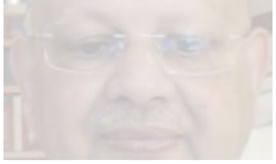
SARS-CoV-2 induced CoVID-19 PANDEMIC

May 19th and May 21st, 2021 ■ 3PM-4PM @ ORCHID



Shoumen Palit Austin Datta

- Research Affiliate, MIT Auto ID Labs, Department of Mechanical Engineering, School of Engineering, Massachusetts Institute of Technology (shoumen@mit.edu)
- Senior Scientist, MDPnP Labs and Cybersecurity Program, Department of Anesthesiology, Massachusetts General Hospital, Harvard Medical School (sdatta8@mgh.harvard.edu)
- Fellow in Medicine (former), Massachusetts General Hospital, Harvard Medical School

May 19th – Part I	Playing TETRIS with CoVID-19: Are we winning?
May 21st – Part II	Rules of the Game: Understanding SARS-CoV-2

Part I

The race to find an effective vaccine is the cornerstone of medical treatment to control mortality and morbidity associated with infectious diseases. If the infectious agent is airborne and it infects humans *agnostic of wealth or poverty*, then the urgency (to TEst, TReat and Isolate, that is, TETRIS) assumes the highest priority, globally. The indiscriminate nature of SARS-CoV-2 infection and fatality has brought the G7 nations to their feet. Vaccines are there (US, EU) and eventually they will be here (India) but the timeline for sufficiency remains speculative. In this short talk, we will analyze a few positive issues that has emerged in the treatment domain and why no one may escape necessary lifestyle adaptations.

Part II

It is imperative that students and teachers, parents and communities, countries and continents, must rapidly become cognizant of the etiology and biology of CoVID-19 and coronaviruses, respectively. In this session we will discuss the salient features of SARS-CoV-2 with respect to the molecular biology of the virus. The wrath of the pandemic will eventually subside in a few years but coronavirus epidemics may become a part of our lives for the next few decades or even centuries. There is nothing to fear if we remember, review and re-evaluate the death and devastation due to the influenza pandemic at the turn of the 20th century and compare to the quantum leaps of progress we also witnessed in the 20th century.

Prepared for OIS discussion with teachers ◆ Brief bio-sketch of speaker may be downloaded from http://bit.ly/BIO-SD

Please lower your expectations from these talks. The topics we are discussing are complicated and I am unskilled in simplification.

Playing TETRIS with CoVID-19?
Are we winning?

Shoumen Palit Austin Datta

19th May 2021 @ ORCHID

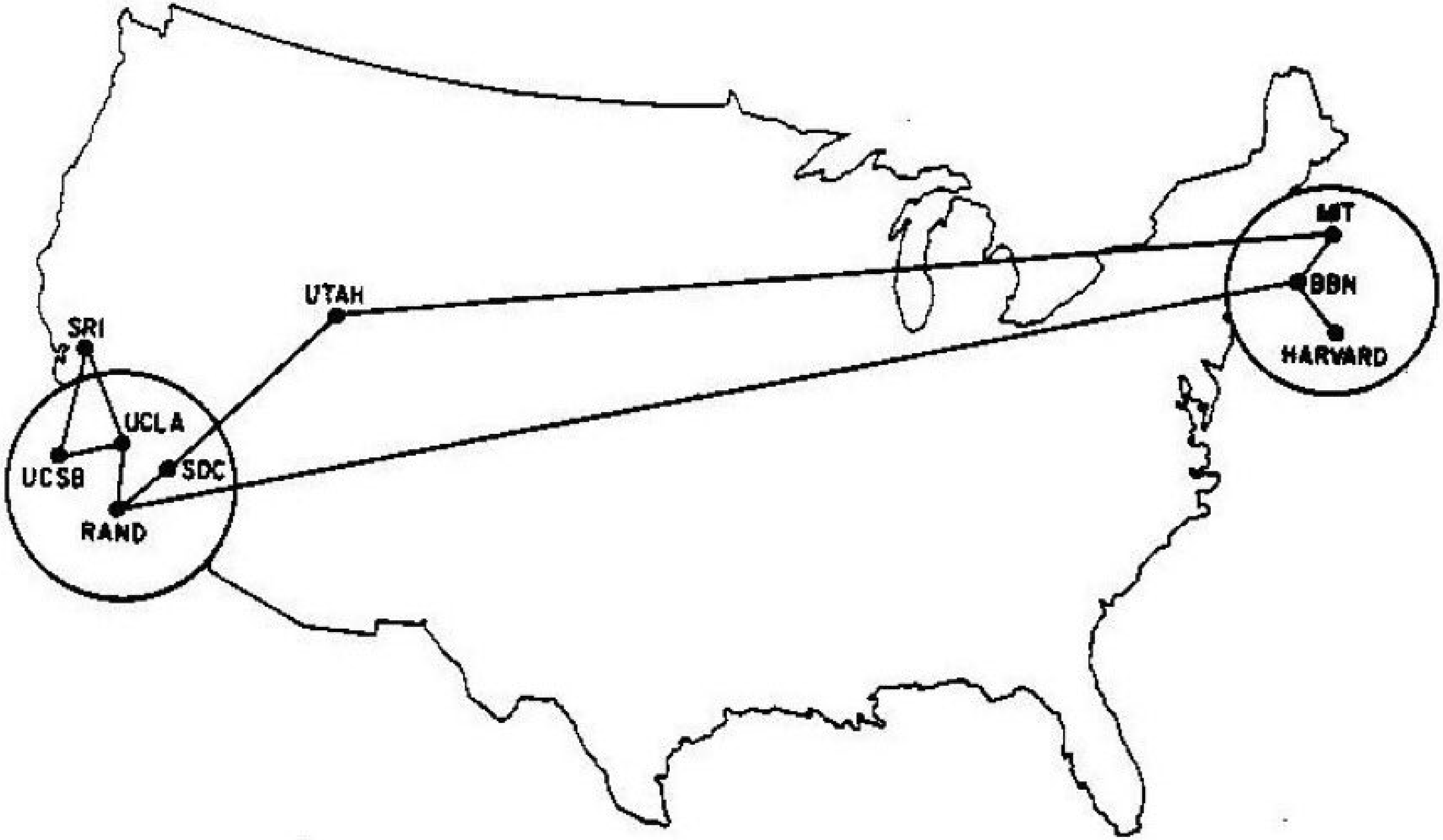
http://bit.ly/BIO-SD

Research Affiliate, MIT Auto ID Labs, Dept of Mechanical Engineering, MIT (shoumen@mit.edu) ▪ Senior Scientist, MDPnP Labs and Cybersecurity Program, Dept of Anesthesiology, Massachusetts General Hospital, Harvard Medical School (sdatta8@mgh.harvard.edu)

Century of Connectivity ?

20th Century

Internet 1970

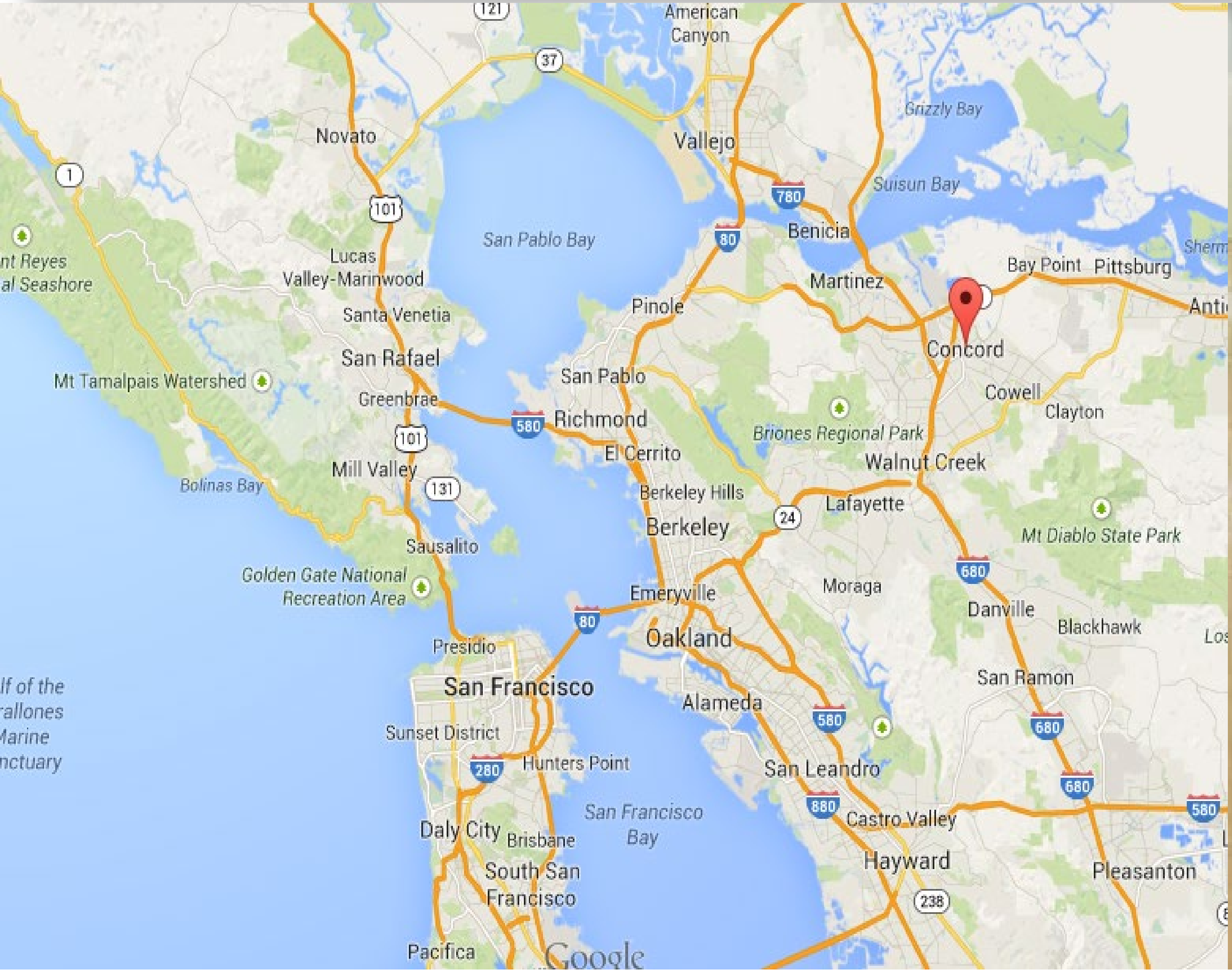


ARPANET → Joseph Carl Robnett Licklider, MIT (March 11, 1915 – June 26, 1990)

From Paradoxes to Paradigms

it takes time …

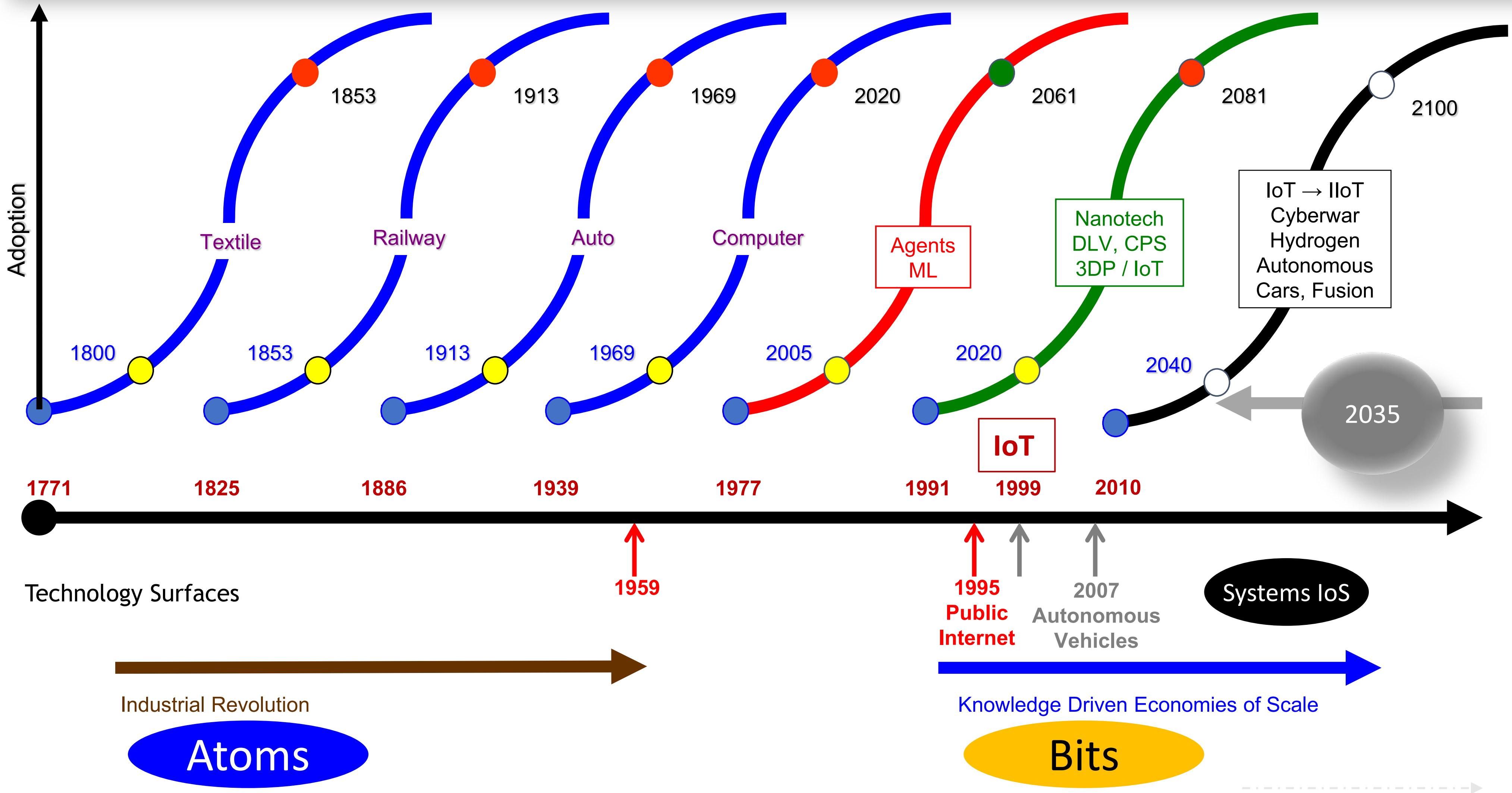
Diffusion of the Internet ▪ NetDay 1996



President Bill Clinton installing computer cables with VP Al Gore on NetDay at Ygnacio Valley High School (Concord, CA - March 9, 1996)

Paradoxes to Paradigms ■ It takes time & transaction cost economics of technology

Economic history and data related to Textile, Railway, Automobiles and Computers taken from work by Norman Poire



Adoption

Textile: 1800, 1853

Railway: 1853, 1913

Auto: 1913, 1969

Computer: 1969, 2020

Agents
ML
2005, 2061

Nanotech
DLV, CPS
3DP / IoT
2020, 2081

IoT → IIoT
Cyberwar
Hydrogen
Autonomous
Cars, Fusion
2040, 2100

2035

IoT

1771 1825 1886 1939 1977 1991 1999 2010

1959

1995
Public
Internet

2007
Autonomous
Vehicles

Systems IoS

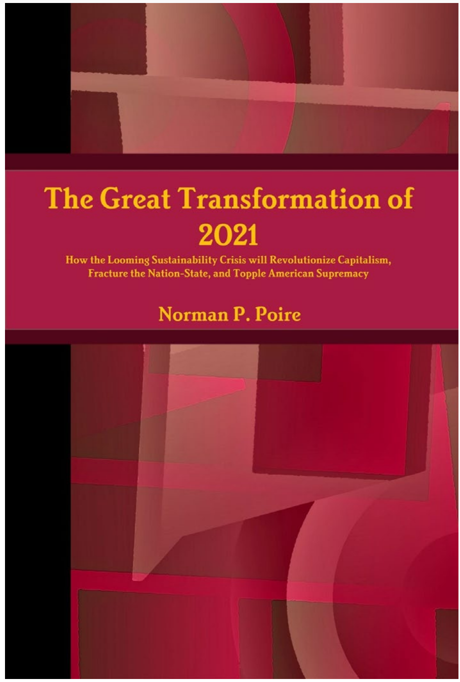
Technology Surfaces

Industrial Revolution

Atoms

Knowledge Driven Economies of Scale

Bits



The Great Transformation of 2021

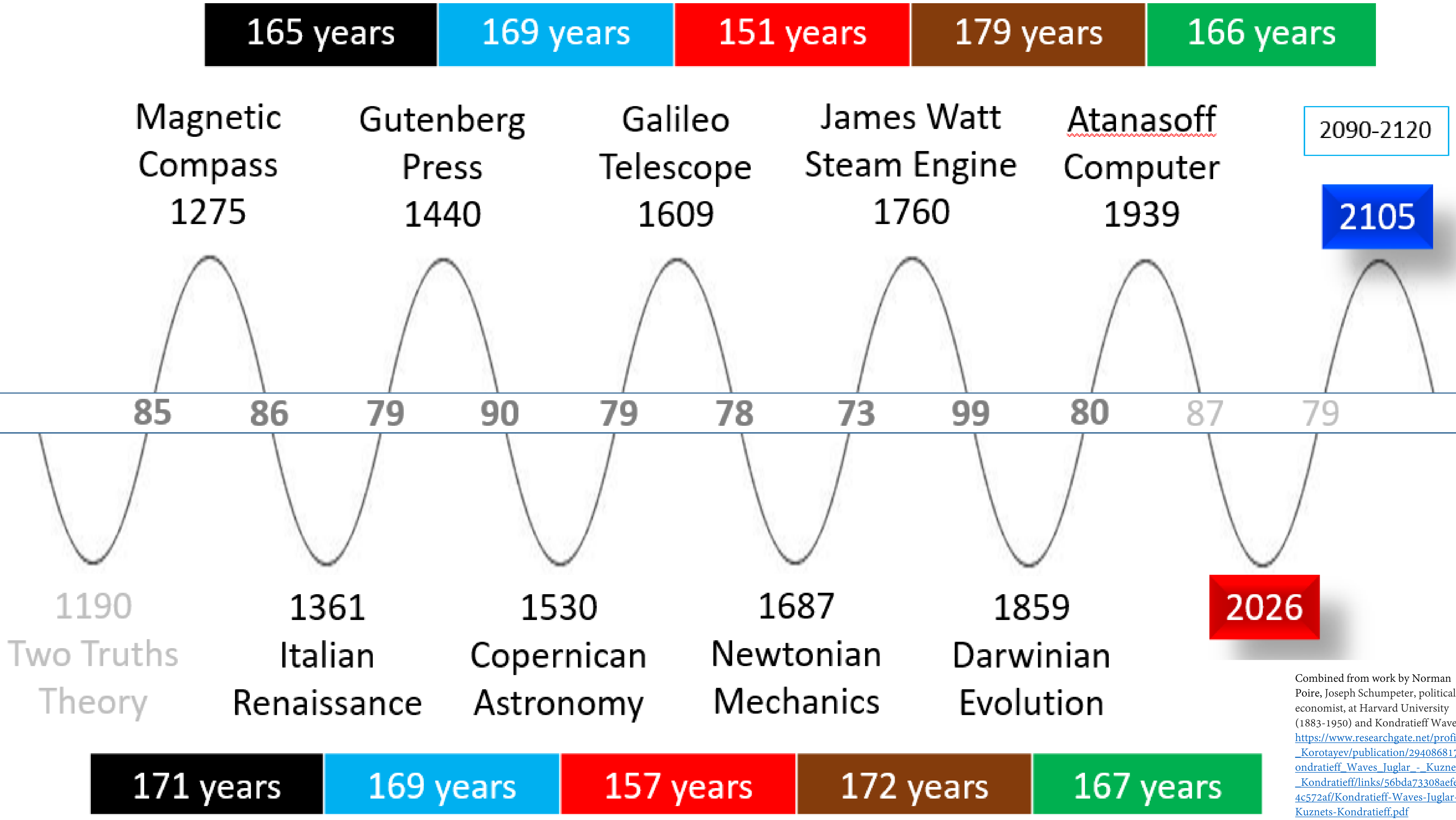
How the Looming Sustainability Crisis will Revolutionize Capitalism, Fracture the Nation-State, and Topple American Supremacy

Norman P. Poire

Poire, Norman P. (2011) The Great Transformation of 2021.

www.lulu.com/shop/norman-poire/the-great-transformation-of-2021/paperback/product-14729057.html

It takes about 28-30 years for some ideas to be socially accepted an adopted as public technology. INTERNET conceptualized in 1950's. ARPANET of 1970 germinated as the public INTERNET in 1995.



165 years | 169 years | 151 years | 179 years | 166 years

Magnetic Compass 1275

Gutenberg Press 1440

Galileo Telescope 1609

James Watt Steam Engine 1760

Atanasoff Computer 1939

2090-2120

2105

85 86 79 90 79 78 73 99 80 87 79

1190 Two Truths Theory

1361 Italian Renaissance

1530 Copernican Astronomy

1687 Newtonian Mechanics

1859 Darwinian Evolution

2026

171 years | 169 years | 157 years | 172 years | 167 years

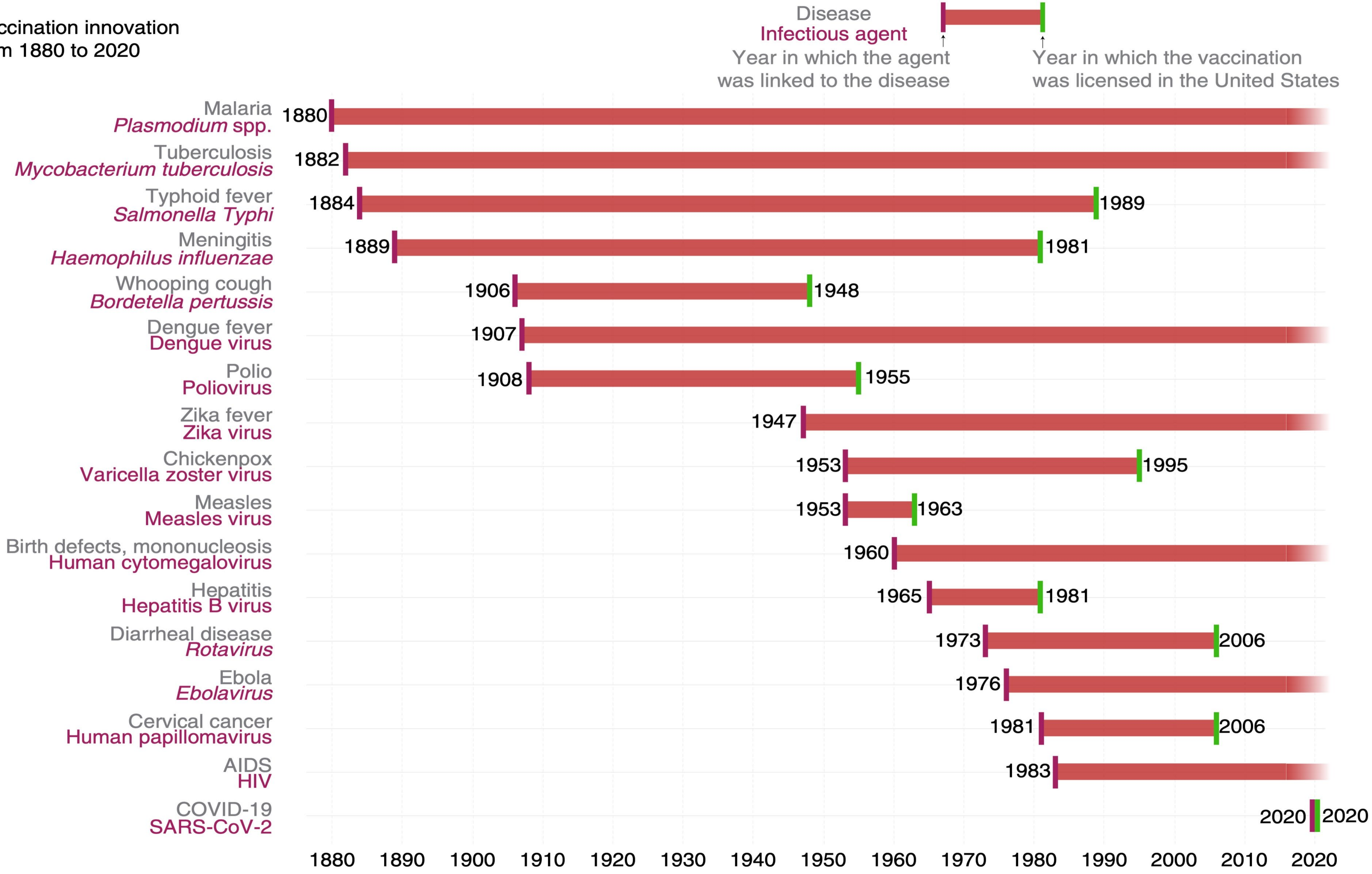
Combined from work by Norman Poire, Joseph Schumpeter, political economist, at Harvard University (1883-1950) and Kondratieff Waves. https://www.researchgate.net/profile/A_Korotayev/publication/294086817_Kondratieff_Waves_Juglar_-_Kuznets_-_Kondratieff/links/56bda73308aefe60e4c572af/Kondratieff-Waves-Juglar-Kuznets-Kondratieff.pdf

Is necessity *still* the mother of invention or is it the wealth of nations?

21st Century

An Inquiry into the Nature and Causes of the Wealth of Nations, generally referred to by its shortened title **The Wealth of Nations**, is the magnum opus of the Scottish economist and moral philosopher Adam Smith. Published March 9, 1776. Download book www.ibiblio.org/ml/libri/s/SmithA_WealthNations_p.pdf

Vaccination innovation from 1880 to 2020



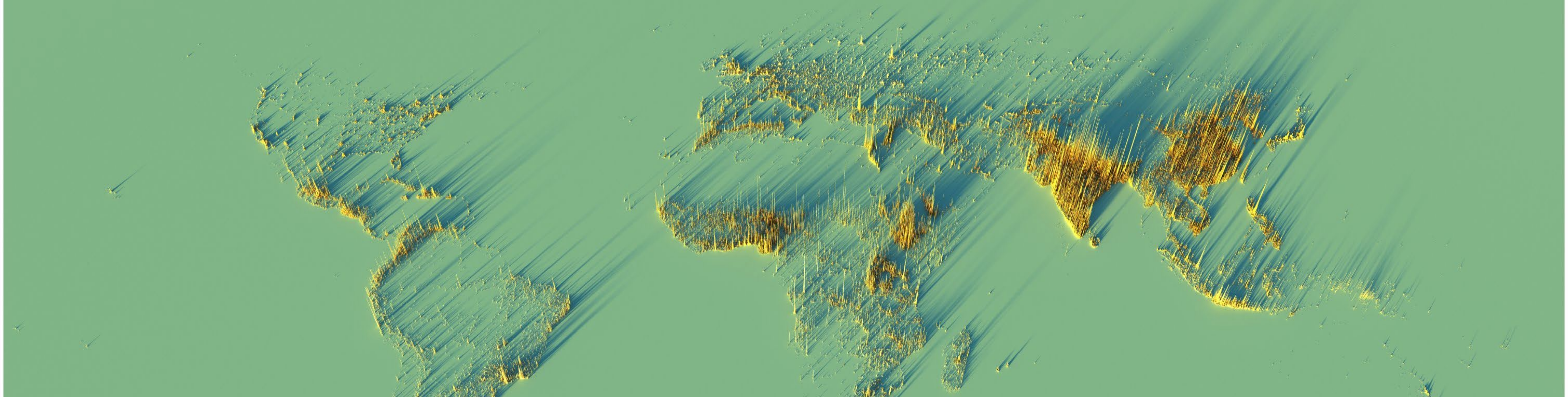
https://ourworldindata.org/vaccination

Published 10th May 2021 ▪ https://doi.org/10.1038/s41562-021-01122-8

EU just bought 900 million doses of PFIZER vaccine for USD $43 BILLION (EUR 35 BILLION)

Ramping Up Its COVID Response, EU Will Buy Up To 1.8B Doses Of Pfizer Vaccine

May 8, 2021 · 10:11 AM ET www.npr.org/sections/coronavirus-live-updates/2021/05/08/995007124/ramping-up-its-covid-response-eu-will-buy-up-to-1-8b-doses-of-pfizer-vaccine



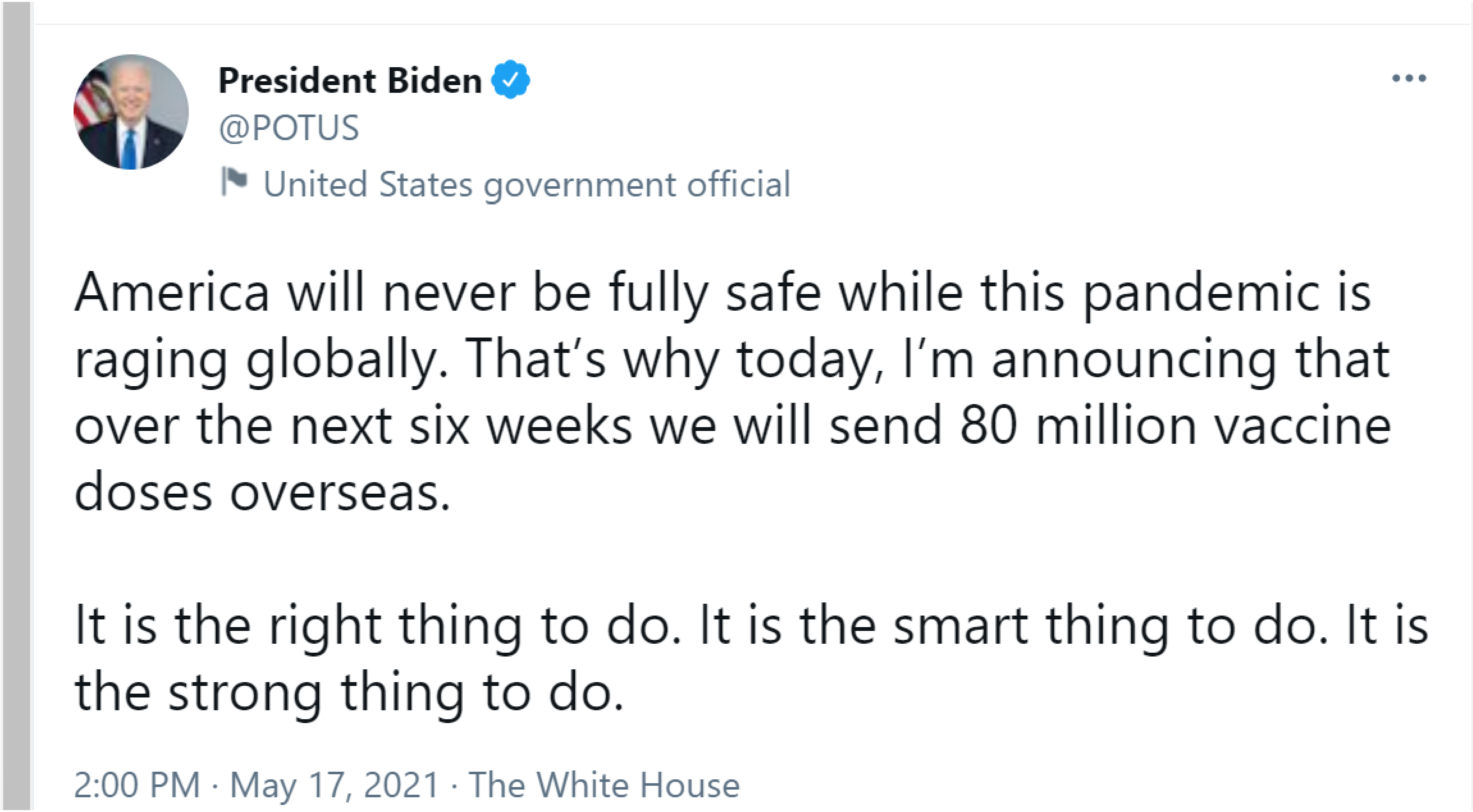
Global Population Density

Ursula von der Leyen ✓
@vonderleyen

Happy to announce that @EU_Commission has just approved a contract for guaranteed 900 million doses (+900 million options) with @BioNTech_Group @Pfizer for 2021-2023.

Other contracts and other vaccine technologies will follow.

5:49 AM · May 8, 2021

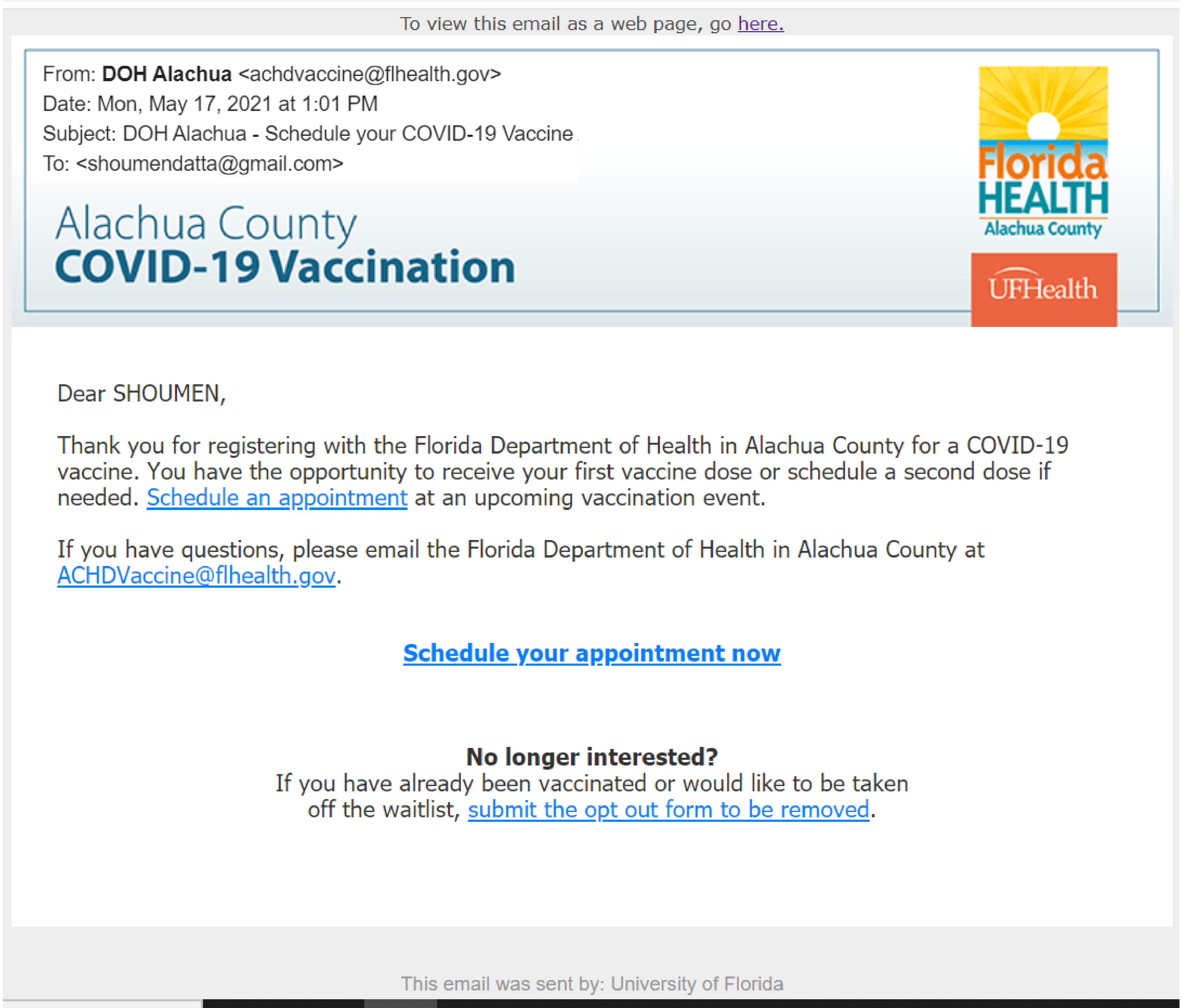


President Biden
@POTUS
United States government official

America will never be fully safe while this pandemic is raging globally. That’s why today, I’m announcing that over the next six weeks we will send 80 million vaccine doses overseas.

It is the right thing to do. It is the smart thing to do. It is the strong thing to do.

2:00 PM · May 17, 2021 · The White House



To view this email as a web page, go here.

From: **DOH Alachua** <achdvaccine@flhealth.gov>
Date: Mon, May 17, 2021 at 1:01 PM
Subject: DOH Alachua - Schedule your COVID-19 Vaccine
To: <shoumendatta@gmail.com>

Alachua County
COVID-19 Vaccination

Dear SHOUMEN,

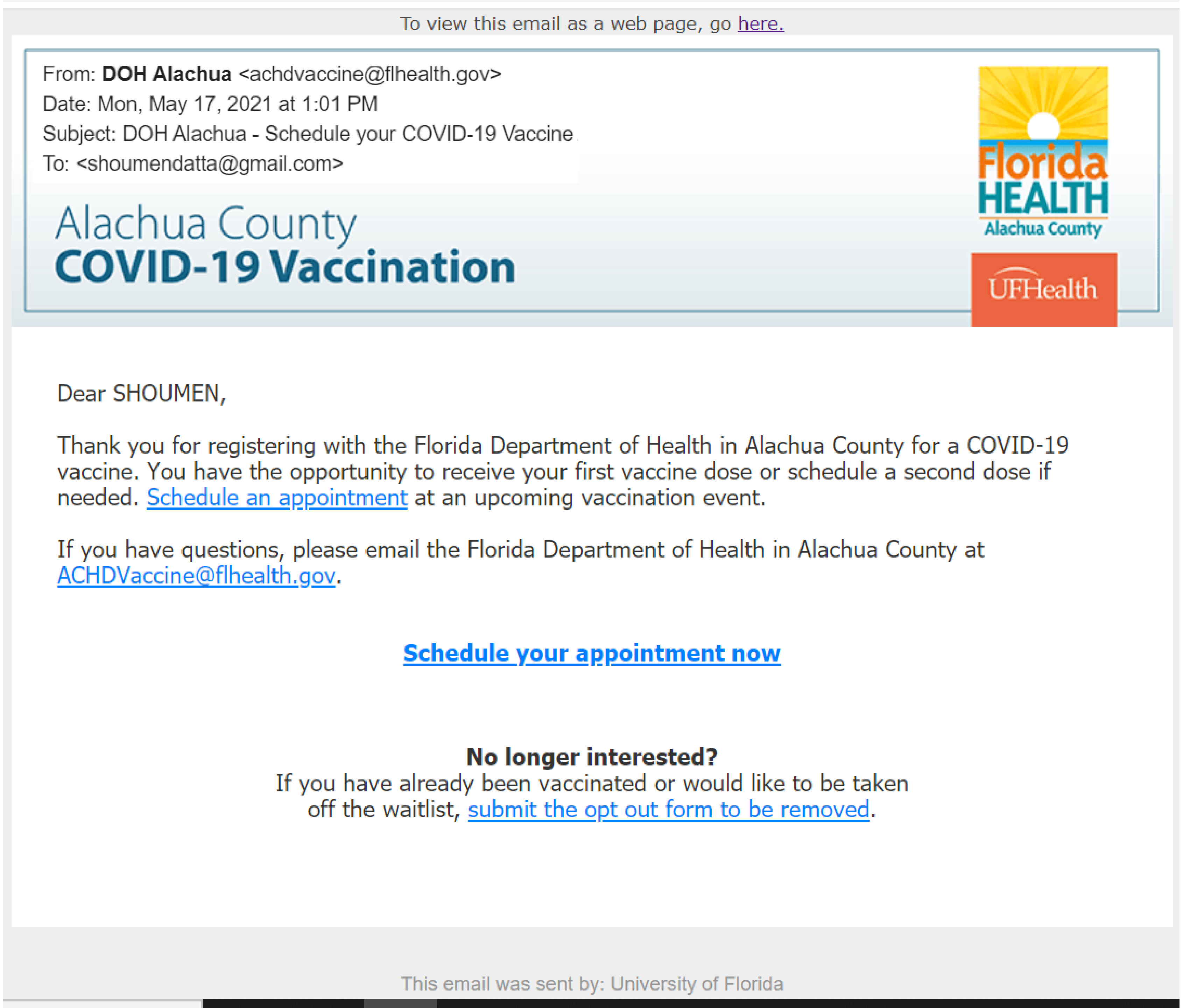
Thank you for registering with the Florida Department of Health in Alachua County for a COVID-19 vaccine. You have the opportunity to receive your first vaccine dose or schedule a second dose if needed. Schedule an appointment at an upcoming vaccination event.

If you have questions, please email the Florida Department of Health in Alachua County at ACHDVaccine@flhealth.gov.

Schedule your appointment now

No longer interested?
If you have already been vaccinated or would like to be taken off the waitlist, submit the opt out form to be removed.

This email was sent by: University of Florida



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Alachua County
COVID-19 Vaccination

Florida HEALTH
Alachua County

UFHealth

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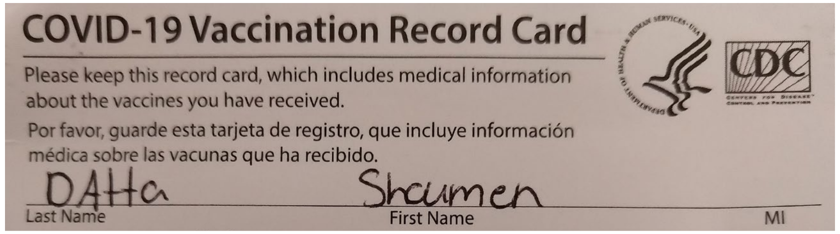


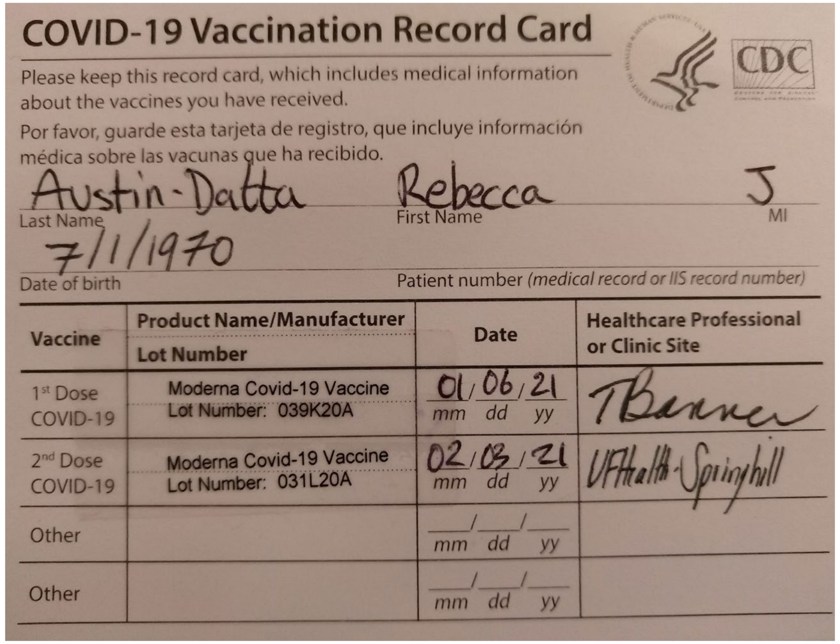
COVID-19 Vaccination Record Card

CDC

Please keep this record card, which includes medical information about the vaccines you have received.

Por favor, guarde esta tarjeta de registro, que incluye información médica sobre las vacunas que ha recibido.

Last Name: DAtta
First Name: Shoumen
MI:



COVID-19 Vaccination Record Card

CDC

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Por favor, guarde esta tarjeta de registro, que incluye información médica sobre las vacunas que ha recibido.

Last Name: Austin-Datta
First Name: Rebecca
MI: J
Date of birth: 7/1/1970
Patient number *(medical record or IIS record number)*:

Vaccine	Product Name/Manufacturer Lot Number	Date	Healthcare Professional or Clinic Site
1st Dose COVID-19	Moderna Covid-19 Vaccine Lot Number: 039K20A	01/06/21 mm dd yy	
2nd Dose COVID-19	Moderna Covid-19 Vaccine Lot Number: 031L20A	02/03/21 mm dd yy	UFHealth-Springhill
Other		__/__/__ mm dd yy	
Other		__/__/__ mm dd yy	

Vaccinated on 6th January 2021

Rich vaccines ◆ Poor vaccines

Moderna ▪ Pfizer

J&J ▪ AZOX

The NEW ENGLAND JOURNAL of MEDICINE

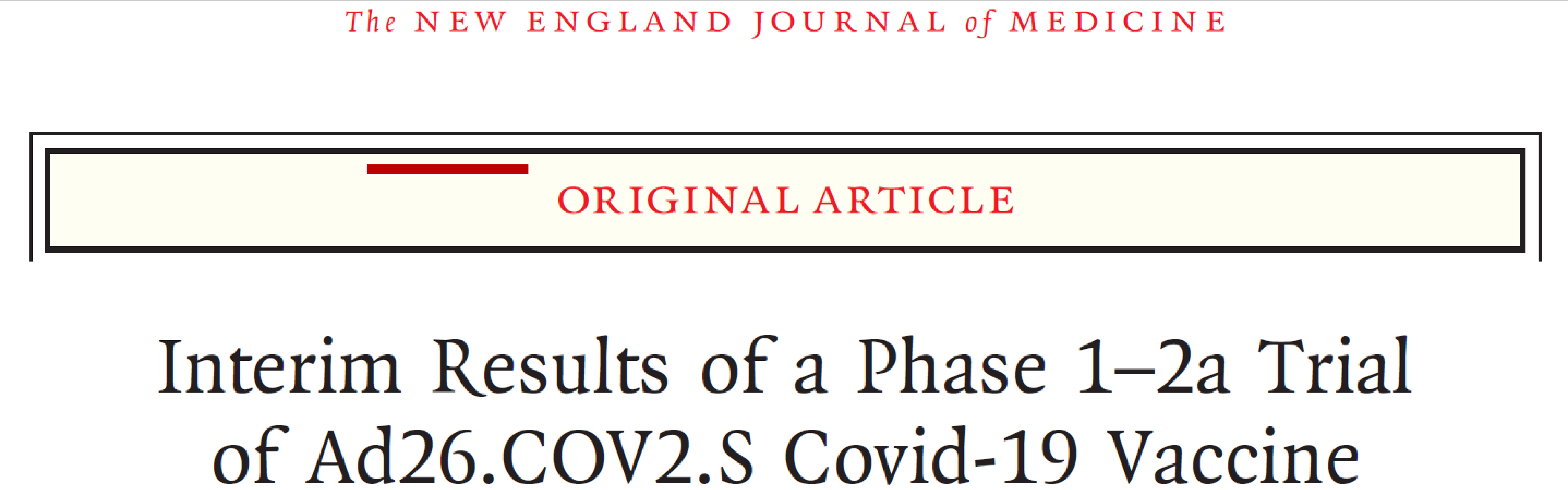
This article was published on January 13, 2021, and last updated on May 13, 2021, at NEJM.org.

N Engl J Med 2021;384:1824-35.
DOI: 10.1056/NEJMoa2034201

ORIGINAL ARTICLE

Interim Results of a Phase 1–2a Trial of Ad26.COV2.S Covid-19 Vaccine

J. Sadoff, M. Le Gars, G. Shukarev, D. Heerwegh, C. Truyers, A.M. de Groot, J. Stoop, S. Tete, W. Van Damme, I. Leroux-Roels, P.-J. Berghmans, M. Kimmel, P. Van Damme, J. de Hoon, W. Smith, K.E. Stephenson, S.C. De Rosa, K.W. Cohen, M.J. McElrath, E. Cormier, G. Scheper, D.H. Barouch, J. Hendriks, F. Struyf, M. Douoguih, J. Van Hoof, and H. Schuitemaker

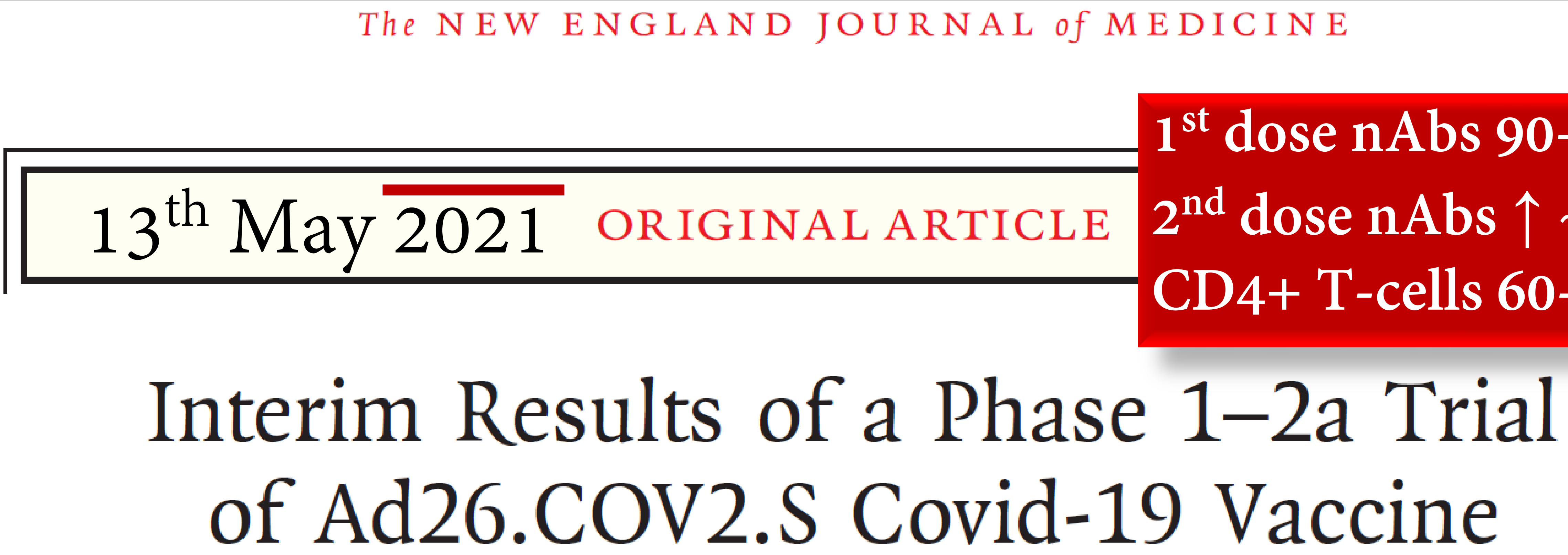


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Interim Results of a Phase 1–2a Trial of Ad26.COV2.S Covid-19 Vaccine

RESULTS: 805 participants (adverse events: fever, fatigue, headache, myalgia). Neutralizing antibody titers against wild-type virus were detected in >90% of all participants on day 29 after first vaccination regardless of vaccine dose or age group and reached 96% by day 57. Titers remained stable until at least day 71. Second dose provided an increase in the titer by a factor of 2.6 to 2.9. SARS-CoV-2 S-protein binding antibody responses were similar to neutralizing-antibody responses. On day 15, CD4+ T-cell responses were detected in 76 to 83% of the participants in cohort 1 and 60 to 67% in cohort 3. CONCLUSIONS: Safety and immunogenicity profiles of Ad26.COV2.S support further development of this J&J vaccine candidate. (ClinicalTrials.gov number is NCT04436276.)



The NEW ENGLAND JOURNAL of MEDICINE

13th May 2021 ORIGINAL ARTICLE

1st dose nAbs 90-96%
2nd dose nAbs ↑ ~3X
CD4+ T-cells 60-83%

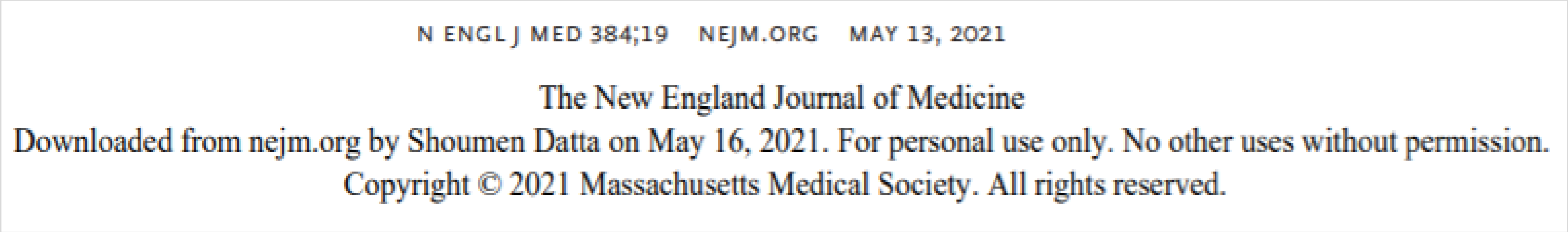
Interim Results of a Phase 1–2a Trial of Ad26.COV2.S Covid-19 Vaccine

CONCLUSION: Safety and immunogenicity profiles of Ad26.COV2.S support further development of the J&J vaccine candidate. ClinicalTrials.gov number NCT04436276

Summary Results on SARS-CoV-2 Vaccine Trial Efficacy and Viral Neutralization of the B.1.1.7, P.1, and 501Y.V2 Variants, as Compared with Preexisting Variants.

Comparative Efficacy

Published 13th May 2021 in New England Journal of Medicine ▪ DOI: 10.1056/NEJMc2100362



N ENGL J MED 384;19 NEJM.ORG MAY 13, 2021

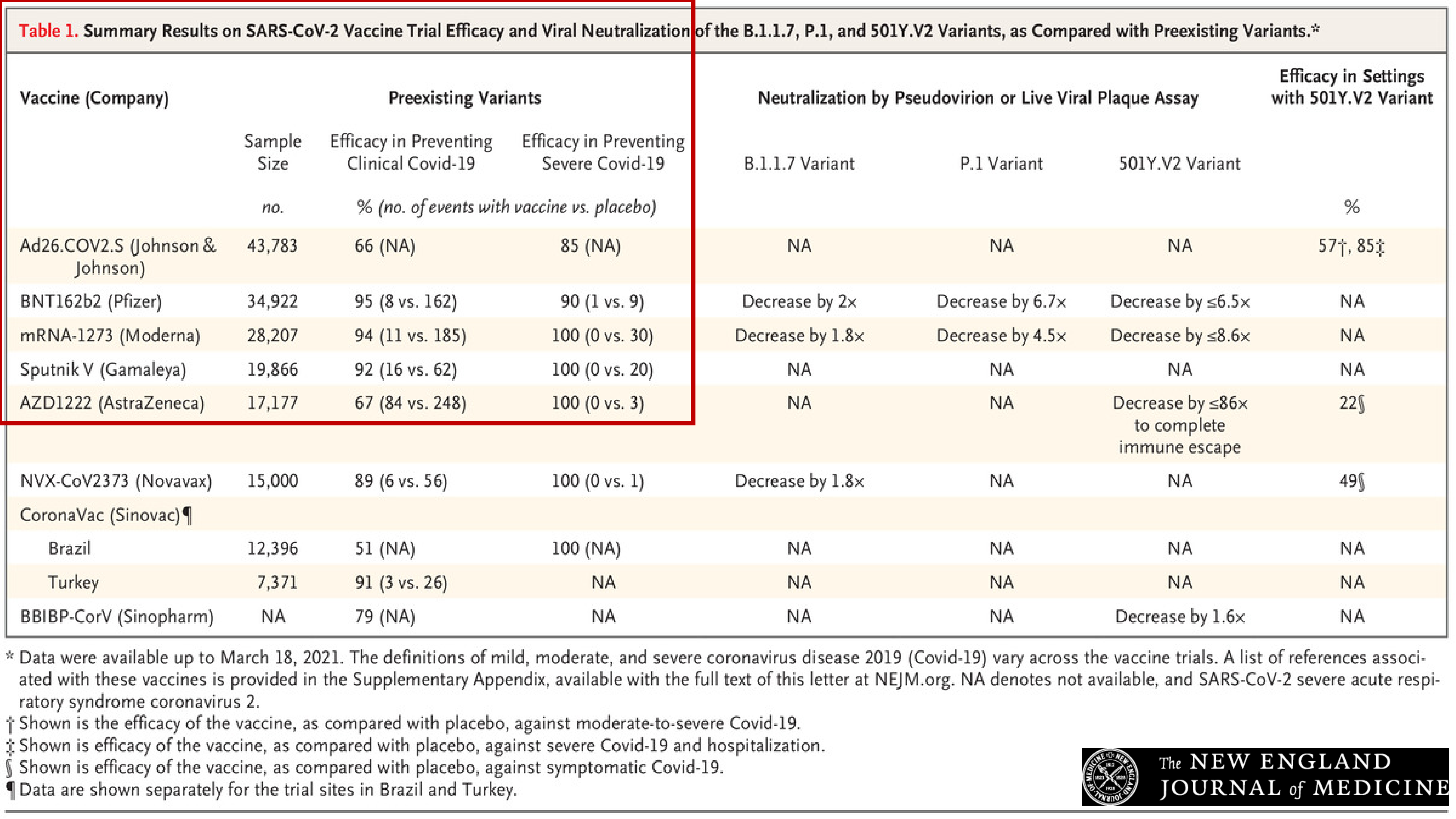


Table 1. **Summary Results on SARS-CoV-2 Vaccine Trial Efficacy and Viral Neutralization of the B.1.1.7, P.1, and 501Y.V2 Variants, as Compared with Preexisting Variants.***

Vaccine (Company)	Preexisting Variants			Neutralization by Pseudovirion or Live Viral Plaque Assay			Efficacy in Settings with 501Y.V2 Variant
	Sample Size	Efficacy in Preventing Clinical Covid-19	Efficacy in Preventing Severe Covid-19	B.1.1.7 Variant	P.1 Variant	501Y.V2 Variant	
	no.	*% (no. of events with vaccine vs. placebo)*					%
Ad26.COV2.S (Johnson & Johnson)	43,783	66 (NA)	85 (NA)	NA	NA	NA	57†, 85‡
BNT162b2 (Pfizer)	34,922	95 (8 vs. 162)	90 (1 vs. 9)	Decrease by 2×	Decrease by 6.7×	Decrease by ≤6.5×	NA
mRNA-1273 (Moderna)	28,207	94 (11 vs. 185)	100 (0 vs. 30)	Decrease by 1.8×	Decrease by 4.5×	Decrease by ≤8.6×	NA
Sputnik V (Gamaleya)	19,866	92 (16 vs. 62)	100 (0 vs. 20)	NA	NA	NA	NA
AZD1222 (AstraZeneca)	17,177	67 (84 vs. 248)	100 (0 vs. 3)	NA	NA	Decrease by ≤86× to complete immune escape	22§
NVX-CoV2373 (Novavax)	15,000	89 (6 vs. 56)	100 (0 vs. 1)	Decrease by 1.8×	NA	NA	49§
CoronaVac (Sinovac)¶							
Brazil	12,396	51 (NA)	100 (NA)	NA	NA	NA	NA
Turkey	7,371	91 (3 vs. 26)	NA	NA	NA	NA	NA
BBIBP-CorV (Sinopharm)	NA	79 (NA)	NA	NA	NA	Decrease by 1.6×	NA

* Data were available up to March 18, 2021. The definitions of mild, moderate, and severe coronavirus disease 2019 (Covid-19) vary across the vaccine trials. A list of references associated with these vaccines is provided in the Supplementary Appendix, available with the full text of this letter at NEJM.org. NA denotes not available, and SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.

† Shown is the efficacy of the vaccine, as compared with placebo, against moderate-to-severe Covid-19.

‡ Shown is efficacy of the vaccine, as compared with placebo, against severe Covid-19 and hospitalization.

§ Shown is efficacy of the vaccine, as compared with placebo, against symptomatic Covid-19.

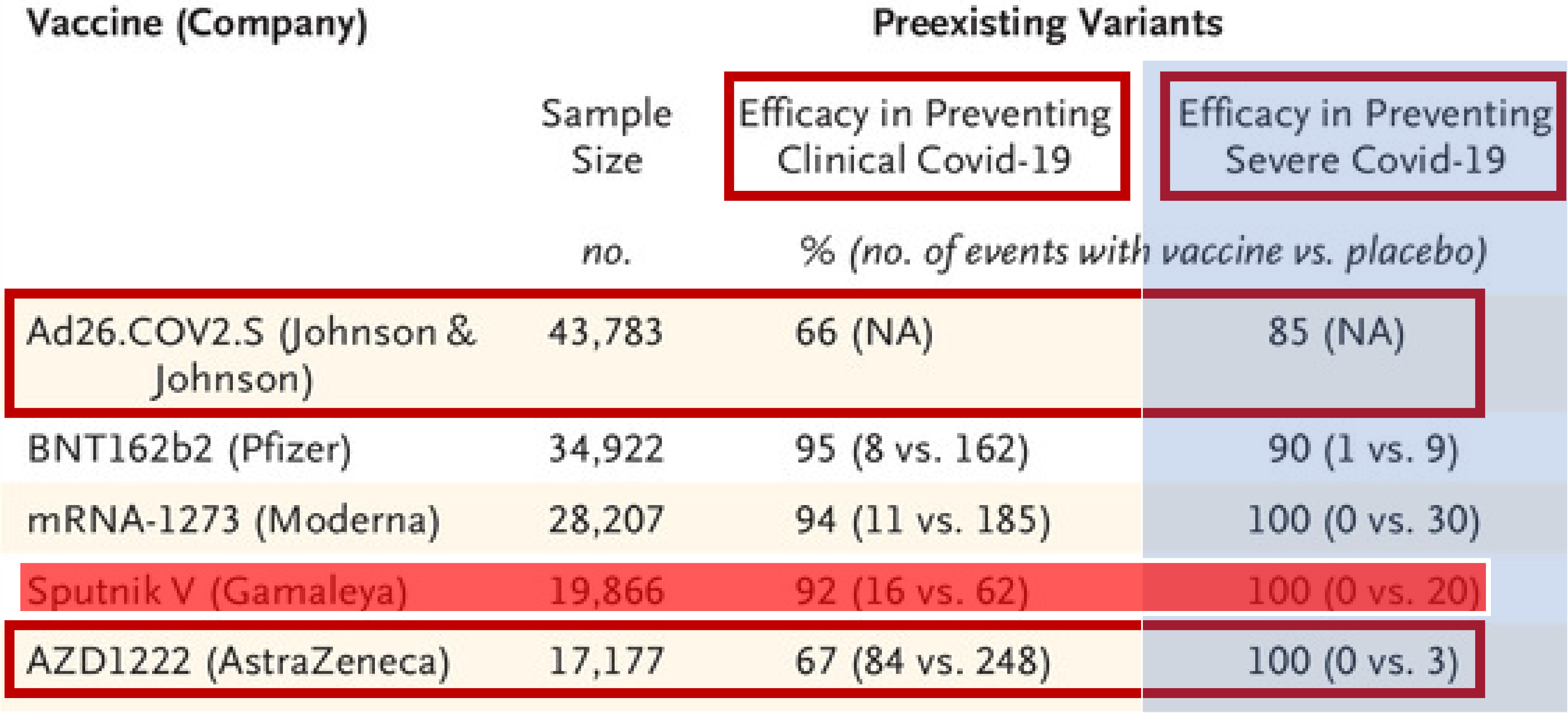
¶ Data are shown separately for the trial sites in Brazil and Turkey.

The NEW ENGLAND JOURNAL of MEDICINE

Table 1. Summary Results on SARS-CoV-2 Vaccine Trial Efficacy and Viral Neutralization

The NEW ENGLAND JOURNAL of MEDICINE

Source: 10.1056/NEJMc2100362 ■ https://www.nejm.org/doi/full/10.1056/NEJMc2100362



Vaccine (Company)		Preexisting Variants	
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Yes, it works. ◆ Poor vaccines

J&J ▪ AZOX

The ***hamsa*** is a palm-shaped amulet popular throughout the Middle East depicting the open right hand, an image recognized and used as a sign of protection in many times throughout history. The *hamsa* holds recognition as a bearer of good fortune among Christians in the Middle East. *Khamsah* is an Arabic word that means "five", but also “5 fingers of the hand”. [Source: Wikipedia]

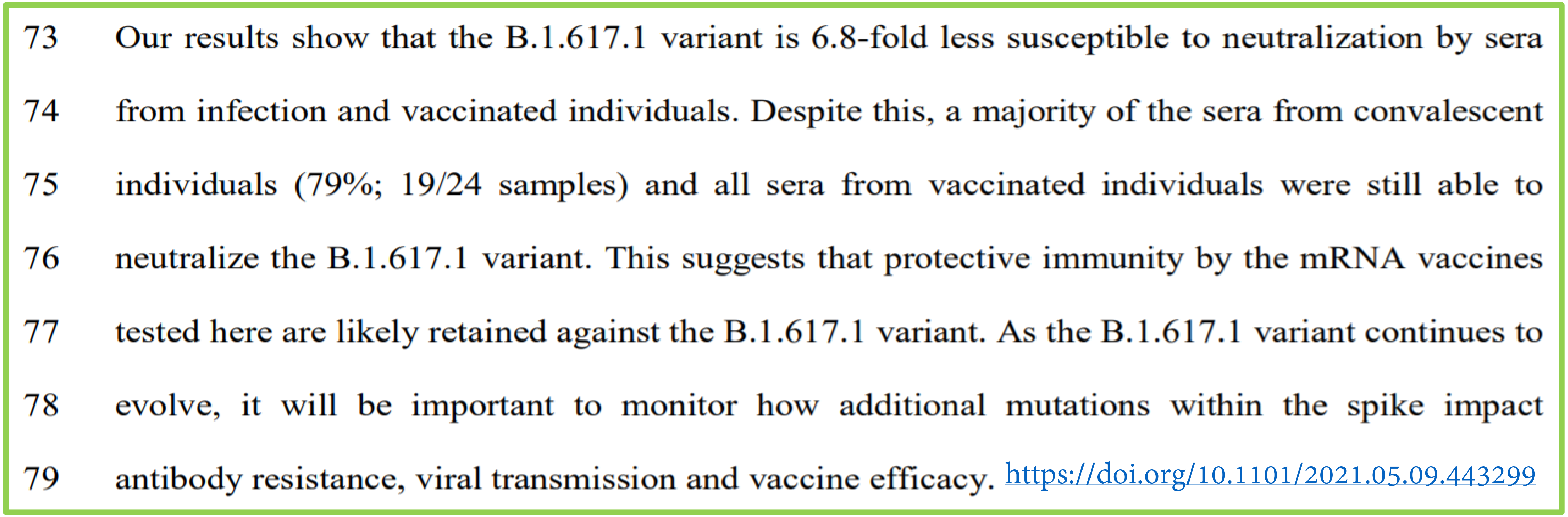
Five Threads of Positivism

1. Vaccinations will work, even against variants.
2. Don’t underestimate the potency of human immune response.
3. If vaccinated individuals are re-infected the severity of the symptoms may be less.
4. Same mutations may re-appear (it is not likely to create new mutants all the time).
5. Booster shots will improve immune response with higher efficacy, with time.

1. Vaccines will work, even against troublesome variants

Effectiveness of PFIZER (BNT162b2) Covid-19 vaccine
[1] against B.1.1.7 variant (UK) ~89% [2] against B.1.351 variant (S. AFRICA) ~75%
NEJM May 5, 2021 DOI: 10.1056/NEJMc2104974 ▪ https://www.nejm.org/doi/full/10.1056/NEJMc2104974

Effectiveness of MODERNA & PFIZER mRNA1273 Covid-19 vaccines
against B.1.617.1 variant (INDIA) is quite high in a small study (n =25)
BIORXIV May 10, 2021▪ https://www.biorxiv.org/content/10.1101/2021.05.09.443299v1.full.pdf



Our results show that the B.1.617.1 variant is 6.8-fold less susceptible to neutralization by sera from infection and vaccinated individuals. Despite this, a majority of the sera from convalescent individuals (79%; 19/24 samples) and all sera from vaccinated individuals were still able to neutralize the B.1.617.1 variant. This suggests that protective immunity by the mRNA vaccines tested here are likely retained against the B.1.617.1 variant. As the B.1.617.1 variant continues to evolve, it will be important to monitor how additional mutations within the spike impact antibody resistance, viral transmission and vaccine efficacy. https://doi.org/10.1101/2021.05.09.443299

2. Our immune machinery is a system of responses

Vaccine efficacy often focuses on **antibodies** and their ability to "neutralize" (**block**) the virus from infecting (**entering**) the human cells. But antibodies are only ONE COMPONENT of our immune system produced by **B cells.**

Immune cells called **T cells** are ANOTHER COMPONENT of our immunity to keep infections in check. These cells can't neutralize the virus, but they can seek out infected cells and **destroy** them. That helps protect against severe disease.

Data from people who have survived CoVID-19 suggests that T-cell response should provide ample **protection** against most of the SARS-CoV-2 **variants**.

Source: MIT Technology Review, May 13, 2021 ■ https://www.technologyreview.com/2021/05/13/1024850/dont-panic-coronavirus-variants

3. Vaccines decrease severity of symptoms if re-infected.

South Africa: one dose of J&J (poor) vaccine provided 85% protection against covid-19-related hospitalizations and deaths (95% of cases caused by the B.1.351 variant).

https://www.nejm.org/doi/full/10.1056/NEJMoa2101544

Israel: B.1.1.7 (UK) has become the dominant strain. Two doses of Pfizer offered 97% protection against symptomatic CoVID-19 and hospitalizations linked to CoVID-19.

www.thelancet.com/action/showPdf?pii=S0140-6736%2821%2900947-8

ORIGINAL ARTICLE

Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19

Jerald Sadoff, M.D., Glenda Gray, M.B., B.Ch., An Vandebosch, Ph.D., Vicky Cárdenas, Ph.D., Georgi Shukarev, M.D., Beatriz Grinsztejn, M.D., Paul A. Goepfert, M.D., Carla Truyers, Ph.D., Hein Fennema, Ph.D., Bart Spiessens, Ph.D., Kim Offergeld, M.Sc., Gert Scheper, Ph.D., et al., for the ENSEMBLE Study Group*

April 21, 2021
DOI: 10.1056/NEJMoa2101544

4. Same mutations re-appearing? Worry less? Yes !!

WHY ?

www.scientificamerican.com/article/the-coronavirus-variants-dont-seem-to-be-highly-variable-so-far

4. Same mutations are re-appearing? Control Infections.

Once the virus enters a cell, it begins to replicate. The more copies it makes, the greater the likelihood that **random errors, or mutations**, will crop up. Most of these **copying errors** are inconsequential. A handful, however, might give the virus a leg up. For example, a spike-protein mutation known as D614G appears to help transmission of SARS-CoV-2. Another, E484K, might help the virus evade the body's antibody response. If the viruses carrying these advantageous mutations get transmitted from one person to the next, they can start to outcompete the viruses that lack them, a process known as natural selection. That's how the B.1.1.7 variant, which is more transmissible, became the predominant strain in the US.

In the case of SARS-CoV-2, the mutations that improve the virus keep popping up in different parts of the globe, a phenomenon known as convergent evolution. **"We are seeing the same combinations** evolving over and over and over again," says Vaughn Cooper, at the University of Pittsburgh. **"A limited number of building blocks can be assembled in different ways, in different combinations, to achieve the same winning structures."**

Cooper and some other researchers see this evidence of convergent evolution as a hopeful sign: the virus may be running out of new ways to adapt to the current environment. "It's actually a small deck of cards right now," he says. "If we can **control infections**, that deck of cards is going to remain small."

www.scientificamerican.com/article/the-coronavirus-variants-dont-seem-to-be-highly-variable-so-far

Control Infection

IF THE VIRUS CAN'T GROW IT CAN'T MUTATE

TETRIS

TE – test

TR – treat

IS – isolate

Cooper and some other researchers see this evidence of convergent evolution as a hopeful sign: the virus may be running out of new ways to adapt to the current environment. "It's actually a small deck of cards right now," he says. "If we can **control infections**, that deck of cards is going to remain small."

5. Booster shots are working ☑ May 5, 2021 https://investors.modernatx.com/node/11836/pdf

Naturally, primary vaccines will become less effective, as physiologically expected. Will low-cost booster shots work? Preliminary results from B.1.351-specific booster increased protection against the variants first identified in South Africa and Brazil. It demonstrates that variant-specific **boosters can work**. Yes, costs may decrease, too.

