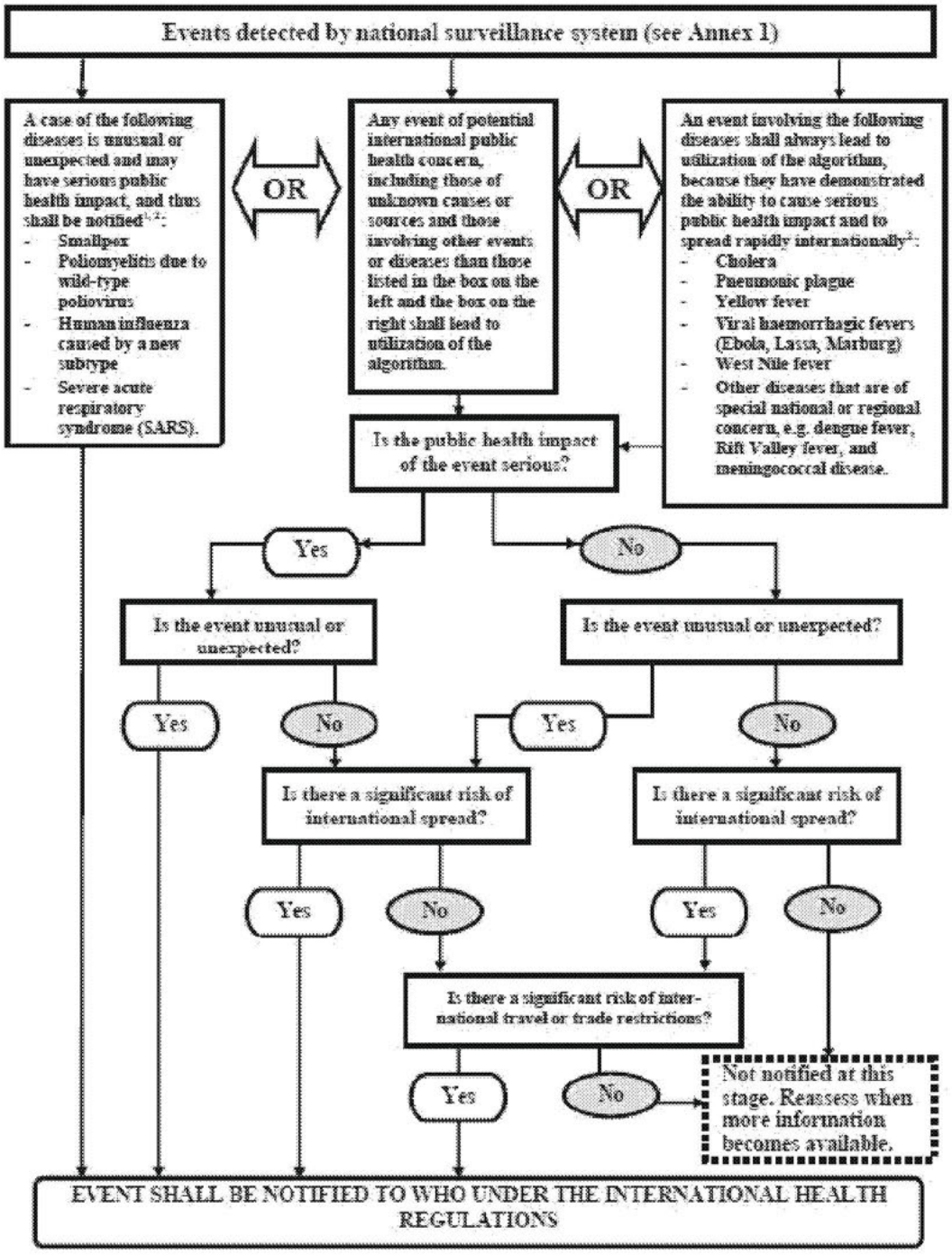
Annex 2 of the 2005 International Health Regulations

ANNEX 2

DECISION INSTRUMENT FOR THE ASSESSMENT AND NOTIFICATION OF EVENTS THAT MAY CONSTITUTE A PUBLIC HEALTH EMERGENCY OF INTERNATIONAL CONCERN



[1] As per WHO case definitions.
[2] The disease list shall be used only for the purposes of these Regulations.

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MRN:	18 BEIJING 138
Date/DTG:	Jan 19, 2018 / 190739Z JAN 18
From:	AMEMBASSY BEIJING
Action:	WASHDC, SECSTATE *ROUTINE*
E.O.:	13526
TAGS:	SHLH, ETRD, ECON, PGOV, CN
Captions:	SENSITIVE
Reference:	17 WUHAN 48
Subject:	China Opens First Bio Safety Level 4 Laboratory

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(b)(5)

(b)(5) **End Summary and Comment.**

China Investing in Infectious Disease Control

2. (U) Between November 2002 and July 2003, China faced an outbreak of Severe Acute Respiratory Syndrome (SARS), which, according to the World Health Organization, resulting in 8,098 cases and leading to 774 deaths reported in 37 countries. A majority of cases occurred in China, where the fatality rate was 9.6%. This incident convinced China to prioritize international cooperation for infectious disease control. An aspect of this prioritization was China's work with the Jean Merieux BSL-4 Laboratory in Lyon, France, to build China's first high containment laboratory at Wuhan's Institute of Virology (WIV), an institute under the auspices of the Chinese Academy of Sciences (CAS). Construction took 11 years and $44 million USD, and construction on the facility was completed on January 31, 2015. Following

two years of effort, which is not unusual for such facilities, the WIV lab was accredited in February 2017 by the China National Accreditation Service for Conformity Assessment. It occupies four floors and consists of over 32,000 square feet. WIV leadership now considers the lab operational and ready for research on class-four pathogens (P4), among which are the most virulent viruses that pose a high risk of aerosolized person-to-person transmission.

Unclear Guidelines on Virus Access and a Lack of Trained Talent Impede Research

3. (SBU) In addition to accreditation, the lab must also receive permission from the National Health and Family Planning Commission (NHFPC) to initiate research on specific highly contagious pathogens. According to some WIV scientists, it is unclear how NHFPC determines what viruses can or cannot be studied in the new laboratory. To date, WIV has obtained permission for research on three viruses: Ebola virus, Nipah virus, and Xinjiang hemorrhagic fever virus (a strain of Crimean Congo hemorrhagic fever found in China's Xinjiang Province). Despite this permission, however, the Chinese government has not allowed the WIV to import Ebola viruses for study in the BSL-4 lab. Therefore, WIV scientists are frustrated and have pointed out that they won't be able to conduct research project with Ebola viruses at the new BSL-4 lab despite of the permission.

(b)(6)

(b)(6) Thus, while the BSL-4 lab is ostensibly fully accredited, its utilization is limited by lack of access to specific organisms and by opaque government review and approval processes. As long as this situation continues, Beijing's commitment to prioritizing infectious disease control - on the regional and international level, especially in relation to highly pathogenic viruses, remains in doubt.

(b)(6) noted that the new lab has a serious shortage of appropriately trained technicians and investigators needed to safely operate this high-containment laboratory. University of Texas Medical Branch in Galveston (UTMB), which has one of several well-established BSL-4 labs in the United States (supported by the National Institute of Allergy and Infectious Diseases (NIAID of NIH)), has scientific collaborations with WIV, which may help alleviate this talent gap over time. Reportedly, researchers from GTMB are helping train technicians who work in the WIV BSL-4 lab. Despite this, (b)(6) they would welcome more help from U.S. and international organizations as they establish "gold standard" operating procedures and training courses for the first time in China. As China is building more BSL-4 labs, including one in Harbin Veterinary Research Institute subordinated to the Chinese Academy of Agricultural Sciences (CAAS) for veterinary research use, (b)(6) the training for technicians and investigators working on dangerous pathogens will certainly be in demand.

Despite Limitations, WIV Researchers Produce SARS Discoveries

6. (SBU) The ability of WIV scientists to undertake productive research despite limitations on the use of the new BSL-4 facility is demonstrated by a recent publication on the origins of SARS. Over a five-year study, (b)(6) (and their research team) widely sampled bats in Yunnan province with funding support from NIAID/NIH, USAID, and several Chinese funding agencies. The study results were published in PLoS Pathogens online on Nov. 30, 2017 (1), and it demonstrated that a SARS-like coronaviruses isolated from horseshoe bats in a single cave contain all the building blocks of the pandemic SARS-coronavirus genome that caused the human outbreak. These results strongly suggest that the highly pathogenic SARS-coronavirus originated in this bat population. Most importantly, the researchers also showed that various SARS-like coronaviruses can interact with ACE2, the human receptor identified for SARS-coronavirus. This finding strongly suggests that SARS-like coronaviruses from bats can be transmitted to humans to cause SARS-like disease. From a public health perspective, this makes the continued surveillance of SARS-like coronaviruses in bats and study of the animal-human interface critical to future emerging coronavirus outbreak prediction and prevention. (b)(5) (b)(5) WIV scientists are allowed to study the SARS-like coronaviruses isolated from bats while they are precluded from studying human-disease causing SARS coronavirus in their new BSL-4 lab until permission for such work is granted by the NHFCP.

1. Hu B, Zeng L-P, Yang X-L, Ge X-Y, Zhang W, Li B, et al. (2017) Discovery of a rich gene pool of bat SARS-related coronaviruses provides new insights into the origin of SARS coronavirus. PLoS Pathog 13(11): e1006698. https://doi.org/10.1371/journal.ppat.1006698

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MRN:	18 WUHAN 38
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From:	AMCONSUL WUHAN
Action:	WASHDC, SECSTATE *ROUTINE*
E.O.:	13526
TAGS:	SHLH, PGOV, CN, PREL, TBIO, KGHI, CDC, EAID, KHIV, IN, JP, TW, TSPL, PINS, SENV
Captions:	SENSITIVE
Reference:	A) 18 BEIJING 138 B) 17 BEIJING 2458 C) 11 MUMBAI 630 D) 17 TOKYO 716 E) 13 SEOUL 790
Subject:	China Virus Institute Welcomes More U.S. Cooperation on Global Health Security

1. (SBU) **Summary with Comment:** China's Wuhan Institute of Virology, a global leader in virus research, is a key partner for the United States in protecting global health security. Its role as operator of the just-launched Biosafety Level 4 (or "P4") lab -- the first such lab in China -- opens up even more opportunities for expert exchange, especially in light of the lab's shortage of trained staff (Ref A). (b)(5)

(b)(5)

(b)(5) **End Summary with Comment.**

2. (U) Wuhan Institute of Virology researchers and staff gave an overview of the lab and current cooperation with the United States to visiting Environment, Science, Technology and Health Counsellor Rick Switzer and Consulate Wuhan Consul General Jamie Fouss in late March. In the last year, the institute has also hosted visits from the National Institutes of Health (NIH), National Science Foundation, and experts from the University of Texas Medical Branch in Galveston. The institute reports to the Chinese Academy of Sciences in Beijing.

P4 Lab is Open and Transparent, Officials Emphasize

3. (SBU) The Wuhan P4 lab, referring to labs with the highest level of safety precautions, became fully operational and began working with live viruses early this year. Institute officials said they believed it is the only operational P4 lab in Asia aside from a U.S. Centers for Disease

Control (CDC)-supported facility in Pune, India (Ref C). China plans to stand up a second P4 lab in Harbin. Institute officials said Japan's biosafety labs are "old" and lack cutting-edge equipment, so they consider Japan's labs to be "P3 Plus" (*Note*: the Japanese government says it has one P4-level lab in the Tokyo suburbs, though its activities are limited, and Japan is building a new P4 lab in Nagasaki, see Ref D. Taiwan operates at least one P4 lab. South Korea was close to opening a P4 lab as of last year, see Ref E. *End.Note.*) Wuhan's lab is located about 20 miles from the city center in Zhengdian district, and the institute plans to gradually consolidate its other training, classroom and lab facilities at that location.

4. (U) Officials described the lab as a "regional node" in the global biosafety system and said it would play an emergency response role in an epidemic or pandemic. The lab's English brochure highlighted a national security role, saying that it "is an effective measure to improve China's availability in safeguarding national bio-safety if [a] possible biological warfare or terrorist attack happens."

5. (SBU) Institute officials said there would be "limited availability" for international and domestic scientists who had gone through the necessary approval process to do research at the lab. They stressed that the lab aimed to be a "worldwide, open platform" for virology. They said they welcomed U.S. Centers for Disease Control (CDC) experts, noting that the Chinese Academy of Sciences was not strong on human disease expertise, having only focused on it in the last 15 years, after the SARS outbreak. A Wuhan-based French consulate official who works on science and technology cooperation with China also emphasized that the lab, which was initiated in 2004 as a France-China joint project, was meant to be "open and transparent" to the global scientific community. "The intent was to set up a lab to international standards, and open to international research," he said. French experts have provided guidance and biosafety training to the lab, which will continue, the French official said. Institute officials said that France provided the lab's design and much of its technology, but that it is entirely China-funded and has been completely China-run since a "handover" ceremony in 2016.

6. (U) In addition to French assistance, experts from the NIH-supported P4 lab at the University of Texas Medical Branch in Galveston have trained Wuhan lab technicians in lab management and maintenance, institute officials said. The Wuhan institute plans to invite scientists from the Galveston lab to do research in Wuhan's lab. One Wuhan Institute of Virology researcher trained for two years at the Galveston lab, and the institute also sent one scientist to U.S. CDC headquarters in Atlanta for six months' work on influenza.

NIH-Supported Research Revises SARS Origin Story

7. (U) NIH was a major funder, along with the Natural Science Foundation of China (NSFC), of SARS research by the Wuhan Institute of Virology's [redacted] This lends weight to the theory that SARS originated in bat populations before jumping first to civet cats (likely via bat feces) and then to humans. [redacted]

(b)(6)
(b)(6) team has provided support in statistical modeling to assess the risk of more coronaaviruses like SARS crossing over to human populations.

Ready to Help with the Global Virome Project

8. (U) Institute officials expressed strong interest in the Global Virome Project (GVP), and said Chinese funding for the project would likely come from Chinese Academy of Sciences funding already earmarked for One Belt, One Road-related initiatives. The GVP aims to launch this year as an international collaborative effort to identify within ten years virtually all of the planet's viruses that have pandemic or epidemic potential and the ability to jump to humans. "We hope China will be one of the leading countries to initiate the Global Virome Project," one Wuhan Institute of Virology official said. China attended a GVP unveiling meeting in January in Thailand and is waiting for more details on the initiative. The officials said that the Chinese government funds projects similar to GVP to investigate the background of viruses and bacteria. This essentially constituted China's own Virome Project, officials said, but they noted the program currently has no official name.

9. (SBU) The Wuhan Institute of Virology's (b)(6) is the (b)(6) (b)(6) (b)(6) which is designed to show "proof of concept" and be a forerunner to the Global Virome Project. (b)(6) with the EcoHealth Alliance (a New York City-based NGO that is working with the University of California, Davis to manage the (b)(6) recently planned to visit Wuhan to meet with (b)(6) (b)(6) noted that China has expressed interest in building the GVP database, which would put China in a leadership position. Other countries have confidence in China's ability to build such a database, but are skeptical on whether China could remain transparent as a "gatekeeper" for this information. (b)(6) said (b)(6) expressed frustration with the slow progress so far in launching GVP, noting that the effort lacked funding sources, needed to hire a CEO, and would have to boost its profile at G7, G20 and other high-level international meetings.

U.S.-China Workshop Explores Research Partnerships

10. (U) The Institute also has ongoing collaboration with the U.S. National Science Foundation, including a just-concluded workshop in Shenzhen, involving about 40 scientists from the United States and China, on the topic of the "Ecology and Evolution of Infectious Diseases." Co-sponsored by the Natural Science Foundation of China (NSFC), (b)(6)
(b)(6)
(b)(6) The workshop explored opportunities for U.S.-China research cooperation in areas like using "big data" to predict emerging infectious diseases, climate change's effect on vector-borne diseases, and pathogen transmission between wildlife, domestic animals and humans.

