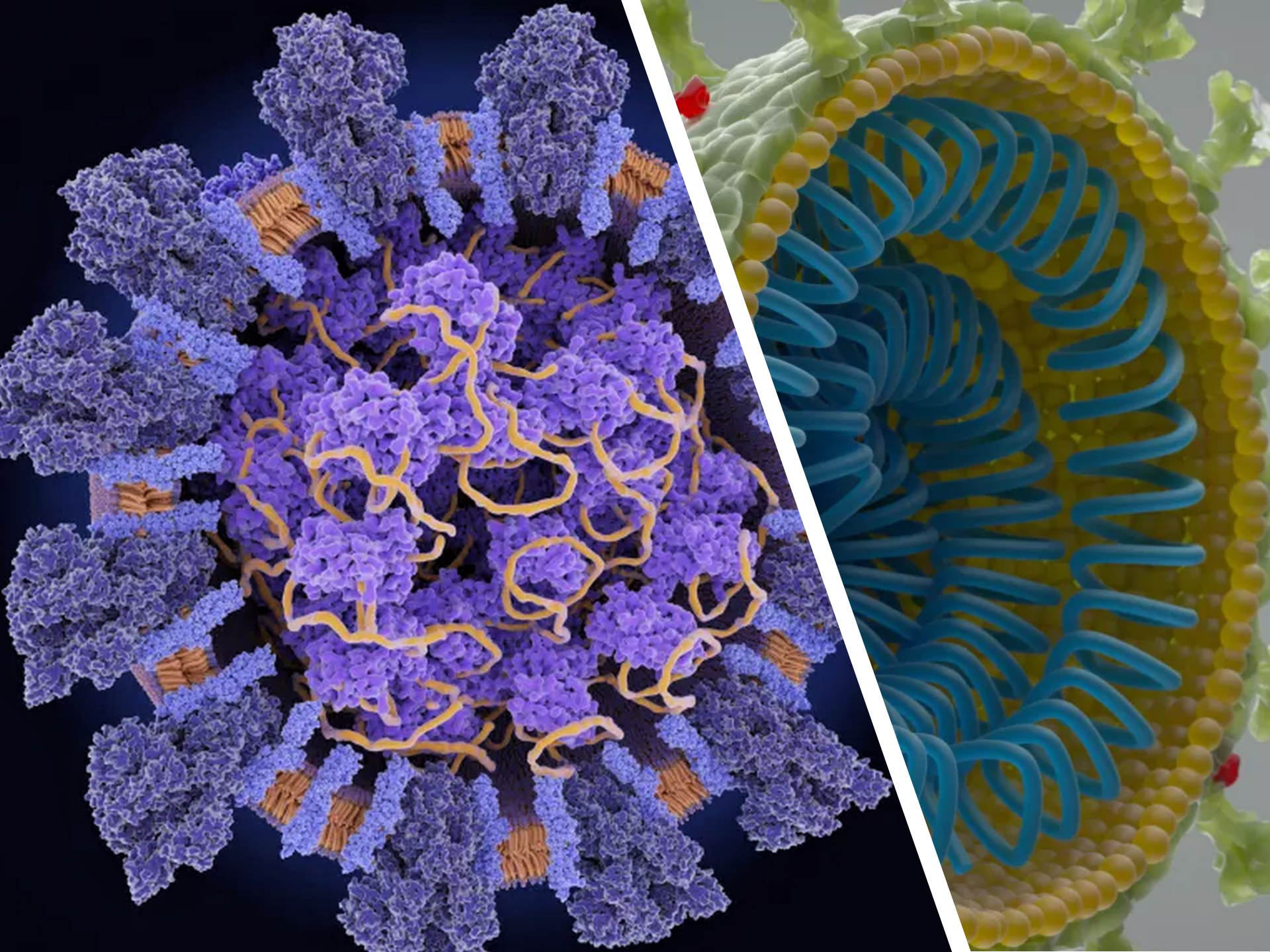
CORONAVIRUS SARS-CoV-2 SCIENCE UPDATE JUNE 2021

С.А. Булат

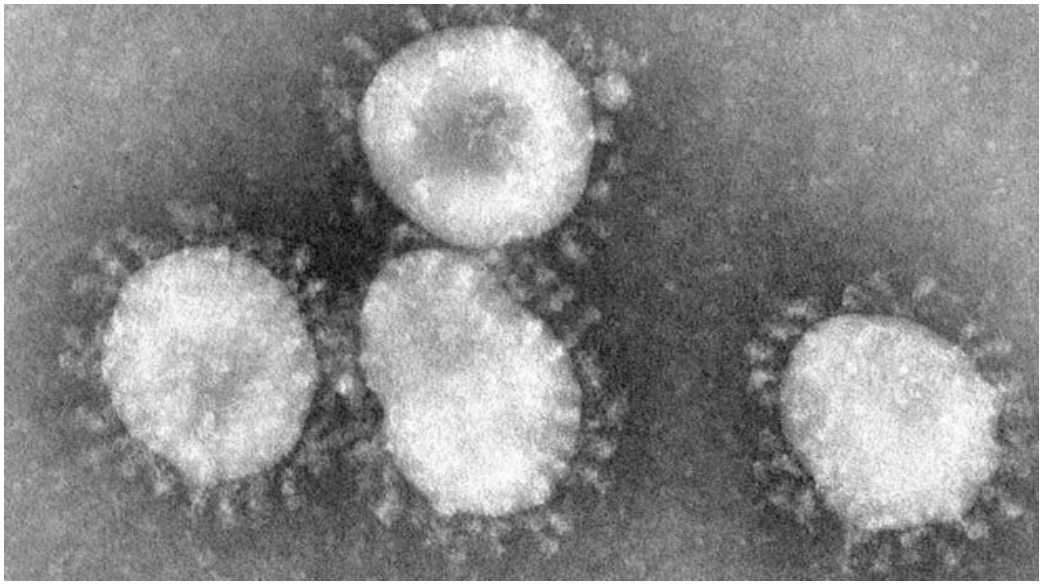
Лаб криоастробиологии

ОМРБ НИЦ КИ-ПИЯФ



Content

- Coronavirus
  - History
  - Structure
  - Disease Covid-19
  - Variants - mutations
- Natural or artificial origin
- Vaccines



The woman who discovered the first coronavirus

June Almeida with her electron microscope at the Ontario Cancer Institute in Toronto in 1963

June Almeida discovered the first human coronavirus - 1964

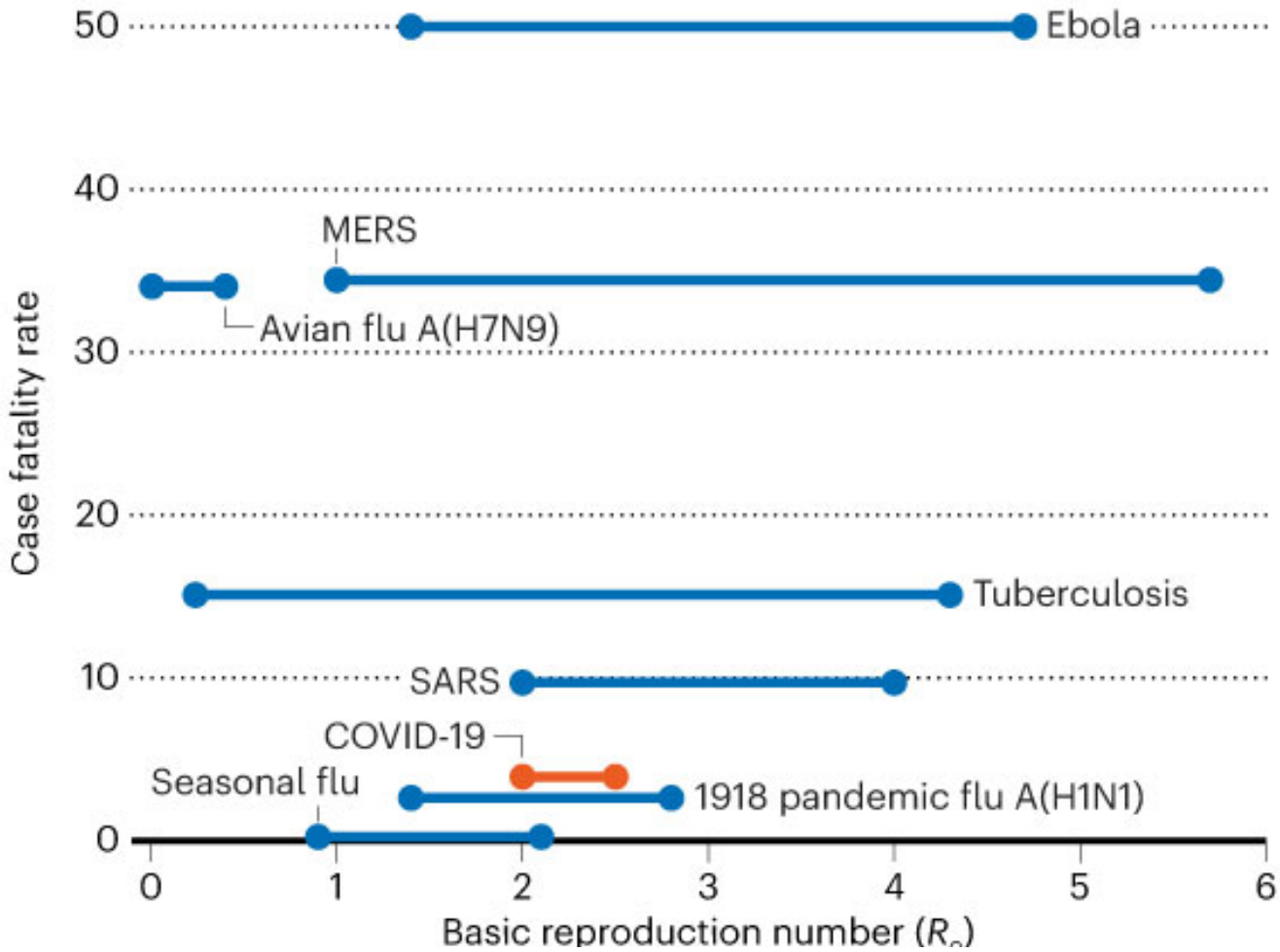
- Covid-19 is a new illness but it is caused by a coronavirus of the type first identified by Dr Almeida in **1964** at her laboratory in St Thomas's Hospital in London.
- …running research at the **common cold unit** in Salisbury in Wiltshire by studying nasal washings from volunteers… were able to grow quite a few common cold-associated viruses but not all of them.
- One sample B814 was from the **nasal washings of a pupil** at a boarding school in Surrey in 1960.
- Researchers found that they were able to transmit common cold symptoms to volunteers but they were unable to grow it in routine cell culture. However, volunteer studies demonstrated its growth in organ cultures → electron microscope.
- June Almeida who saw the virus particles in the specimens described them as **like influenza viruses but not exactly the same**. She identified what became known as the first human coronavirus.
- The new discovery from strain B814 was written up in the British Medical Journal in **1965** and the first photographs of what she had seen were published in the Journal of General Virology **two years later**.
- Dr Tyrrell and Dr Almeida, along with Prof Tony Waterson named virus as coronavirus because of the crown or halo surrounding it on the viral image.