Positivism

IF THE VIRUS CAN'T GROW IT CAN'T MUTATE

TETRIS

TE – test

TR – treat

IS – isolate

TEST

Rich test ◆ Poor test

Mobile Phone

news.berkeley.edu/story_jump/new-crispr-based-covid-19-test-uses-smartphone-cameras-to-spot-virus-rna/

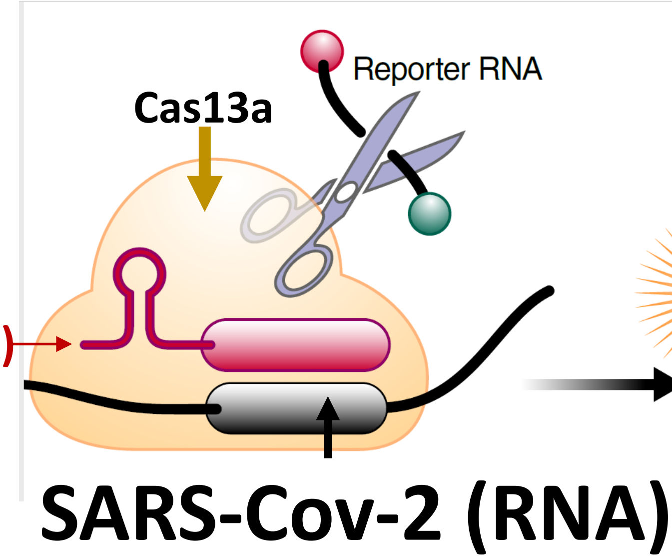
Berkeley News

MIND & BODY, RESEARCH, TECHNOLOGY & ENGINEERING

New CRISPR-based COVID-19 test uses smartphone cameras to spot virus RNA

By Kara Manke | DECEMBER 4, 2020

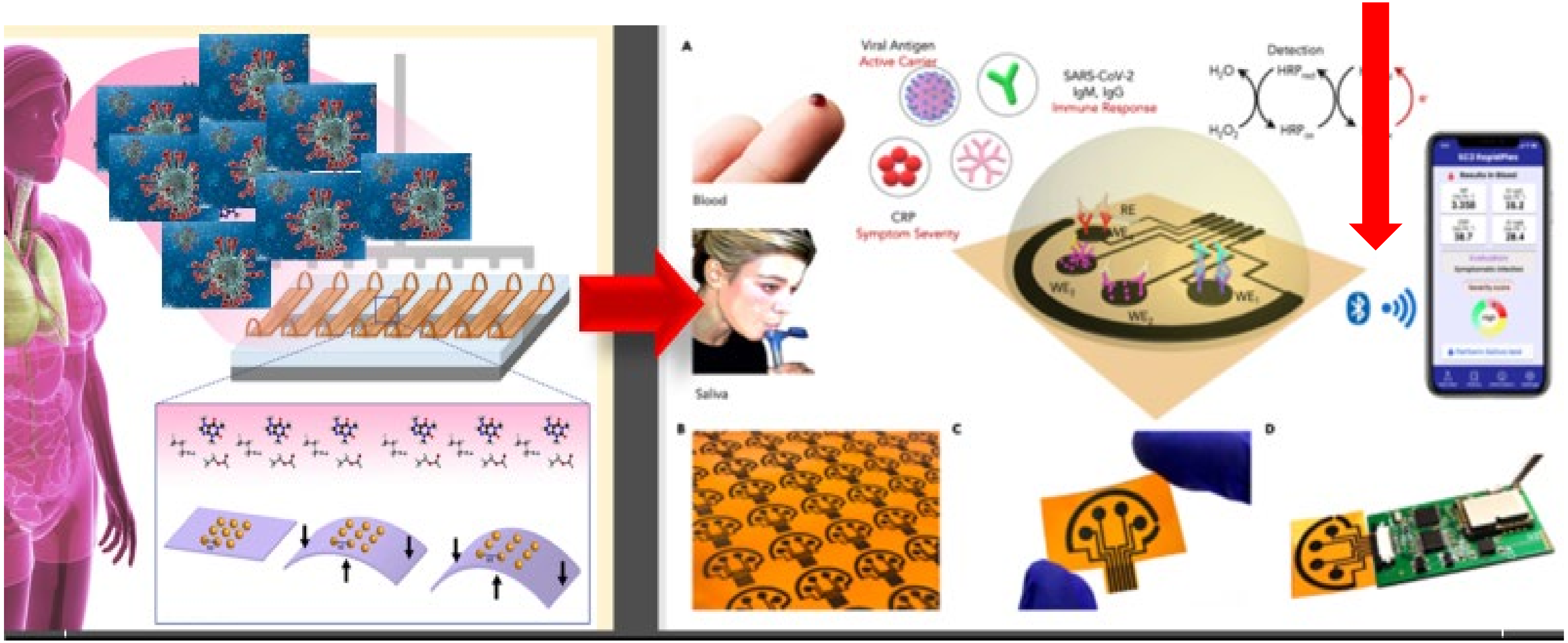
https://www.cell.com/cell/pdf/S0092-8674(20)31623-8.pdf



https://dspace.mit.edu/handle/1721.1/128017

Mobile Phone Data

WiFi, Bluetooth, 802.11
wireless data transfer
(signal transduction)

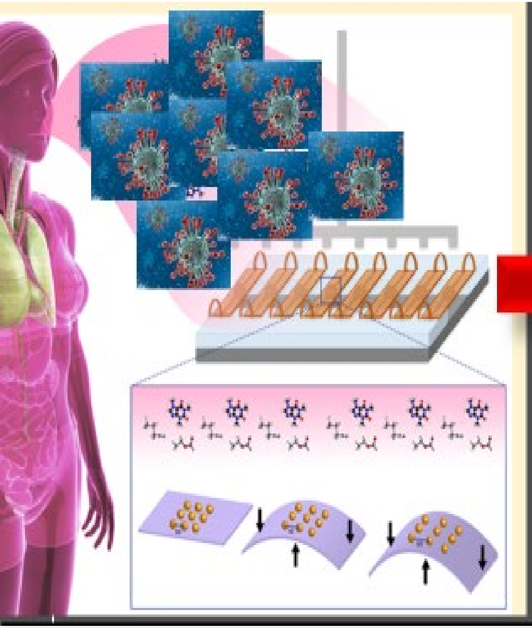


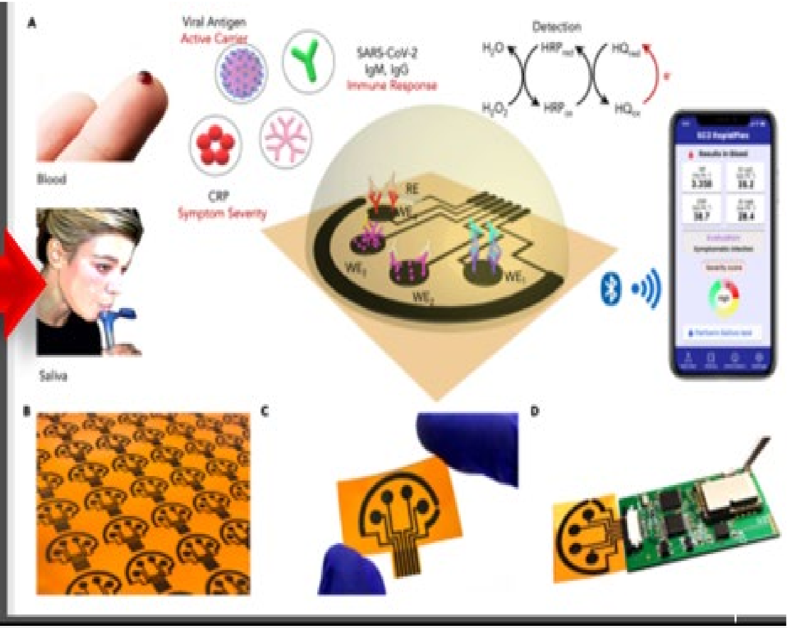
https://dspace.mit.edu/handle/1721.1/128017

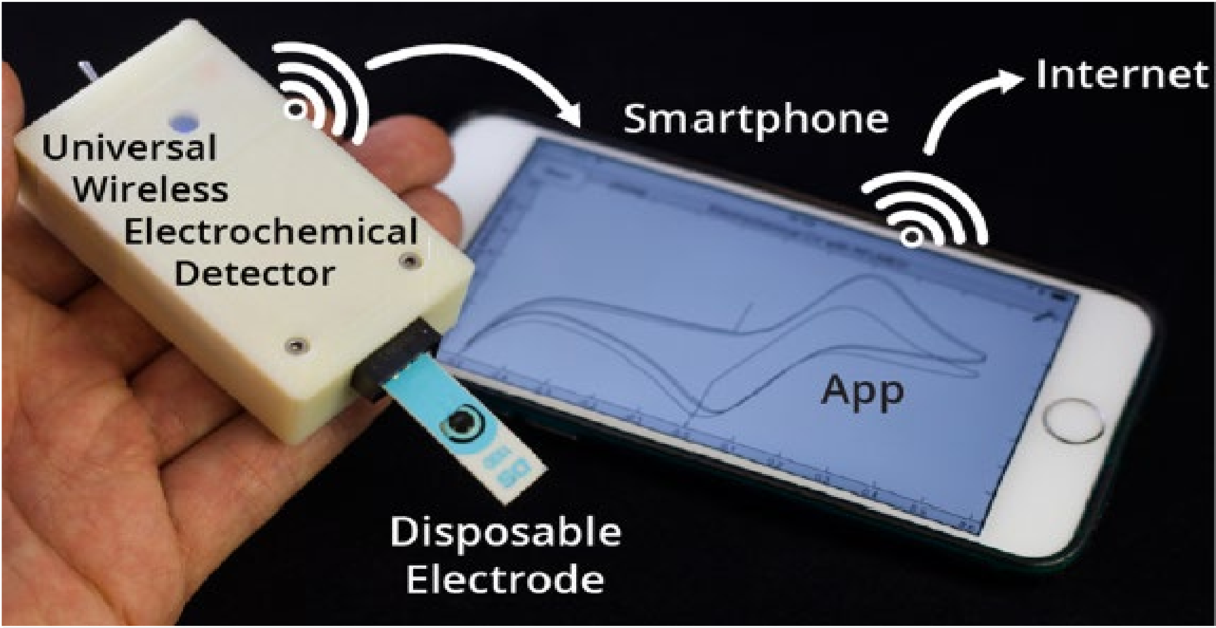
Low-cost
laser inscribed
turbostrat graphene sensors

TEST

Detection of airborne SARS-CoV-2 from breath/saliva (sputum)



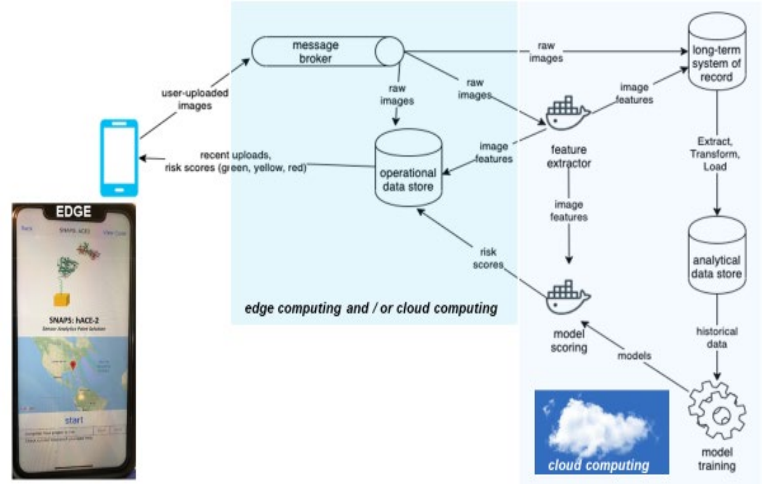




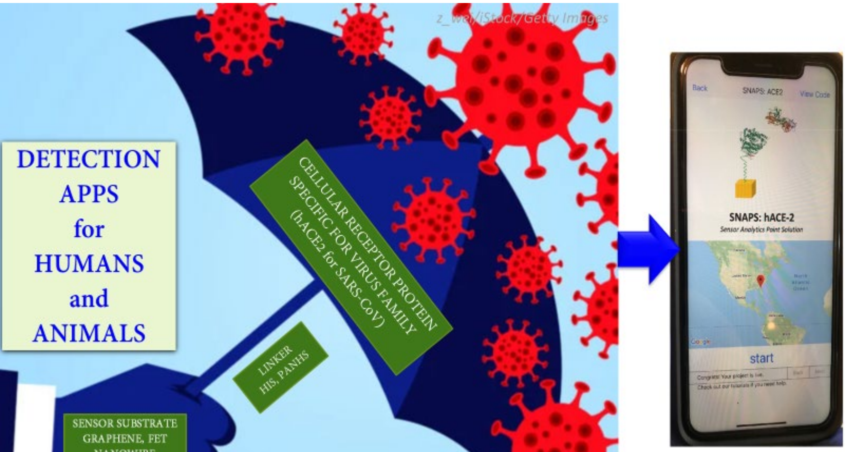
For the rest of the world can low-cost sensors linked to mobile phones help to test frequently & control infection?

https://dspace.mit.edu/handle/1721.1/128017

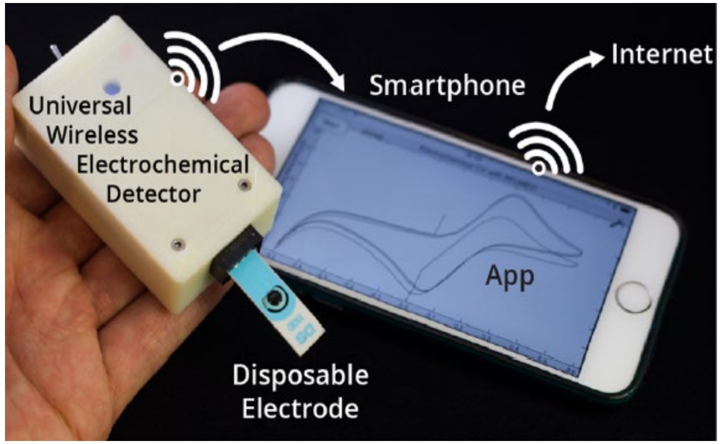
TEST ANYTHING ?
HUMANS, ANIMALS, CROP, FOOD, WATER, SEWERS

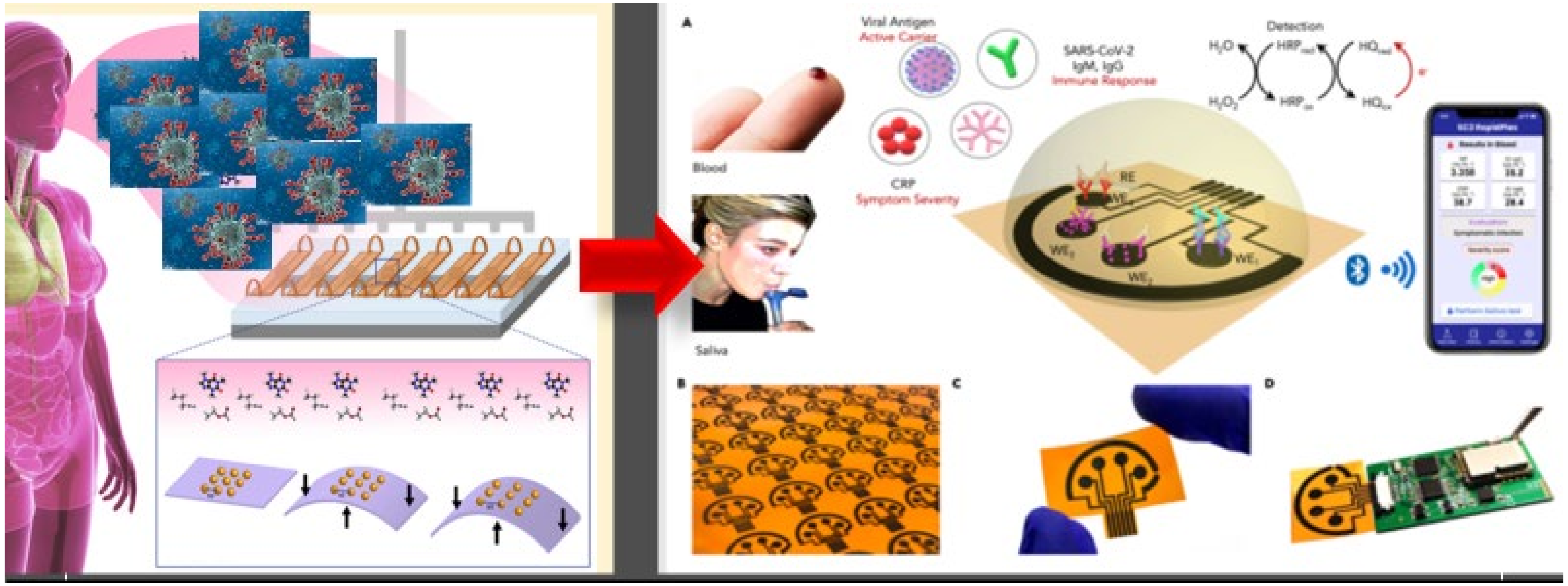


Mobile Phone



Eric McLamore • Smartphone Surveillance
https://emclamor.wixsite.com/mclamorelab

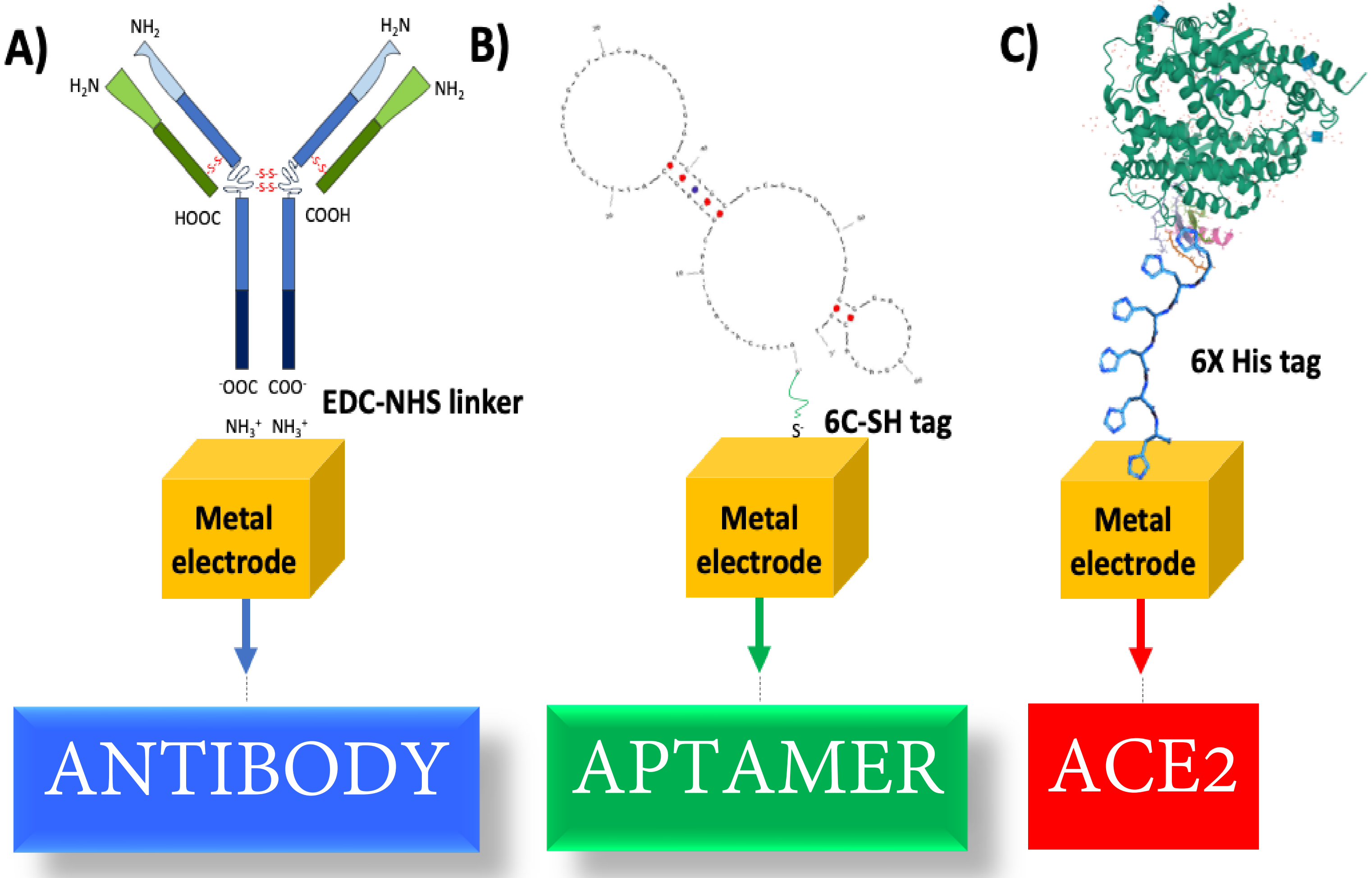




https://dspace.mit.edu/handle/1721.1/128017

- Mobile
- Phone
- Data

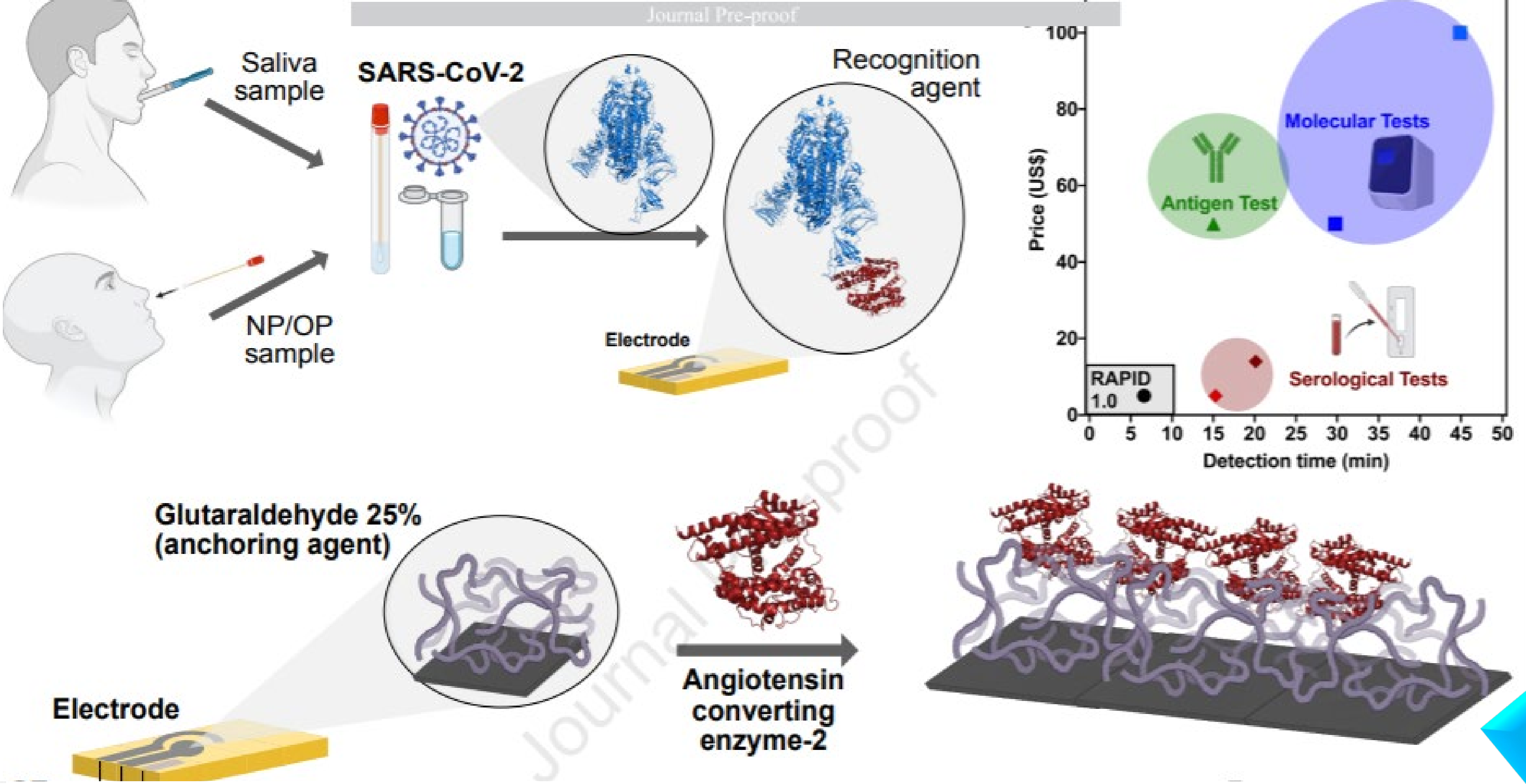
What can we use in low-cost sensors to detect SARS-CoV-2?

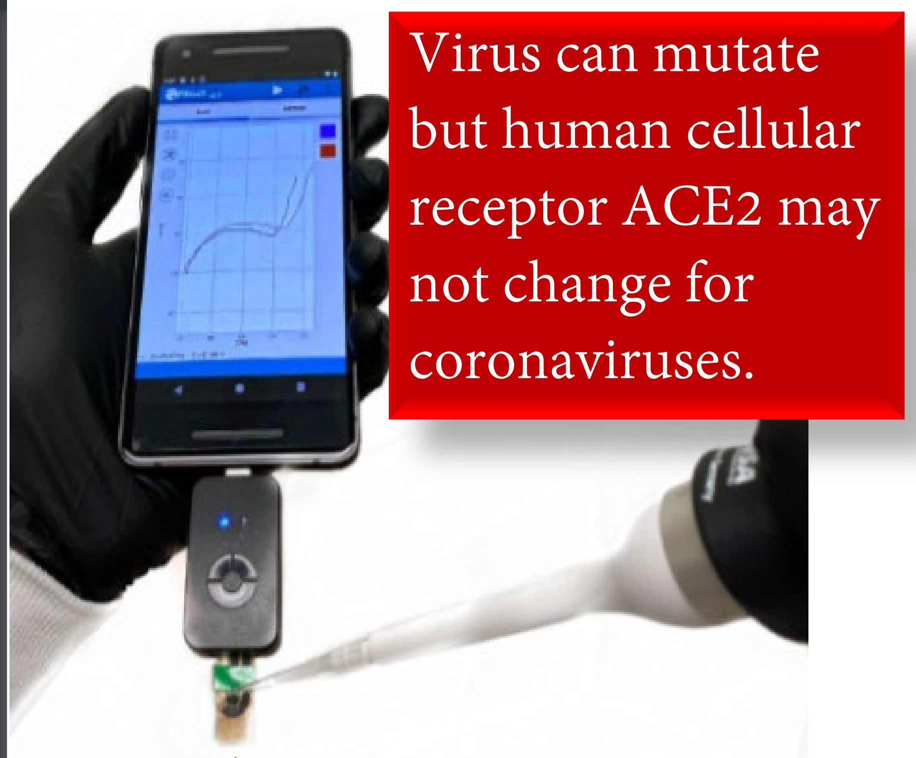


Cartoon: Eric McLamore and Diana Vanegas https://dspace.mit.edu/handle/1721.1/128017

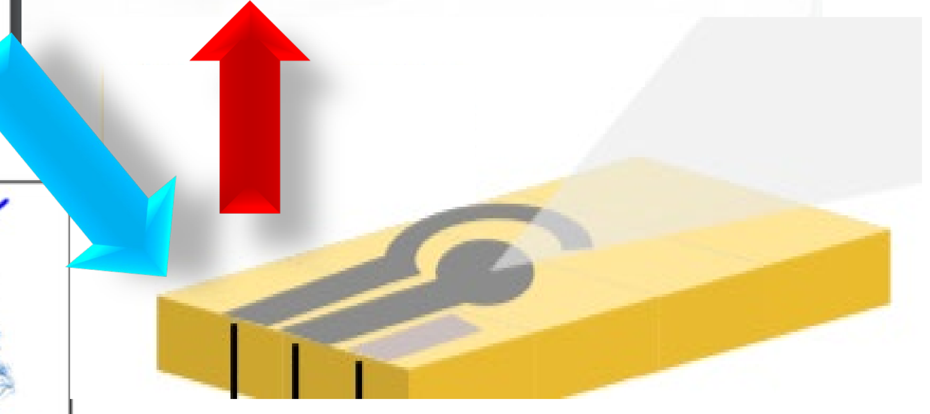
Low-cost
laser inscribed
turbostrat graphene sensors ?

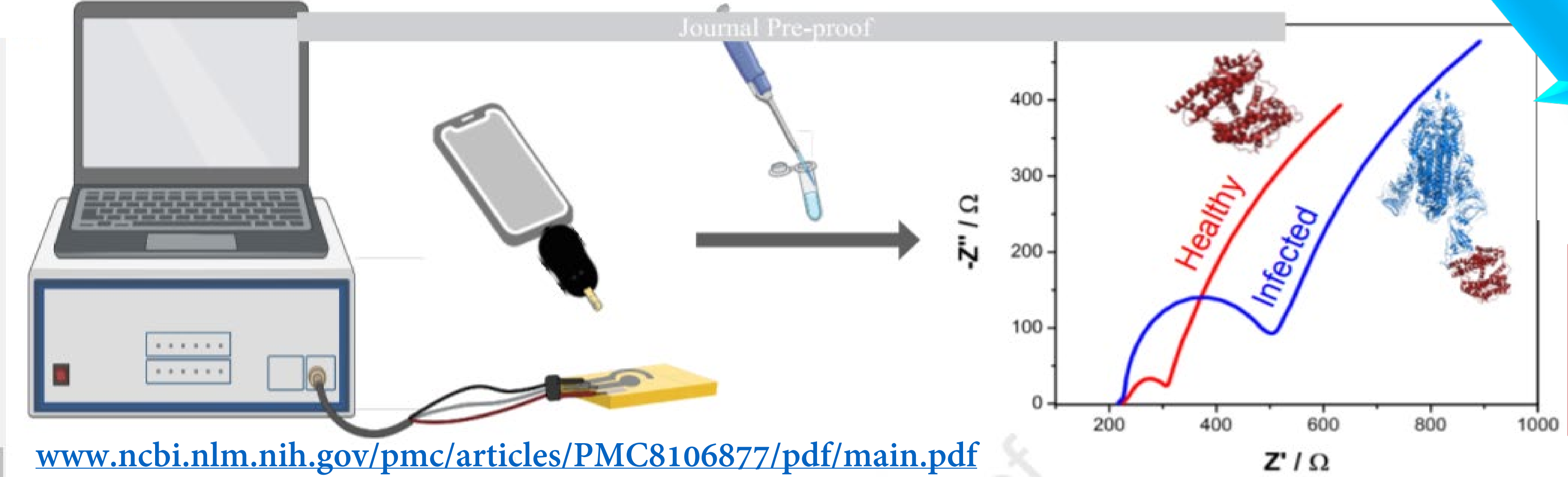
LOW-COST ACE2 SENSOR DETECTS SARS-CoV-2





Virus can mutate but human cellular receptor ACE2 may not change for coronaviruses.





ACE2 SENSOR

www.ncbi.nlm.nih.gov/pmc/articles/PMC8106877/pdf/main.pdf

Positivism
Pandemic
Progress

Education and Research to bring science to society

All Advantages are Temporary

- Protection (masks) from airborne pathogens is quintessential for all.
- Testing is key to controlling infection.
- Lifestyle must adapt daily exposure to limit risk of infection (for 2 to 5 years).
- This disaster is a great opportunity to advance math and biomedical education.
- Dealing with this catastrophe will require convergence of science and engineering to create tools for mobile digital healthcare.

The pandemic as a blessing?

Digital Health and Healthcare

Pay-Per-Pee Home Health - IoT Wireless Metabolomics & Vitals - Connected Healthcare

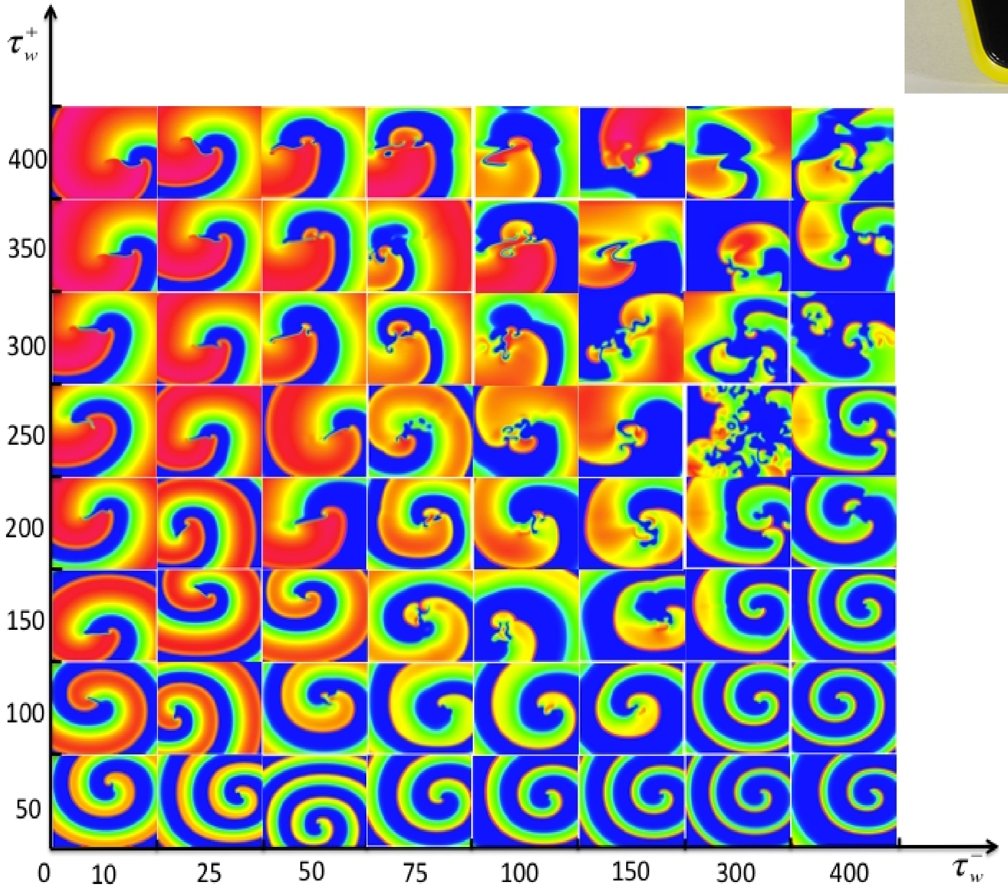
1.WELCOME
The e-urinal is your health partner who can tell you your health condition.

2.HEALTH SCORE
With a touch screen, the e-urinal can measure your PH/SG/URO/BLO/WBC/PRO/GLU/BIL/KET with your urine. What's more, she can give your health Score!

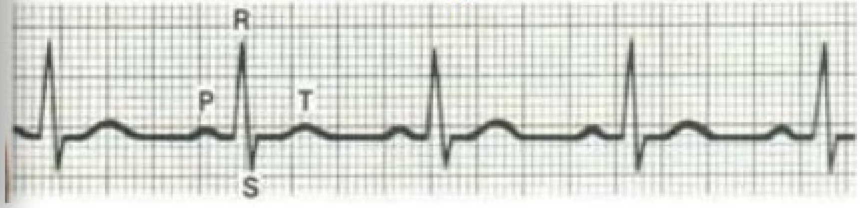
3.DETAILS
If you wanna know the details, just press she icon, she can record your past measuring data and can give you some heath advice.

Weigh-scale, BMI, FOBT, urine analysis, sugar, ketone body analysis, blood pressure monitor, pulse oximeter, networked to phone via WiFi and/or Bluetooth with biometrics and face recognition for secure communication with physician and hospital or clinic, globally.

CARDIAC ARRHYTHMIA
DIAGNOSIS & REPORTING
CARDIOLOGIST-in-a-POCKET



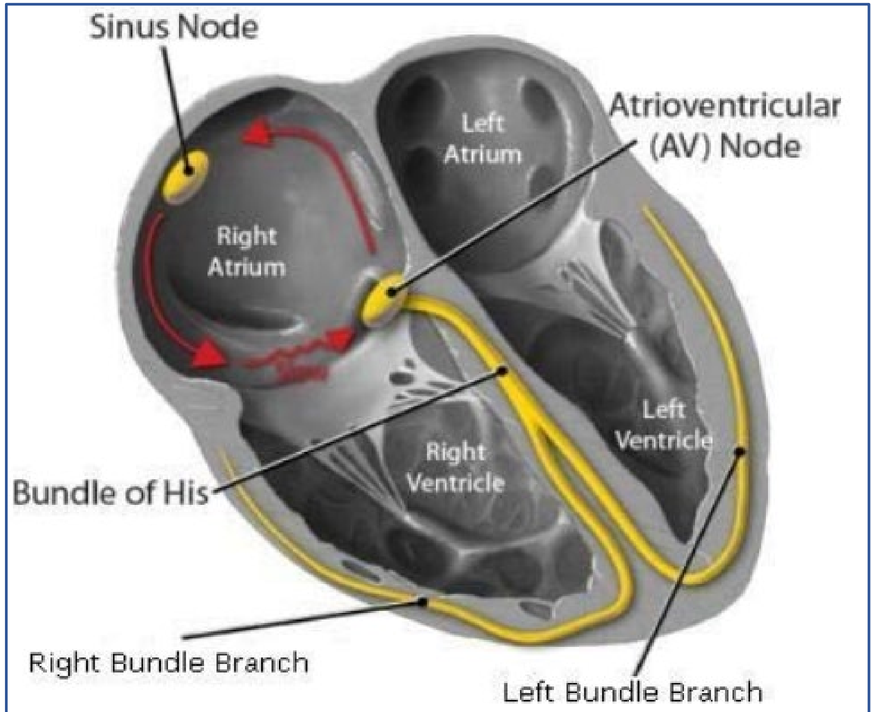
Normal Sinus Rhythm



Circular pathways in the heart conduction system is a common cause of arrhythmias

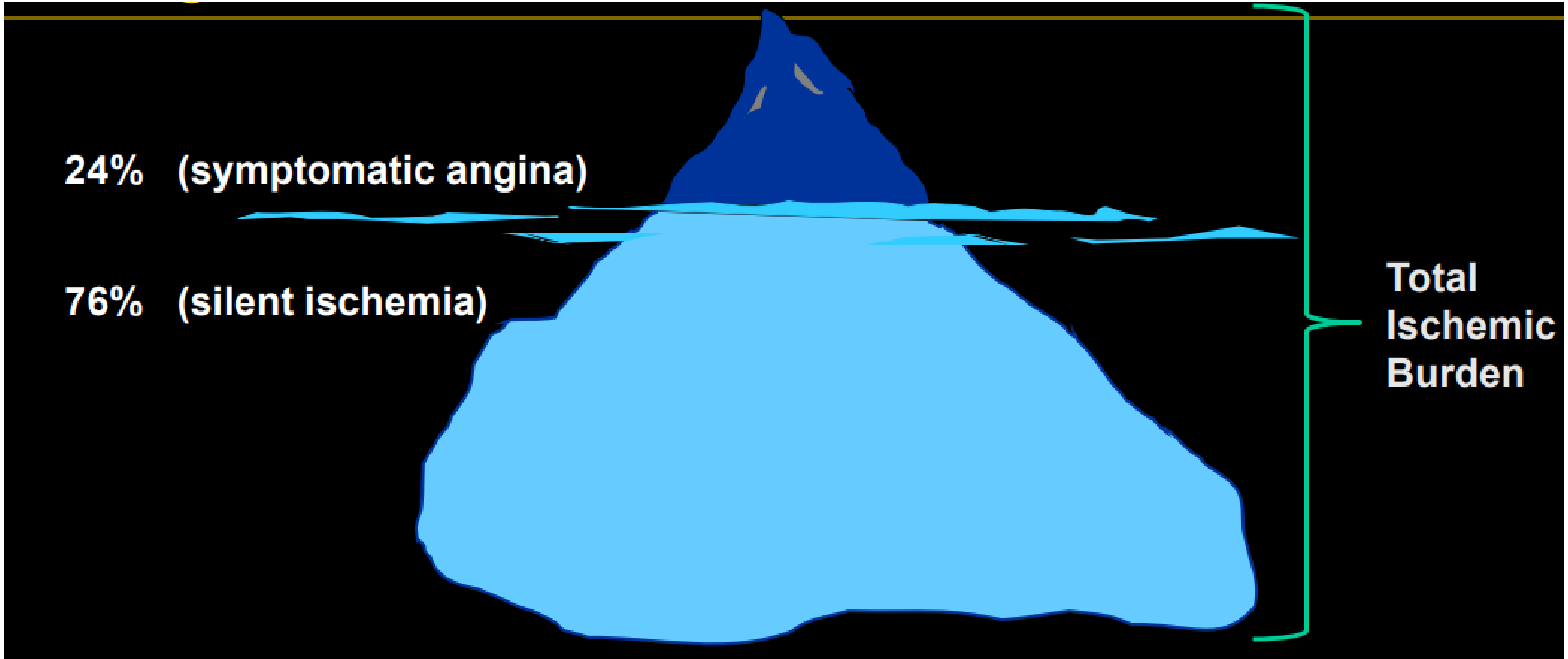
Arrhythmic Rhythm

www.seas.upenn.edu/sunfest/docs/slides/MALAMASPETER.pdf



Symptomatic Angina: The Tip of the Ischemic Iceberg

www.escardio.org/static_file/Escardio/education/live-events/courses/education-resource/Fri-11-SMI-Gutterman.pdf



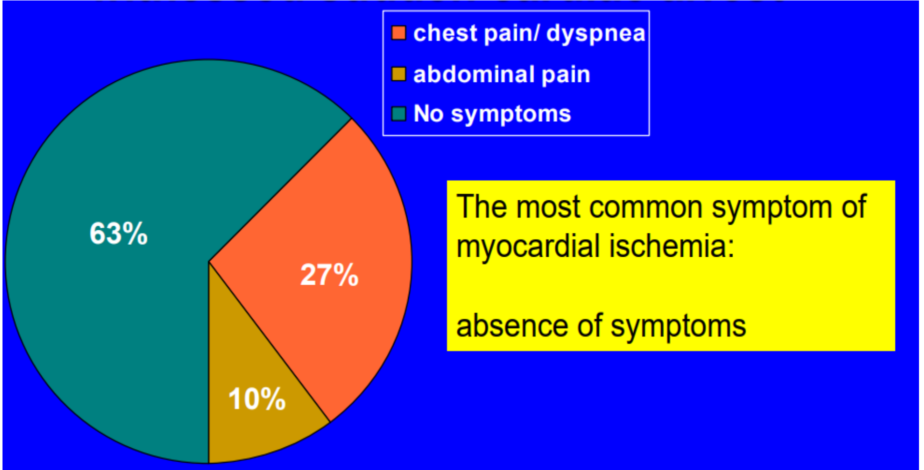
If you cannot sense, you cannot detect.

If you cannot predict, you cannot prevent.

If you cannot measure, you do not have metrics.

If you do not have data, you cannot take a decision.

https://dspace.mit.edu/handle/1721.1/107893

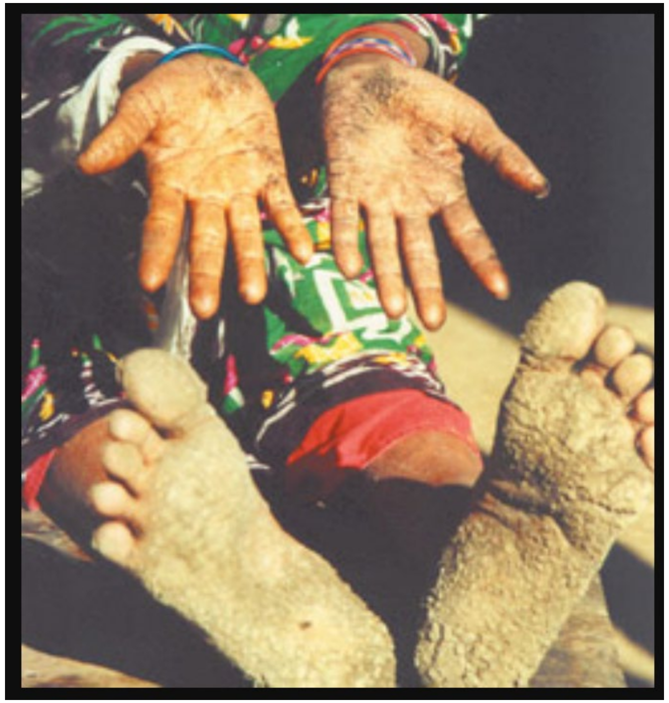


The most common symptom of myocardial ischemia:

absence of symptoms

Reality Check ☑ Arsenic in Water (Bangladesh)



Digital Health IoT – Water and Soil Monitoring

http://bit.ly/ROHIT-KARNIK_MIT

U=Araihazar
M=Khaserkandi
V=Khaser Kandi
Start>=85'
Fail=22/100
Average arsenic 44 ppb
42 safe of 71 wells
 45- 90' 40 of 69
115-130'   2 of   2

HUMANS / ANIMALS / PLANTS / ENVIRONMENT SYNERGISTIC SYSTEMS INTEGRATION OneHealth

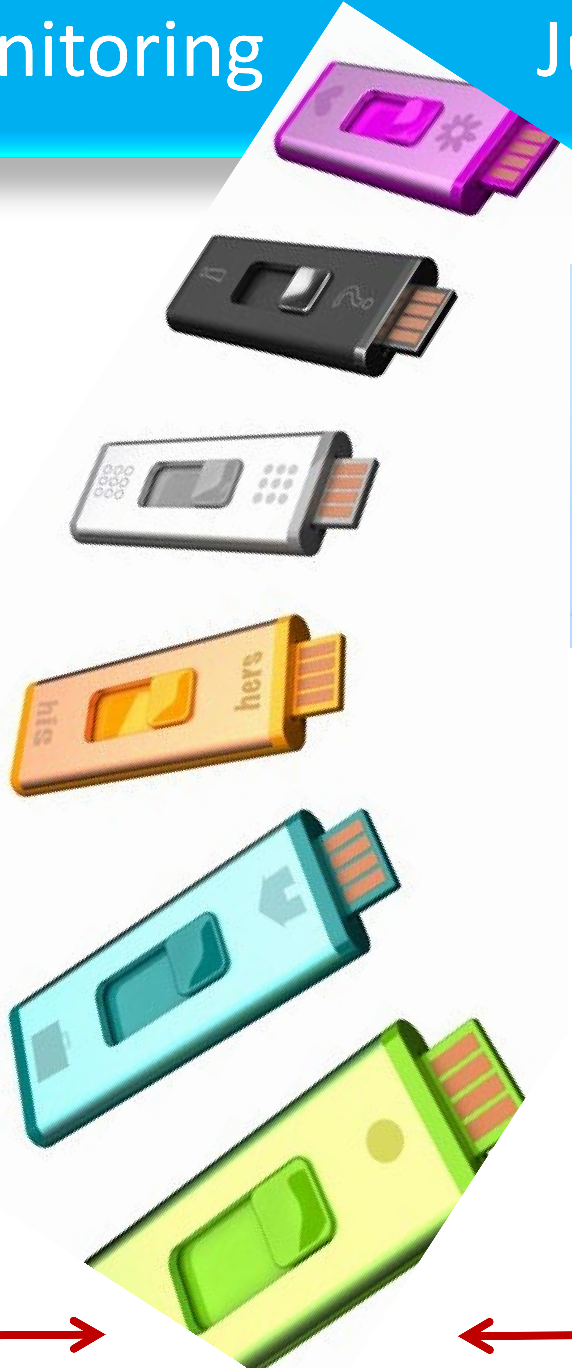
Nutritional SARA⇨ Real-Time Digestive Analytics
Nutritional ⇨ sense, analyze, respond, actuate

- **In vivo** rates of digestion will enable precision mixed ration formulation and better dairy health to increase milk


Pandemic may improve healthcare

Digital Health & Monitoring

Just Pay-A-Penny-Per-Use **(PAPPU)**



Glucose Sensor

Cholesterol Sensor

SARS-CoV-2 Sensor

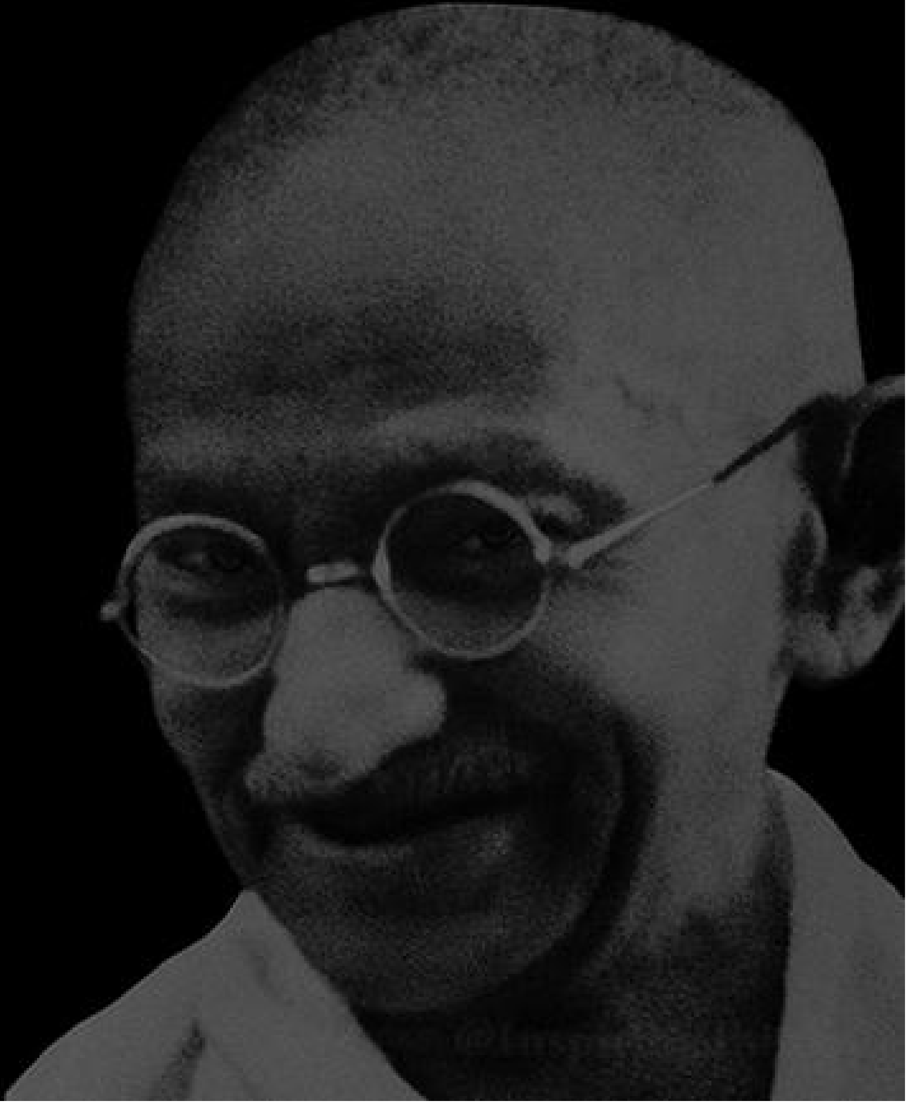
What does the data suggest about my health?

Hot swappable, modular, smart

NK Labs
ARA Prototype

THE WORLD HAS ENOUGH
FOR EVERYONE'S NEED,
BUT NOT ENOUGH FOR
EVERYONE'S GREED.

MAHATMA GANDHI (1869-1948)

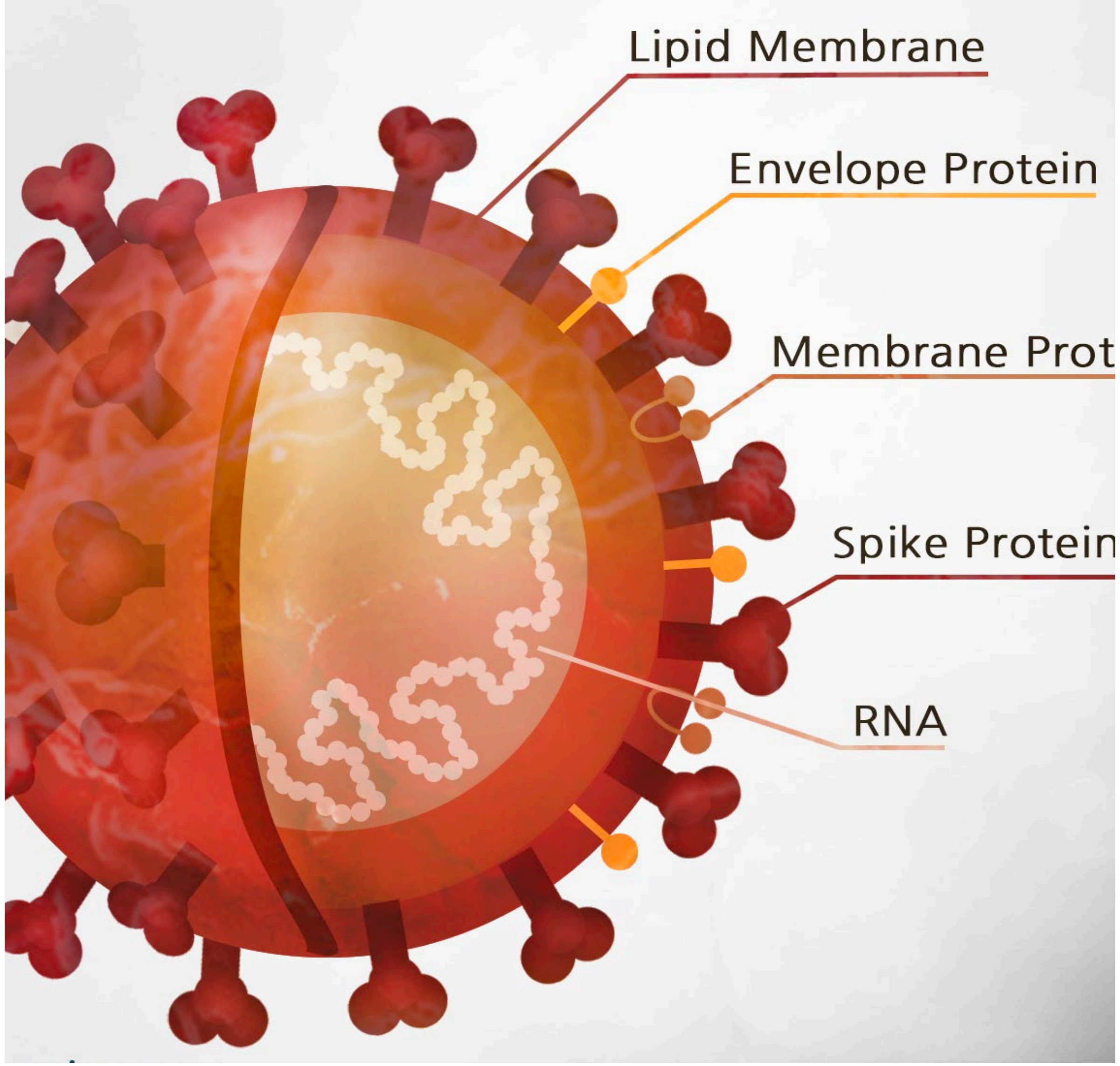


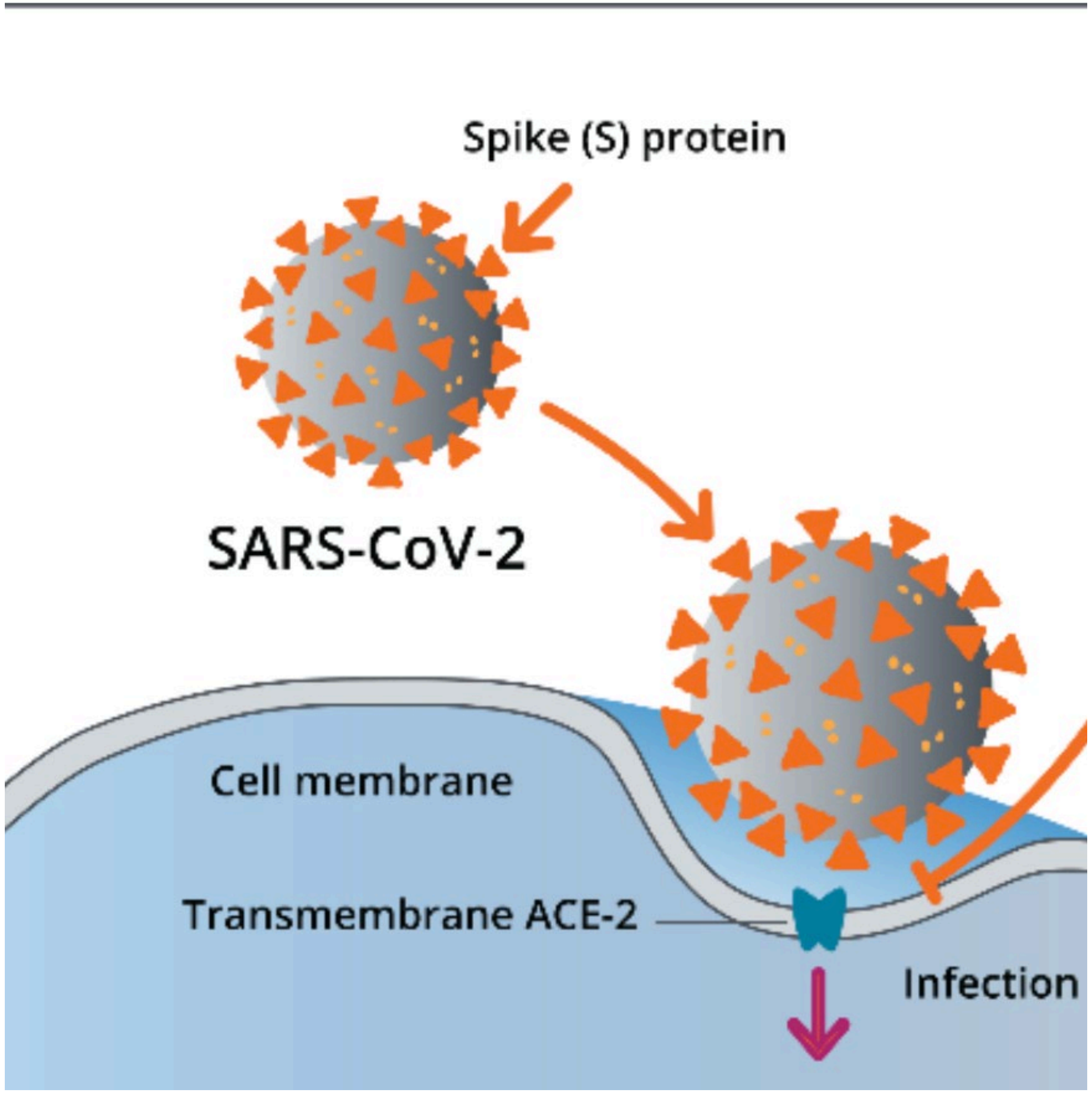
Additional Explanation

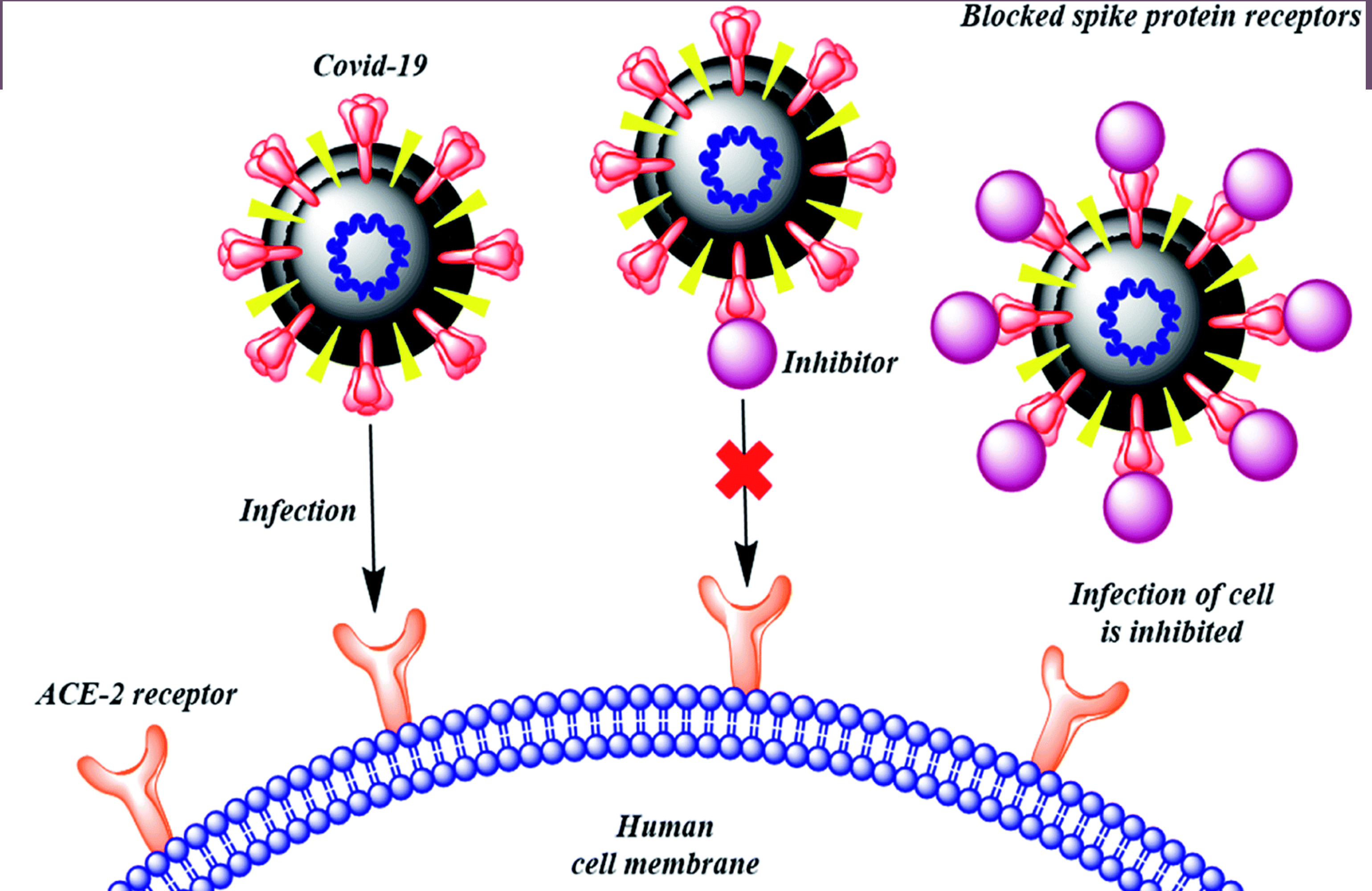
4. Same mutations re-appearing? Molecular Messages.

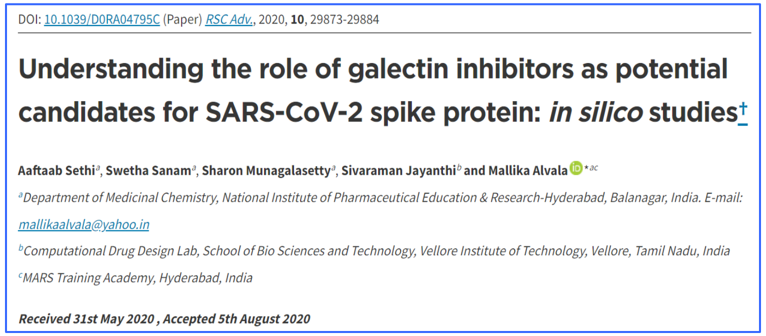
WHY ?

www.scientificamerican.com/article/the-coronavirus-variants-dont-seem-to-be-highly-variable-so-far


Lipid Membrane
Envelope Protein
Membrane Prot
Spike Protein
RNA


Spike (S) protein
SARS-CoV-2
Cell membrane
Transmembrane ACE-2
Infection




DOI: 10.1039/D0RA04795C (Paper) RSC Adv., 2020, 10, 29873-29884

Understanding the role of galectin inhibitors as potential candidates for SARS-CoV-2 spike protein: *in silico* studies†

Aaftaab Sethi[a], **Swetha Sanam**[a], **Sharon Munagalasetty**[a], **Sivaraman Jayanthi**[b] and **Mallika Alvala**[*ac]

[a] *Department of Medicinal Chemistry, National Institute of Pharmaceutical Education & Research-Hyderabad, Balanagar, India. E-mail: mallikaalvala@yahoo.in*

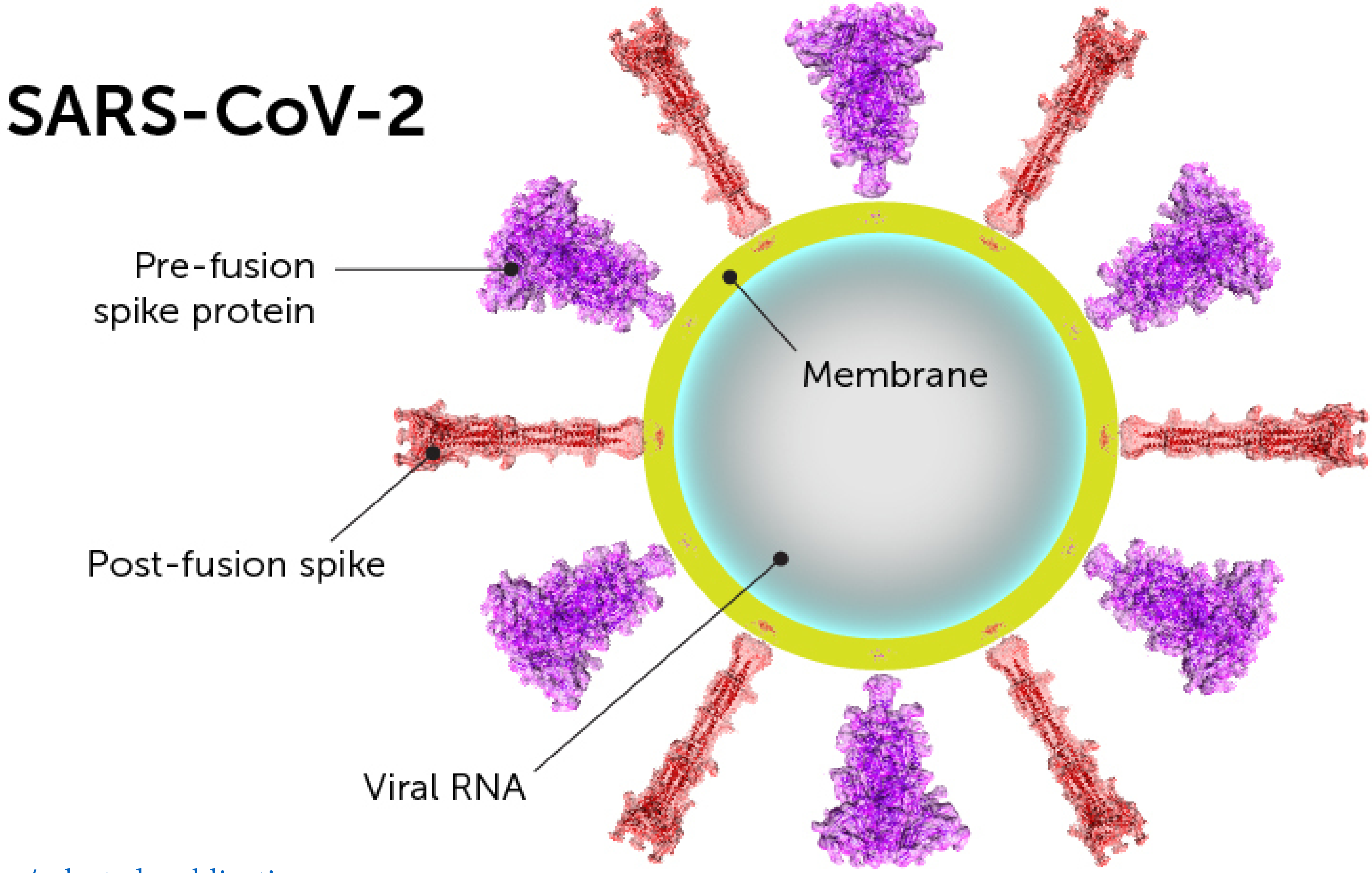
[b] *Computational Drug Design Lab, School of Bio Sciences and Technology, Vellore Institute of Technology, Vellore, Tamil Nadu, India*

[c] *MARS Training Academy, Hyderabad, India*

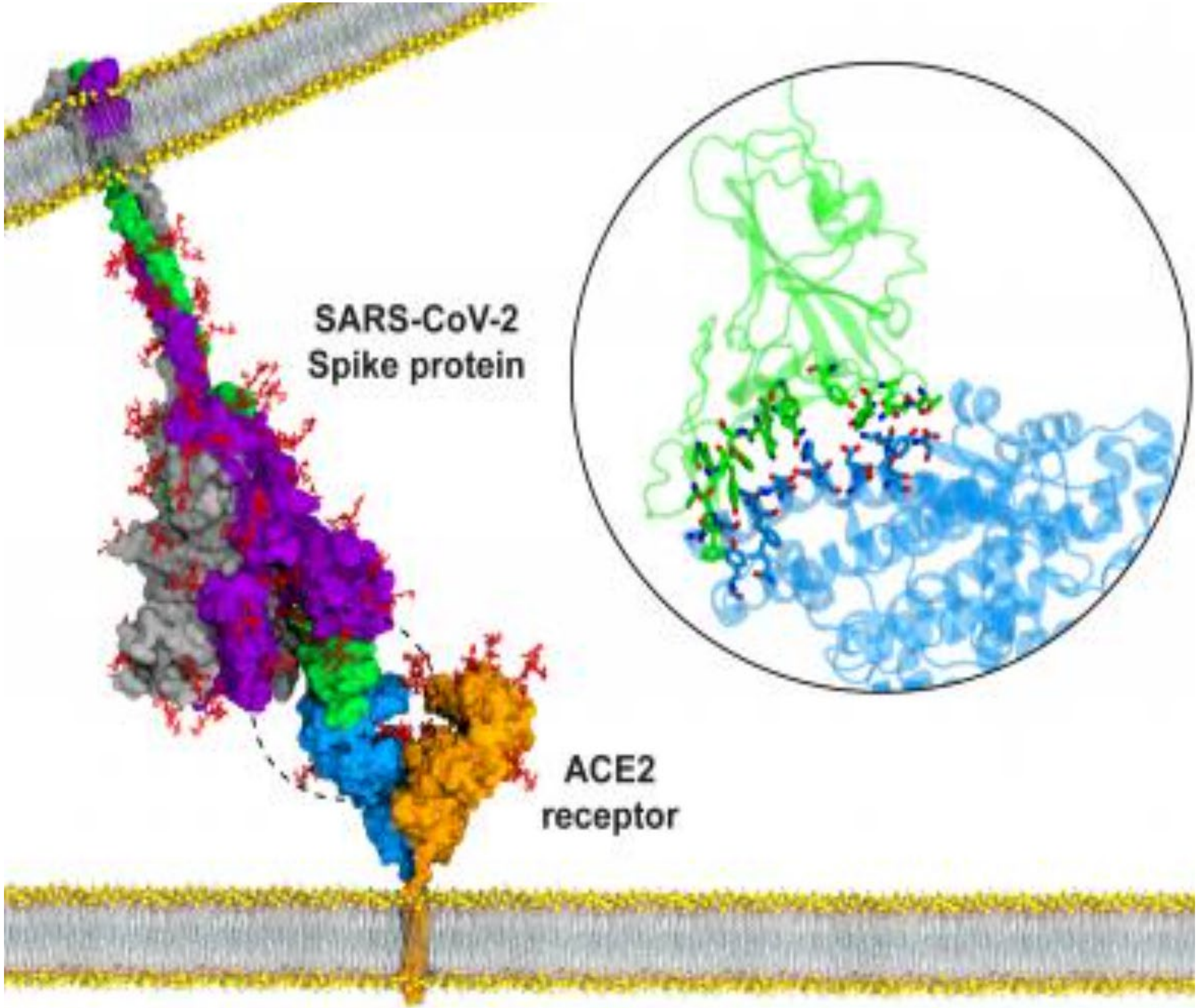
Received 31st May 2020 , Accepted 5th August 2020

https://pubs.rsc.org/en/content/articlepdf/2020/ra/d0ra04795c

BREAKTHROUGH DISCOVERY

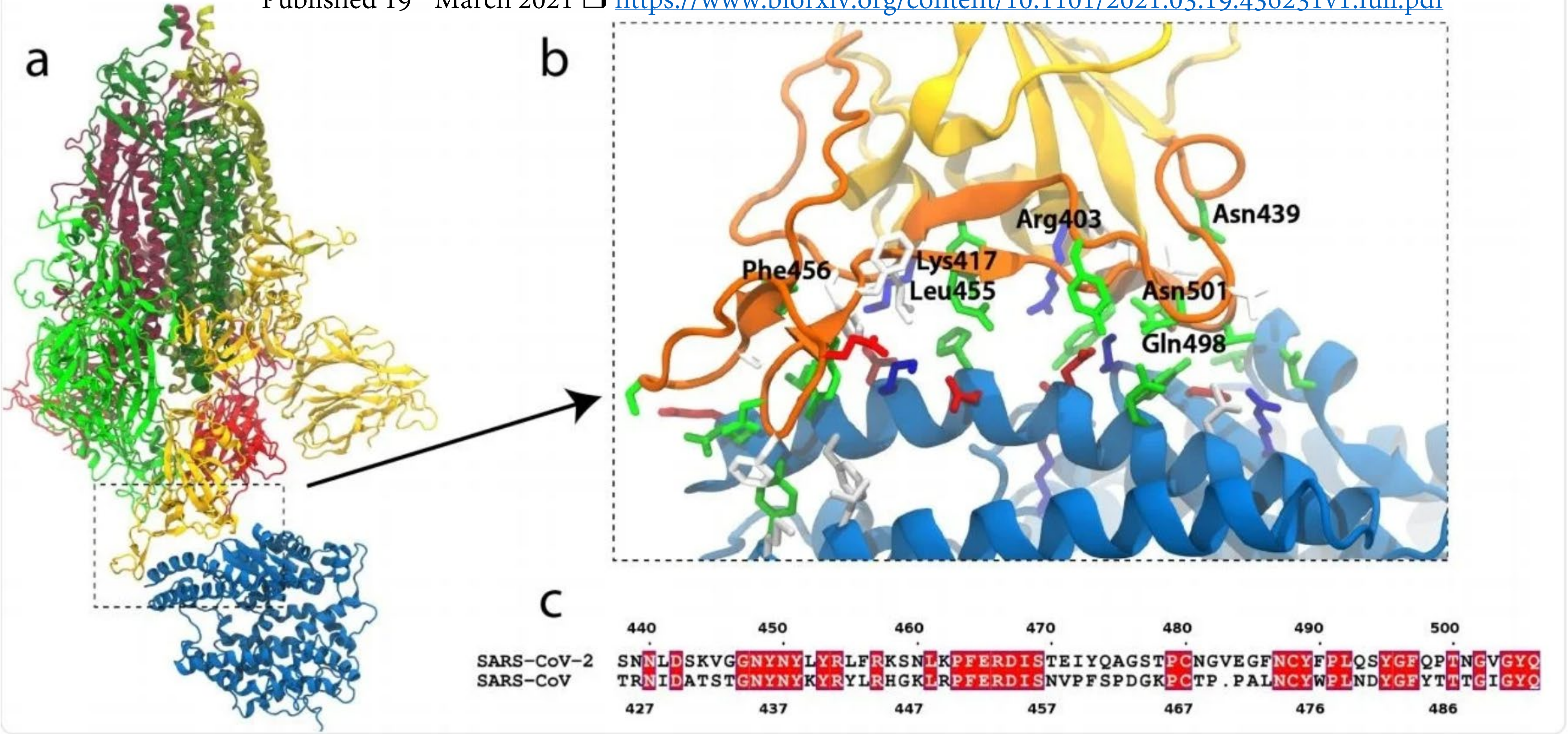


https://www.mclellanlab.org/selected-publications



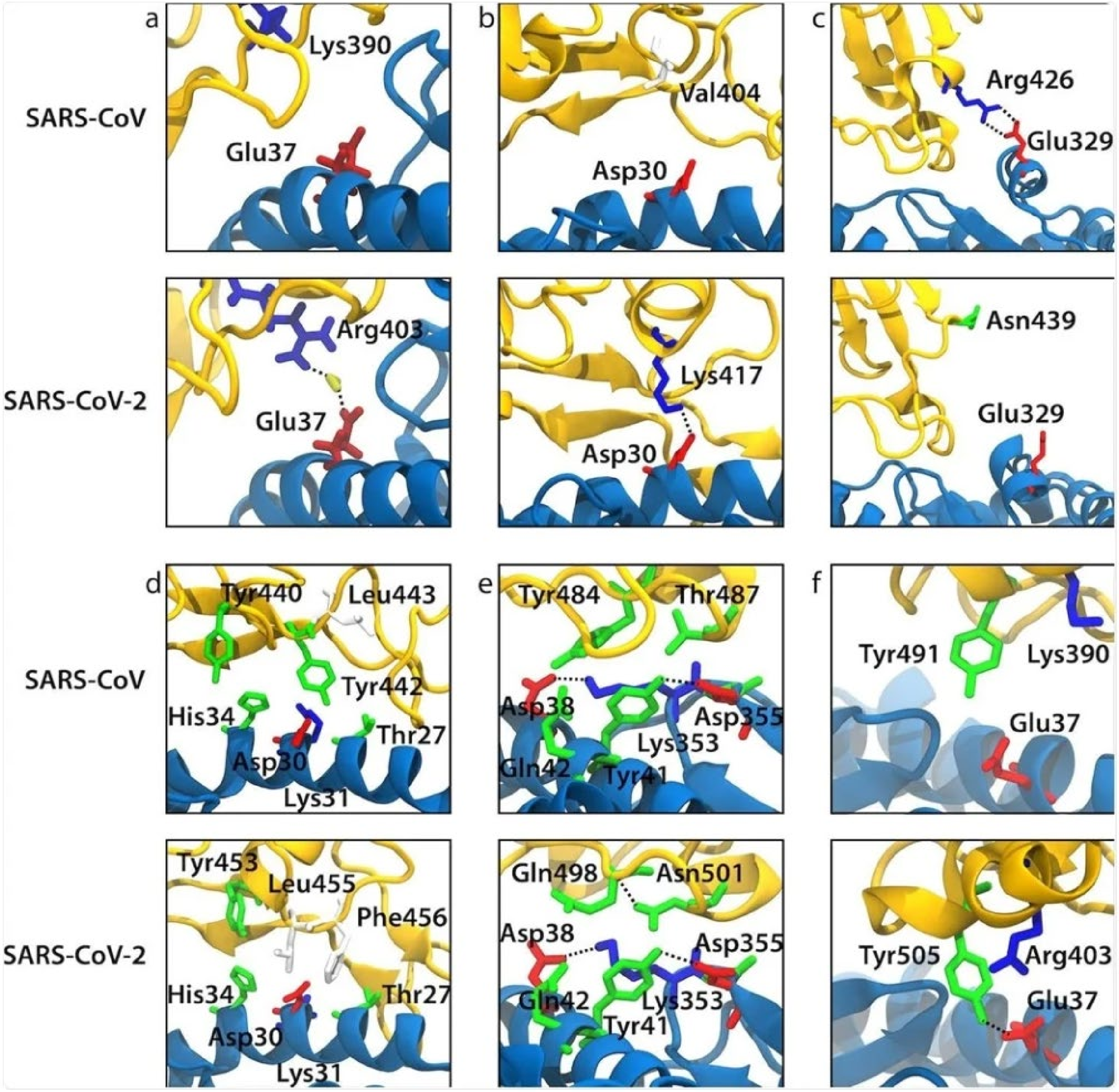
Source:
Ahmet Yildiz
University of California, Berkeley

Published 19th March 2021 ❐ https://www.biorxiv.org/content/10.1101/2021.03.19.436231v1.full.pdf



SARS-CoV-2 S-protein binding to ACE2. (a) S-protein trimer (green, yellow, red) bound to the peptidase domain of ACE2 (blue). The lighter and darker shades of the trimer are S1 and S2, respectively. The viral envelope would be at the top and the host cell membrane at the bottom. (b) Close-up of the RBM (orange) interacting with ACE2. Residues near the interface are shown in a stick representation, colored by residue type (blue and red are positively and negatively charged, respectively, green is polar, white is hydrophobic). Specific residues in SARS-CoV-2 are labeled. (c) Alignment of the RBMs of SARS-CoV-2 and SARS-CoV19. Identical residues are white on red background.

4. Same mutations re-appearing? Why?

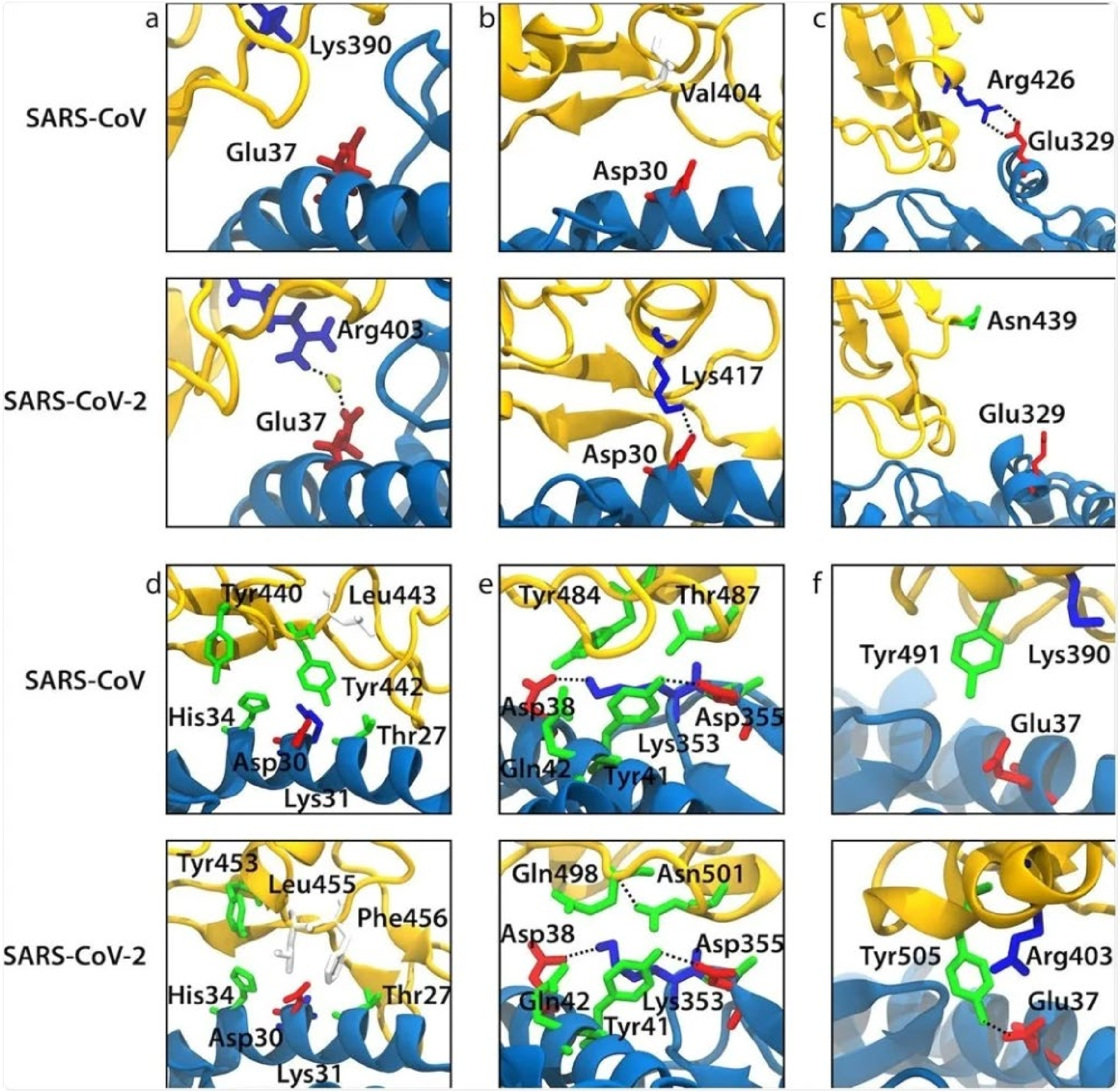


Critical interactions for SARS-CoV-2 spike protein binding to ACE2 identified by machine learning, Anna Pavlova, Zijian Zhang, Atanu Acharya, Diane L Lynch, Yui Tik Pang, Zhongyu Mou, Jerry M Parks, Chris Chipot, James C. Gumbart, bioRxiv, 2021.03.19.436231;
https://doi.org/10.1101/2021.03.19.436231
https://www.biorxiv.org/content/10.1101/2021.03.19.436231v1
https://www.biorxiv.org/content/10.1101/2021.03.19.436231v1.full.pdf

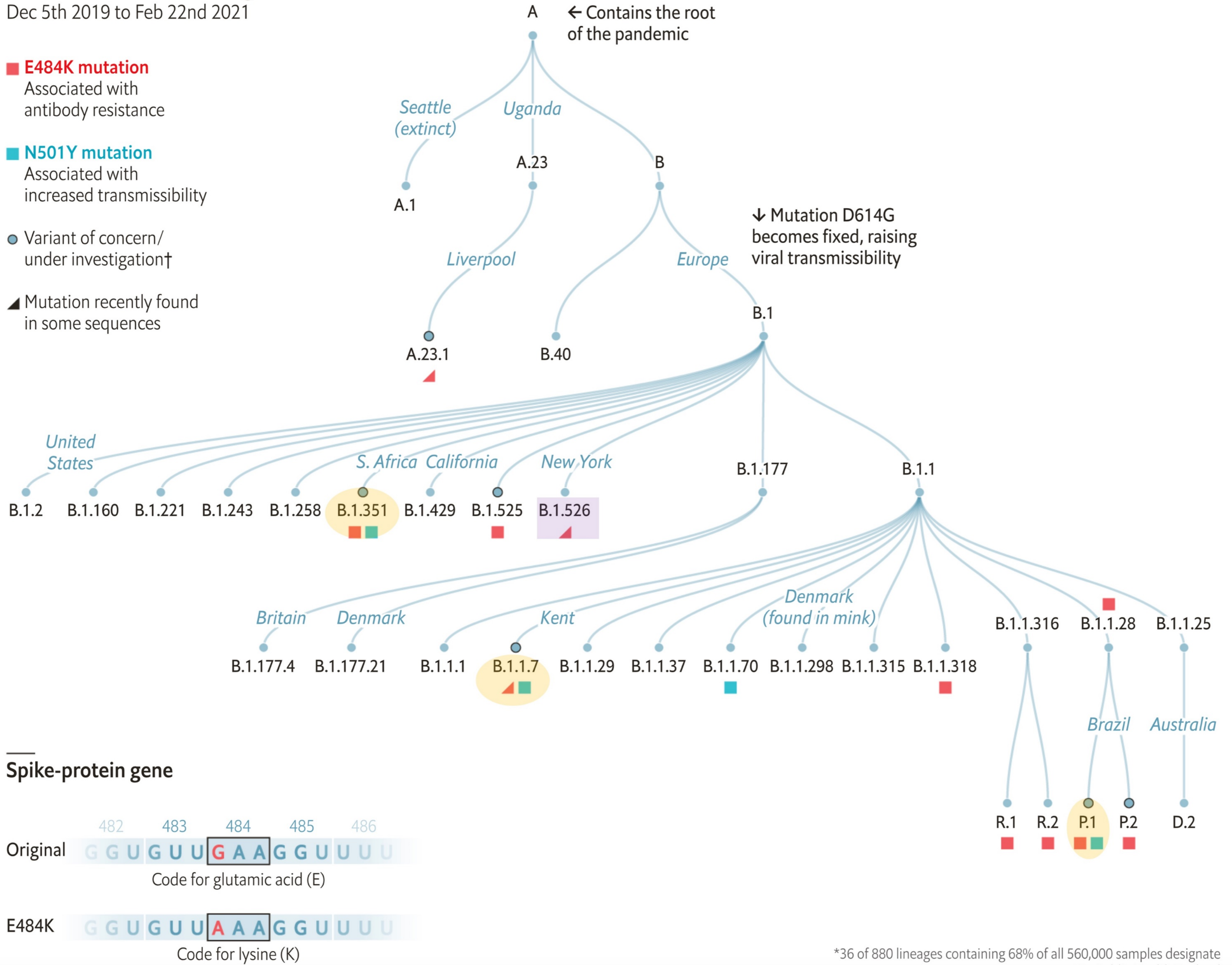
4. Same mutations re-appearing? Why?