11. (SBU) Some workshop participants also expressed skepticism about the Global Virome Project's (GVP) approach, saying that gaining a predictive understanding of viruses with pandemic potential would require going beyond the GVP's strategy of sample collection, to take an "ecological" approach that considers the virome beyond vertebrate systems to identify

mechanisms driving pathogen evolution. A follow-on workshop will be held in June at the University of Berkeley. NSF and NSFC hope to jointly announce a funding call for collaborative projects later this year.

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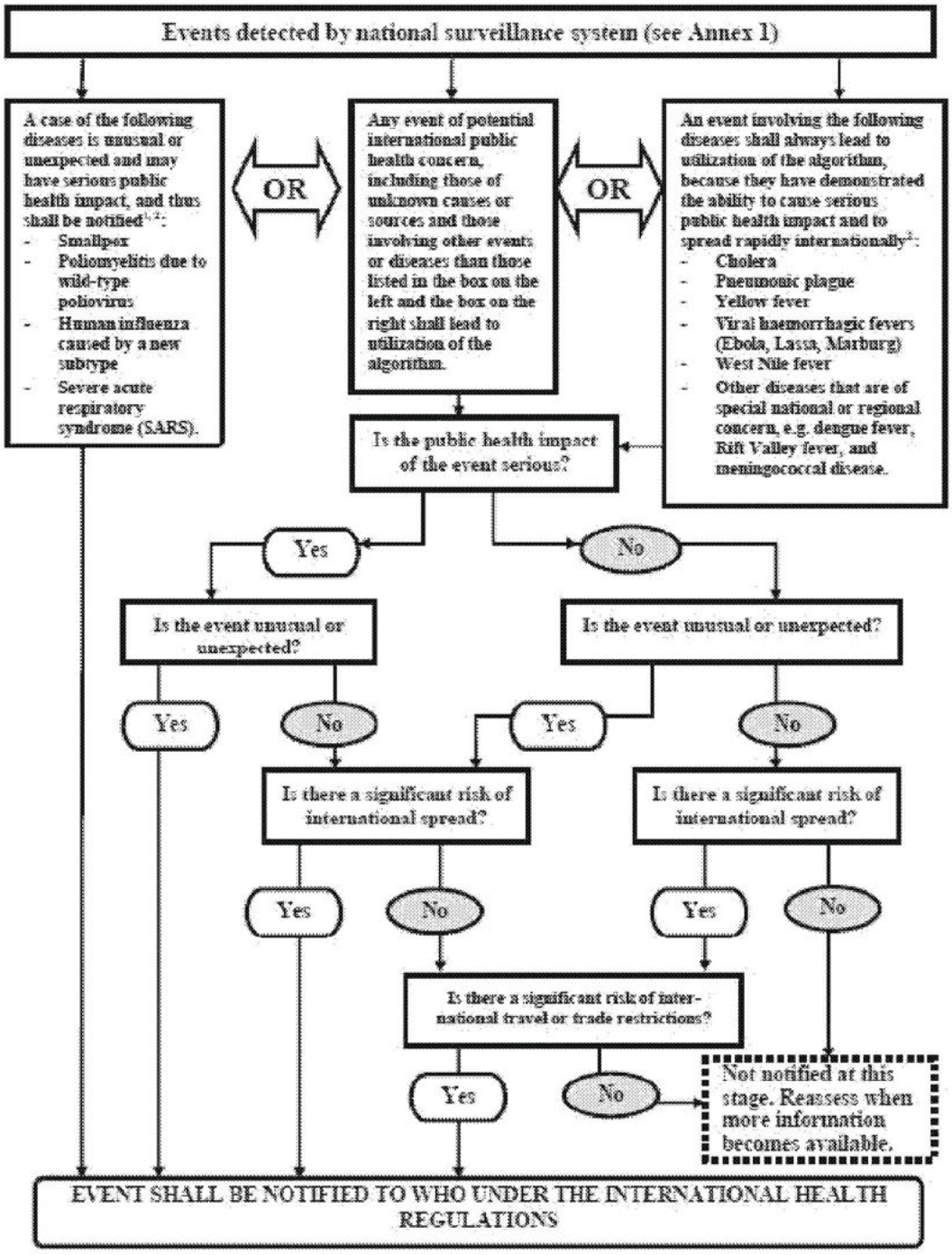
Annex 2 of the 2005 International Health Regulations

ANNEX 2

DECISION INSTRUMENT FOR THE ASSESSMENT AND NOTIFICATION OF EVENTS THAT MAY CONSTITUTE A PUBLIC HEALTH EMERGENCY OF INTERNATIONAL CONCERN



[1] As per WHO case definitions.
[2] The disease list shall be used only for the purposes of these Regulations.

Response to Rodgers Guthrie Griffith WIV origins COVID 19 draft

1. An assessment from a classified U.S. Defense Intelligence Agency (DIA) report included the possibility that the origins of SARS CoV-2 could have emerged accidentally from a laboratory in Wuhan, China due to unsafe laboratory practices.[19] The DIA report cited U.S. government and Chinese researchers who found "about 33 percent of the original 41 identified cases did not have direct exposure" to the market.[20] That, along with what is known of the WIV's work in past few years, raised reasonable suspicion that the pandemic may have been caused by a lab error, not a wet market.[21] Further, a WHO inspector on the recent mission noted that "we know not all of those first 174 early COVID-19 cases visited the market, including the man diagnosed in December 2019 with the earliest onset date."[22] What information does the NIH have on the earliest COVID-19 cases?

(b) (5)

2. According to an editorial on February 23, 2021, in *The Wall Street Journal* by former Secretary of State Mike Pompeo and Miles Yu, "[China's] army of scientists claim to have discovered almost 2,000 new viruses in a little over a decade."[23] How many of these discovered viruses does the NIH have information on and were any of these viruses discovered at the WIV?

(b) (5)

1. According to *The Wall Street Journal* editorial mentioned in the previous question, some have alleged that the WIV's virus-carrying animals were sold as pets and may even show up at local wet markets.[24] Is the NIH aware of these allegations? If so, please provide any information the NIH has related to these allegations.

(b) (5)

2. Please provide all information that NIH has about laboratory accidents and/or biosafety practices at the WIV since January 1, 2015.

(b) (5)

3. Please provide all information that NIH has from NIH staff, grantees, sub-grantees, contractors, or subcontractors about communications and events at the WIV from August 2019 to the present.

(b) (5)

4. Please provide all information that NIH has from NIH staff, grantees, sub-grantees, contractors, or subcontractors about their communications with China-based NIH,

Chinese National Science Foundation, CDC, and China CDC about events at the WIV from August 2019 to the present.

(b) (5)

State Department Cables

1. What information does NIH have about the WIV's responses to the 2018 U.S. Department of State cables (attached to this letter) regarding safety concerns?

(b) (5)

2. The April 2018 cable from the U.S. Department of State stated that the WIV planned to invite University of Texas Medical Branch Galveston (UTMBG) researchers to do research in Wuhan's labs. Please provide any information NIH received that indicates whether the WIV invited UTMBG researchers, and whether UTMBG researchers conducted any research in Wuhan's labs.

    a. If there was such research, please provide information and any documents related to this research.

(b) (5)

3. Why was it pertinent to the NIH investigation that the "nonprofit [EcoHealth Alliance] must provide the "WIV's responses to the 2018 Department of State cables regarding safety concerns"?[25]

    a. Did EcoHealth Alliance provide this information? If so, how did NIH use the information to further its investigation?

(b) (5)

EcoHealth Alliance, Columbia University Health Sciences

4. Was the 2019 NIH federal award to EcoHealth Alliance reviewed and approved by the HHS Potential Pandemic Pathogen Care and Oversight (P3CO) committee?[26]

    a. If so, please provide the documentation with the committee's decision.

    b. Please also provide the names of the individuals who were members of the committee at the time.

Response: NIAID

5. Please provide all correspondence and communications between NIH and EcoHealth Alliance, since January 1, 2020, related to federal funding involving the WIV. The documentation should include, but not be limited to, correspondence between NIH and EcoHealth Alliance dated sometime in April 2020, on July 8, 2020, and sometime in August 2020.

(b) (5)

6. In April 2020, NIH suspended a 2019 federal award to EcoHealth Alliance, in part, because NIH did not believe the work aligned with "program goals and agency priorities."[27] Please specify the work that was done by the EcoHealth Alliance that did not align with the agency's program goals and priorities, and when that work was conducted.

    a. Was an evaluation of EcoHealth Alliance's work and whether it aligned with the agency's program goals and priorities conducted by the NIH before the award was issued? If yes, please provide any related documentation. If not, why not?

(b) (5)

7. In April 2020 correspondence with EcoHealth Alliance, NIH wrote that it "received reports that the Wuhan Institute of Virology…has been conducting research at its facilities in China that pose serious bio-safety concerns."[28] What are the sources for those reports to NIH and what were the specific allegations reported?

(b) (5)

8. Why did the NIH request that EcoHealth Alliance provide a sample of the pandemic coronavirus that the WIV used to determine its genetic sequence for SARS CoV-2?[29]

    a. Why is this information important to NIH's investigation?

    b. Has NIH obtained the sample and if so, what evaluations have been done, and for what purpose?

    c. If NIH has not yet obtained the sample, what are the planned studies

andevaluations NIH will conduct with the sample when it is obtained?

(b) (5)

9. What is the nature of NIH's concerns about purported restrictions at the WIV including "diminished cell-phone traffic in October 2019, and the evidence that there may have been roadblocks surrounding the facility from October 14-19, 2019[,]" aboutthe WIV lab or virus origin?[30]

    a. What is the basis of information to NIH about the purported restrictions at theWIV?

    b. What are the other purported restrictions at the WIV in October 2019?

(b) (5)

10. After terminating EcoHealth Alliance's 2019 project entitled "Understanding the Risk ofBat Coronavirus Emergence," the NIH later offered to reinstate the EcoHealth Alliance funding in July 2020 if EcoHealth Alliance agreed to meet certain conditions.[31]

    a. Please provide all of the information presented to NIH from EcoHealth Alliancein response to NIH's conditions for reinstatement.

    b. What actions did NIH take based upon the information received? How has theinformation been used in NIH's investigation?

    c. One condition for the federal award reinstatement was for EcoHealth Alliance toarrange for an outside inspection of the WIV and its records, "with specific attention to addressing the question of whether WIV staff had SARS-CoV-2theirpossession prior to December 2019."[32] Why is it pertinent to the NIH's investigation if staff at WIV had SARS-CoV-2 in their possession prior to December 2019? What is the potential significance if the staff did have the virusin their possession prior to December 2019?

    d. What information does NIH have that was used for the basis of requesting that theEcoHealth Alliance "must 'explain the apparent disappearance' of a scientist whoworked in the Wuhan lab," and on social media was rumored to be "patient zero" of the pandemic?[33]

        i. What is the potential significance about the whereabouts of this scientistand the photo being removed from the website?

(b) (5)

11. Please provide all correspondence and communications between NIH and Columbia University related to federal funding involving the WIV, including email correspondencein April 2020 between Dr. Michael Lauer, Deputy Director of extramural research, and Naomi Schrag of Columbia University.

    a. In an April 2020 email, Dr. Lauer advised Naomi Schrag of Columbia Universitythat it would be helpful for NIH "to know about all China-based participants in this work since the Type 1 grant started in 2014 - who they were and how much money they received."[34] Why did NIH request that Columbia University provideinformation about all of the China-based participants?

        i. What is the pertinence of the timeframe starting in 2014 for the requestedinformation?

        ii. Did Columbia University provide the NIH with the requested information about all of the China-based participants from all grantees since 2014? Ifso, please provide the information1. If not, why not?

(b) (5)

Federal Funding Records

1. Please provide ledgers or any accounting for dispersion of all NIH federal funding awards that EcoHealth Alliance has sent to the WIV, including through contracts, grants,donations, cooperative agreements, staffing, or any other support or means. In addition, please provide the results and outcomes from the funding and support.[35]

(b) (5)

2. What is the totalamount of NIH federal funding per year from 2017 through 2021 that has directly or indirectly supported the WIV scientists or research through grant recipients, including to EcoHealth Alliance; Wildlife Trust, Inc.; Columbia

University Health Sciences; Trustees of Columbia University; University of North Carolina ChapelHill; Vanderbilt University; University of Virginia; and Oregon Health and Science University?[36]

(b) (5)

3. According to a report in *The Washington Post* on April 14, 2020, the WIV issued a news release in English about the final visit from U.S. Embassy scientist diplomats in Beijing, which occurred on March 27, 2018.[37] Does the NIH have a copy of this news release? Ifso, please provide a copy.

(b) (5)

4. For NIH award recipients that have provided support to the WIV since January 1, 2012,please provide annual reports, trip reports related to the WIV, documentation of any survey or field trips by the WIV, and interim data summaries from the WIV.

(b) (5)

5. Please provide copies of all grantee annual reports, progress reports, projects, studies, andobservations since 2014 where foreign sites for all Type 1 and Type 2 awards have been documented as involving the WIV.

(b) (5)

6. Please provide copies of all grantee annual reports, progress reports, projects, studies, andobservations since 2014 for NIH domestic grantee awards with a foreign component involving the WIV.

(b) (5)

7. Please provide the name(s) of the NIH program manager(s) or officer(s) responsible foroverseeing the grants to EcoHealth Alliance and time period(s) of responsibility.

(b) (5)

8. Please provide the name(s) of the NIH Scientific Review Officers responsible for reviewing and approving any NIH financial awards to EcoHealth Alliance and any otherfunding recipients that supported the WIV.

(b) (5)

9. According to an editorial in *The Wall Street Journal*, the WIV housed tens of thousands of bat samples and laboratory animals in 2019.[38] Please provide any information the NIH has on the number of bat samples and animals at the WIV.

    a. Did any NIH scientists who are fluent in Mandarin review the Chinese scientific literature on the WIV research related to coronaviruses that is dated before February 1, 2020?

(b) (5)

10. Does the NIH have the unpublished sequences of bat coronaviruses that were maintained in the WIV database before December 30, 2019, or before the database was removed from the internet?[39] Does NIH have the full sequences of the eight viruses sampled in the Yunnan province on an EcoHealth Alliance bat-virus sampling trip in 2015?

    a. Please provide NIH's analysis if the sequences have been analyzed.

    b. If NIH does not have the sequences, can NIH get this information from the EcoHealth Alliance or from other NIH-funded sources?

(b) (5)

11. Please provide the original version of "Origin and cross-species transmission of bat coronaviruses in China" that was submitted to *Nature* by EcoHealth Alliance on October 6, 2019, published August 25, 2020, and funded in part by NIAID (award number R01AI110964).[40] If NIH does not have the October 6, 2019 report, can NIH obtain it from EcoHealth Alliance for this response? If so, please provide the report.

(b) (5)

12. Have NIH, EcoHealth Alliance, or other NIH award recipient(s) been denied permission or access to results of any WIV research, which indirectly received financial support from NIH awards? If so, please provide the date(s), individuals involved, and circumstances of each denial.

(b) (5)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Institute of Allergy
and Infectious Diseases
Bethesda, Maryland 20892

8 July 2020

Drs. Aleksei Chmura and Peter Daszak
EcoHealth Alliance, Inc.
460 W 34th St
Suite 1701
New York, NY 10001

Re: NIH Grant R01AI110964

Dear Drs. Chmura and Daszak:

In follow-up to my previous letter of April 24, 2020, I am writing to notify you that the National Institute of Allergy and Infectious Diseases (NIAID), an Institute within the National Institutes of Health (NIH), under the Department of Health and Human Services (HHS), has withdrawn its termination of grant R01AI110964, which supports the project *Understanding the Risk of Bat Coronavirus Emergence*. Accordingly, the grant is reinstated.