June Almeida died in 2007, at the age of 77

Coronavirus-2 genome and Bad News Wrapped in Protein.pdf

COVID-19 VS OTHER DISEASES

Estimates suggest the COVID-19 coronavirus is less deadly than the related illnesses SARS or MERS, but more infectious (R_0) than seasonal influenza.



SYMPTOMS

Symptoms can range from mild to severe, and some people don't have any symptoms at all. The following symptoms may appear 2-14 days after exposure.*

PRIMARY SYMPTOMS:

- Fever
- Dry Cough
- Fatigue

LESS COMMON SYMPTOMS:

- Diarrhea
- Runny Nose
- Sore Throat
- Aches And Pains

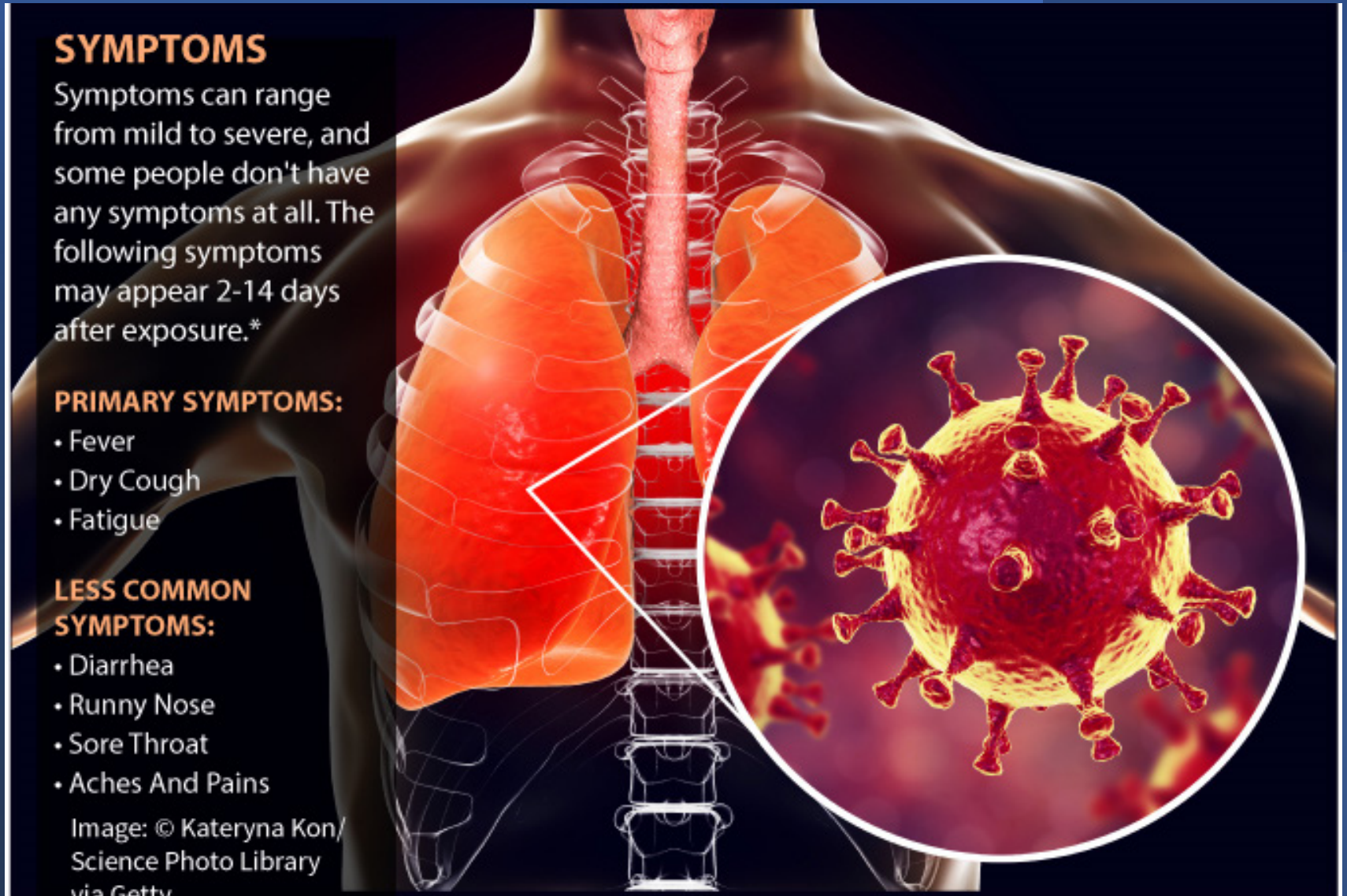
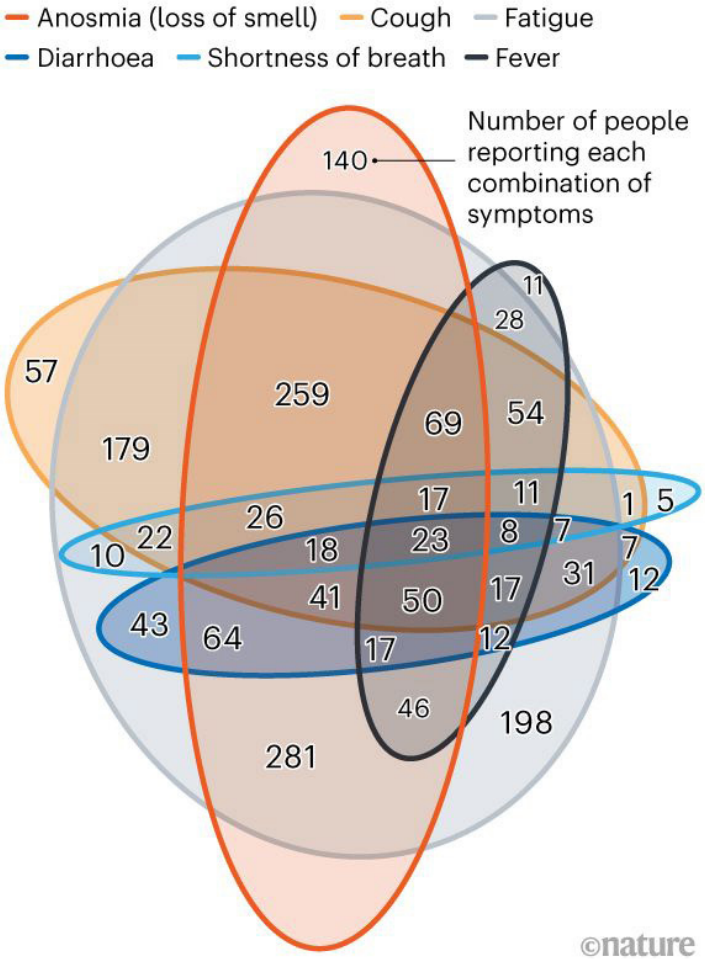


Image: © Kateryna Kon/ Science Photo Library via Getty

*This is based on what has been seen previously for the incubation period of similar viruses.