There are only a few different ways amino acids can best fit inside the groove (interaction site) between the viral SARS-CoV-2 Spike protein and the human cell receptor protein ACE2 (blue).

Critical interactions for SARS-CoV-2 spike protein binding to ACE2 identified by machine learning, Anna Pavlova, Zijian Zhang, Atanu Acharya, Diane L Lynch, Yui Tik Pang, Zhongyu Mou, Jerry M Parks, Chris Chipot, James C. Gumbart, bioRxiv, 2021.03.19.436231;
https://doi.org/10.1101/2021.03.19.436231
https://www.biorxiv.org/content/10.1101/2021.03.19.436231v1
https://www.biorxiv.org/content/10.1101/2021.03.19.436231v1.full.pdf



Selected SARS-CoV-2 lineages*
Dec 5th 2019 to Feb 22nd 2021



🟥 **E484K mutation**
Associated with antibody resistance

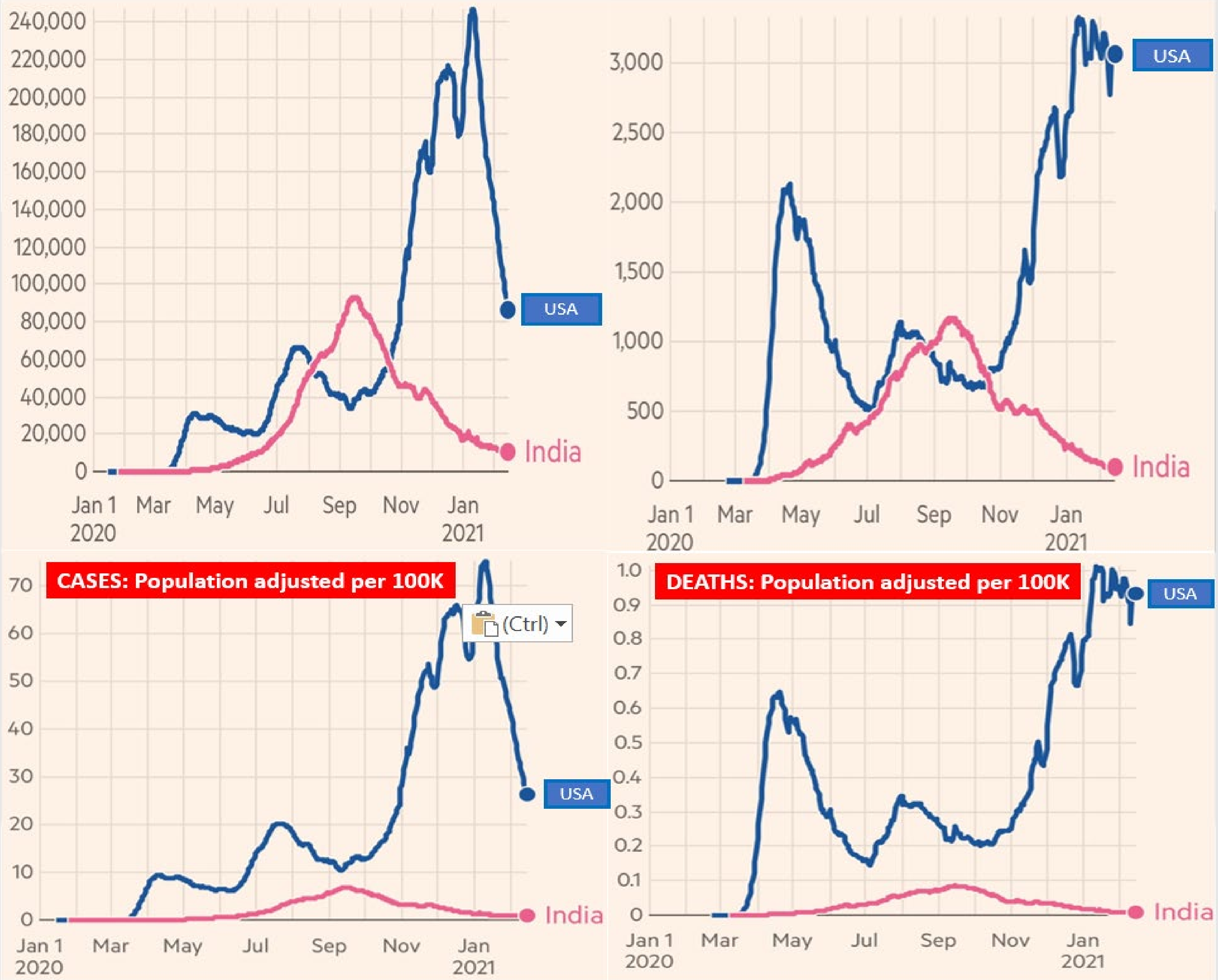
🟦 **N501Y mutation**
Associated with increased transmissibility

● Variant of concern/under investigation†

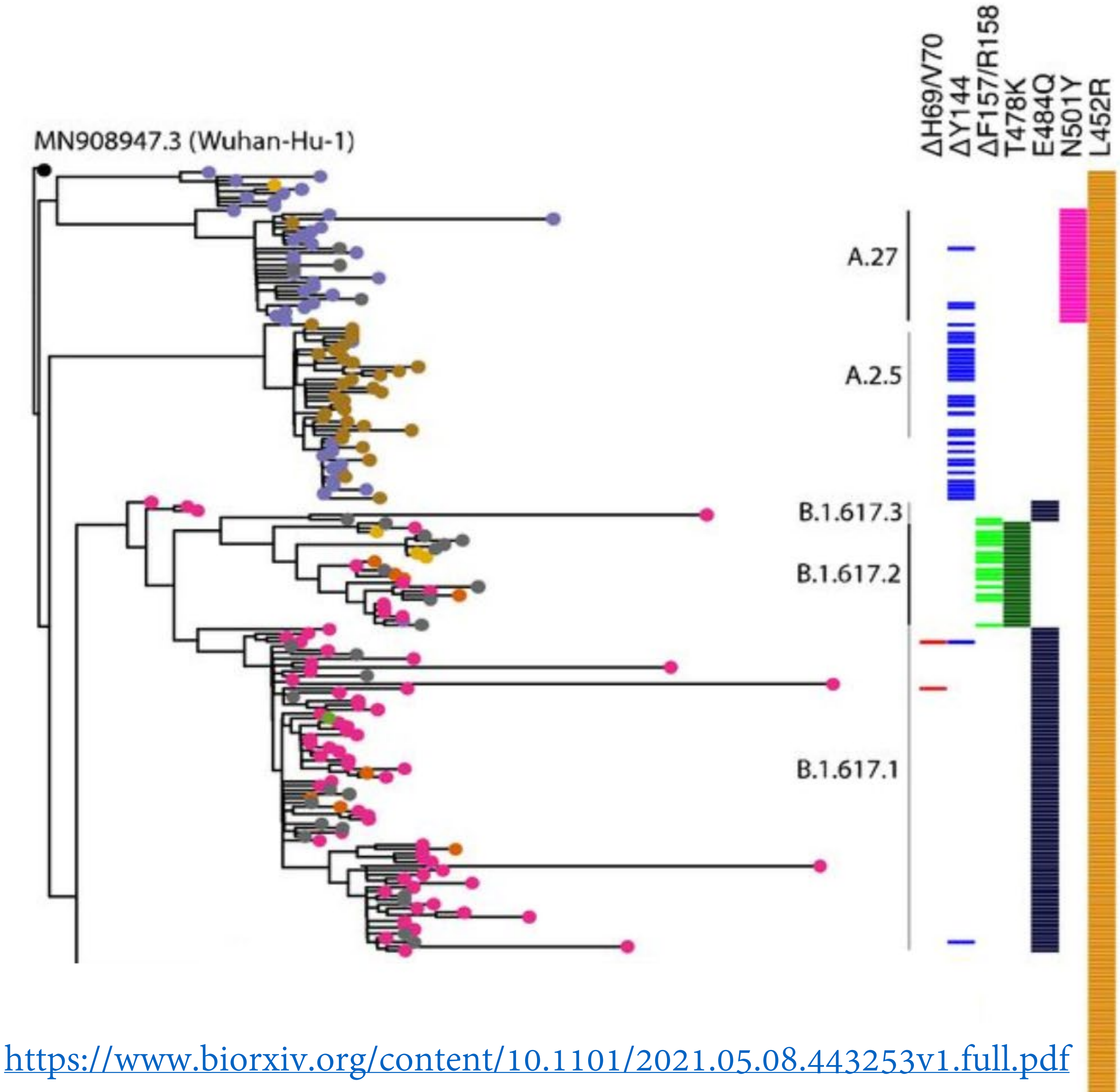
◢ Mutation recently found in some sequences

Spike-protein gene

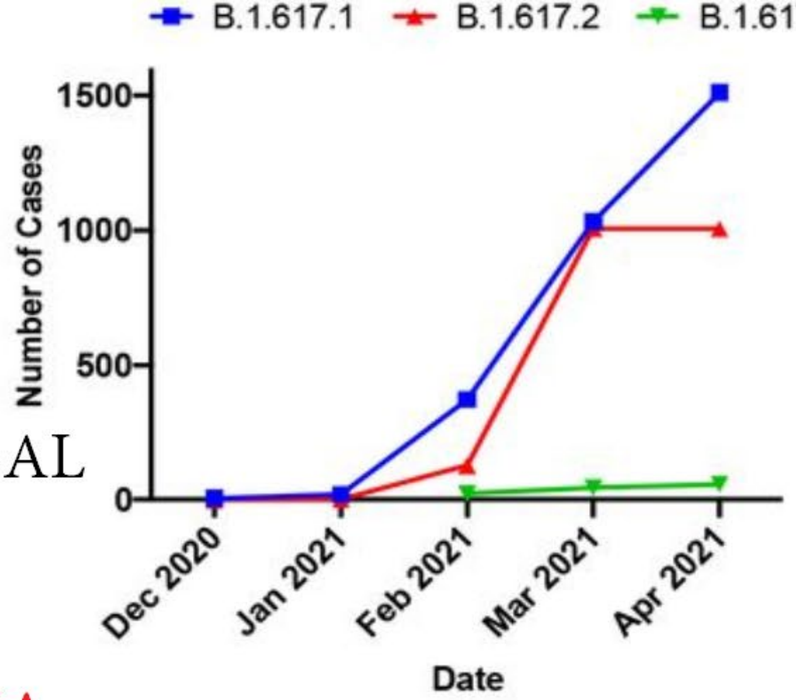
*36 of 880 lineages containing 68% of all 560,000 samples designate
†By Public Health England


CASES: Population adjusted per 100K

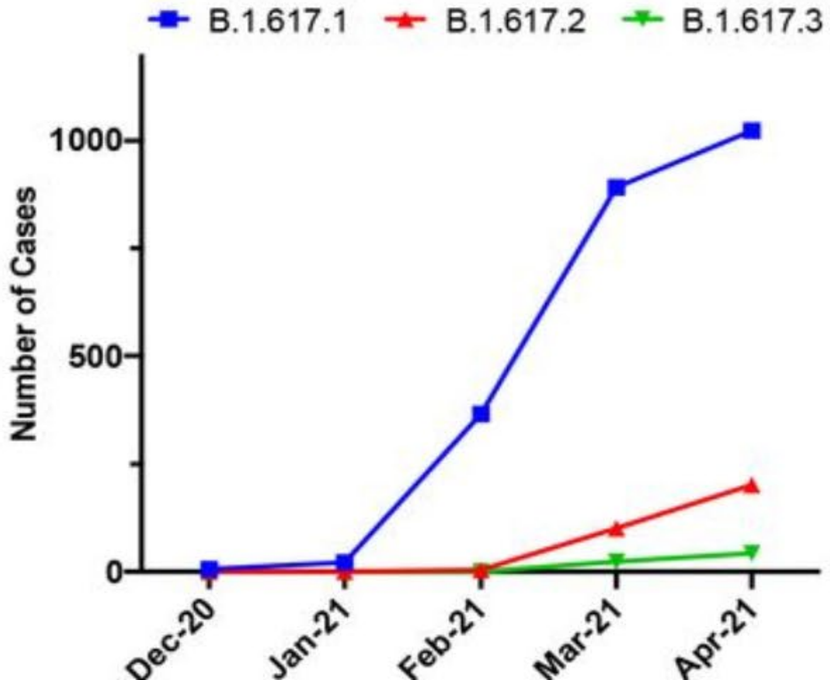
DEATHS: Population adjusted per 100K



GLOBAL

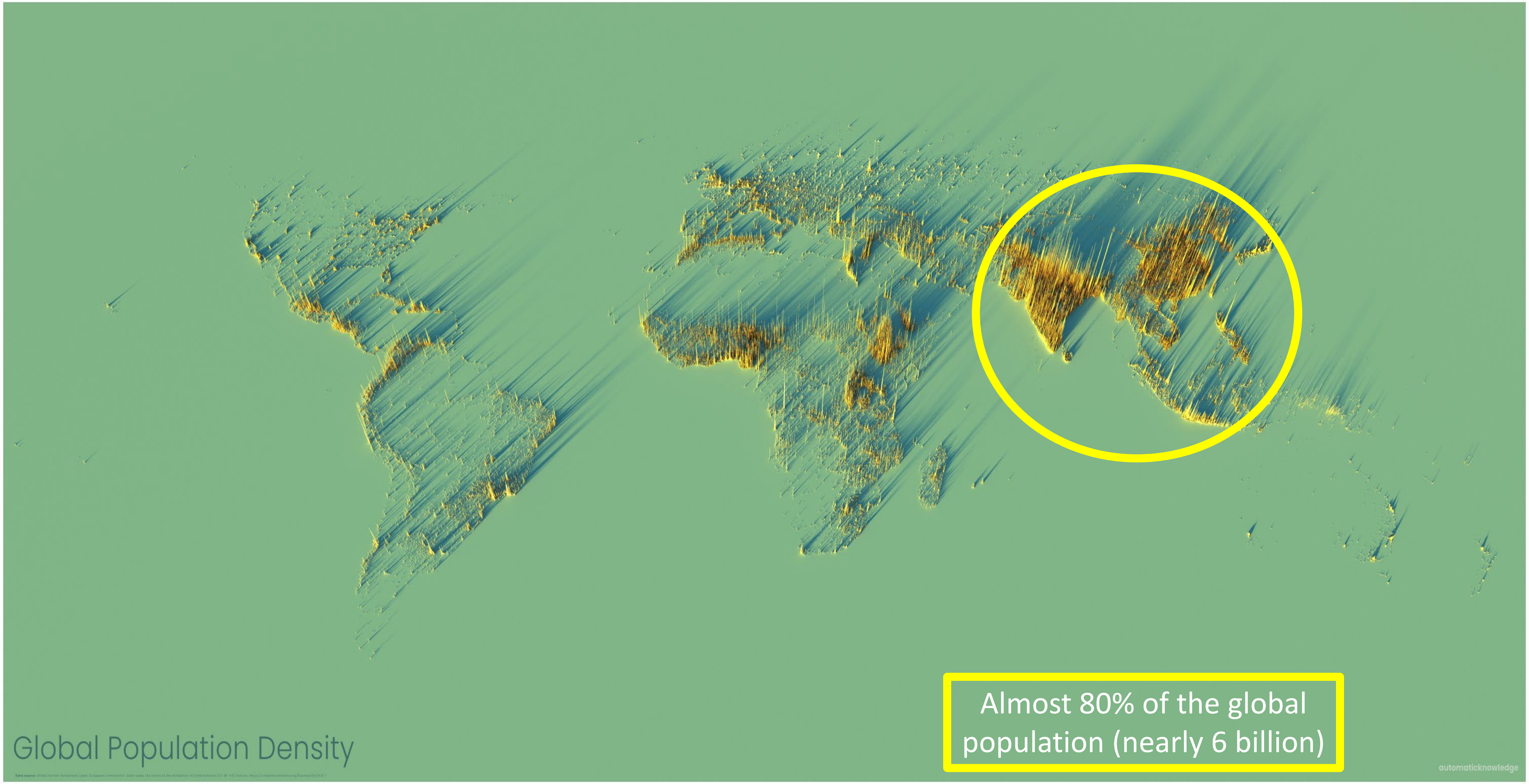


INDIA



https://www.biorxiv.org/content/10.1101/2021.05.08.443253v1.full.pdf

Can people power progress? Can India define the ethical agenda for socio-economic good for the next few centuries?


Global Population Density

Data source: Global Human Settlement Layer, European Commission. Used under the terms of the Attribution 4.0 International (CC BY 4.0) licence. https://creativecommons.org/licenses/by/4.0/

Almost 80% of the global population (nearly 6 billion)

The education of a boy may change the fate of a man. The education of a girl may change the destiny of a nation.

Playing TETRIS with CoVID-19?
Are we winning?

Yes. Thank you.

Shoumen Datta

Playing by the rules of the game ?

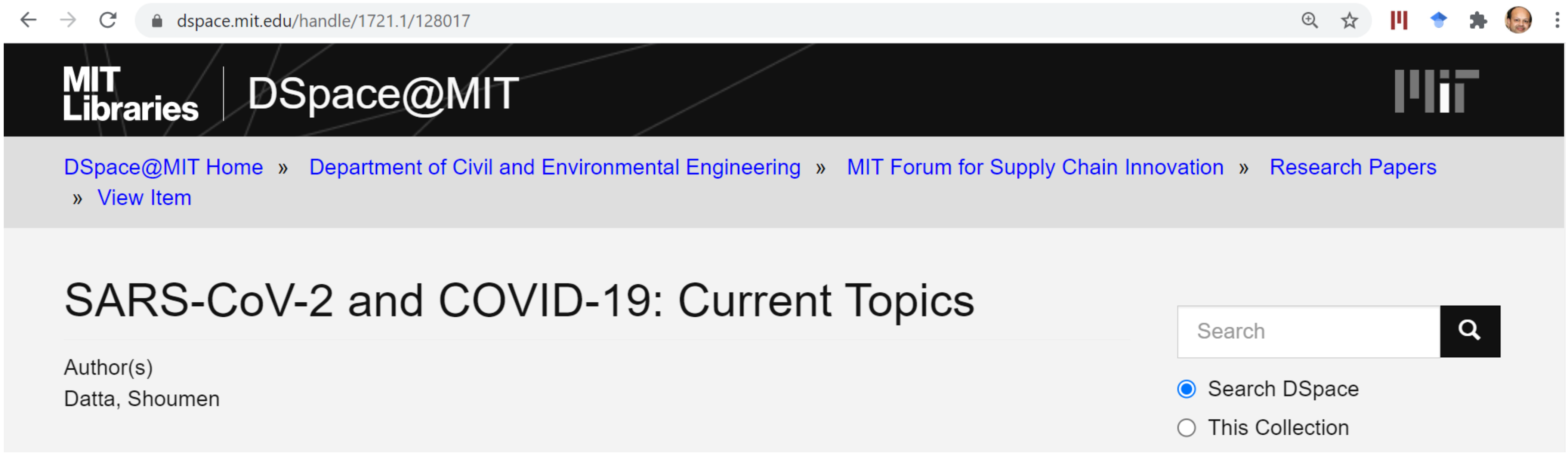
Understanding or Under-estimating SARS-CoV-2 ?

Shoumen Palit Austin Datta

21st May 2021 @ ORCHID

http://bit.ly/BIO-SD

Research Affiliate, MIT Auto ID Labs, Dept of Mechanical Engineering, MIT (shoumen@mit.edu) ▪ Senior Scientist, MDPnP Labs and Cybersecurity Program, Dept of Anesthesiology, Massachusetts General Hospital, Harvard Medical School (sdatta8@mgh.harvard.edu)



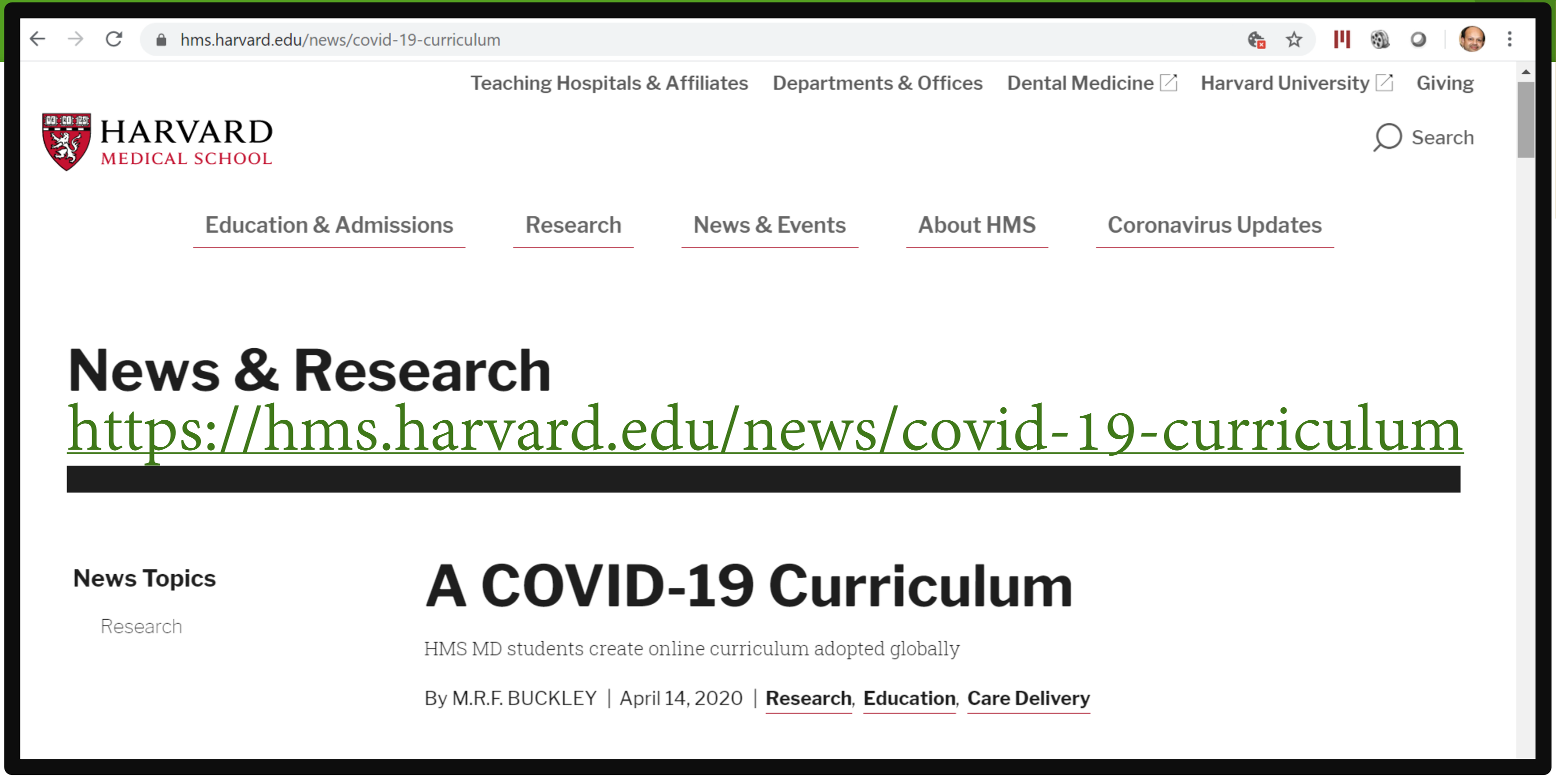
dspace.mit.edu/handle/1721.1/128017

DSpace@MIT Home » Department of Civil and Environmental Engineering » MIT Forum for Supply Chain Innovation » Research Papers » View Item

SARS-CoV-2 and COVID-19: Current Topics

Author(s)
Datta, Shoumen

References to material in this presentation are in the MIT Library ▪ https://dspace.mit.edu/handle/1721.1/128017



News & Research

https://hms.harvard.edu/news/covid-19-curriculum

News Topics

Research

A COVID-19 Curriculum

HMS MD students create online curriculum adopted globally

By M.R.F. BUCKLEY | April 14, 2020 | **Research**, **Education**, **Care Delivery**

If you have any questions:
Please email me (S. Datta)
sdatta8@mgh.harvard.edu

https://ocw.mit.edu/courses/biology/7-00-covid-19-sars-cov-2-and-the-pandemic-fall-2020/

https://ocw.mit.edu/courses/biology/

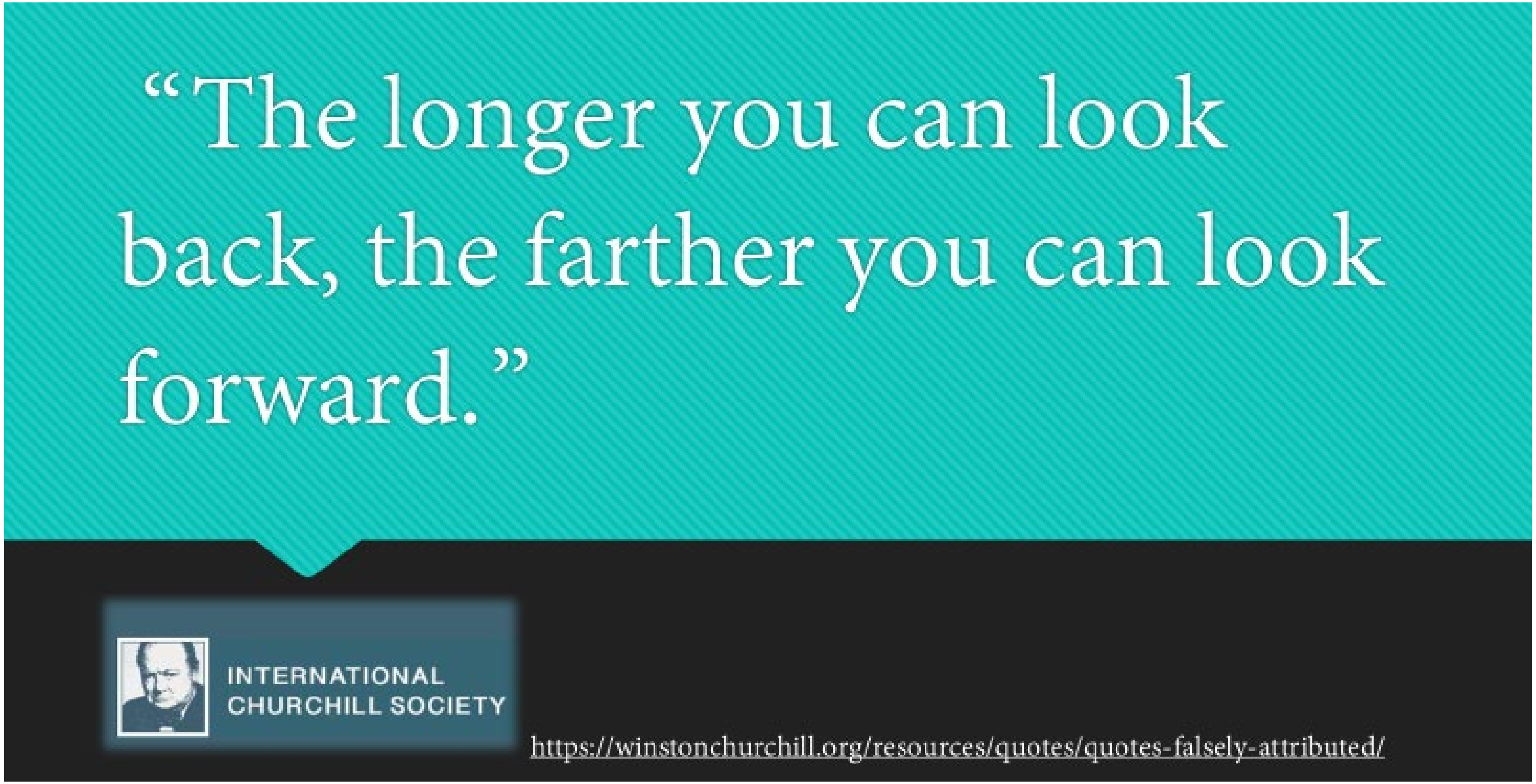
“COVID-19, SARS-CoV-2 and the Pandemic” (7.00)

If you have any questions:
Please email me (S. Datta)
shoumen@mit.edu

https://biology.mit.edu/undergraduate/current-students/subject-offerings/covid-19-sars-cov-2-and-the-pandemic/

History

History of human civilization is inextricably linked with history of science and engineering.



> "The longer you can look back, the farther you can look forward."

INTERNATIONAL
CHURCHILL SOCIETY

https://winstonchurchill.org/resources/quotes/quotes-falsely-attributed/

Princeton University Press

- Roman history might be considered the age of pandemic disease. Three times the empire was rocked by mortality events with stunning geographical reach. **In AD 165** an event known as the Antonine Plague, probably caused by smallpox, erupted. **In AD 249**, an uncertain pathogen swept the territories under Rome. **In AD 541**, the pandemic of Yersinia pestis, the agent that causes bubonic plague, arrived and **lingered for over 200 years.** To understand how the Romans lived and died, much less the fate of their empire, we must try to reconstruct the specific juncture of human civilization and disease history that the Romans encountered.

Harper, Kyle (2019) *Fate of Rome: Climate, Disease, and End of an Empire.* https://delong.typepad.com/fate-of-rome.pdf

Timeline ? of the Spanish ? Flu (1888-1922). *It wasn't just 1918-1919.*

The **1889-1890 influenza pandemic** may have originated in China (following the **1888 flooding**); Athabasca in Canada (May 1889); Greenland (summer of 1889), Tomsk in Siberia or Bukhara in Uzbekistan (October 1889). First cases appeared in St. Petersburg (Russia) on 27th October 1889 and expanded via railway to whole Europe. In Paris, 1st cases were recorded on 17th November; in Berlin and Vienna on 30th November; in London around middle of December and in southern European countries, from Italy to Portugal towards the end of December. The influenza spread overseas to America in January 1890, with the first cases appearing in Boston and New York. During the first months of the year, it spread throughout North and South America, Africa, Asia and Oceania, arriving by August 1890 to island of Madagascar, Jamaica and Santa Helena. In Paris, the first cases (17th Nov 1889) were benign but from 15th December (1889) onwards, the virus became extremely virulent and mortality rose steeply between 16 December 1889 and 31st January 1890, when over 5,042 deaths were recorded in Paris.

Bertillon J. (1892) La grippe a Paris et dans quelques autres villes de France et de l'étranger en 1889-1890. *Annuaire Statistique de la ville de Paris pour l'année 1890, 97-131*
www.numdam.org/article/JSFS_1893__34__60_0.pdf◆www.ncbi.nlm.nih.gov/pmc/articles/PMC2805838/pdf/jmgm-03-190.pdf◆https://doi.org/10.4172/1747-0862.1000033

The Spanish ? Flu Pandemic begin in France (Étaples 1916) or China (1888)?

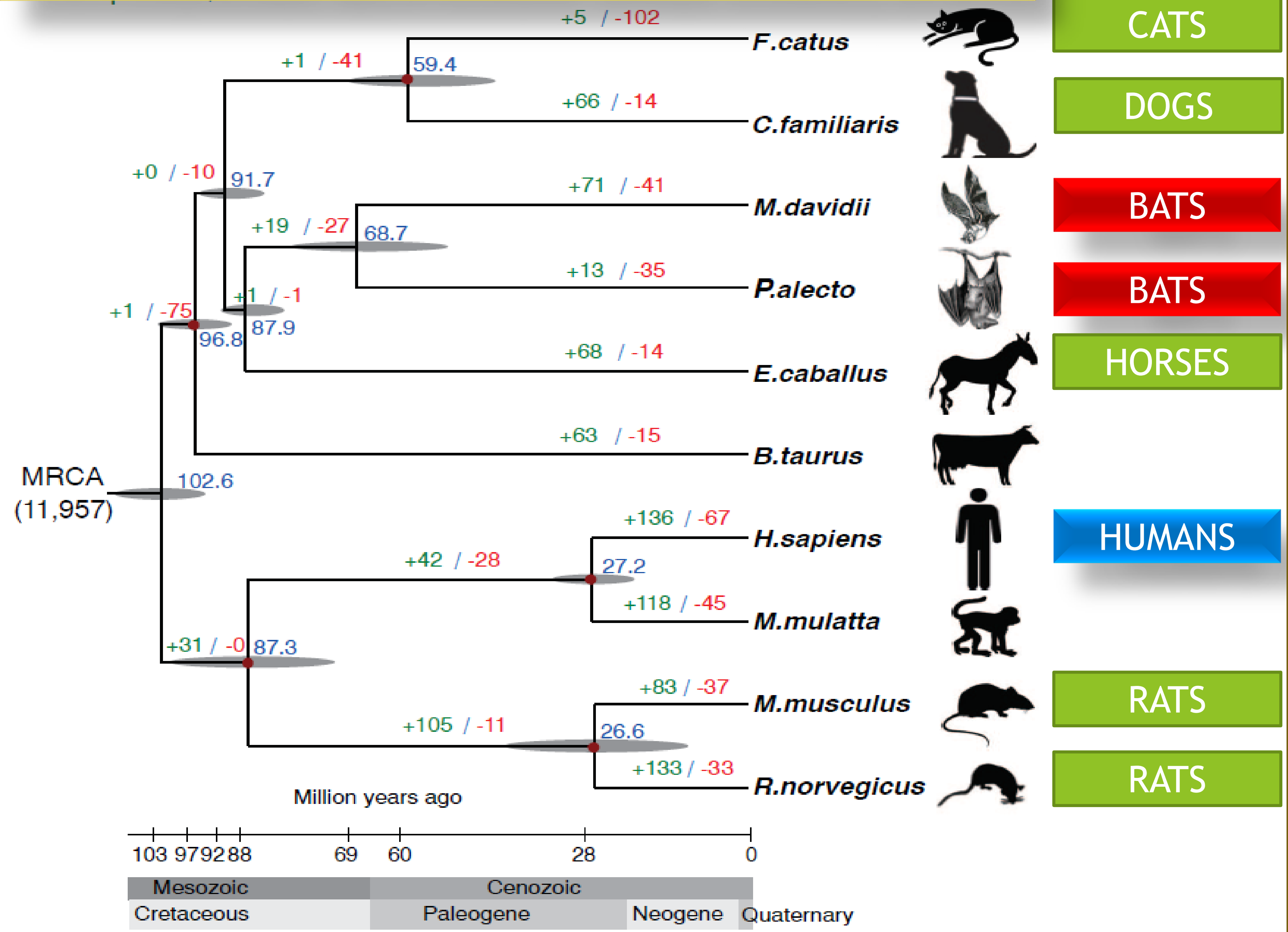
The pandemic started in the British WWI military base in **Étaples** (**1916**-1917), north of France (Dept of Pas-de-Calais). The base was occupied by 100,000 soldiers in a space of 12 sq km. It was situated near sea, with birds, **cats, dogs, rats**. Bats? Pigs, ducks and geese served as food for soldiers, and **horses** were used as a means of transport. **Mix of crowded soldiers, animals** and 24 types of **war gasses (mutagens)** might have caused the appearance of the first outbreak of the epidemic between December 1916 and March 1917. Soldiers suffered from acute respiratory infection, high temperature, and cough to confirm influenza. Clinical signs of bronchopneumonia were supported by pathology data (acute purulent bronchitis). Outbreak was clinically characterised by heliotrope cyanosis described extensively in the ensuing 1918 outbreak, with high mortality. The influenza pneumococcal purulent bronchitis described in 1916 and 1917 is the same condition as the influenza pneumonia of the **1918 influenza pandemic**.

These findings were revisited in 2002 & 2005. Did the USAID under Obama Administration pick up this in 2009?

Oxford, J.S., *et al.* (2002) World War I May Have Allowed the Emergence of 'Spanish' Influenza. *The Lancet Infectious Diseases*, vol. 2, no. 2, Feb. 2002, pp. 111–114. doi:10.1016/S1473-3099(02)00185-8

Oxford, J.S., *et al.* (2005) Hypothesis: The Conjunction of Soldiers, Gas, Pigs, Ducks, Geese and Horses in Northern France during the Great War Provided the Conditions for the Emergence of the 'Spanish' Influenza Pandemic of 1918–1919. *Vaccine*, vol. 23, no. 7, Jan. 2005, pp. 940–945. doi:10.1016/j.vaccine.2004.06.035

PHYLOGENOMIC RELATIONSHIP between ANIMALS, ÉTAPLES



Phylogenomic analysis. Maximum-likelihood phylogenomic analysis of 2492 genes from *M. davidii*, *P. alecto*, and eight mammalian species. Divergence time estimates in blue, gene family expansion events in green, and gene family contraction events in red. MRCA, most recent common ancestor.

USAID PREDICT (USA) gathered specimens from more than 10,000 bats and 2,000 other mammals. They detected about 1,200 viruses that could spread from wild animals to humans. ~160 were novel coronaviruses, much like SARS-CoV-2, as well as a new Ebola virus. How and when these viruses will infect other species ***related by phylogenomics*** is a dangerous uncertainty.

Are pandemics inevitable?

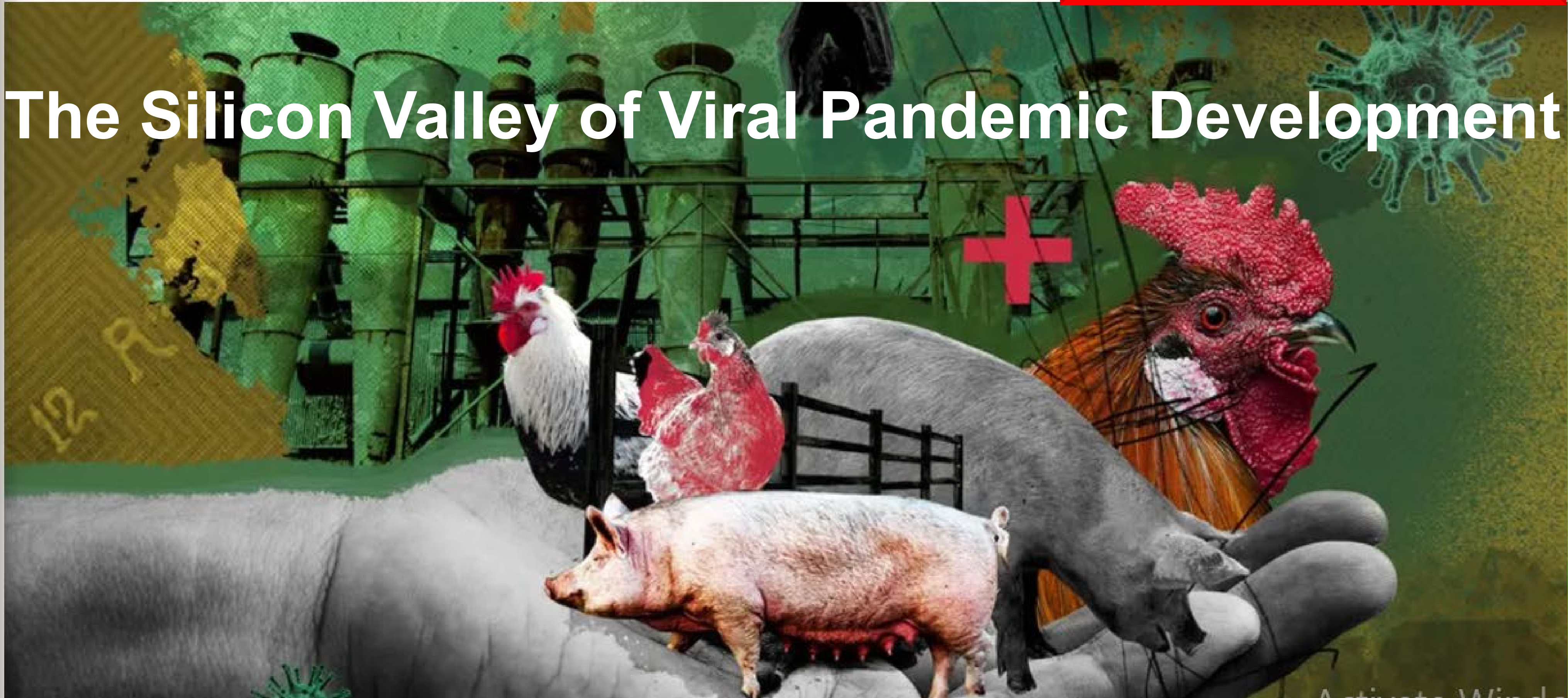
theguardian.com/commentisfree/2020/apr/20/factory-farms-pandemic-risk-covid-animal-human-health

Influenza viruses H1N1 (swine flu) and H5N1 (bird flu) evolved on pig & chicken farms. Genetics reveal that H1N1 emerged from a virus circulating in US pigs. Wet markets and the **poultry farms are the Silicon Valley of viral pandemic development.**

We have to wake up: factory farms are breeding grounds for pandemics

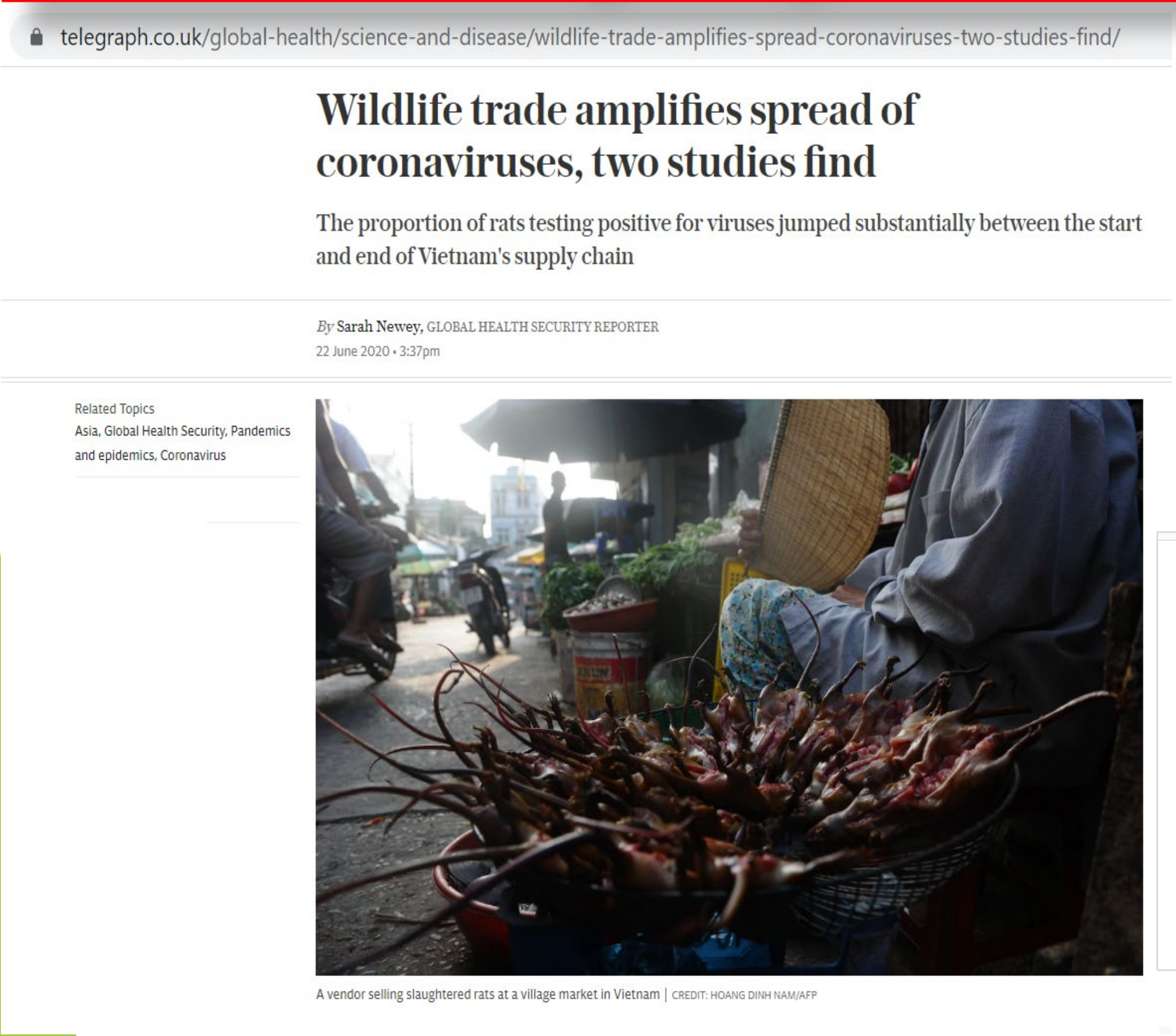
Covid-19's history is not yet fully known, but the links between animal and human health could not be clearer

- Coronavirus - latest updates
- See all our coronavirus coverage



The Silicon Valley of Viral Pandemic Development

A vendor selling slaughtered rats at a market in Viet Nam



telegraph.co.uk/global-health/science-and-disease/wildlife-trade-amplifies-spread-coronaviruses-two-studies-find/

Wildlife trade amplifies spread of coronaviruses, two studies find

The proportion of rats testing positive for viruses jumped substantially between the start and end of Vietnam's supply chain

By Sarah Newey, GLOBAL HEALTH SECURITY REPORTER

22 June 2020 • 3:37pm

Related Topics

Asia, Global Health Security, Pandemics and epidemics, Coronavirus

A vendor selling slaughtered rats at a village market in Vietnam | CREDIT: HOANG DINH NAM/AFP

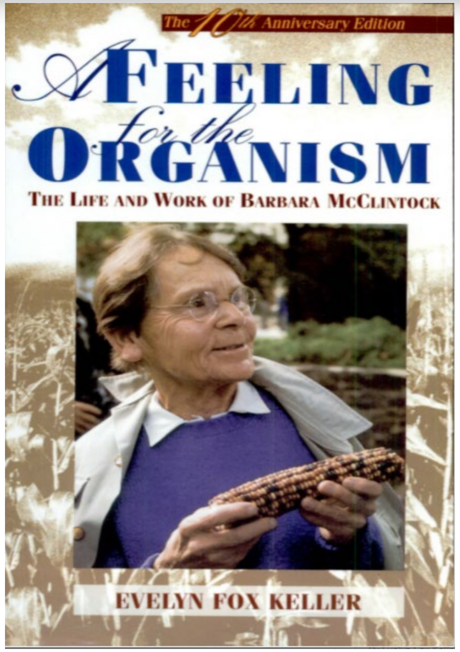
bioRxiv preprint doi: https://doi.org/10.1101/2020.06.05.098590. this version posted June 17, 2020. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Coronavirus testing indicates transmission risk increases along wildlife supply chains for human consumption in Viet Nam, 2013-2014

Nguyen Quynh Huong[1¶], Nguyen Thi Thanh Nga[1¶], Nguyen Van Long[2], Bach Duc Luu[2], Alice Latinne[1,3,4], Mathieu Pruvot[3], Nguyen Thanh Phuong[5], Le Tin Vinh Quang[5], Vo Van Hung[5],

WHY PHYLOGEMNOMIC RELATIONSHIPS MATTER?

GENES "JUMP" AND VIRUSES CAN JUMP, TOO, BETWEEN ANIMALS SHARING ANCESTRAL GENOMIC RELATIONSHIPS.



The 10th Anniversary Edition

A FEELING for the ORGANISM

THE LIFE AND WORK OF BARBARA McCLINTOCK

EVELYN FOX KELLER

Discovery of transposons in maize by **BARBARA MCCLINTOCK** made it abundantly clear that genes and segments of genes "jump" from one genome to another (displayed as variation in kernel color in the photograph). Phylogenomic ancestry supports the fact that zoonotic viruses are "jumping" (may be undetected) and can/will "jump" between species. McClintock, B. (1950) *The origin and behavior of mutable loci in maize.* Proceedings of the National Academy of Sciences USA 36(6): 344–355 https://www.pnas.org/content/pnas/36/6/344.full.pdf

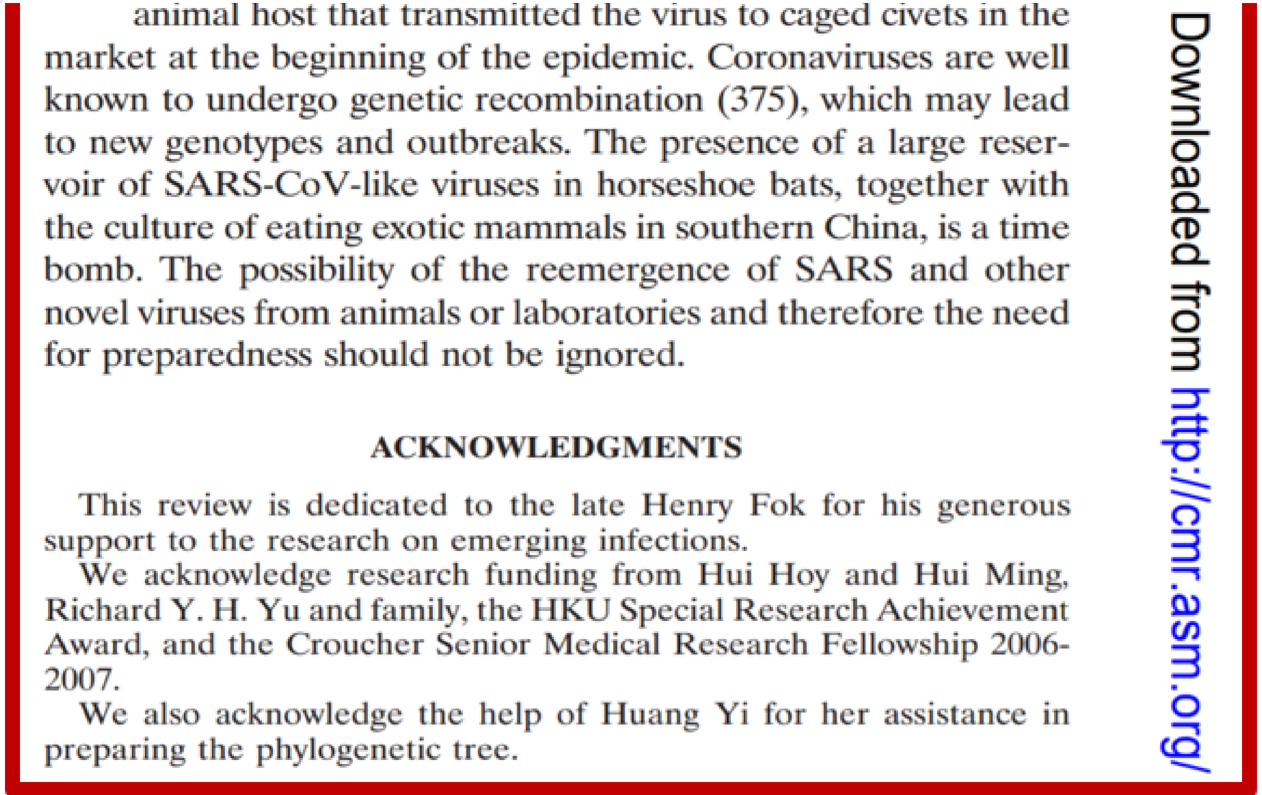
www.nobelprize.org/prizes/medicine/1983/mcclintock/facts/ ◆ www.wired.com/2012/06/happy-birthday-barbara-mcclintock/

CLINICAL MICROBIOLOGY REVIEWS, Oct. 2007, p. 660–694 Vol. 20, No. 4
0893-8512/07/$08.00+0 doi:10.1128/CMR.00023-07

Severe Acute Respiratory Syndrome Coronavirus as an Agent of Emerging and Reemerging Infection

Vincent C. C. Cheng, Susanna K. P. Lau, Patrick C. Y. Woo, and Kwok Yung Yuen*

State Key Laboratory of Emerging Infectious Diseases, Department of Microbiology, Research Centre of Infection and Immunology, The University of Hong Kong, Hong Kong Special Administrative Region, China



animal host that transmitted the virus to caged civets in the market at the beginning of the epidemic. Coronaviruses are well known to undergo genetic recombination (375), which may lead to new genotypes and outbreaks. The presence of a large reservoir of SARS-CoV-like viruses in horseshoe bats, together with the culture of eating exotic mammals in southern China, is a time bomb. The possibility of the reemergence of SARS and other novel viruses from animals or laboratories and therefore the need for preparedness should not be ignored.

ACKNOWLEDGMENTS

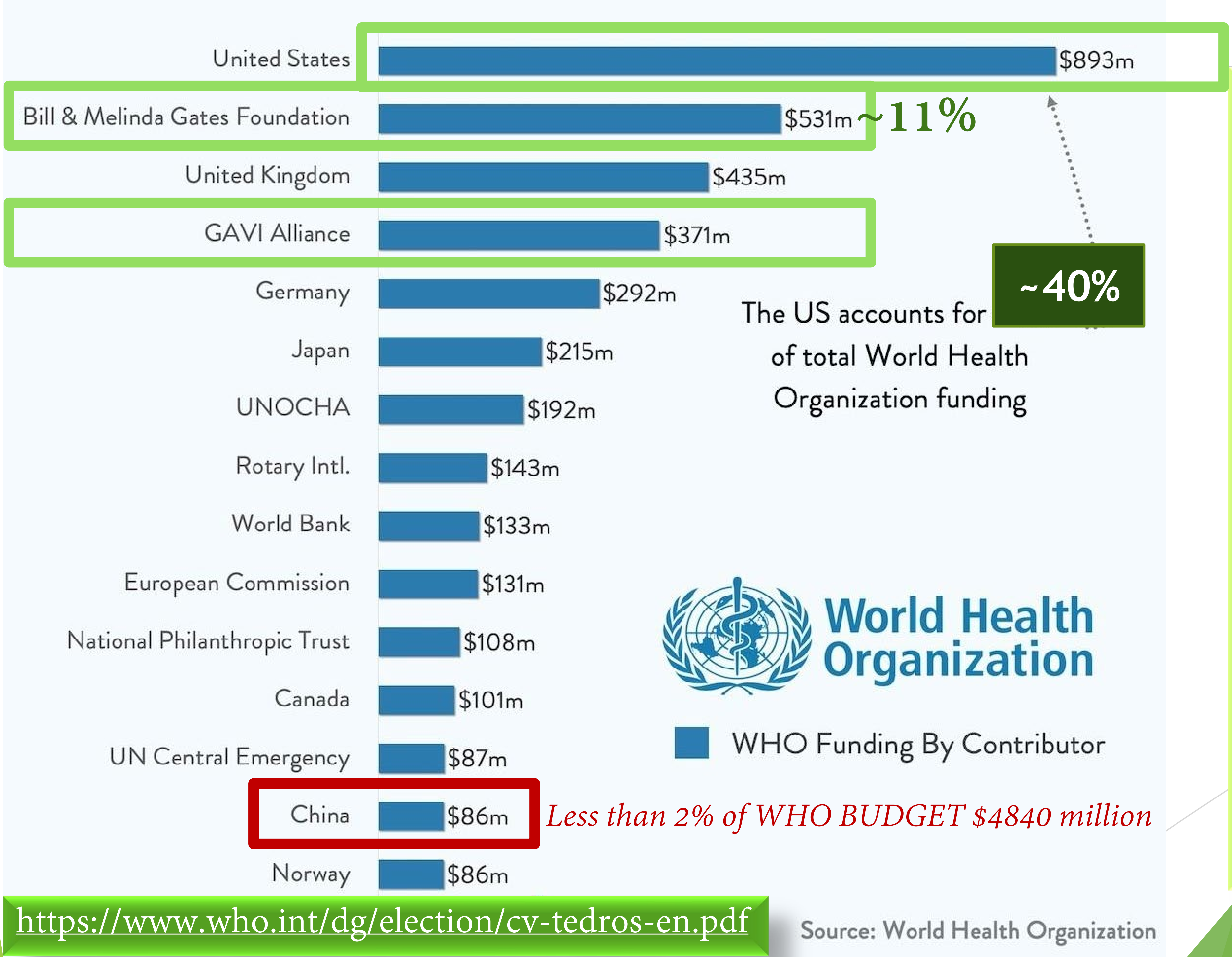
This review is dedicated to the late Henry Fok for his generous support to the research on emerging infections.

We acknowledge research funding from Hui Hoy and Hui Ming, Richard Y. H. Yu and family, the HKU Special Research Achievement Award, and the Croucher Senior Medical Research Fellowship 2006-2007.

We also acknowledge the help of Huang Yi for her assistance in preparing the phylogenetic tree.

2007
WHO IGNORED
THE WRITING
ON THE WALL

Who Funds WHO



~11%

The US accounts for ~40% of total World Health Organization funding

Less than 2% of WHO BUDGET $4840 million

Source: World Health Organization

https://www.who.int/dg/election/cv-tedros-en.pdf

https://www.who.int/about/finances-accountability/budget/WHOPB-PRP-19.pdf?ua=1

AUGUST

2009

statnews.com/2020/05/17/the-art-of-the-pandemic-how-donald-trump-walked-the-u-s-into-the-covid-19-era/

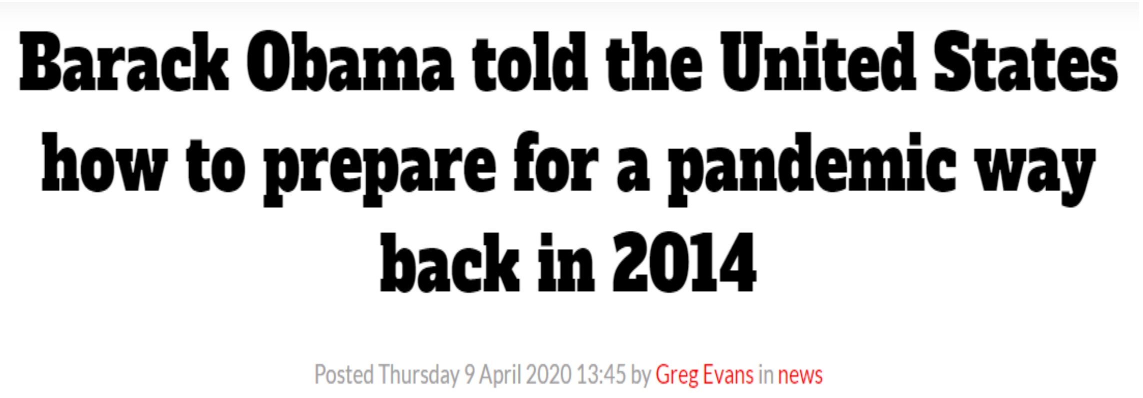
A pandemic plan was in place. Trump abandoned it — and science — in the face of Covid-19

By JASON KARLAWISH / MAY 17, 2020

President Obama met with his science advisers in August 2009 to talk about preparations for a possible swine flu pandemic.

PETE SOUZA/WIKIMEDIA COMMONS

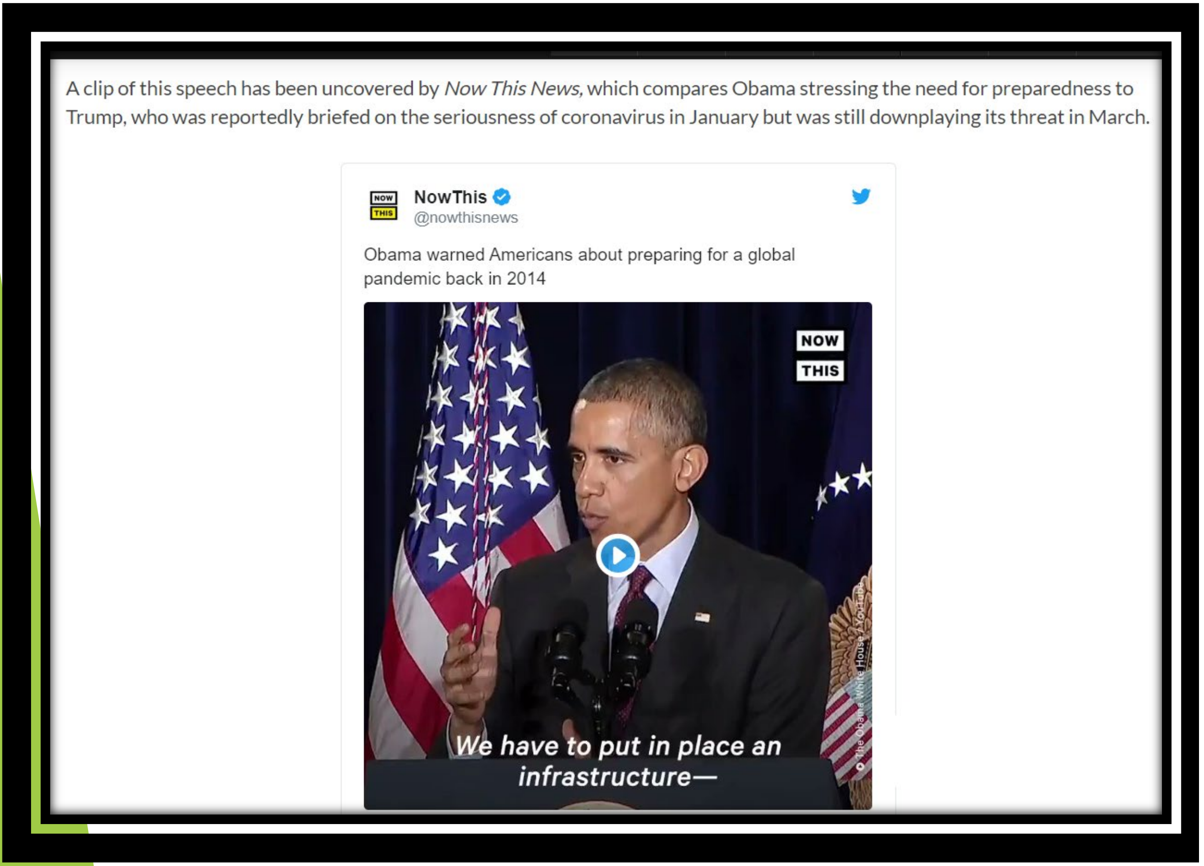
https://bit.ly/USAID-PREDICT-508



Barack Obama told the United States how to prepare for a pandemic way back in 2014

Posted Thursday 9 April 2020 13:45 by Greg Evans in news

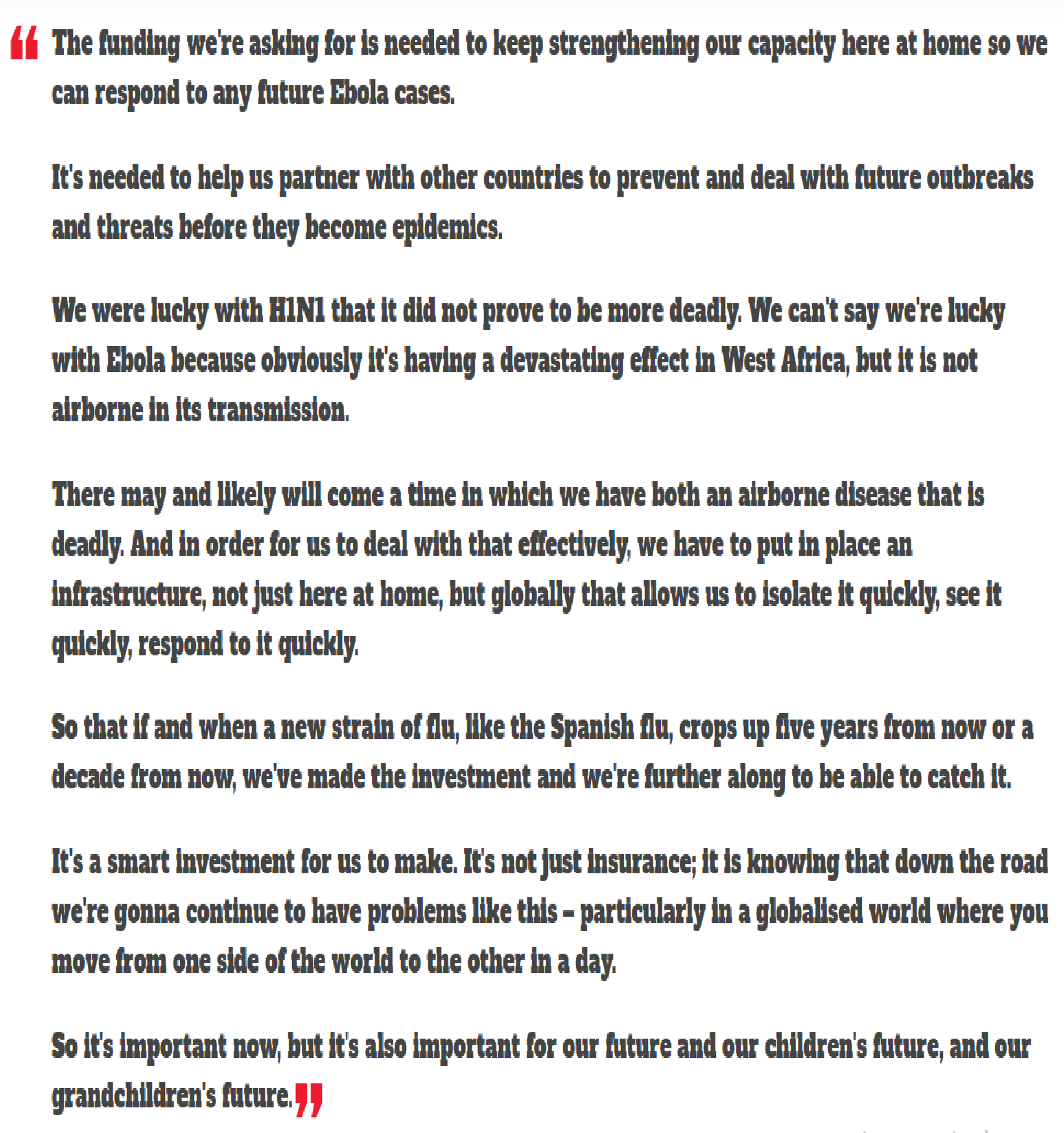
www.indy100.com/article/obama-trump-coronavirus-prepare-pandemic-2014-speech-watch-video-9457926



A clip of this speech has been uncovered by *Now This News*, which compares Obama stressing the need for preparedness to Trump, who was reportedly briefed on the seriousness of coronavirus in January but was still downplaying its threat in March.

NowThis @nowthisnews

Obama warned Americans about preparing for a global pandemic back in 2014



“The funding we're asking for is needed to keep strengthening our capacity here at home so we can respond to any future Ebola cases.

It's needed to help us partner with other countries to prevent and deal with future outbreaks and threats before they become epidemics.

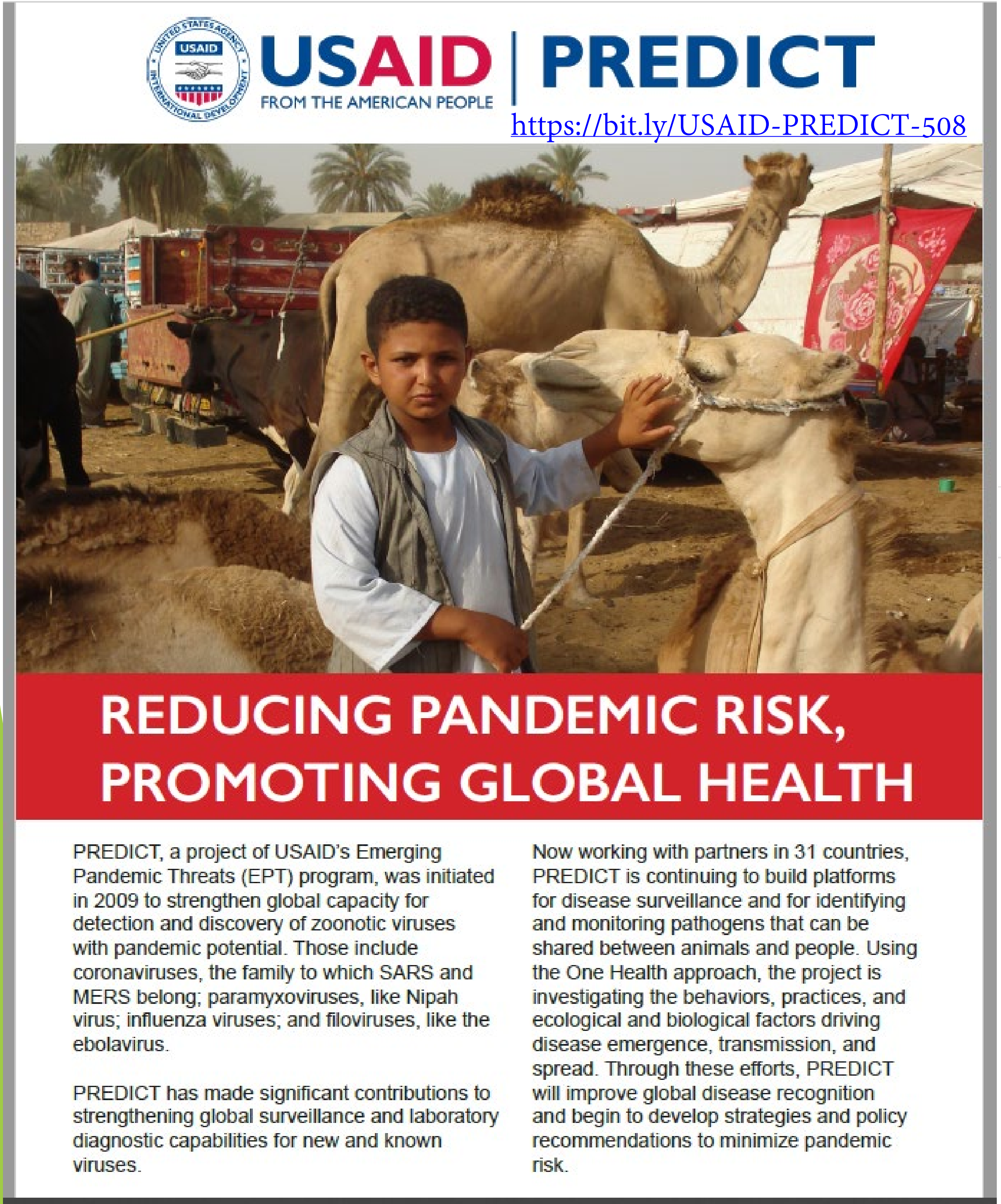
We were lucky with H1N1 that it did not prove to be more deadly. We can't say we're lucky with Ebola because obviously it's having a devastating effect in West Africa, but it is not airborne in its transmission.

There may and likely will come a time in which we have both an airborne disease that is deadly. And in order for us to deal with that effectively, we have to put in place an infrastructure, not just here at home, but globally that allows us to isolate it quickly, see it quickly, respond to it quickly.

So that if and when a new strain of flu, like the Spanish flu, crops up five years from now or a decade from now, we've made the investment and we're further along to be able to catch it.

It's a smart investment for us to make. It's not just insurance; it is knowing that down the road we're gonna continue to have problems like this – particularly in a globalised world where you move from one side of the world to the other in a day.

So it's important now, but it's also important for our future and our children's future, and our grandchildren's future.”



USAID | PREDICT
FROM THE AMERICAN PEOPLE

https://bit.ly/USAID-PREDICT-508

REDUCING PANDEMIC RISK, PROMOTING GLOBAL HEALTH

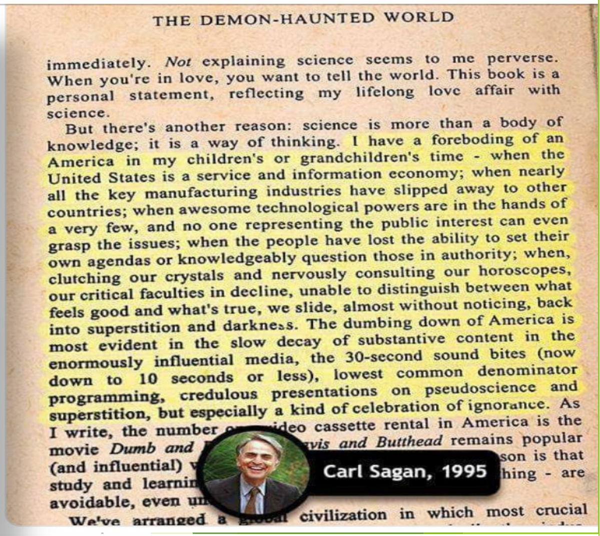
PREDICT, a project of USAID's Emerging Pandemic Threats (EPT) program, was initiated in 2009 to strengthen global capacity for detection and discovery of zoonotic viruses with pandemic potential. Those include coronaviruses, the family to which SARS and MERS belong; paramyxoviruses, like Nipah virus; influenza viruses; and filoviruses, like the ebolavirus.

PREDICT has made significant contributions to strengthening global surveillance and laboratory diagnostic capabilities for new and known viruses.

Now working with partners in 31 countries, PREDICT is continuing to build platforms for disease surveillance and for identifying and monitoring pathogens that can be shared between animals and people. Using the One Health approach, the project is investigating the behaviors, practices, and ecological and biological factors driving disease emergence, transmission, and spread. Through these efforts, PREDICT will improve global disease recognition and begin to develop strategies and policy recommendations to minimize pandemic risk.

The Demon-Haunted World
Carl Sagan, 1995

“kind of celebration of ignorance”



THE DEMON-HAUNTED WORLD

immediately. *Not* explaining science seems to me perverse. When you're in love, you want to tell the world. This book is a personal statement, reflecting my lifelong love affair with science.

But there's another reason: science is more than a body of knowledge; it is a way of thinking. I have a foreboding of an America in my children's or grandchildren's time - when the United States is a service and information economy; when nearly all the key manufacturing industries have slipped away to other countries; when awesome technological powers are in the hands of a very few, and no one representing the public interest can even grasp the issues; when the people have lost the ability to set their own agendas or knowledgeably question those in authority; when, clutching our crystals and nervously consulting our horoscopes, our critical faculties in decline, unable to distinguish between what feels good and what's true, we slide, almost without noticing, back into superstition and darkness. The dumbing down of America is most evident in the slow decay of substantive content in the enormously influential media, the 30-second sound bites (now down to 10 seconds or less), lowest common denominator programming, credulous presentations on pseudoscience and superstition, but especially a kind of celebration of ignorance. As I write, the number ideo cassette rental in America is the movie *Dumb and* *vis and Butthead* remains popular (and influential) son is that study and learnin hing - are avoidable, even u

We've arranged a civilization in which most crucial

latimes.com/science/story/2020-04-02/coronavirus-trump-pandemic-program-viruses-detection

Trump administration ended pandemic early-warning program to detect coronaviruses

By EMILY BAUMGAERTNER, JAMES RAINEY

APRIL 2, 2020 | 4:35 PM

emily.baumgaertner@latimes.com

We are drowning in data, inundated with information, but do we know which specific knowledge is of what value, when, for humanity?

Data is not information. Information does not create knowledge. Knowledge does not guarantee wisdom.

https://twitter.com/JReinerMD/status/1246236090249478145/photo/1

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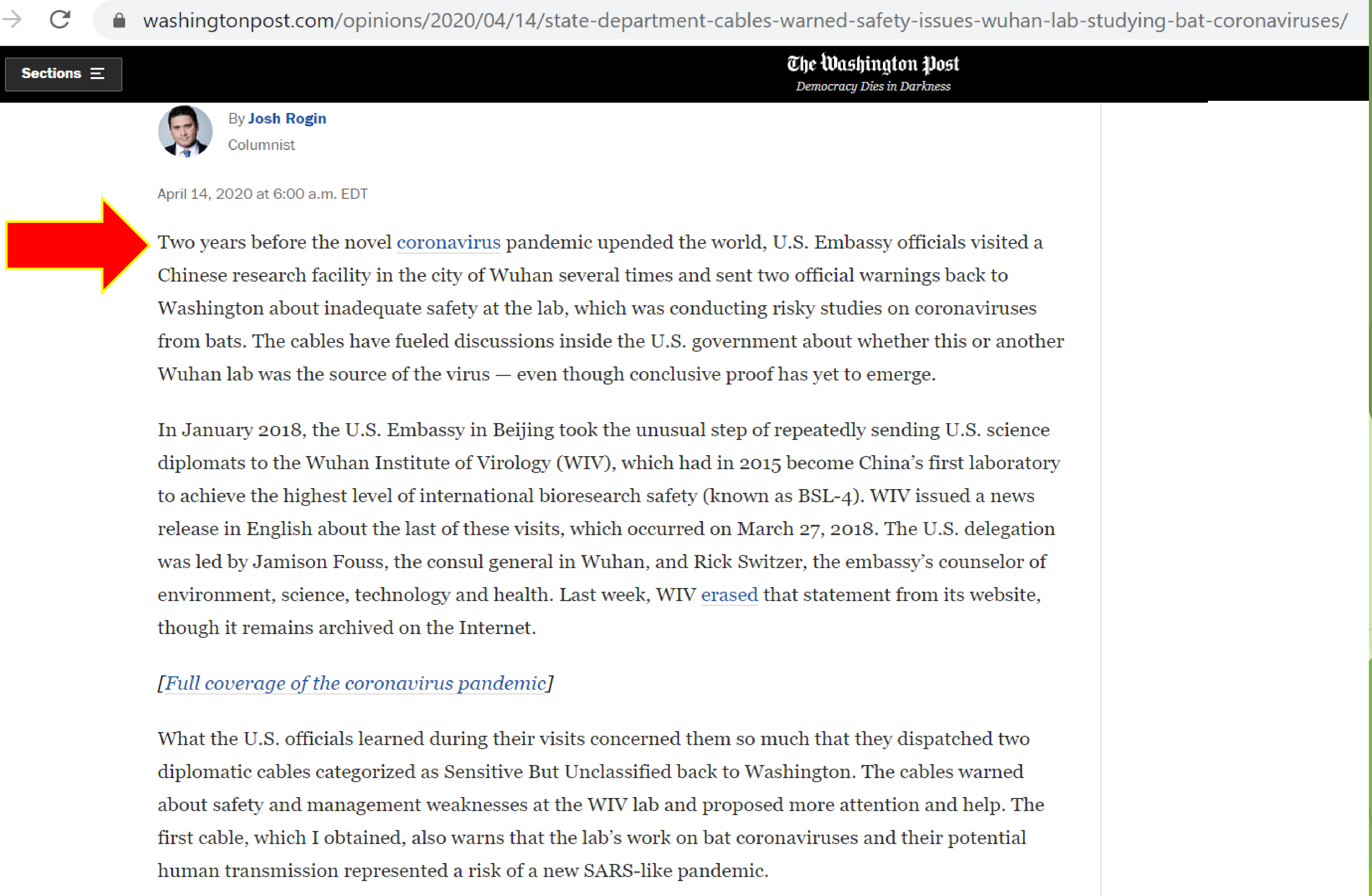

By **Josh Rogin**
Columnist

April 14, 2020 at 6:00 a.m. EDT

Two years before the novel coronavirus pandemic upended the world, U.S. Embassy officials visited a Chinese research facility in the city of Wuhan several times and sent two official warnings back to Washington about inadequate safety at the lab, which was conducting risky studies on coronaviruses from bats. The cables have fueled discussions inside the U.S. government about whether this or another Wuhan lab was the source of the virus — even though conclusive proof has yet to emerge.