However, as you are aware, the NIH has received reports that the Wuhan Institute of Virology (WIV), a subrecipient of EcoHealth Alliance under R01AI110964, has been conducting research at its facilities in China that pose serious bio-safety concerns and, as a result, create health and welfare threats to the public in China and other countries, including the United States. Grant award R01AI110964 is subject to biosafety requirements set forth in the NIH Grants Policy Statement (e.g., NIH GPS, Section 4.1.24 "Public Health Security") and the Notice of Award (e.g., requiring that "Research funded under this grant must adhere to the [CDC/NIH Biosafety in Microbiological and Biomedical Laboratories (BMBL)]."). Moreover, NIH grant recipients are expected to provide safe working conditions for their employees and foster work environments conducive to high-quality research. NIH GPS, Section 4. The terms and conditions of the grant award flow down to subawards to subrecipients. 45 C.F.R. § 75.101.

As the grantee, EcoHealth Alliance was required to "monitor the activities of the subrecipient as necessary to ensure that the subaward is used for authorized purposes, in compliance with Federal statutes, regulations, and the terms and conditions of the subaward . . ." 45 C.F.R. § 75.352(d). We have concerns that WIV has not satisfied safety requirements under the award, and that EcoHealth Alliance has not satisfied its obligations to monitor the activities of its subrecipient to ensure compliance.

Moreover, as we have informed you through prior Notices of Award, this award is subject to the Transparency Act subaward and executive compensation reporting requirement of 2 C.F.R. Part

170. To date you have not reported any subawards in the Federal Subaward Reporting System.

Therefore, effective the date of this letter, July 8, 2020, NIH is suspending all activities related to R01AI110964, until such time as these concerns have been addressed to NIH's satisfaction. This suspension is taken in accordance with 45 C.F.R. § 75.371, Remedies for Noncompliance, which permits suspension of award activities in cases of non-compliance, and the NIH GPS, Section 8.5.2, which permits NIH to take immediate action to suspend a grant when necessary to protect the public health and welfare. This action is not appealable in accordance with 42 C.F.R. § 50.404 and the NIH GPS Section 8.7, Grant Appeals Procedures. However, EcoHealth Alliance has the opportunity to provide information and documentation demonstrating that WIV and EcoHealth Alliance have satisfied the above-mentioned requirements.

Specifically, to address the NIH's concerns, EcoHealth must provide the NIH with the following information and materials, which must be complete and accurate:

1. Provide an aliquot of the actual SARS-CoV-2 virus that WIV used to determine the viral sequence.
2. Explain the apparent disappearance of Huang Yanling, a scientist / technician who worked in the WIV lab but whose lab web presence has been deleted.
3. Provide the NIH with WIV's responses to the 2018 U.S. Department of State cables regarding safety concerns.
4. Disclose and explain out-of-ordinary restrictions on laboratory facilities, as suggested, for example, by diminished cell-phone traffic in October 2019, and the evidence that there may have been roadblocks surrounding the facility from October 14-19, 2019.
5. Explain why WIV failed to note that the RaTG13 virus, the bat-derived coronavirus in its collection with the greatest similarity to SARS-CoV-2, was actually isolated from an abandoned mine where three men died in 2012 with an illness remarkably similar to COVID-19, and explain why this was not followed up.
6. Additionally, EcoHealth Alliance must arrange for WIV to submit to an outside inspection team charged to review the lab facilities and lab records, with specific attention to addressing the question of whether WIV staff had SARS-CoV-2 in their possession prior to December 2019. The inspection team should be granted full access to review the processes and safety of procedures of all of the WIV field work (including but not limited to collection of animals and biospecimens in caves, abandoned man-made underground cavities, or outdoor sites). The inspection team could be organized by NIAID, or, if preferred, by the U.S. National Academy of Sciences.
7. Lastly, EcoHealth Alliance must ensure that all of its subawards are fully reported in the Federal Subaward Reporting System

During this period of suspension, NIH will continue to review the activities under this award, taking into consideration information provided by EcoHealth Alliance, to further asses compliance by EcoHealth Alliance and WIV, including compliance with other terms and conditions of award that may be implicated. Additionally, during the period of suspension, EcoHealth Alliance may not allow research under this project to be conducted. Further, no funds from grant R01AI110964 may be provided to or expended by EcoHealth Alliance or any subrecipients; all such charges are unallowable. It is EcoHealth Alliance's responsibility as the

recipient of this grant award to ensure that the terms of this suspension are communicated to and understood by all subrecipients. EcoHealth Alliance must provide adequate oversight to ensure compliance with the terms of the suspension. Any noncompliance of the terms of this suspension must be immediately reported to NIH. Once the original award is reinstated, NIH will take additional steps to restrict all funding in the HHS Payment Management System in the amount of $369,819. EcoHealth Alliance will receive a revised Notice of Award from NIAID indicating the suspension of these research activities and funding restrictions as a specific condition of award.

Please note that this action does not preclude NIH from taking additional corrective or enforcement actions pursuant to 45 CFR Part 75, including, but not limited to, terminating the grant award. NIH may also take other remedies that may be legally available if NIH discovers other violations of terms and conditions of award on the part of EcoHealth Alliance or WIV.

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Sincerely,

Michael S. Lauer -S Digitally signed by Michael S. Lauer -S
Date: 2020.07.08 21:43:41 -04'00'

Michael S Lauer, MD
NIH Deputy Director for Extramural Research
Email: (b) (6)

cc: Dr. Erik Stemmy
Ms. Emily Linde

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
National Institute of Allergy
and Infectious Diseases
Bethesda, Maryland 20892

24 April 2020

Drs. Aleksei Chmura and Peter Daszak
EcoHealth Alliance, Inc.
460 W 34th St
Suite 1701
New York, NY 10001

Re: Termination of NIH Grant R01 AI 110964

Dear Drs. Chmura and Daszak:

I am writing to notify you that the National Institute of Allergy and Infectious Diseases (NIAID), an Institute within the National Institutes of Health (NIH), under the Department of Health and Human Services (HHS) has elected to terminate the project *Understanding the Risk of Bat Coronavirus Emergence*, funded under grant R01 AI110964, for convenience. This grant project was issued under the authorization of Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284). This grant was funded as a discretionary grant as outlined in the NIH Grants Policy Statement, which states that the decision not to award a grant, or to award a grant at a particular funding level, is at the discretion of the agency, in accordance with NIH's dual review system.

At this time, NIH does not believe that the current project outcomes align with the program goals and agency priorities. NIAID has determined there are no animal and human ethical considerations, as this project is not a clinical trial, but rather an observational study.

As a result of this termination, a total of $369,819.56 will be remitted to NIAID and additional drawdowns will not be supported. The remaining funds have been restricted in the HHS Payment Management System, effective immediately.

Please let me know if you have any questions concerning the information in this letter.

Sincerely,

Lauer, Michael (NIH/OD) [E] Digitally signed by Lauer, Michael (NIH/OD) [E]
Date: 2020.04.24 16:41:16 -04'00'

Michael S Lauer, MD
NIH Deputy Director for Extramural Research
Email: (b) (6)

cc: Dr. Erik Stemmy
Ms. Emily Linde

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Institute of Allergy
and Infectious Diseases
Bethesda, Maryland 20892

23 October 2020

Drs. Aleksei Chmura and Peter Daszak
EcoHealth Alliance, Inc.
460 W 34th St
Suite 1701
New York, NY 10001

Re: NIH Grant R01AI110964

Dear Drs. Chmura and Daszak:

I am following up on Mr. Krinsky's August 13, 2020, letter on behalf of EcoHealth Alliance, Inc. ("EcoHealth") responding to NIH's suspension of grant R01AI110964, which funds the project *Understanding the Risk of Bat Coronavirus Emergence* (the "Project"). Per my letter of July 8, 2020, NIH reinstated the grant but suspended all award activities because we have concerns that the Wuhan Institute of Virology (WIV), which previously served as a subrecipient of the Project, had not satisfied safety requirements that applied to its subawards with EcoHealth, and that EcoHealth had not satisfied its obligations to monitor the activities of its subrecipient to ensure compliance. EcoHealth objected to the suspension on the grounds that WIV has no *current* connection to the Project or EcoHealth's research, and EcoHealth had not issued any subawards in connection with the Grant *at the time of the suspension*.

The fact that EcoHealth does not currently have a subrecipient relationship with WIV and had not issued subawards to WIV at the time of suspension does not absolve EcoHealth of any past non-compliance with the terms and conditions of award for grant R01AI110964. While EcoHealth did not issue a subaward to WIV for year 6 of the grant, WIV served as a subrecipient for years 1 through 5. NIH awarded EcoHealth grant R01AI110964 in 2014, with a project period of June 1, 2014, through June 30, 2024, as renewed. In EcoHealth's grant application, EcoHealth listed Drs. Zheng Li Shi and Xing Yi Ge of WIV as co-investigators and senior/key personnel. It stated that "Drs. Shi, Zhang, and Daszak have collaborated together since 2002 and have been involved in running joint conferences, and shipping samples into and out of China." EcoHealth listed WIV as a Project/Performance Site Location. In describing WIV's facilities, EcoHealth described WIV as China's premier institute for virological research" and touted WIV's "fully equipped biosafety level 3 laboratory" and "a newly opened BLS-4 laboratory." In support of the application, Dr. Zheng Li Shi's personal statement indicated that "My lab will be responsible for diagnosis, genomics and isolation of coronavirus from wild and domestic animals in Southern China and for analyzing their receptor binding domains." The application stated that "Wuhan Institute of Virology and the Wuhan University Center for Animal Experiment BSL-3

lab have an Internal Biosafety Committee and are accredited BSL-2 and BSL 3 laboratories. All experimental work using infectious material will be conducted under appropriate biosafety standards. Disposal of hazardous materials will be conducted according to the institutional biosafety regulations."

EcoHealth requested funding specifically for activities to be carried out by WIV. NIH awarded EcoHealth a total of $749,976 for WIV's work in the following annual amounts for years 1 through 5:

	-Yr 1	-Yr 2	-Yr 3	-Yr 4	-Yr 5
Total Direct Costs	$123,699	$128,718	$147,335	$147,335	$147,335
F&A Costs @ 8%	$9,896	$10,297	$11,787	$11,787	$11,787
TOTAL COSTS	$133,595	$139,015	$159,122	$159,122	$159,122

As stated in the Notices of Award for each budget period of the grant, the awards were subject to terms and conditions, which include the NIH Grants Policy Statement (GPS) and applicable HHS grant regulations. As I indicated in my letter of July 8, 2020, as a term and condition of award EcoHealth was required to "monitor the activities of the subrecipient as necessary to ensure that the subaward is used for authorized purposes, in compliance with Federal statutes, regulations, and the terms and conditions of the subaward . . ." 45 C.F.R. § 75.352(d). See also, 45 C.F.R. § 75.342(a) ("The non-Federal entity is responsible for oversight of the operations of the Federal award supported activities."). Moreover, EcoHealth was required to "Establish and maintain effective internal control over the Federal award that provides reasonable assurance that the non-Federal entity is managing the Federal award in compliance with Federal statutes, regulations, and the terms and conditions of the Federal award[.]" 45 C.F.R. § 75.303(a). The Notice of Award stated that as a term and condition of award, "Research funded under this grant must adhere to the [CDC/NIH Biosafety in Microbiological and Biomedical Laboratories (BMBL)]." Moreover, the NIH GPS provides that NIH grant recipients are expected to provide safe working conditions for their employees and foster work environments conducive to high-quality research. NIH GPS, Section 4. The terms and conditions of the grant award flow down to subawards to subrecipients, so these terms applied to WIV. 45 C.F.R. § 75.101.

As I stated, NIH has concerns of non-compliance with terms and conditions of award—namely, that WIV had not satisfied safety requirements under the award and that EcoHealth Alliance had not satisfied its obligations to monitor the activities of its subrecipient to ensure compliance. Accordingly, NIH suspended all activities related to R01AI110964, pursuant to 45 C.F.R. § 75.371, Remedies for Noncompliance, which permits suspension of award activities in cases of non-compliance, and the NIH GPS, Section 8.5.2, which permits NIH to take immediate action to suspend a grant when necessary to protect the public health and welfare.

In my letter of July 8, 2020, I provided EcoHealth with the opportunity to object and to provide information and documentation challenging the suspension. Specifically, I sought information and materials that speak to WIV's lab safety and EcoHealth's oversight of its subrecipient, and an inspection of WIV's laboratory records and facilities. I indicated that as a specific condition of award, during the period of suspension, EcoHealth Alliance may not allow research under this

project to be conducted and that no funds from grant R01AI110964 may be provided to or expended by EcoHealth Alliance or any subrecipients.

EcoHealth objected to the requests on the grounds that "NIAID is not authorized under 45 CFR§§ 75.371, 75.205, and 75.207, entitled *Specific Award Conditions*, to impose, *inter alia*, conditions that consist of demands for information regarding entities that are neither subrecipients of grant funds nor project affiliates."

These provisions are irrelevant to NIH's requests. NIH is required to permit the opportunity for recipients to object and provide information and documentation challenging a suspension, 45 C.F.R. § 75.374, so we specifically gave EcoHealth the opportunity to provide information that speaks to NIH's concerns. Moreover, as a granting agency, NIH is required to "manage and administer the Federal award in a manner so as to ensure that Federal funding is expended and associated programs are implemented in full accordance with U.S. statutory and public policy requirements: Including, but not limited to, those protecting public welfare [and] the environment[.]" 45 C.F.R. § 75.300(a). In addition to seeking information that speaks to compliance with terms and conditions of award, NIH is entitled to "make site visits as warranted by program needs." 45 C.F.R. § 75.342. As a term and condition of award, NIH "must have the right of access to any documents, papers, or other records of the non-Federal entity which are pertinent to the Federal award, in order to make audits, examinations, excerpts, and transcripts" (45 C.F.R. § 75.364); and must have "timely and reasonable access to the non-Federal entity's personnel for the purpose of interview and discussion related to such documents" (id.). These requirements flow down to subawards to subrecipients. 45 C.F.R. § 75.101. "Non-Federal entities must comply with requirements in [45 C.F.R. Part 75] regardless of whether the non-Federal entity is a recipient or subrecipient of a Federal award." 45 C.F.R. 75.101. As the grantee, EcoHealth was required to have in place, "A requirement that the subrecipient permit the pass-through entity and auditors to have access to the subrecipient's records and financial statements as necessary for the pass-through entity to meet the requirements of this part." 45 C.F.R. § 75.352(a)(5). For each of these reasons, NIH is justified in seeking the materials, information, and a site visit specified in my letter of July 8, 2020.

In addition to objecting to NIH's authority to seek the materials, information, and a site visit, EcoHealth has responded that it lacks knowledge or information regarding the requests; that it is not in possession, custody, or control of the specified items; and that it has no authority to grant NIAID and the U.S. National Academy of Sciences access to WIV's facility to conduct an inspection. EcoHealth's responses have not satisfied NIH's concerns that EcoHealth had failed to adequately monitor the compliance of its subrecipient, and that the subrecipient, WIV, had failed to comply with safety requirements.

Notwithstanding this, NIH is providing an additional opportunity for EcoHealth to provide information and documentation challenging these concerns of non-compliance. Accordingly, in addition to reiterating our prior requests (1) through (6) per our letter of July 8, 2020, NIH requests the following information and materials, which must be complete and accurate:

1. Provide copies of all EcoHealth Alliance – WIV subrecipient agreements as well as any other documents and information describing how EcoHealth Alliance monitored WIV's compliance with the terms and conditions of award, including with respect to biosafety.
2. Describe EcoHealth's efforts to evaluate WIV's risk of noncompliance with Federal statutes, regulations, and the terms and conditions of the subaward.
3. Provide copies of all WIV biosafety reports from June 1, 2014 through May 31, 2019.