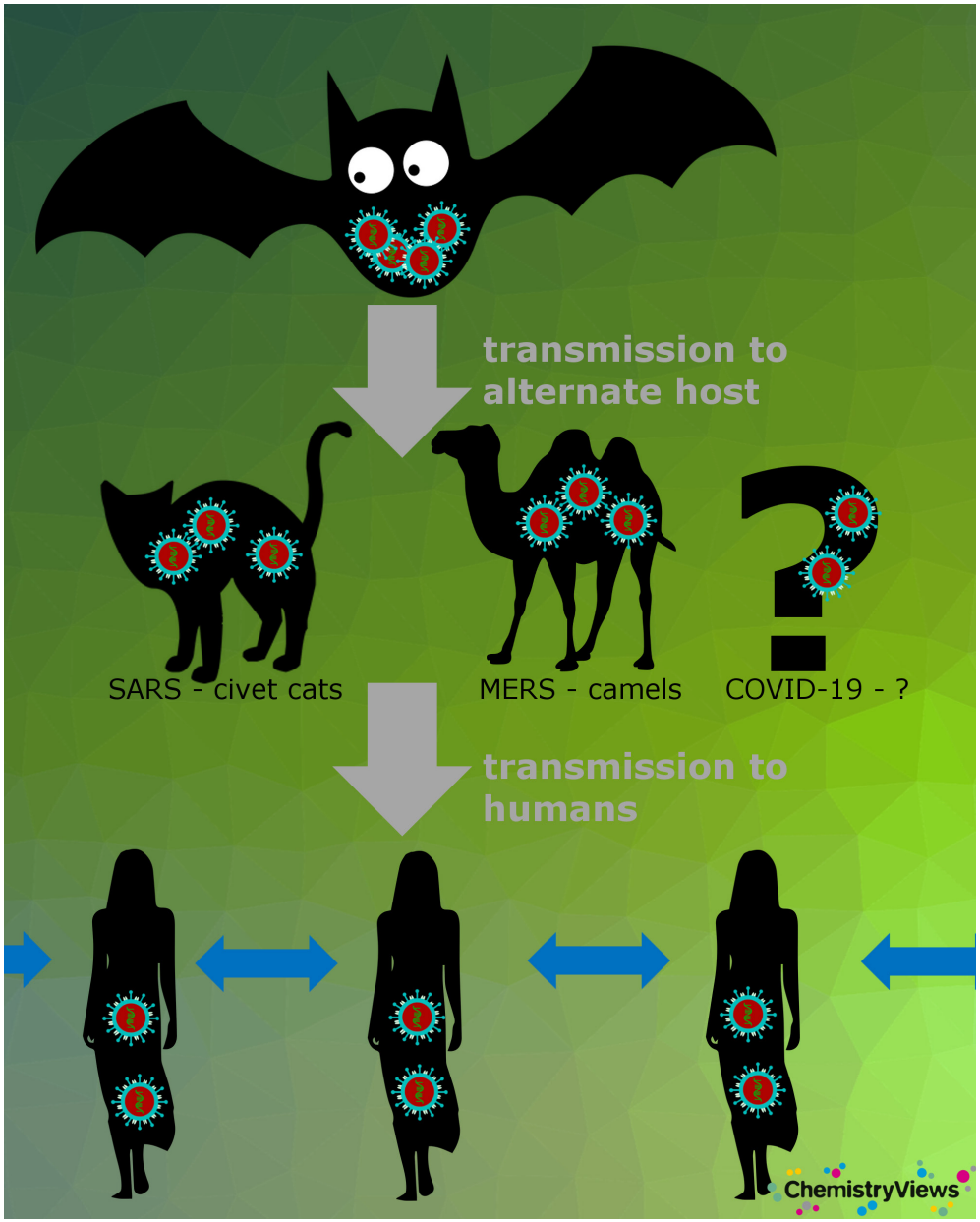
TRACKING SYMPTOMS

On 7 April, around 60% of app users who tested positive for COVID-19 and reported symptoms had lost their sense of smell.



Coronavirus Entering and Replicating in a Host Cell

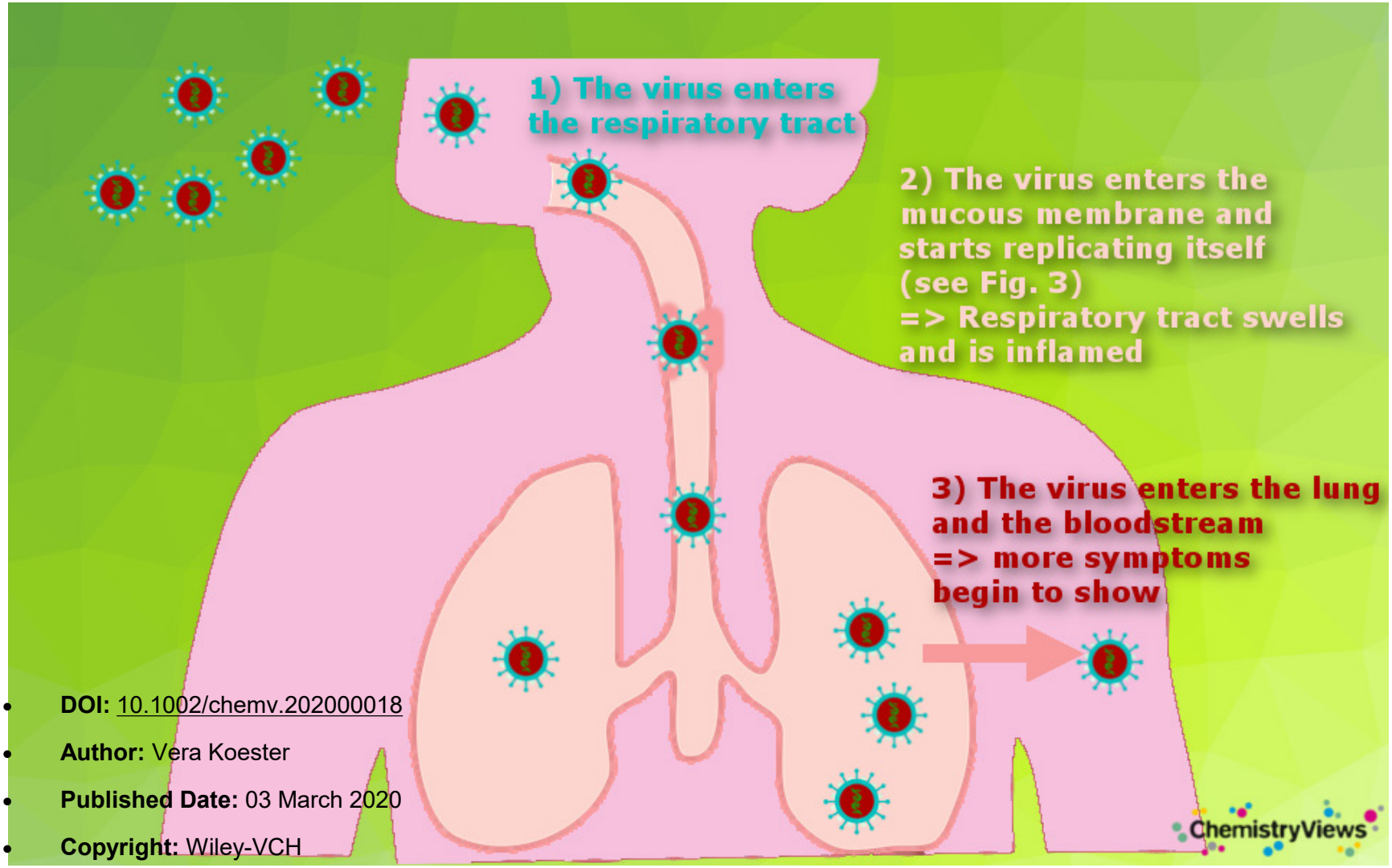
- **DOI:** 10.1002/chemv.202000018
- **Author:** Vera Koester
- **Published Date:** 03 March 2020



SARS-CoV-2 causing the current COVID-19 outbreak

- SARS-CoV-2 shares a strong homology with its better-studied cousin SARS-CoV, responsible for an outbreak of SARS (Severe Acute Respiratory Syndrome) between 2002 and 2003
- MERS-CoV, another member of this genus, has caused the Middle East respiratory syndrome (MERS) first reported in 2012.
- Most coronaviruses are known to infect only non-human species.