In January 2018, the U.S. Embassy in Beijing took the unusual step of repeatedly sending U.S. science diplomats to the Wuhan Institute of Virology (WIV), which had in 2015 become China's first laboratory to achieve the highest level of international bioresearch safety (known as BSL-4). WIV issued a news release in English about the last of these visits, which occurred on March 27, 2018. The U.S. delegation was led by Jamison Fouss, the consul general in Wuhan, and Rick Switzer, the embassy's counselor of environment, science, technology and health. Last week, WIV erased that statement from its website, though it remains archived on the Internet.

[Full coverage of the coronavirus pandemic]

What the U.S. officials learned during their visits concerned them so much that they dispatched two diplomatic cables categorized as Sensitive But Unclassified back to Washington. The cables warned about safety and management weaknesses at the WIV lab and proposed more attention and help. The first cable, which I obtained, also warns that the lab's work on bat coronaviruses and their potential human transmission represented a risk of a new SARS-like pandemic.

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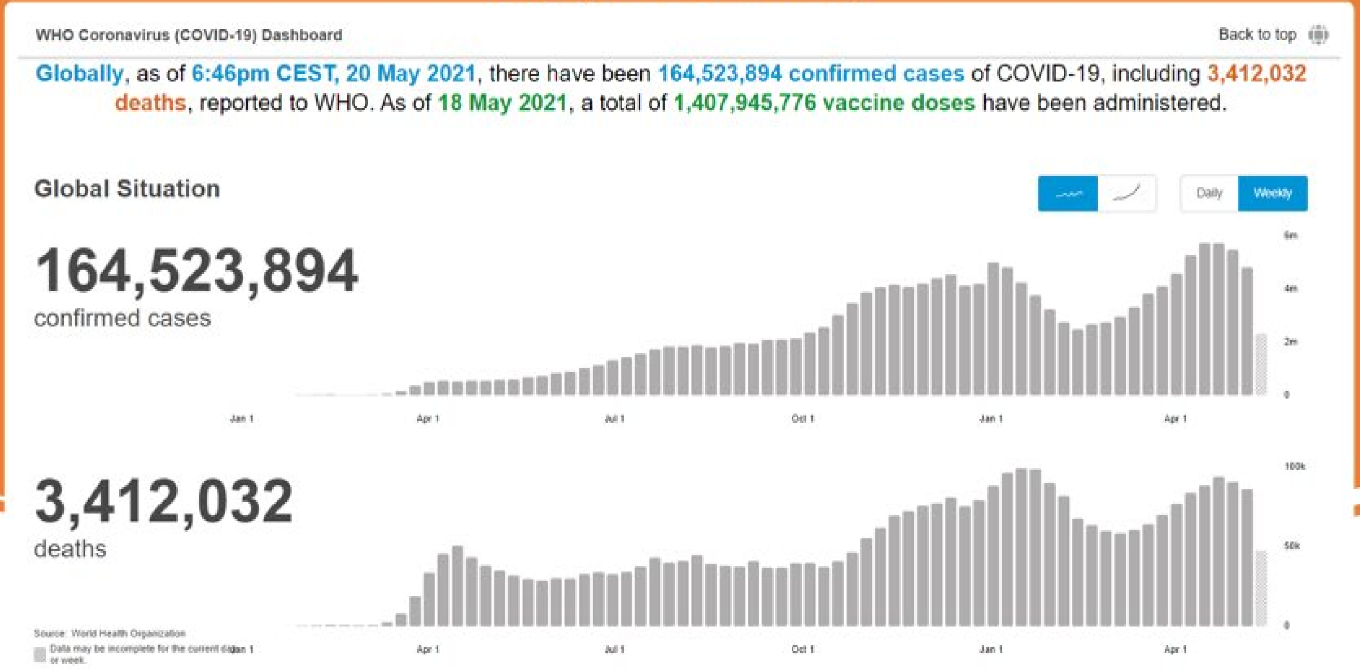
	Emergence	Cases	Fatality Rate	Transmissibility
SARS	2003	8,098	11%	+
MERS	2011	2,519	34%	+
SARS-CoV-2	2019	➢ 200 million	0.5-1% Est	+++
SARS-CoV-3?	??	??	??	??
SARS-CoV-4?	??	??	??	??

https://covid19.who.int/



WHO Coronavirus (COVID-19) Dashboard

Globally, as of 6:46pm CEST, 20 May 2021, there have been 164,523,894 confirmed cases of COVID-19, including 3,412,032 deaths, reported to WHO. As of 18 May 2021, a total of 1,407,945,776 vaccine doses have been administered.

Global Situation

164,523,894
confirmed cases

3,412,032
deaths

Source: World Health Organization

Data may be incomplete for the current day or week.

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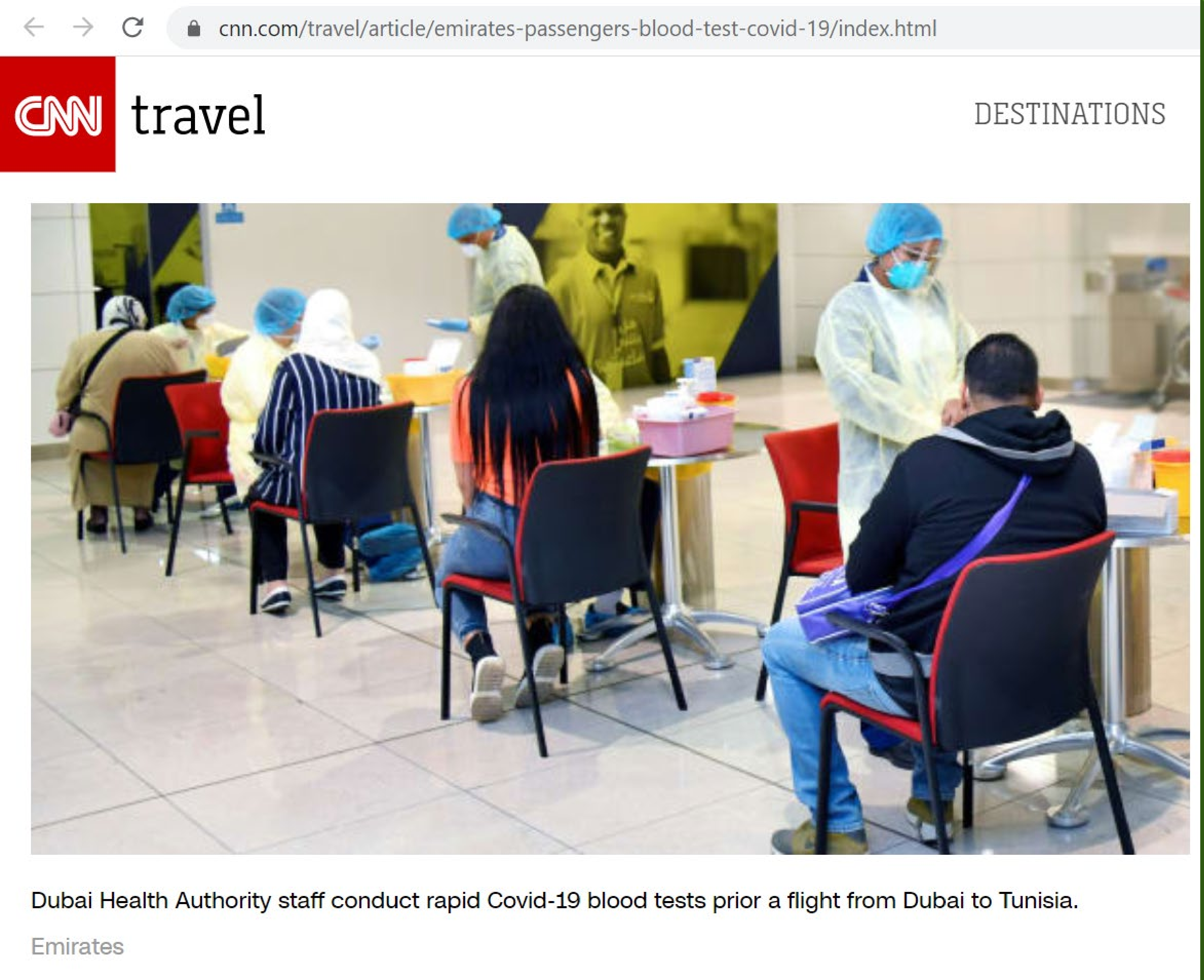
Life, Style and Lifestyle Changes

Is a post-Pandemic world a threat to democracy?

Gandhi's Salt March to Dandi – Postcolonial Studies



cnn.com/travel/article/emirates-passengers-blood-test-covid-19/index.html

Dubai Health Authority staff conduct rapid Covid-19 blood tests prior a flight from Dubai to Tunisia.

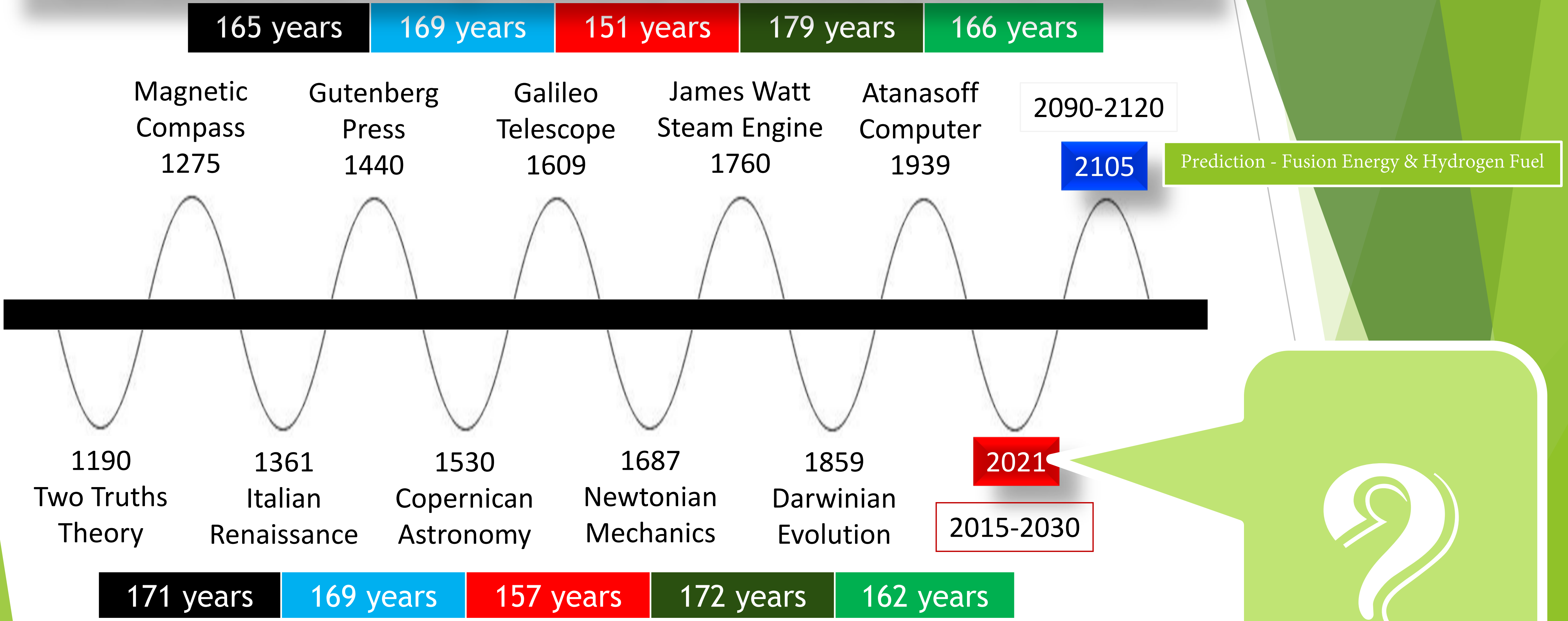
Emirates

(CNN) — Perhaps a sign of what the future holds for air travelers, Dubai-based airline Emirates has begun carrying out Covid-19 blood tests on passengers at the airport prior to flights.

According to a statement released by the airline, the first rapid Covid-19 blood tests took place on Wednesday at Dubai International Airport, with passengers on a flight to Tunisia all reportedly tested before departure. The tests were conducted by the Dubai Health Authority in Terminal 3 and results were available within 10 minutes. Emirates claims to be the world's first airline to conduct such tests.

"We are working on plans to scale up testing capabilities in the future and extend it to other flights," said Adel Al Redha, Emirates Chief Operating Officer, in the statement. "This will enable us to conduct on-site tests and provide immediate confirmation for Emirates passengers traveling to countries that require COVID-19 test certificates."

Continuious Imagination, Invention, Innovation



165 years | 169 years | 151 years | 179 years | 166 years

Magnetic Compass 1275

Gutenberg Press 1440

Galileo Telescope 1609

James Watt Steam Engine 1760

Atanasoff Computer 1939

2090-2120

2105

Prediction - Fusion Energy & Hydrogen Fuel

1190 Two Truths Theory

1361 Italian Renaissance

1530 Copernican Astronomy

1687 Newtonian Mechanics

1859 Darwinian Evolution

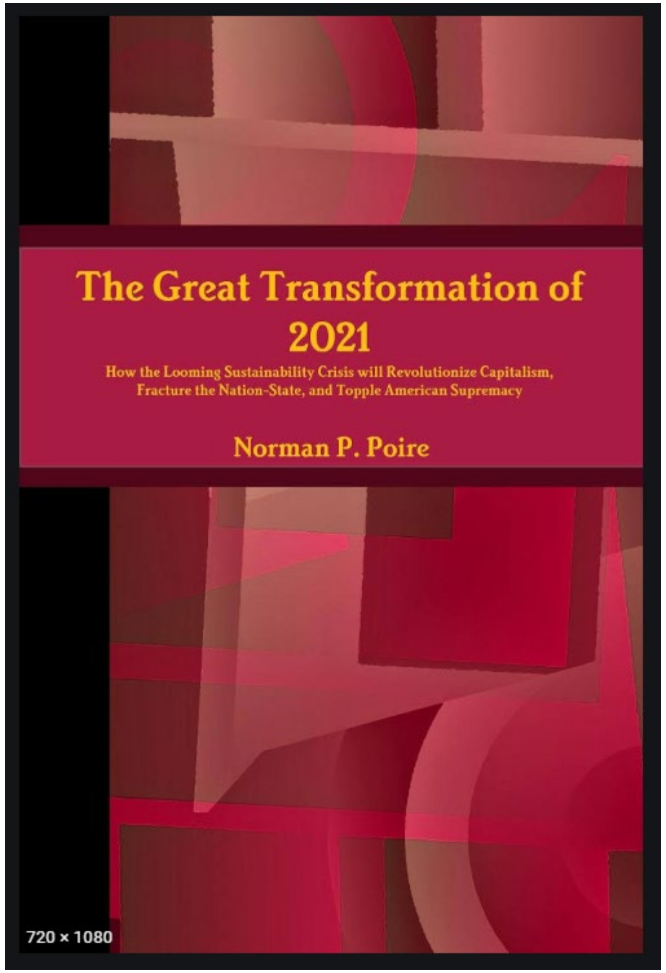
2021

2015-2030

171 years | 169 years | 157 years | 172 years | 162 years

Continuous Ideological Changes and Social Shifts

Adapted from Norman Poire and loosely based on Kondratieff Waves

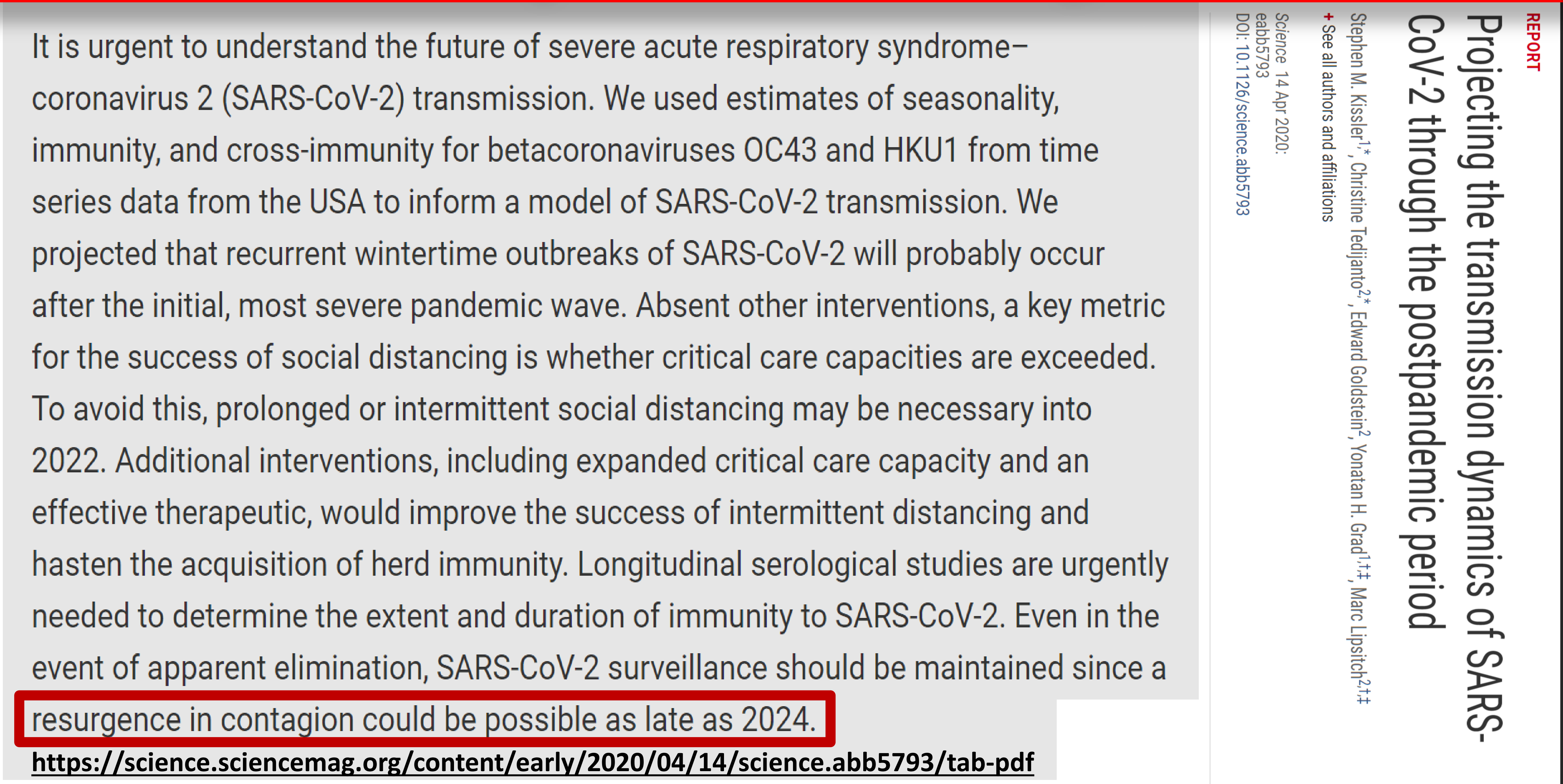


The Great Transformation of 2021

How the Looming Sustainability Crisis will Revolutionize Capitalism, Fracture the Nation-State, and Topple American Supremacy

Norman P. Poire

Pandemic is a partner through 2024-2025



REPORT

Projecting the transmission dynamics of SARS-CoV-2 through the postpandemic period

Stephen M. Kissler[1,*], Christine Tedijanto[2,*], Edward Goldstein[2], Yonatan H. Grad[1,†,‡], Marc Lipsitch[2,†,‡]

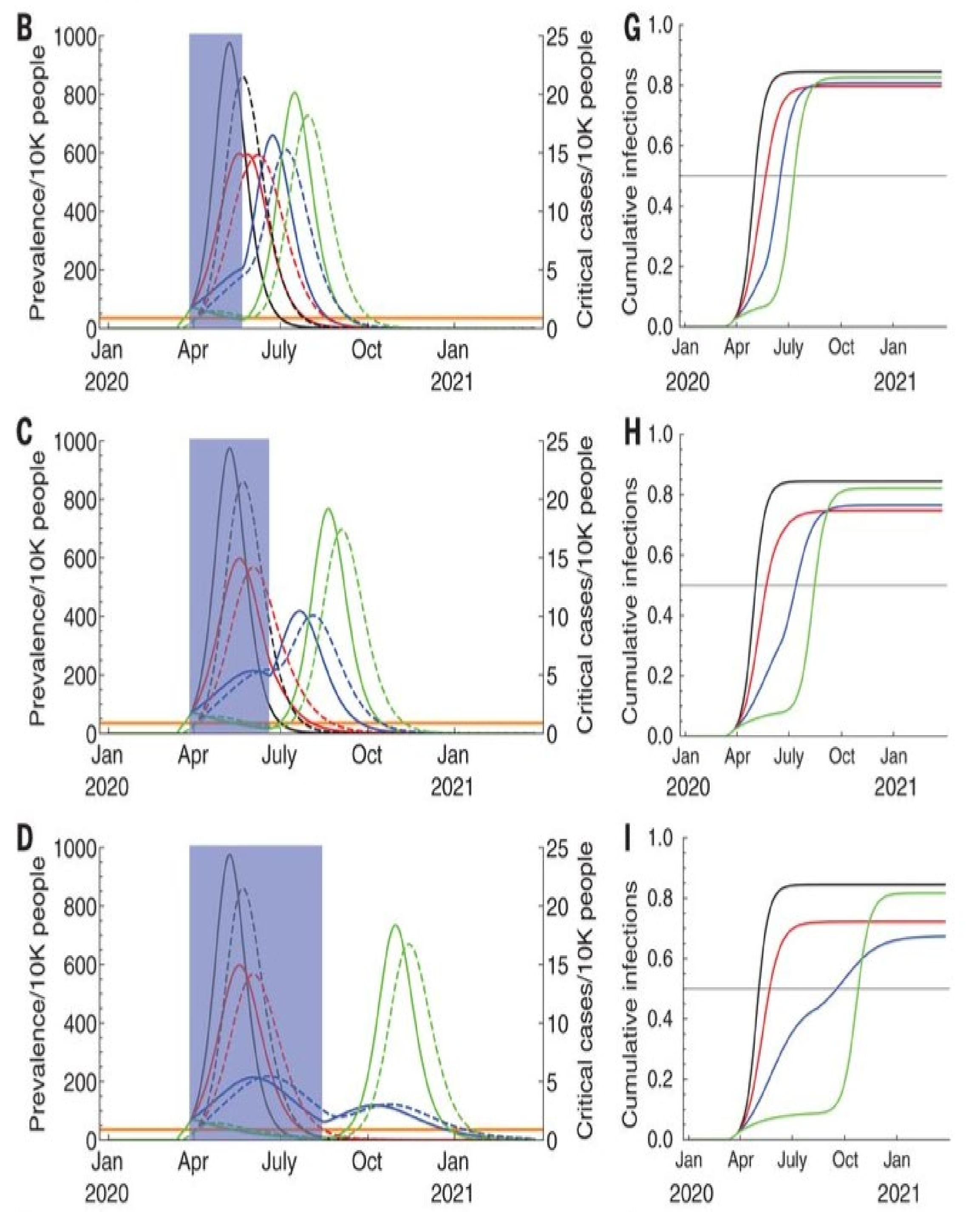
+ See all authors and affiliations

Science 14 Apr 2020:
eabb5793
DOI: 10.1126/science.abb5793

It is urgent to understand the future of severe acute respiratory syndrome–coronavirus 2 (SARS-CoV-2) transmission. We used estimates of seasonality, immunity, and cross-immunity for betacoronaviruses OC43 and HKU1 from time series data from the USA to inform a model of SARS-CoV-2 transmission. We projected that recurrent wintertime outbreaks of SARS-CoV-2 will probably occur after the initial, most severe pandemic wave. Absent other interventions, a key metric for the success of social distancing is whether critical care capacities are exceeded. To avoid this, prolonged or intermittent social distancing may be necessary into 2022. Additional interventions, including expanded critical care capacity and an effective therapeutic, would improve the success of intermittent distancing and hasten the acquisition of herd immunity. Longitudinal serological studies are urgently needed to determine the extent and duration of immunity to SARS-CoV-2. Even in the event of apparent elimination, SARS-CoV-2 surveillance should be maintained since a resurgence in contagion could be possible as late as 2024.

https://science.sciencemag.org/content/early/2020/04/14/science.abb5793/tab-pdf

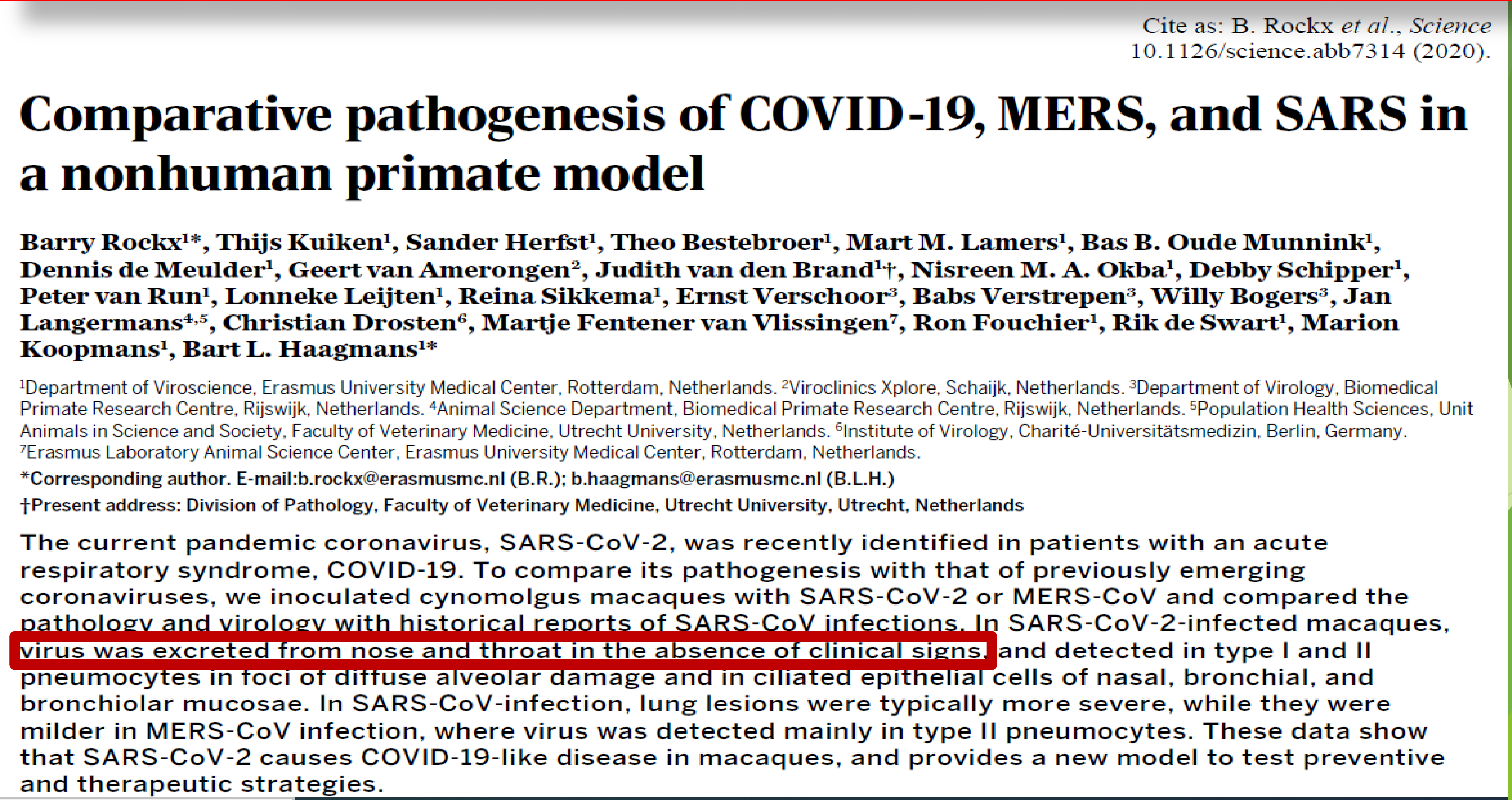
Intermittent distancing may be required into 2022 unless critical care capacity is increased substantially or a treatment or vaccine becomes available. Resurgence in contagion could be possible as late as 2024. Kissler et al. used existing data to build US models of multiyear interactions between existing coronaviruses, to project the potential epidemic dynamics and pressures on critical care capacity over the next 5 years. The long-term dynamics of SARS-CoV-2 strongly depends on immune responses and immune cross-reactions between the coronaviruses, as well as the timing of introduction of the new virus into a population. One scenario is that a resurgence in SARS-CoV-2 could occur as far into the future as 2025.
SOURCE: Projecting the transmission dynamics of SARS-CoV-2 through the postpandemic period.
Stephen M. Kissler, Christine Tedijanto, Edward Goldstein, Yonatan H. Grad, Marc Lipsitch. Harvard T.H. Chan School of Public Health, Boston. DOI: 10.1126/science.abb5793
Eml: mlipsitc@hsph.harvard.edu; ygrad@hsph.harvard.edu
Published: Science 22 May 2020: Vol. 368, pp. 860-868.
https://science.sciencemag.org/content/368/6493/860



Pandemic is a partner through 2024-2025

WHY ?

WHY ~ 50 days of separation / distancing may be crucial for our safety "virus was excreted from nose and throat in the absence of clinical signs"



Cite as: B. Rockx *et al.*, *Science*
10.1126/science.abb7314 (2020).

Comparative pathogenesis of COVID-19, MERS, and SARS in a nonhuman primate model

Barry Rockx[1]*, Thijs Kuiken[1], Sander Herfst[1], Theo Bestebroer[1], Mart M. Lamers[1], Bas B. Oude Munnink[1], Dennis de Meulder[1], Geert van Amerongen[2], Judith van den Brand[1]†, Nisreen M. A. Okba[1], Debby Schipper[1], Peter van Run[1], Lonneke Leijten[1], Reina Sikkema[1], Ernst Verschoor[3], Babs Verstrepen[3], Willy Bogers[3], Jan Langermans[4,5], Christian Drosten[6], Martje Fentener van Vlissingen[7], Ron Fouchier[1], Rik de Swart[1], Marion Koopmans[1], Bart L. Haagmans[1]*

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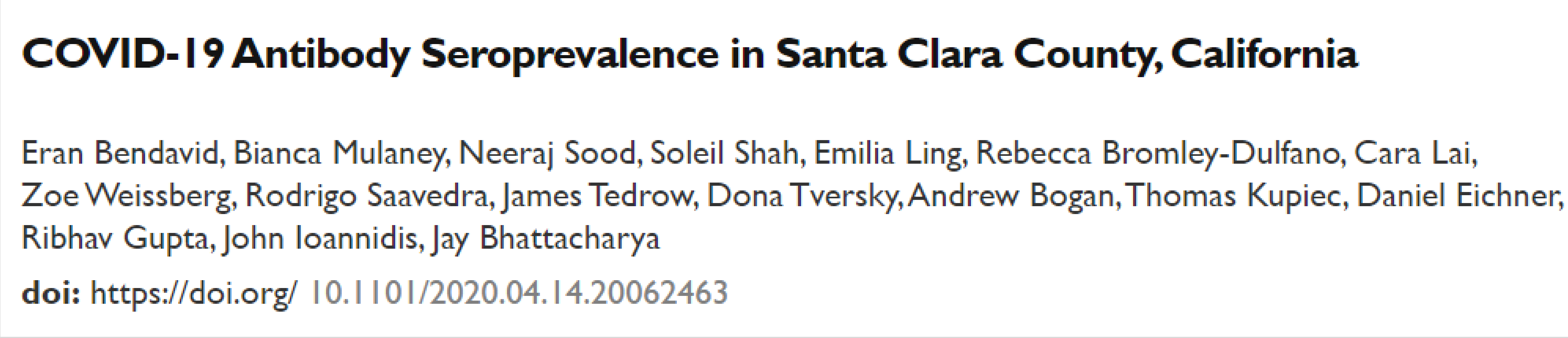
The current pandemic coronavirus, SARS-CoV-2, was recently identified in patients with an acute respiratory syndrome, COVID-19. To compare its pathogenesis with that of previously emerging coronaviruses, we inoculated cynomolgus macaques with SARS-CoV-2 or MERS-CoV and compared the pathology and virology with historical reports of SARS-CoV infections. In SARS-CoV-2-infected macaques, virus was excreted from nose and throat in the absence of clinical signs, and detected in type I and II pneumocytes in foci of diffuse alveolar damage and in ciliated epithelial cells of nasal, bronchial, and bronchiolar mucosae. In SARS-CoV-infection, lung lesions were typically more severe, while they were milder in MERS-CoV infection, where virus was detected mainly in type II pneumocytes. These data show that SARS-CoV-2 causes COVID-19-like disease in macaques, and provides a new model to test preventive and therapeutic strategies.

https://science.sciencemag.org/content/early/2020/04/16/science.abb7314/tab-pdf
www.medrxiv.org/content/10.1101/2020.03.15.20036707v2
https://arxiv.org/pdf/2003.12055.pdf
www.medrxiv.org/content/10.1101/2020.03.22.20040071v1

Number of people infected by COVID-19 may be 50-80 times higher than official count, Stanford study.

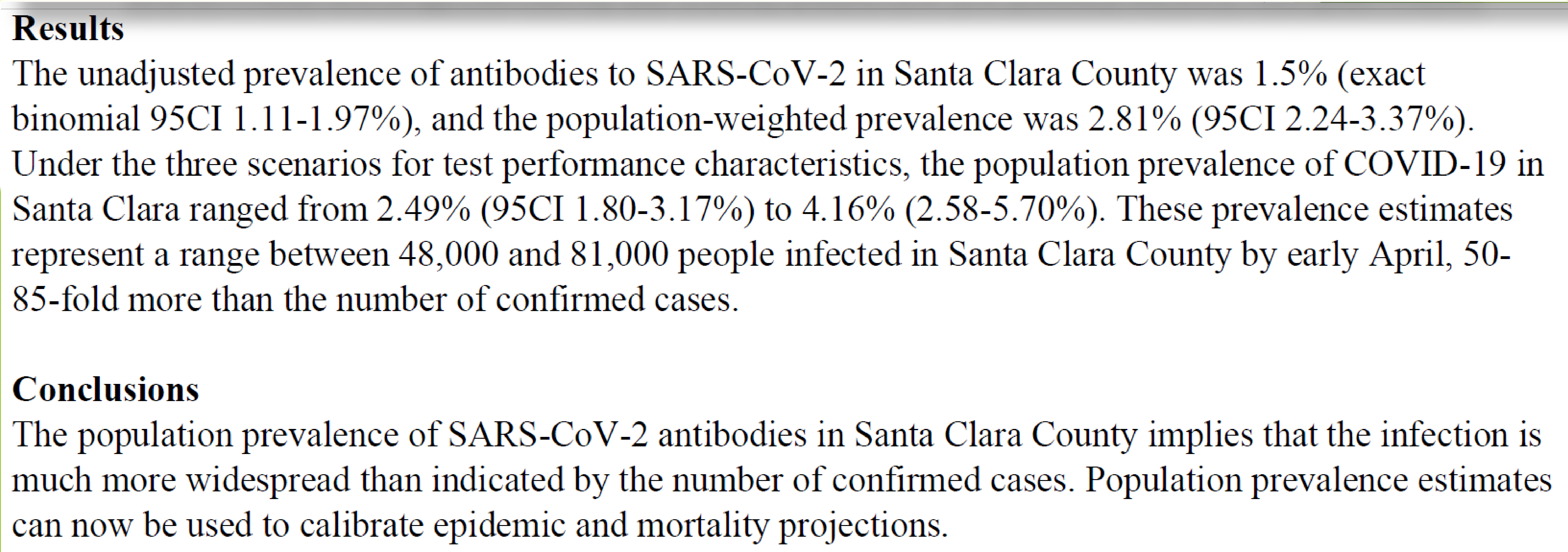


COVID-19 Antibody Seroprevalence in Santa Clara County, California

Eran Bendavid, Bianca Mulaney, Neeraj Sood, Soleil Shah, Emilia Ling, Rebecca Bromley-Dulfano, Cara Lai, Zoe Weissberg, Rodrigo Saavedra, James Tedrow, Dona Tversky, Andrew Bogan, Thomas Kupiec, Daniel Eichner, Ribhav Gupta, John Ioannidis, Jay Bhattacharya

doi: https://doi.org/ 10.1101/2020.04.14.20062463

www.medrxiv.org/content/10.1101/2020.04.14.20062463v1.full.pdf+html



Results

The unadjusted prevalence of antibodies to SARS-CoV-2 in Santa Clara County was 1.5% (exact binomial 95CI 1.11-1.97%), and the population-weighted prevalence was 2.81% (95CI 2.24-3.37%). Under the three scenarios for test performance characteristics, the population prevalence of COVID-19 in Santa Clara ranged from 2.49% (95CI 1.80-3.17%) to 4.16% (2.58-5.70%). These prevalence estimates represent a range between 48,000 and 81,000 people infected in Santa Clara County by early April, 50-85-fold more than the number of confirmed cases.

Conclusions

The population prevalence of SARS-CoV-2 antibodies in Santa Clara County implies that the infection is much more widespread than indicated by the number of confirmed cases. Population prevalence estimates can now be used to calibrate epidemic and mortality projections.

TEST

Control Infection

TETRIS

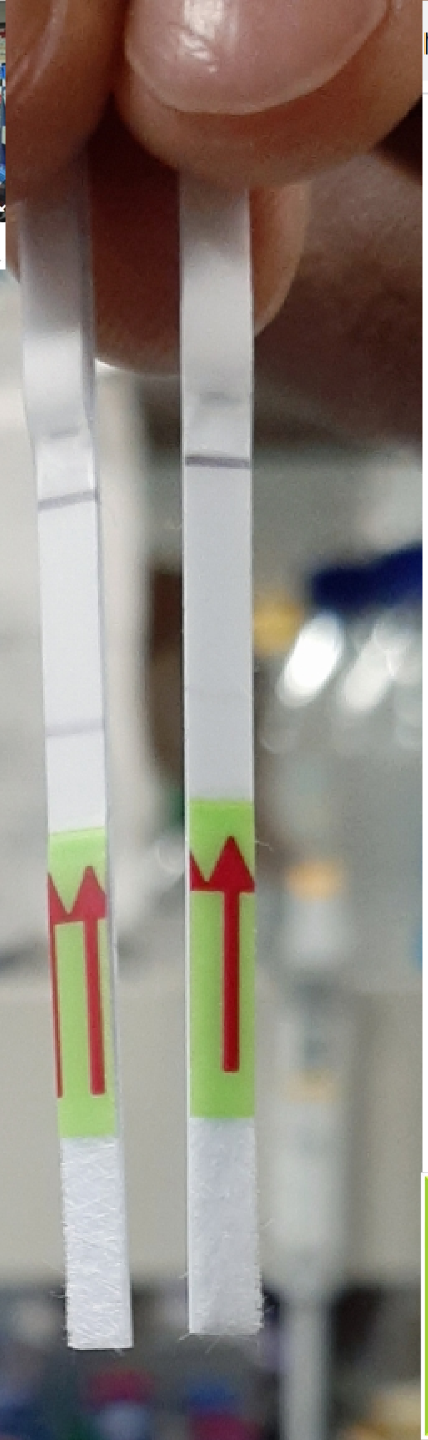
TE – test

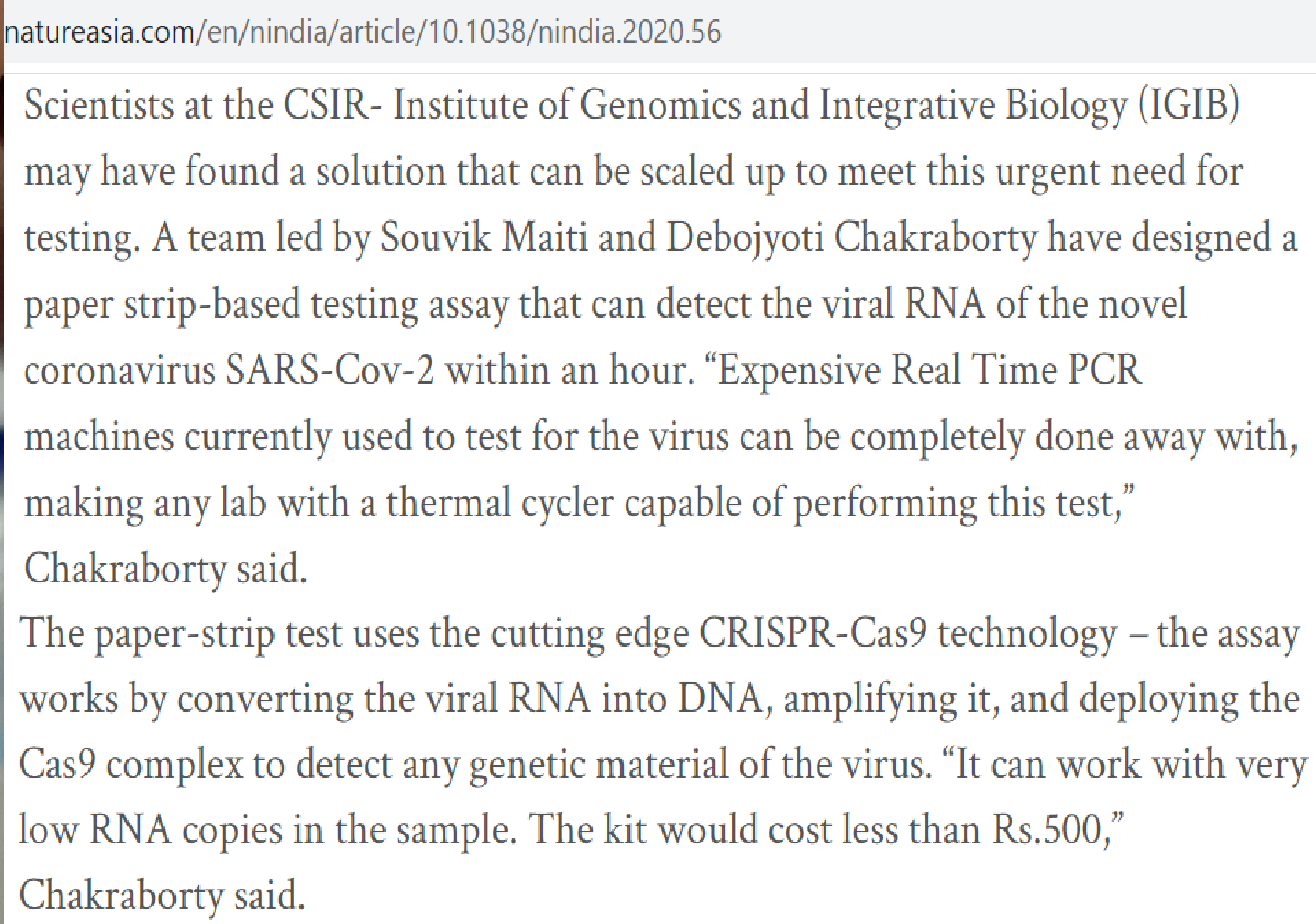
TR – treat

IS – isolate

India has a solution?

Team Feluda: (Left to right) Dr Debojyoti Chakraborty, Dr Souvik Maiti, Rhythm Phutela, Mohd Azhar and Manoj Kumar have worked around the clock to produce the rapid paper-





natureasia.com/en/nindia/article/10.1038/nindia.2020.56

Scientists at the CSIR- Institute of Genomics and Integrative Biology (IGIB) may have found a solution that can be scaled up to meet this urgent need for testing. A team led by Souvik Maiti and Debojyoti Chakraborty have designed a paper strip-based testing assay that can detect the viral RNA of the novel coronavirus SARS-Cov-2 within an hour. “Expensive Real Time PCR machines currently used to test for the virus can be completely done away with, making any lab with a thermal cycler capable of performing this test,” Chakraborty said.

The paper-strip test uses the cutting edge CRISPR-Cas9 technology – the assay works by converting the viral RNA into DNA, amplifying it, and deploying the Cas9 complex to detect any genetic material of the virus. “It can work with very low RNA copies in the sample. The kit would cost less than Rs.500,” Chakraborty said.

Under $7 paper-strip for SARS-CoV2 testing with results in about an hour. Is it reliable?

India, we have a problem.

Not unique to India. But, India may suffer the most.

35.5 Crore Women Don't Have Access To Toilet In India: Report

The Logical Indian

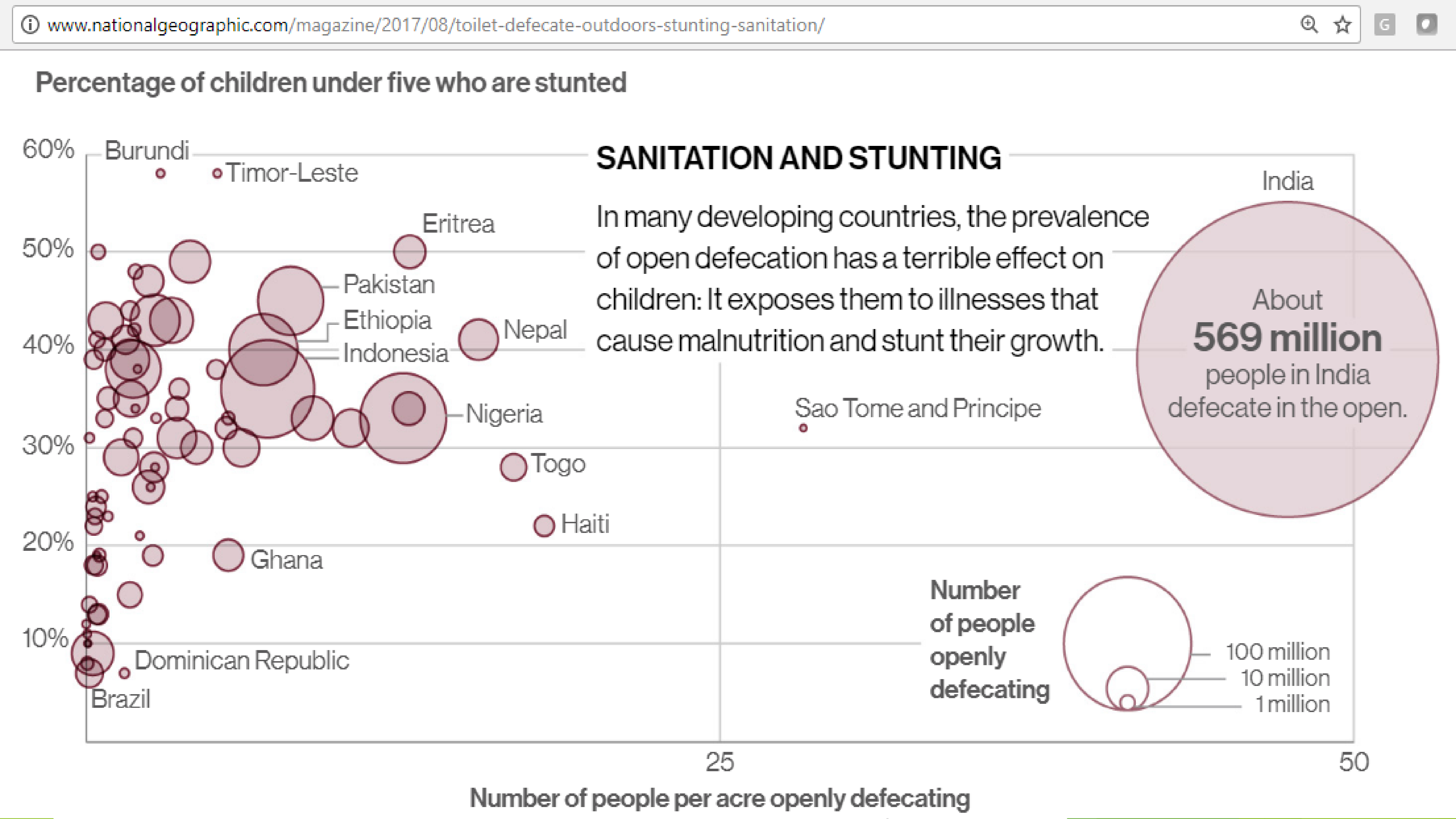
20 Nov 2017

Editor : The Logical Indian

https://thelogicalindian.com/story-feed/awareness/india-worst-in-the-world-for-the-highest-number-of-people-without-basic-sanitation

https://www.nationalgeographic.com/magazine/2017/08/toilet-defecate-outdoors-stunting-sanitation/

Sanitation in a post-pandemic world?


www.nationalgeographic.com/magazine/2017/08/toilet-defecate-outdoors-stunting-sanitation/

SANITATION AND STUNTING

In many developing countries, the prevalence of open defecation has a terrible effect on children: It exposes them to illnesses that cause malnutrition and stunt their growth.

About **569 million** people in India defecate in the open.

cen.acs.org/biological-chemistry/infectious-disease/Novel-coronavirus-found-surprisingly-high/98/i15

INFECTIOUS DISEASE

Novel coronavirus found in surprisingly high levels in sewage

Viral levels higher than expected based on confirmed COVID-19 cases

by ***Celia Henry Arnaud***

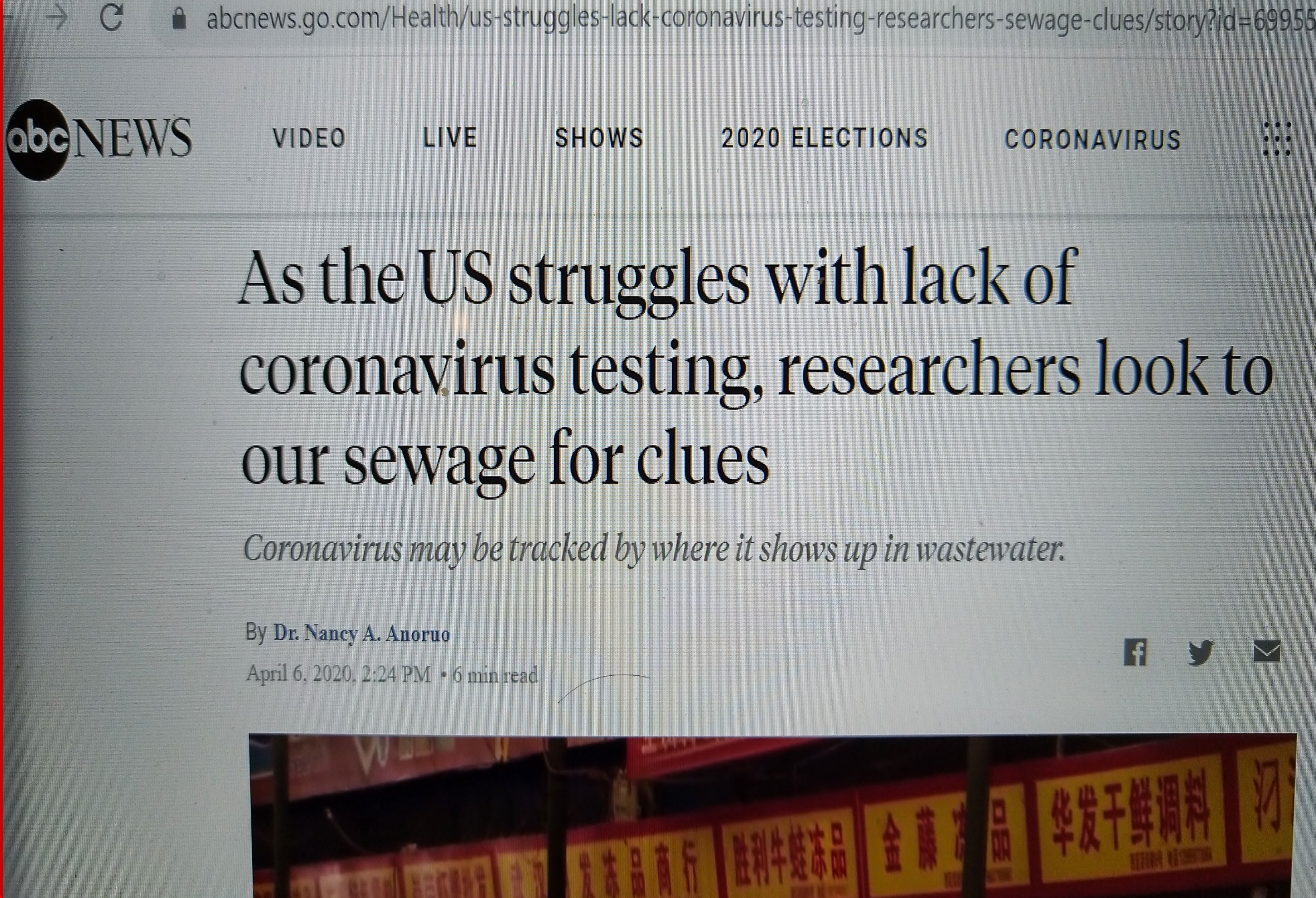
APRIL 16, 2020 | APPEARED IN **VOLUME 98, ISSUE 15**

In a
Post-COVID
World:

New
Metaphors?
Paradigms?

CITCOM
Canaries in the
Coal Mine

SENSEW
Sensors in the
Sewer
Seawater
Wastewater



As the US struggles with lack of coronavirus testing, researchers look to our sewage for clues

Coronavirus may be tracked by where it shows up in wastewater.

By **Dr. Nancy A. Anoruo**

April 6, 2020, 2:24 PM • 6 min read

Pandemic's blessing?

Digital Health and Healthcare

In a Post-COVID World: New lines of business – pay per pee healthcare

www.newsweek.com/coronavirus-traces-massachusetts-wastewater-levels-higher-expected-1497141

vice.com/en_us/article/m7qygn/your-poop-might-be-key-for-predicting-the-end-of-the-pandemic

Your Poop Might Be Key For Predicting End of the Pandemic

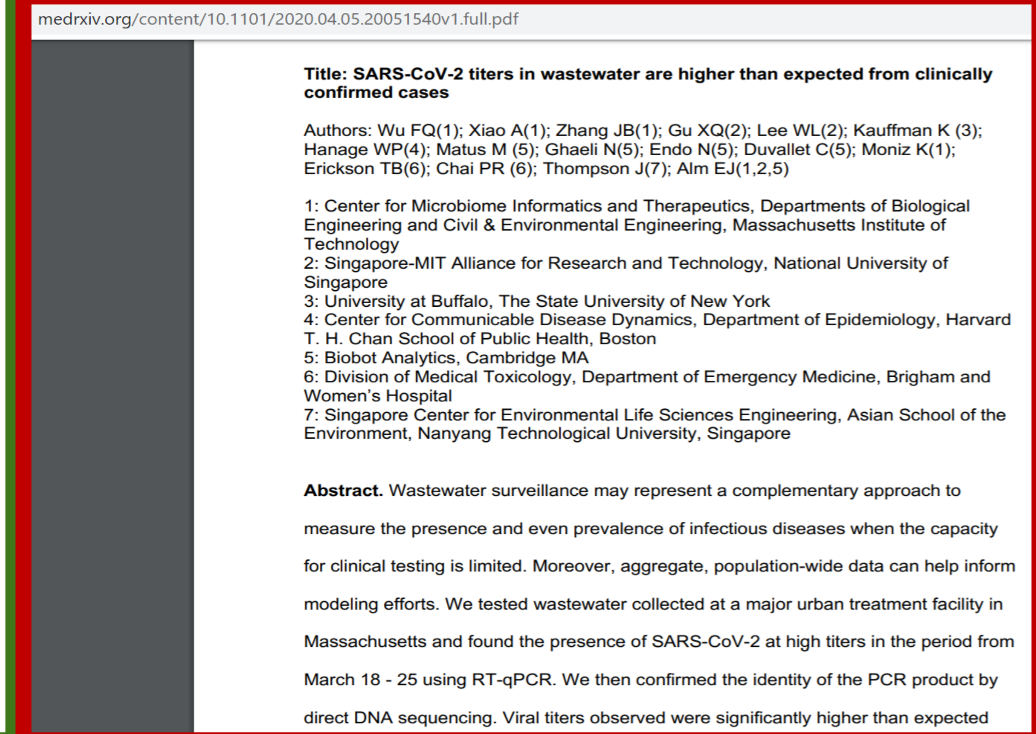
Looking for the new coronavirus in wastewater could give us a heads up about where the outbreak is spreading – and when it has started to dissipate.

By **Shayla Love**

Apr 8 2020, 4:55pm Share Tweet Snap

PAOLO CORDONI / EYEEM | GETTY

On March 5, there had not yet been a clinical diagnosis of COVID-19 in Amersfoort, a Dutch city of more than 150,000 people to the east of Amsterdam. But underneath Amersfoort's streets, dotted with Medieval buildings, the sewage pipes containing people's fecal matter told another story.



medrxiv.org/content/10.1101/2020.04.05.20051540v1.full.pdf

Title: SARS-CoV-2 titers in wastewater are higher than expected from clinically confirmed cases

Authors: Wu FQ(1); Xiao A(1); Zhang JB(1); Gu XQ(2); Lee WL(2); Kauffman K (3); Hanage WP(4); Matus M (5); Ghaeli N(5); Endo N(5); Duvallet C(5); Moniz K(1); Erickson TB(6); Chai PR (6); Thompson J(7); Alm EJ(1,2,5)

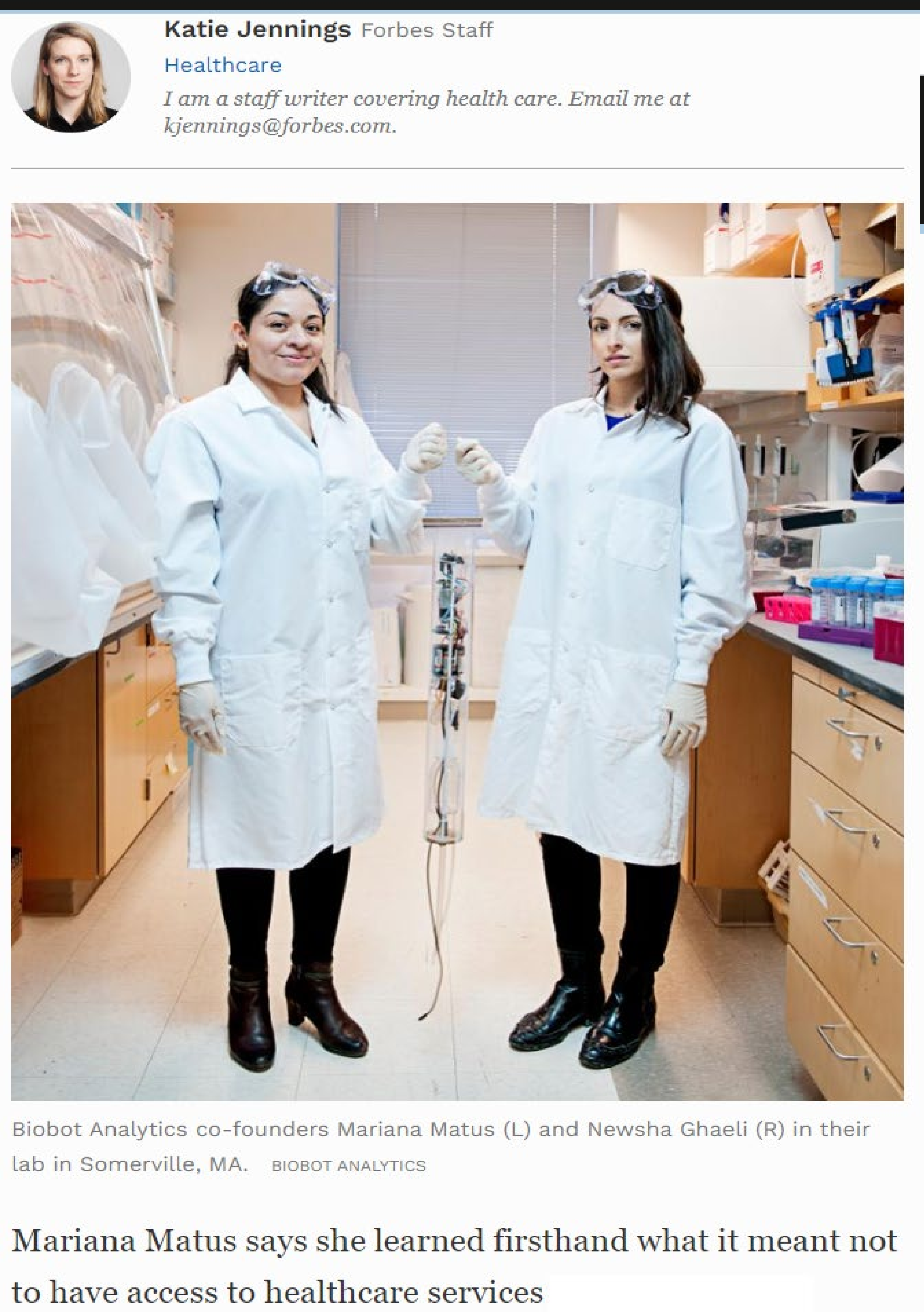
1: Center for Microbiome Informatics and Therapeutics, Departments of Biological Engineering and Civil & Environmental Engineering, Massachusetts Institute of Technology
2: Singapore-MIT Alliance for Research and Technology, National University of Singapore
3: University at Buffalo, The State University of New York
4: Center for Communicable Disease Dynamics, Department of Epidemiology, Harvard T. H. Chan School of Public Health, Boston
5: Biobot Analytics, Cambridge MA
6: Division of Medical Toxicology, Department of Emergency Medicine, Brigham and Women's Hospital
7: Singapore Center for Environmental Life Sciences Engineering, Asian School of the Environment, Nanyang Technological University, Singapore

Abstract. Wastewater surveillance may represent a complementary approach to measure the presence and even prevalence of infectious diseases when the capacity for clinical testing is limited. Moreover, aggregate, population-wide data can help inform modeling efforts. We tested wastewater collected at a major urban treatment facility in Massachusetts and found the presence of SARS-CoV-2 at high titers in the period from March 18 - 25 using RT-qPCR. We then confirmed the identity of the PCR product by direct DNA sequencing. Viral titers observed were significantly higher than expected

www.medrxiv.org/content/10.1101/2020.04.05.20051540v1.full.pdf

Pay-Per-Pee Home Health - IoT Wireless Metabolomics & Vitals - Connected Healthcare

Weigh-scale, BMI, FOBT, urine analysis, sugar, ketone body analysis, blood pressure monitor, pulse oximeter, networked to phone via WiFi and/or Bluetooth with biometrics and face recognition for secure communication



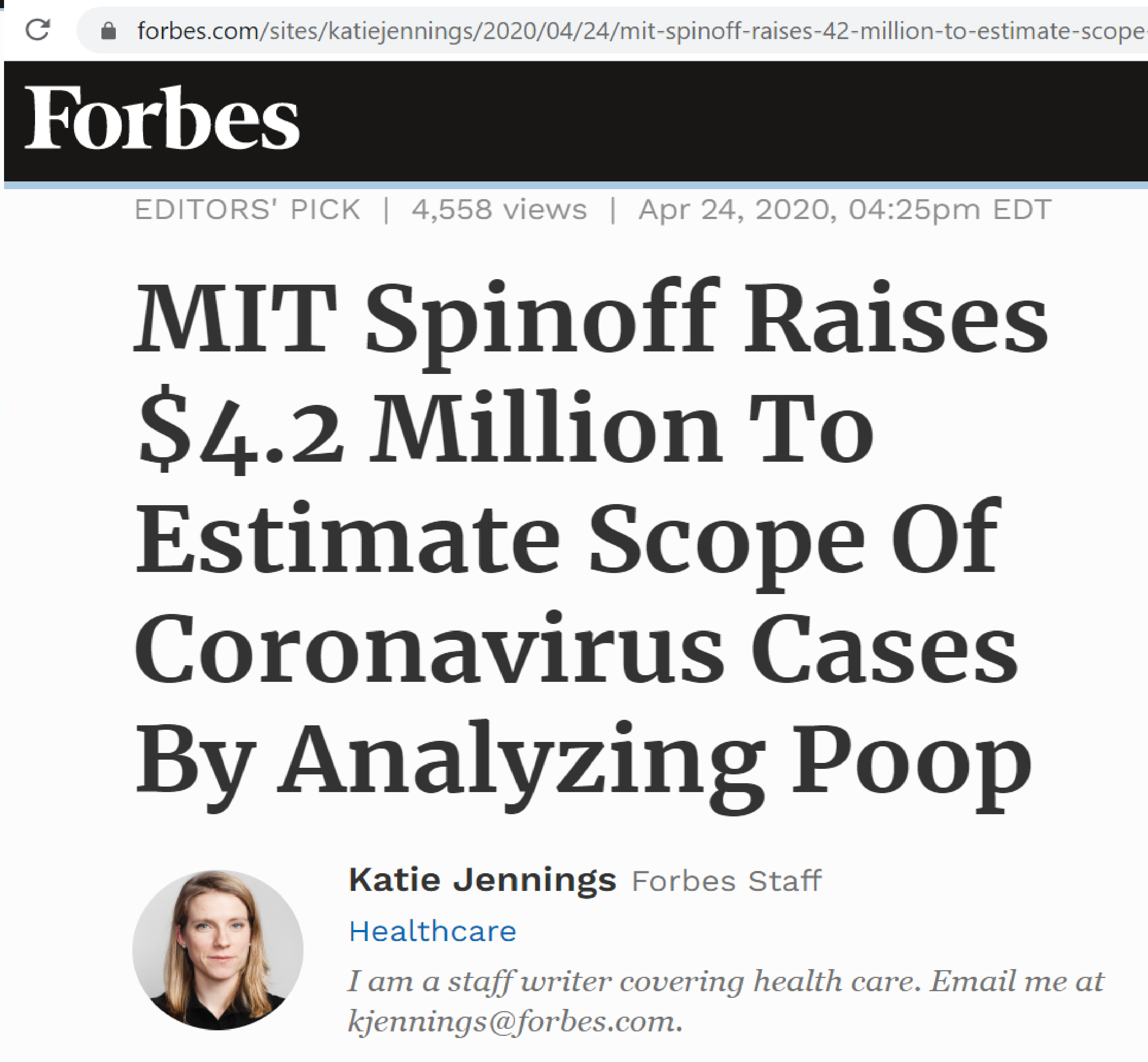
Katie Jennings Forbes Staff

Healthcare

I am a staff writer covering health care. Email me at kjennings@forbes.com.

Biobot Analytics co-founders Mariana Matus (L) and Newsha Ghaeli (R) in their lab in Somerville, MA. BIOBOT ANALYTICS

Mariana Matus says she learned firsthand what it meant not to have access to healthcare services



forbes.com/sites/katiejennings/2020/04/24/mit-spinoff-raises-42-million-to-estimate-scope

Forbes

EDITORS' PICK | 4,558 views | Apr 24, 2020, 04:25pm EDT

MIT Spinoff Raises $4.2 Million To Estimate Scope Of Coronavirus Cases By Analyzing Poop

Katie Jennings Forbes Staff

Healthcare

I am a staff writer covering health care. Email me at kjennings@forbes.com.

TEST

Control Infection

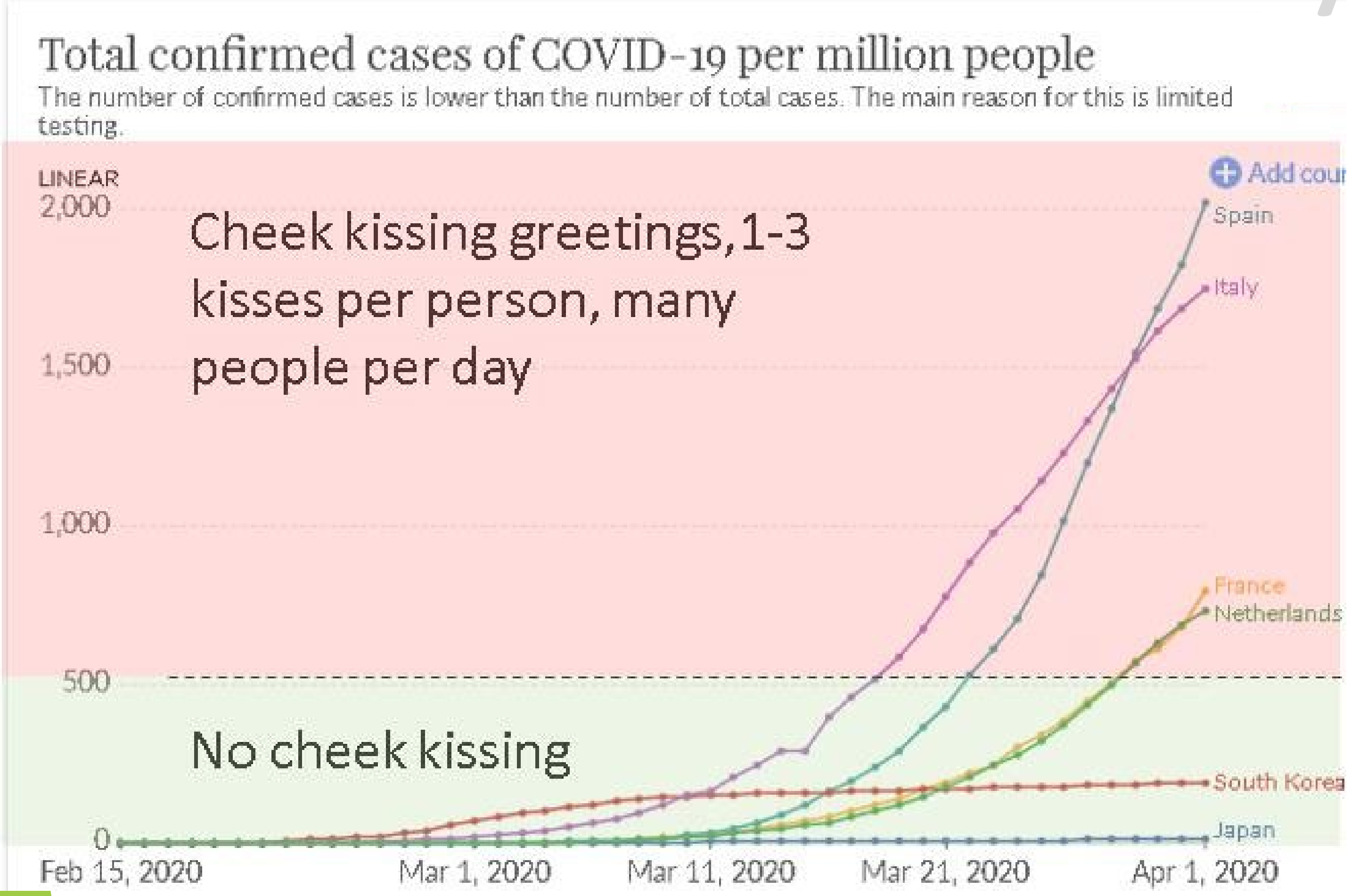
TETRIS

TE – test

TR – treat

IS – isolate

Life and Lifestyle Changes


Total confirmed cases of COVID-19 per million people

The number of confirmed cases is lower than the number of total cases. The main reason for this is limited testing.

Cheek kissing greetings, 1-3 kisses per person, many people per day

No cheek kissing

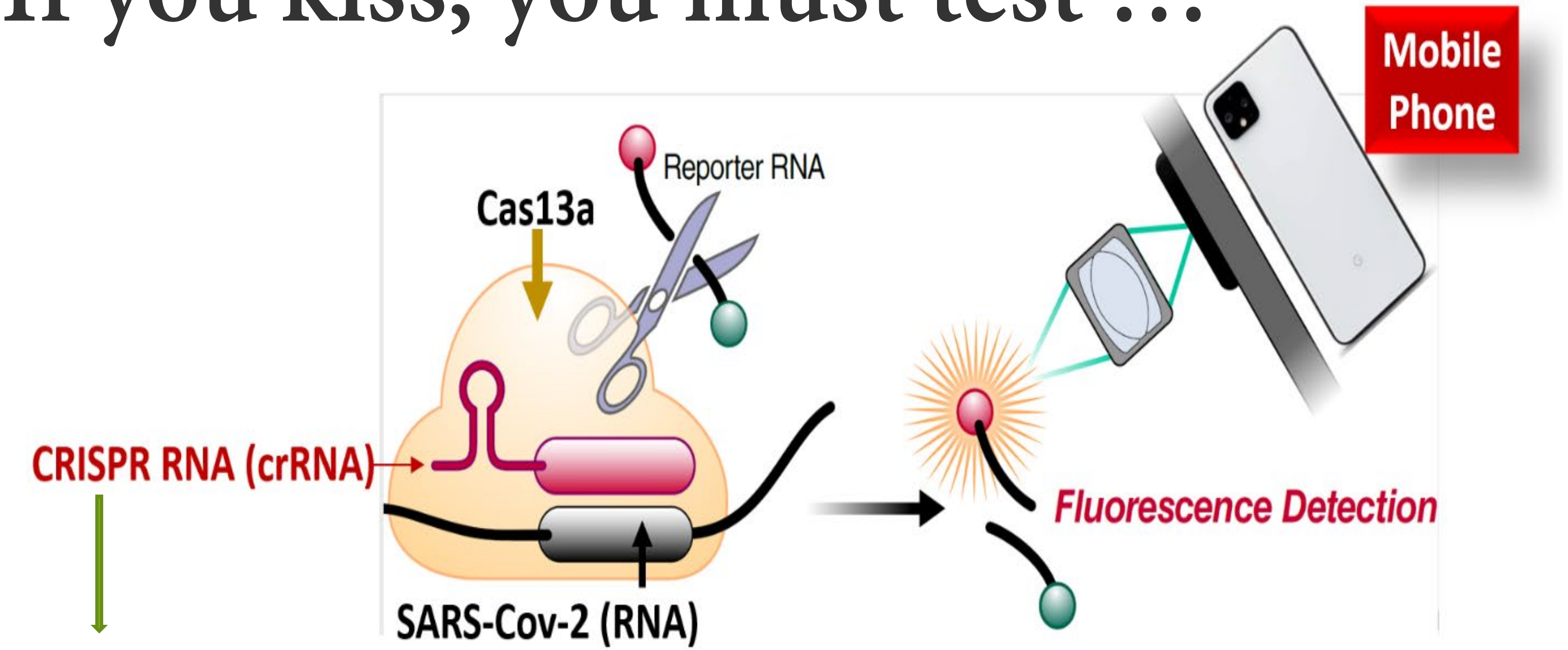

Kissing friends and acquaintances hello is an everyday part of French culture - as demonstrated by French First Lady Carla Bruni (r.) and President Barack Obama.(Triboullard/Getty)

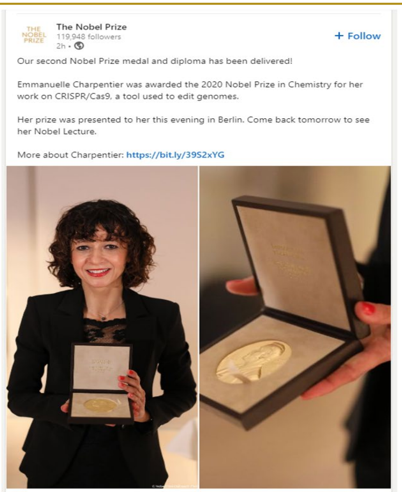
Swine flu has put an end to a beloved French custom, at least for now.

France's health ministry has issued a warning that the air kiss, or "la bise," could spread the H1N1 virus.

KISS & TELL

If you kiss, you must test …





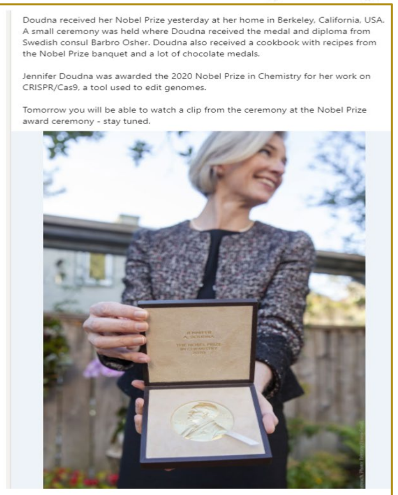
The Nobel Prize
119,948 followers
2h •

Our second Nobel Prize medal and diploma has been delivered!

Emmanuelle Charpentier was awarded the 2020 Nobel Prize in Chemistry for her work on CRISPR/Cas9, a tool used to edit genomes.

Her prize was presented to her this evening in Berlin. Come back tomorrow to see her Nobel Lecture.

More about Charpentier: https://bit.ly/39S2xYG



Doudna received her Nobel Prize yesterday at her home in Berkeley, California, USA. A small ceremony was held where Doudna received the medal and diploma from Swedish consul Barbro Osher. Doudna also received a cookbook with recipes from the Nobel Prize banquet and a lot of chocolate medals.

Jennifer Doudna was awarded the 2020 Nobel Prize in Chemistry for her work on CRISPR/Cas9, a tool used to edit genomes.

Tomorrow you will be able to watch a clip from the ceremony at the Nobel Prize award ceremony - stay tuned.

CRISPR - clustered regularly interspaced short palindromic repeats

Detection of one copy RNA per μL (microL) from SARS-CoV-2 with mobile phone camera. Cas13a (C2c2) is complexed with a CRISPR RNA (crRNA) containing a programmable spacer sequence (red tube) to form a nuclease-inactive ribonucleoprotein complex (RNP). When the RNP binds to a complementary ***target*** RNA, it activates HEPN (higher eukaryotes and prokaryotes nucleotide-binding domain) motifs of Cas13a that then indiscriminately cleaves surrounding ssRNAs. Target RNA binding and subsequent Cas13 cleavage activity can therefore be detected with a fluorophore-quencher pair linked by an ssRNA, which will fluoresce after cleavage by active Cas13. Ott et al used the SARS-CoV-2 nucleocapsid (N) gene as the template (detection ***target***) to create an array of crRNA spacer (red tube).