During the ongoing period of suspension, NIH will continue to review the activities under this award, taking into consideration information provided by EcoHealth Alliance, to further assess whether EcoHealth Alliance and WIV complied with the terms and conditions of award, including compliance with other terms and conditions of award that may be implicated. We remind you that during the period of suspension, EcoHealth Alliance may not allow research under this project to be conducted. Further, no funds from grant R01AI110964 may be provided to or expended by EcoHealth Alliance or any subrecipients; all such charges are unallowable. It is EcoHealth Alliance's responsibility as the recipient of this grant award to ensure that the terms of this suspension are communicated to and understood by all subrecipients. EcoHealth Alliance must provide adequate oversight to ensure compliance with the terms of the suspension. Any noncompliance of the terms of this suspension must be immediately reported to NIH. EcoHealth Alliance will receive a revised Notice of Award from NIAID indicating the continued suspension of these research activities and funding restrictions as a specific condition of award.

Please note that this action does not preclude NIH from taking additional corrective or enforcement actions pursuant to 45 C.F.R. Part 75, including, but not limited to, terminating the grant award or disallowing costs. NIH may also take other remedies that may be legally available if NIH discovers other violations of terms and conditions of award on the part of EcoHealth Alliance or WIV.

Sincerely,

Michael S. Lauer -S Digitally signed by Michael S. Lauer -S
Date: 2020.10.23 13:34:25 -04'00'

Michael S Lauer, MD
NIH Deputy Director for Extramural Research
Email: (b) (6)

cc: Dr. Erik Stemmy (NIAID)
Ms. Emily Linde (NIAID)

Theory That COVID Came From A Chinese Lab Takes On New Life In Wake Of WHO Report

John Ruwitch

Members of the World Health Organization team investigating the origins of the coronavirus leave the Wuhan Institute of Virology in Wuhan, China, on Feb. 3.

Hector Retamal/AFP via Getty Images

Before COVID-19, few scientists would have pegged the city of Wuhan, in temperate central China, as a likely starting point for a global coronavirus pandemic. Its climate and fauna don't fit the bill.

But the city of 11 million straddling the Yangtze River is home to some of China's most advanced biological research laboratories. And one of the secretive, state-run institutions, the Wuhan Institute of Virology, is known to

conduct experiments on the kind of virus that has killed nearly 3 million people worldwide so far since late 2019.

"I think there were a lot of people who did put together the fact that you had an outbreak in Wuhan and you have these laboratories in Wuhan fairly immediately," said David Feith, who was an Asia adviser in the Trump administration's State Department when the coronavirus emerged.

"The question was: What does the evidence tell us?" said Feith, who is currently at the Center for a New American Security, a Washington, D.C., think tank.

At the time, not much.

Former President Donald Trump and some in his administration latched onto the theory. But scientists focused on stopping the pandemic, and China dragged its feet on an international investigation.

Article continues after sponsor message

Now, though, the lab leak hypothesis seems to have found new life.

On Tuesday, the World Health Organization released a joint report with Beijing on the origins of the pandemic following a four-week investigation in China. It concluded, among other things, that the lab leak hypothesis was "extremely unlikely."

But WHO Director-General Tedros Adhanom Ghebreyesus said he does not believe the team's assessment of the lab leak possibility was extensive enough.

"Although the team has concluded that a laboratory leak is the least likely hypothesis, this requires further investigation, potentially with additional

missions involving specialist experts, which I am ready to deploy," he told WHO members, according to a written statement.

Jamie Metzl, a senior fellow at the Atlantic Council, has been an outspoken proponent of such an investigation.

"I'm not saying that I am certain that COVID-19 stems from an accidental lab leak, but it would be absolutely irresponsible and could only be politically motivated to say that it's not even worth having a full investigation," he said.

A State Department fact sheet from mid-January highlights reports of sick lab researchers at the Wuhan Institute of Virology in the fall of 2019, notes the dangerous type of coronavirus research the lab was conducting and said there was also secret military activity at the lab.

China has refuted the claims. Critics of the WHO report, such as Metzl, said the expert team that visited the lab took their Chinese interlocutors at their word and didn't dig. Metzl said that's insufficient.

"If in the middle of the worst pandemic in a century, China wants to tell the rest of the world, 'Screw you, it's not even worth investigating,' that's on them. But we shouldn't give them a free pass," he said.

While Metzl and others, like Feith, believe there is more circumstantial evidence that SARS-CoV-2, the virus that causes COVID-19, came from a lab than naturally, many scientists say the opposite. Based on the available evidence, they believe, like the WHO team, that the coronavirus appears far more likely to have emerged naturally.

Alina Chan, a postdoctoral scientist working on genetics at the Broad Institute in Boston, said this is a critical juncture.

"This time it's China that's in the hot spot. ... But next time, maybe it's not China. So, if we decide that we cannot investigate, we just give up this time, then other countries might feel that there isn't an accountability mechanism in place," she said.

That could potentially lead to less stringent, and more dangerous, lab conditions, she said.

Politics at play

Meanwhile, not far beneath the surface of the debate are geopolitical tensions between China and the United States — relations between the two countries soured in the last year under Trump and show no signs of improving under the Biden administration.

Trump sought to place maximum blame for COVID-19 on China — and pushed the lab leak theory — in what some of his critics saw as an effort to deflect criticism of his own handling of the pandemic.

But Scott Kennedy at the Center for Strategic and International Studies said China's foot-dragging on an investigation, counter-accusations and secrecy haven't helped its case.

"The West prides itself on its openness and transparency relative to authoritarian places like China, so in the competition for soft power and legitimacy this is a useful topic to continue to push," he said.

For its part, the Biden administration joined 13 other governments to criticize the WHO report and call for more openness from China on Tuesday. In a joint statement, they did not mention the lab leak theory, but the Biden administration hasn't ruled it out.

"I think the administration has made it pretty clear that given the lack of

Chinese transparency, it is not comfortable eliminating the lab escape theory," said Elizabeth Economy, a senior fellow at Stanford University's Hoover Institution.

"The fact that WHO head Tedros, who has previously championed China's transparency, stated that more extensive research was needed before eliminating the possibility that the virus escaped from the lab signals that continued skepticism is merited," Economy said.

Impact on U.S.-China relations

Still, some worry that a hard-charging focus on hypothetical lab accidents might further bog down U.S.-China relations, which are at their rockiest in decades.

Deborah Seligsohn, an assistant professor at Pennsylvania's Villanova University, was in charge of science and health issues at the U.S. Embassy in Beijing during the SARS epidemic in the early 2000s. She said there's been a lot of cooperation between China and the United States in the field of science and public health, including on this pandemic, and it's not best served by piling pressure on Beijing.

"I think that leads to a lot of accusations and eventually someone decides to diffuse it by coming up with some sort of face-saving agreement, but I don't think it actually leads to science," she said.

And, for better or worse, pushing hard might make it tougher to get answers about the origins of the pandemic — which will be difficult to do under any circumstances.

"I think the genetics will tell you about the virus. I think it would be very difficult to tell you where it got into the human population and how it spread

and whether it came from a lab or it didn't come from the lab. I think that's going to be very hard," said Barry Bloom, an immunologist and infectious disease expert at Harvard T.H. Chan School of Public Health.

"And no matter how good the rational explanations of another WHO committee, there's a subset of people in both countries that will not believe the most likely answers."

The Lab-Leak Hypothesis

Nicholson Baker Jan. 4, 2021

For decades, scientists have been hot-wiring viruses in hopes of preventing a pandemic, not causing one. But what if ...?

By

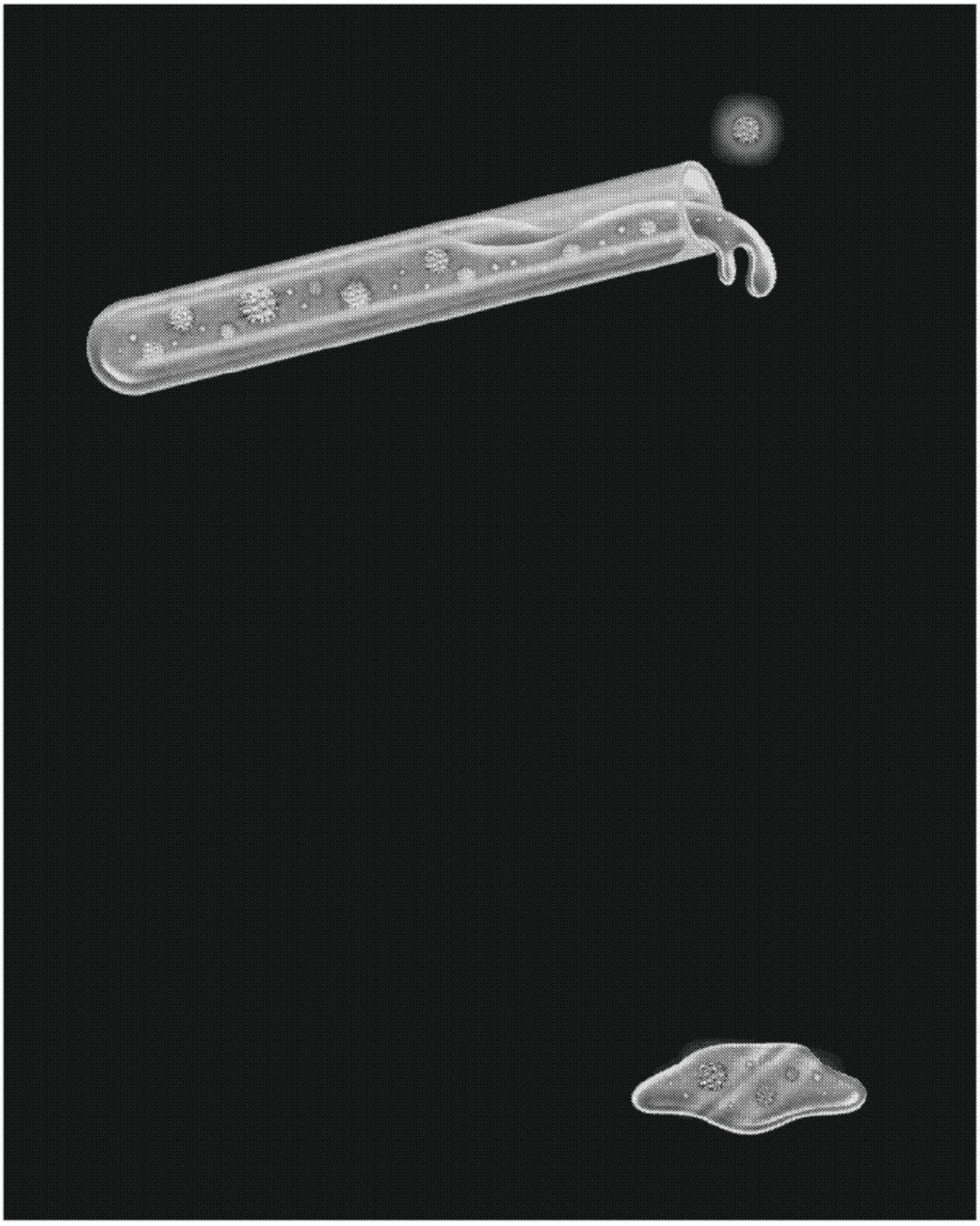

Illustration: Illustration by Robert Beatty for New York Magazine

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I.

Flask Monsters

What happened was fairly simple, I've come to believe. It was an accident. A virus spent some time in a laboratory, and eventually it got out. SARS-CoV-2, the virus that causes COVID-19, began its existence inside a bat, then it learned how to infect people in a claustrophobic mine shaft, and then it was made more infectious in one or more laboratories, perhaps as part of a scientist's well-intentioned but risky effort to create a broad-spectrum vaccine. SARS-2 was not designed as a biological weapon. But it was, I think, designed. Many thoughtful people dismiss this notion, and they may be right. They sincerely believe that the coronavirus arose naturally, "zoonotically," from animals, without having been previously studied, or hybridized, or sluiced through cell cultures, or otherwise worked on by trained professionals. They hold that a bat, carrying a coronavirus, infected some other creature, perhaps a pangolin, and that the pangolin may have already been sick with a different coronavirus disease, and out of the conjunction and commingling of those two diseases within the pangolin, a new disease, highly infectious to humans, evolved. Or they hypothesize that two coronaviruses recombined in a bat, and this new virus spread to other bats, and then the bats infected a person directly — in a rural setting, perhaps — and that this person caused a simmering undetected outbreak of respiratory disease, which over a period of months or years evolved to become virulent and highly transmissible but was not noticed until it appeared in Wuhan.

There is no direct evidence for these zoonotic possibilities, just as there is no direct evidence for an experimental mishap — no written confession, no incriminating notebook, no official accident report. Certainty craves detail, and detail requires an investigation. It has been a full year, 80 million people

have been infected, and, surprisingly, no public investigation has taken place. We still know very little about the origins of this disease.

Nevertheless, I think it's worth offering some historical context for our yearlong medical nightmare. We need to hear from the people who for years have contended that certain types of virus experimentation might lead to a disastrous pandemic like this one. And we need to stop hunting for new exotic diseases in the wild, shipping them back to laboratories, and hot-wiring their genomes to prove how dangerous to human life they might become.

Over the past few decades, scientists have developed ingenious methods of evolutionary acceleration and recombination, and they've learned how to trick viruses, coronaviruses in particular, those spiky hairballs of protein we now know so well, into moving quickly from one species of animal to another or from one type of cell culture to another. They've made machines that mix and mingle the viral code for bat diseases with the code for human diseases — diseases like SARS, severe acute respiratory syndrome, for example, which arose in China in 2003, and MERS, Middle East respiratory syndrome, which broke out a decade later and has to do with bats and camels. Some of the experiments — "gain of function" experiments — aimed to create new, more virulent, or more infectious strains of diseases in an effort to predict and therefore defend against threats that might conceivably arise in nature. The term *gain of function* is itself a euphemism; the Obama White House more accurately described this work as "experiments that may be reasonably anticipated to confer attributes to influenza, MERS, or SARS viruses such that the virus would have enhanced pathogenicity and/or transmissibility in mammals via the respiratory route." The virologists who carried out these experiments have accomplished amazing feats of genetic transmutation, no question, and there have been very few publicized accidents over the years. But there have been some.

And we were warned, repeatedly. The intentional creation of new microbes that combine virulence with heightened transmissibility "poses extraordinary risks to the public," wrote infectious-disease experts Marc Lipsitch and Thomas Inglesby in 2014. "A rigorous and transparent risk-assessment process for this work has not yet been established." That's still true today. In 2012, in *Bulletin of the Atomic Scientists*, Lynn Klotz warned that there was an 80 percent chance, given how many laboratories were then handling virulent viro-varietals, that a leak of a potential pandemic pathogen would occur sometime in the next 12 years.

A lab accident — a dropped flask, a needle prick, a mouse bite, an illegibly labeled bottle — is apolitical. Proposing that something unfortunate happened during a scientific experiment in Wuhan — where COVID-19 was first diagnosed and where there are three high-security virology labs, one of which held in its freezers the most comprehensive inventory of sampled bat viruses in the world — isn't a conspiracy theory. It's just a theory. It merits attention, I believe, alongside other reasoned attempts to explain the source of our current catastrophe.

II.

"A Reasonable Chance"

Seeking Ebola strains in Sierra Leone's wild-animal population for USAID's Predict project in 2018. Photo: Simon Townsley

From early 2020, the world was brooding over the origins of COVID-19. People were reading research papers, talking about what kinds of live animals were or were not sold at the Wuhan seafood market — wondering where the new virus had come from.

Meanwhile, things got strange all over the world. The Chinese government shut down transportation and built hospitals at high speed. There were video clips of people who'd suddenly dropped unconscious in the street. A doctor on YouTube told us how we were supposed to scrub down our produce when we got back from the supermarket. A scientist named Shi Zhengli of the Wuhan Institute of Virology published a paper saying that the novel coronavirus was 96 percent identical to a bat virus, RaTG13, found in

Yunnan province in southern China. On March 13, I wrote in my journal that there seemed to be something oddly artificial about the disease: "It's too airborne — too catching — it's something that has been selected for infectivity. That's what I suspect. No way to know so no reason to waste time thinking about it."