SUS SCROFA DOMESTICUS
AKA
PIG
FELIS CATUS
AKA
CAT
NEOVISON VISON
AKA
MINK
ROUSETTUS AEGYPTIACUS
AKA
EGYPTIAN FRUIT BAT
MUSTELA PUTORIUS FURO
AKA
FERRET
RHINOLOPHUS
AKA
HORSESHOE BAT

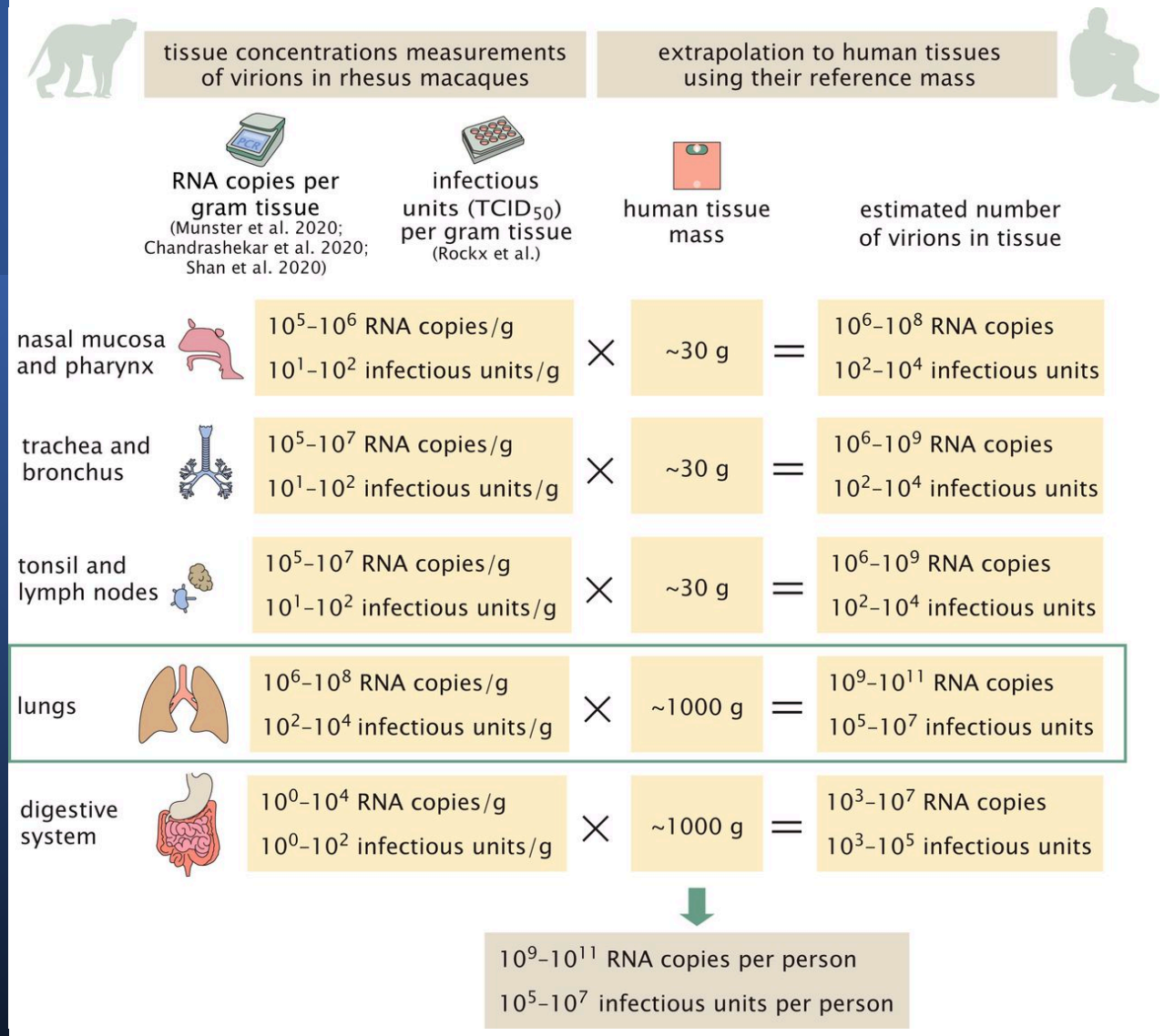


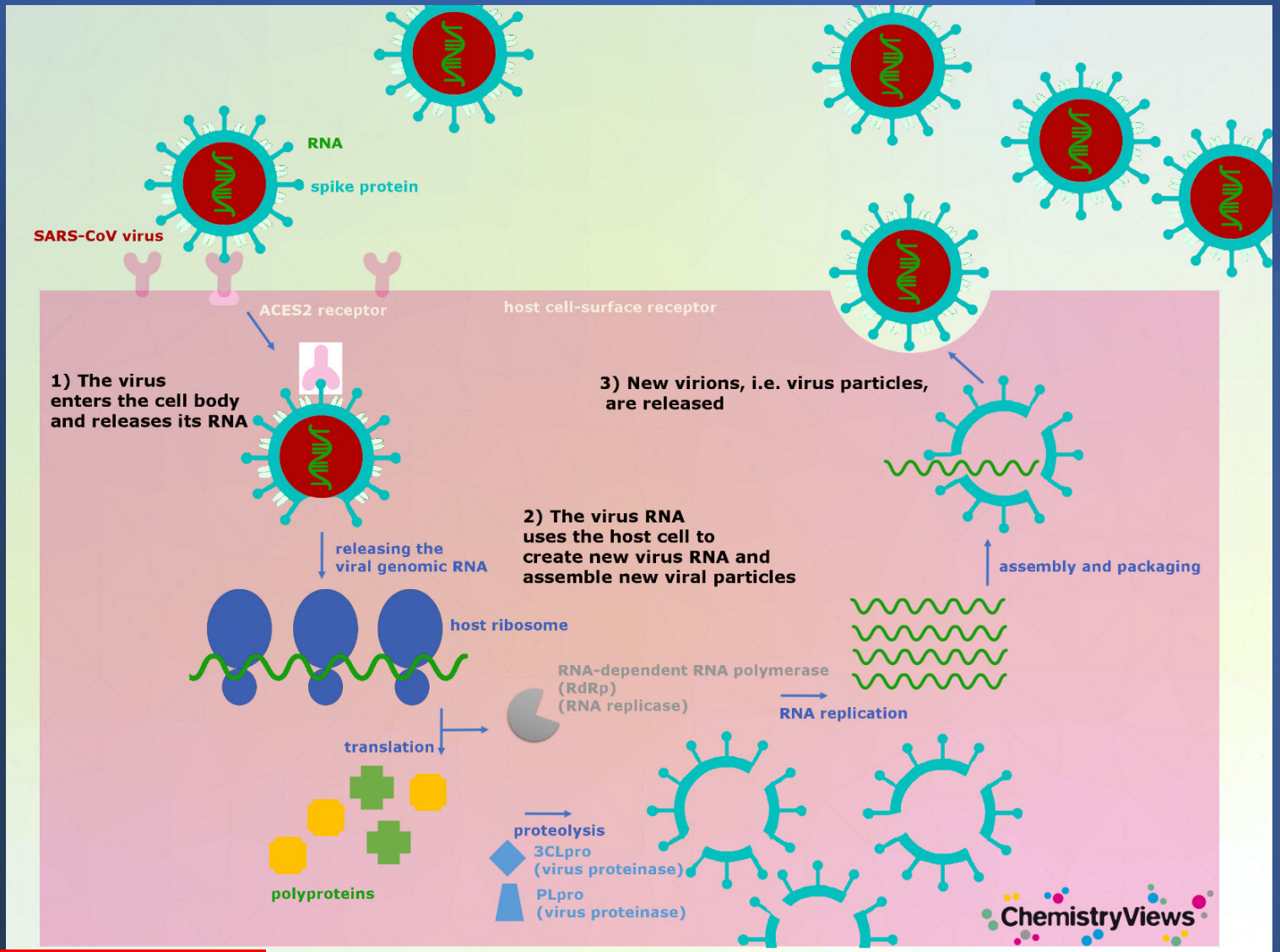
- **DOI:** 10.1002/chemv.202000018
- **Author:** Vera Koester
- **Published Date:** 03 March 2020

The total number and mass of **SARS-CoV-2** virions – Sender et al., 2021 PNAS 118, e2024815118

- Each infected individual carries about **10 billion to 100 billion** individual SARS-CoV-2 particles at the peak of their infection.
- Each viral particle has a mass of **1 femtogram** - each person, at peak infection, carries about **1 microgram to 10 micrograms** of virus particles.