Parinaz Fozouni, Jennifer A. Doudna, Daniel A. Fletcher and Melanie Ott (2020) *Direct detection of SARS-CoV-2 using CRISPR-Cas13a and a mobile phone.* Pub 30 Sep 2020 https://doi.org/10.1101/2020.09.28.20201947

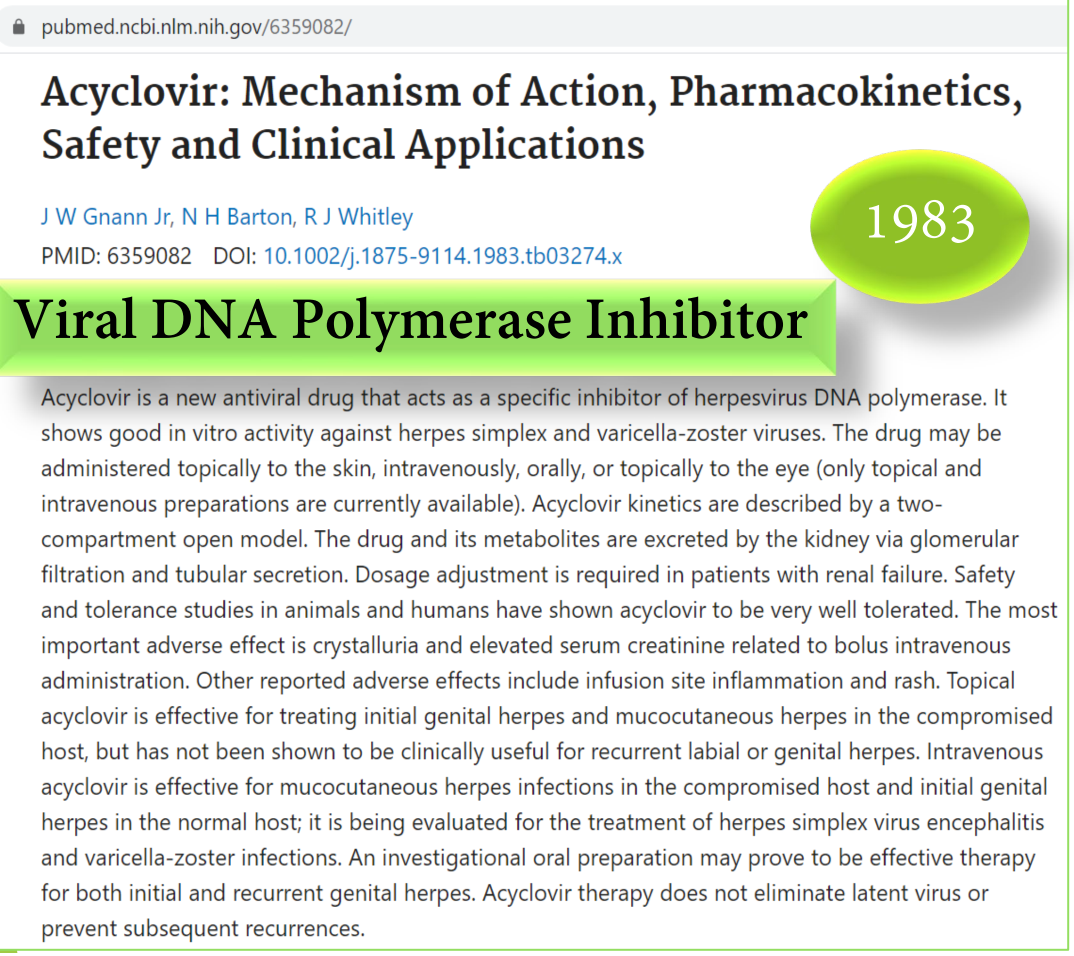
In the absence of vaccines …

Stop the virus from replicating inside the cell, even if it enters !

This the foundation of most cancer chemotherapy. Stop actively growing cells (cancer cells are actively growing) from growing by interfering/inhibiting their ability to replicate the genetic material (for humans, it is DNA).

For SARS-CoV-2 we need RNA inhibitors

RNA POLYMERASE INHIBITOR



pubmed.ncbi.nlm.nih.gov/6359082/

Acyclovir: Mechanism of Action, Pharmacokinetics, Safety and Clinical Applications

J W Gnann Jr, N H Barton, R J Whitley

PMID: 6359082 DOI: 10.1002/j.1875-9114.1983.tb03274.x

1983

Viral DNA Polymerase Inhibitor

Acyclovir is a new antiviral drug that acts as a specific inhibitor of herpesvirus DNA polymerase. It shows good in vitro activity against herpes simplex and varicella-zoster viruses. The drug may be administered topically to the skin, intravenously, orally, or topically to the eye (only topical and intravenous preparations are currently available). Acyclovir kinetics are described by a two-compartment open model. The drug and its metabolites are excreted by the kidney via glomerular filtration and tubular secretion. Dosage adjustment is required in patients with renal failure. Safety and tolerance studies in animals and humans have shown acyclovir to be very well tolerated. The most important adverse effect is crystalluria and elevated serum creatinine related to bolus intravenous administration. Other reported adverse effects include infusion site inflammation and rash. Topical acyclovir is effective for treating initial genital herpes and mucocutaneous herpes in the compromised host, but has not been shown to be clinically useful for recurrent labial or genital herpes. Intravenous acyclovir is effective for mucocutaneous herpes infections in the compromised host and initial genital herpes in the normal host; it is being evaluated for the treatment of herpes simplex virus encephalitis and varicella-zoster infections. An investigational oral preparation may prove to be effective therapy for both initial and recurrent genital herpes. Acyclovir therapy does not eliminate latent virus or prevent subsequent recurrences.

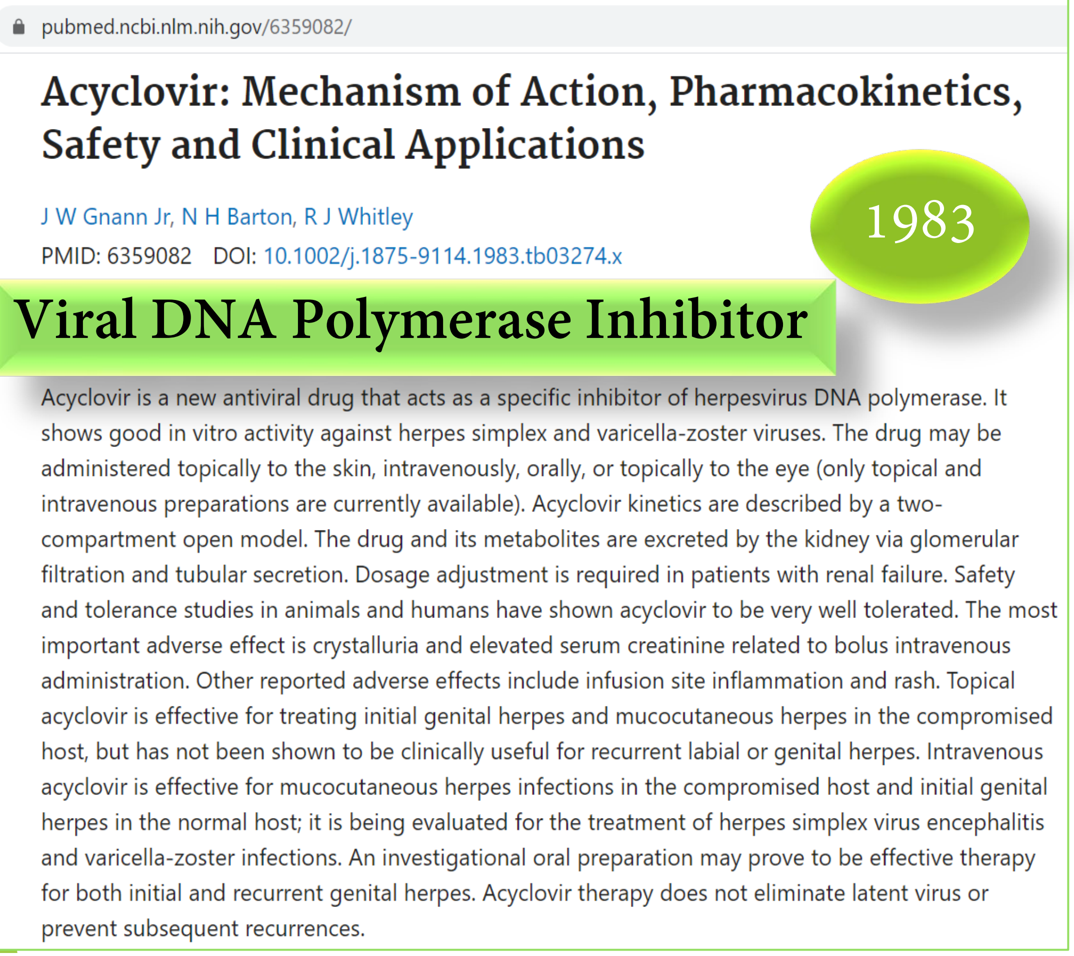
Current status and prospects for oral acyclovir treatment of first episode and recurrent genital herpes simplex virus

Yvonne J. Bryson

Journal of Antimicrobial Chemotherapy, Volume 12, Issue suppl_B, 1983, 61–65, https://doi.org/10.1093/jac/12.suppl_B.61

Published: 01 June 1983

https://pubmed.ncbi.nlm.nih.gov/6306847/



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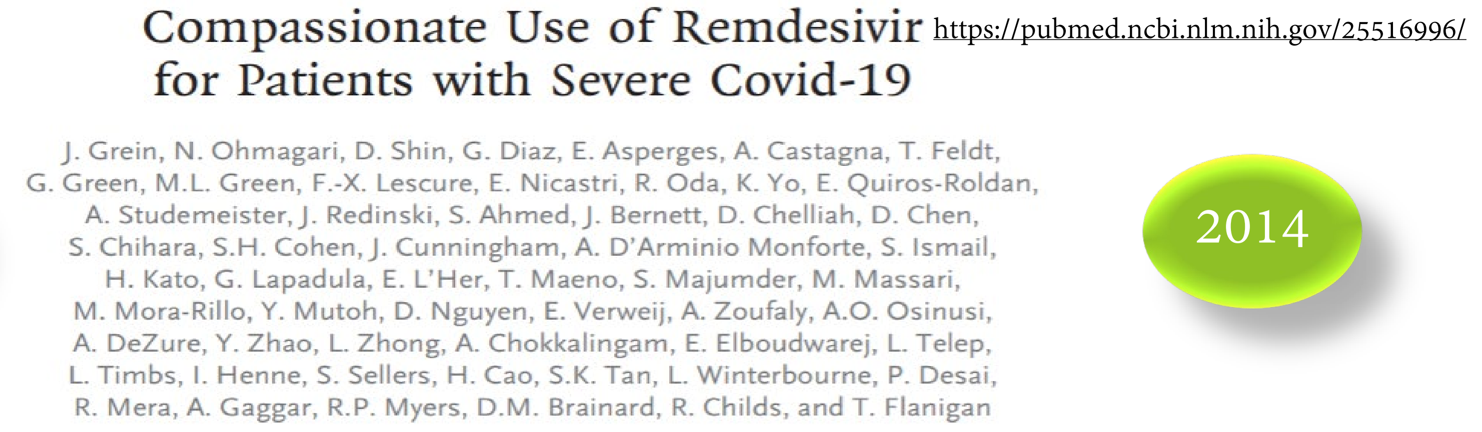
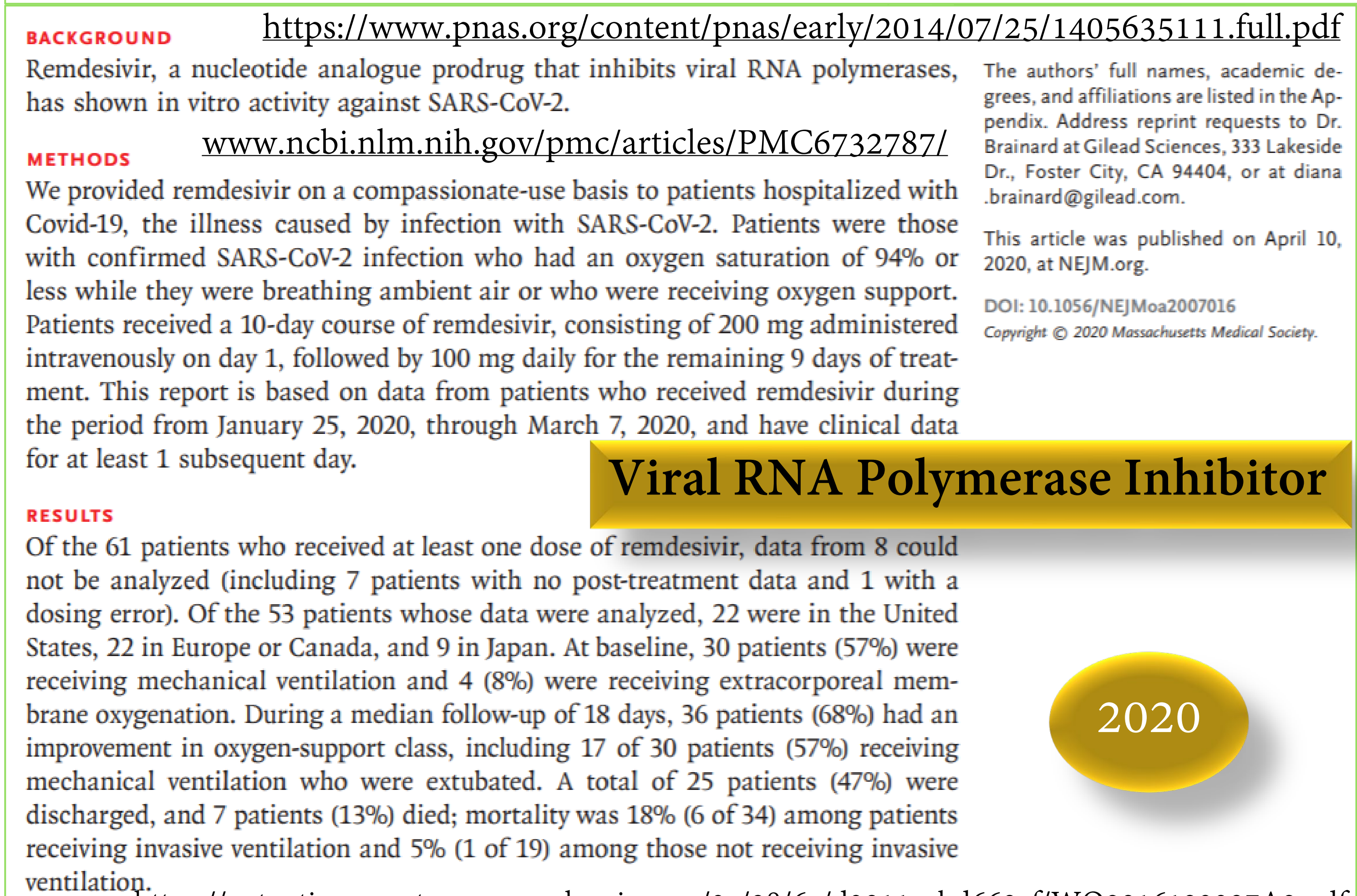


Compassionate Use of Remdesivir for Patients with Severe Covid-19

https://pubmed.ncbi.nlm.nih.gov/25516996/

J. Grein, N. Ohmagari, D. Shin, G. Diaz, E. Asperges, A. Castagna, T. Feldt, G. Green, M.L. Green, F.-X. Lescure, E. Nicastri, R. Oda, K. Yo, E. Quiros-Roldan, A. Studemeister, J. Redinski, S. Ahmed, J. Bernett, D. Chelliah, D. Chen, S. Chihara, S.H. Cohen, J. Cunningham, A. D'Arminio Monforte, S. Ismail, H. Kato, G. Lapadula, E. L'Her, T. Maeno, S. Majumder, M. Massari, M. Mora-Rillo, Y. Mutoh, D. Nguyen, E. Verweij, A. Zoufaly, A.O. Osinusi, A. DeZure, Y. Zhao, L. Zhong, A. Chokkalingam, E. Elboudwarej, L. Telep, L. Timbs, I. Henne, S. Sellers, H. Cao, S.K. Tan, L. Winterbourne, P. Desai, R. Mera, A. Gaggar, R.P. Myers, D.M. Brainard, R. Childs, and T. Flanigan

2014



https://www.pnas.org/content/pnas/early/2014/07/25/1405635111.full.pdf

BACKGROUND

Remdesivir, a nucleotide analogue prodrug that inhibits viral RNA polymerases, has shown in vitro activity against SARS-CoV-2.

www.ncbi.nlm.nih.gov/pmc/articles/PMC6732787/

METHODS

We provided remdesivir on a compassionate-use basis to patients hospitalized with Covid-19, the illness caused by infection with SARS-CoV-2. Patients were those with confirmed SARS-CoV-2 infection who had an oxygen saturation of 94% or less while they were breathing ambient air or who were receiving oxygen support. Patients received a 10-day course of remdesivir, consisting of 200 mg administered intravenously on day 1, followed by 100 mg daily for the remaining 9 days of treatment. This report is based on data from patients who received remdesivir during the period from January 25, 2020, through March 7, 2020, and have clinical data for at least 1 subsequent day.

Viral RNA Polymerase Inhibitor

RESULTS

Of the 61 patients who received at least one dose of remdesivir, data from 8 could not be analyzed (including 7 patients with no post-treatment data and 1 with a dosing error). Of the 53 patients whose data were analyzed, 22 were in the United States, 22 in Europe or Canada, and 9 in Japan. At baseline, 30 patients (57%) were receiving mechanical ventilation and 4 (8%) were receiving extracorporeal membrane oxygenation. During a median follow-up of 18 days, 36 patients (68%) had an improvement in oxygen-support class, including 17 of 30 patients (57%) receiving mechanical ventilation who were extubated. A total of 25 patients (47%) were discharged, and 7 patients (13%) died; mortality was 18% (6 of 34) among patients receiving invasive ventilation and 5% (1 of 19) among those not receiving invasive ventilation.

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Brainard at Gilead Sciences, 333 Lakeside Dr., Foster City, CA 94404, or at diana.brainard@gilead.com.

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2020

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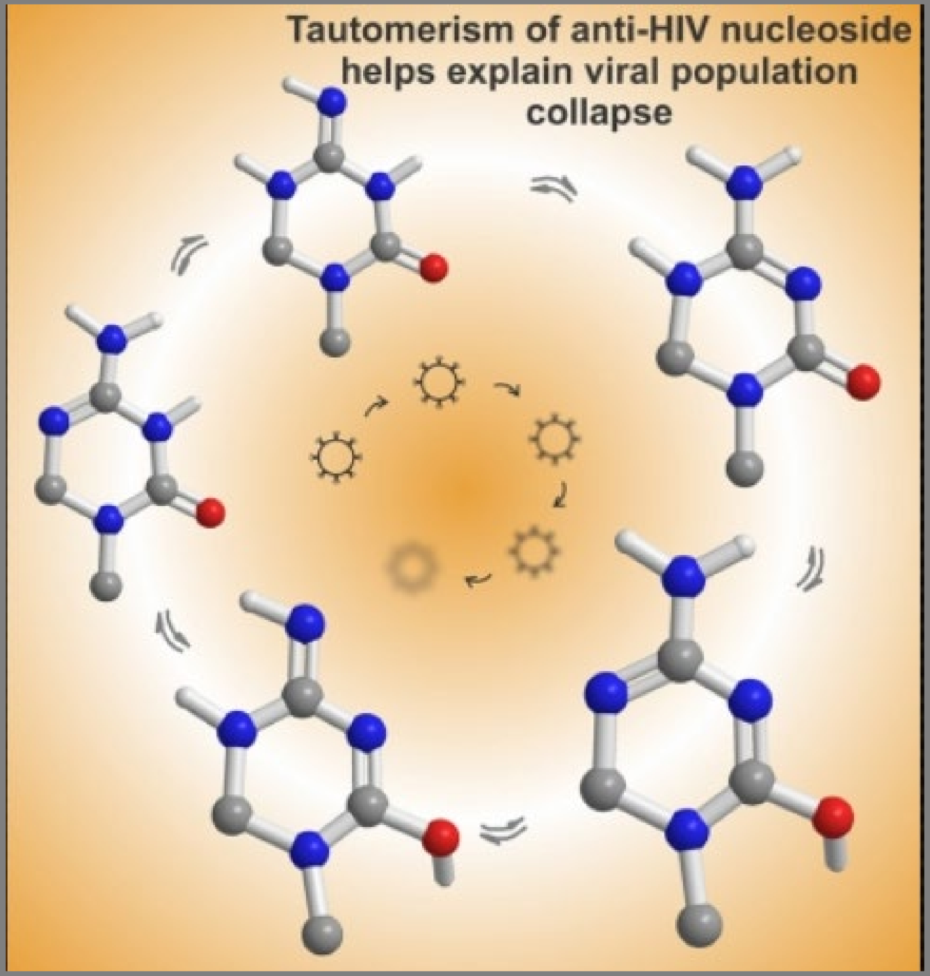
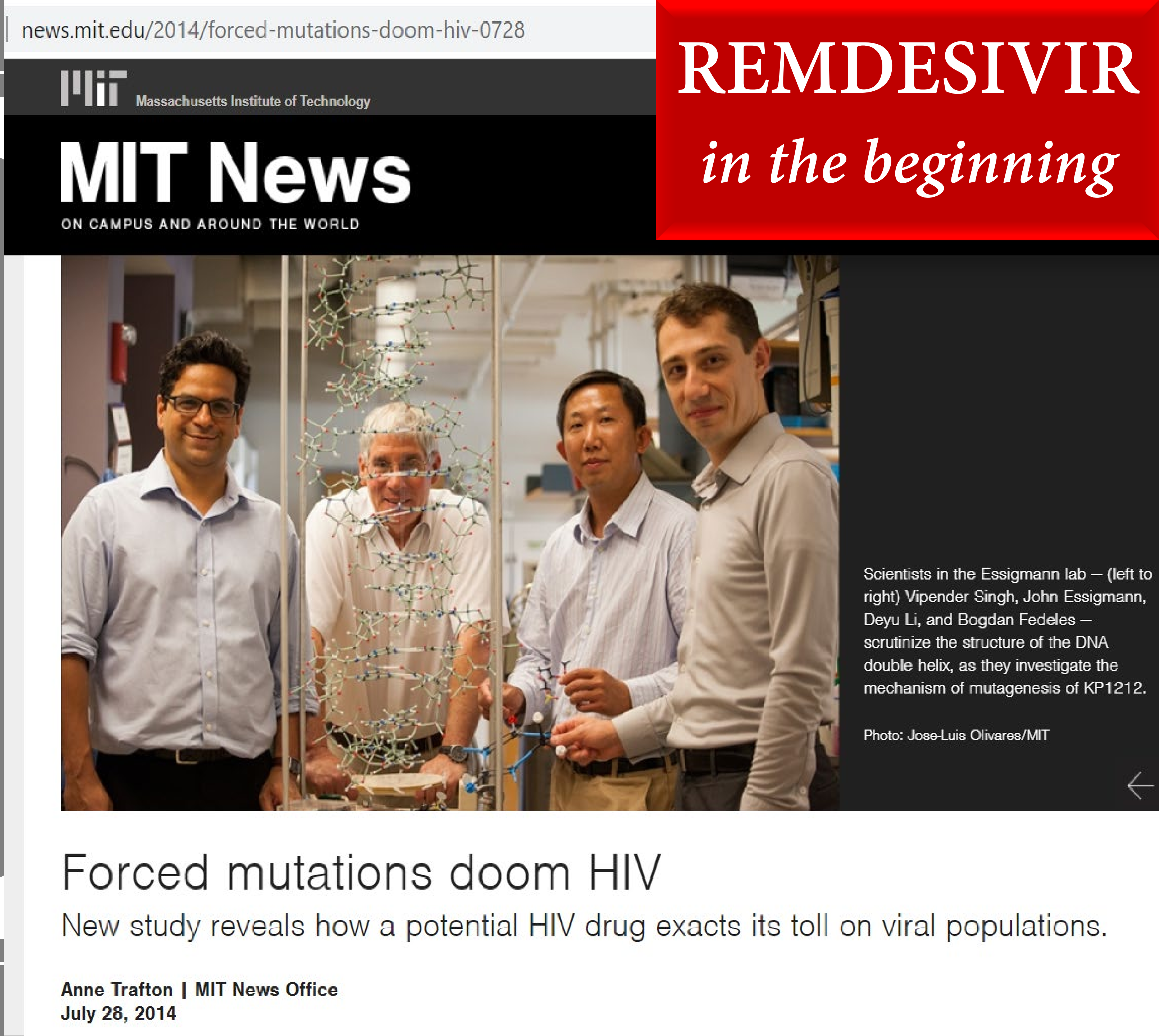
REMDESIVIR
in the beginning

https://rnajournal.cshlp.org/content/21/1/1.full.pdf+html


Tautomerism of anti-HIV nucleoside helps explain viral population collapse

www.pnas.org/content/pnas/early/2014/07/25/1405635111.full.pdf


news.mit.edu/2014/forced-mutations-doom-hiv-0728

MIT News

ON CAMPUS AND AROUND THE WORLD

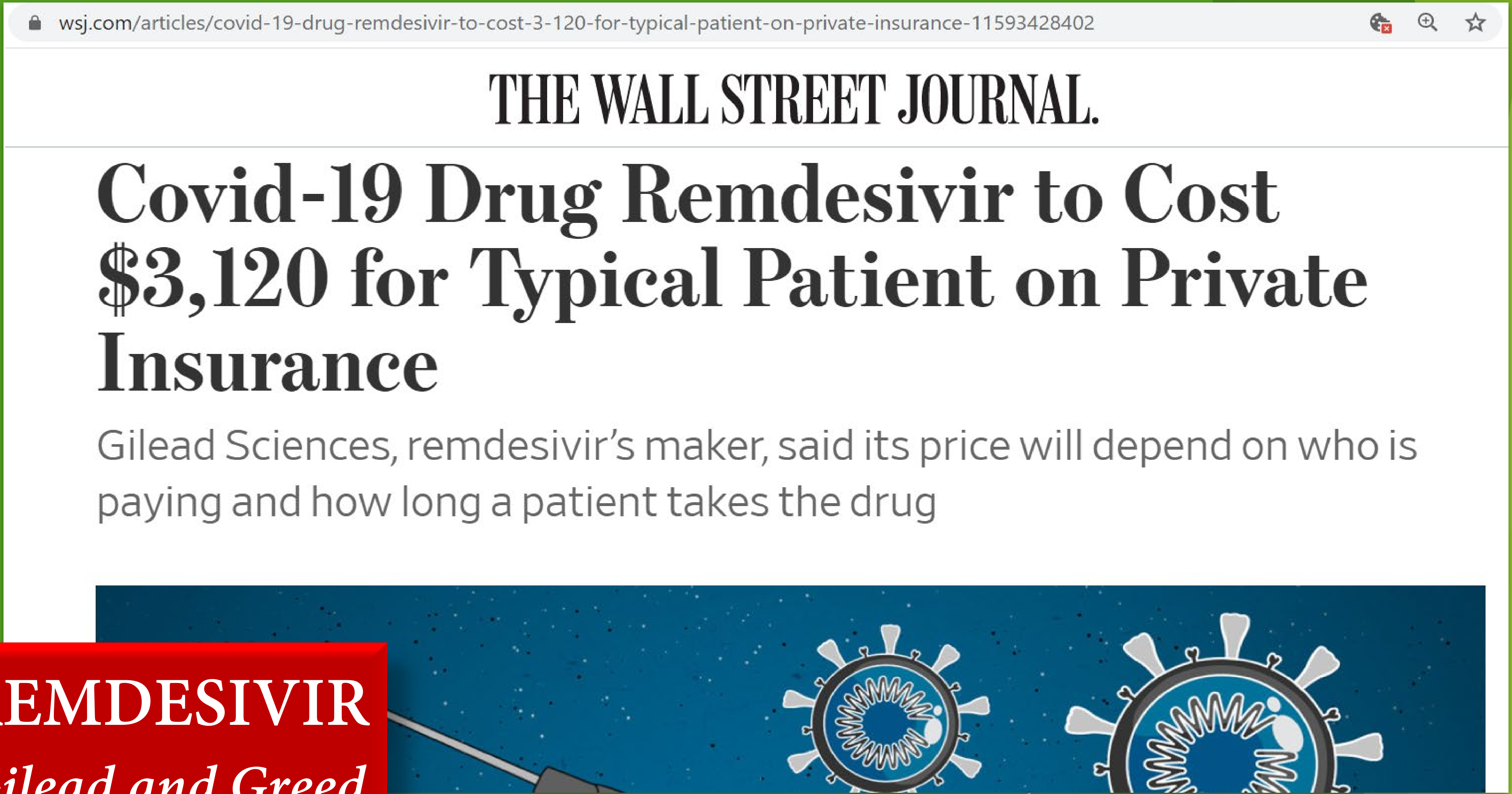
Scientists in the Essigmann lab — (left to right) Vipender Singh, John Essigmann, Deyu Li, and Bogdan Fedeles — scrutinize the structure of the DNA double helix, as they investigate the mechanism of mutagenesis of KP1212.

Photo: Jose-Luis Olivares/MIT

Forced mutations doom HIV

New study reveals how a potential HIV drug exacts its toll on viral populations.

Anne Trafton | MIT News Office
July 28, 2014



wsj.com/articles/covid-19-drug-remdesivir-to-cost-3-120-for-typical-patient-on-private-insurance-11593428402

THE WALL STREET JOURNAL.

Covid-19 Drug Remdesivir to Cost $3,120 for Typical Patient on Private Insurance

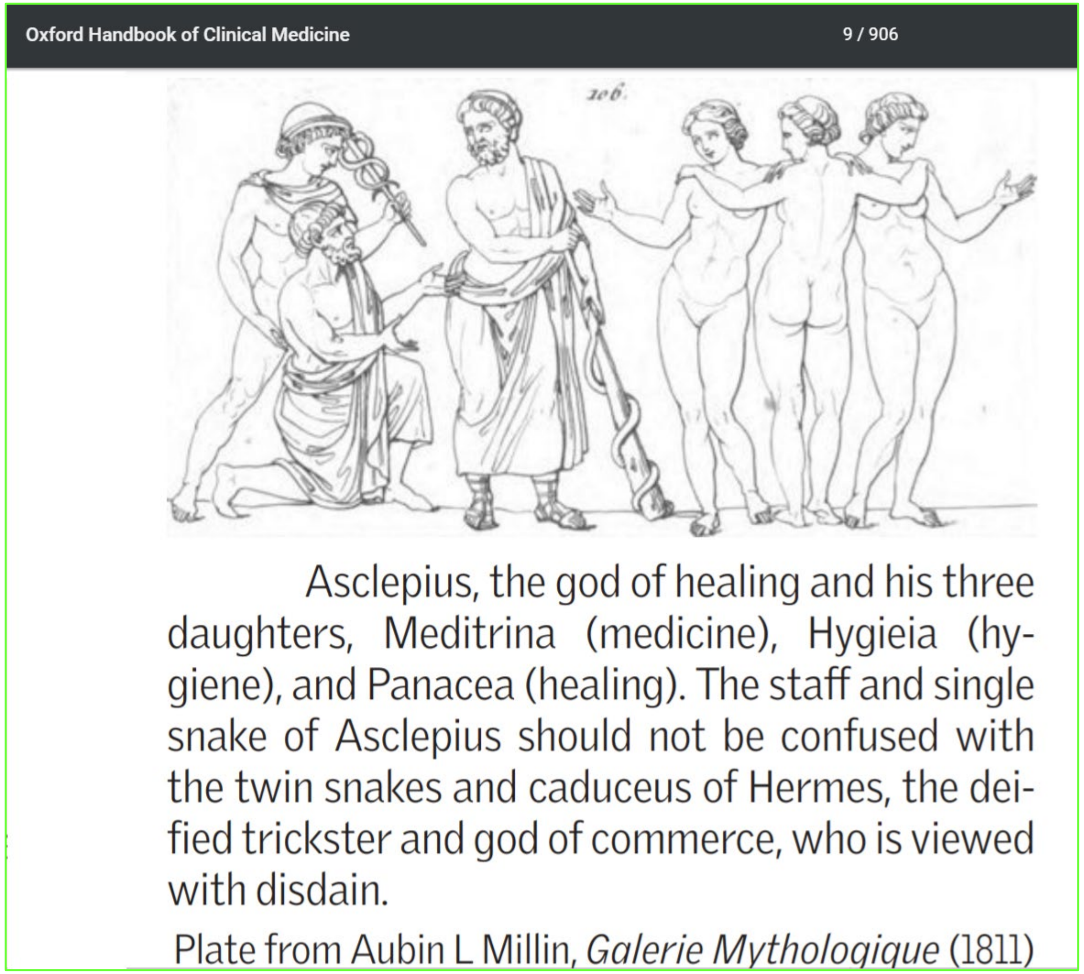
Gilead Sciences, remdesivir's maker, said its price will depend on who is paying and how long a patient takes the drug

REMDESIVIR

Gilead and Greed

Covid-19 Drug Remdesivir to Cost $3,120 for Typical Patient on Private Insurance

Gilead Sciences, remdesivir's maker, said its price will depend on who is paying and how long a patient takes the drug



Asclepius, the god of healing and his three daughters, Meditrina (medicine), Hygieia (hygiene), and Panacea (healing). The staff and single snake of Asclepius should not be confused with the twin snakes and caduceus of Hermes, the deified trickster and god of commerce, who is viewed with disdain.

Plate from Aubin L Millin, *Galerie Mythologique* (1811)

Gluttony

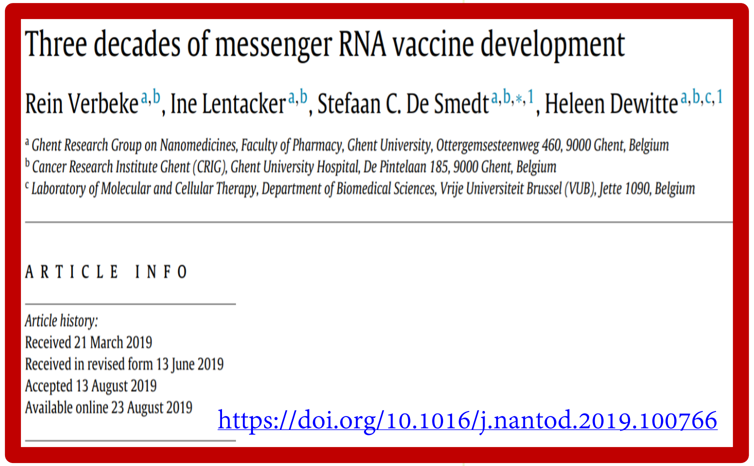
Greed

&

Gilead

The investment in basic science

Molecular Biology



Three decades of messenger RNA vaccine development

Rein Verbeke[a,b], Ine Lentacker[a,b], Stefaan C. De Smedt[a,b,*,1], Heleen Dewitte[a,b,c,1]

[a] Ghent Research Group on Nanomedicines, Faculty of Pharmacy, Ghent University, Ottergemsesteenweg 460, 9000 Ghent, Belgium
[b] Cancer Research Institute Ghent (CRIG), Ghent University Hospital, De Pintelaan 185, 9000 Ghent, Belgium
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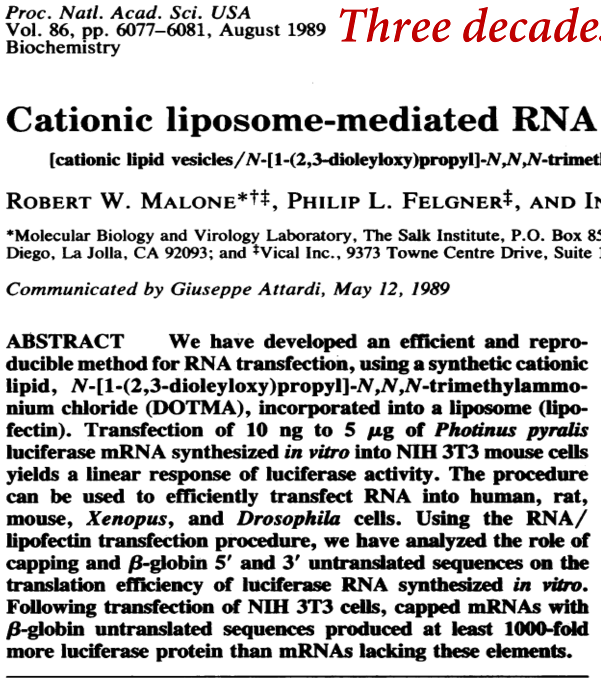
30 years !

The ex-pharma exec leading Trump's COVID-19 vaccine program has $10 million in stock options for a company getting federal funding

Dr Moncef Slaoui speaks at a White House press conference on May 15, 2020, announcing a program to rapidly develop a coronavirus vaccine.

https://www.businessinsider.com/moncef-slaoui-leading-trump-vaccine-push-10m-holding-moderna-conflict-2020-5

Three decades of mRNA vaccine development



Proc. Natl. Acad. Sci. USA
Vol. 86, pp. 6077–6081, August 1989
Biochemistry

Cationic liposome-mediated RNA transfection

[cationic lipid vesicles/*N*-[1-(2,3-dioleyloxy)propyl]-*N*,*N*,*N*-trimethylammonium chloride (DOTMA)/translation]

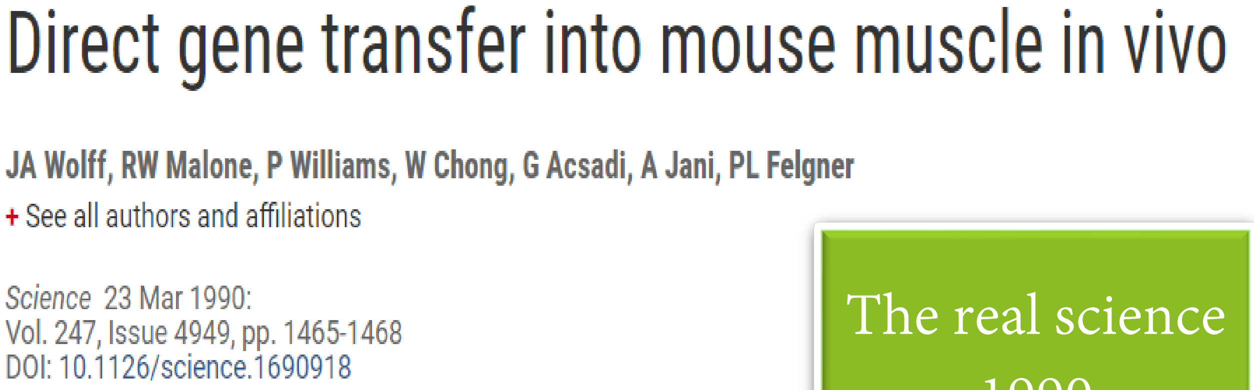
ROBERT W. MALONE*†‡, PHILIP L. FELGNER‡, AND INDER M. VERMA*§

*Molecular Biology and Virology Laboratory, The Salk Institute, P.O. Box 85800, San Diego, CA 92138; †Department of Biology, University of California–San Diego, La Jolla, CA 92093; and ‡Vical Inc., 9373 Towne Centre Drive, Suite 100, San Diego, CA 92121

Communicated by Giuseppe Attardi, May 12, 1989

ABSTRACT We have developed an efficient and reproducible method for RNA transfection, using a synthetic cationic lipid, *N*-[1-(2,3-dioleyloxy)propyl]-*N*,*N*,*N*-trimethylammonium chloride (DOTMA), incorporated into a liposome (lipofectin). Transfection of 10 ng to 5 μg of *Photinus pyralis* luciferase mRNA synthesized *in vitro* into NIH 3T3 mouse cells yields a linear response of luciferase activity. The procedure can be used to efficiently transfect RNA into human, rat, mouse, *Xenopus*, and *Drosophila* cells. Using the RNA/lipofectin transfection procedure, we have analyzed the role of capping and β-globin 5′ and 3′ untranslated sequences on the translation efficiency of luciferase RNA synthesized *in vitro*. Following transfection of NIH 3T3 cells, capped mRNAs with β-globin untranslated sequences produced at least 1000-fold more luciferase protein than mRNAs lacking these elements.

The basic science
1989

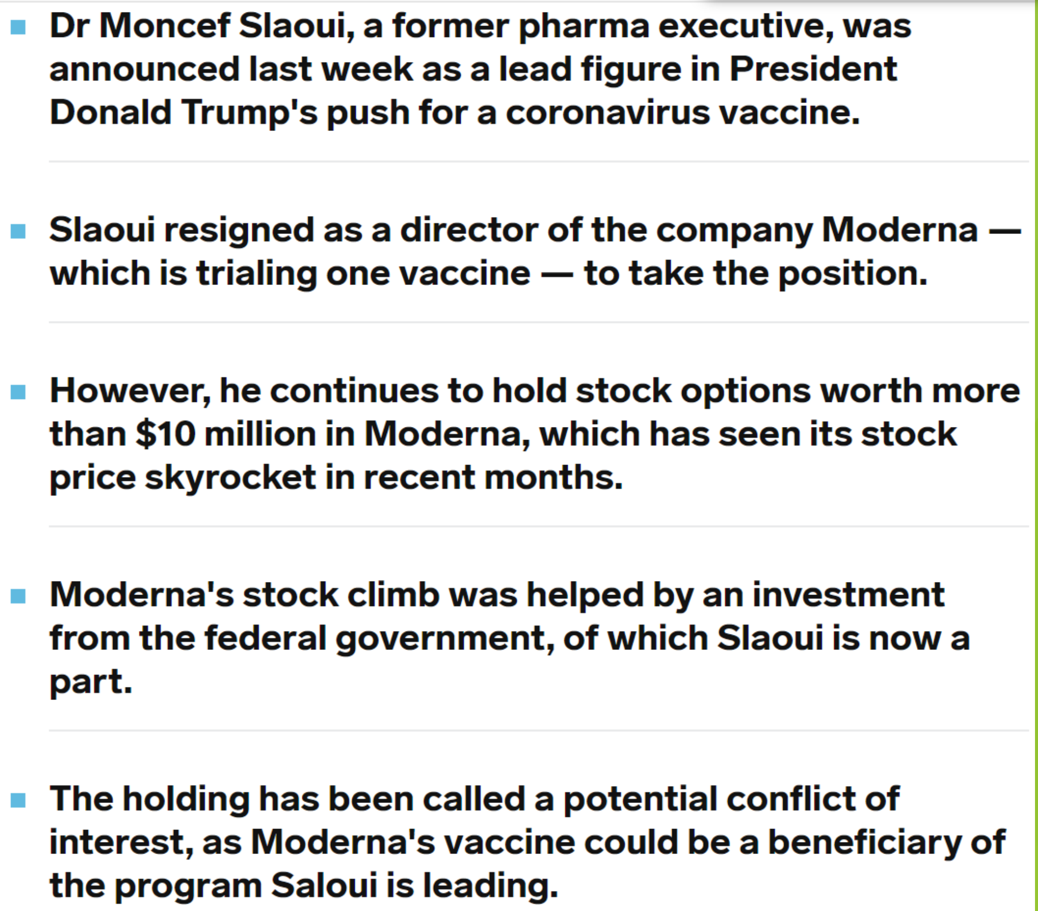


Direct gene transfer into mouse muscle in vivo

JA Wolff, RW Malone, P Williams, W Chong, G Acsadi, A Jani, PL Felgner
+ See all authors and affiliations

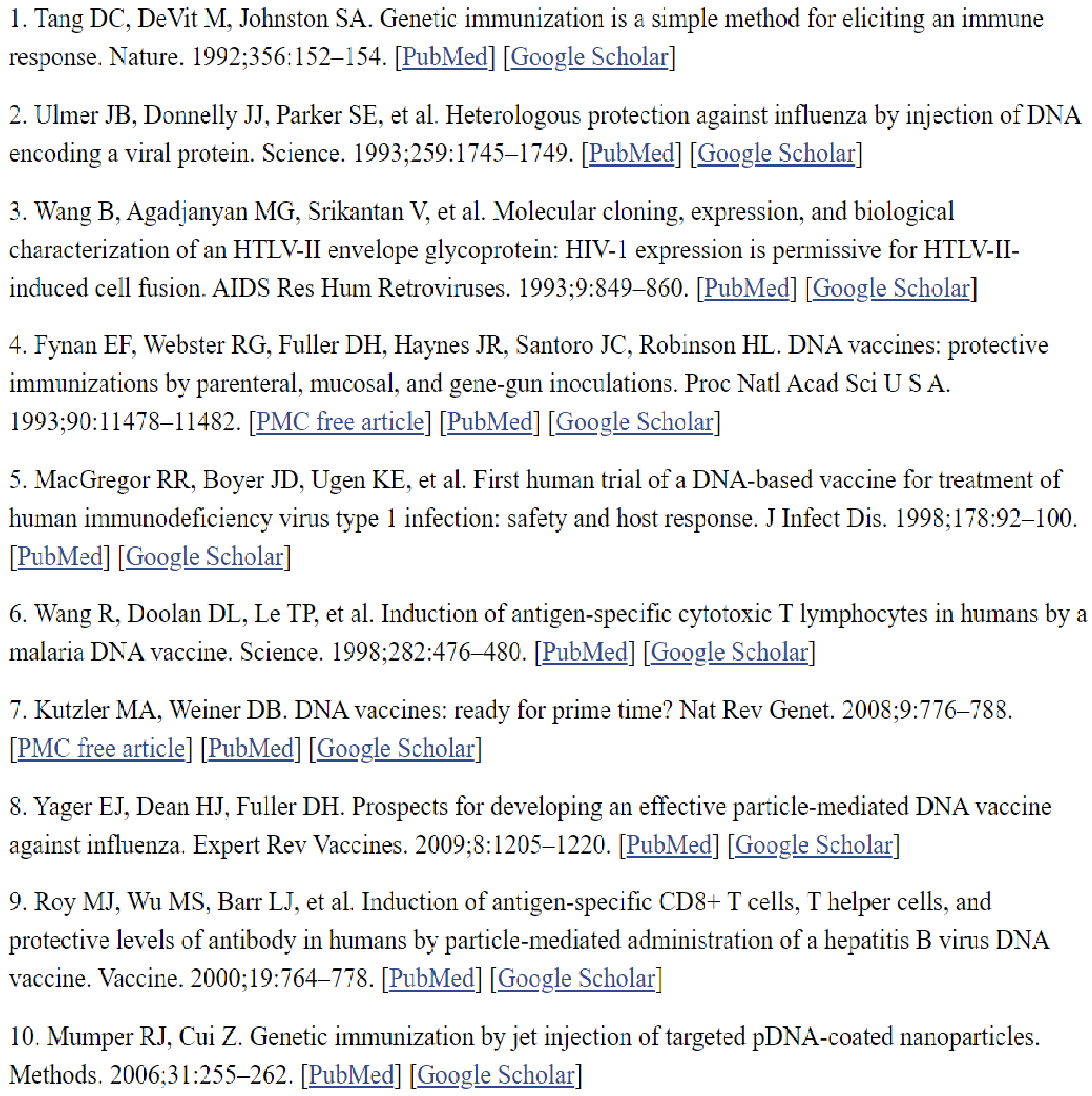
Science 23 Mar 1990:
Vol. 247, Issue 4949, pp. 1465-1468
DOI: 10.1126/science.1690918

The real science
1990



- **Dr Moncef Slaoui, a former pharma executive, was announced last week as a lead figure in President Donald Trump's push for a coronavirus vaccine.**
- **Slaoui resigned as a director of the company Moderna — which is trialing one vaccine — to take the position.**
- **However, he continues to hold stock options worth more than $10 million in Moderna, which has seen its stock price skyrocket in recent months.**
- **Moderna's stock climb was helped by an investment from the federal government, of which Slaoui is now a part.**
- **The holding has been called a potential conflict of interest, as Moderna's vaccine could be a beneficiary of the program Saloui is leading.**

Three decades of DNA vaccine development



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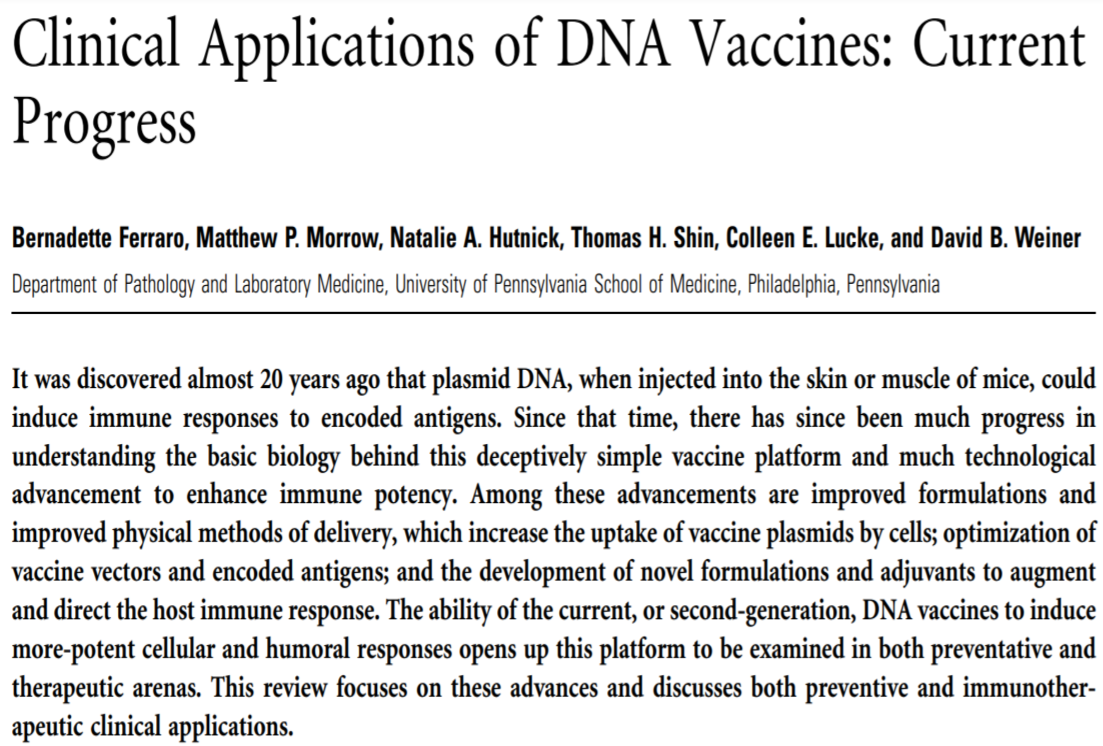


Clinical Applications of DNA Vaccines: Current Progress

Bernadette Ferraro, Matthew P. Morrow, Natalie A. Hutnick, Thomas H. Shin, Colleen E. Lucke, and David B. Weiner

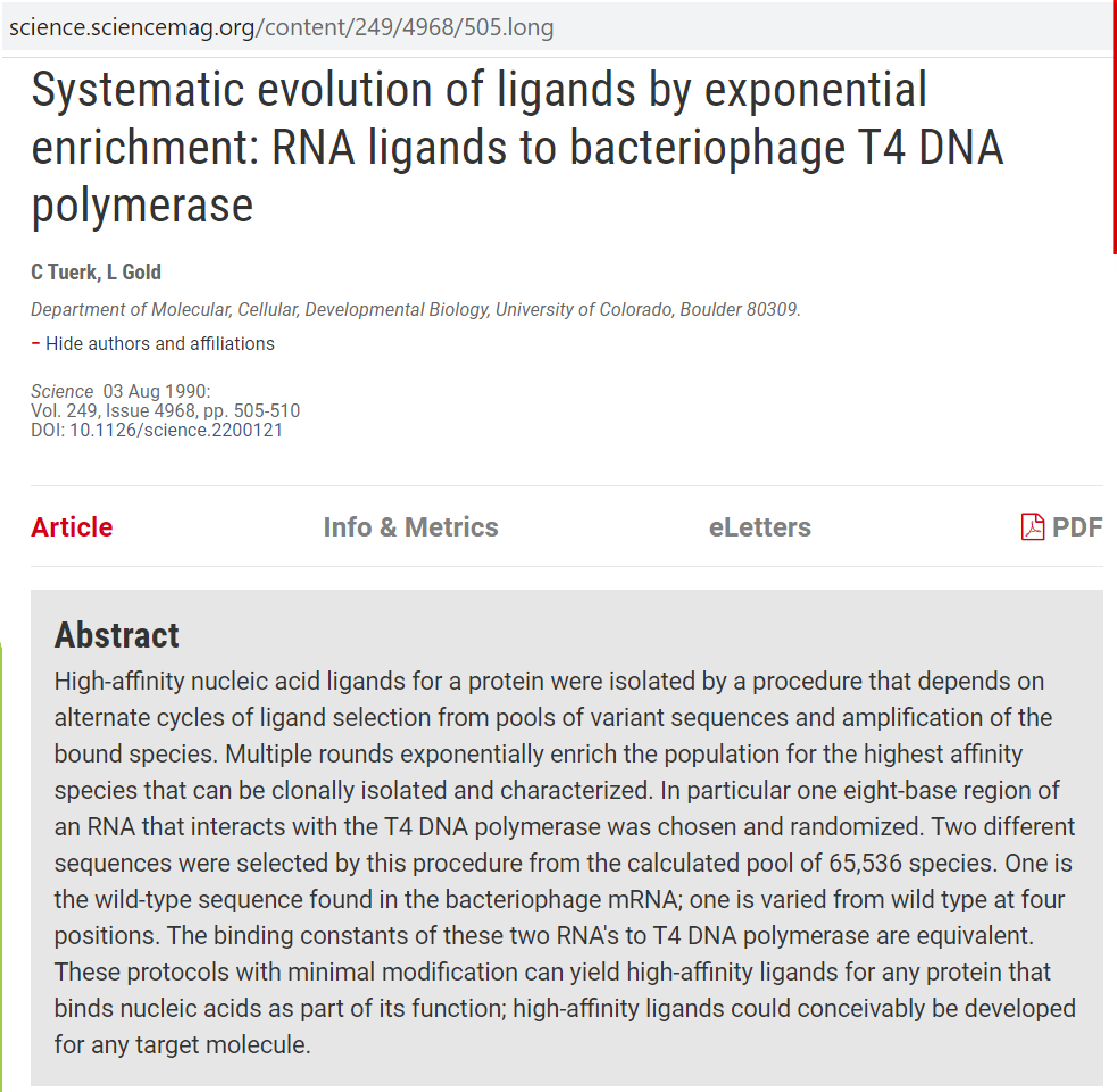
Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

It was discovered almost 20 years ago that plasmid DNA, when injected into the skin or muscle of mice, could induce immune responses to encoded antigens. Since that time, there has since been much progress in understanding the basic biology behind this deceptively simple vaccine platform and much technological advancement to enhance immune potency. Among these advancements are improved formulations and improved physical methods of delivery, which increase the uptake of vaccine plasmids by cells; optimization of vaccine vectors and encoded antigens; and the development of novel formulations and adjuvants to augment and direct the host immune response. The ability of the current, or second-generation, DNA vaccines to induce more-potent cellular and humoral responses opens up this platform to be examined in both preventative and therapeutic arenas. This review focuses on these advances and discusses both preventive and immunotherapeutic clinical applications.

30 years !

c/articles/PMC3202319/pdf/cir334.pdf

30 years!



science.sciencemag.org/content/249/4968/505.long

Systematic evolution of ligands by exponential enrichment: RNA ligands to bacteriophage T4 DNA polymerase

C Tuerk, L Gold

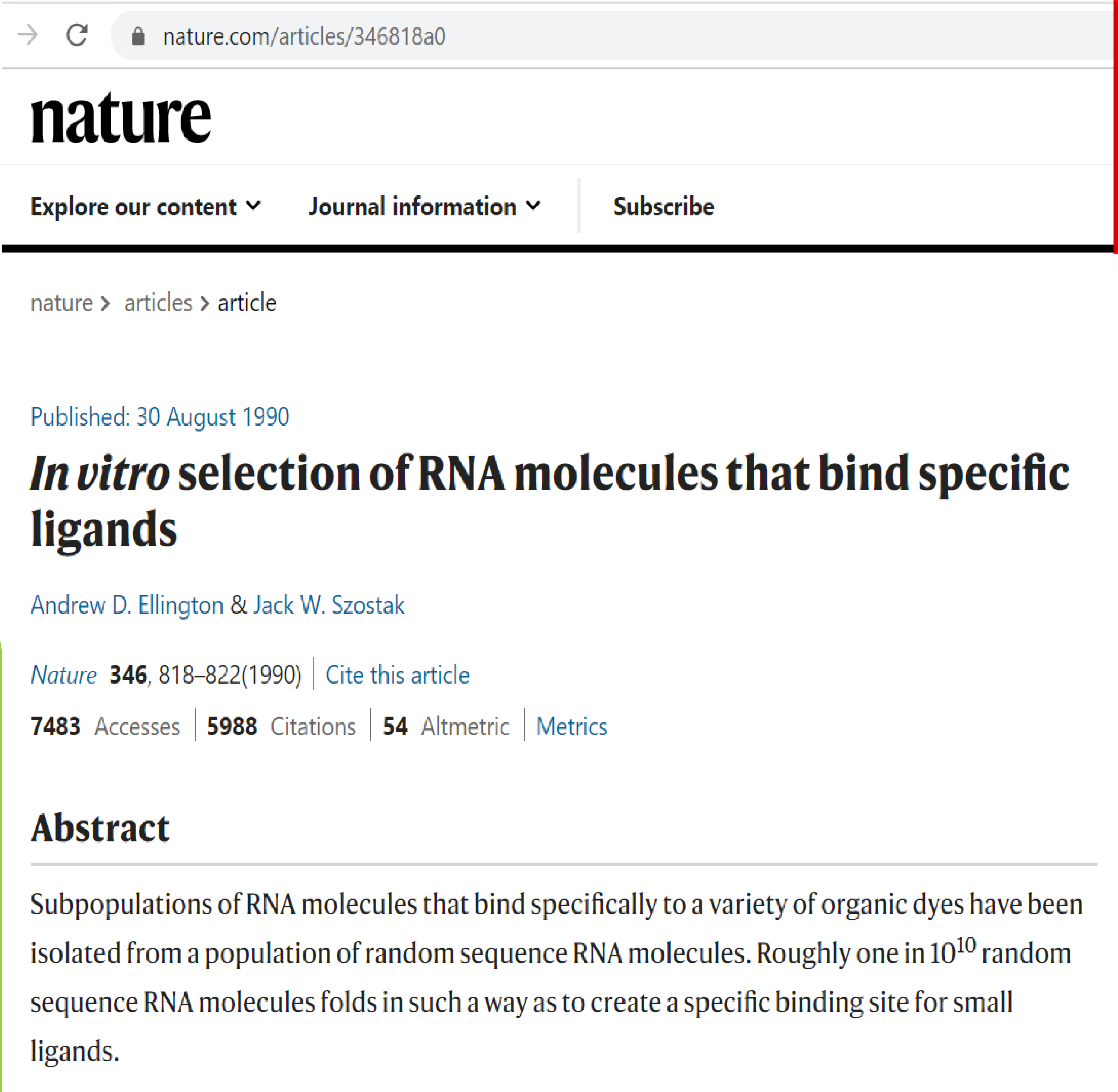
Department of Molecular, Cellular, Developmental Biology, University of Colorado, Boulder 80309.

Science 03 Aug 1990:
Vol. 249, Issue 4968, pp. 505-510
DOI: 10.1126/science.2200121

Abstract

High-affinity nucleic acid ligands for a protein were isolated by a procedure that depends on alternate cycles of ligand selection from pools of variant sequences and amplification of the bound species. Multiple rounds exponentially enrich the population for the highest affinity species that can be clonally isolated and characterized. In particular one eight-base region of an RNA that interacts with the T4 DNA polymerase was chosen and randomized. Two different sequences were selected by this procedure from the calculated pool of 65,536 species. One is the wild-type sequence found in the bacteriophage mRNA; one is varied from wild type at four positions. The binding constants of these two RNA's to T4 DNA polymerase are equivalent. These protocols with minimal modification can yield high-affinity ligands for any protein that binds nucleic acids as part of its function; high-affinity ligands could conceivably be developed for any target molecule.

30 years !



Published: 30 August 1990

In vitro selection of RNA molecules that bind specific ligands

Andrew D. Ellington & Jack W. Szostak

Nature **346**, 818–822(1990) | Cite this article

7483 Accesses | **5988** Citations | **54** Altmetric | Metrics

Abstract

Subpopulations of RNA molecules that bind specifically to a variety of organic dyes have been isolated from a population of random sequence RNA molecules. Roughly one in 10^{10} random sequence RNA molecules folds in such a way as to create a specific binding site for small ligands.

CoVID-19 mRNA vaccine: Women in Science

Dr Susan Berget
https://www.bcm.edu/people-search/susan-berget-18269

Dr Claire Moore
https://gsbs.tufts.edu/facultyResearch/faculty/moore-claire

Dr Kizzmekia Corbett
https://directorsblog.nih.gov/tag/kizzmekia-corbett/

https://doi.org/10.1073/pnas.1919416116
https://irp.nih.gov/podcast/2020/05/dr-kizzmekia-corbett-the-novel-coronavirus-vaccine

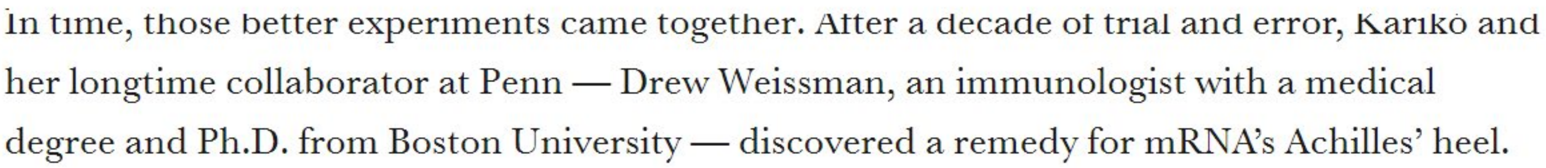
Fig. 1. Members of the MIT Center for Cancer Research (Robert Weinberg, *Second Row from Bottom, Far Left*; Susan Berget, *Third Row from Bottom, Third from Left*; Claire Moore, *Back Row, Fourth from Left*; Philip Sharp, *Back Row, Far Right*). Image courtesy of Robert Weinberg. https://news.mit.edu/2020/phillip-sharp-rna-vaccines-1211

Katalin Karikó spent the 1990s collecting rejections. Her work, attempting to harness the power of mRNA to fight disease, was too far-fetched for government grants, corporate funding, and even support from her own colleagues. By 1995, after six years on the faculty at the University of Pennsylvania, Karikó got demoted. She had been on the path to full professorship, but with no money coming in to support her work on mRNA, her bosses succumbed to myopia.

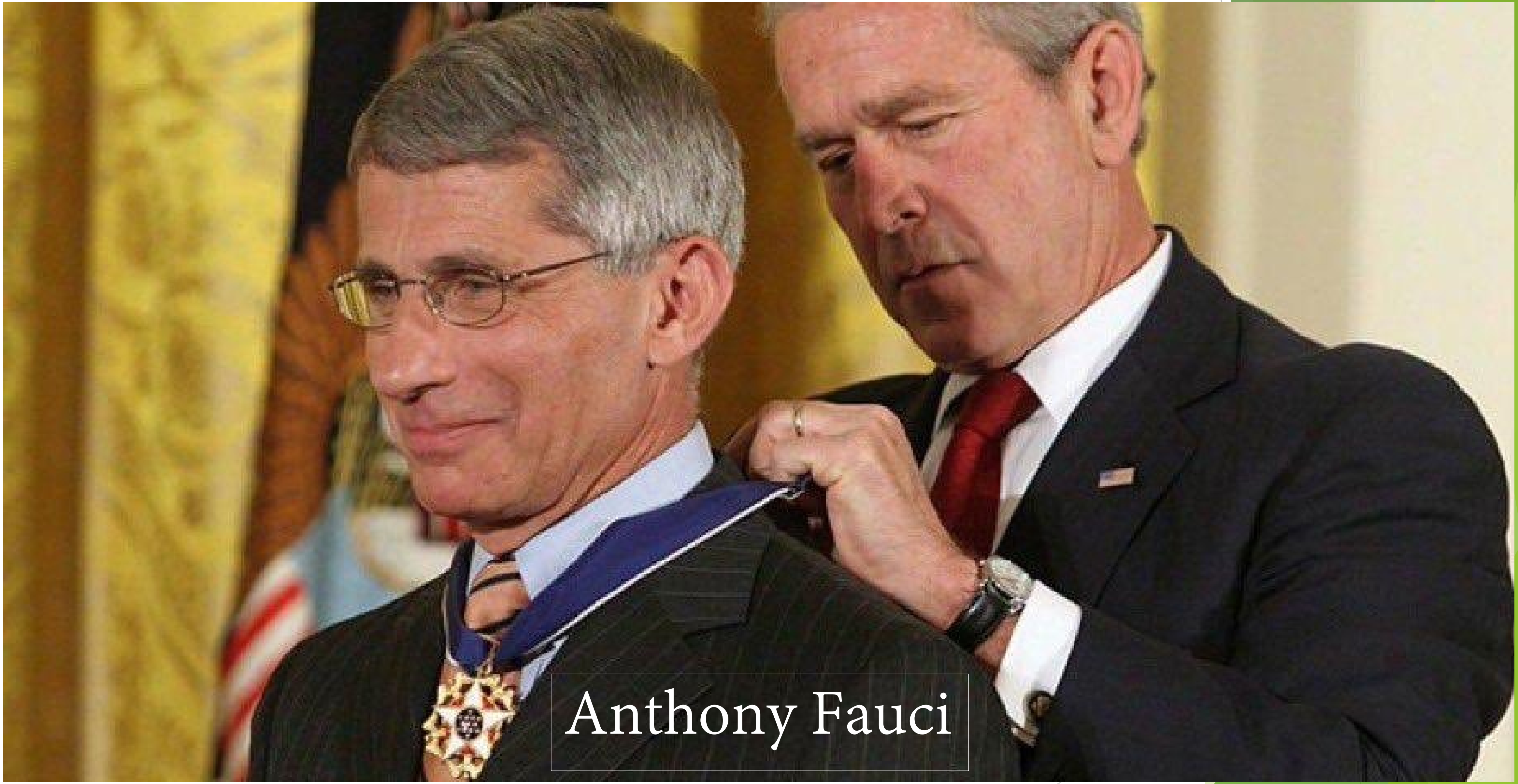
Katalin Karikó, a senior vice president at BioNTech overseeing its mRNA work, in her home office in Rydal, Penn.

JESSICA KOURKOUNIS FOR THE BOSTON GLOBE

www.statnews.com/2020/11/10/the-story-of-mrna-how-a-once-dismissed-idea-became-a-leading-technology-in-the-covid-vaccine-race/

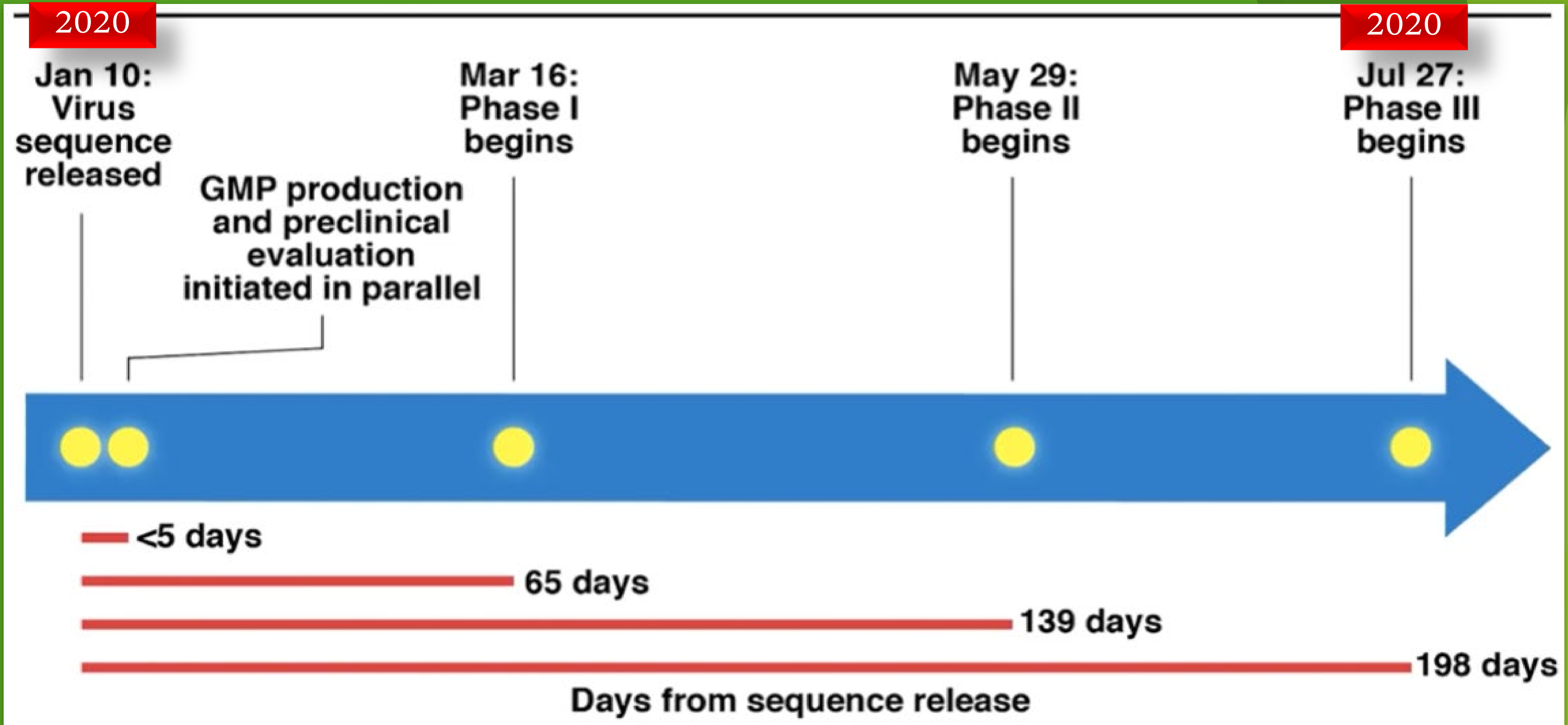


In time, those better experiments came together. After a decade of trial and error, Karikó and her longtime collaborator at Penn — Drew Weissman, an immunologist with a medical degree and Ph.D. from Boston University — discovered a remedy for mRNA's Achilles' heel.



Anthony Fauci

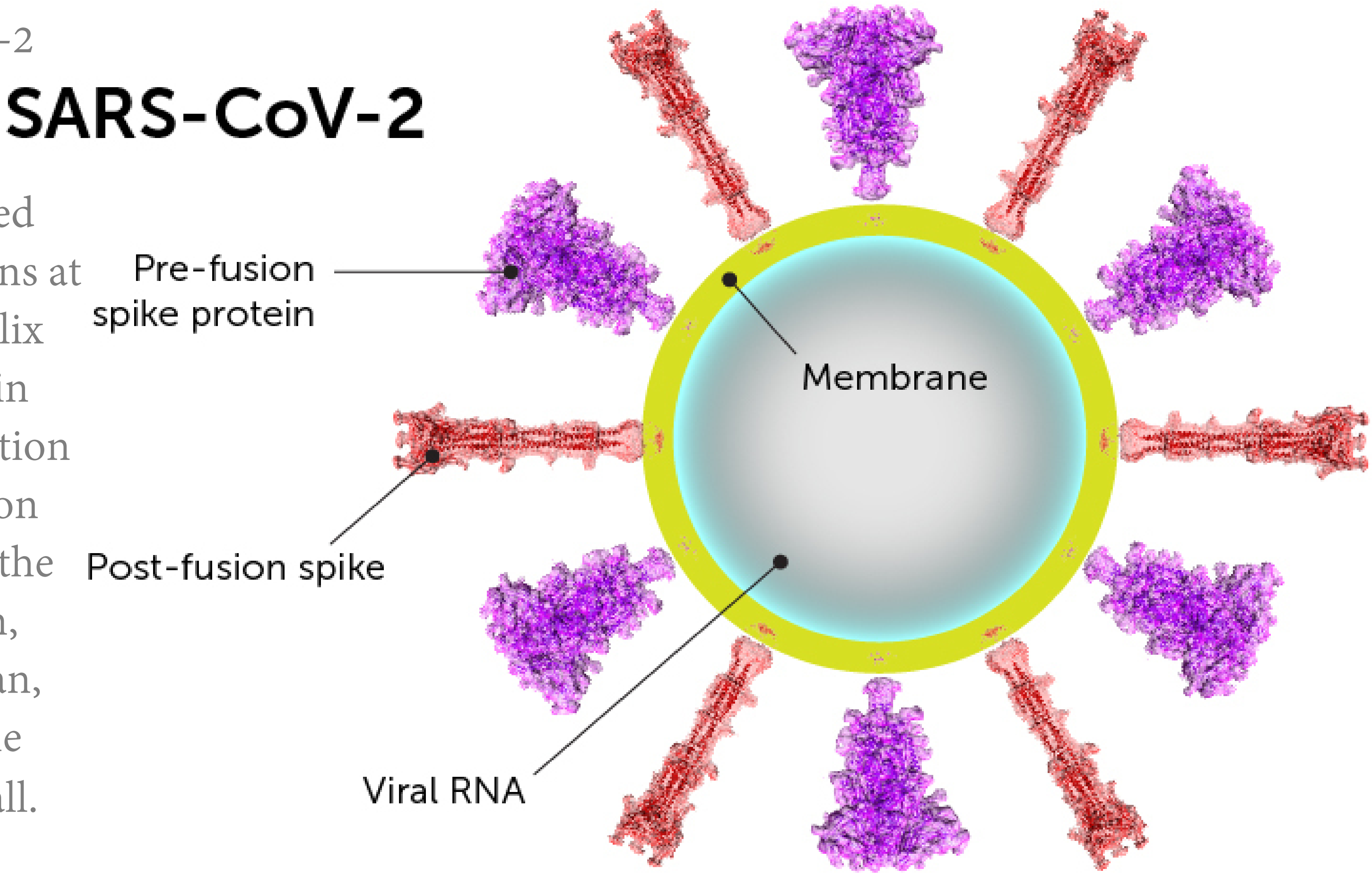
Timeline of SARS-CoV-2 mRNA-1273 Vaccine Development. NIAID, NIH & Moderna (Cambridge, MA).



SARS-CoV-2 mRNA-1273 encodes the SARS-CoV-2 full-length spike glycoprotein trimer, S-2P (stabilized with 2 Proline substitutions at the top of the central helix in S2 subunit). mRNA is encapsulated in lipid nanoparticles (0.5 mg per mL).

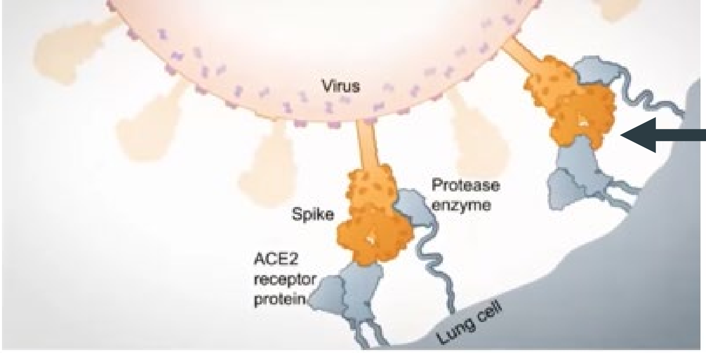
https://www.mclellanlab.org/selected-publications

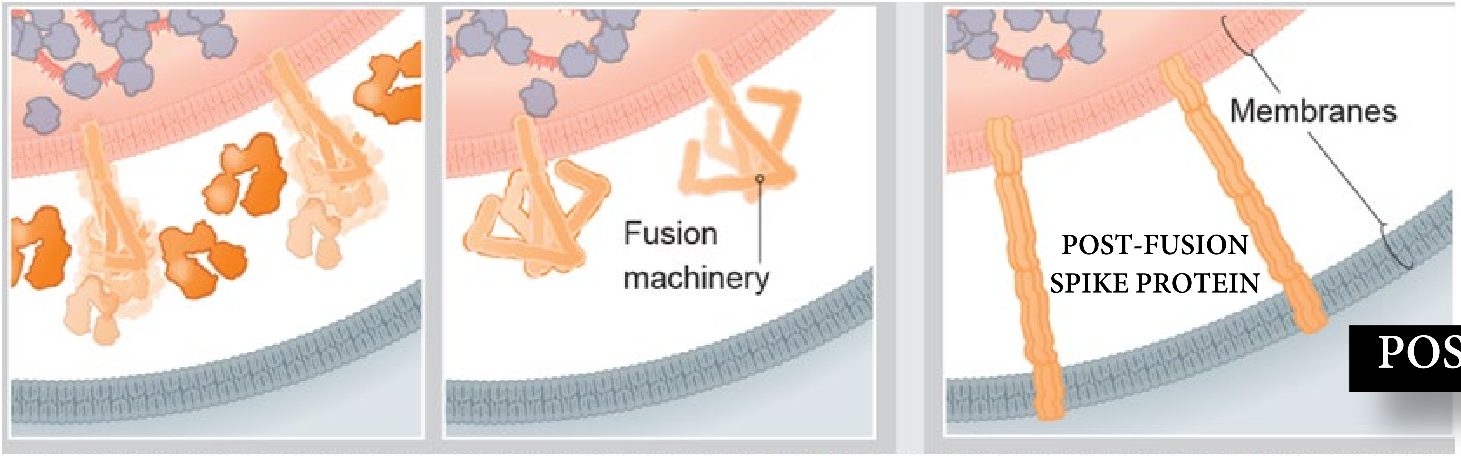
SARS-CoV-2 mRNA-1273 encodes the SARS-CoV-2 full-length spike glycoprotein trimer, S-2P which was stabilized with Proline substitutions at the top of the central helix in S2 subunit to maintain the structural configuration resembling the pre-fusion Spike protein. Without the two Proline substitution, (S-2P by Jason McClellan, NIH) the mRNA vaccine may not be effective at all.