This was just a note to self — at the time, I hadn't interviewed scientists about SARS-2 or read their research papers. But I did know something about pathogens and laboratory accidents; I published a book last year, *Baseless*, that talks about some of them. The book is named after a Pentagon program, Project Baseless, whose goal, as of 1951, was to achieve "an Air Force–wide combat capability in biological and chemical warfare at the earliest possible date."

A vast treasure was spent by the U.S. on the amplification and aerial delivery of diseases — some well known, others obscure and stealthy. America's biological-weapons program in the '50s had A1-priority status, as high as nuclear weapons. In preparation for a total war with a numerically superior communist foe, scientists bred germs to be resistant to antibiotics and other drug therapies, and they infected lab animals with them, using a technique called "serial passaging," in order to make the germs more virulent and more catching.

And along the way, there were laboratory accidents. By 1960, hundreds of American scientists and technicians had been hospitalized, victims of the diseases they were trying to weaponize. Charles Armstrong, of the National Institutes of Health, one of the consulting founders of the American germ-warfare program, investigated Q fever three times, and all three times, scientists and staffers got sick. In the anthrax pilot plant at Camp Detrick, Maryland, in 1951, a microbiologist, attempting to perfect the "foaming process" of high-volume production, developed a fever and died. In 1964,

veterinary worker Albert Nickel fell ill after being bitten by a lab animal. His wife wasn't told that he had Machupo virus, or Bolivian hemorrhagic fever. "I watched him die through a little window to his quarantine room at the Detrick infirmary," she said.

In 1977, a worldwide epidemic of influenza A began in Russia and China; it was eventually traced to a sample of an American strain of flu preserved in a laboratory freezer since 1950. In 1978, a hybrid strain of smallpox killed a medical photographer at a lab in Birmingham, England; in 2007, live foot-and-mouth disease leaked from a faulty drainpipe at the Institute for Animal Health in Surrey. In the U.S., "more than 1,100 laboratory incidents involving bacteria, viruses and toxins that pose significant or bioterror risks to people and agriculture were reported to federal regulators during 2008 through 2012," reported *USA Today* in an exposé published in 2014.
In 2015, the Department of Defense discovered that workers at a germ-warfare testing center in Utah had mistakenly sent close to 200 shipments of live anthrax to laboratories throughout the United States and also to Australia, Germany, Japan, South Korea, and several other countries over the past 12 years. In 2019, laboratories at Fort Detrick — where "defensive" research involves the creation of potential pathogens to defend against — were shut down for several months by the Centers for Disease Control and Prevention for "breaches of containment." They reopened in December 2019.

High-containment laboratories have a whispered history of near misses. Scientists are people, and people have clumsy moments and poke themselves and get bitten by the enraged animals they are trying to nasally inoculate. Machines can create invisible aerosols, and cell solutions can become contaminated. Waste systems don't always work properly. Things can go wrong in a hundred different ways.

Hold that human fallibility in your mind. And then consider the cautious words of Alina Chan, a scientist who works at the Broad Institute of MIT and Harvard. "There is a reasonable chance that what we are dealing with is the result of a lab accident," Chan told me in July of last year. There was also, she added, a reasonable chance that the disease had evolved naturally — both were scientific possibilities. "I don't know if we will ever find a smoking gun, especially if it was a lab accident. The stakes are so high now. It would be terrifying to be blamed for millions of cases of COVID-19 and possibly up to a million deaths by year end, if the pandemic continues to grow out of control. The Chinese government has also restricted their own scholars and scientists from looking into the origins of SARS-CoV-2. At this rate, the origin of SARS-CoV-2 may just be buried by the passage of time."

I asked Jonathan A. King, a molecular biologist and biosafety advocate from MIT, whether he'd thought *lab accident* when he first heard about the epidemic. "Absolutely, absolutely," King answered. Other scientists he knew were concerned as well. But scientists, he said, in general were cautious about speaking out. There were "very intense, very subtle pressures" on them not to push on issues of laboratory biohazards. Collecting lots of bat viruses, and passaging those viruses repeatedly through cell cultures, and making bat-human viral hybrids, King believes, "generates new threats and desperately needs to be reined in."

"All possibilities should be on the table, including a lab leak," a scientist from the NIH, Philip Murphy — chief of the Laboratory of Molecular Immunology — wrote me recently. Nikolai Petrovsky, a professor of endocrinology at Flinders University College of Medicine in Adelaide, Australia, said in an email, "There are indeed many unexplained features of this virus that are hard if not impossible to explain based on a completely natural origin." Richard Ebright, a molecular biologist at Rutgers University, wrote that he'd been concerned for some years about the Wuhan laboratory and about the

work being done there to create "chimeric" (i.e., hybrid) SARS-related bat coronaviruses "with enhanced human infectivity." Ebright said, "In this context, the news of a novel coronavirus in Wuhan ***screamed*** lab release."

III.

"No Credible Evidence"

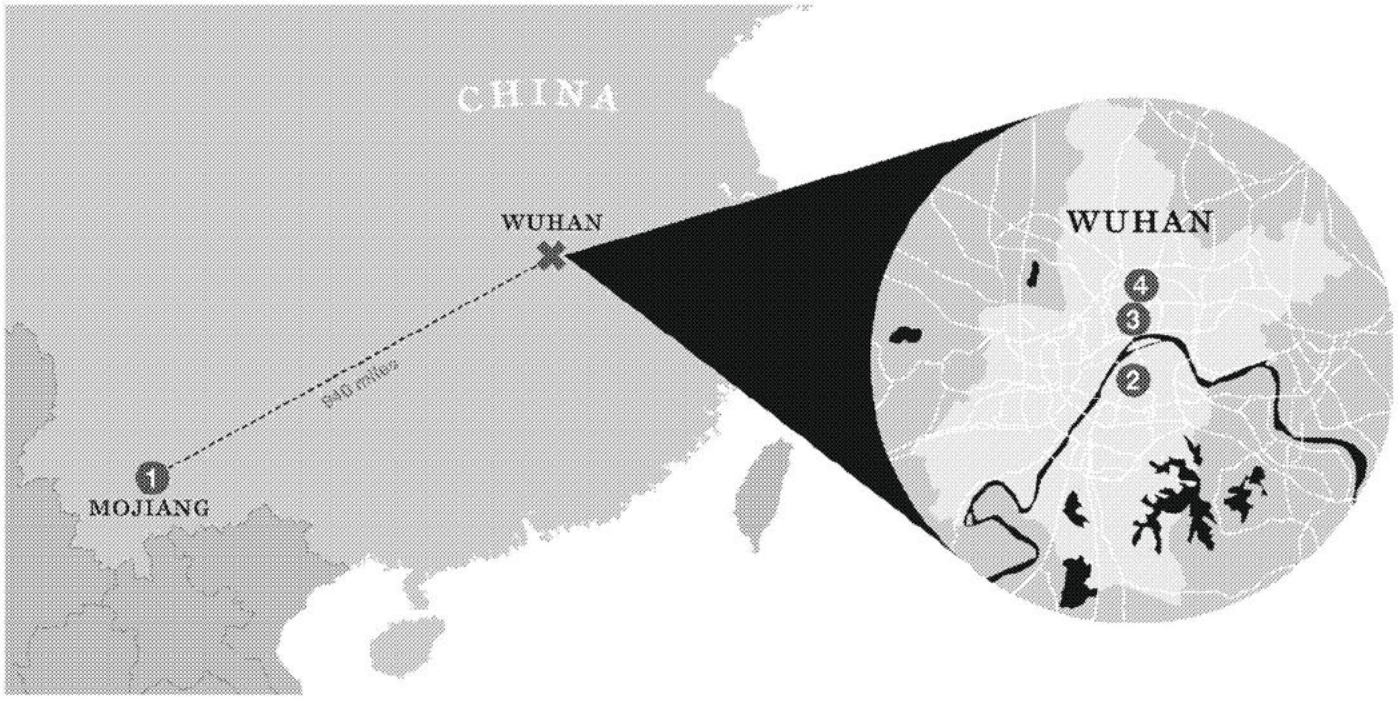
The new disease, as soon as it appeared, was intercepted — stolen and politicized by people with ulterior motives. The basic and extremely interesting scientific question of what happened was sucked up into an ideological sharknado.

Some Americans boycotted Chinese restaurants; others bullied and harassed Asian Americans. Steve Bannon, broadcasting from his living room, in a YouTube series called *War Room*, said that the Chinese Communist Party had made a biological weapon and intentionally released it. He called it the "CCP virus." And his billionaire friend and backer, Miles Guo, a devoted Trump supporter, told a right-wing website that the communists' goal was to "use the virus to infect selective people in Hong Kong, so that the Chinese Communist Party could use it as an excuse to impose martial law there and ultimately crush the Hong Kong pro-democracy movement. But it backfired terribly."

In *The Lancet*, in February, a powerful counterstatement appeared, signed by 27 scientists. "We stand together to strongly condemn conspiracy theories suggesting that COVID-19 does not have a natural origin," the statement said. "Scientists from multiple countries have published and analyzed genomes of the causative agent, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and they overwhelmingly conclude

that this coronavirus originated in wildlife, as have so many other emerging pathogens."

The behind-the-scenes organizer of this *Lancet* statement, Peter Daszak, is a zoologist and bat-virus sample collector and the head of a New York nonprofit called EcoHealth Alliance — a group that (as veteran science journalist Fred Guterl explained later in *Newsweek*) has channeled money from the National Institutes of Health to Shi Zhengli's laboratory in Wuhan, allowing the lab to carry on recombinant research into diseases of bats and humans. "We have a choice whether to stand up and support colleagues who are being attacked and threatened daily by conspiracy theorists or to just turn a blind eye," Daszak said in February in *Science* magazine.



How Did It Get Out? 1. The Tongguan Mine Shaft in Mojiang, Yunnan, where, in 2013, fragments of RaTG13, the closest known relative of SARSCoV-2, were recovered and transported to the Wuhan Institute of Virology; **2. The Wuhan Institute of Virology,** where Shi Zhengli's team brought the RaTG13 sample, sequenced its genome, then took it out of the freezer several times in recent years; **3. The Wuhan Center for Disease Control and Prevention,** which first reported signs of the novel coronavirus in hospital patients; **4. The Huanan Seafood Wholesale Market,** an early suspected origin of the pandemic, where the first major outbreak occurred. Illustration: Map by Jason Lee

Vincent Racaniello, a professor at Columbia and a co-host of a podcast called *This Week in Virology*, said on February 9 that the idea of an accident in Wuhan was "complete bunk." The coronavirus was 96 percent similar to a bat virus found in 2013, Racaniello said. "It's not a man-made virus. It wasn't released from a lab."

Racaniello's dismissal was seconded by a group of scientists from Ohio State, the University of Pennsylvania, and the University of North Carolina, who put out a paper in *Emerging Microbes and Infections* to quiet the "speculations, rumors, and conspiracy theories that SARS-CoV-2 is of laboratory origin." There was "currently no credible evidence" that SARS-2 leaked from a lab, these scientists said, using a somewhat different argument from Racaniello's. "Some people have alleged that the human SARS-CoV-2 was leaked directly from a laboratory in Wuhan where a bat CoV (RaTG13) was recently reported," they said. But RaTG13 could not be the source because it differed from the human SARS-2 virus by more than a thousand nucleotides. One of the paper's authors, Susan Weiss, told the Raleigh *News & Observer*, "The conspiracy theory is ridiculous."

The most influential natural-origin paper, "The Proximal Origin of SARS-CoV-2," by a group of biologists that included Kristian Andersen of Scripps Research, appeared online in a preliminary version in mid-February. "We do not believe any type of laboratory-based scenario is plausible," the scientists said. Why? Because molecular-modeling software predicted that if you wanted to optimize an existing bat virus so that it would replicate well in human cells, you would arrange things a different way than how the SARS-2 virus actually does it — even though the SARS-2 virus does an extraordinarily good job of replicating in human cells. The laboratory-based scenario was implausible, the paper said, because, although it was true that the virus could conceivably have developed its unusual genetic features in a laboratory, a stronger and "more parsimonious" explanation was that the

features came about through some kind of natural mutation or recombination. "What we think," explained one of the authors, Robert F. Garry of Tulane University, on YouTube, "is that this virus is a recombinant. It probably came from a bat virus, plus perhaps one of these viruses from the pangolin." Journalists, for the most part, echoed the authoritative pronouncements of Daszak, Racaniello, Weiss, Andersen, and other prominent natural-originists. "The balance of the scientific evidence strongly supports the conclusion that the new coronavirus emerged from nature — be it the Wuhan market or somewhere else," said the Washington *Post*'s "Fact Checker" column. "Dr. Fauci Again Dismisses Wuhan Lab As Source of Coronavirus," said CBS News, posting a video interview of Anthony Fauci by *National Geographic*. "If you look at the evolution of the virus in bats, and what's out there now," Fauci said, "it's very, very strongly leaning toward 'This could not have been artificially or deliberately manipulated' — the way the mutations have naturally evolved."

Everyone took sides; everyone thought of the new disease as one more episode in an ongoing partisan struggle. Think of Mike Pompeo, that landmass of Cold War truculence; think of Donald Trump himself. They stood at their microphones saying, in a winking, I-know-something-you-don't-know sort of way, that this disease escaped from a Chinese laboratory. Whatever they were saying must be wrong. It became impermissible, almost taboo, to admit that, of course, SARS-2 could have come from a lab accident. "The administration's claim that the virus spread from a Wuhan lab has made the notion politically toxic, even among scientists who say it could have happened," wrote science journalist Mara Hvistendahl in the Intercept.

IV.

"Is It a Complete Coincidence?"

Even so, in January and February of 2020, there were thoughtful people who were speaking up, formulating their perplexities.

One person was Sam Husseini, an independent journalist. He went to a CDC press conference at the National Press Club on February 11, 2020. By then, 42,000 people had gotten sick in China and more than a thousand had died. But there were only 13 confirmed cases in the U.S. Halfway through the Q&A period, Husseini went to the microphone and asked the CDC's representative, Anne Schuchat, where the virus had come from. His head was spinning, he told me later.

"Obviously the main concern is how to stop the virus," Husseini said; nonetheless, he wanted to know more about its source. "Is it the CDC's contention," he asked, "that there's absolutely no relation to the BSL-4 lab in Wuhan? It's my understanding that this is the only place in China with a BSL-4 lab. We in the United States have, I think, two dozen or so, and there have been problems and incidents." (A BSL-4 laboratory is a maximum-security biosafety-level-four facility, used to house research on the most dangerous known pathogens. *New York* has confirmed there are at least 11 BSL-4 facilities currently operating in the U.S.) Husseini hastened to say that he wasn't implying that what happened in Wuhan was in any way intentional. "I'm just asking, Is it a complete coincidence that this outbreak happened in the one city in China with a BSL-4 lab?"

Schuchat thanked Husseini for his questions and comments. Everything she'd seen was quite consistent with a natural, zoonotic origin for the disease, she said.

That same month, a group of French scientists from Aix-Marseille University posted a paper describing their investigation of a small insertion in the genome of the new SARS-2 virus. The virus's spike protein contained a

sequence of amino acids that formed what Etienne Decroly and colleagues called a "peculiar furin-like cleavage site" — a chemically sensitive region on the lobster claw of the spike protein that would react in the presence of an enzyme called furin, which is a type of protein found everywhere within the human body, but especially in the lungs. When the spike senses human furin, it shudders, chemically speaking, and the enzyme opens the protein, commencing the tiny morbid ballet whereby the virus burns a hole in a host cell's outer membrane and finds its way inside.

The code for this particular molecular feature — not found in SARS or any SARS-like bat viruses, but present in a slightly different form in the more lethal MERS virus — is easy to remember because it's a roar: "R-R-A-R." The letter code stands for amino acids: arginine, arginine, alanine, and arginine. Its presence, so Decroly and his colleagues observed, may heighten the "pathogenicity" — that is, the god-awfulness — of a disease.