The total number and mass of SARS-CoV-2 virions – Sender et al., 2021 PNAS 118, e2024815118





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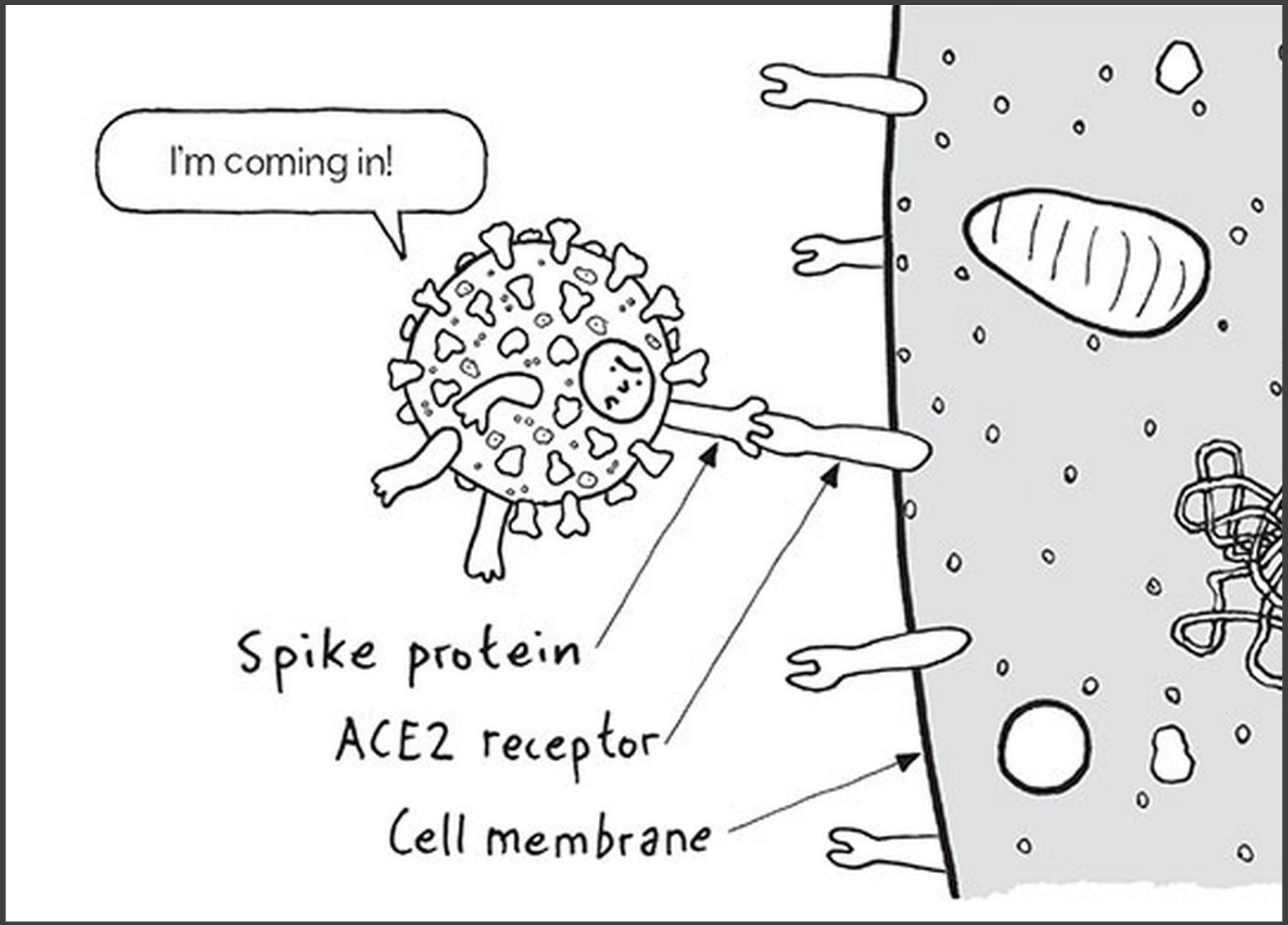
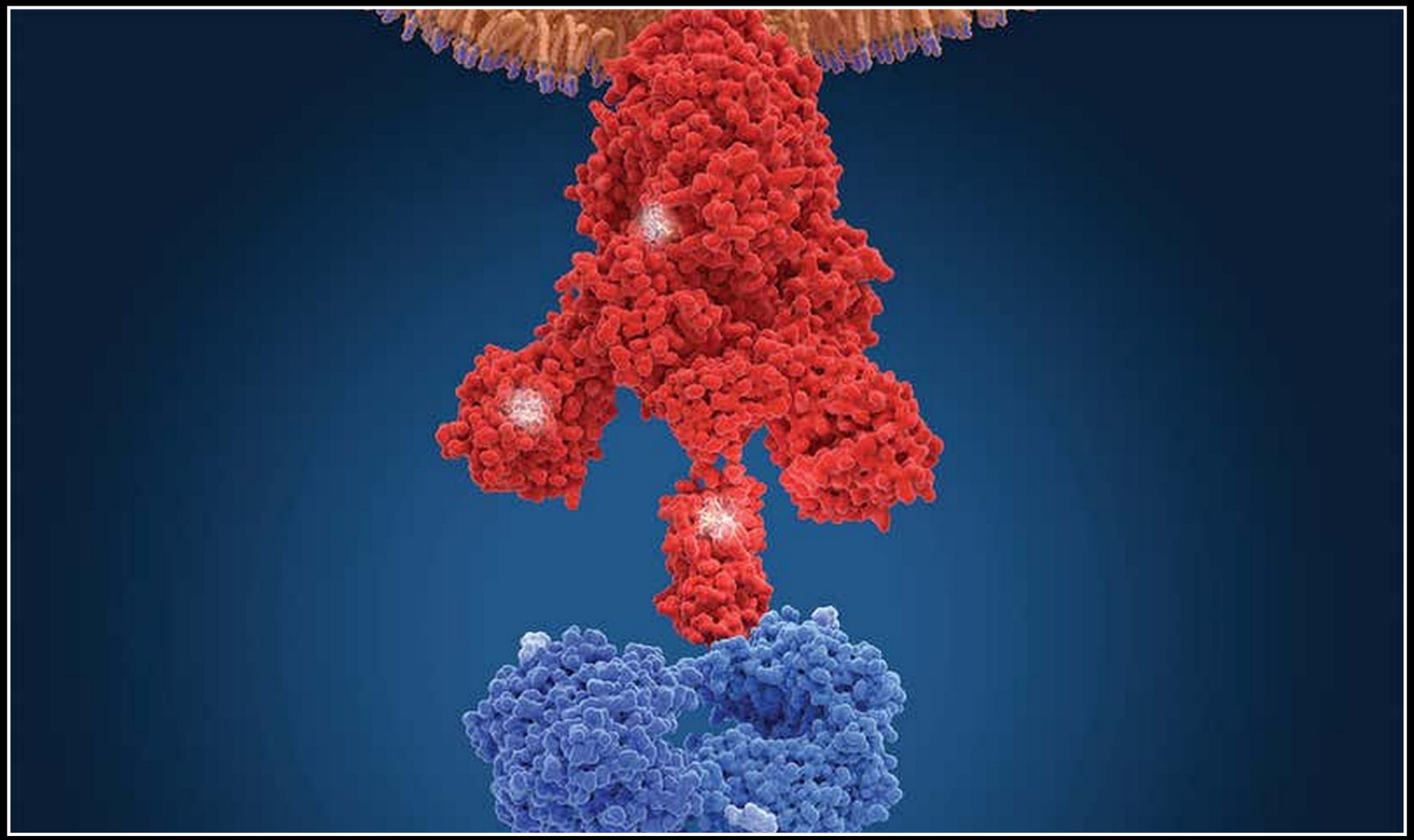

I'm coming in!
Spike protein
ACE2 receptor
Cell membrane

Human ACE2 receptors

- ACE2 receptors are found in **ciliated epithelial cells in the upper and lower airway** and in **type II pneumocytes** in the alveoli in the lower airway.
  - Type II pneumocytes produce lung-lubricating proteins important for lung function.
- **ACE2** (**Angiotensin-converting enzyme 2)** is a protein on the surface of many cell types. It is an **enzyme** that generates small proteins – by cutting up the larger protein angiotensinogen – that then go on to regulate functions in the cell.