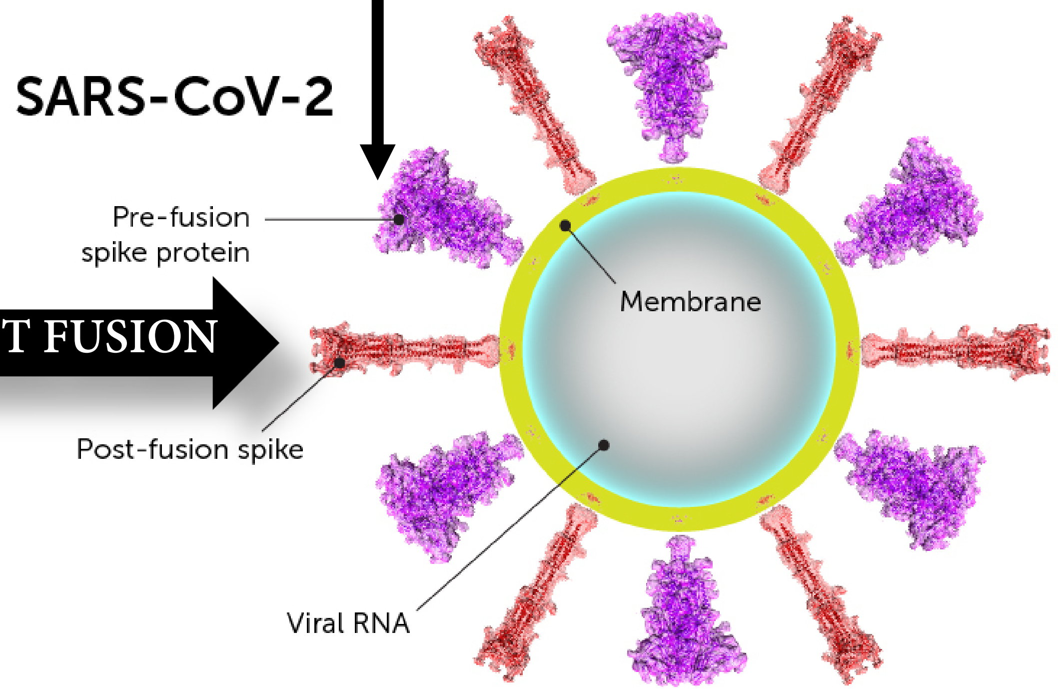
BREAKTHROUGH

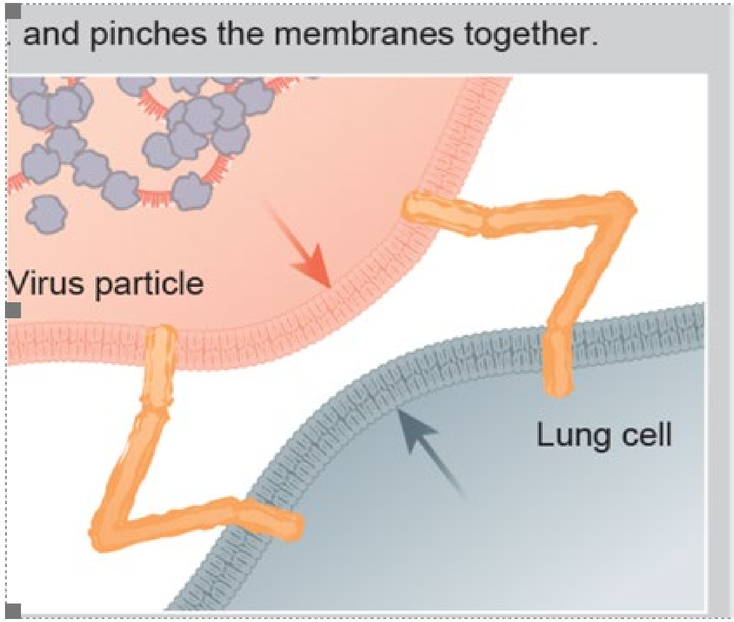
Significant change in configuration between PRE-fusion and POST-fusion Spike proteins

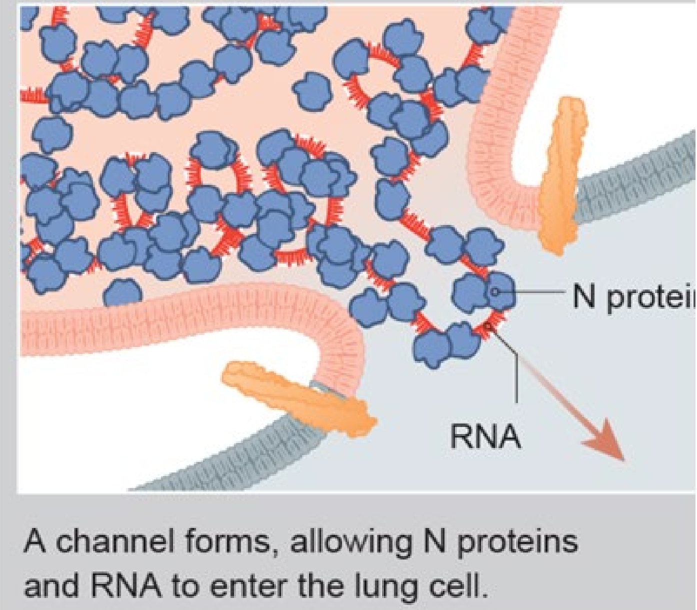




POST FUSION

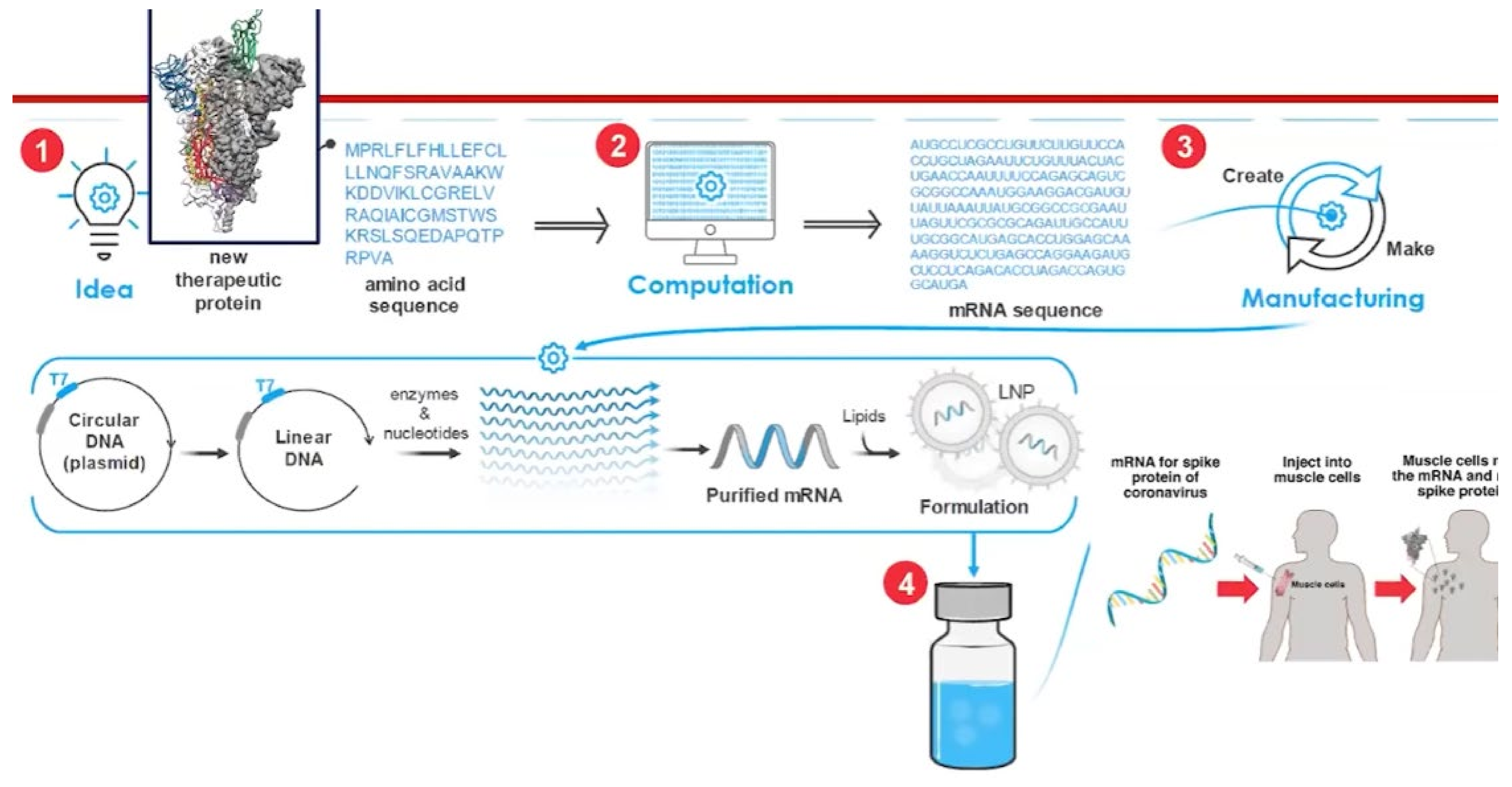



and pinches the membranes together.



A channel forms, allowing N proteins and RNA to enter the lung cell.

Cartoon by Brit Glausinger, University of California Berkeley

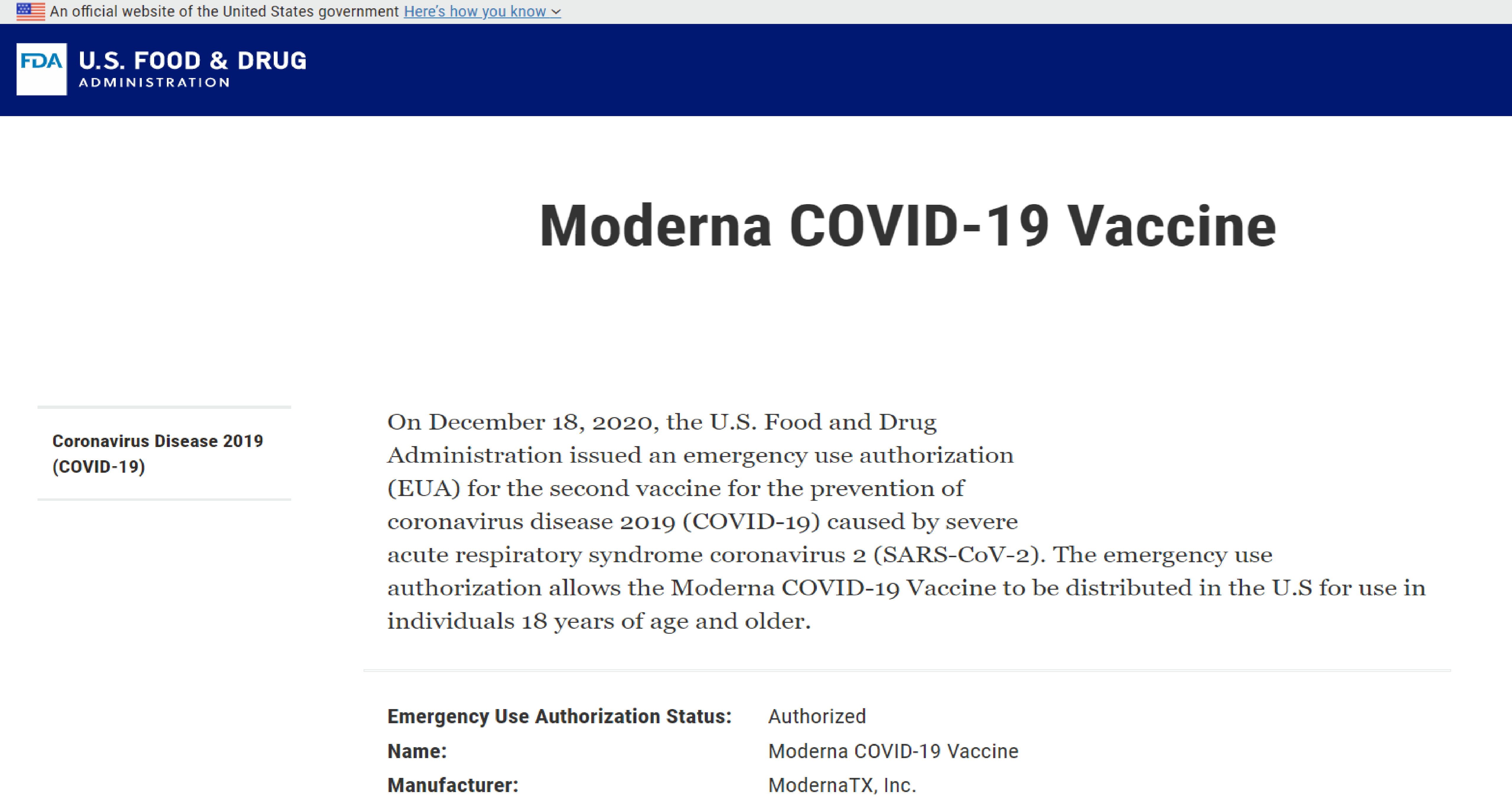


The mRNA vaccine → 30+ years in the making …

Pfizer-BioNTech COVID-19 Vaccine

On December 11, 2020, the U.S. Food and Drug Administration issued the first emergency use authorization (EUA) for a vaccine for the prevention of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older. The emergency use authorization allows the Pfizer-BioNTech COVID-19 Vaccine to be distributed in the U.S.

Emergency Use Authorization Status:	Authorized
Name:	Pfizer-BioNTech COVID-19 Vaccine
Manufacturer:	Pfizer Inc.



Moderna COVID-19 Vaccine

On December 18, 2020, the U.S. Food and Drug Administration issued an emergency use authorization (EUA) for the second vaccine for the prevention of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The emergency use authorization allows the Moderna COVID-19 Vaccine to be distributed in the U.S for use in individuals 18 years of age and older.

Emergency Use Authorization Status:	Authorized
Name:	Moderna COVID-19 Vaccine
Manufacturer:	ModernaTX, Inc.

FDA NEWS RELEASE

FDA Issues Emergency Use Authorization for Third COVID-19 Vaccine

For Immediate Release: February 27, 2021

Español

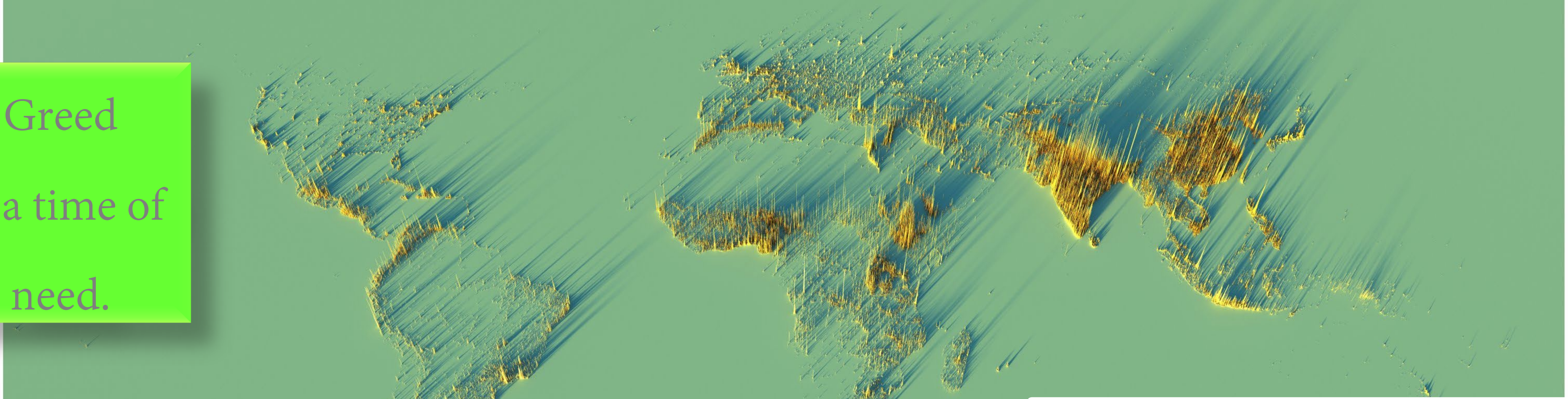
Today, the U.S. Food and Drug Administration issued an emergency use authorization (EUA) for the third vaccine for the prevention of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The EUA allows the Janssen COVID-19 Vaccine to be distributed in the U.S for use in individuals 18 years of age and older.

EU just bought 900 million doses of PFIZER vaccine for USD $43 BILLION (EUR 35 BILLION)

Ramping Up Its COVID Response, EU Will Buy Up To 1.8B Doses Of Pfizer Vaccine

May 8, 2021 · 10:11 AM ET www.npr.org/sections/coronavirus-live-updates/2021/05/08/995007124/ramping-up-its-covid-response-eu-will-buy-up-to-1-8b-doses-of-pfizer-vaccine

Greed
at a time of
need.



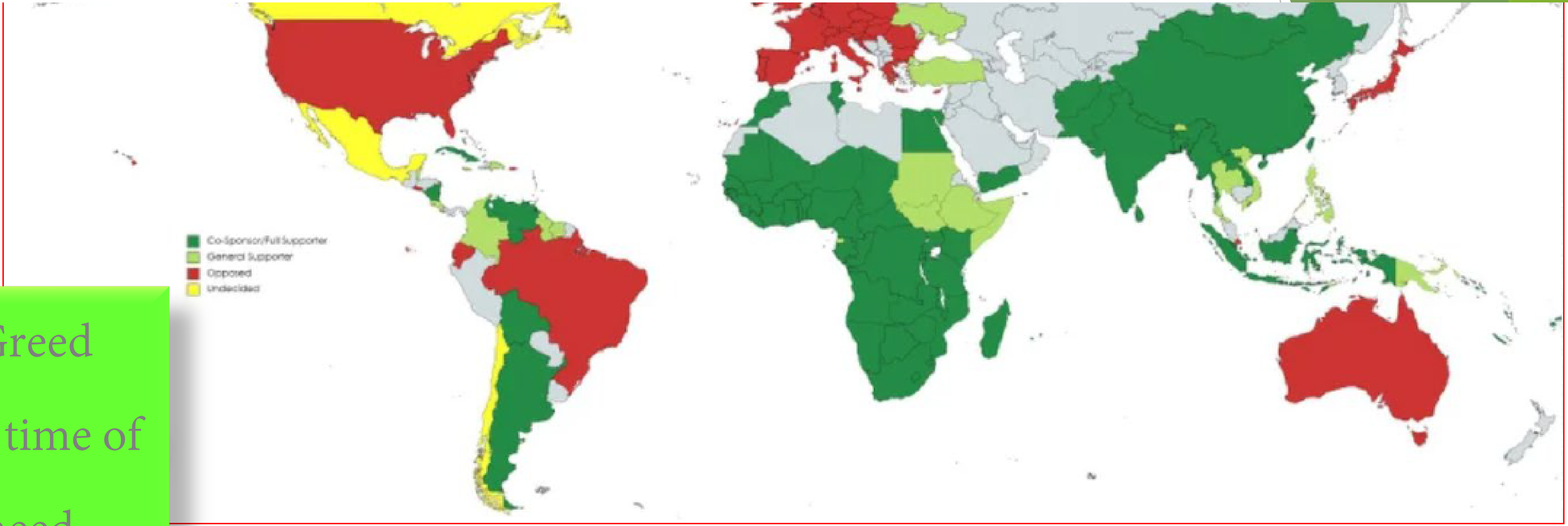
Global Population Density

Ursula von der Leyen
@vonderleyen

Happy to announce that @EU_Commission has just approved a contract for guaranteed 900 million doses (+900 million options) with @BioNTech_Group @Pfizer for 2021-2023.

Other contracts and other vaccine technologies will follow.

5:49 AM · May 8, 2021



Greed
at a time of
need.

Figure 45: Countries shown in RED are the nations which OPPOSED[623] and *voted against* the UN call for waiving patent law for life-saving CoVID-19 vaccines. Countries in RED blocked the proposal which called for the right to manufacture and import affordable CoVID-19 vaccines. The proposal[624] was led by India and South Africa. Countries shown in yellow are "undecided" after >100 million CoVID-19 cases and nearly 3 million deaths due to CoVID-19, globally. https://doi.org/10.26434/chemrxiv.13102877

Why truth matters …

Dates of discovery of the novel coronavirus causing COVID-19 and implementation of control measures in China, from 31 Dec 2019.

31 Dec. Respiratory disease due to novel coronavirus detected in Wuhan city

20 Jan. Novel coronavirus disease categorized as a Category B infectious disease and managed under Category A infectious diseases

21 Jan. Ministry of Transport launches Level 2 emergency

23 Jan. Wuhan city travel ban; first 3 provinces begin Level 1 response

24 Jan. 14 provinces begin Level 1 response

25 Jan. 13 provinces begin Level 1 response

26 Jan. China State Council approves an extension of the Spring Festival holiday to 2 Feb

27 Jan. Ministry of Education postpones start of the spring semester in 2020

28 Jan. Ministry of Transport refunds all public rail, road, and water travel tickets

29 Jan. Last province begins Level 1 response

30 Jan. 14,000 health checkpoints set up at bus and boat terminals, service centers, and toll gates nationwide

3 Feb. Travel permits to Hong Kong and Macau suspended

10 Feb. Residential districts in Hubei province put under closed management

31 … 20 21 23 24 25 26 27 28 29 30 3 10

Huaiyu Tian et al. Science 2020;368:638-642

nature.com/news/polopoly_fs/1.12413!/menu/main/topColumns/topLeftColumn/pdf/494155a.pdf

The latest US influenza season is more severe and has caused more deaths than usual.

EPIDEMIOLOGY

When Google got flu wrong

US outbreak foxes a leading web-based method for tracking seasonal flu.

Mistrust any article that uses a visual which superimposes a Gaussian distribution. Evidence suggests that the bells must herald heteroskedasticity as the new normal.

Tarun Khanna • 1st

Jorge Paulo Lemann Professor, Harvard Business School Director, Lakshmi Mittal an...

2h •

Which Covid-19 Data Can You Trust?
I spend a lot of time working on data and algorithm rich methods for entrepreneurship of all stripes. It's hugely fun! But lately, watching the barrage of Covid-19-motivated data provided by the well-meaning tech and advisory community, I began to wonder. Two colleagues, an epidemiologist and a physician, and I wrote this today. Please share your comments

Which Covid-19 Data Can You Trust?

hbr.org

51 • 6 Comments

Shoumen Datta • You 16m ...

MIT

Mistrust any article that uses a visual which superimposes a Gaussian distribution. Evidence indicates that the bells must herald heteroskedasticity as the new normal.

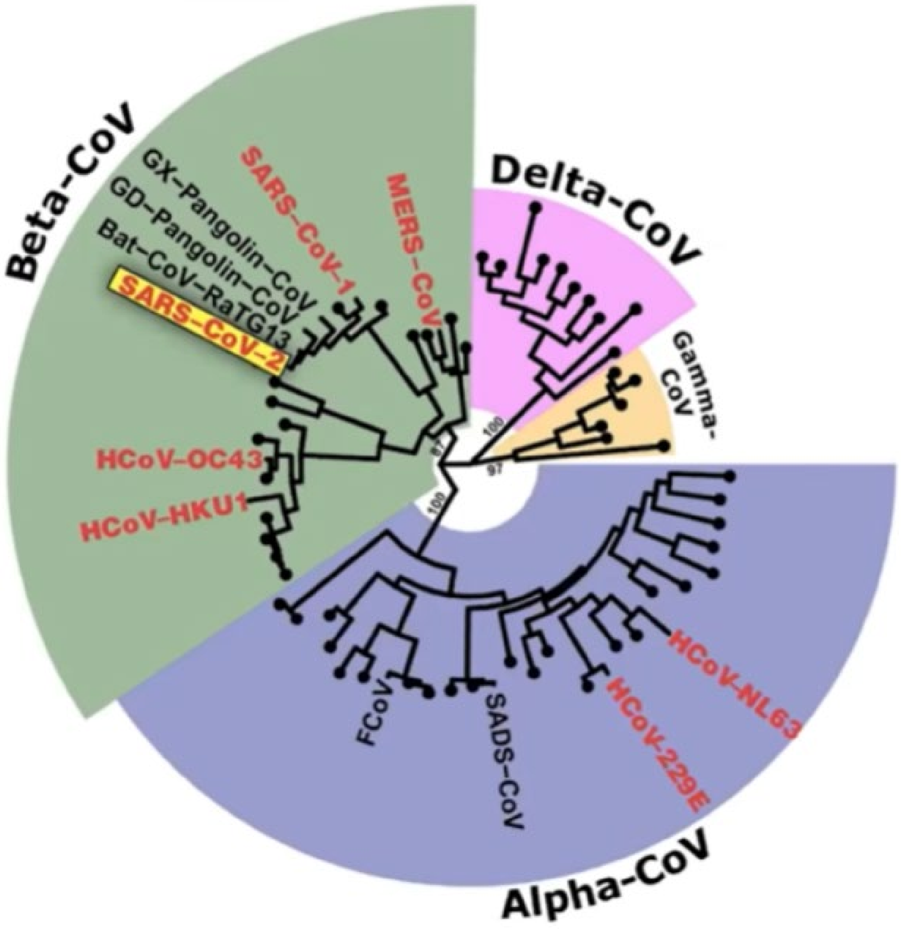
· 2 Likes

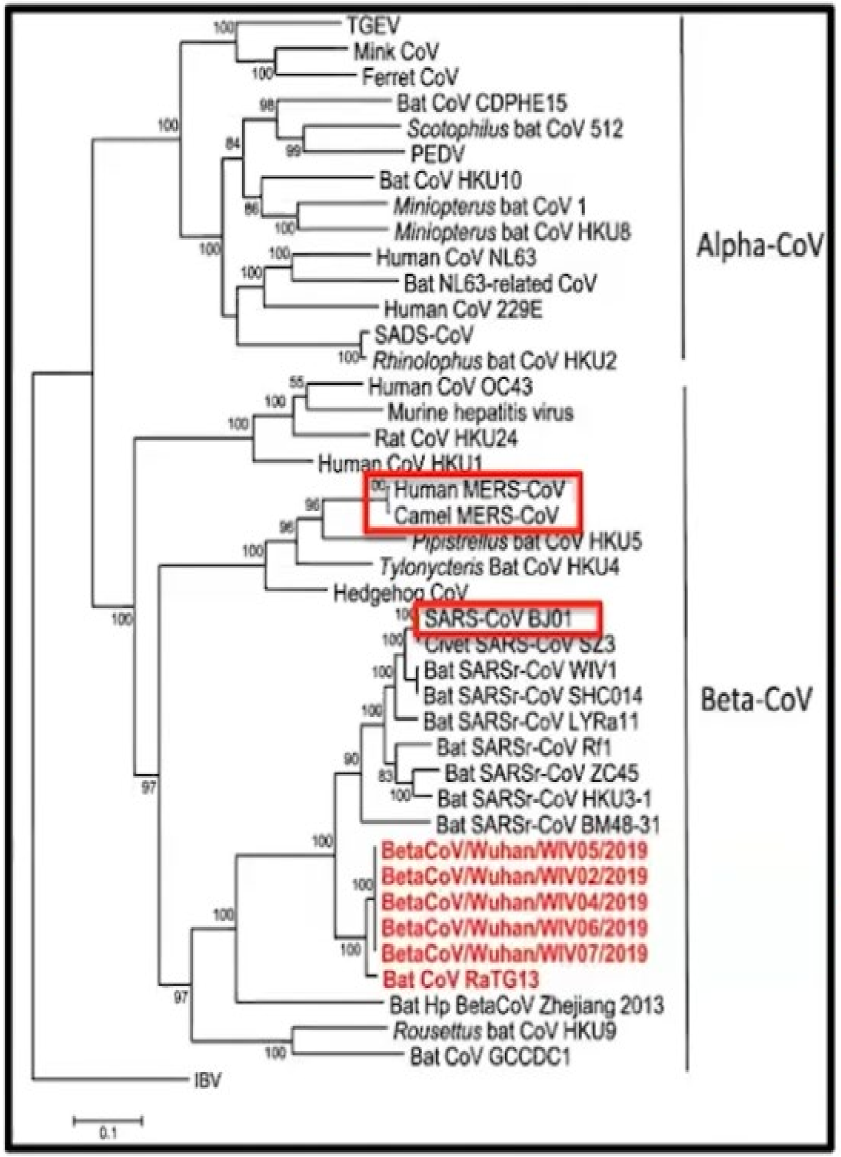
We can't deal with half truths, lies, fake news but we can explore science.

Very brief and select Molecular Biology and Molecular Medicine of SARS-CoV-2 & CoVID-19

Plethora of unknown unknowns …

Phylogenomic Map of Coronavirus Family





MERS Epidemiology

Up to November 2019

Cases: 2494

Deaths: 854

Countries: 27

SARS Epidemiology

Cases: 8437

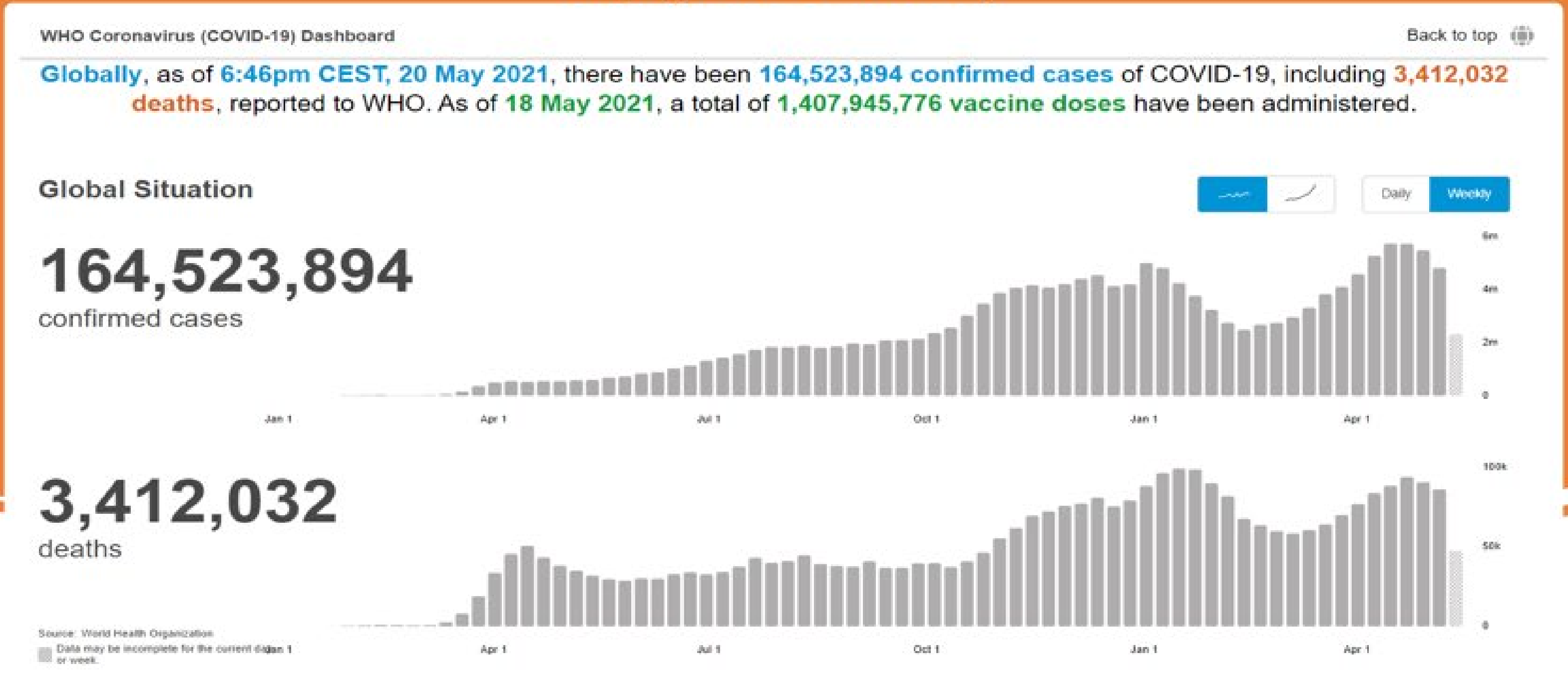
Deaths: 813

Countries: 32

From Anthony Fauci, NIAID. Courtesy of Sebastian M. Gygli, NIAID ■ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6496161/pdf/AAC.02175-18.pdf

	Emergence	Cases	Fatality Rate	Transmissibility
SARS	2003	8,098	11%	+
MERS	2011	2,519	34%	+
SARS-CoV-2	2019	➢ 200 million	0.5-1% Est	+++
SARS-CoV-3?	??	??	??	??
SARS-CoV-4?	??	??	??	??

https://covid19.who.int/



WHO Coronavirus (COVID-19) Dashboard

Globally, as of 6:46pm CEST, 20 May 2021, there have been 164,523,894 confirmed cases of COVID-19, including 3,412,032 deaths, reported to WHO. As of 18 May 2021, a total of 1,407,945,776 vaccine doses have been administered.

Global Situation

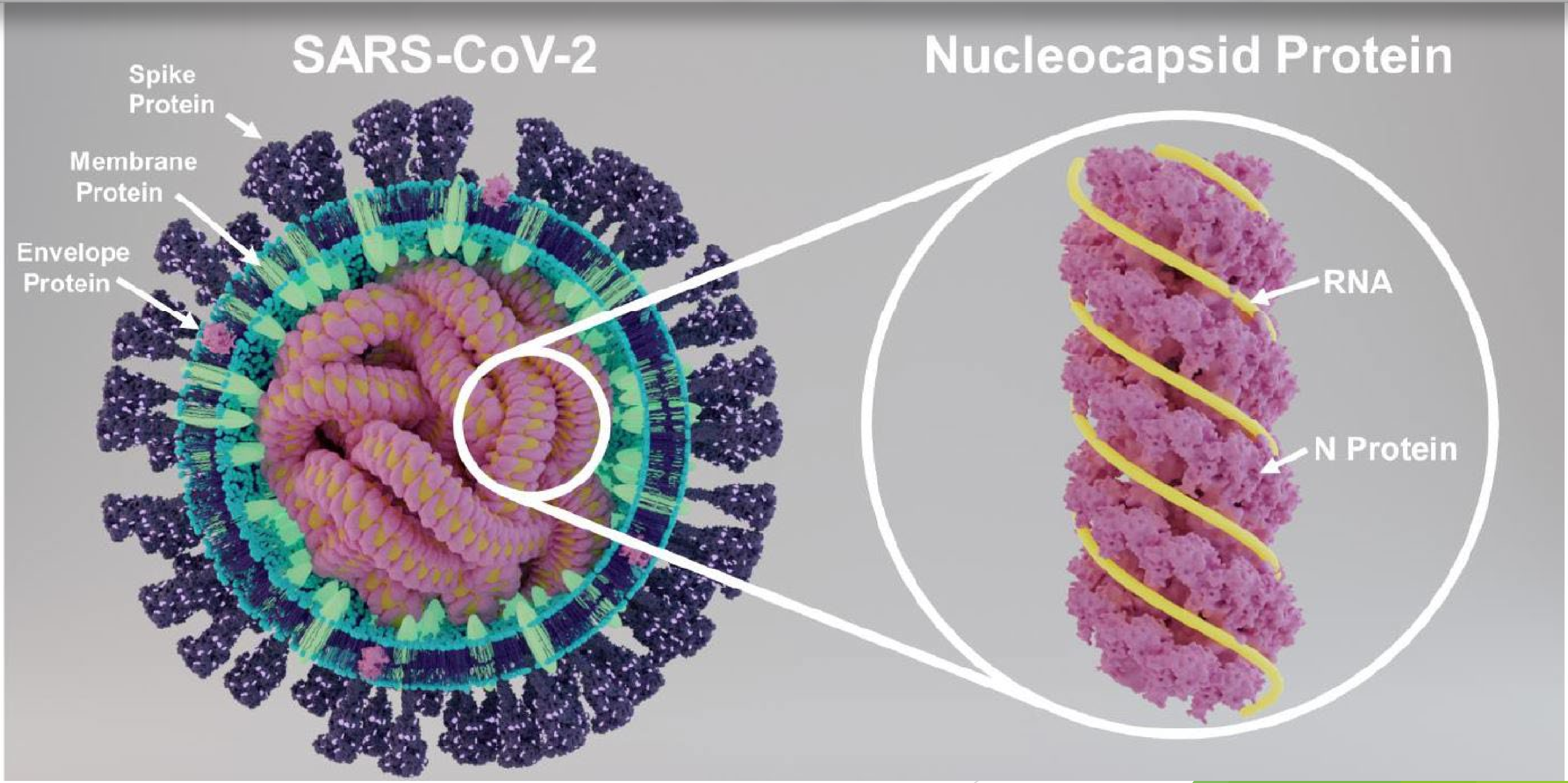
164,523,894
confirmed cases

3,412,032
deaths

Source: World Health Organization

Data may be incomplete for the current day or week.

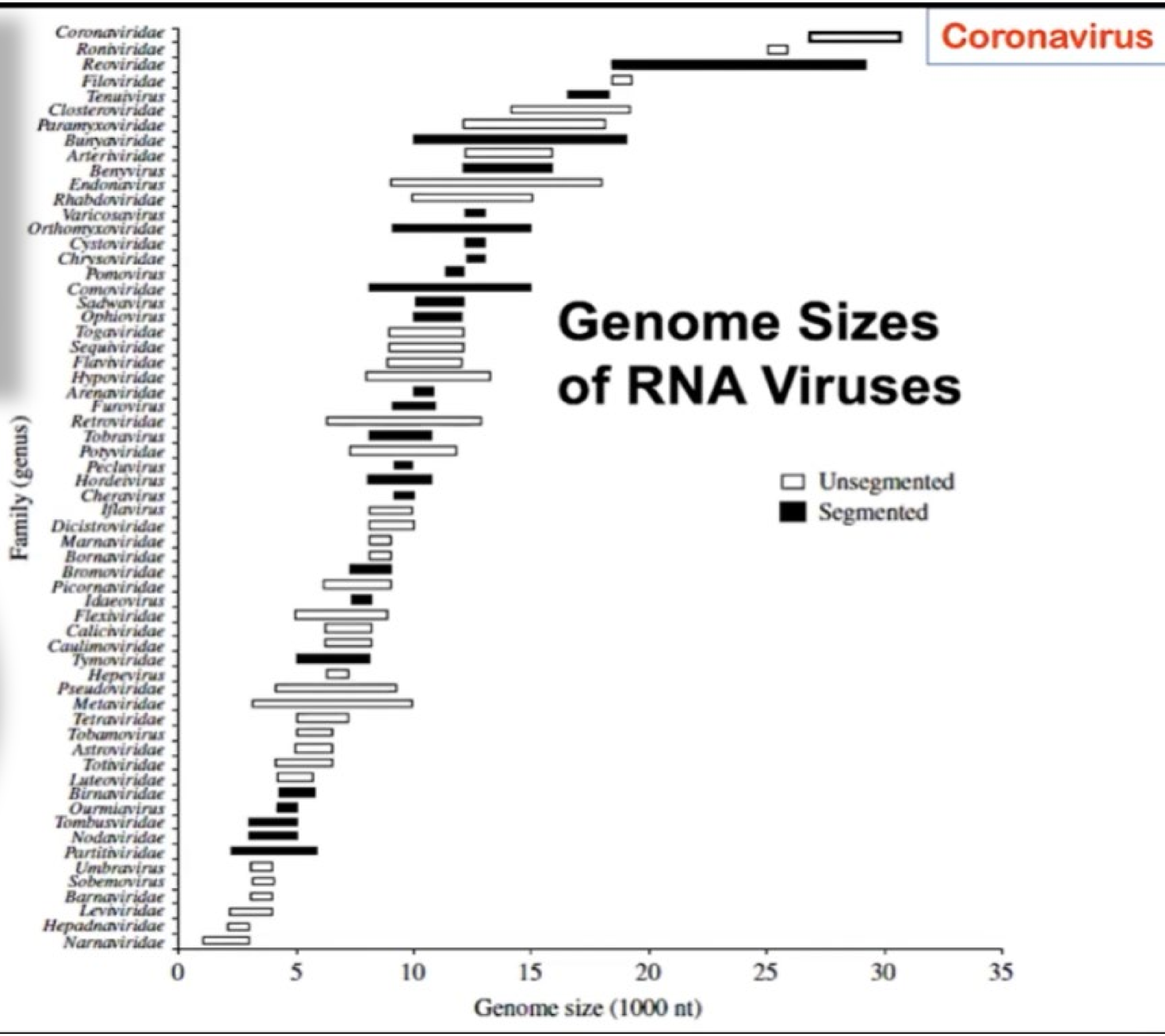
SARS-CoV-2 is a member of the Coronavirus Family This virus family has the largest genome among RNA viruses.



Coronaviridae: Largest genome size of RNA viruses

WHY

?



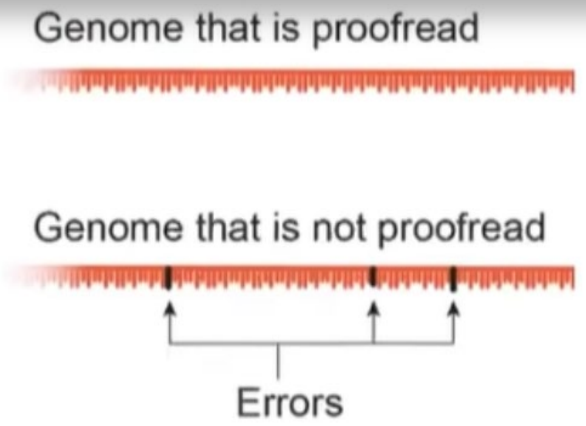
Coronaviridae: Largest genome size of RNA viruses

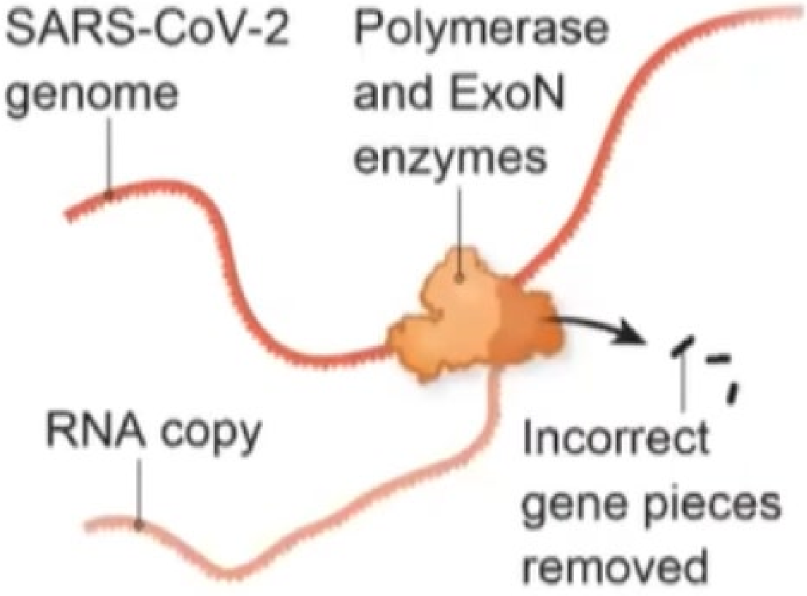
WHY

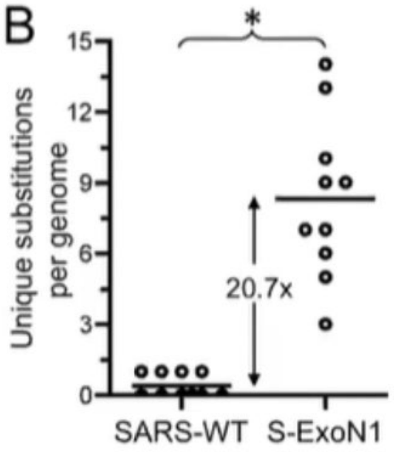
?

We don't know !!

SARS-CoV-2 proofreading: removes incorrect pieces







Mutated or inactivated Nsp14-ExoN results in >20-fold increase (Eckerle *et al* 2010) in genomic errors (B, right). ExoN in RdRp of SARS-CoV-2 enables error correction (left).

SARS-CoV-2 proofreading: removes incorrect pieces

Then WHY so many mutations?

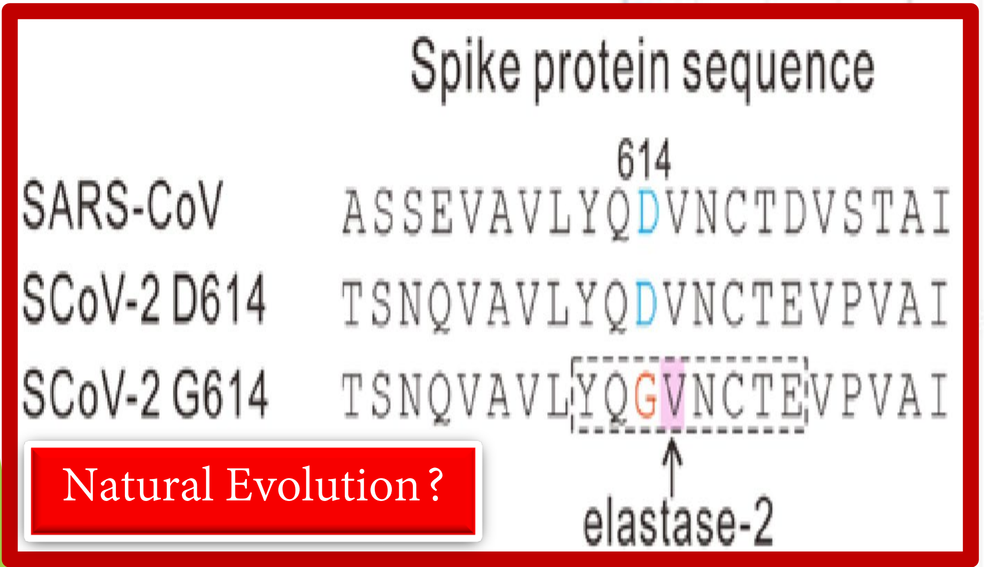
SARS-CoV-2 proofreading: removes incorrect pieces

Then WHY so many mutations?

We don't know !!

D614G is the most abundant (~65%) non-synonymous mutations observed in S protein (creates neutrophil elastase-2 cleavage site). Phylogenetic analysis of SARS-CoV-2 genomes (n = 2,834) shows D614G mutant (BLUE, clade G) highest around the world. D⟶G is an “up-mutation” advantageous to the virus. D614G creates a host serine protease elastase-2 cleavage site. The coronavirus S protein must be cleaved by host proteases to enable membrane fusion, critical for viral entry. D614G mutation in S protein promotes virus entry (2X in pseudovirus assays). Data indicates that D614G mutation changes the antigenicity of S protein, thereby decreasing (3 to 5 fold) neutralization sensitivity to individual convalescent sera.

www.biorxiv.org/content/10.1101/2020.06.20.161323v1.full.pdf



Spike protein sequence

614

SARS-CoV ASSEVAVLYQDVNCTDVSTAI

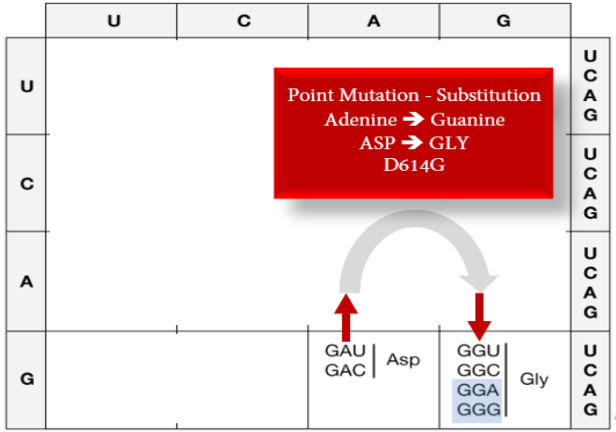
SCoV-2 D614 TSNQVAVLYQDVNCTEVPVAI

SCoV-2 G614 TSNQVAVLYQGVNCTEVPVAI

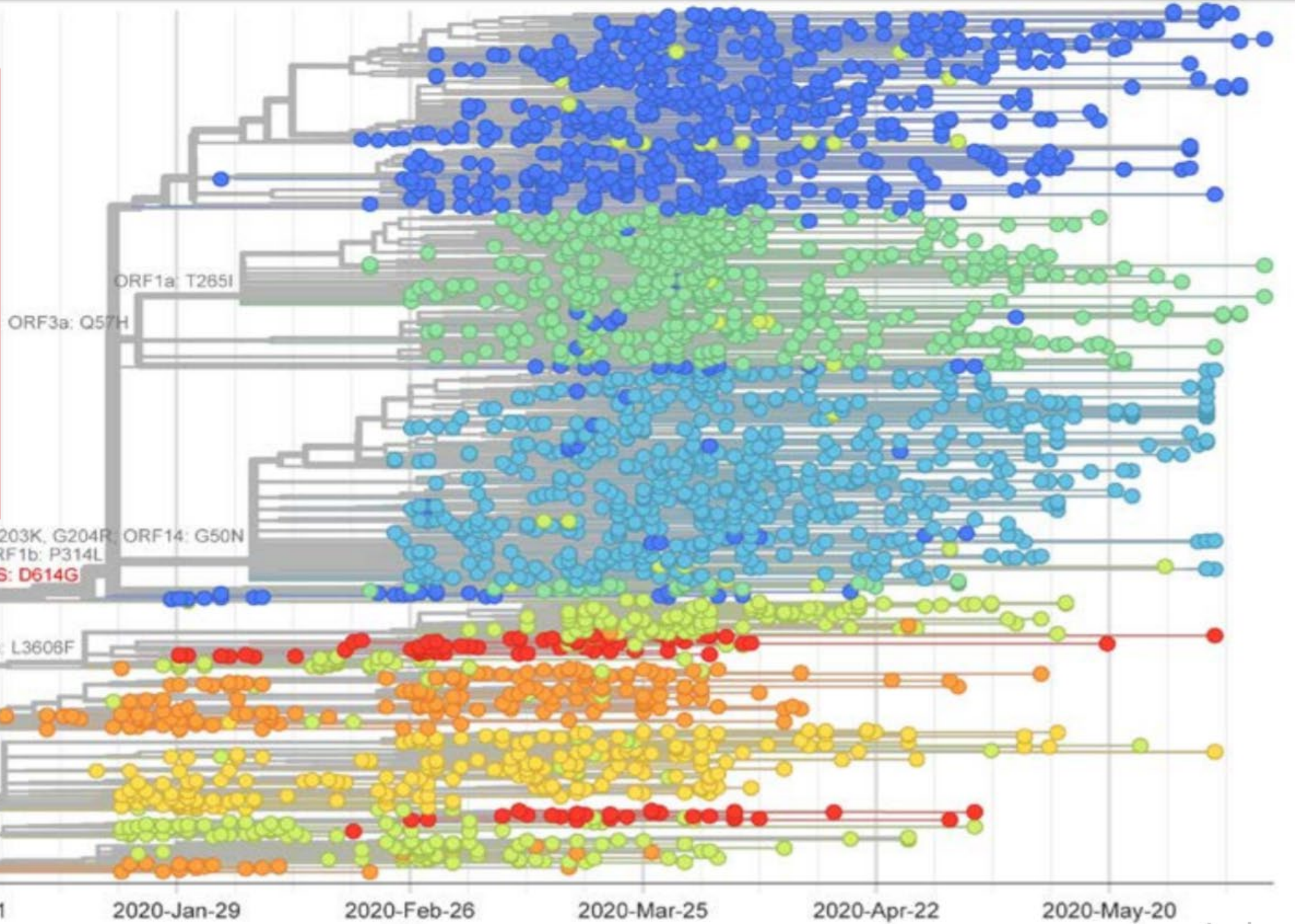
elastase-2

Natural Evolution ?

www.ncbi.nlm.nih.gov/pmc/articles/PMC4369385/pdf/978-1-4939-2438-7_Chapter_1.pdf



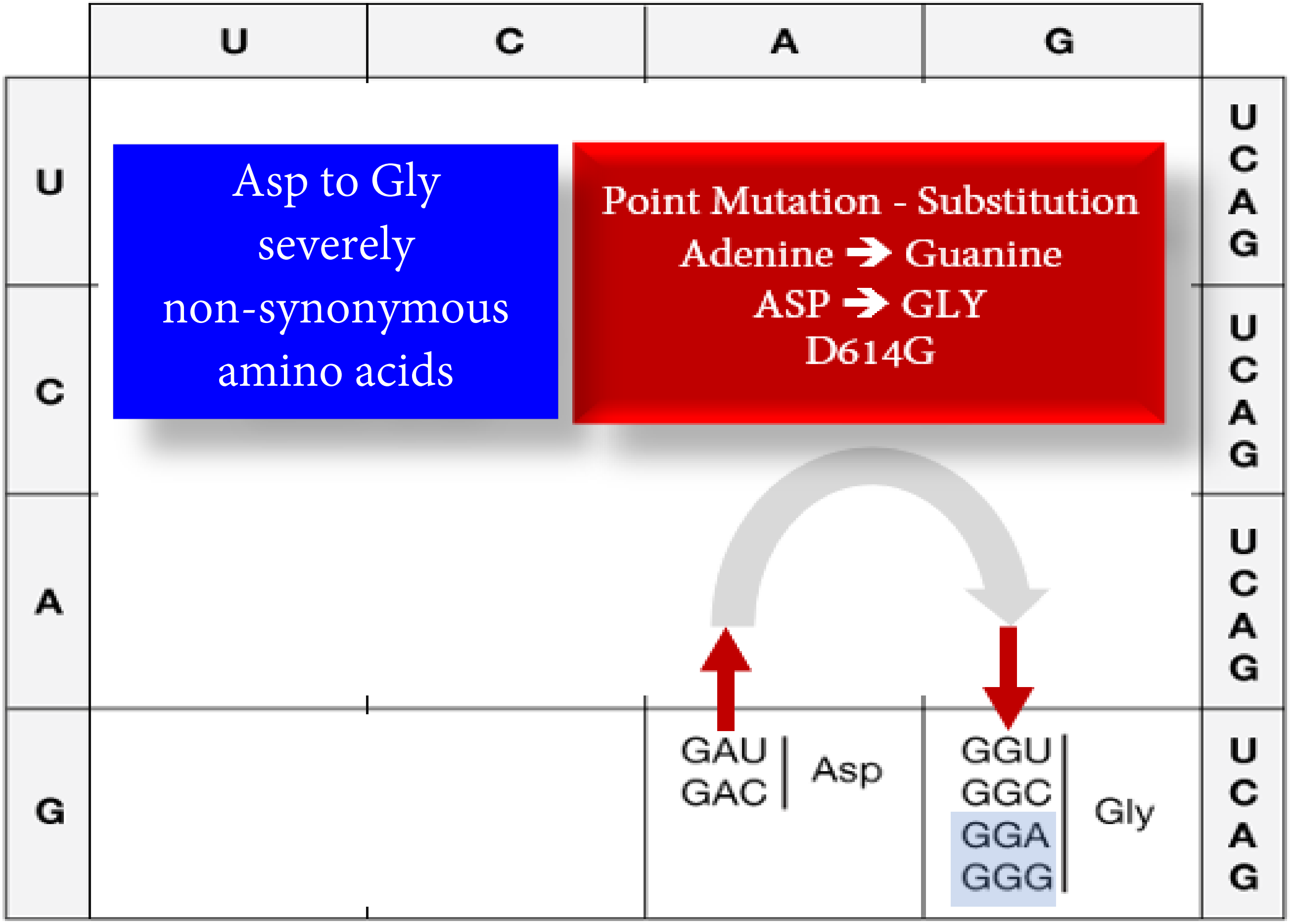
Point Mutation - Substitution
Adenine → Guanine
ASP → GLY
D614G



D614G is the most abundant (~65%) non-synonymous mutations observed in the S protein (creates neutrophil elastase-2 cleavage site). Natural evolution ?

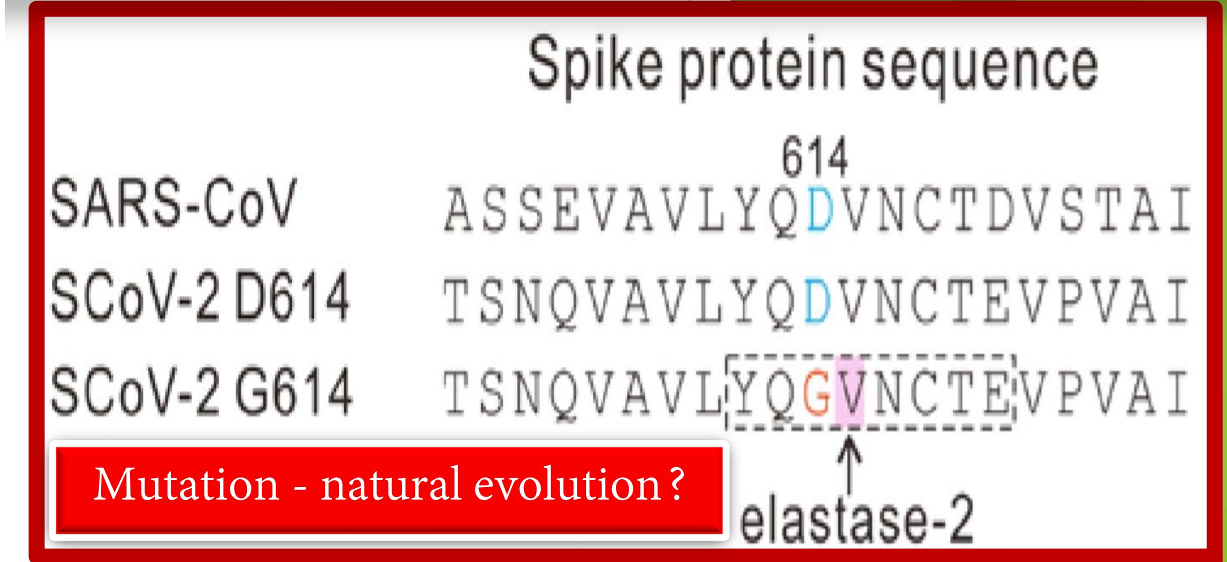
The D614G mutation of SARS-CoV-2 spike protein enhances viral infectivity and decreases neutralization sensitivity to individual convalescent sera

www.biorxiv.org/content/10.1101/2020.06.20.161323v1.full.pdf



Asp to Gly severely non-synonymous amino acids

Point Mutation - Substitution
Adenine ➔ Guanine
ASP ➔ GLY
D614G



Mutation - natural evolution ?

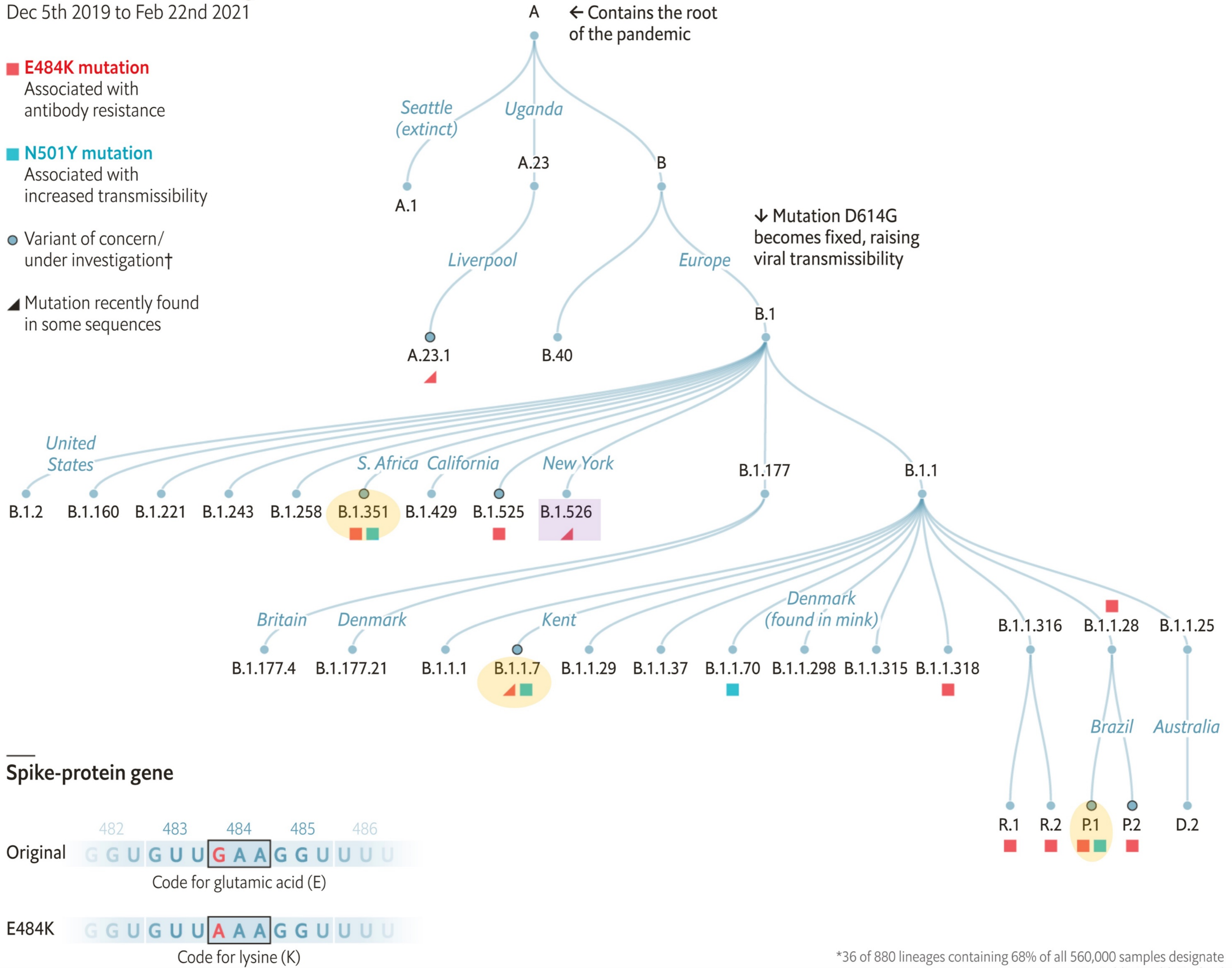
Mutations in Spike Protein	No. of mutation	No. of wildtype	Total No. of sequences	Mutation (%)
D614G	2995	1637	4632	64.659
A829T	37	4602	4639	0.798
L5F	33	4614	4647	0.710
H146Y	26	4594	4620	0.563
P1263L	15	4631	4646	0.323
V483A	12	4387	4399	0.273
S939F	12	4626	4638	0.259
R78M	10	4623	4633	0.216
E583D	9	4639	4648	0.194
A845S	9	4632	4641	0.194

Top 10 abundant non-synonymous mutations observed in S protein

www.ncbi.nlm.nih.gov/pmc/articles/PMC4369385/pdf/978-1-4939-2438-7_Chapter_1.pdf

Selected SARS-CoV-2 lineages*

Dec 5th 2019 to Feb 22nd 2021



- 🟥 **E484K mutation** Associated with antibody resistance
- 🟦 **N501Y mutation** Associated with increased transmissibility
- ● Variant of concern/ under investigation†
- ◢ Mutation recently found in some sequences

Spike-protein gene

Original G G U G U U G A A G G U U U U

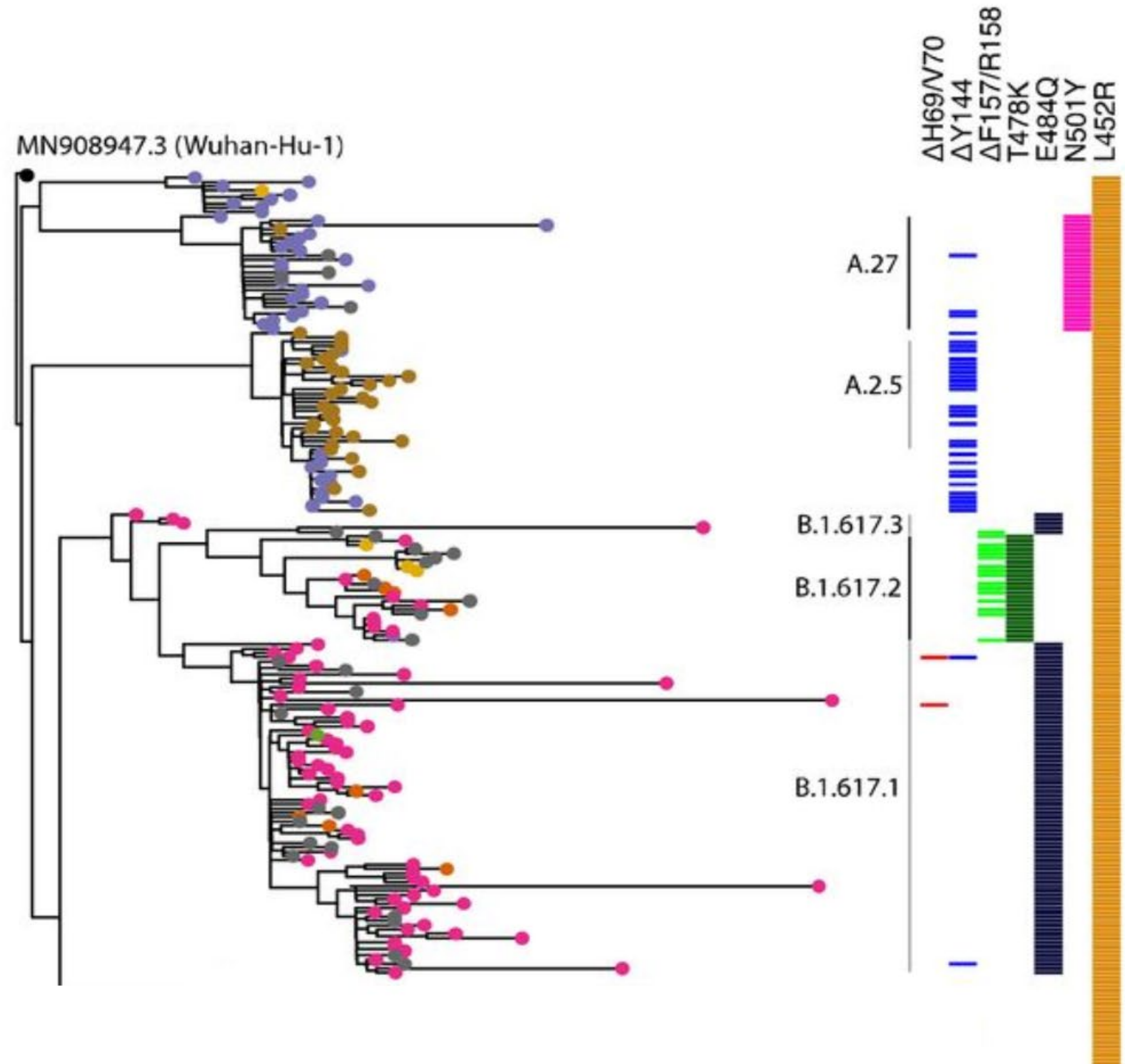
Code for glutamic acid (E)

E484K G G U G U U A A A G G U U U U

Code for lysine (K)

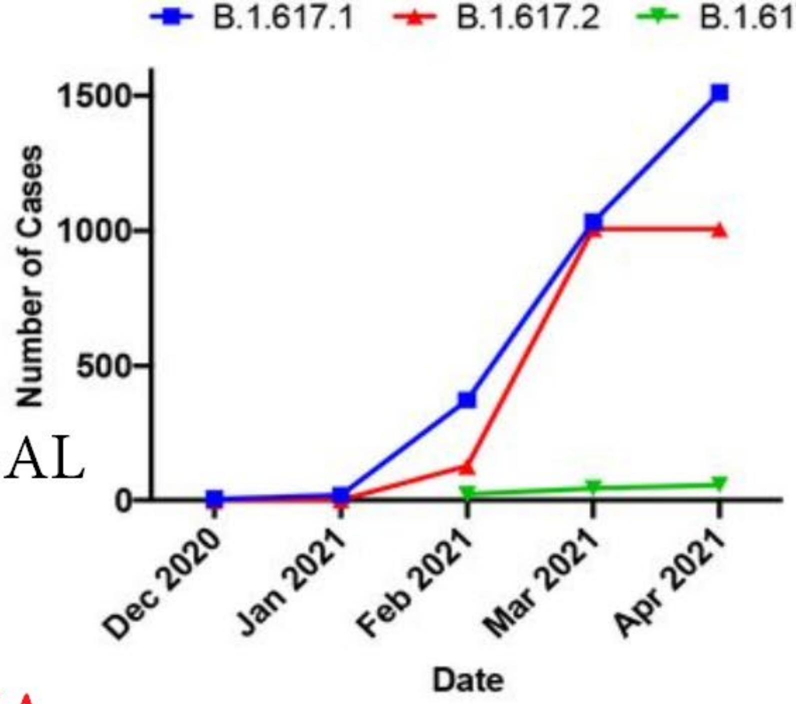
*36 of 880 lineages containing 68% of all 560,000 samples designate

†By Public Health England

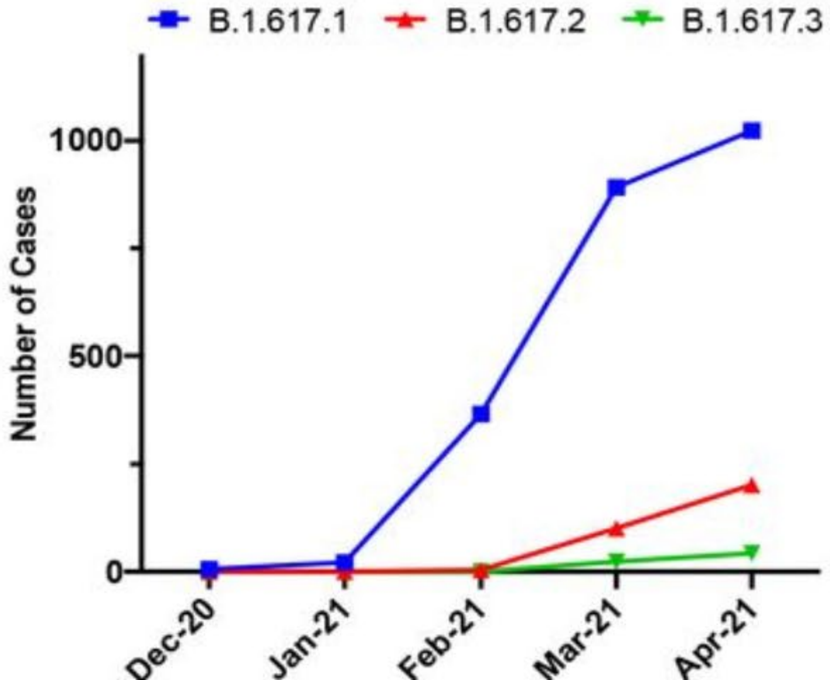


https://www.biorxiv.org/content/10.1101/2021.05.08.443253v1.full.pdf

GLOBAL



INDIA

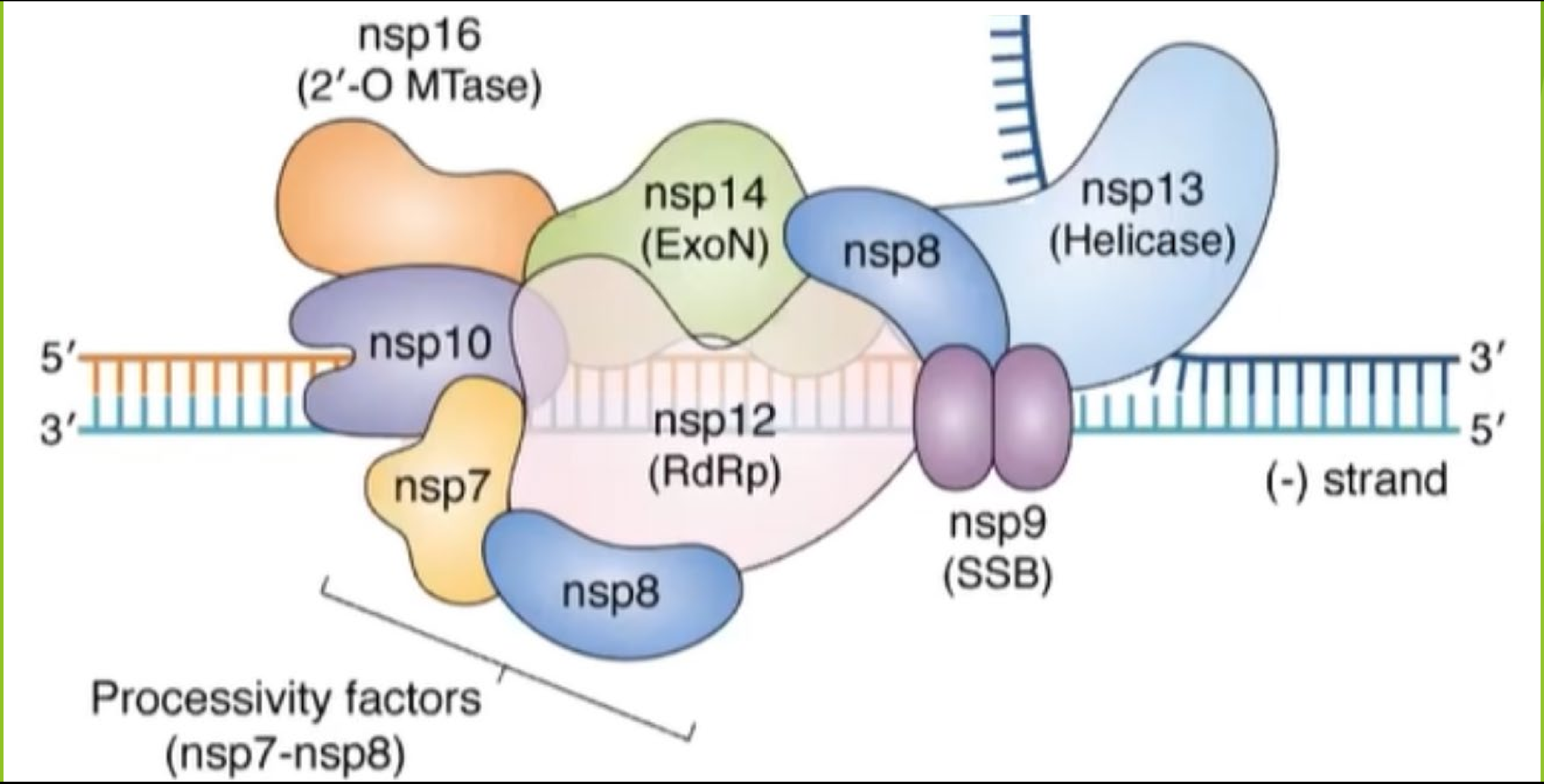


SARS-CoV-2 proofreading: removes incorrect pieces

Who is the proofreader?

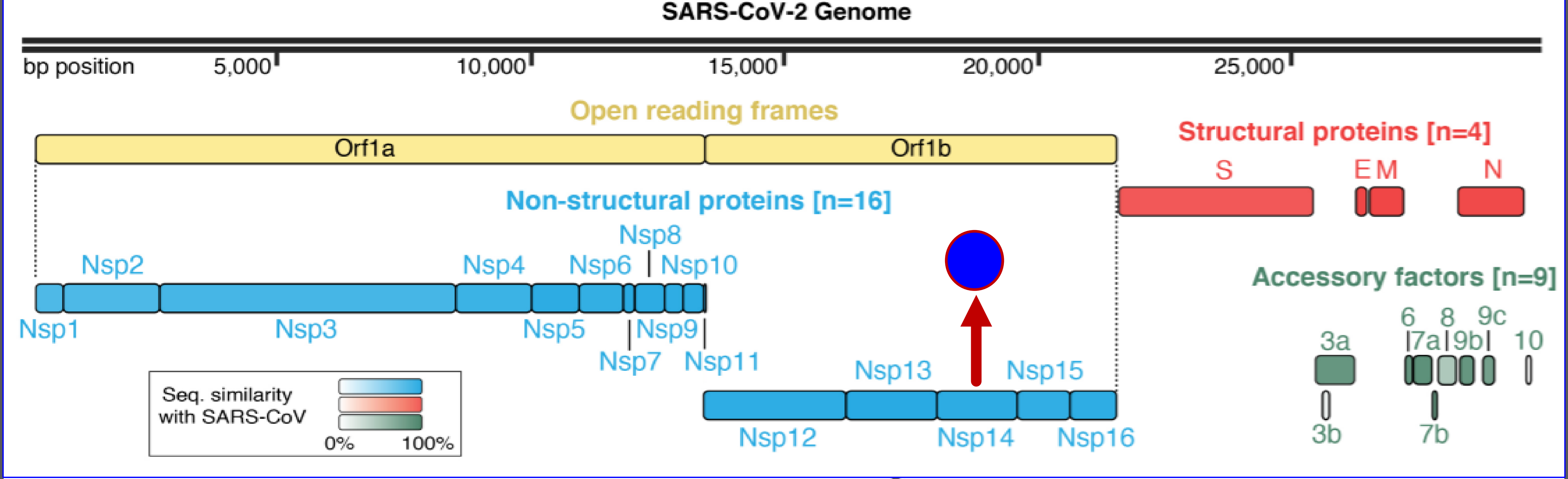
ExoN – part of the SARS-CoV-2 RNA Polymerase – RdRp (RNA-dependent RNA polymerase)

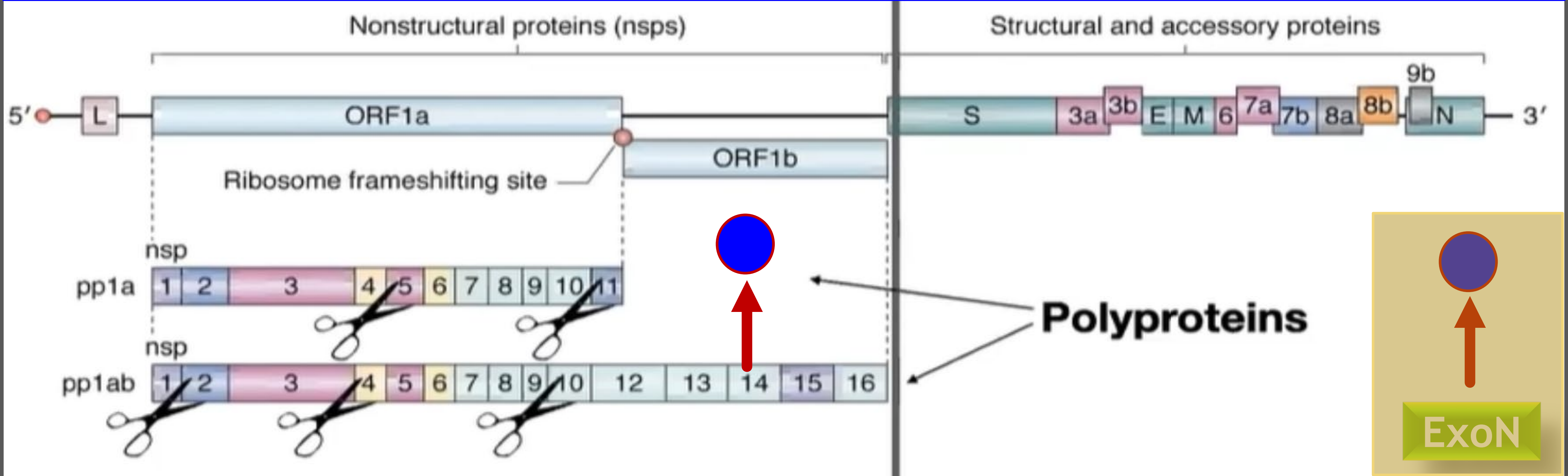
SARS-CoV-2 RNA Polymerase – RdRp (RNA-dependent RNA polymerase)



- SARS-CoV-2 Proofreader is ExoN (nsp14). It is a part of the RdRp complex.

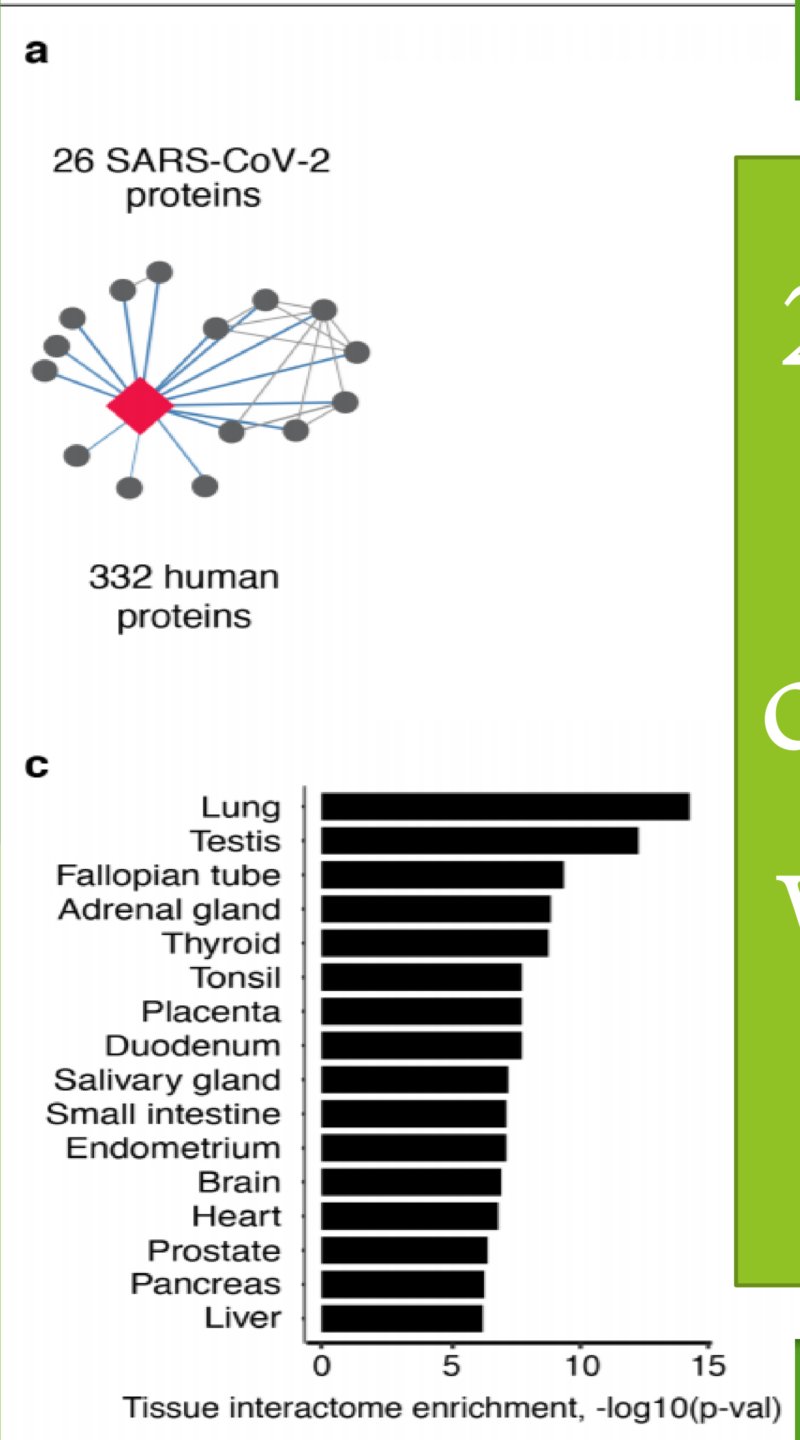
How does the virus obtain/get RdRp?