Botao Xiao, a professor at the South China University of Technology, posted a short paper on a preprint server titled "The Possible Origins of 2019-nCoV Coronavirus." Two laboratories, the Wuhan Center for Disease Control and Prevention (WHCDC) and the Wuhan Institute of Virology, were not far from the seafood market, which was where the disease was said to have originated, Xiao wrote — in fact, the WHCDC was only a few hundred yards away from the market — whereas the horseshoe bats that hosted the disease were hundreds of miles to the south. (No bats were sold in the market, he pointed out.) It was unlikely, he wrote, that a bat would have flown to a densely populated metropolitan area of 15 million people. "The killer coronavirus probably originated from a laboratory in Wuhan," Xiao believed. He urged the relocation of "biohazardous laboratories" away from densely populated places. His article disappeared from the server.

And late in the month, a professor at National Taiwan University, Fang Chi-

tai, gave a lecture on the coronavirus in which he described the anomalous R-R-A-R furin cleavage site. The virus was "unlikely to have four amino acids added all at once," Fang said — natural mutations were smaller and more haphazard, he argued. "From an academic point of view, it is indeed possible that the amino acids were added to COVID-19 in the lab by humans." When the Taiwan *News* published an article about Fang's talk, Fang disavowed his own comments, and the video copy of the talk disappeared from the website of the Taiwan Public Health Association. "It has been taken down for a certain reason," the association explained. "Thank you for your understanding."

V.

"A Serious Shortage of Appropriately Trained Technicians"

In the spring, I did some reading on coronavirus history. Beginning in the 1970s, dogs, cows, and pigs were diagnosed with coronavirus infections; dog shows were canceled in 1978 after 25 collies died in Louisville, Kentucky. New varieties of coronaviruses didn't start killing humans, though, until 2003 — that's when restaurant chefs, food handlers, and people who lived near a live-animal market got sick in Guangzhou, in southern China, where the shredded meat of a short-legged raccoonlike creature, the palm civet, was served in a regional dish called "dragon-tiger-phoenix soup." The new disease, SARS, spread alarmingly in hospitals, and it reached 30 countries and territories. More than 800 people died; the civet-borne virus was eventually traced to horseshoe bats.

Later, smaller outbreaks of SARS in Taiwan, Singapore, and China's National Institute of Virology in Beijing were all caused by laboratory accidents. Of the Beijing Virology Institute, the World Health Organization's safety

investigators wrote, in May 2004, that they had "serious concerns about biosafety procedures." By one account, a SARS storage room in the Beijing lab was so crowded that the refrigerator holding live virus was moved out to the hallway. "Scientists still do not fully understand exactly where or how SARS emerged 18 months ago," wrote Washington *Post* reporter David Brown in June 2004. "But it is clear now that the most threatening source of the deadly virus today may be places they know intimately — their own laboratories."

I'm just asking, Is it a complete coincidence that this outbreak happened in the one city in China with a BSL-4 lab?

MERS arose in 2012, possibly spread by camels that had contracted the disease from bats or bat guano, then passed it to human drinkers of raw camel milk and butchers of camel meat. It was an acute sickness, with a high fatality rate, mostly confined to Saudi Arabia. Like SARS, MERS ebbed quickly — it all but disappeared outside the Middle East, except for an outbreak in 2015 at the Samsung Medical Center in South Korea, where a single case of MERS led to more than 180 infections, many involving hospital workers.

In January 2015, the brand-new BSL-4 lab in Wuhan, built by a French contractor, celebrated its opening, but full safety certification came slowly. According to State Department cables from 2018 leaked to the Washington *Post*, the new BSL-4 lab had some start-up problems, including "a serious shortage of appropriately trained technicians and investigators needed to safely operate this high-containment laboratory." The staff had gotten some training at a BSL-4 lab in Galveston, Texas, but they were doing potentially dangerous work with SARS-like viruses, the memo said, and they needed more help from the U.S.

In November or December of 2019, the novel coronavirus began to spread. Chinese scientists initially named it "Wuhan seafood market pneumonia virus," but soon that idea went away. The market, closed and decontaminated by Chinese officials on January 1, 2020, was an amplifying hub, not the source of the outbreak, according to several studies by Chinese scientists. Forty-five percent of the earliest SARS-2 patients had no link with the market.

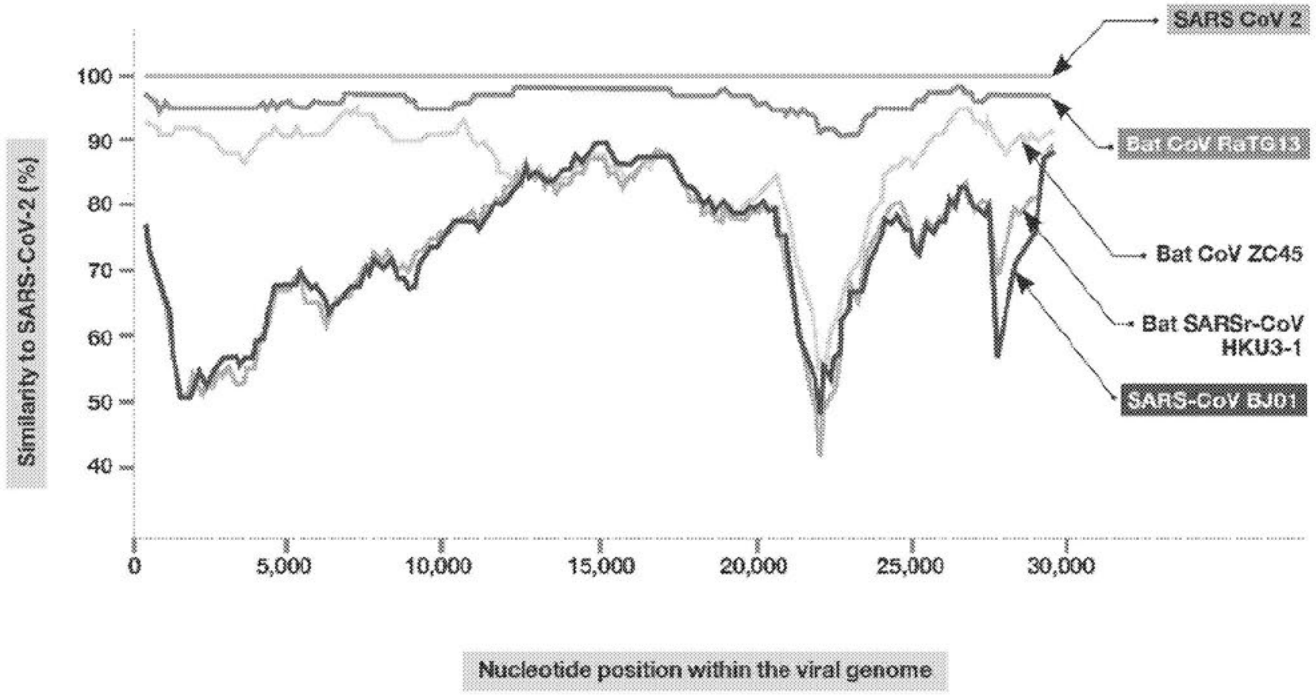
VI.

Emergence

Now let's take a step back. AIDS, fatal and terrifying and politically charged, brought on a new era in government-guided vaccine research, under the guidance of Anthony Fauci. A virologist at Rockefeller University, Stephen S. Morse, began giving talks on "emerging viruses" — other plagues that might be in the process of coming out of nature's woodwork. In 1992, Richard Preston wrote a horrific account of one emergent virus, Ebola, in *The New Yorker*, which became a best-selling book in 1994; Laurie Garrett's *The Coming Plague: Newly Emerging Diseases in a World Out of Balance* appeared that same year and was also a best seller. The idea seemed to be everywhere: We were on the verge of a wave of zoonotic, emergent plagues.

This new, useful term, *emerging*, began to glow in the research papers of some coronavirologists, who were out of the spotlight, working on common colds and livestock diseases. The term was useful because it was fluid. An emerging disease could be real and terrifying, as AIDS was — something that had just arrived on the medical scene and was confounding our efforts to combat it — or it could be a disease that hadn't arrived, and might never arrive, but could be shown in a laboratory to be waiting in the wings, just a

few mutations away from a human epidemic. It was real and unreal at the same time — a quality that was helpful when applying for research grants.



Where Did It Come From? This chart measures the genetic similarity of known viruses to the novel coronavirus (which appears in yellow). By far the closest is the bat virus RaTG13, which appears in blue, and which was recovered in 2013 and brought to the Wuhan Institute of Virology. The first SARS, marked in red, is a much more distant relative. Graphic: Zhou, P., Yang, XL., Wang, XG. et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 579, 270–273 (2020)

Take, for instance, this paper from 1995: "High Recombination and Mutation Rates in Mouse Hepatitis Viruses Suggest That Coronaviruses May Be Potentially Important Emerging Viruses." It was written by Dr. Ralph Baric and his bench scientist, Boyd Yount, at the University of North Carolina. Baric, a gravelly voiced former swim champion, described in this early paper how his lab was able to train a coronavirus, MHV, which causes hepatitis in mice, to jump species, so that it could reliably infect BHK (baby-hamster kidney) cell cultures. They did it using serial passaging: repeatedly dosing a mixed solution of mouse cells and hamster cells with mouse-hepatitis virus,

while each time decreasing the number of mouse cells and upping the concentration of hamster cells. At first, predictably, the mouse-hepatitis virus couldn't do much with the hamster cells, which were left almost free of infection, floating in their world of fetal-calf serum. But by the end of the experiment, after dozens of passages through cell cultures, the virus had mutated: It had mastered the trick of parasitizing an unfamiliar rodent. A scourge of mice was transformed into a scourge of hamsters. And there was more: "It is clear that MHV can rapidly alter its species specificity and infect rats and primates," Baric said. "The resulting virus variants are associated with demyelinating diseases in these alternative species." (A demyelinating disease is a disease that damages nerve sheaths.) With steady prodding from laboratory science, along with some rhetorical exaggeration, a lowly mouse ailment was morphed into an emergent threat that might potentially cause nerve damage in primates. That is, nerve damage in us.

A few years later, in a further round of "interspecies transfer" experimentation, Baric's scientists introduced their mouse coronavirus into flasks that held a suspension of African-green-monkey cells, human cells, and pig-testicle cells. Then, in 2002, they announced something even more impressive: They'd found a way to create a full-length infectious clone of the entire mouse-hepatitis genome. Their "infectious construct" replicated itself just like the real thing, they wrote.

Not only that, but they'd figured out how to perform their assembly seamlessly, without any signs of human handiwork. Nobody would know if the virus had been fabricated in a laboratory or grown in nature. Baric called this the "no-see'm method," and he asserted that it had "broad and largely unappreciated molecular biology applications." The method was named, he wrote, after a "very small biting insect that is occasionally found on North Carolina beaches."

In 2006, Baric, Yount, and two other scientists were granted a patent for their invisible method of fabricating a full-length infectious clone using the seamless, no-see'm method. But this time, it wasn't a clone of the mouse-hepatitis virus — it was a clone of the entire deadly human SARS virus, the one that had emerged from Chinese bats, via civets, in 2002. The Baric Lab came to be known by some scientists as "the Wild Wild West." In 2007, Baric said that we had entered "the golden age of coronavirus genetics."

"I would be afraid to look in their freezers," one virologist told me.

Baric and Shi Zhengli of the Wuhan Institute of Virology, the two top experts on the genetic interplay between bat and human coronaviruses, began collaborating in 2015.

VII.

"I Had Not Slept a Wink"

Virologist Shi Zhengli at the Wuhan Institute of Virology in 2017. Photo: Feature China / Barcroft Studios / Future Publishing / Getty Images

Early in the pandemic, *Scientific American* profiled Shi Zhengli, known in China as the "bat woman." Shi trapped hundreds of bats in nets at the mouths of caves in southern China, sampled their saliva and their blood, swabbed their anuses, and gathered up their fecal pellets. Several times, she visited and sampled bats in a mine in Mojiang, in southern China, where, in 2012, six men set to work shoveling bat guano were sickened by a severe lung disease, three of them fatally. Shi's team took the samples back to Wuhan and analyzed whatever fragments of bat virus she could find. In some cases, when she found a sequence that seemed particularly significant, she experimented with it in order to understand how it might potentially infect humans. Some of her work was funded by the National Institutes of Health and some of it by the U.S. Defense Threat Reduction

Agency of the Department of Defense via Peter Daszak's EcoHealth Alliance.

As Shi explained to *Scientific American*, late in December 2019, she heard from the director of the Wuhan Institute that there was an outbreak of a new disease in the city. Medical samples taken from hospital patients arrived at her lab for analysis. Shi determined that the new virus was related to SARS but even more closely related to a bat disease that her own team had found on a virus-hunting trip: the now-famous RaTG13. Shi was surprised that the outbreak was local, she said: "I had never expected this kind of thing to happen in Wuhan, in central China." The bat hiding places that she'd been visiting were, after all, as far away as Orlando, Florida, is from New York City. Could this new virus, she wondered, have come from her own laboratory? She checked her records and found no exact matches. "That really took a load off my mind," she said. "I had not slept a wink for days."

If one of the first thoughts that goes through the head of a lab director at the Wuhan Institute of Virology is that the new coronavirus could have come from her lab, then we are obliged to entertain the scientific possibility that it could indeed have come from her lab. Right then, there should have been a comprehensive, pockets-inside-out, fully public investigation of the Virology Institute, along with the other important virus labs in Wuhan, including the one close by the seafood market, headquarters of the Wuhan CDC. There should have been interviews with scientists, interviews with biosafety teams, close parsings of laboratory notebooks, freezer and plumbing and decontamination systems checks — everything. It didn't happen. The Wuhan Institute of Virology closed down its databases of viral genomes, and the Chinese Ministry of Education sent out a directive: "Any paper that traces the origin of the virus must be strictly and tightly managed."

Shi made some WeChat posts early in 2020. "The novel 2019 coronavirus is nature punishing the human race for keeping uncivilized living habits," she wrote. "I, Shi Zhengli, swear on my life that it has nothing to do with our laboratory." She advised those who believed rumors, and gave credence to unreliable scientific papers, to "shut their stinking mouths."

VIII.

" 'Bug to Drug' in 24 Hours"

It wasn't only AIDS that changed the way the NIH funded research. The War on Terror also influenced which diseases got the most attention. In the late '90s, under Bill Clinton and then George W. Bush, biodefense specialists became interested — again — in anthrax. The Defense Threat Reduction Agency built a small anthrax factory in Nevada, using simulants, to demonstrate how easy it would be for a terrorist to build a small anthrax factory. And in the first year of the Bush presidency, the Defense Intelligence Agency wrote up plans to create a vaccine-resistant form of anthrax using state-of-the-art gene-splicery. A front-page article describing these initiatives, "U.S. Germ Warfare Research Pushes Treaty Limits," appeared in the New York *Times* on September 4, 2001, one week before 9/11. "Pentagon Says Projects Are Defense, Is Pressing Ahead," was the subtitle.

After the 9/11 attacks, and the mysterious anthrax mailings that began a week later (which said, "TAKE PENACILIN [*sic*] NOW / DEATH TO AMERICA / DEATH TO ISRAEL / ALLAH IS GREAT"), the desire for biopreparedness became all consuming. Now there were emerging biothreats from humans as well as from the evolving natural world. Fauci's anti-terror budget went from $53 million in 2001 to $1.7 billion in 2003. Setting aside his work toward an AIDS vaccine, which was taking longer than he'd foreseen, Fauci

said he would be going all out to defend against a suite of known Cold War agents, all of which had been bred and perfected in American weapons programs many years before — brucellosis, anthrax, tularemia, and plague, for instance. "We are making this the highest priority," Fauci said. "We are really marshaling all available resources."