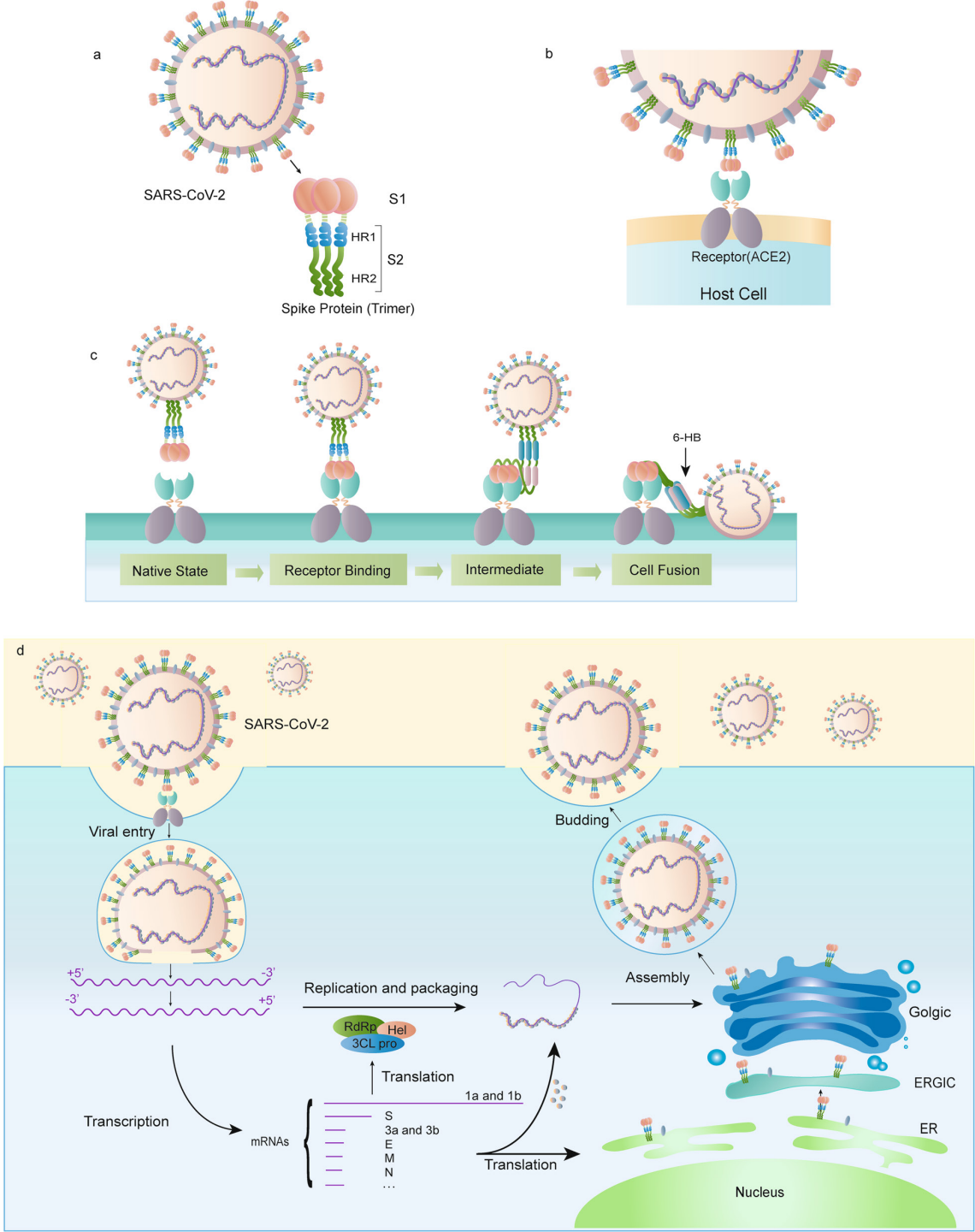
B.1.1.7 spike protein

a The schematic structure of the S protein

b The S protein binds to the receptor ACE2

c The binding and virus–cell fusion process mediated by the S protein

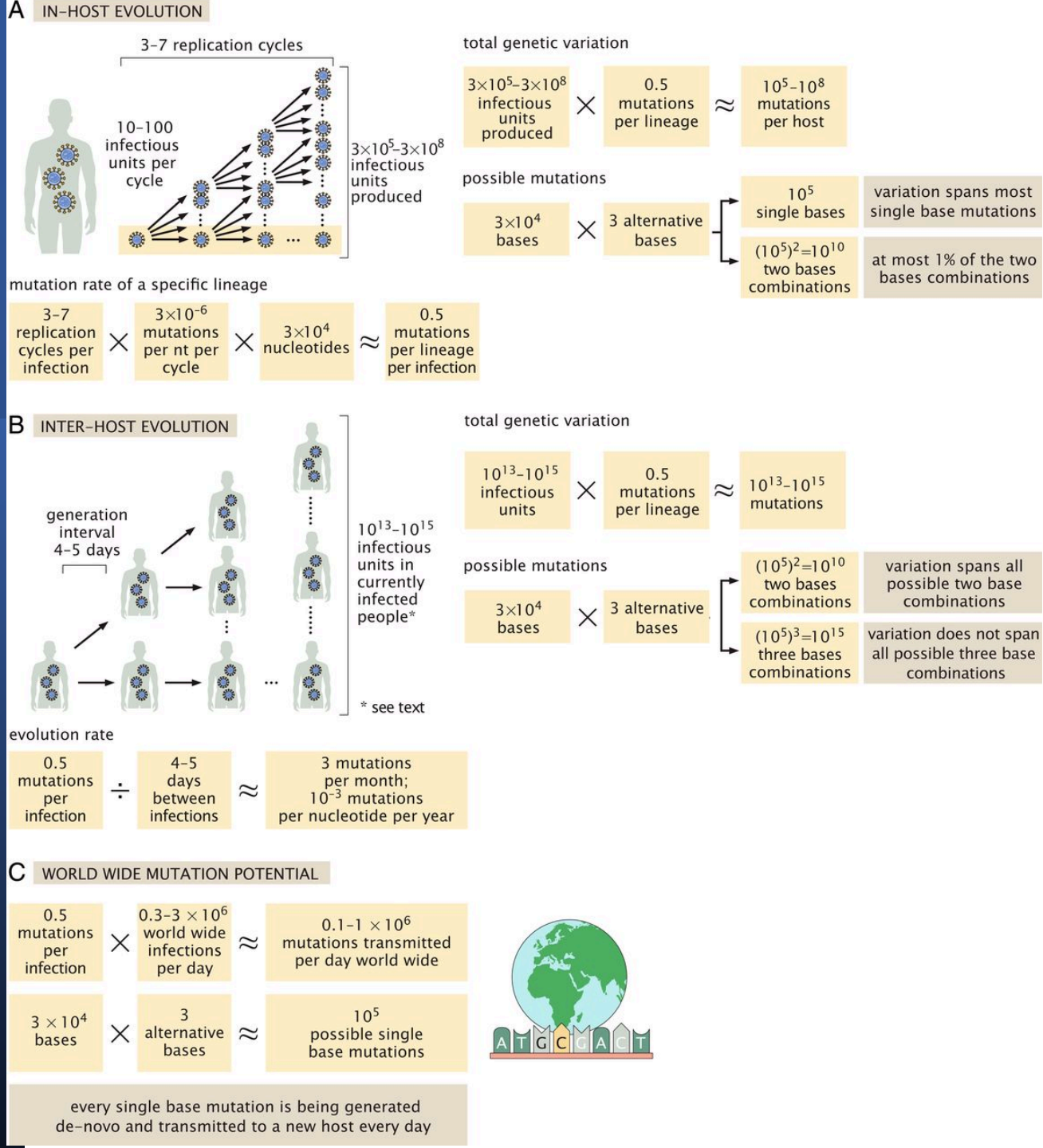
d The life cycle of SARS-CoV-2 in host cells



Huang et al., 2020

SARS-CoV-2
EVOLUTION

The total number and mass of SARS-CoV-2 virions – Sender et al., 2021 PNAS 118, e2024815118



The total number and mass of SARS-CoV-2 virions – Sender et al., 2021 PNAS 118, e2024815118

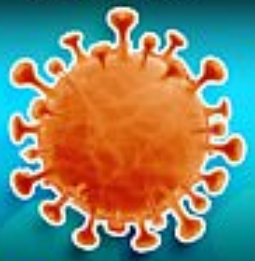
The relationship between the number of virions produced in an infected individual and the evolution of SARS-CoV-2.

We use our estimates for the total number of virions produced during an infection, along with other epidemiological and biochemical characteristics of SARS-CoV-2, to estimate the rate of mutation accumulation within an infected host (*A*) and within the population (*B*). We consider both the evolution along a specific genetic lineage of virions and the diversity among a population of virions—either within an infected host (*A*) or within the total population (*B*).
In addition, we look at the de novo mutation generated and transmitted to the newly infected in comparison to all possible single base mutations (*C*).