SARS-CoV-2 Genome
bp position
5,000
10,000
15,000
20,000
25,000
Open reading frames
Orf1a
Orf1b
Structural proteins [n=4]
S
E M
N
Non-structural proteins [n=16]
Nsp8
Nsp2
Nsp4
Nsp6
Nsp10
Nsp1
Nsp3
Nsp5
Nsp9
Nsp7
Nsp11
Nsp13
Nsp15
Nsp12
Nsp14
Nsp16
Accessory factors [n=9]
3a
6
8
9c
7a
9b
10
3b
7b
Seq. similarity with SARS-CoV
0%
100%

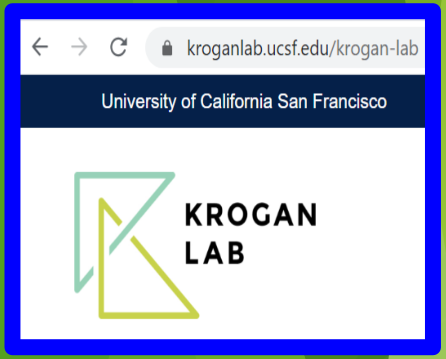

Nonstructural proteins (nsps)
Structural and accessory proteins
5′
L
ORF1a
ORF1b
Ribosome frameshifting site
S
3a
3b
E
M
6
7a
7b
8a
8b
9b
N
3′
nsp
pp1a
1
2
3
4
5
6
7
8
9
10
11
nsp
pp1ab
1
2
3
4
5
6
7
8
9
10
12
13
14
15
16
Polyproteins
ExoN

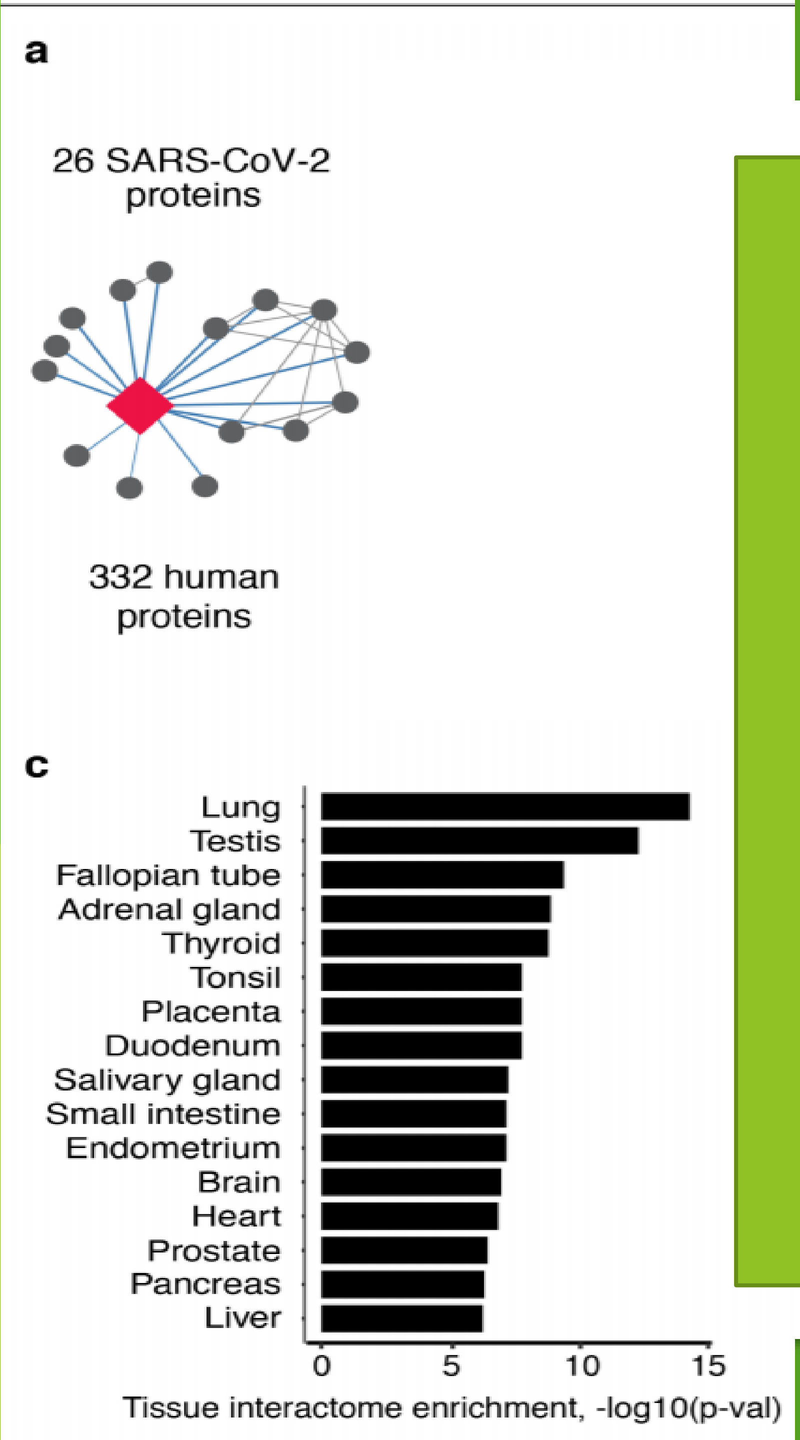
What are the functions of viral proteins?

We don’t know enough !!



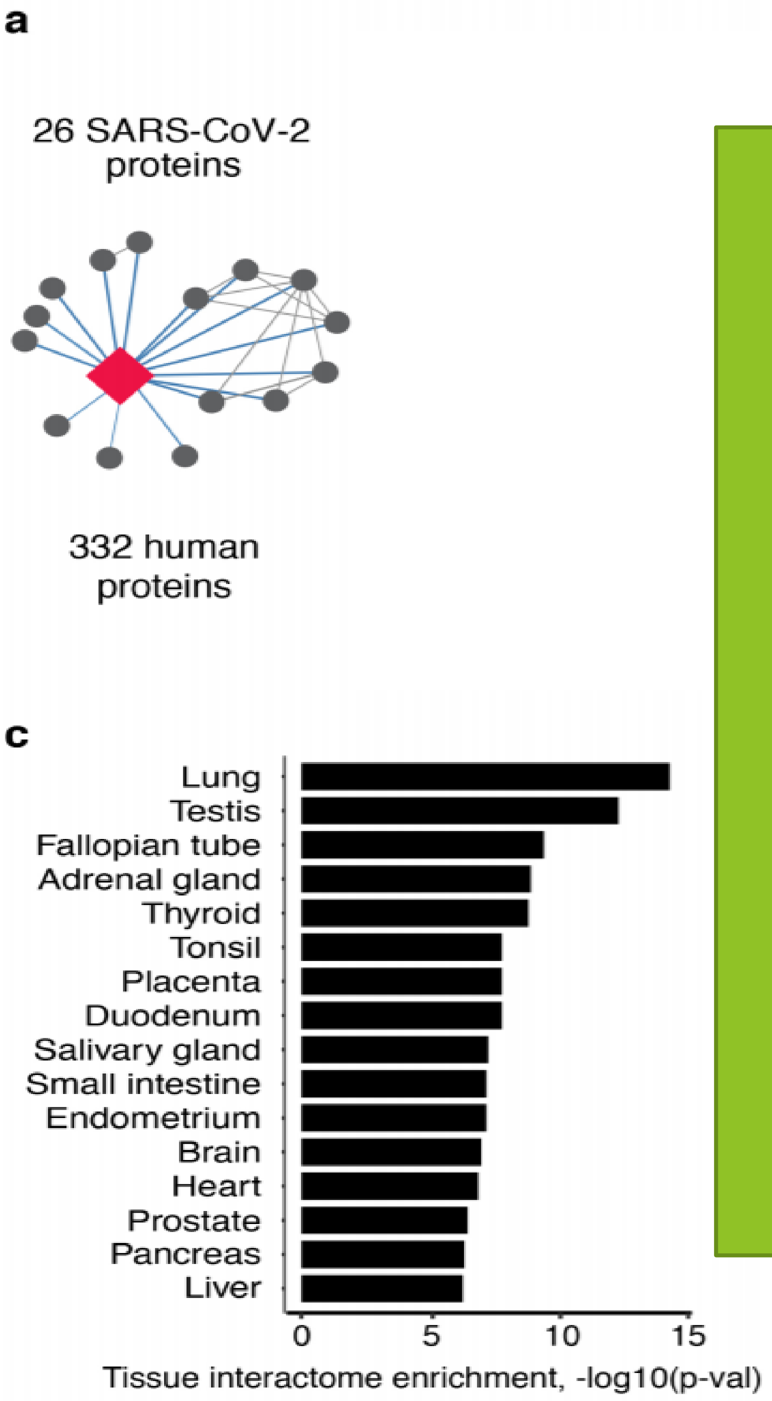
26 SARS-CoV-2 proteins can/may interact with 332 human proteins.





What are these interactions ?

We don’t know !



What do we know?

We don’t know !

nature.com/articles/s41586-020-2286-9_reference.pdf

kroganlab.ucsf.edu/krogan-lab

University of California San Francisco

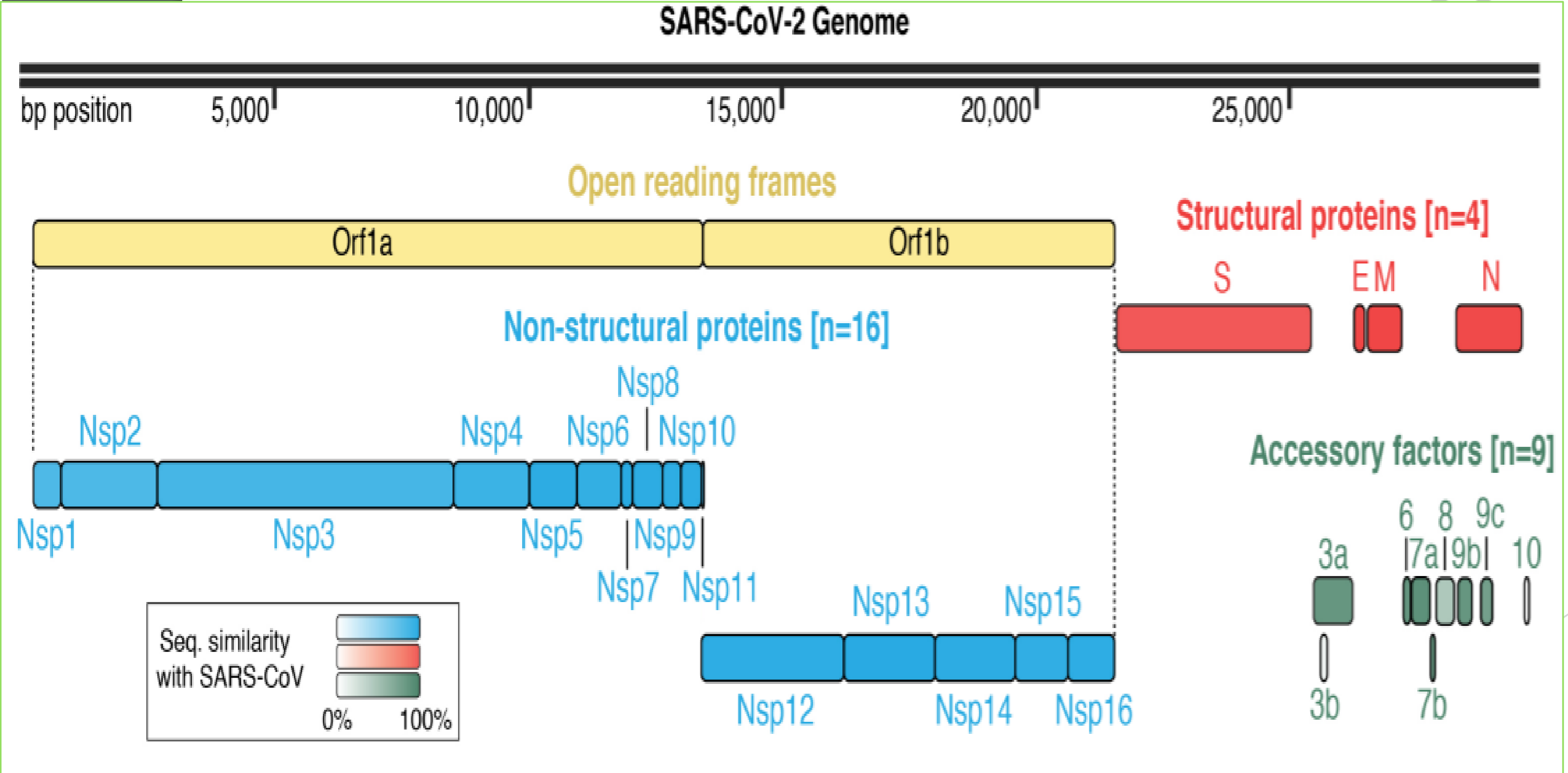
KROGAN LAB

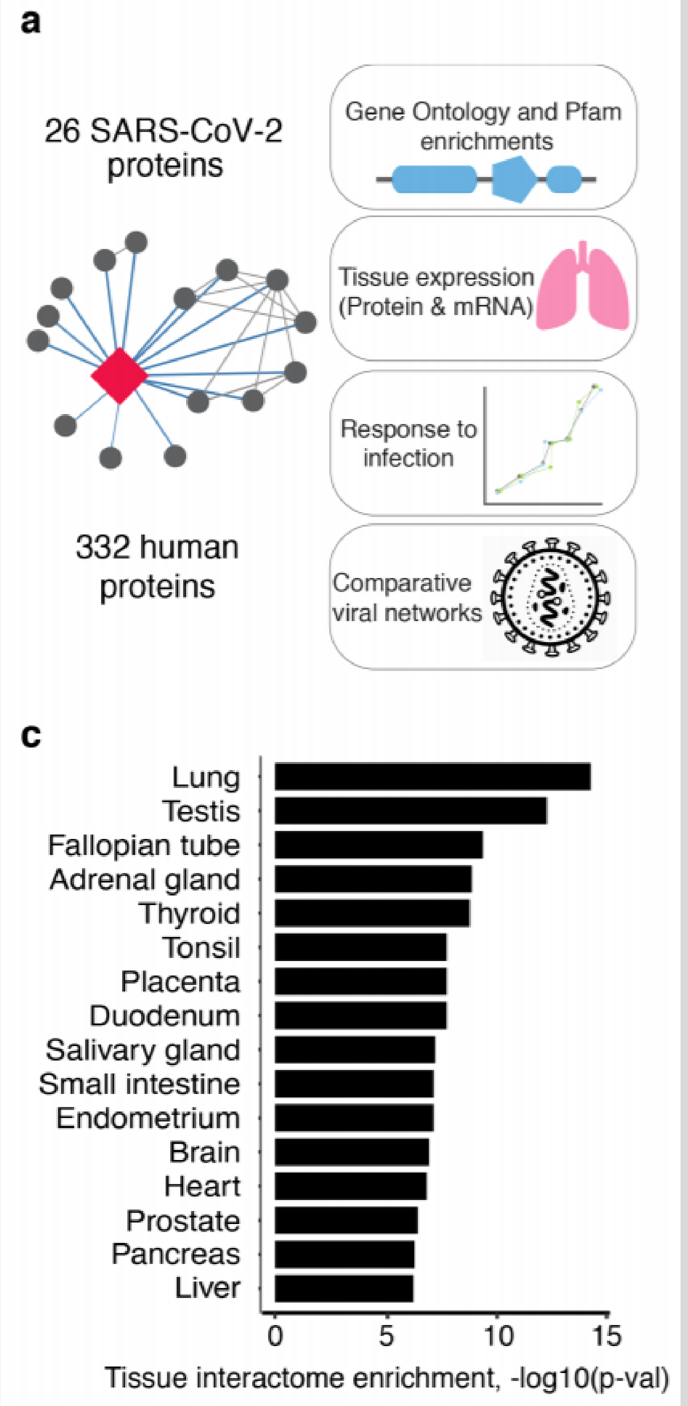
nature

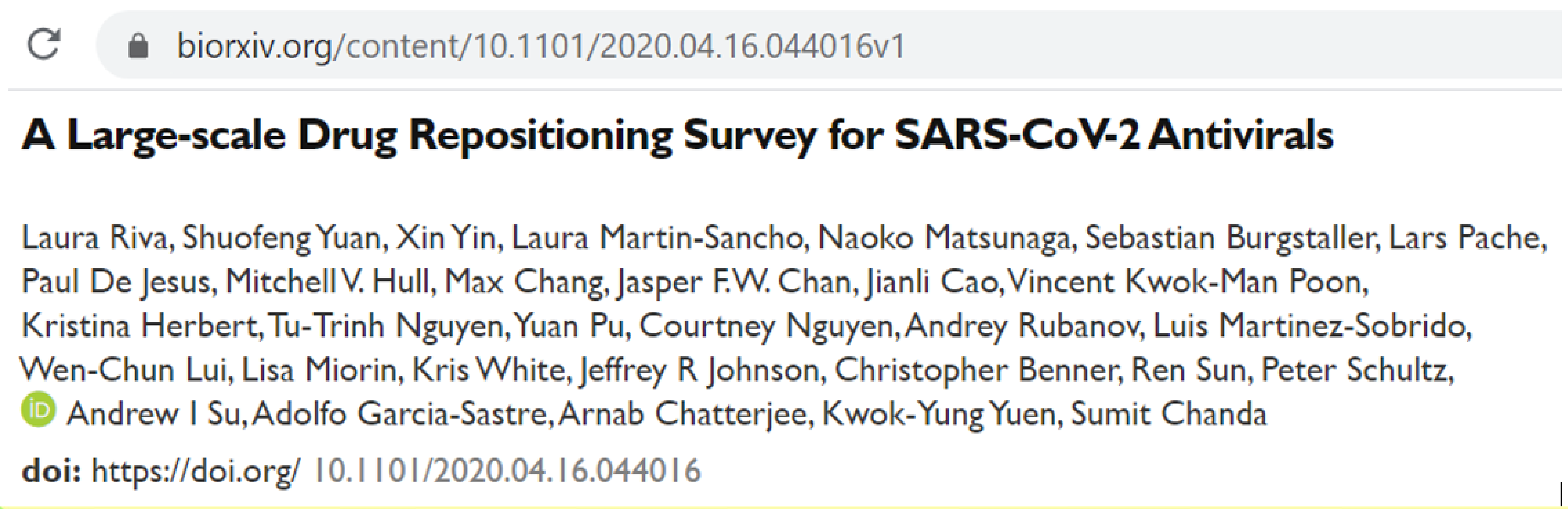
https://doi.org/10.1038/s41586-020-2286-9

Accelerated Article Preview

A SARS-CoV-2 protein interaction map reveals targets for drug repurposing







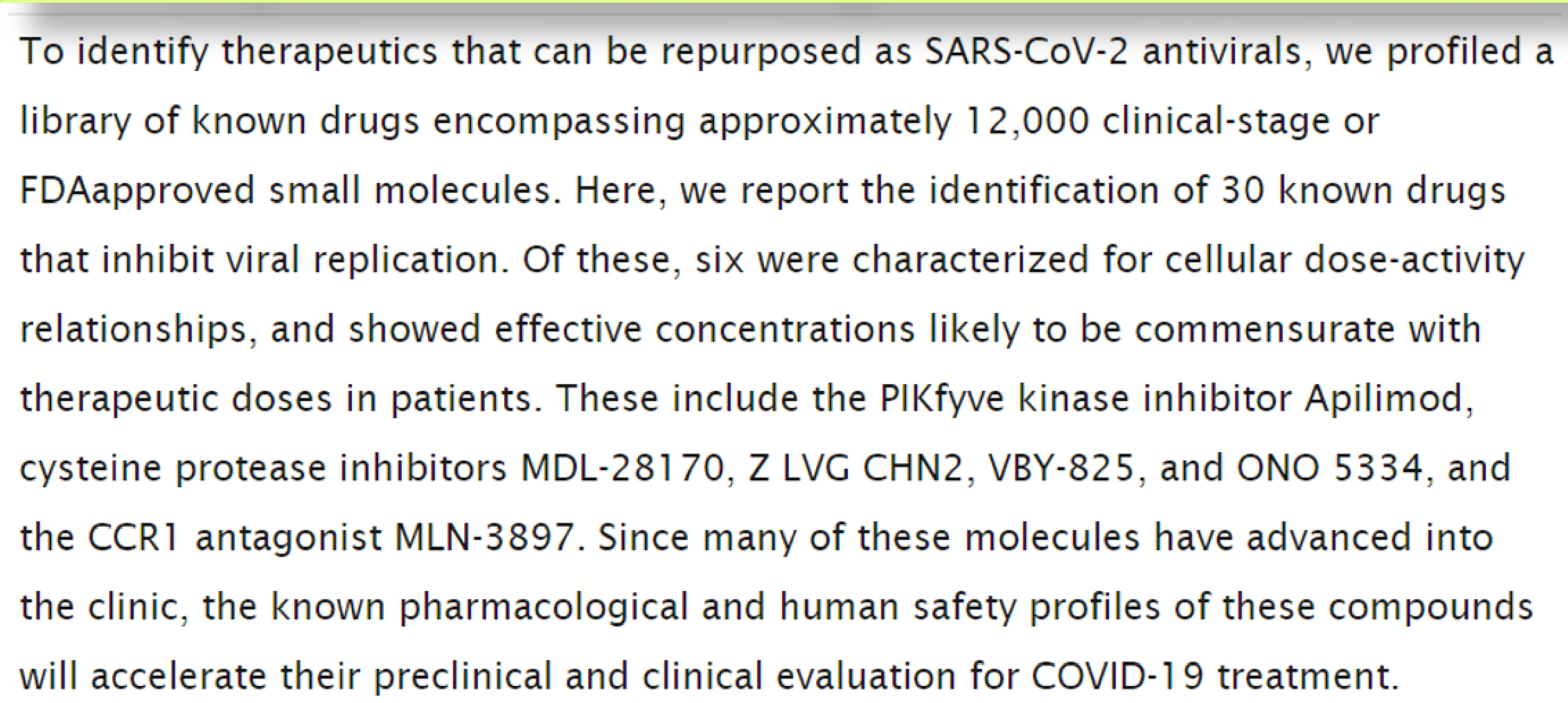
biorxiv.org/content/10.1101/2020.04.16.044016v1

A Large-scale Drug Repositioning Survey for SARS-CoV-2 Antivirals

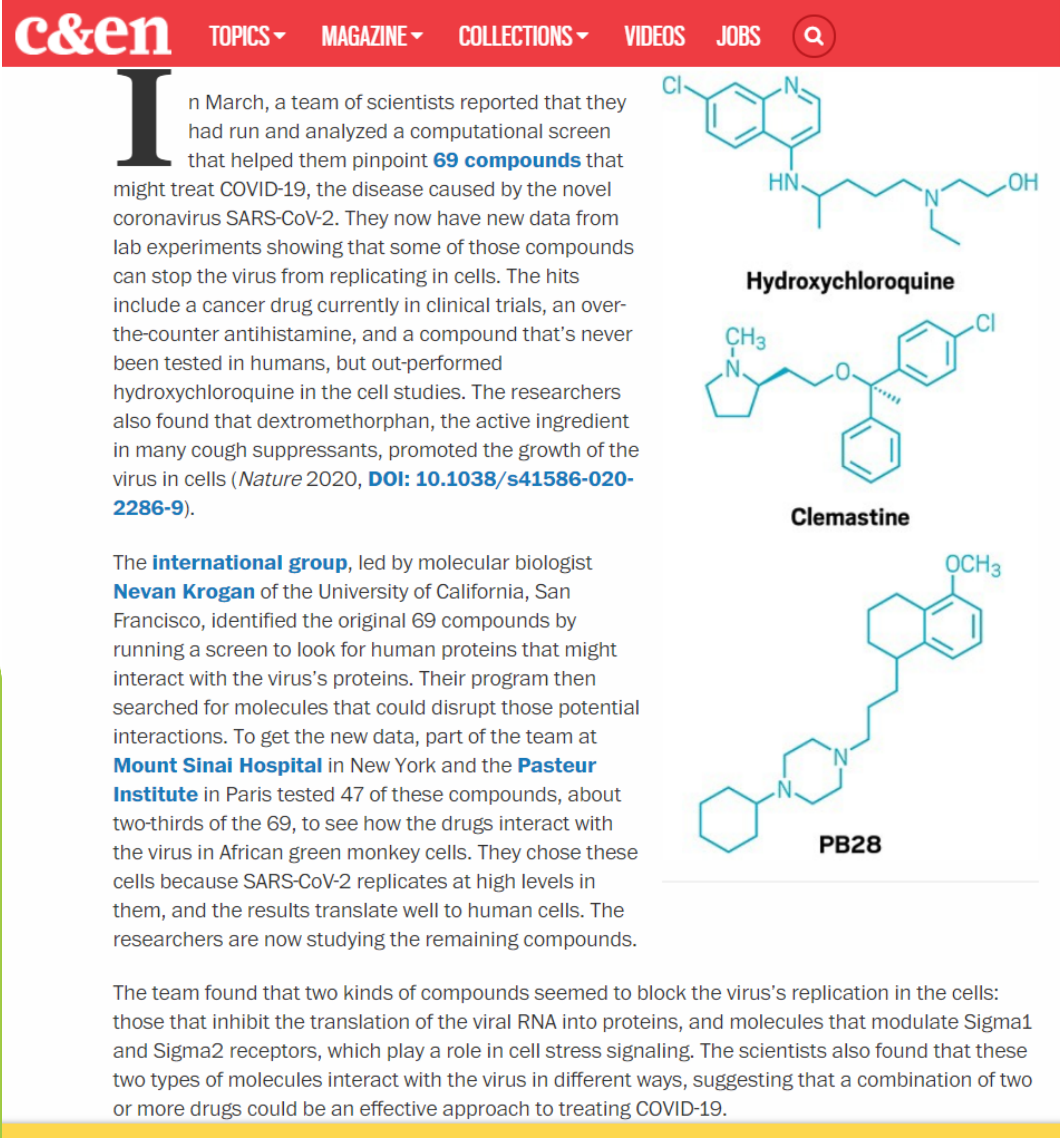
Laura Riva, Shuofeng Yuan, Xin Yin, Laura Martin-Sancho, Naoko Matsunaga, Sebastian Burgstaller, Lars Pache, Paul De Jesus, Mitchell V. Hull, Max Chang, Jasper F.W. Chan, Jianli Cao, Vincent Kwok-Man Poon, Kristina Herbert, Tu-Trinh Nguyen, Yuan Pu, Courtney Nguyen, Andrey Rubanov, Luis Martinez-Sobrido, Wen-Chun Lui, Lisa Miorin, Kris White, Jeffrey R Johnson, Christopher Benner, Ren Sun, Peter Schultz, Andrew I Su, Adolfo Garcia-Sastre, Arnab Chatterjee, Kwok-Yung Yuen, Sumit Chanda

doi: https://doi.org/ 10.1101/2020.04.16.044016

https://www.biorxiv.org/content/10.1101/2020.04.16.044016v1.full.pdf



To identify therapeutics that can be repurposed as SARS-CoV-2 antivirals, we profiled a library of known drugs encompassing approximately 12,000 clinical-stage or FDAapproved small molecules. Here, we report the identification of 30 known drugs that inhibit viral replication. Of these, six were characterized for cellular dose-activity relationships, and showed effective concentrations likely to be commensurate with therapeutic doses in patients. These include the PIKfyve kinase inhibitor Apilimod, cysteine protease inhibitors MDL-28170, Z LVG CHN2, VBY-825, and ONO 5334, and the CCR1 antagonist MLN-3897. Since many of these molecules have advanced into the clinic, the known pharmacological and human safety profiles of these compounds will accelerate their preclinical and clinical evaluation for COVID-19 treatment.



In March, a team of scientists reported that they had run and analyzed a computational screen that helped them pinpoint **69 compounds** that might treat COVID-19, the disease caused by the novel coronavirus SARS-CoV-2. They now have new data from lab experiments showing that some of those compounds can stop the virus from replicating in cells. The hits include a cancer drug currently in clinical trials, an over-the-counter antihistamine, and a compound that's never been tested in humans, but out-performed hydroxychloroquine in the cell studies. The researchers also found that dextromethorphan, the active ingredient in many cough suppressants, promoted the growth of the virus in cells (*Nature* 2020, **DOI: 10.1038/s41586-020-2286-9**).

The **international group**, led by molecular biologist **Nevan Krogan** of the University of California, San Francisco, identified the original 69 compounds by running a screen to look for human proteins that might interact with the virus's proteins. Their program then searched for molecules that could disrupt those potential interactions. To get the new data, part of the team at **Mount Sinai Hospital** in New York and the **Pasteur Institute** in Paris tested 47 of these compounds, about two-thirds of the 69, to see how the drugs interact with the virus in African green monkey cells. They chose these cells because SARS-CoV-2 replicates at high levels in them, and the results translate well to human cells. The researchers are now studying the remaining compounds.

The team found that two kinds of compounds seemed to block the virus's replication in the cells: those that inhibit the translation of the viral RNA into proteins, and molecules that modulate Sigma1 and Sigma2 receptors, which play a role in cell stress signaling. The scientists also found that these two types of molecules interact with the virus in different ways, suggesting that a combination of two or more drugs could be an effective approach to treating COVID-19.

kroganlab.ucsf.edu/krogan-lab

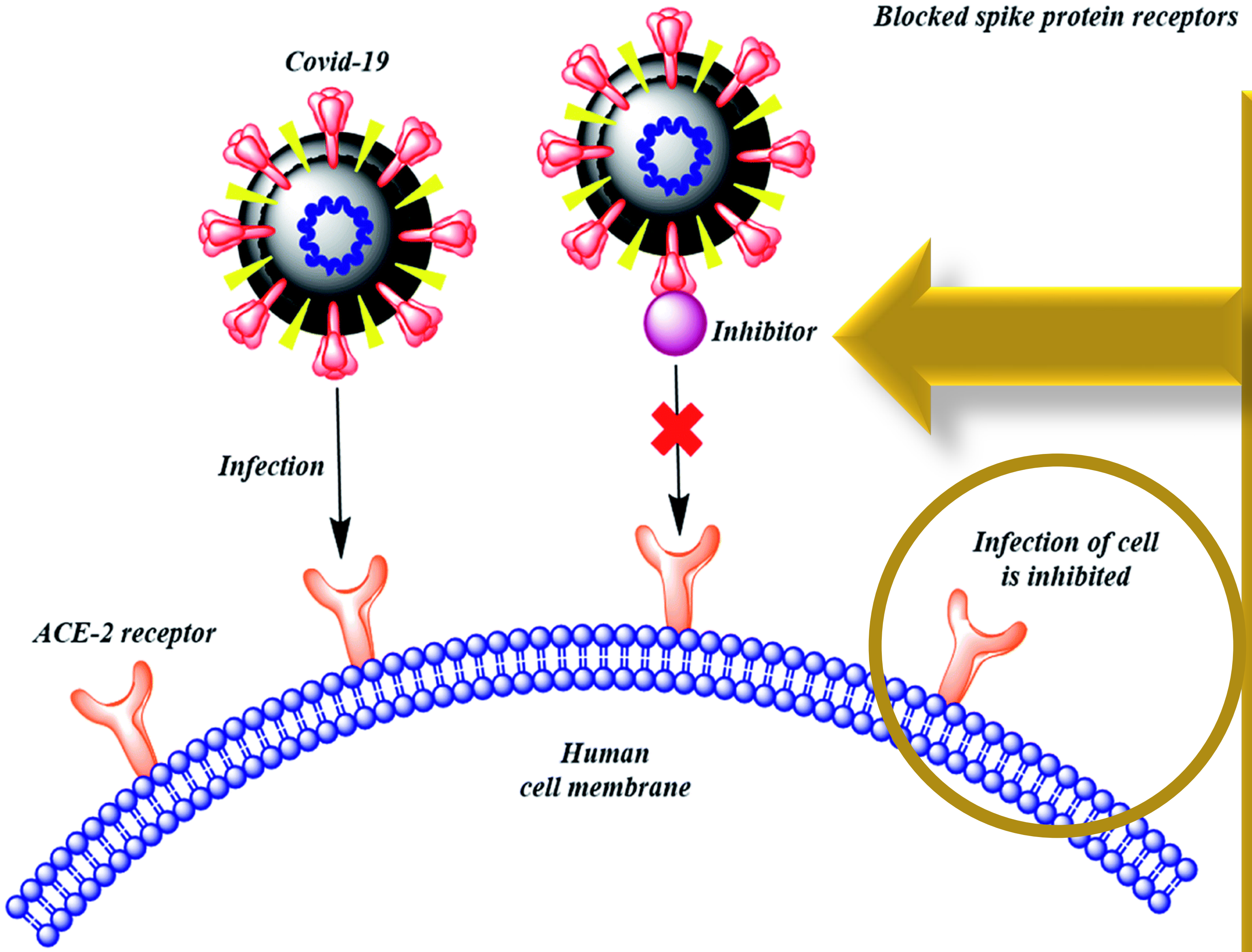
University of California San Francisco

https://cen.acs.org/biological-chemistry/infectious-disease/Cell-studies-suggest-repurposed-drugs-could-block-replication-of-SARS-CoV-2/98/web/2020/05

What is drug repurposing?

Re-use a drug (chemical molecule) created for another purpose.

How will it help us from SARS-CoV-2?



Discovering or repurposing a molecule to inhibit or prevent the virus from entering the cell may be a major step forward in infection control.

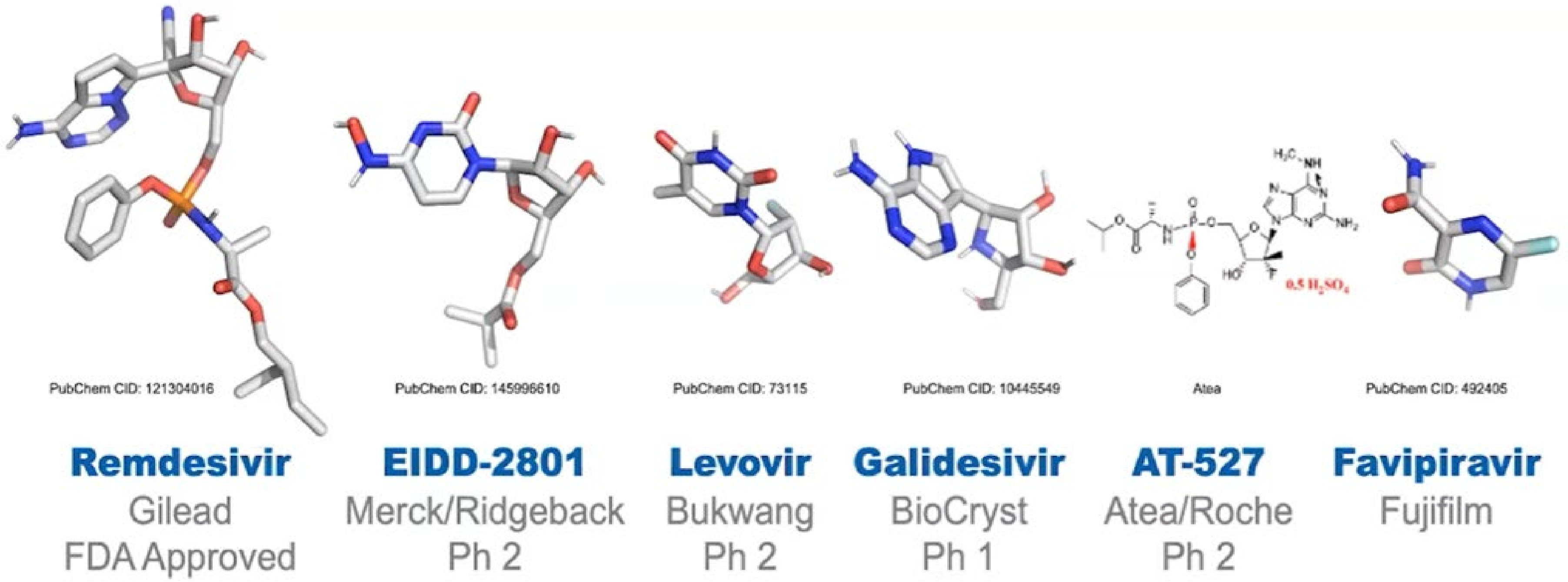
https://pubs.rsc.org/en/content/articlepdf/2020/ra/d0ra04795c

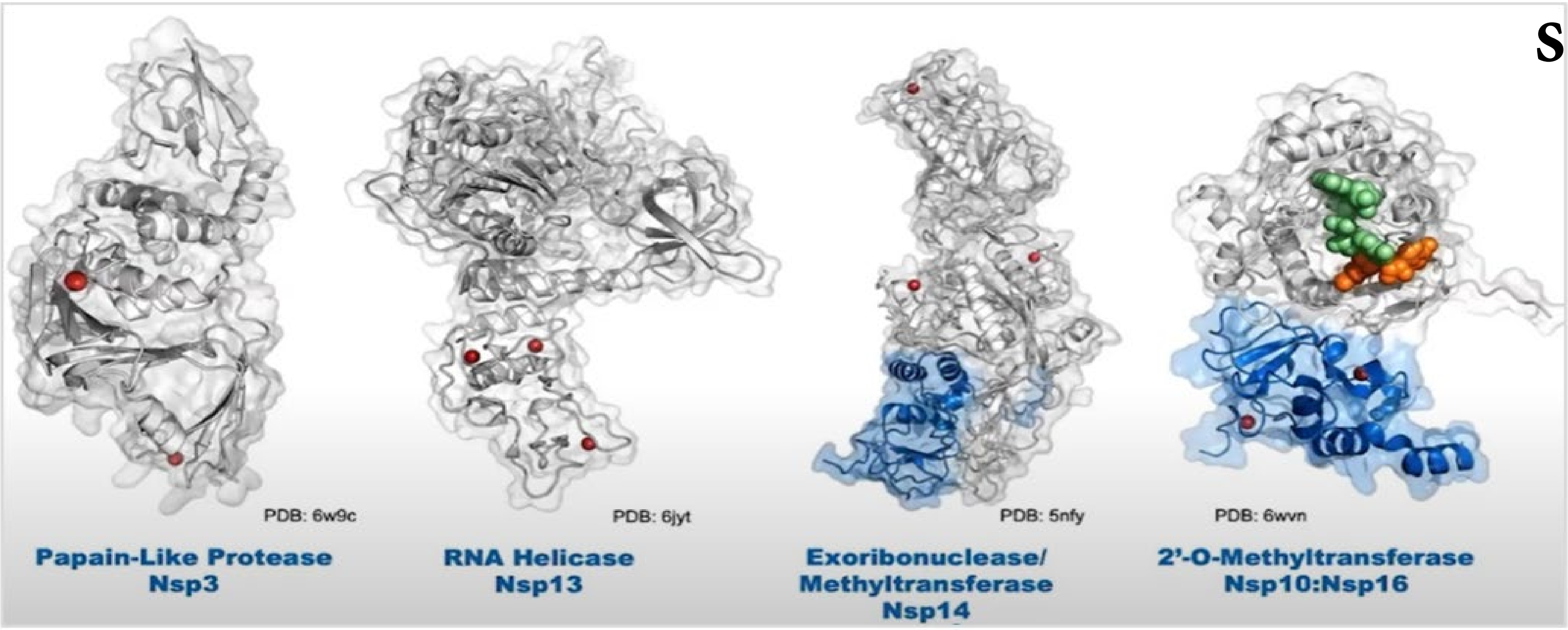
Do we have clues for drug re-purposing?

Yes, there are several candidates that are being intensely studied.

The one candidate that is in limited use is Remdesivir from Gilead.

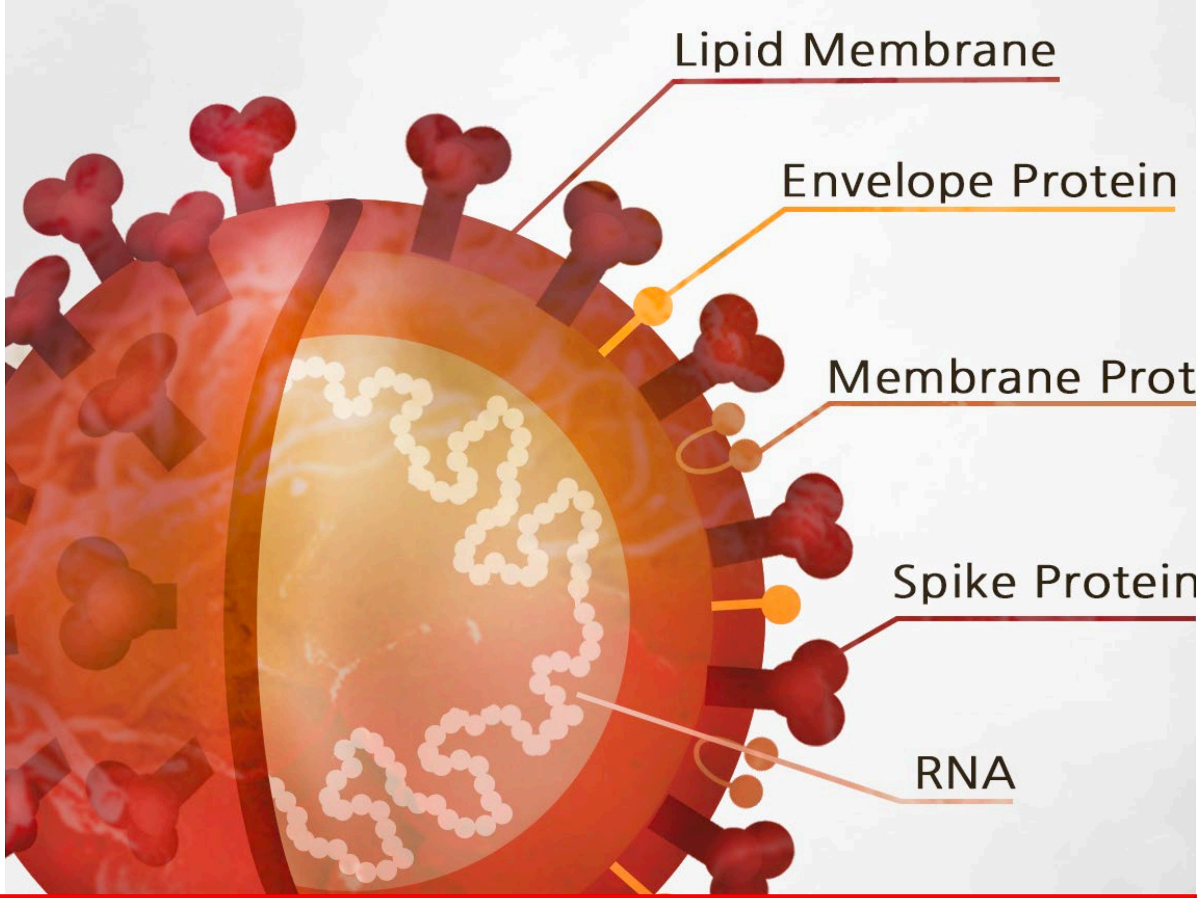
Search for small molecule inhibitors for SARS-CoV-2



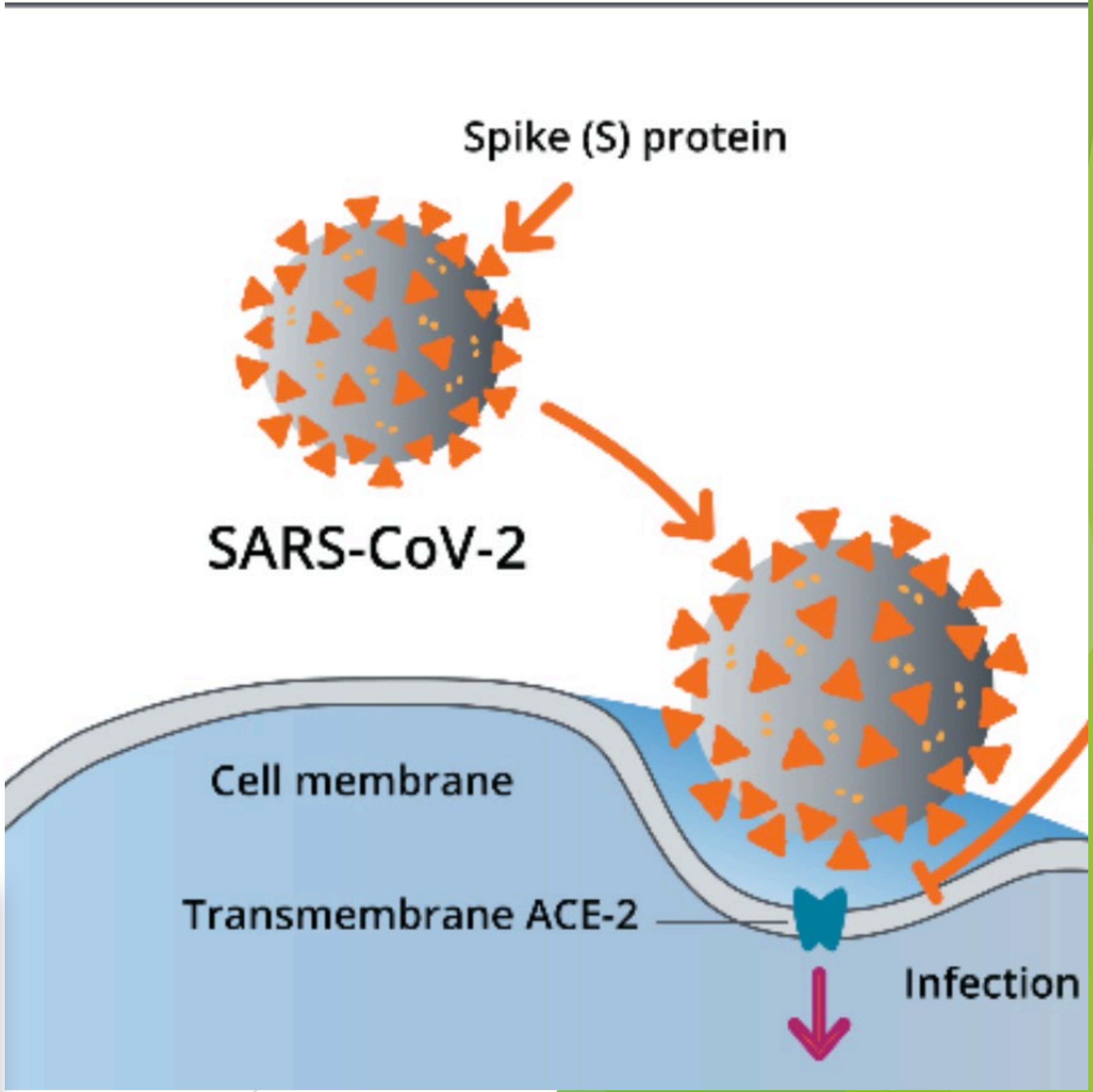


Anything else we think we do know?

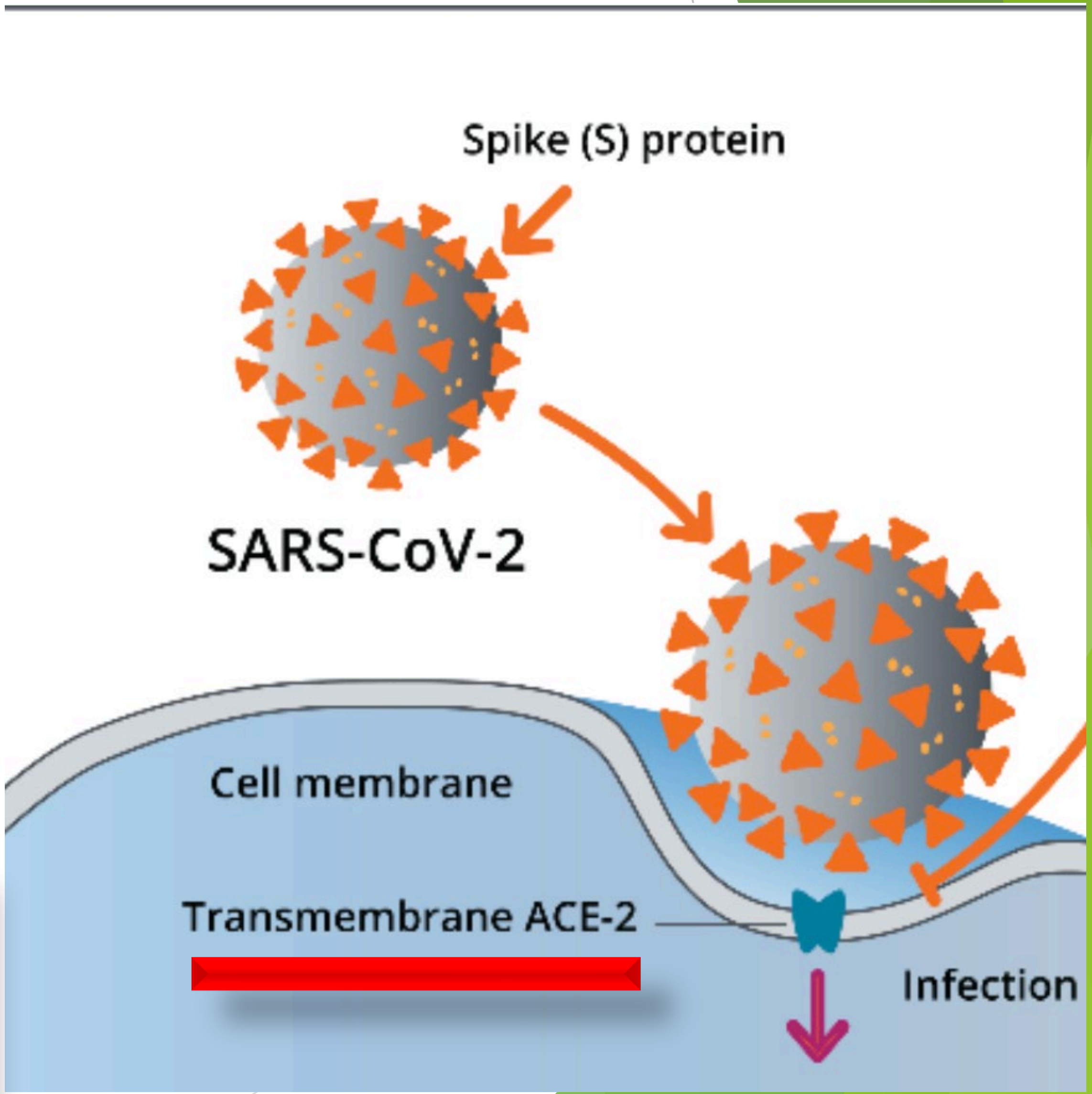
Coronavirus family members, including SARS, MERS & SARS-CoV-2 uses **human protein ACE2** to enter our cell



Why hACE2 ??



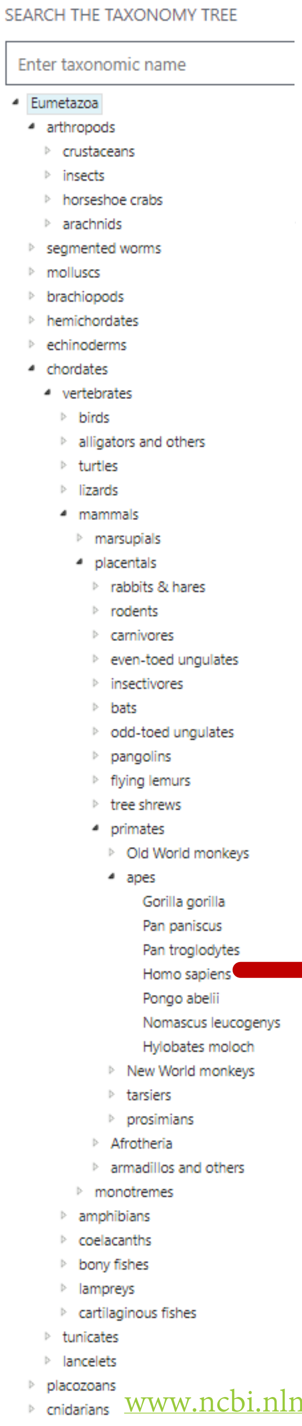
We don’t know !!



Why hACE2 ??

What is ACE2?

ACE and ACE2 genes are orthologs which are highly conserved in evolution.

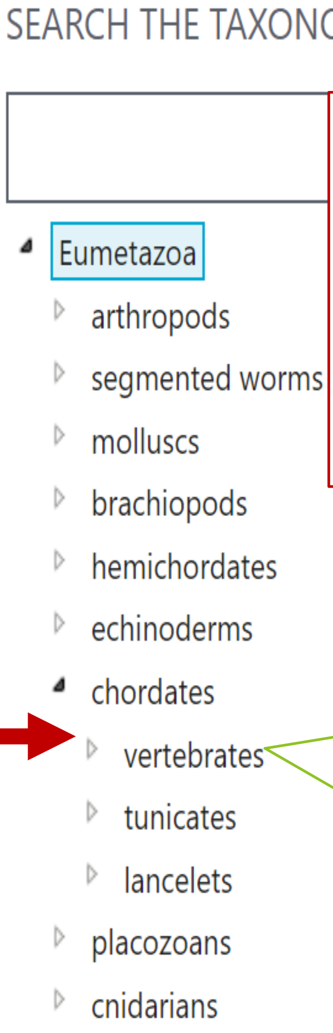


SEARCH THE TAXONOMY TREE

Enter taxonomic name

- Eumetazoa
  - arthropods
    - crustaceans
    - insects
    - horseshoe crabs
    - arachnids
  - segmented worms
  - molluscs
  - brachiopods
  - hemichordates
  - echinoderms
  - chordates
    - vertebrates
      - birds
      - alligators and others
      - turtles
      - lizards
      - mammals
        - marsupials
        - placentals
          - rabbits & hares
          - rodents
          - carnivores
          - even-toed ungulates
          - insectivores
          - bats
          - odd-toed ungulates
          - pangolins
          - flying lemurs
          - tree shrews
          - primates
            - Old World monkeys
            - apes
              - Gorilla gorilla
              - Pan paniscus
              - Pan troglodytes
              - Homo sapiens
              - Pongo abelii
              - Nomascus leucogenys
              - Hylobates moloch
            - New World monkeys
            - tarsiers
            - prosimians
          - Afrotheria
          - armadillos and others
        - monotremes
      - amphibians
      - coelacanths
      - bony fishes
      - lampreys
      - cartilaginous fishes
    - tunicates
    - lancelets
  - placozoans
  - cnidarians

Angiotensin I Converting Enzyme 2 (ACE2) encoded by this gene belongs to the angiotensin-converting enzyme family of dipeptidyl carboxydipeptidases and has homology to human angiotensin 1 converting enzyme (ACE). This secreted protein catalyzes the cleavage of angiotensin I into angiotensin 1-9, and angiotensin II into the vasodilator angiotensin 1-7. The organ- and cell-specific expression of this gene suggests that it may play a role in the regulation of cardiovascular and renal function, as well as fertility. The encoded protein is a receptor for the spike glycoprotein of human coronavirus HCoV-NL63 and the human severe acute respiratory syndrome coronaviruses, SARS-CoV and SARS-nCoV2-2019.

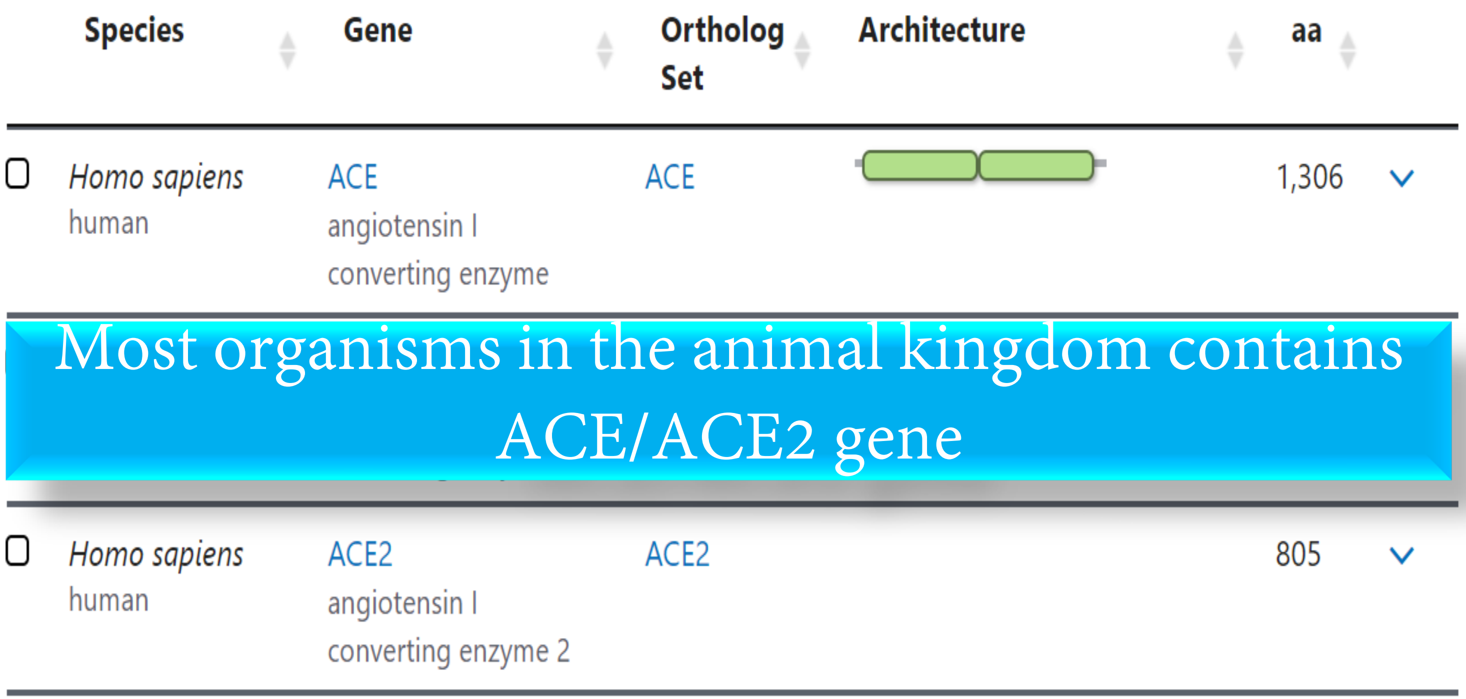


SEARCH THE TAXONOMY TREE

1,308 genes for: *Eumetazoa*

- Eumetazoa
  - arthropods
  - segmented worms
  - molluscs
  - brachiopods
  - hemichordates
  - echinoderms
  - chordates
    - vertebrates
    - tunicates
    - lancelets
  - placozoans
  - cnidarians

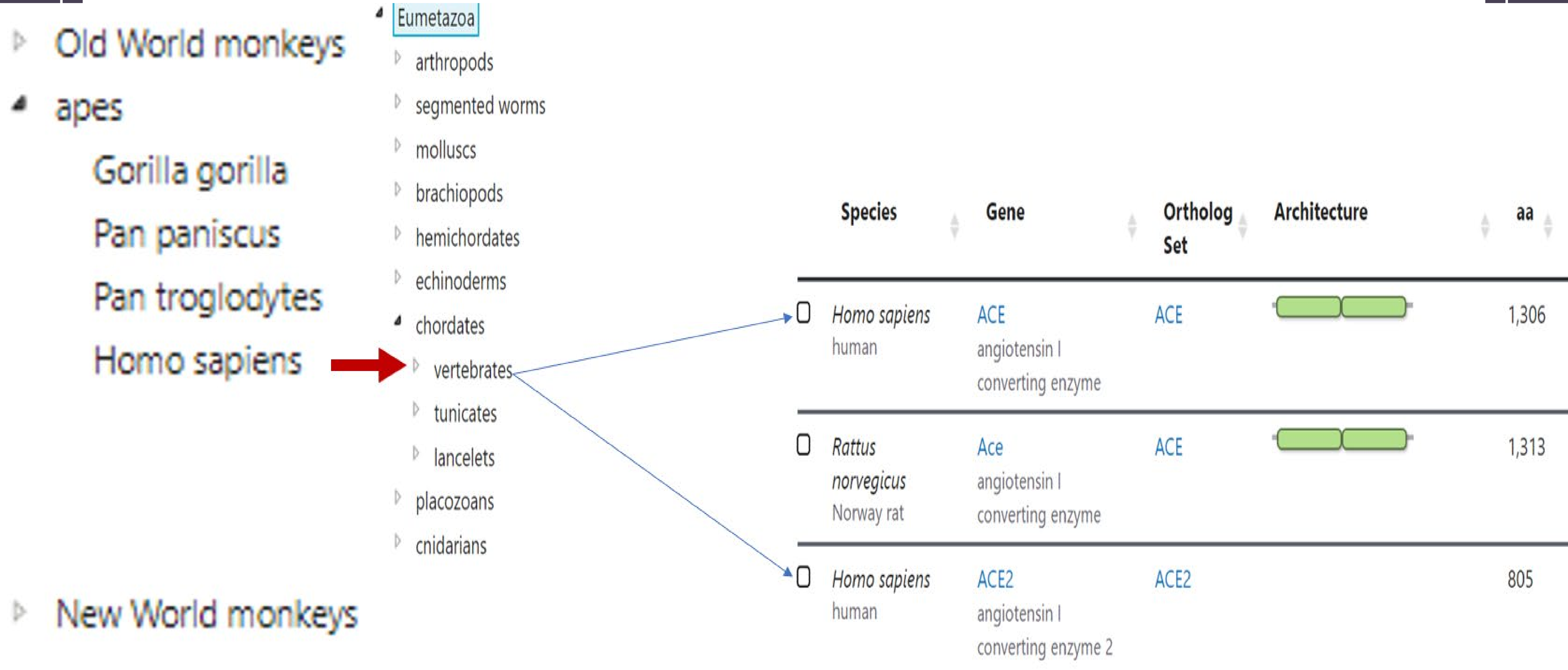
Raccoon dog (rd), native to East Asia, is one of the suspected intermediate hosts of severe acute respiratory syndrome coronavirus (SARS-CoV). The amino acid sequence of rdACE2 has identities of 99.3, 89.2, 83.9 and 80.4% to ACE2 proteins from dog, masked palm civet (pcACE2), human (huACE2) and bat, respectively. There are six amino acid changes in rdACE2 compared with huACE2, and four changes compared with pcACE2, within the 18 residues of ACE2 known to make direct contact with the SARS-CoV S protein. Spike proteins derived from human SARS-CoV or SARS-CoV-like viruses of masked palm civets and raccoon dogs were tested for their entry efficiency into human cell lines. The results showed that rdACE2 is a more efficient receptor for human SARS-CoV, but not for SARS-CoV-like viruses of masked palm civets and raccoon dogs, than huACE2 or pcACE2. This study provides useful data to elucidate the role of raccoon dog in SARS outbreaks (https://pubmed.ncbi.nlm.nih.gov/19625462/). In China, raccoon dogs are skinned alive. Video shows workers on these farms cutting the skin and fur from an animal's leg while the free limbs kick and writhe. When the fur is finally peeled off over the animals' heads, the bloody bodies are discarded. http://advocacy.britannica.com/blog/advocacy/2010/02/raccoon-dogs-are-skinned-alive-in-china/



	Species	Gene	Ortholog Set	Architecture	aa
☐	*Homo sapiens* human	ACE angiotensin I converting enzyme	ACE	🟩🟩	1,306
☐	*Homo sapiens* human	ACE2 angiotensin I converting enzyme 2	ACE2		805

Most organisms in the animal kingdom contains ACE/ACE2 gene

www.ncbi.nlm.nih.gov/gene/59272/ortholog/similargenes/?scope=6072

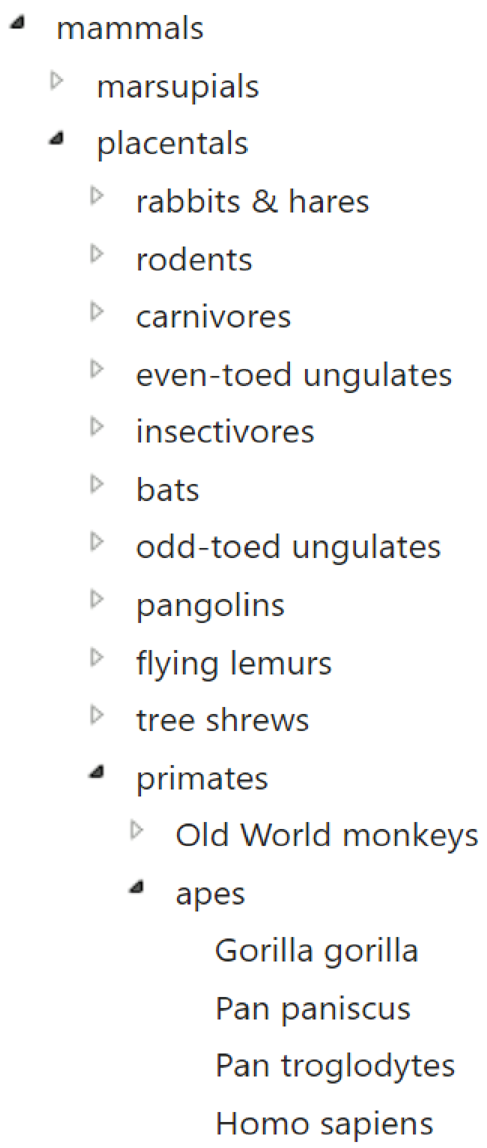


- Old World monkeys
- apes
  - Gorilla gorilla
  - Pan paniscus
  - Pan troglodytes
  - Homo sapiens
- New World monkeys

- Eumetazoa
  - arthropods
  - segmented worms
  - molluscs
  - brachiopods
  - hemichordates
  - echinoderms
  - chordates
    - vertebrates
    - tunicates
    - lancelets
  - placozoans
  - cnidarians

	Species	Gene	Ortholog Set	Architecture	aa
☐	*Homo sapiens* human	ACE angiotensin I converting enzyme	ACE	🟩🟩	1,306
☐	*Rattus norvegicus* Norway rat	Ace angiotensin I converting enzyme	ACE	🟩🟩	1,313
☐	*Homo sapiens* human	ACE2 angiotensin I converting enzyme 2	ACE2		805

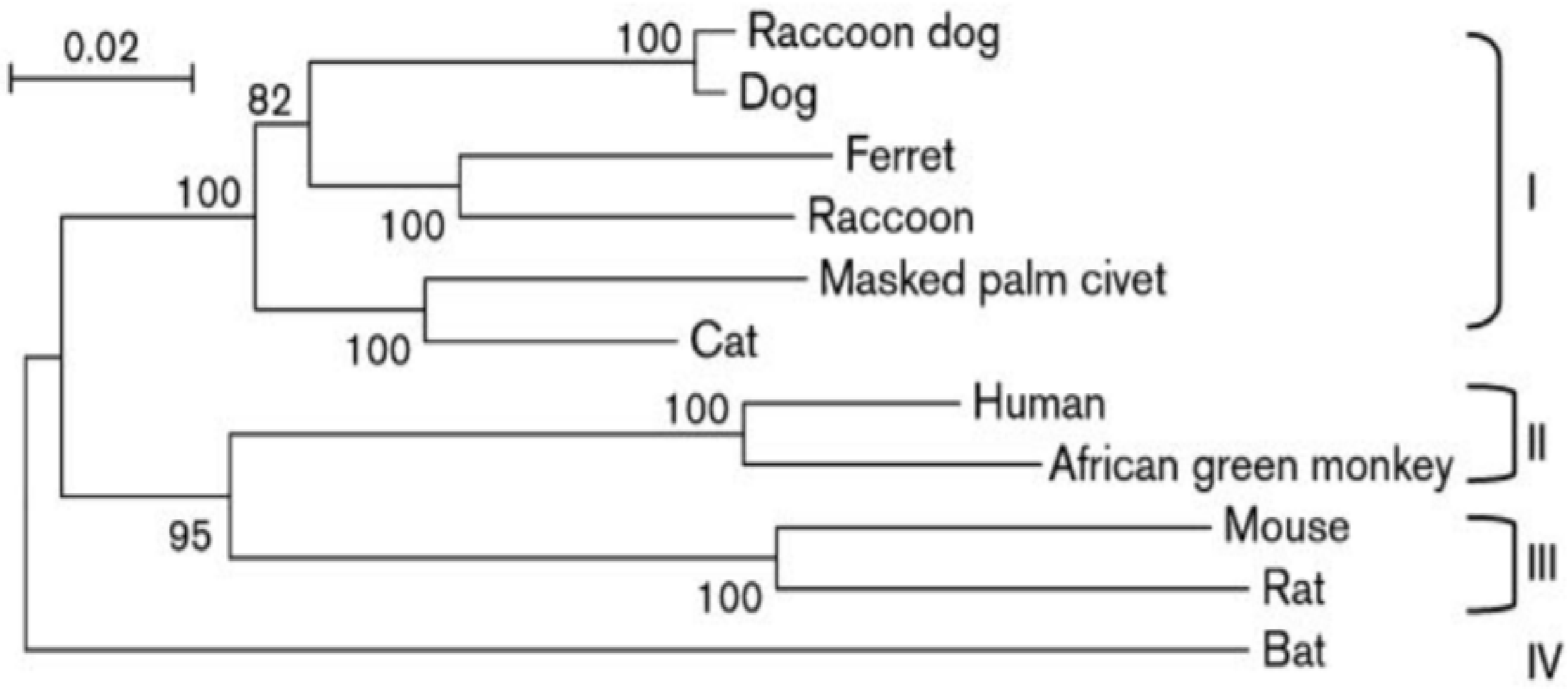
Evolutionary Conservation of ACE2 Gene from Dogs to Humans



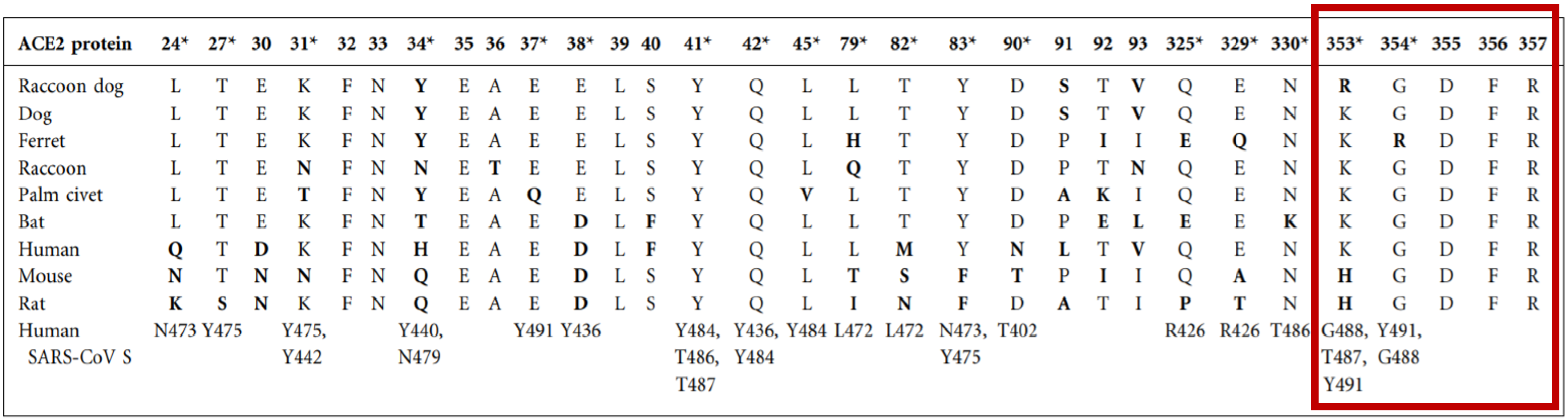
- mammals
  - marsupials
  - placentals
    - rabbits & hares
    - rodents
    - carnivores
    - even-toed ungulates
    - insectivores
    - bats
    - odd-toed ungulates
    - pangolins
    - flying lemurs
    - tree shrews
    - primates
      - Old World monkeys
      - apes
        - Gorilla gorilla
        - Pan paniscus
        - Pan troglodytes
        - Homo sapiens

Figure 11: The evolutionary journey of the ACE2 gene from racoon dogs which are closer to dogs (domestic dogs evolved approximately 6 million years ago) to humans (0.2 million years ago, MYA). Over this time period (6MYA – 0.2MYA) the ACE2 protein appears to be well conserved.

Serpell, James, ed. *The Domestic Dog: Its Evolution, Behaviour, and Interactions with People.* Cambridge University Press, 1995.



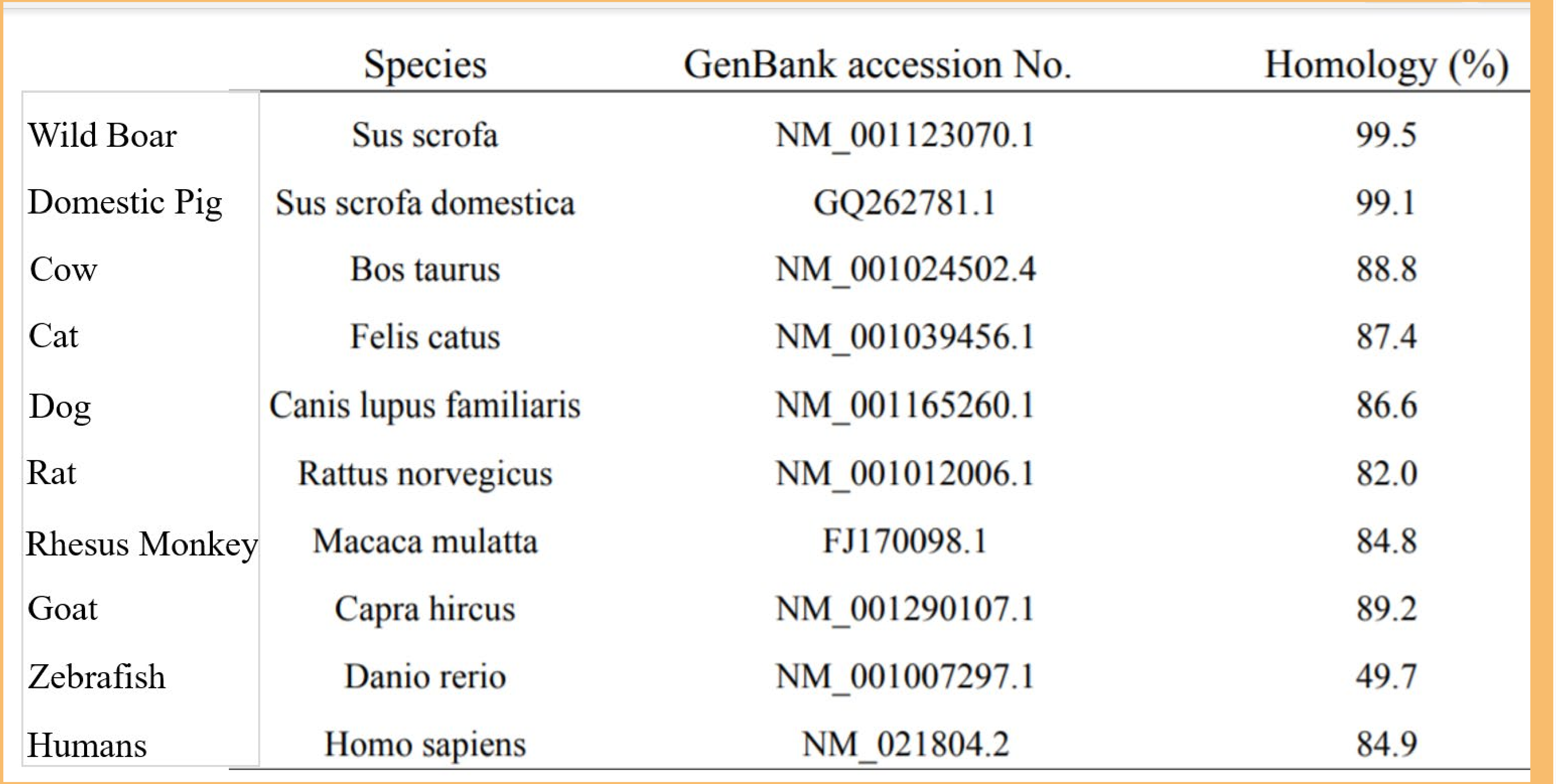
Partial Conservation of ACE2 Protein Contacts between ACE2 and SARS-CoV



ACE2 protein	**24***	**27***	**30**	**31***	**32**	**33**	**34***	**35**	**36**	**37***	**38***	**39**	**40**	**41***	**42***	**45***	**79***	**82***	**83***	**90***	**91**	**92**	**93**	**325***	**329***	**330***	**353***	**354***	**355**	**356**	**357**
Raccoon dog	L	T	E	K	F	N	**Y**	E	A	E	E	L	S	Y	Q	L	L	T	Y	D	**S**	T	**V**	Q	E	N	**R**	G	D	F	R
Dog	L	T	E	K	F	N	**Y**	E	A	E	E	L	S	Y	Q	L	L	T	Y	D	**S**	T	**V**	Q	E	N	K	G	D	F	R
Ferret	L	T	E	K	F	N	**Y**	E	A	E	E	L	S	Y	Q	L	**H**	T	Y	D	P	**I**	I	**E**	**Q**	N	K	**R**	D	F	R
Raccoon	L	T	E	**N**	F	N	**N**	E	**T**	E	E	L	S	Y	Q	L	**Q**	T	Y	D	P	T	**N**	Q	E	N	K	G	D	F	R
Palm civet	L	T	E	**T**	F	N	**Y**	E	A	**Q**	E	L	S	Y	Q	**V**	L	T	Y	D	**A**	**K**	I	Q	E	N	K	G	D	F	R
Bat	L	T	E	K	F	N	**T**	E	A	E	**D**	L	**F**	Y	Q	L	L	T	Y	D	P	**E**	**L**	**E**	E	**K**	K	G	D	F	R
Human	**Q**	T	**D**	K	F	N	**H**	E	A	E	**D**	L	**F**	Y	Q	L	L	**M**	Y	**N**	**L**	T	**V**	Q	E	N	K	G	D	F	R
Mouse	**N**	T	**N**	**N**	F	N	**Q**	E	A	E	**D**	L	S	Y	Q	L	**T**	**S**	**F**	**T**	P	**I**	I	Q	**A**	N	**H**	G	D	F	R
Rat	**K**	**S**	**N**	K	F	N	**Q**	E	A	E	**D**	L	S	Y	Q	L	**I**	**N**	**F**	D	**A**	T	I	**P**	**T**	N	**H**	G	D	F	R
Human SARS-CoV S	N473	Y475		Y475, Y442			Y440, N479			Y491	Y436			Y484, T486, T487	Y436, Y484	Y484	L472	L472	N473, Y475	T402				R426	R426	T486	G488, T487, Y491	Y491, G488			

Figure 13: Contacts between ACE2 and SARS-CoV RBD (receptor binding domain or RBM, receptor binding motif). ACE2 residues in contact with S1 RBD are listed by their position and aa. Non-identical amino acid residues are shown in bold. The residues in the viral S protein from human isolates that contact ACE2 are shown at the bottom of each column. Columns with a star (*) denote 18 residues of ACE2 known to make direct contact with the SARS-CoV Spike protein. A loop and β5 (residues 353–357) had one variation in rdACE2 (K353R) and Histidine in mouse and rat ACE2 proteins (K353H). This position is critical for ACE2 binding to SARS-CoV Spike protein. Differences in the RBDs of SARS-CoV-2 and SARS-CoV are expected. In particular, of the 33 amino acids in the region 460–492 in the SARS-CoV S protein that contains the critical residues that contact ACE2, half (15/33) are conserved in SARS-CoV-2 (cross-neutralizing antibodies may not be effective).