> ***I would be afraid to look in their freezers.***

Vaccine development had to progress much faster, Fauci believed; he wanted to set up "vaccine systems" and "vaccine platforms," which could be quickly tailored to defend against a particular emergent strain some terrorist with an advanced biochemistry degree might have thrown together in a laboratory. "Our goal within the next 20 years is 'bug to drug' in 24 hours," Fauci said. "This would specifically meet the challenge of genetically engineered bioagents." The first Project BioShield contract Fauci awarded was to VaxGen, a California pharmaceutical company, for $878 million worth of shots of anthrax vaccine.

By 2005, so much money was going toward biothreat reduction and preparedness that more than 750 scientists sent a protest letter to the NIH. Their claim was that grants to study canonical biowar diseases — anthrax, plague, brucellosis, and tularemia, all exceptionally rare in the U.S. — had increased by a factor of 15 since 2001, whereas funds for the study of widespread "normal" diseases, of high public-health importance, had decreased.

Fauci was firm in his reply: "The United States through its leaders made the decision that this money was going to be spent on biodefense," he said. "We disagree with the notion that biodefense concerns are of 'low public-health significance.' "

In 2010, by one count, there were 249 BSL-3 laboratories and seven BSL-4 laboratories in the U.S., and more than 11,000 scientists and staffers were authorized to handle the ultralethal germs on the government's select pathogen list. And yet the sole bioterrorist in living memory who actually killed American citizens, according to the FBI — the man who sent the anthrax letters — turned out to be one of the government's own researchers. Bruce Ivins, an eccentric, suicidal laboratory scientist from Ohio who worked in vaccine development at Fort Detrick, allegedly wanted to boost the fear level so as to persuade the government to buy more of the patented, genetically engineered anthrax VaxGen vaccine, of which he was a co-inventor. (See David Willman's fascinating biography of Ivins, *Mirage Man*.) Fauci's staff at NIH funded Ivins's vaccine laboratory and gave $100 million to VaxGen to accelerate vaccine production. (The NIH's $878 million contract with VaxGen, however, was quietly canceled in 2006; Ivins, who was never charged, killed himself in 2008.)

"The whole incident amounted to a snake eating its own tail," wrote Wendy Orent in an August 2008 piece titled "Our Own Worst Bioenemy" in the Los Angeles *Times*. "No ingenious biowarrior from Al Qaeda sent the lethal envelopes through the U.S. postal system. An American scientist did." What confirmed Ivins's guilt, according to the FBI, was that there was a genetic match between the anthrax used in the killings and the strain held at Fort Detrick.

IX.

"Weapons of Mass Disruption"

After SARS appeared in 2003, Ralph Baric's laboratory moved up the NIH funding ladder. SARS was a "dual use" organism — a security threat and a zoonotic threat at the same time. In 2006, Baric wrote a long, fairly creepy

paper on the threat of "weaponizable" viruses. Synthetic biology had made possible new kinds of viral "weapons of mass disruption," he wrote, involving, for example, "rapid production of numerous candidate bioweapons that can be simultaneously released," a scattershot terror tactic Baric called the " 'survival of the fittest' approach."

Baric hoped to find a SARS vaccine, but he couldn't; he kept looking for it, year after year, supported by the NIH, long after the disease itself had been contained. It wasn't really gone, Baric believed. Like other epidemics that pop up and then disappear, as he told a university audience some years later, "they don't go extinct. They are waiting to return." What do you do if you run a well-funded laboratory, an NIH "center of excellence," and your emergent virus is no longer actually making people sick? You start squeezing it and twisting it into different shapes. Making it stand on its hind legs and quack like a duck, or a bat. Or breathe like a person.

Baric's safety record is good — although there was a minor mouse-bite incident in 2016, uncovered by ProPublica — and his motives are beyond reproach: "Safe, universal, vaccine platforms are needed that can be tailored to new pathogens as they emerge, quickly tested for safety, and then strategically used to control new disease outbreaks in human populations," he wrote in a paper on public health. But the pioneering work he did over the past 15 years — generating tiny eager single-stranded flask monsters and pitting them against human cells, or bat cells, or gene-spliced somewhat-human cells, or monkey cells, or humanized mice — was not without risk, and it may have led others astray.

In 2006, for instance, Baric and his colleagues, hoping to come up with a "vaccine strategy" for SARS, produced noninfectious virus replicon particles (or VRPs) using the Venezuelan-equine-encephalitis virus (another American germ-warfare agent), which they fitted with various SARS spike

proteins. Then, wearing Tyvek suits and two pairs of gloves each, and working in a biological safety cabinet in a BSL-3-certified laboratory, they cloned and grew recombinant versions of the original SARS virus in an incubator in a medium that held African-green-monkey cells. When they had grown enough virus, the scientists swapped out one kind of spike protein for a carefully chosen mutant, and they challenged their prototype vaccine with it in mice.

The scientists also tried their infectious SARS clones in something called an air-liquid interface, using a relatively new type of cell culture developed by Raymond Pickles of the University of North Carolina's Cystic Fibrosis Center. Pickles had perfected a method of emulating the traits of human airway tissue by cultivating cells taken from lung-disease patients — nurturing the culture over four to six weeks in such a way that the cells differentiated and developed a crop of tiny moving hairs, or cilia, on top and goblet cells within that produced real human mucus. In fact, before infecting these HAE (human airway epithelial) cells with a virus, the lab worker must sometimes rinse off some of the accumulated mucus, as if helping the lab-grown tissue to clear its throat. So Baric was exposing and adapting his engineered viruses to an extraordinarily true-to-life environment — the juicy, sticky, hairy inner surface of our breathing apparatus.

SARS-2 seems almost perfectly calibrated to grab and ransack our breathing cells and choke the life out of them. "By the time SARS-CoV-2 was first detected in late 2019, it was already pre-adapted to human transmission," Alina Chan and her co-authors have written, whereas SARS, when it first appeared in 2003, underwent "numerous adaptive mutations" before settling down. Perhaps viral nature hit a bull's-eye of airborne infectivity, with almost no mutational drift, no period of accommodation and adjustment, or perhaps some lab worker somewhere, inspired by Baric's

work with human airway tissue, took a spike protein that was specially groomed to colonize and thrive deep in the ciliated, mucosal tunnels of our inner core and cloned it onto some existing viral bat backbone. It could have happened in Wuhan, but — because anyone can now "print out" a fully infectious clone of any sequenced disease — it could also have happened at Fort Detrick, or in Texas, or in Italy, or in Rotterdam, or in Wisconsin, or in some other citadel of coronaviral inquiry. No conspiracy — just scientific ambition, and the urge to take exciting risks and make new things, and the fear of terrorism, and the fear of getting sick. Plus a whole lot of government money.

X.

"Risky Areas for Spillover"

Project Bioshield began to fade by the end of the Bush administration, although the expensive high-containment laboratories, controversial preservers and incubators of past and future epidemics, remain. By 2010, some BioShield projects had dissolved into Obama's Predict program, which paid for laboratories and staff in 60 "risky areas for spillover" around the world. Jonna Mazet, a veterinary scientist from the University of California, Davis, was in charge of Predict, which was a component of USAID's "Emerging Pandemic Threats" program. Her far-flung teams collected samples from 164,000 animals and humans and claimed to have found "almost 1,200 potentially zoonotic viruses, among them 160 novel coronaviruses, including multiple SARS- and MERS-like coronaviruses." The fruits of Predict's exotic harvest were studied and circulated in laboratories worldwide, and their genetic sequences became part of GenBank, the NIH's genome database, where any curious RNA wrangler anywhere could quickly synthesize snippets of code and test out a new disease on human cells.

Baric, Jonna Mazet, and Peter Daszak of EcoHealth worked together for years — and Daszak also routed Predict money to Shi Zhengli's bat-surveillance team in Wuhan through his nonprofit, mingling it with NIH money and money from the U.S. Defense Threat Reduction Agency. In 2013, Mazet announced that Shi Zhengli's virus hunters, with Predict's support, had, for the first time, isolated and cultured a live SARS-like virus from bats and demonstrated that this virus could bind to the human ACE2, or "angiotensin-converting enzyme 2," receptor, which Baric's laboratory had determined to be the sine qua non of human infectivity. "This work shows that these viruses can directly infect humans and validates our assumption that we should be searching for viruses of pandemic potential before they spill over to people," Mazet said.

Daszak, for his part, seems to have viewed his bat quests as part of an epic, quasi-religious death match. In a paper from 2008, Daszak and a co-author described Bruegel's painting *The Fall of the Rebel Angels* and compared it to the contemporary human biological condition. The fallen angels could be seen as pathogenic organisms that had descended "through an evolutionary (not spiritual) pathway that takes them to a netherworld where they can feed only on our genes, our cells, our flesh," Daszak wrote. "Will we succumb to the multitudinous horde? Are we to be cast downward into chthonic chaos represented here by the heaped up gibbering phantasmagory against which we rail and struggle?"

XI.

"Lab-Made?"

There are, in fact, some helpful points of agreement between zoonoticists — those who believe in a natural origin of the SARS-2 virus — and those who believe that it probably came from a laboratory. Both sides agree, when

pressed, that a lab origin can't be conclusively ruled out and a natural origin can't be ruled out either — because nature, after all, is capable of improbable, teleological-seeming achievements. Both sides also agree, for the most part, that the spillover event that began the human outbreak probably happened only once, or a few times, quite recently, and not many times over a longer period. They agree that bat virus RaTG13 (named for the *Rinolophus affinus* bat, from Tongguan, in 2013) is the closest match to the human virus that has yet been found, and that although the two viruses are very similar, the spike protein of the bat virus lacks the features the human spike protein possesses that enable it to work efficiently with human tissue.

Zoonoticists hold that SARS-2's crucial features — the furin cleavage site and the ACE2 receptor — are the result of a recombinant event involving a bat coronavirus (perhaps RaTG13 or a virus closely related to it) and another, unknown virus. Early on, researchers proposed that it could be a snake sold at the seafood market — a Chinese cobra or a banded krait — but no: Snakes don't typically carry coronaviruses. Then there was a thought that the disease came from sick smuggled pangolins, because there existed a certain pangolin coronavirus that was, inexplicably, almost identical in its spike protein to the human coronavirus — but then, no: There turned out to be questions about the reliability of the genetic information in that diseased-pangolin data set, on top of which there were no pangolins for sale at the Wuhan market. Then a group from China's government veterinary laboratory at Harbin tried infecting beagles, pigs, chickens, ducks, ferrets, and cats with SARS-2 to see if they could be carriers. (Cats and ferrets got sick; pigs, ducks, and most dogs did not.)

In September, some scientists at the University of Michigan, led by Yang Zhang, reported that they had created a "computational pipeline" to screen nearly a hundred possible intermediate hosts, including the Sumatran orangutan, the Western gorilla, the Olive baboon, the crab-eating macaque,

and the bonobo. All these primates were "permissive" to the SARS-2 coronavirus and should undergo "further experimentational investigation," the scientists proposed.

Despite this wide-ranging effort, there is at the moment no animal host that zoonoticists can point to as the missing link. There's also no single, agreed-upon hypothesis to explain how the disease may have traveled from the bat reservoirs of Yunnan all the way to Wuhan, seven hours by train, without leaving any sick people behind and without infecting anyone along the way.

The zoonoticists say that we shouldn't find it troubling that virologists have been inserting and deleting furin cleavage sites and ACE2-receptor-binding domains in experimental viral spike proteins for years: The fact that virologists have been doing these things in laboratories, in advance of the pandemic, is to be taken as a sign of their prescience, not of their folly. But I keep returning to the basic, puzzling fact: This patchwork pathogen, which allegedly has evolved without human meddling, first came to notice in the only city in the world with a laboratory that was paid for years by the U.S. government to perform experiments on certain obscure and heretofore unpublicized strains of bat viruses — which bat viruses then turned out to be, out of all the organisms on the planet, the ones that are most closely related to the disease. What are the odds?

In July, I discovered a number of volunteer analysts who were doing a new kind of forensic, samizdat science, hunched over the letter code of the SARS-2 genome like scholars deciphering the cuneiform impressions in Linear B tablets. There were the anonymous authors of Project Evidence, on GitHub, who "disavow all racism and violent attacks, including those which are aimed at Asian or Chinese people," and there was Yuri Deigin, a biotech entrepreneur from Canada, who wrote a massive, lucid paper on Medium, "Lab-Made?," which illumined the mysteries of the spike protein. Jonathan

Latham of the Bioscience Resource Project, with his co-author Allison Wilson, wrote two important papers: one a calm, unsparing overview of laboratory accidents and rash research and the other a close look at the small outbreak of an unexplained viral pneumonia in a bat-infested copper mine in 2012. I corresponded with Alina Chan (now the subject of a nicely turned piece in *Boston* magazine by Rowan Jacobsen) and with the pseudonymous Billy Bostickson, a tireless researcher whose Twitter photo is a cartoon of an injured experimental monkey, and Monali Rahalkar, of the Agharkar Research Institute in Pune, India, who wrote a paper with her husband, Rahul Bahulikar, that also sheds light on the story of the bat-guano-shoveling men whose virus was remarkably like SARS-2, except that it was not nearly as catching. I talked to Rossana Segreto, a molecular biologist at the University of Innsbruck, whose paper, "Is Considering a Genetic-Manipulation Origin for SARS-CoV-2 a Conspiracy Theory That Must Be Censored?," co-authored with Yuri Deigin, was finally published in November under a milder title; it argued that SARS-2's most notable features, the furin site and the human ACE2-binding domain, were unlikely to have arisen simultaneously and "might be the result of lab manipulation techniques such as site directed mutagenesis." Segreto is also the person who first established that a bat-virus fragment named BtCoV/4991, identified in 2013, was 100 percent identical to the closest known cousin to SARS-CoV-2, the bat virus RaTG13, thereby proving that the virus closest to the SARS-2-pandemic virus was linked back not to a bat cave but to a mine shaft, and that this same virus had been stored and worked on in the Wuhan Institute for years. This made possible the first big investigative piece on SARS-2's origins, in the *Times* of London, in July: "Nobody can deny the bravery of scientists who risked their lives harvesting the highly infectious virus," the *Times* authors write. "But did their courageous detective work lead inadvertently to a global disaster?"

XII.

"A New, Non-Natural Risk"

In 2011, a tall, confident Dutch scientist, Ron Fouchier, using grant money from Fauci's group at NIH, created a mutant form of highly pathogenic avian influenza, H5N1, and passaged it ten times through ferrets in order to prove that he could "force" (his word) this potentially fatal disease to infect mammals, including humans, "via aerosols or respiratory droplets." Fouchier said his findings indicated that these avian influenza viruses, thus forced, "pose a risk of becoming pandemic in humans."

This experiment was too much for some scientists: Why, out of a desire to prove that something extremely infectious could happen, would you make it happen? And why would the U.S. government feel compelled to pay for it to happen? Late in 2011, Marc Lipsitch of the Harvard School of Public Health got together with several other dismayed onlookers to ring the gong for caution. On January 8, 2012, the New York *Times* published a scorcher of an editorial, "An Engineered Doomsday." "We cannot say there would be no benefits at all from studying the virus," the *Times* said. "But the consequences, should the virus escape, are too devastating to risk."

These gain-of-function experiments were an important part of the NIH's approach to vaccine development, and Anthony Fauci was reluctant to stop funding them. He and Francis Collins, director of the National Institutes of Health, along with Gary Nabel, NIAID director of vaccine research, published an opinion piece in the Washington *Post* in which they contended that the ferret flu experiments, and others like them, were "a risk worth taking." "Important information and insights can come from generating a potentially dangerous virus in the laboratory," they wrote; the work can "help delineate the principles of virus transmission between species." The

work was safe because the viruses were stored in a high-security lab, they believed, and the work was necessary because nature was always coming up with new threats. "Nature is the worst bioterrorist," Fauci told a reporter. "We know that through history."