KENT

Name: B.1.1.7
In UK? 76,203
Key mutations:
N501Y – speeds up transmission

BRISTOL



Name: VOC-202102/02
In UK? 26
Key mutations: Kent variant with E484K, which can 'escape' antibodies for other variants

LIVERPOOL

Name: VUI-202102/01
In UK? 71
Key mutations: 2020 version of virus with E484K

NEW

Name: : B.1.525
In UK? 50
Key mutations: E484K can 'escape' antibodies from vaccines
Q677H unknown effects
F888L unknown effects

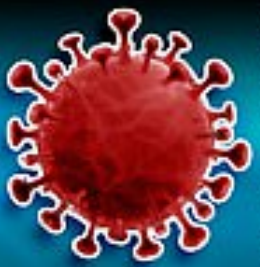
SOUTH AFRICA

Name: 501Y.V2 or B.1.351
In UK? 235
Key mutations: N501Y speeds up transmission
E484K can 'escape' antibodies for other variants

BRAZIL #1

Name: P.1
In UK? 0
Key mutations: N501Y speeds up transmission
E484K can 'escape' antibodies for other variants
K417T unknown effects

BRAZIL #2



Name: P.2
In UK? 31
Key mutations: E484K can 'escape' antibodies

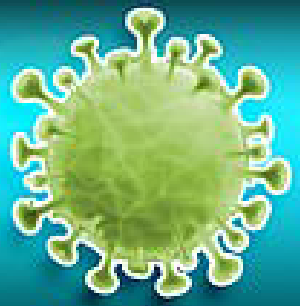
CALIFORNIA

Name: B.1.429
In UK? 7
Key mutations: L452R can 'escape' some antibodies from vaccines

NEW

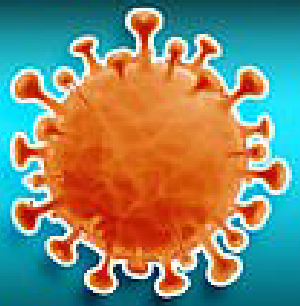
Name: B.1.1.7 + B.1.429
In UK? 0
Key mutations: N501Y speeds up transmission
L452R can 'escape' some antibodies from vaccines

KENT



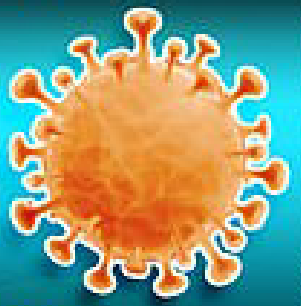
Name: B.1.1.7
In UK? 218,169
Key mutations:
N501Y – speeds up transmission

BRISTOL



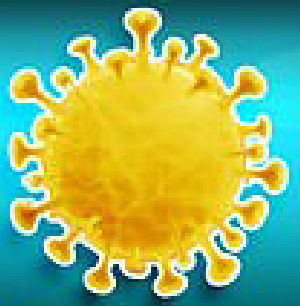
Name: VOC-202102/02
B.1.1.7
In UK? 43
Key mutations: Kent variant with E484K, which can 'escape' antibodies for other variants

LIVERPOOL



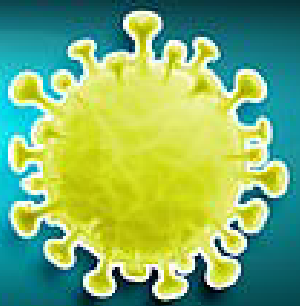
Name: VUI-202102/01
A.23.1
In UK? 79
Key mutations: 2020 version of virus with E484K

NIGERIA



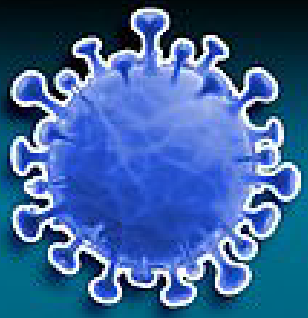
Name: B.1.525
In UK? 372
Key mutations: E484K can 'escape' antibodies from vaccines
Q677H unknown effects
F888L unknown effects

ANTIGUA



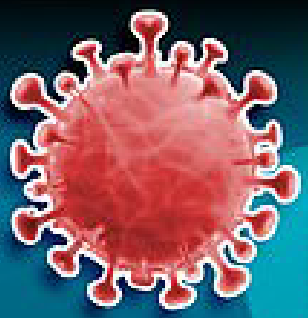
Name: B1.324.1 with E484K
In UK? 2
Key mutations: E484K and N501Y, which helps it spread.

SOUTH AFRICA



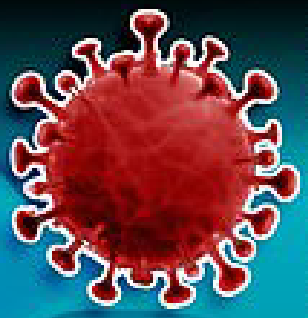
Name: 501Y.V2 or B.1.351
In UK? 670
Key mutations: N501Y speeds up transmission
E484K can 'escape' antibodies for other variants

BRAZIL #1



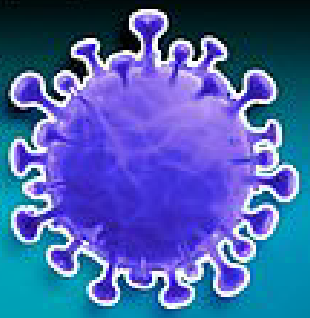
Name: P.1
In UK? 60
Key mutations: N501Y speeds up transmission
E484K can 'escape' antibodies for other variants
K417T unknown effects

BRAZIL #2



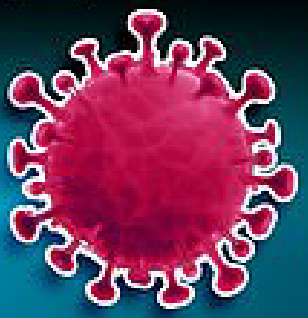
Name: P.2
In UK? 59
Key mutations: E484K can 'escape' antibodies

PHILIPPINES



Name: P.3
In UK? 5
Key mutations: E484K and N501Y, which help it spread and evade antibodies

INDIA



Name: B.1.617
In UK? 132
Key mutations: E484Q and L452R which speed up transmission and can escape antibodies


India
Name: B.1617
In UK? 77
Key mutations: E484Q
which help it spread and
L452R can 'escape' some
antibodies from vaccines

NEPAL

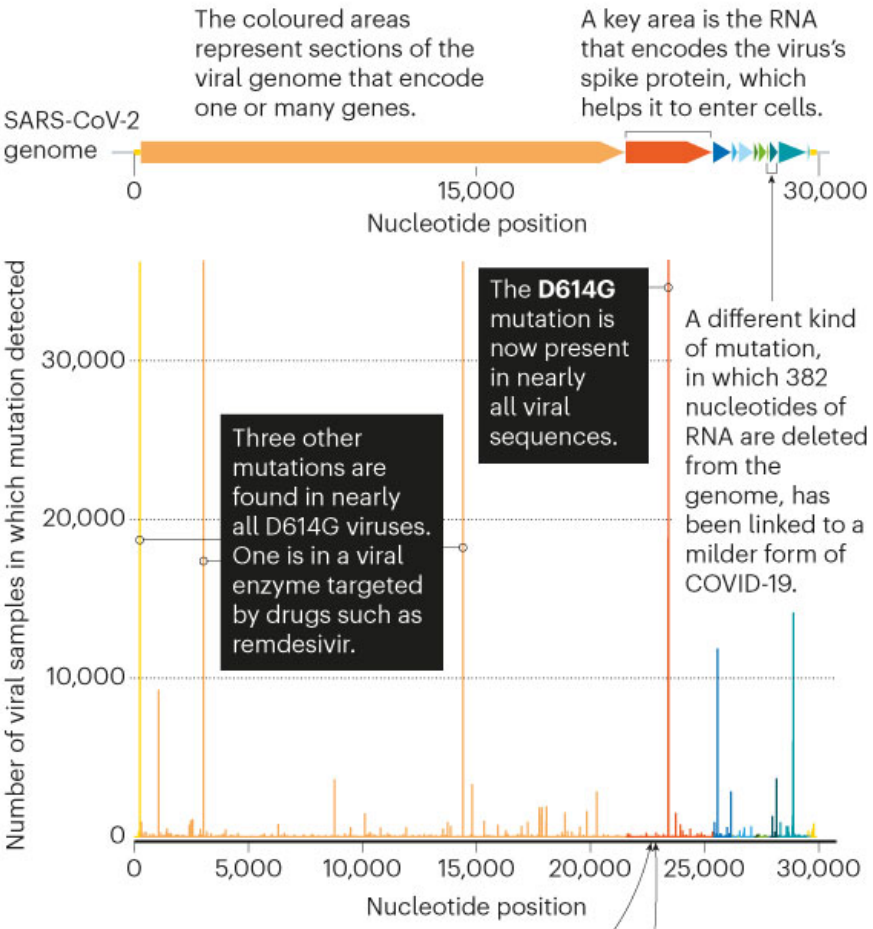
Name: Delta plus or AY.1
Origin: Believed to be Nepal
In UK? Spotted 52 times
Where else has it been spotted? Nepal, Japan, Portugal, US and India
What is it? It's a more mutated version of the Indian variant that is dominant in the UK, known now as 'Delta'.
What mutations? All the ones which make the Indian variant so infectious, as well as K417N, thought to make vaccines weaker
What is K417N? A mutation on the virus' spike protein also found on the jab-resistant South African variant

Lambda or C.37 6 July 2021

- The strain was first sequenced in Peru in August 2020.
- The variant has been spotted in 30 other countries, including the US, Australia and Germany.
- It has two concerning mutations on its spike protein — known as L452Q and F490S.
- The mutations are feared play a role in making it **more infectious** and able to **dodge some immunity**.
- Scientists in Peru have claimed the mutation is more infectious because of its rapid spread in the country. But there is no significant proof the virus is actually any more contagious than existing strains, including Delta.
- Experts insist there is no evidence to suggest it is deadlier, despite some doctors linking its spread to Peru having the world's worst Covid mortality rate.