Evolutionary Conservation of ACE2 Gene



	Species	GenBank accession No.	Homology (%)
Wild Boar	Sus scrofa	NM_001123070.1	99.5
Domestic Pig	Sus scrofa domestica	GQ262781.1	99.1
Cow	Bos taurus	NM_001024502.4	88.8
Cat	Felis catus	NM_001039456.1	87.4
Dog	Canis lupus familiaris	NM_001165260.1	86.6
Rat	Rattus norvegicus	NM_001012006.1	82.0
Rhesus Monkey	Macaca mulatta	FJ170098.1	84.8
Goat	Capra hircus	NM_001290107.1	89.2
Zebrafish	Danio rerio	NM_001007297.1	49.7
Humans	Homo sapiens	NM_021804.2	84.9

Genomic Organization and conserved regions of the ACE2 gene. Top shows single nucleotide polymorphisms (SNPs).

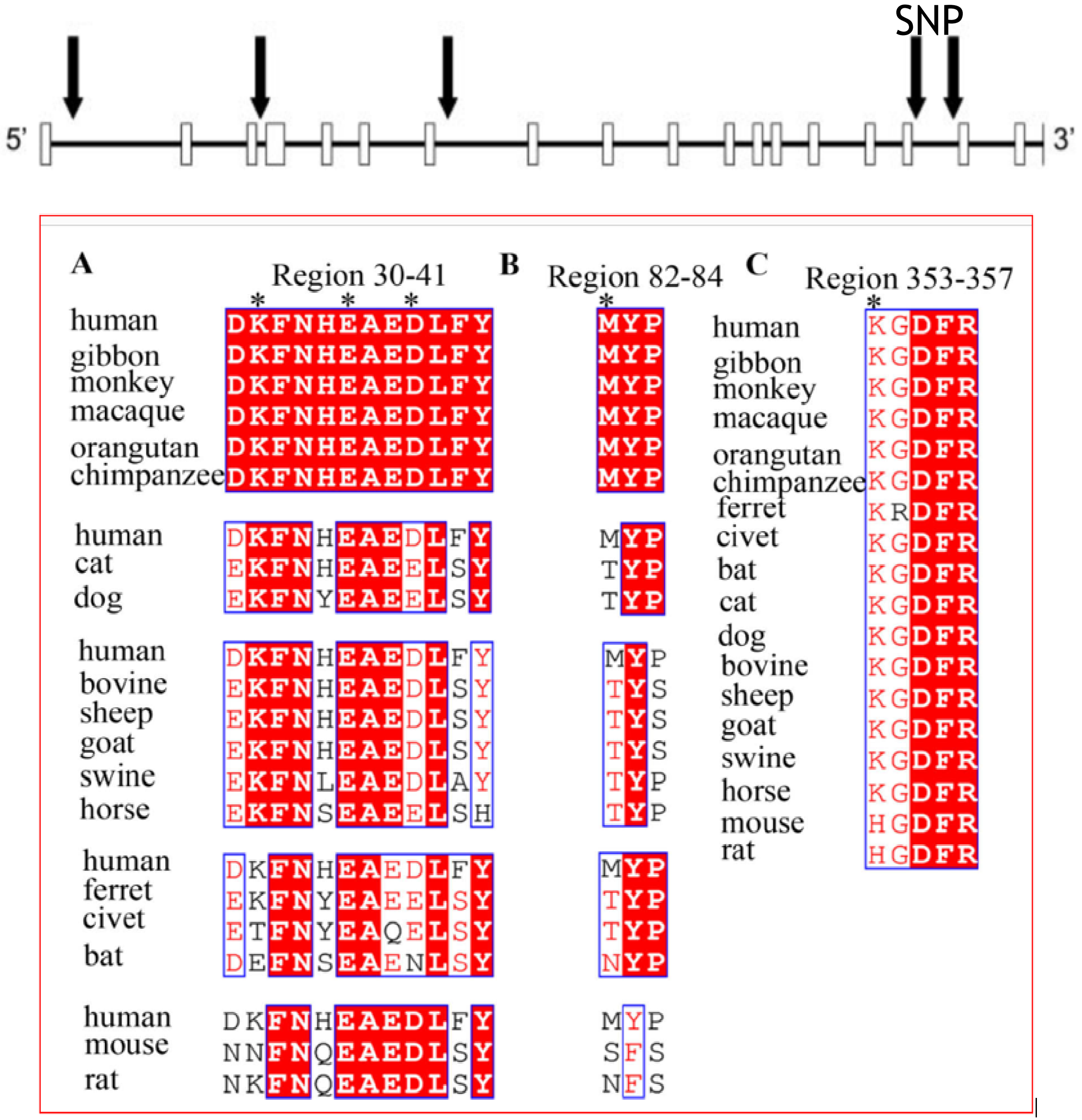


Figure 20: (TOP) Genomic organization of ACE2 (arrows mark SNP, single nucleotide polymorphisms, ref 215). hACE2 contains 18 exons and codes for 805 amino acid protein. ACE2 is a homolog of ACE (may be a duplication of the ACE gene and then fused with another gene). (BOTTOM PANEL) Compare ACE2 based peptides (Figure 19) with sequence

What is the role of ACE and ACE2?

ACE – Angiotension Converting Enzyme

ACE2 – Angiotensin Converting Enzyme 2

ACE & ACE2 is an integral part of the Renin-Angiotensin Axis in Physiology

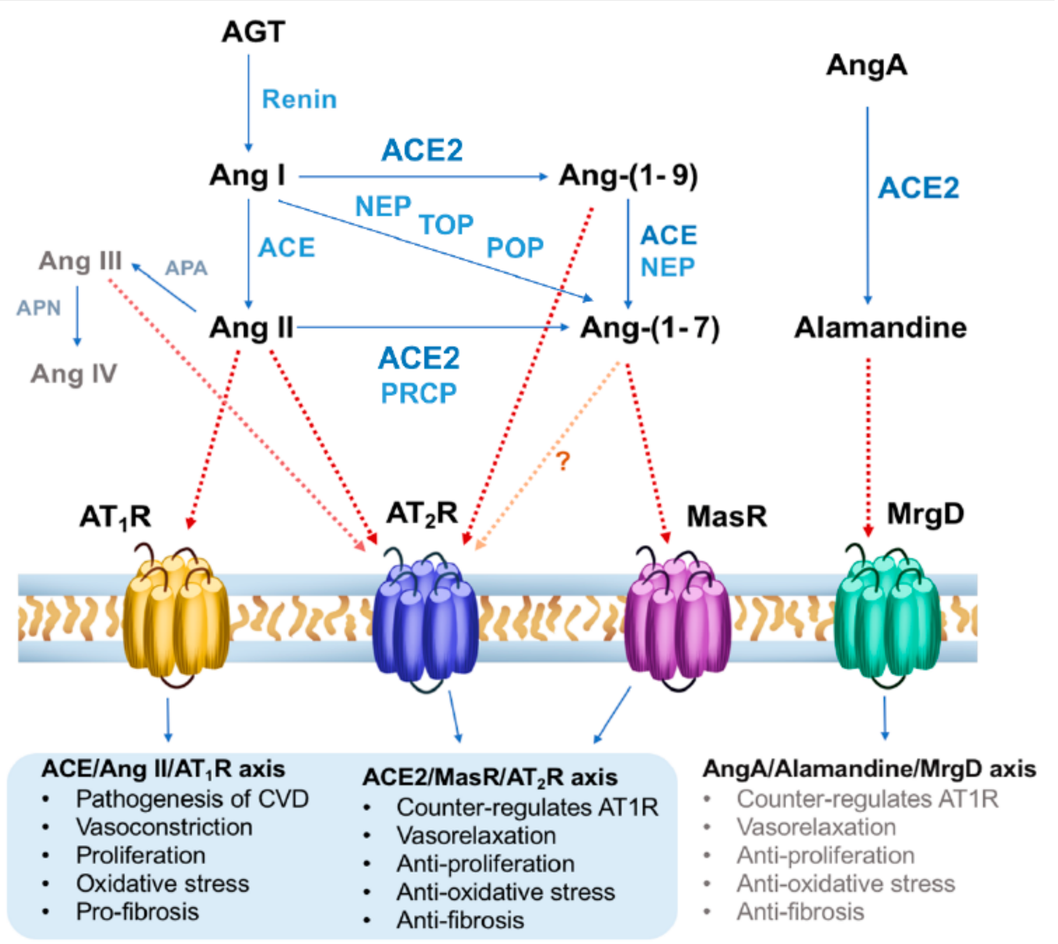
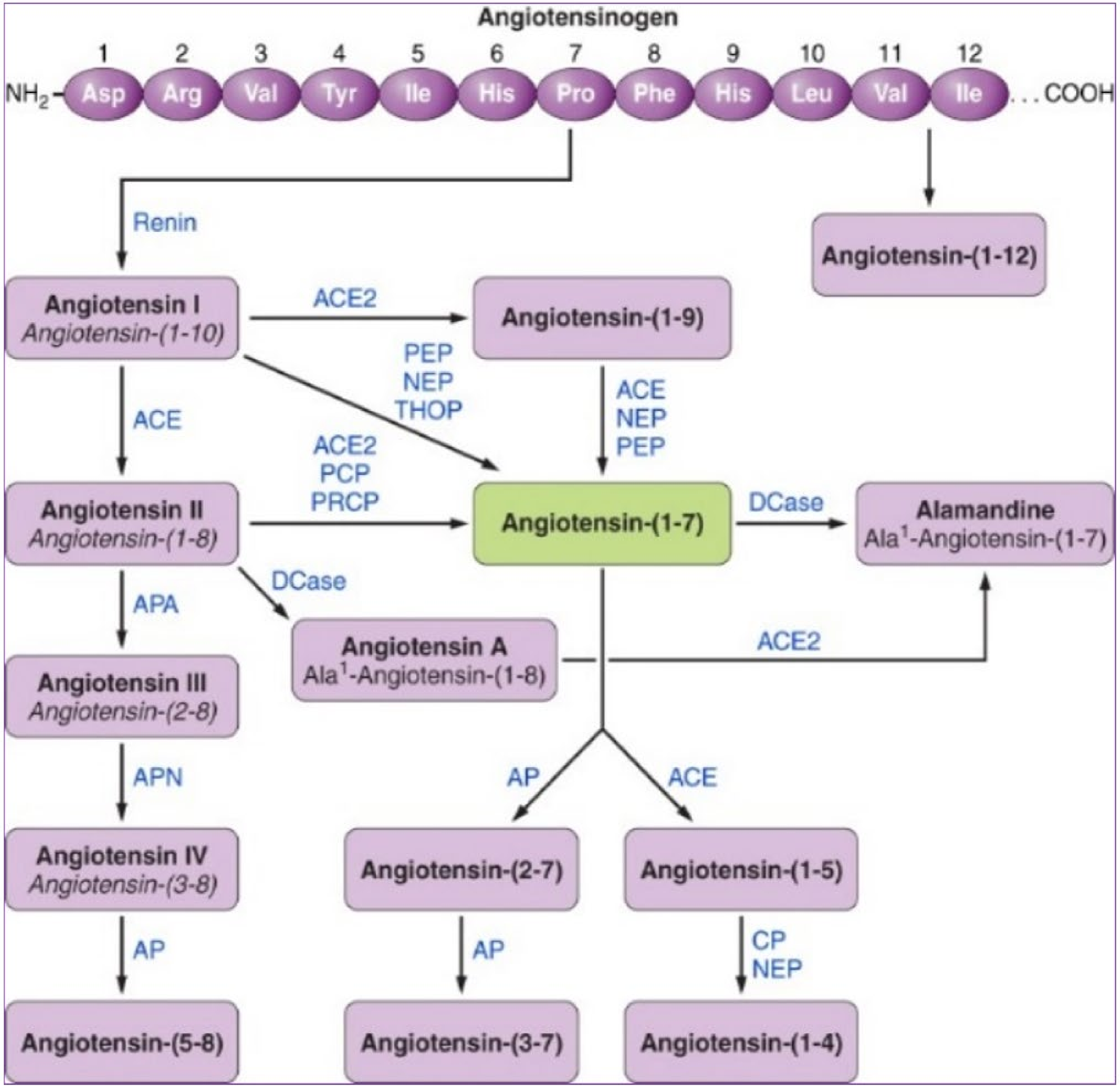
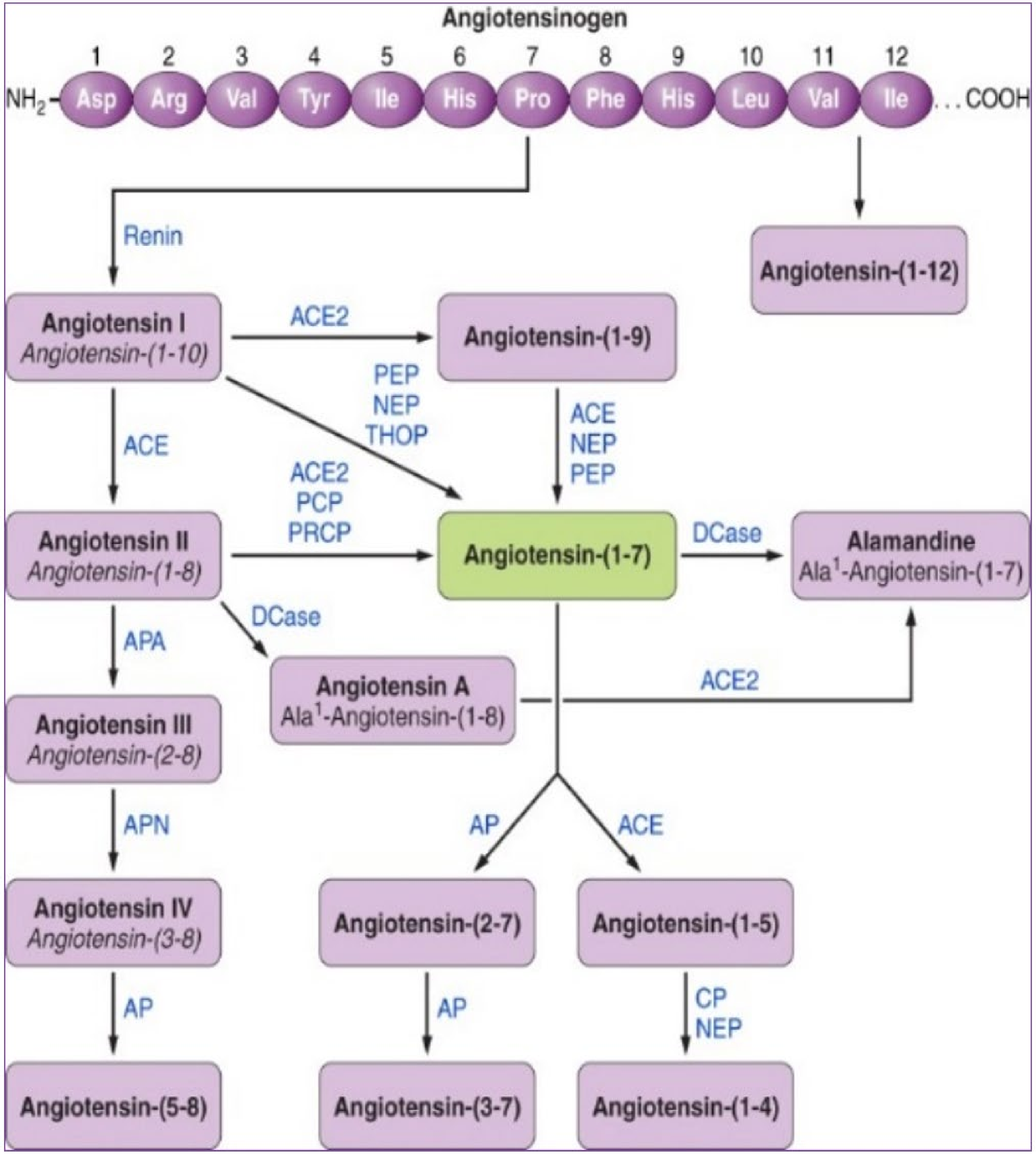
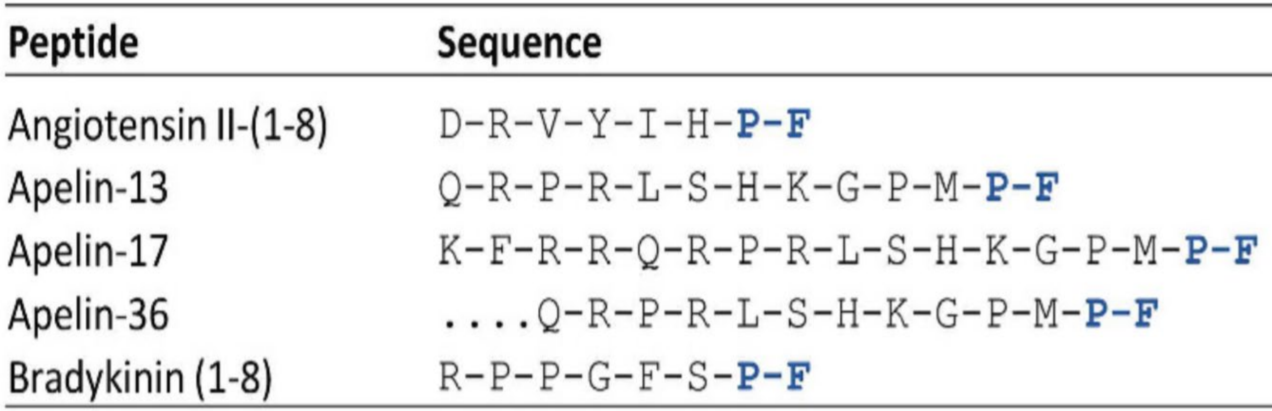


Figure 1. Schematic overview of the renin/ACE/Ang-II/AT$_1$R axis, ACE2/MasR/AT$_2$R axis and AngA/Alamandine-MrgD axis, modified from [22]. ACE, Angiotensin converting enzyme; AGT, angiotensinogen; Ang, angiotensin; APA, aminopeptidase A; APN, aminopeptidase N; AT$_1$R, angiotensin II type 1 receptor; AT$_2$R, angiotensin II type 2 receptor; MasR, Mas receptor; MrgD, Mas-related G-protein coupled receptor type D; NEP, neutral endopeptidase, POP, prolyloligopeptidase; PRCP, prolylcarboxypeptidase; TOP, thimet oligopeptidase.



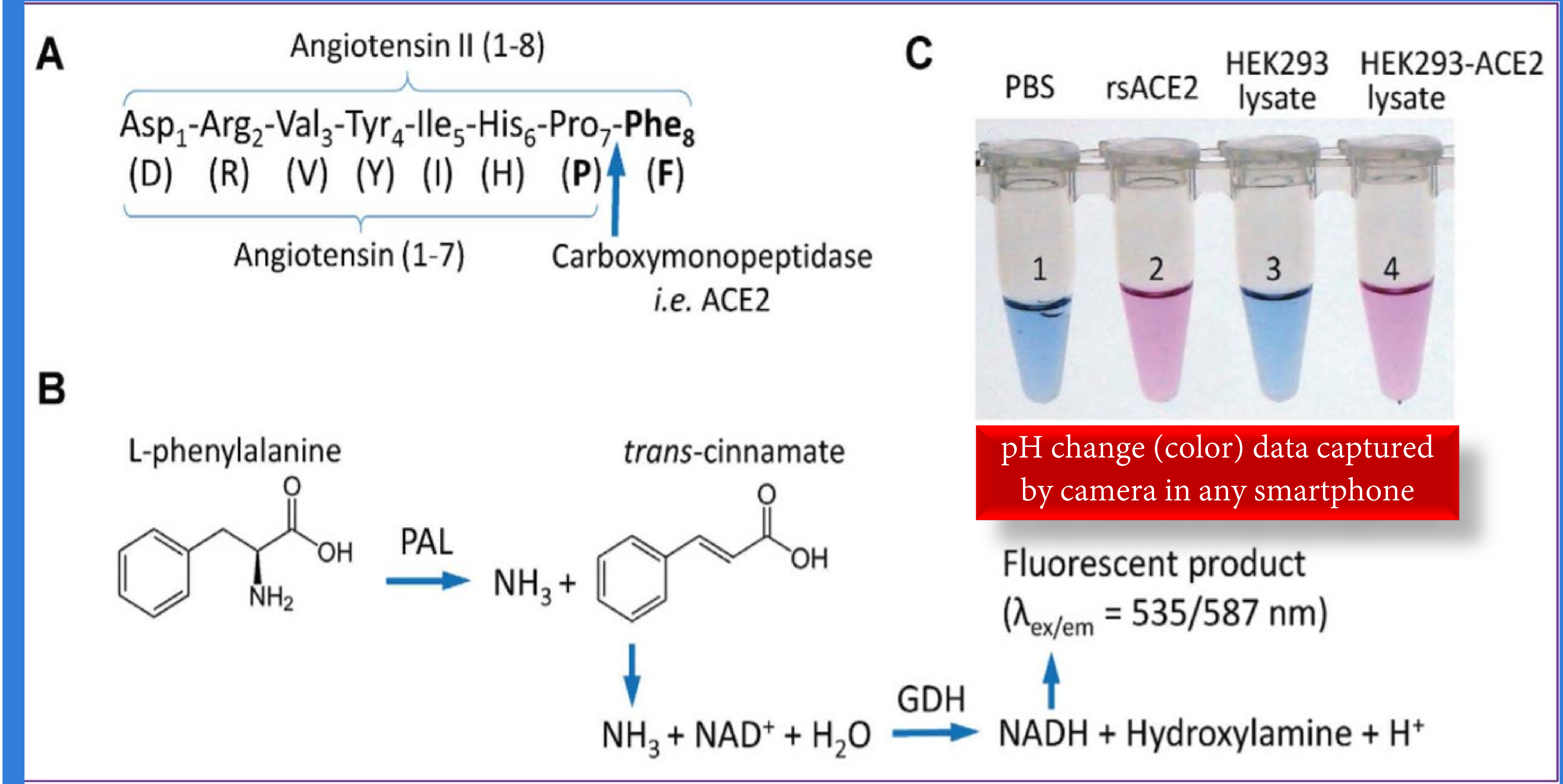
Vasoactive Peptide Hormones in Cardiovascular & Renal Function





Peptide	Sequence
Angiotensin II-(1-8)	D-R-V-Y-I-H-**P-F**
Apelin-13	Q-R-P-R-L-S-H-K-G-P-M-**P-F**
Apelin-17	K-F-R-R-Q-R-P-R-L-S-H-K-G-P-M-**P-F**
Apelin-36	....Q-R-P-R-L-S-H-K-G-P-M-**P-F**
Bradykinin (1-8)	R-P-P-G-F-S-**P-F**

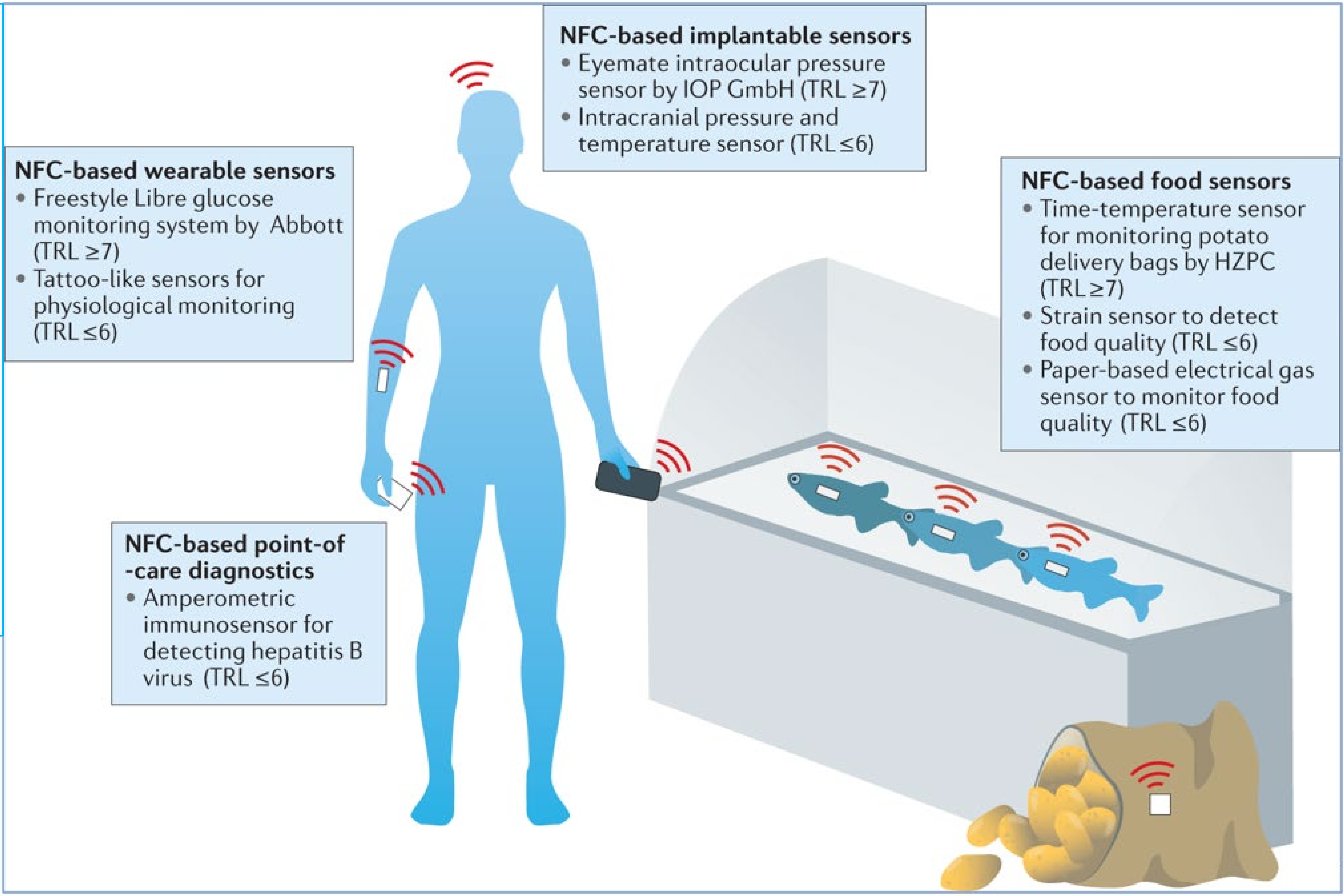
Assay to Determine Conversion of Angiotensin II to Angiotensin may detect SARS-CoV-2 in saliva



pH change (color) data captured by camera in any smartphone

A pie in the sky?

Near-field communication (NFC) based SARS-CoV-2 sensor in our mobile future?



NFC-based implantable sensors
- Eyemate intraocular pressure sensor by IOP GmbH (TRL ≥7)
- Intracranial pressure and temperature sensor (TRL ≤6)

NFC-based wearable sensors
- Freestyle Libre glucose monitoring system by Abbott (TRL ≥7)
- Tattoo-like sensors for physiological monitoring (TRL ≤6)

NFC-based food sensors
- Time-temperature sensor for monitoring potato delivery bags by HZPC (TRL ≥7)
- Strain sensor to detect food quality (TRL ≤6)
- Paper-based electrical gas sensor to monitor food quality (TRL ≤6)

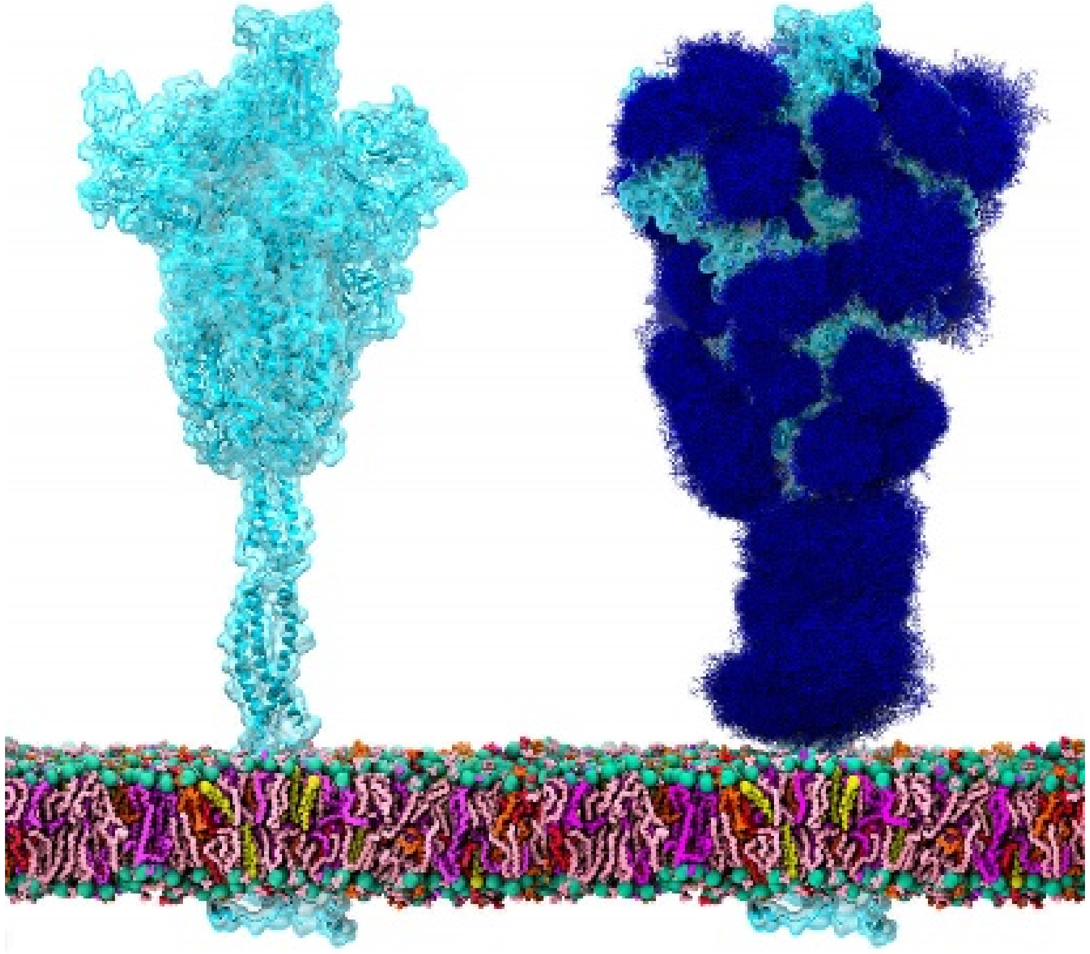
NFC-based point-of-care diagnostics
- Amperometric immunosensor for detecting hepatitis B virus (TRL ≤6)

What are the roadblocks to rapid testing?

Low-cost detection of Spike protein and many others …

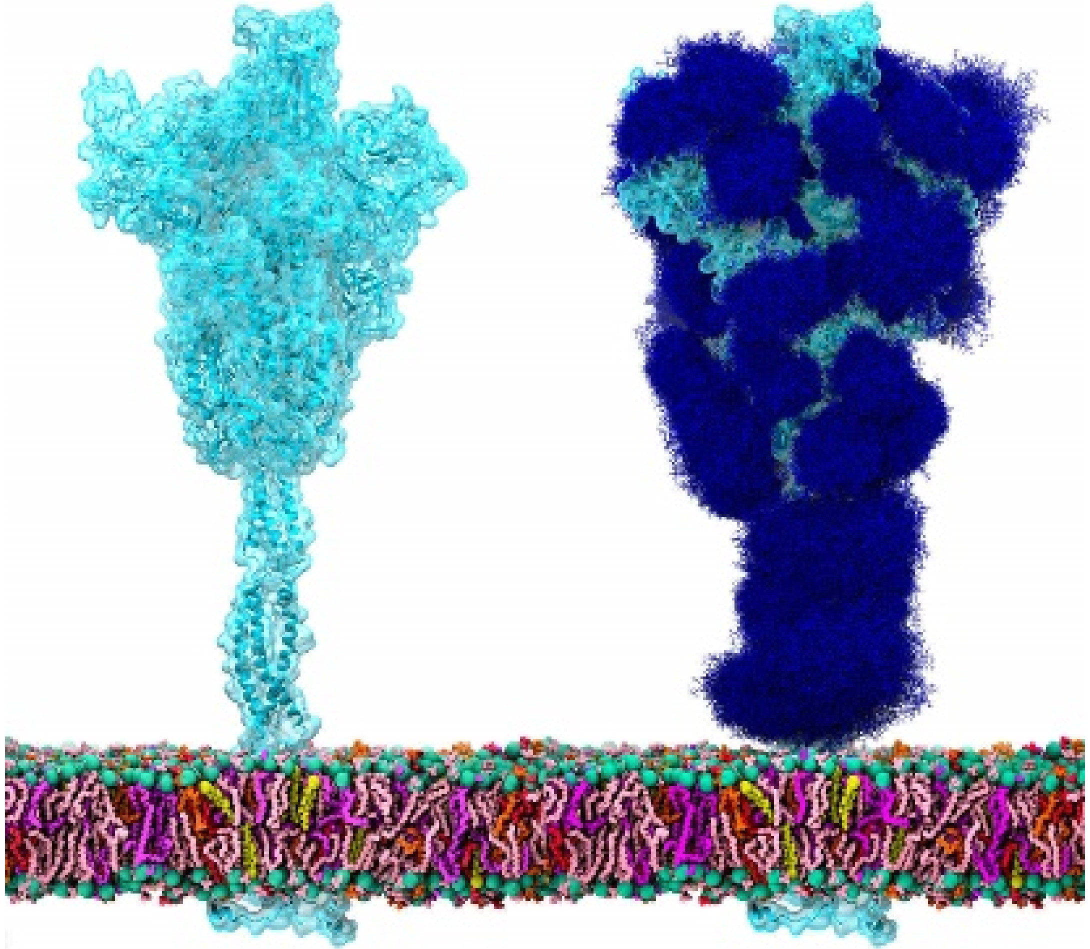
- Why is the detection of the SARS-CoV-2 Spike protein such a problem ?

- Because it is covered by a glycan shield to avoid recognition by the immune system.



- Is the sensitivity of detection reduced because of uncertain access to the Spike protein when testing for SARS-CoV-2 ?

YES.



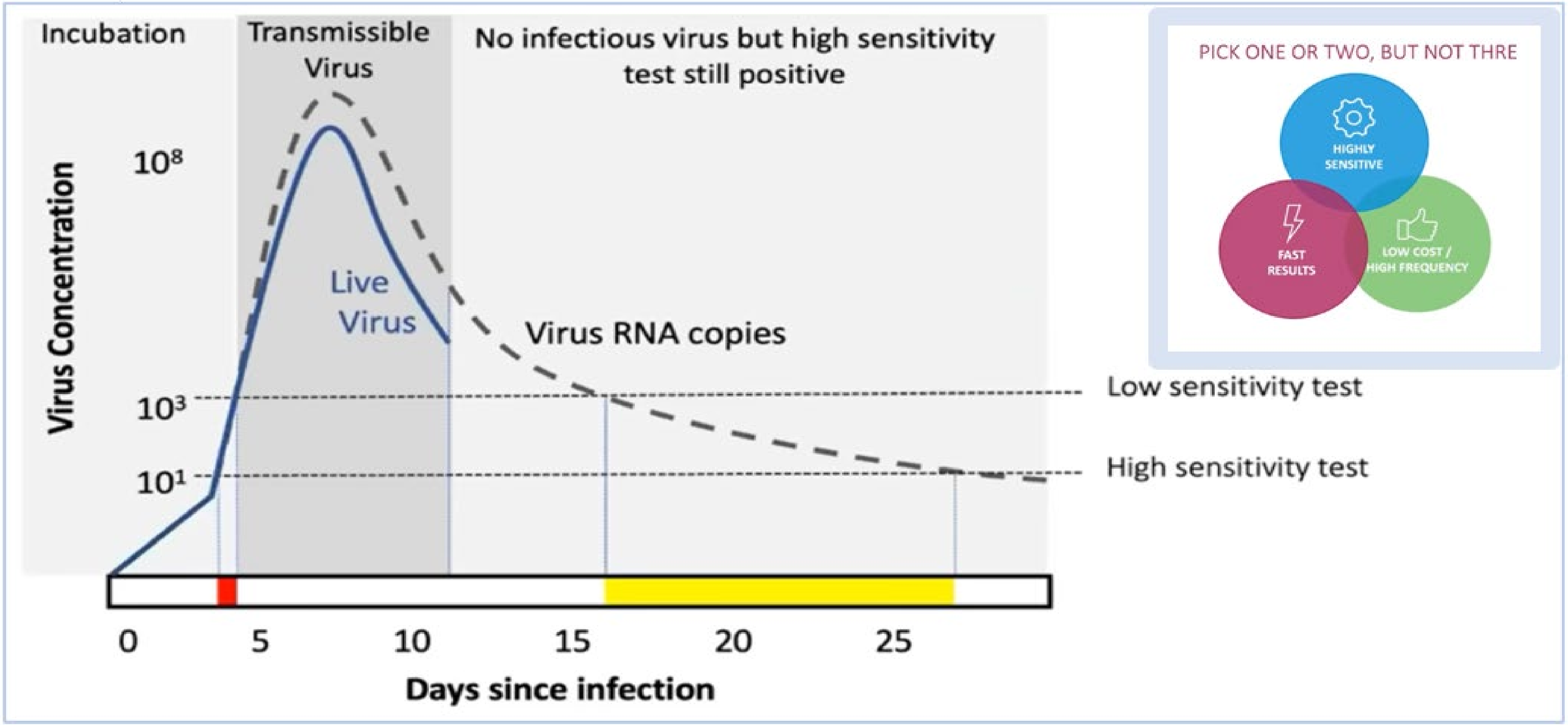
Sensitivity of detection

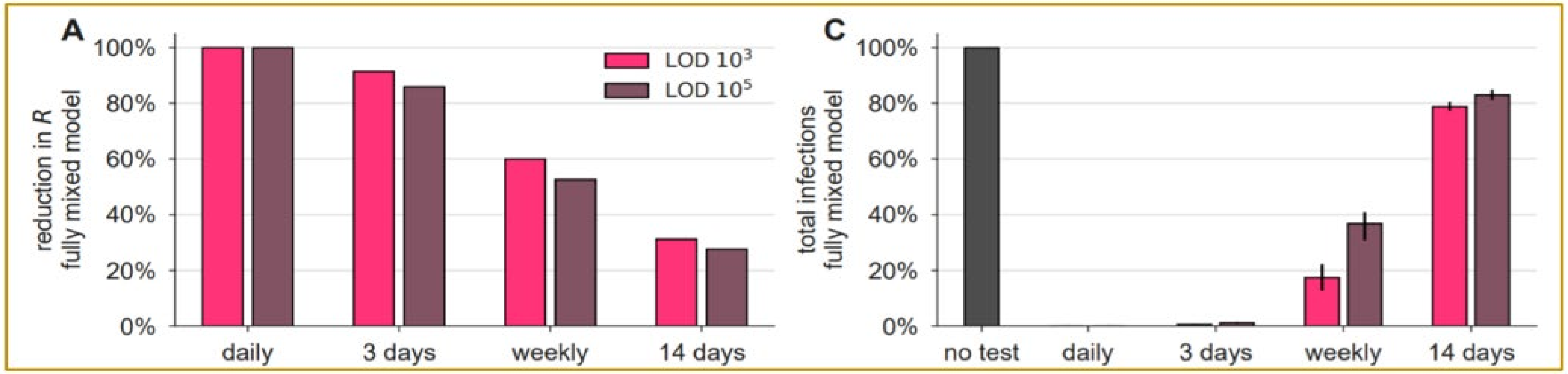
may not be a barrier

for using low-cost

SARS-CoV-2 tests.

Why?

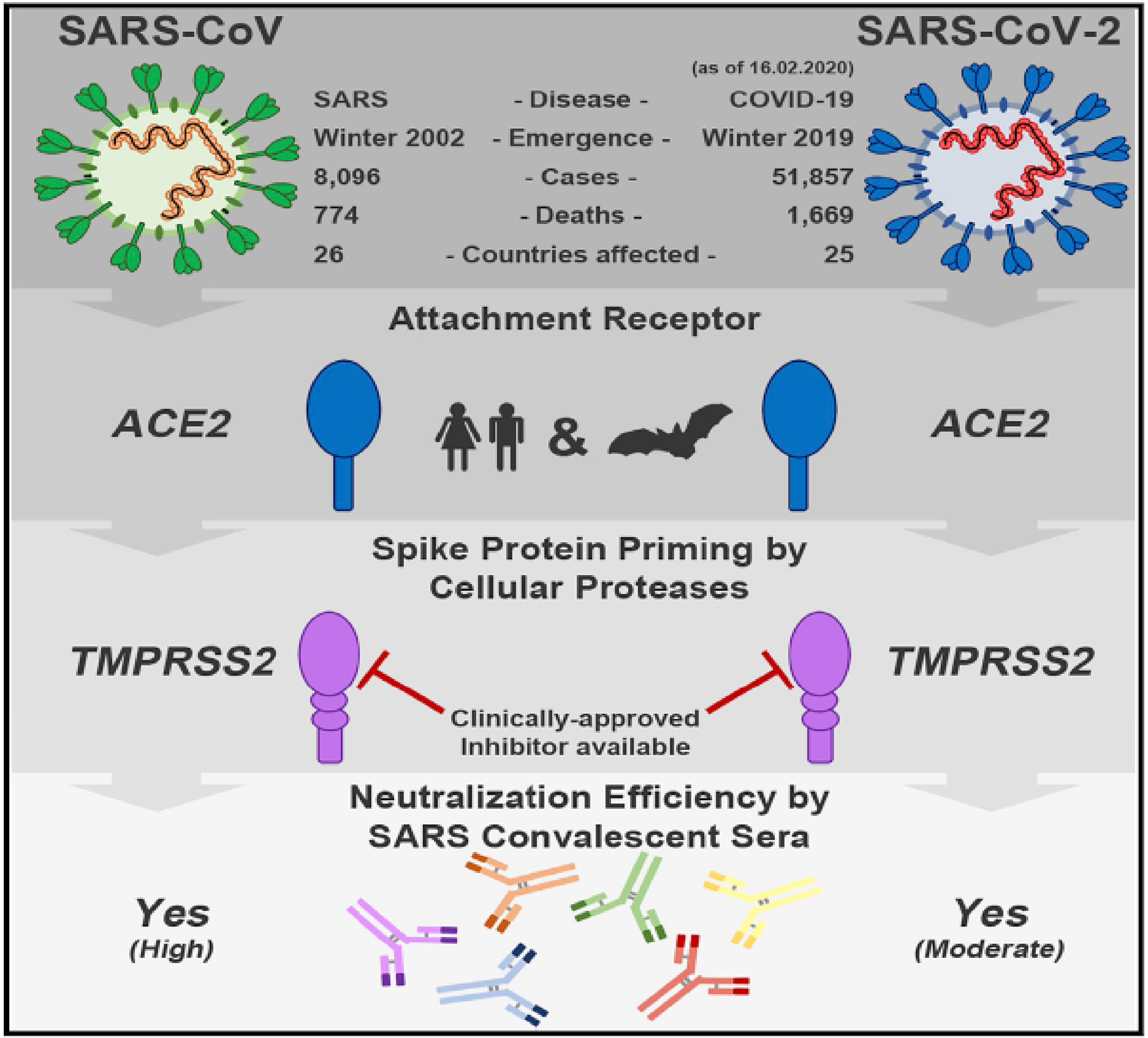




Is there an ACE2 helper for viral entry?

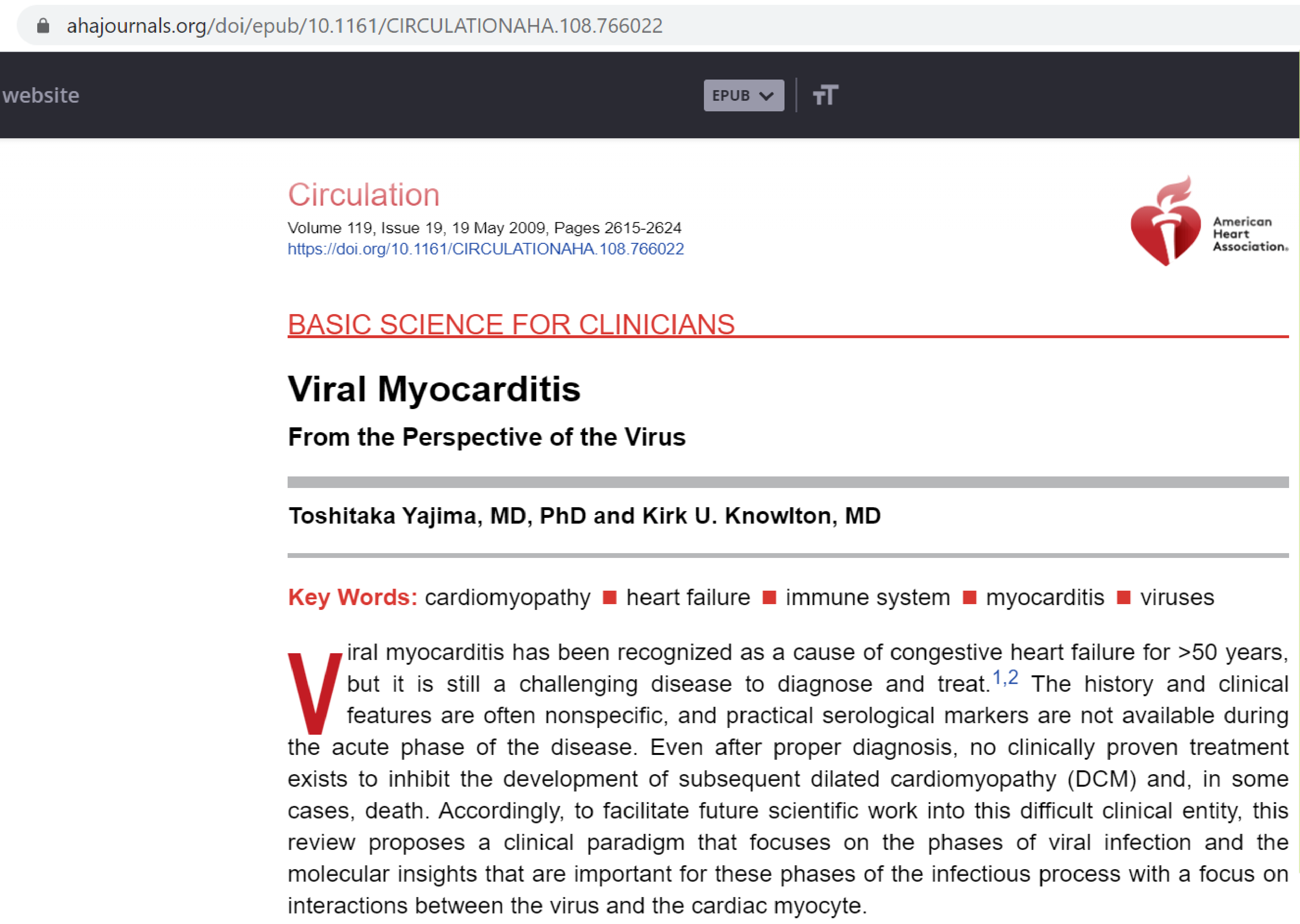
Yes. TMPRSS2. That’s all what we know, at present. What is TMPRSS2?

TMPRSS2 gene produces transmembrane protease serine 2 which acts with ACE2 for SARS-CoV-2 infection. Androgen-induced TMPRSS2 activates several substrates that include pro-hepatocyte growth factor/HGF, the protease activated receptor-2/F2RL1 or matriptase/ST14 leading to extracellular matrix disruption and leads to metastasis of human prostate cancer cells.



SARS-CoV		SARS-CoV-2
SARS	- Disease -	COVID-19
Winter 2002	- Emergence -	Winter 2019
8,096	- Cases -	51,857
774	- Deaths -	1,669
26	- Countries affected -	25

Why are symptoms for CoVID-19 often extremely varied & acute?



Circulation
Volume 119, Issue 19, 19 May 2009, Pages 2615-2624
https://doi.org/10.1161/CIRCULATIONAHA.108.766022

BASIC SCIENCE FOR CLINICIANS

Viral Myocarditis

From the Perspective of the Virus

Toshitaka Yajima, MD, PhD and Kirk U. Knowlton, MD

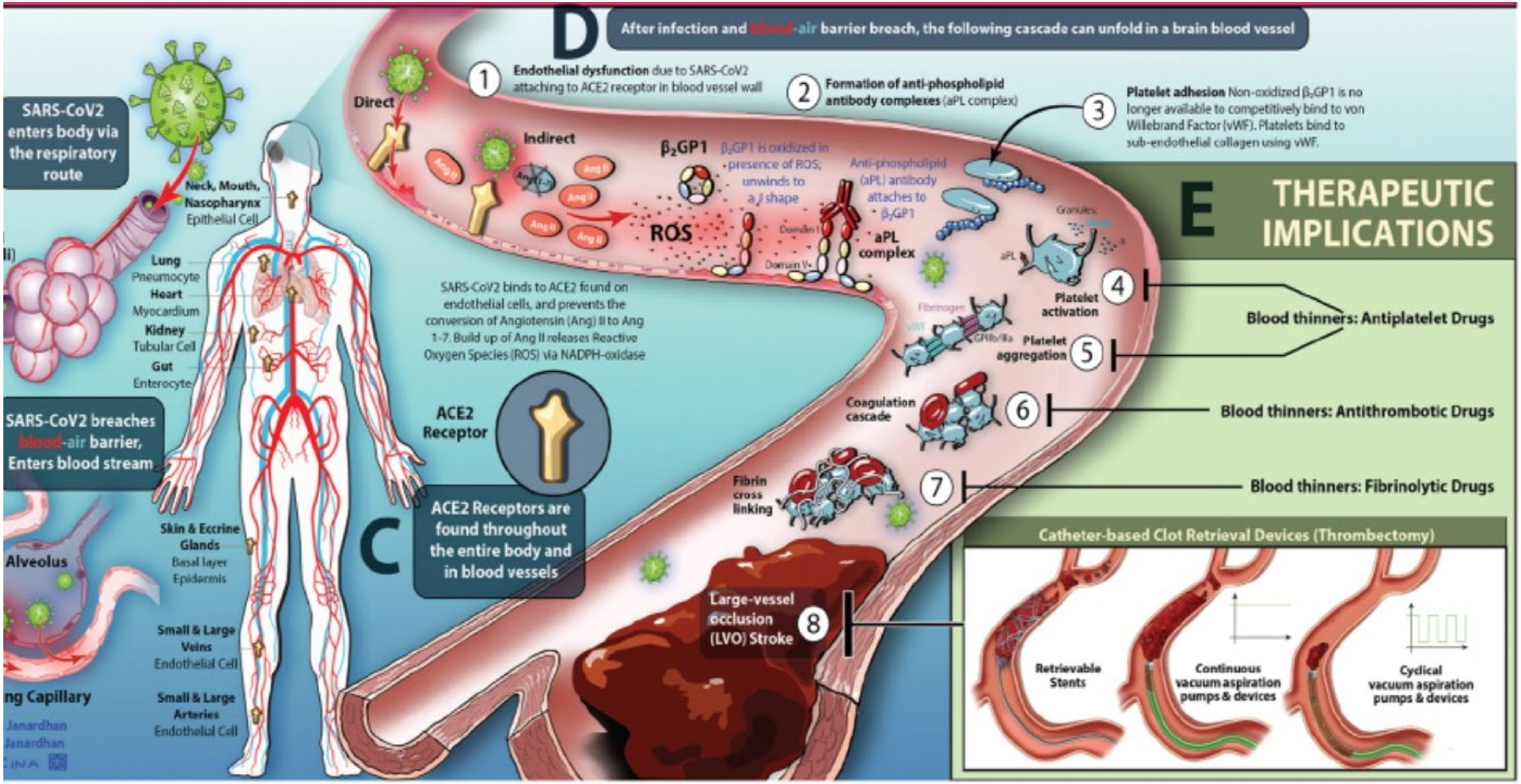
Key Words: cardiomyopathy ■ heart failure ■ immune system ■ myocarditis ■ viruses

Viral myocarditis has been recognized as a cause of congestive heart failure for >50 years, but it is still a challenging disease to diagnose and treat.[1,2] The history and clinical features are often nonspecific, and practical serological markers are not available during the acute phase of the disease. Even after proper diagnosis, no clinically proven treatment exists to inhibit the development of subsequent dilated cardiomyopathy (DCM) and, in some cases, death. Accordingly, to facilitate future scientific work into this difficult clinical entity, this review proposes a clinical paradigm that focuses on the phases of viral infection and the molecular insights that are important for these phases of the infectious process with a focus on interactions between the virus and the cardiac myocyte.

Inevitable?

We have known about viral myocarditis for more than 50 years.

ACE2 receptor is almost ubiquitous and directly affects the cardiovascular system and renal function.



After infection and blood-air barrier breach, the following cascade can unfold in a brain blood vessel

① **Endothelial dysfunction** due to SARS-CoV2 attaching to ACE2 receptor in blood vessel wall

② **Formation of anti-phospholipid antibody complexes** (aPL complex)

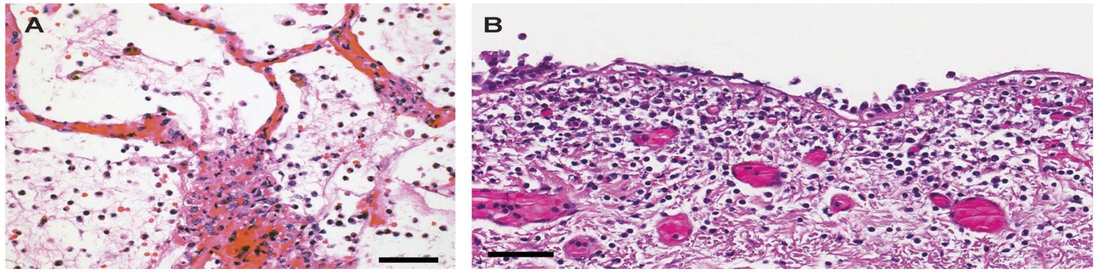
③ **Platelet adhesion** Non-oxidized β_2GP1 is no longer available to competitively bind to von Willebrand Factor (vWF). Platelets bind to sub-endothelial collagen using vWF.

β_2GP1 is oxidized in presence of ROS; unwinds to a J shape

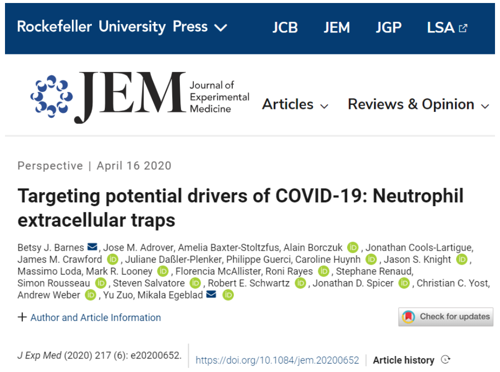
Anti-phospholipid (aPL) antibody attaches to β_2GP1

SARS-CoV2 binds to ACE2 found on endothelial cells, and prevents the conversion of Angiotensin (Ang) II to Ang 1-7. Build up of Ang II releases Reactive Oxygen Species (ROS) via NADPH-oxidase

Jonathan Spicer, M.D., Ph.D., a clinician scientist at the RI-MUHC and Assistant Professor of Surgery at McGill University is a thoracic surgeon who has witnessed the devastating effects of COVID-19 infection at the bedside. “We see in these patients severe lung damage known as ARDS, another serious problem caused by excess NETs and seen in cases of severe influenza,” he said. “In addition, their airways are often clogged with thick mucus and unlike most severe lung infections, these patients tend to form small clots throughout their body at much higher rates than normal. NETs have also been found in the blood of patients with sepsis or cancer, where they can facilitate the formation of such blood clots.”



Neutrophils in an autopsy specimen from the lungs of a patient who succumbed from COVID-19. (A) Extensive neutrophil infiltration in pulmonary capillaries, with acute capillaritis with fibrin deposition, extravasation into the alveolar space. (B) Neutrophilic mucositis of the trachea.



Perspective | April 16 2020

Targeting potential drivers of COVID-19: Neutrophil extracellular traps

Betsy J. Barnes, Jose M. Adrover, Amelia Baxter-Stoltzfus, Alain Borczuk, Jonathan Cools-Lartigue, James M. Crawford, Juliane Daßler-Plenker, Philippe Guerci, Caroline Huynh, Jason S. Knight, Massimo Loda, Mark R. Looney, Florencia McAllister, Roni Rayes, Stephane Renaud, Simon Rousseau, Steven Salvatore, Robert E. Schwartz, Jonathan D. Spicer, Christian C. Yost, Andrew Weber, Yu Zuo, Mikala Egeblad

+ Author and Article Information

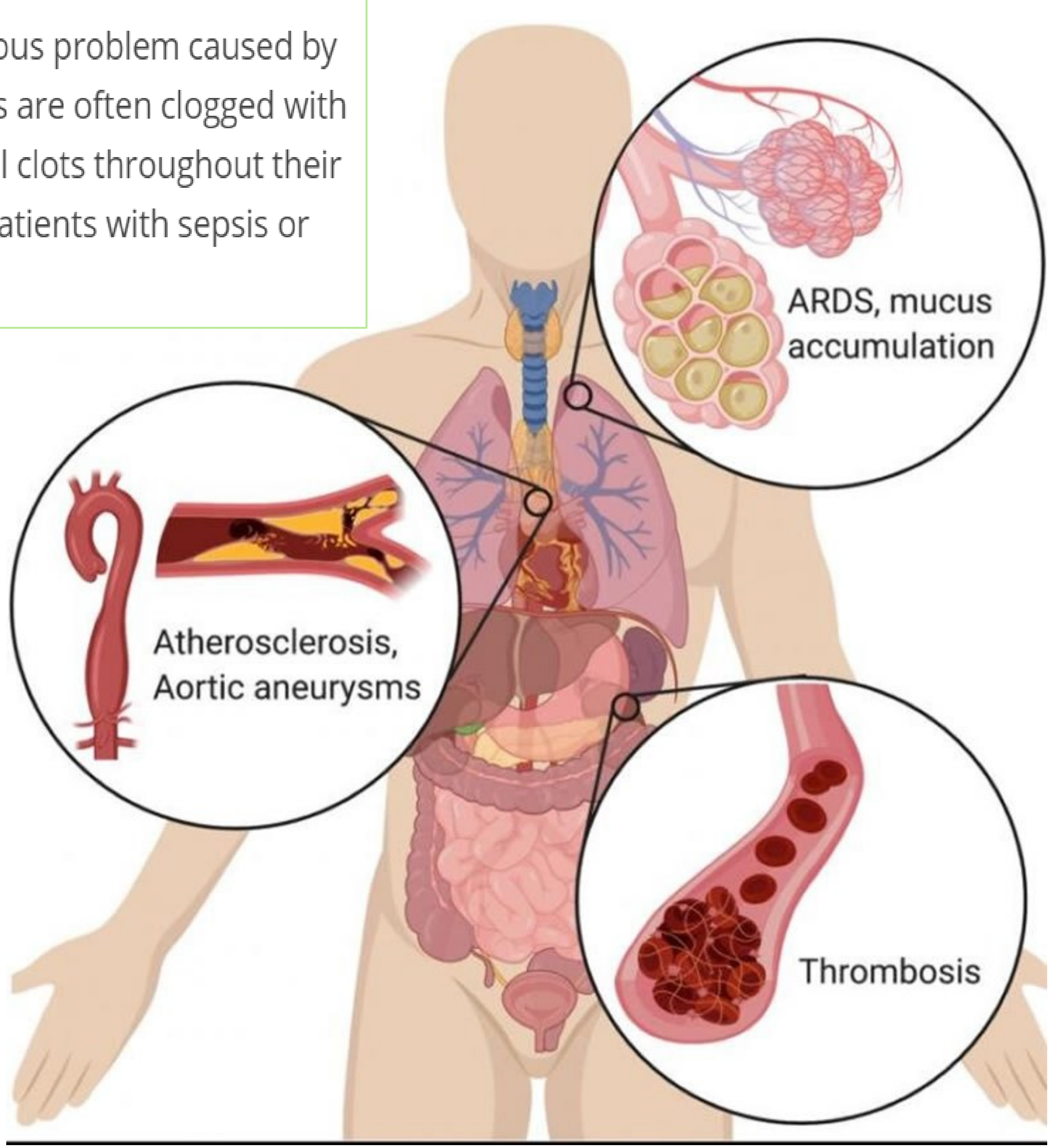
J Exp Med (2020) 217 (6): e20200652. https://doi.org/10.1084/jem.20200652 | Article history

International consortium investigates cells as cause of COVID-19 deaths

News

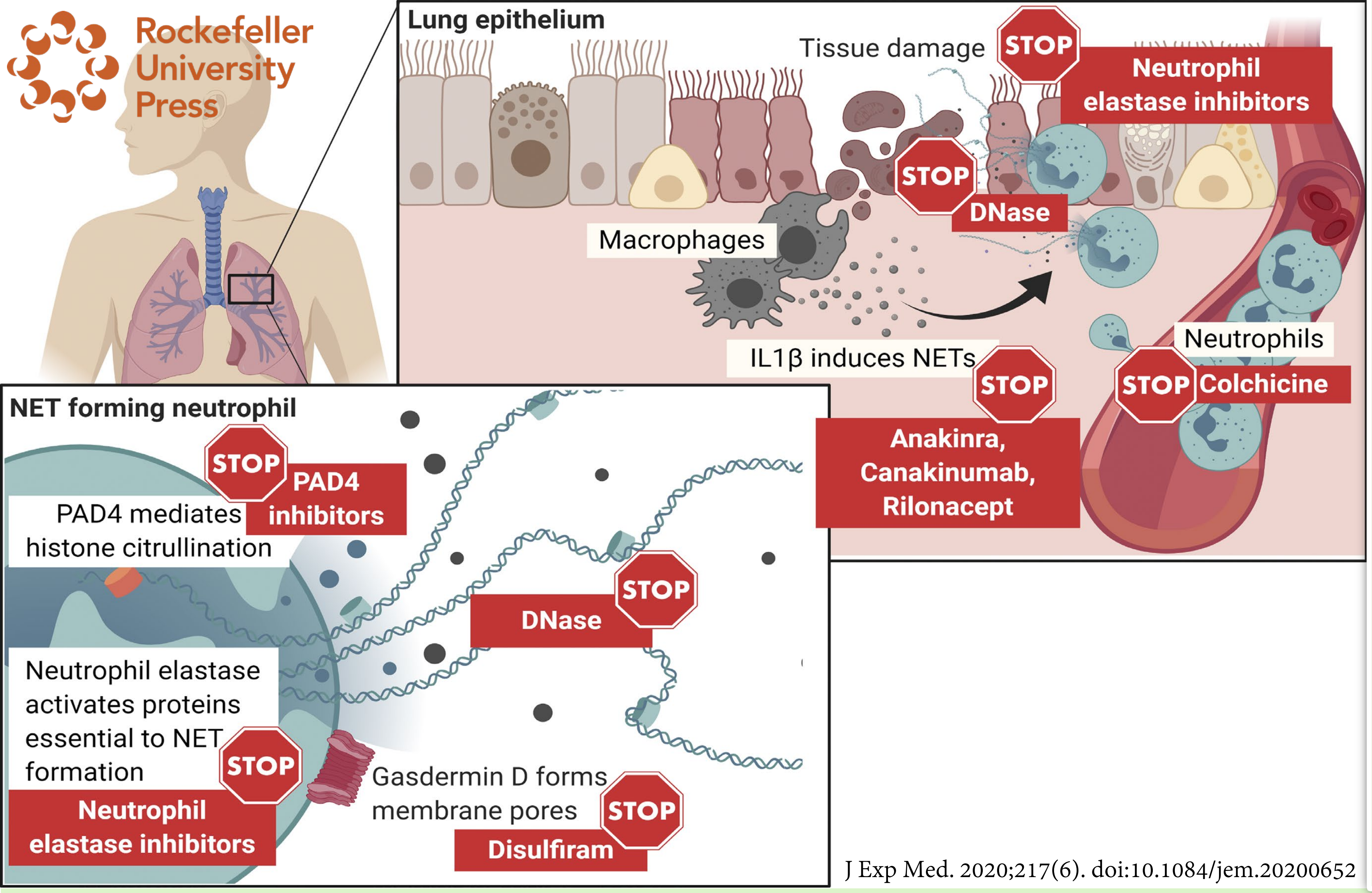
New publication links neutrophil infiltration in the lungs of patients to COVID-19 symptoms

PUBLISHED: 17 APR 2020



www.mcgill.ca/newsroom/channels/news/international-consortium-investigates-overactive-immune-cells-cause-covid-19-deaths-321710

Targeting potential drivers of COVID-19: Neutrophil Extracellular Traps (NET)

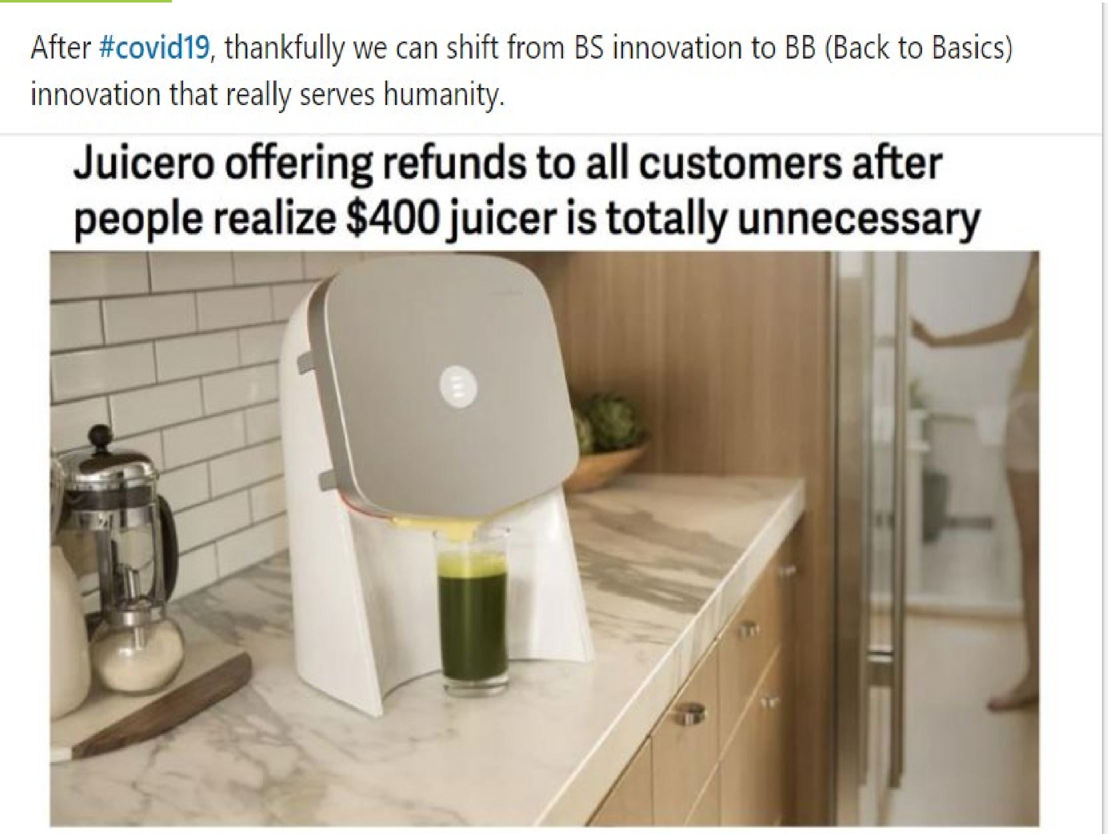


J Exp Med. 2020;217(6). doi:10.1084/jem.20200652

NETs can be targeted by existing drugs through several means. NE, PAD4, and gasdermin D inhibitors will prevent NET formation. DNase has been used safely to digest NETs in the mucous secretions of the airways of CF patients. Colchicine inhibits neutrophil migration and infiltration to sites of inflammation. IL1β blockers will prevent an inflammatory loop between NETs and IL1β. Of these approaches, trials to treat COVID-19 with colchicine and anakinra are ongoing (ClinicalTrials.gov id: NCT04324021, NCT04330638, NCT02735707, NCT04326790, NCT04328480, NCT04322565, NCT04322682).

Summary: How little we know !

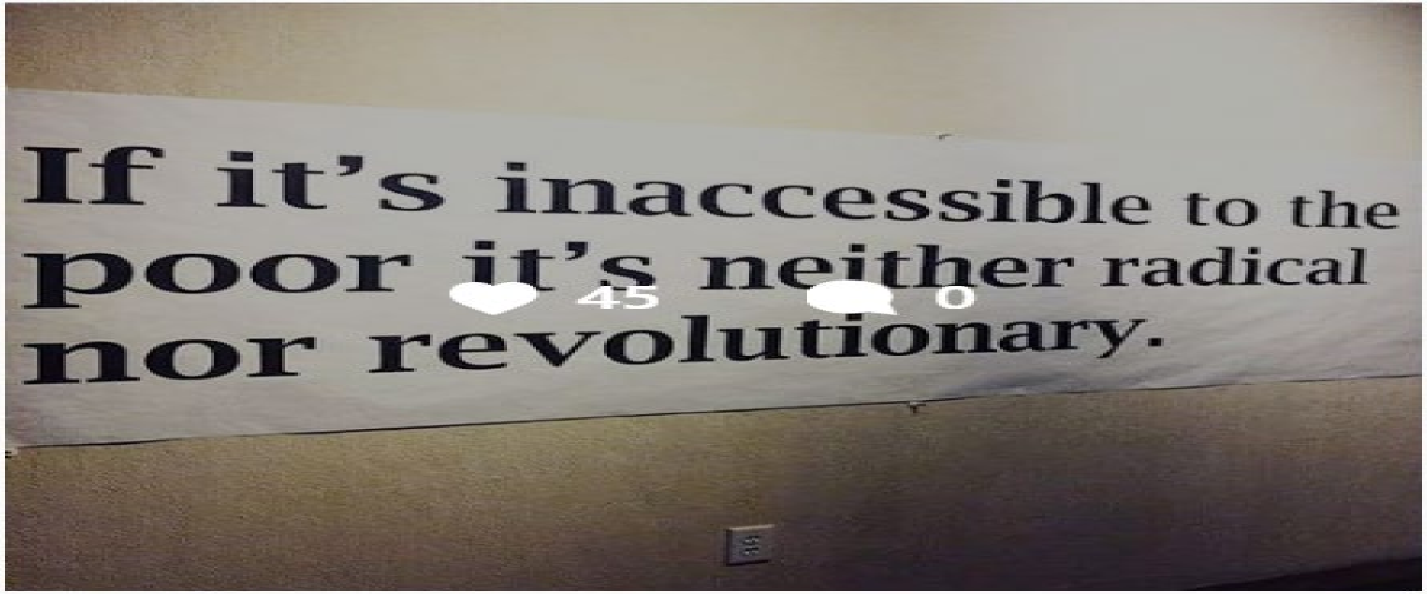
TETRIS is the best key at hand.
Sensors for early detection may save lives.
We will have to live with this virus for decades.
We know very little about the biology of the virus.
Vaccines, small molecules and all forms are treatment are welcome.
We know almost nothing about interactions between virus and physiology.
Build even better bridges between molecular biology and molecular medicine.
Basic science research is our best path to progress.
Mathematics is central to rigor in science.
Always try to un-learn and re-learn.
Don’t polish the chrome.
Tune the engine.



After #covid19, thankfully we can shift from BS innovation to BB (Back to Basics) innovation that really serves humanity.

Juicero offering refunds to all customers after people realize $400 juicer is totally unnecessary

« The best brains in the world are busy solving the problems of the rich, who really don't have problems »



If it's inaccessible to the poor it's neither radical nor revolutionary.

The education of a boy may change the fate of a man.
The education of a girl can change the destiny of a nation.

https://www.forbes.com/sites/avivahwittenbergcox/2020/04/13/what-do-countries-with-the-best-coronavirus-reponses-have-in-common-women-leaders/#6c5c6c9c3dec

Playing by the rules of the game ?

Understanding or Under-estimating SARS-CoV-2 ?

Break all rules. Ask correct questions.

Understand that many unknown unknowns exist.

What counts, often cannot be counted. Hubris kills.

Shoumen Palit Austin Datta

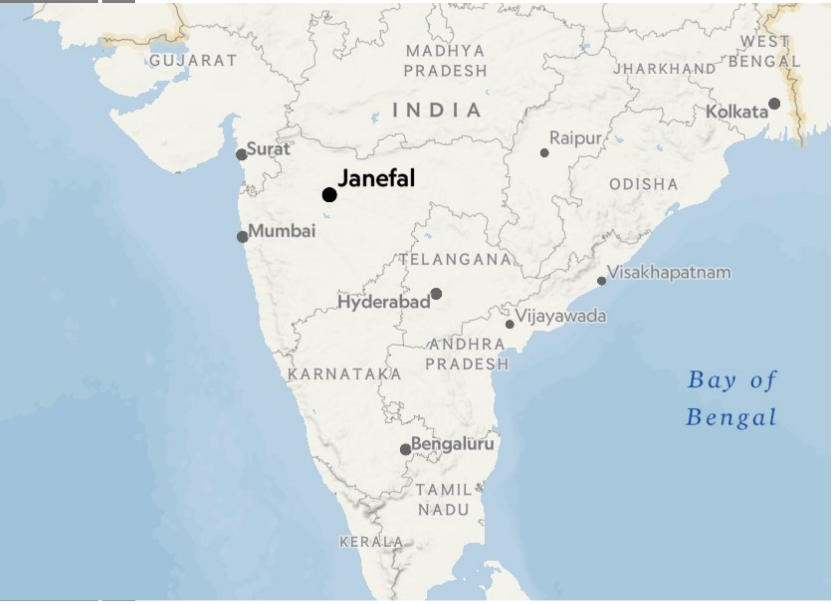
21st May 2021 @ ORCHID

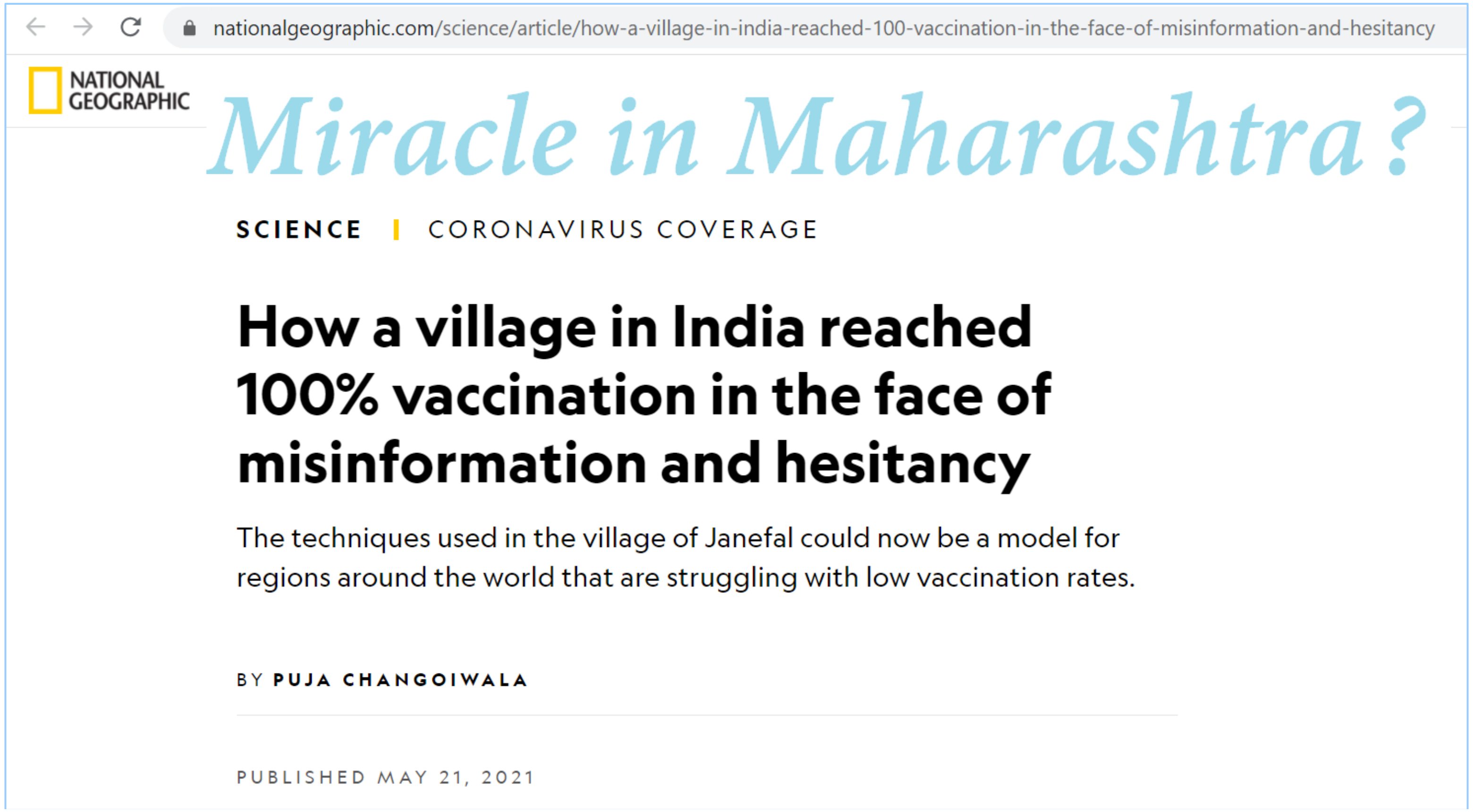
http://bit.ly/BIO-SD

Research Affiliate, MIT Auto ID Labs, Dept of Mechanical Engineering, MIT (shoumen@mit.edu) ▪ Senior Scientist, MDPnP Labs and Cybersecurity Program, Dept of Anesthesiology, Massachusetts General Hospital, Harvard Medical School (sdatta8@mgh.harvard.edu)

HOPE … brewing

Miracle in Maharashtra ?





SCIENCE | CORONAVIRUS COVERAGE

How a village in India reached 100% vaccination in the face of misinformation and hesitancy

The techniques used in the village of Janefal could now be a model for regions around the world that are struggling with low vaccination rates.

BY **PUJA CHANGOIWALA**

PUBLISHED MAY 21, 2021

When health workers tried to convince Munir Pathan to take the COVID-19 vaccine in February, the 52-year-old farmer refused. The jab would kill him, he was certain. A resident of Janefal village in the western Indian state of Maharashtra, roughly a 228-mile drive from Mumbai, Pathan had read messages on WhatsApp, stating that vaccine shots are lethal and that if a doctor errs while administering the shot, it leads to an infection in the arm. The only way to save the person thereafter is by amputating the limb. On April 27, 2021 (3 months after the vaccination drive first commenced in India), Pathan took his first shot at a vaccination camp organized in his village. That day, health workers managed to inoculate 65 residents of Janefal (100% of its eligible population), setting an example for rural India and prompting vaccination drives in 16 nearby villages. “Now, every village wants to be Janefal,” says Sunil Chavan, collector of the Aurangabad district (village base). **Janefal stands out as a role model.**

"Sometimes our fate resembles a fruit tree in winter. Who would think that those branches would turn green again and blossom?" ~ Johann Wolfgang von Goethe