Soon afterward, there followed some distressing screwups in secure federal laboratories involving live anthrax, live smallpox, and live avian influenza. These got attention in the science press. Then Lipsitch's activists (calling themselves the Cambridge Working Group) sent around a strong statement on the perils of research with "Potential Pandemic Pathogens," signed by more than a hundred scientists. The work might "trigger outbreaks that would be difficult or impossible to control," the signers said. Fauci reconsidered, and the White House in 2014 announced that there would be a "pause" in the funding of new influenza, SARS, and MERS gain-of-function research.

Baric, in North Carolina, was not happy. He had a number of gain-of-function experiments with pathogenic viruses in progress. "It took me ten seconds to realize that most of them were going to be affected," he told NPR. Baric and a former colleague from Vanderbilt University wrote a long letter to an NIH review board expressing their "profound concerns." "This decision will significantly inhibit our capacity to respond quickly and effectively to future outbreaks of SARS-like or MERS-like coronaviruses, which continue to circulate in bat populations and camels," they wrote. The funding ban was itself dangerous, they argued. "Emerging coronaviruses in nature do not observe a mandated pause."

Hoping to smooth over controversy by showing due diligence, the National Science Advisory Board for Biosecurity, founded in the BioShield era under President Bush, paid a consulting firm, Gryphon Scientific, to write a report on gain-of-function research, which by now was simply referred to as GoF.

In chapter six of this thousand-page dissertation, published in April 2016, the consultants take up the question of coronaviruses. "Increasing the transmissibility of the coronaviruses could significantly increase the chance of a global pandemic due to a laboratory accident," they wrote.

The Cambridge Working Group continued to write letters of protest and plead for restraint and sanity. Steven Salzberg, a professor of biomedical engineering at Johns Hopkins, said, "We have enough problems simply keeping up with the current flu outbreaks — and now with Ebola — without scientists creating incredibly deadly new viruses that might accidentally escape their labs." David Relman of Stanford Medical School said, "It is unethical to place so many members of the public at risk and then consult only scientists — or, even worse, just a small subset of scientists — and exclude others from the decision-making and oversight process." Richard Ebright wrote that creating and evaluating new threats very seldom increases security: "Doing so in biology — where the number of potential threats is nearly infinite, and where the asymmetry between the ease of creating threats and the difficulty of addressing threats is nearly absolute — is especially counterproductive." Lynn Klotz wrote, "Awful as a pandemic brought on by the escape of a variant H5N1 virus might be, it is SARS that now presents the greatest risk. The worry is less about recurrence of a natural SARS outbreak than of yet another escape from a laboratory researching it to help protect against a natural outbreak." Marc Lipsitch argued that gain-of-function experiments can mislead, "resulting in worse not better decisions," and that the entire gain-of-function debate as overseen by the NIH was heavily weighted in favor of scientific insiders and "distinctly unwelcoming of public participation."

Nariyoshi Shinomiya, a professor of physiology and nano-medicine at the National Defense Medical College in Japan, offered this warning: "Similar to nuclear or chemical weapons there is no going back once we get a thing in

our hands."

But in the end, Baric was allowed to proceed with his experiments, and the research papers that resulted, showered with money, became a sort of *Anarchist's Cookbook* for the rest of the scientific world. In November 2015, Baric and colleagues published a collaboration paper with Shi Zhengli titled "A SARS-like Cluster of Circulating Bat Coronaviruses Shows Potential for Human Emergence." Into a human SARS virus that they had adapted so that it would work in mice, Baric and Shi et al. inserted the spike protein of a bat virus, SHC014, discovered by Shi in southern China. They dabbed the mice nasally with virus and waited, looking for signs of sickness: "hunching, ruffled fur." They also infected human airway cells with the mouse-adapted bat-spike-in-a-human-virus backbone. In both mice and human airway cells, the chimeric virus caused a "robust infection."

This proved, Baric and Shi believed, that you did not need civets or other intermediate hosts in order for bats to cause an epidemic in humans and that therefore all the SARS-like viruses circulating in bat populations "may pose a future threat." Peter Daszak, who had used Predict funds to pay Shi for her work on the paper, was impressed by this conclusion; the findings, he said, "move this virus from a candidate emerging pathogen to a clear and present danger."

Richard Ebright was trenchantly unenthusiastic. "The only impact of this work," he said, "is the creation, in a lab, of a new, non-natural risk."

Early in 2016, Baric and Shi again collaborated. Shi sent Baric a fresh bat virus spike protein, and Baric inserted it into the backbone of a human SARS virus and then used that infectious clone to attack human airway cells. "The virus readily and efficiently replicated in cultured human airway tissues, suggesting an ability to potentially jump directly to humans,"

reported the UNC's website. This time, they also used the bat-human hybrid virus to infect transgenic humanized mice that grew human ACE2 protein. The mice, young and old, lost weight and died, proving, again, that this particular bat virus was potentially "poised to emerge in human populations." It was "an ongoing threat," Baric wrote. But was it? Civets and camels that are exposed to a lot of bat-guano dust may be an ongoing threat and a manageable one. But the bats themselves just want to hang in their caves and not be bothered by frowning sightseers in spacesuits who want to poke Q-tips in their bottoms. This 2016 "poised for human emergence" paper was supported by eight different NIH grants. In 2015, Baric's lab received $8.3 million from the NIH; in 2016, it received $10.5 million.

Gain-of-function research came roaring back under Trump and Fauci. "The National Institutes of Health will again fund research that makes viruses more dangerous," said an article in *Nature* in December 2017. Carrie Wolinetz of the NIH's office of science policy defended the decision. "These experiments will help us get ahead of viruses that are already out there and pose a real and present danger to human health," she told *The Lancet*. The NIH, Wolinetz said, was committed to a leadership role with gain-of-function research internationally. "If we are pursuing this research in an active way, we will be much better positioned to develop protection and countermeasures should something bad happen in another country."

A reporter asked Marc Lipsitch what he thought of the resumption of NIH funding. Gain-of-function experiments "have done almost nothing to improve our preparedness for pandemics," he said, "yet they risked creating an accidental pandemic."

XIII.

"Proximity Is a Problem"

In April, four months into the coronavirus emergency, a deputy director at the NIH wrote an email to EcoHealth Alliance. "You are instructed to cease providing any funds to Wuhan Institute of Virology," it said. In response, Daszak and the chief scientific officer of New England Biolabs (a company that sells seamless gene-splicing products to laboratories, among other things) got 77 Nobel Prize winners to sign a statement saying that the cancellation deprived the "nation and the world of highly regarded science that could help control one of the greatest health crises in modern history and those that may arise in the future." Later, as a condition of further funding, the NIH wrote to say it wanted Daszak to arrange an outside inspection of the Wuhan lab and to procure from Wuhan's scientists a sample of whatever they'd used to sequence the SARS-2 virus. Daszak was outraged ("I am not trained as a private detective"), and again he fought back. He was reluctant to give up his own secrets, too. "Conspiracy-theory outlets and politically motivated organizations have made Freedom of Information Act requests on our grants and all of our letters and emails to the NIH," he told *Nature*. "We don't think it's fair that we should have to reveal everything we do."

But Daszak has survived — even prospered. Recently, *The Lancet* made him the lead investigator in its inquiry into the origins of the pandemic, and the World Health Organization named him to its ten-person origins investigation. ("We're still close enough to the origin to really find out more details about where it has come from," Daszak told *Nature*.)

The NIH has also set up an ambitious new international program, called CREID, which stands for Centers for Research in Emerging Infectious Diseases, and it has put Daszak's EcoHealth in charge of trapping animals and looking for obscure bat viruses in Singapore, Malaysia, and Thailand.

Baric is one of Daszak's partners in CREID. The virus hunting and collecting, which Richard Ebright likens to "looking for a gas leak with a lighted match," will continue and widen with U.S. funding. "We're going to work in remote parts of Malaysia and Thailand to get to the front line of where the next pandemic is going to start," Daszak told NPR.

In May, an interviewer from the People's Pharmacy website asked Baric if he had any thoughts on whether the coronavirus began with a natural bat-to-human transfer. "Or was there something a little bit more, perhaps, insidious involved?"

"Well, of course the answers to those questions are in China," Baric replied. "Exactly how they work in that facility is something that would be very difficult for a Westerner to know," he said. "The main problems that the Institute of Virology has is that the outbreak occurred in close proximity to that Institute. That Institute has in essence the best collection of virologists in the world that have gone out and sought out, and isolated, and sampled bat species throughout Southeast Asia. So they have a very large collection of viruses in their laboratory. And so it's — you know — proximity is a problem. It's a problem."

Over the course of the fall, and especially after the election muffled Donald Trump's influence over the country's public-health apparatus, that proximity problem — and the uncomfortable questions of origins it raised — began to grow somewhat more discussable. The BBC, *Le Monde*, and Italy's RAI have all recently taken seriously the scientific possibility of a lab leak. In late October, the World Health Organization convened the first meeting of its second inquiry into the origins of the disease. The WHO's effort is perhaps the world's best chance to satisfy its curiosity about goings-on at the Wuhan Institute of Virology and at the Wuhan CDC's virus lab near the Wuhan seafood market. But, as the New York *Times* has reported, the

WHO's information gathering has been hindered by Chinese secretiveness since February, when an initial investigative team sent to Beijing was told its members' access to scientists would be restricted and that it couldn't visit the seafood market, then considered a hub of the pandemic.

When a BBC video team tried to inspect the Yunnan mine shaft, they found the road to the mine blocked by a strategically parked truck that had "broken down" shortly before they arrived. Reporter John Sudworth asked Daszak, one of the ten members of the second WHO investigative team, whether he would push for access to the Wuhan Institute of Virology. "That's not my job to do that," Daszak replied.

In November, David Relman, the Stanford microbiologist, one of the most thoughtful of the voices warning against gain-of-function research, published a paper in *Proceedings of the National Academy of Sciences* on the urgent need to unravel the origins of COVID-19. "If SARS-CoV-2 escaped from a lab to cause the pandemic," he wrote, "it will become critical to understand the chain of events and prevent this from happening again." Conflicts of interest by researchers and administrators will need to be addressed, Relman wrote; to reach the truth, the investigation must be transparent, international, and, as much as possible, unpolitical. "A more complete understanding of the origins of COVID-19 clearly serves the interests of every person in every country on this planet."

"The world is sitting on a precedent-setting decision right now," wrote Alina Chan on December 8. "It is unclear if SARS2 is 100 percent natural or emerged due to lab/research activities. If we walk away from this, demonstrating that we cannot effectively investigate its origins, it will pave the way for future COVIDS."

Just before this issue of *New York* went to press, I reached Ralph Baric by

phone and asked him where he now believed SARS-2 came from. (Anthony Fauci, Shi Zhengli, and Peter Daszak didn't respond to emails, and Kristian Andersen said he was busy with other things.) Baric said he still thought the virus came from bats in southern China, perhaps directly, or possibly via an intermediate host, although the smuggled pangolins, in his view, were a red herring. The disease evolved in humans over time without being noticed, he suspected, becoming gradually more infectious, and eventually a person carried it to Wuhan "and the pandemic took off." Then he said, "Can you rule out a laboratory escape? The answer in this case is probably not."

XIV.

Transmission

So how did we actually get this disease?

Here's what I think happened. In April 2012, in a copper mine in Mojiang, China, three men were given an awful job — they were told to shovel bat guano out of a mine shaft. They went to work and shoveled guano for seven hours a day in the confined, insufficiently ventilated space of the mine shaft, and by the end of the week, they were sick with a viral pneumonia of unknown etiology. Three more, younger shovelers were hired to replace the ones who were out sick.

The viral load in their lungs was so huge, because of all the guano dust, that their lungs became a kind of accelerated laboratory passaging experiment, as Jonathan Latham and Allison Wilson have written, forcing the virus to switch its allegiance from bats to humans. SARS experts were consulted, and the disease was judged to be SARS-like but not SARS. It was something new. (Shi Zhengli told *Scientific American* that the guano shovelers had died of a fungal disease, but, as Monali Rahalkar pointed out,

they were treated with antivirals, and their symptoms were consistent with viral pneumonia with attendant secondary fungal infections.)

Although it was a severe disease, and in the end three of the shovelers died, there was no resultant epidemic. It was actually a case of industrial overexposure to an infectious substance — what we might call a massive OSHA violation. The bat disease that the men encountered wasn't necessarily all that dangerous except in an environment of immunosuppressive overload.

Peter Daszak and Shi Zhengli were interested, of course, because this unidentified coronavirus disease involved bats and people. Of the fragmentary bits of virus Shi retrieved from the mine shaft, one was SARS-like, and Shi sequenced it and called it BtCoV/4991 and published a paper about it. Several times — in 2016 and 2018 and 2019 — this most interesting sample, a portion of what we now know as RaTG13, was taken out of the freezers in Shi's lab and worked on in undisclosed ways. (Peter Daszak claims that these samples have disintegrated and can't be validated or studied.) Samples of the nameless human disease also traveled back to the Wuhan Institute of Virology — few specifics about these valuable specimens have been released by Chinese sources, however.

This is the period in the story that demands a very close investigation, when chimeric assemblages may have been created and serially passaged, using BtCoV/4991, a.k.a. RaTG13, and other bat viruses, perhaps along with forms of the human virus. It's when Shi and Baric both published papers that were about what happened when you hot-swapped mutant spike proteins between bat viruses and human viruses.

The link, via the renamed sample BtCoV/4991, to the copper mine is of exceptional importance because of the one huge difference between the

unnamed guano shovelers' virus and the SARS-2 virus that is now ravaging, for example, California: transmissibility. Airborne human-to-human transmissibility — the kind of thing that gain-of-functioneers like Ron Fouchier and Ralph Baric were aiming at, in order to demonstrate what Baric called "lurking threats" — is COVID-19's crucial distinguishing feature. If six men had gotten extremely sick with COVID-19 back in 2012 in southern China, doctors and nurses in the hospital where they lay dying would likely have gotten sick as well. There might have been hundreds or thousands of cases. Instead, only the shovelers themselves, who had breathed a heavy concentration of guano dust for days, got it.

The existence of bat virus RaTG13 is therefore not necessarily evidence of a natural bat origin. In fact, it seems to me to imply the opposite: New functional components may have been overlaid onto or inserted into the RaTG13 genome, new Tinkertoy intermolecular manipulations, especially to its spike protein, which have the effect of making it unprecedentedly infectious in human airways.

This is where the uniquely peculiar furin insert and/or the human-tuned ACE2-receptor-binding domain may come in — although it's also possible that either of these elements could have evolved as part of some multistep zoonotic process. But in the climate of gonzo laboratory experimentation, at a time when all sorts of tweaked variants and amped-up substitutions were being tested on cell cultures and in the lungs of humanized mice and other experimental animals, isn't it possible that somebody in Wuhan took the virus that had been isolated from human samples, or the RaTG13 bat virus sequence, or both (or other viruses from that same mine shaft that Shi Zhengli has recently mentioned in passing), and used them to create a challenge disease for vaccine research — a chopped-and-channeled version of RaTG13 or the miners' virus that included elements that would make it thrive and even rampage in people? And then what if, during an

experiment one afternoon, this new, virulent, human-infecting, furin-ready virus got out?

For more than 15 years, coronavirologists strove to prove that the threat of SARS was ever present and must be defended against, and they proved it by showing how they could doctor the viruses they stored in order to force them to jump species and go directly from bats to humans. More and more bat viruses came in from the field teams, and they were sequenced and synthesized and "rewired," to use a term that Baric likes. In this international potluck supper of genetic cookery, hundreds of new variant diseases were invented and stored. And then one day, perhaps, somebody messed up. It's at least a reasonable, "parsimonious" explanation of what might have happened.

This may be the great scientific meta-experiment of the 21st century. Could a world full of scientists do all kinds of reckless recombinant things with viral diseases for many years and successfully avoid a serious outbreak? The hypothesis was that, yes, it was doable. The risk was worth taking. There would be no pandemic.

I hope the vaccine works.

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