A CATALOGUE OF CORONAVIRUS MUTATIONS

Various mutations have been detected in SARS-CoV-2 genomes, including the most prevalent one, D614G. The virus's genetic code has just under 30,000 nucleotides of RNA, or letters, that spell out at least 29 genes. The most common mutations are single-nucleotide changes.



SARS-CoV-2
ORIGIN

Identification of novel **bat coronaviruses** sheds light on the evolutionary origins of **SARS-CoV-2** and related viruses
Zhou et al., 2021 Cell 12082 (3 June 2021)

411 samples from 342 bats

Oral swabs Feces Urine

24 full-length coronavirus genomes

SARS-CoV-2
SARS-CoV
RpYN06
Alpha-CoV
RsYN04/RmYN05/RmYN08
RsYN03/RmYN07/RsYN09

RpYN06, two deletions in the RBD

RsYN04, one deletion in the RBD

Differential binding affinity

RsYN04
RpYN06
hACE2
hACE2

49 *Rhinolophus* bat species

R. accuminatus
R. affinis
R. pusillus
R. shameli
R. stheno
R. malayanus
....

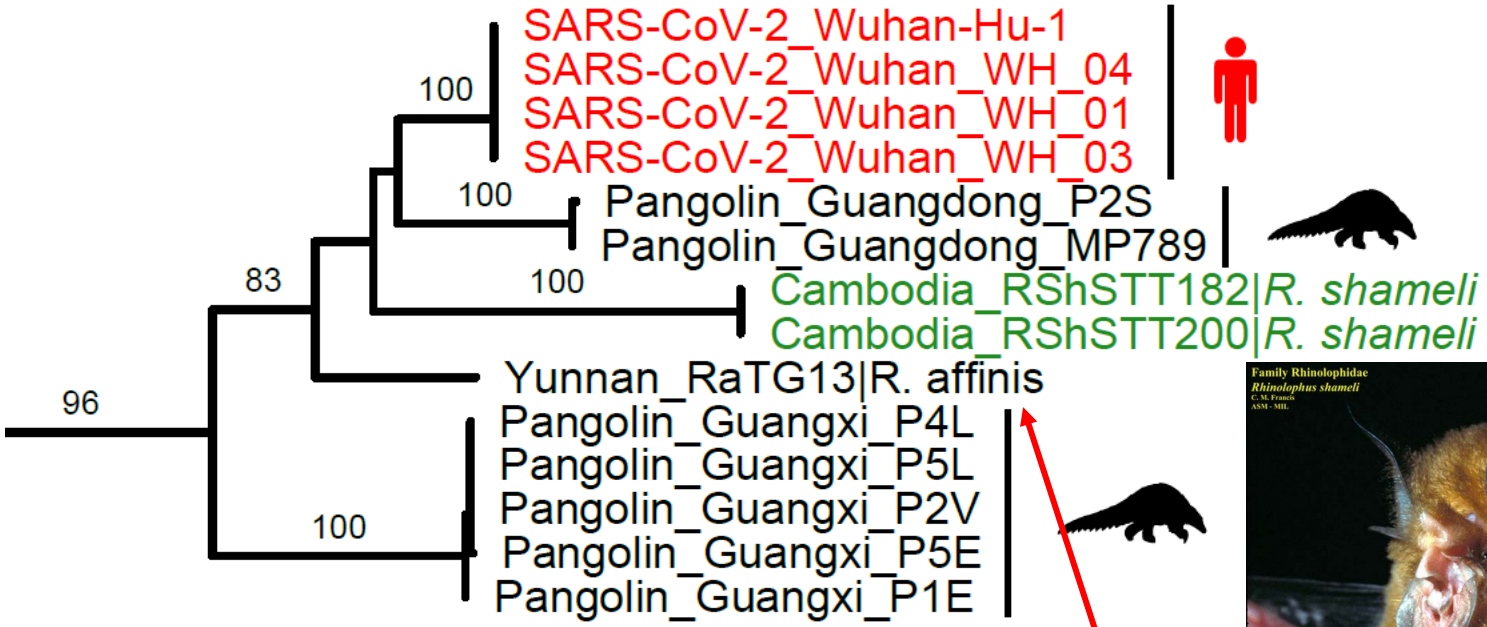
Ecological modeling

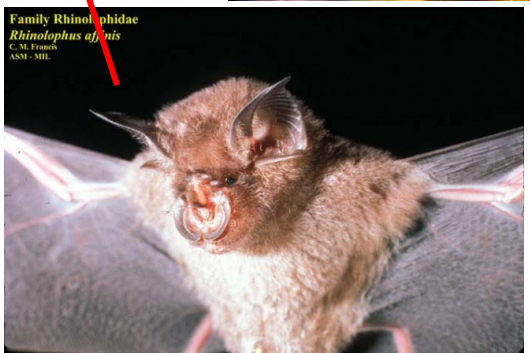
A broad geographic range of rhinolophid bats in parts of Asia

Summary

Despite the discovery of animal coronaviruses related to SARS-CoV-2, the evolutionary origins of this virus are elusive. We describe a meta-transcriptomic study of 411 bat samples collected from a small geographical region in Yunnan province, China, between May 2019 and November 2020. We identified 24 full-length coronavirus genomes, including four novel SARS-CoV-2 related and three SARS-CoV related viruses. *Rhinolophus pusillus* virus RpYN06 was the closest relative of SARS-CoV-2 in most of the genome, although it possessed a more divergent spike gene. The other three SARS-CoV-2 related coronaviruses carried a genetically distinct spike gene that could weakly bind to the hACE2 receptor *in vitro*. Ecological modeling predicted the co-existence of up to 23 *Rhinolophus* bat species, with the largest contiguous hotspots extending from South Laos and Vietnam to southern China. Our study highlights the remarkable diversity of bat coronaviruses at the local scale, including close relatives of both SARS-CoV-2 and SARS-CoV.

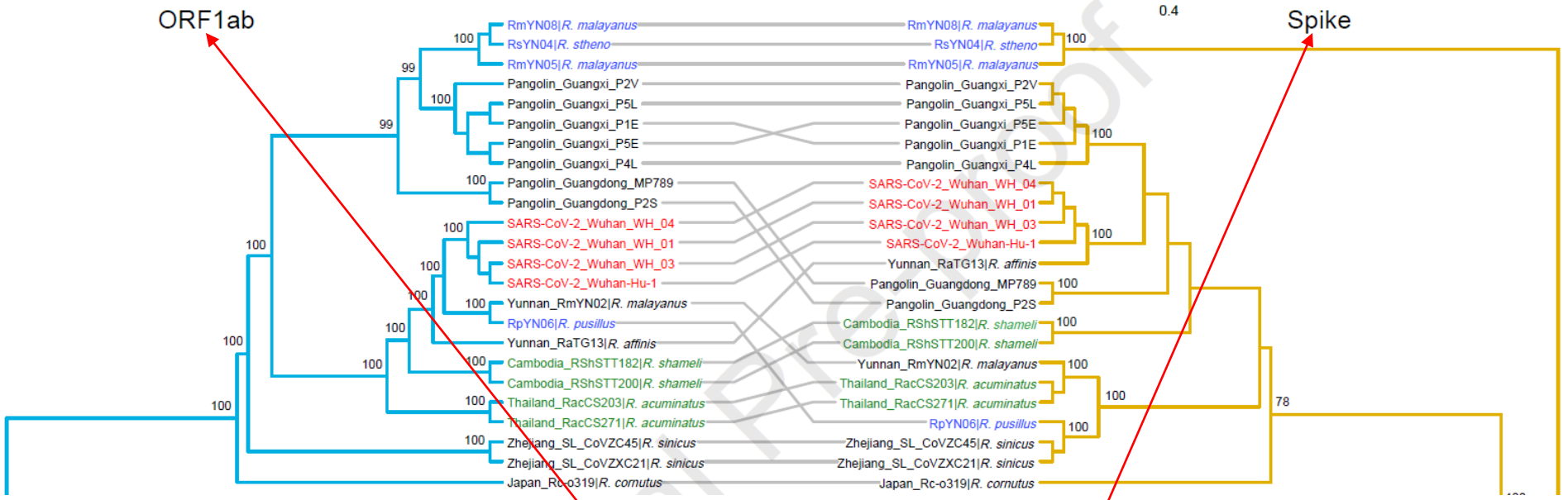
Phylogenetic analysis of the RBD regions of SARS-CoV-2 and representative betacoronaviruses

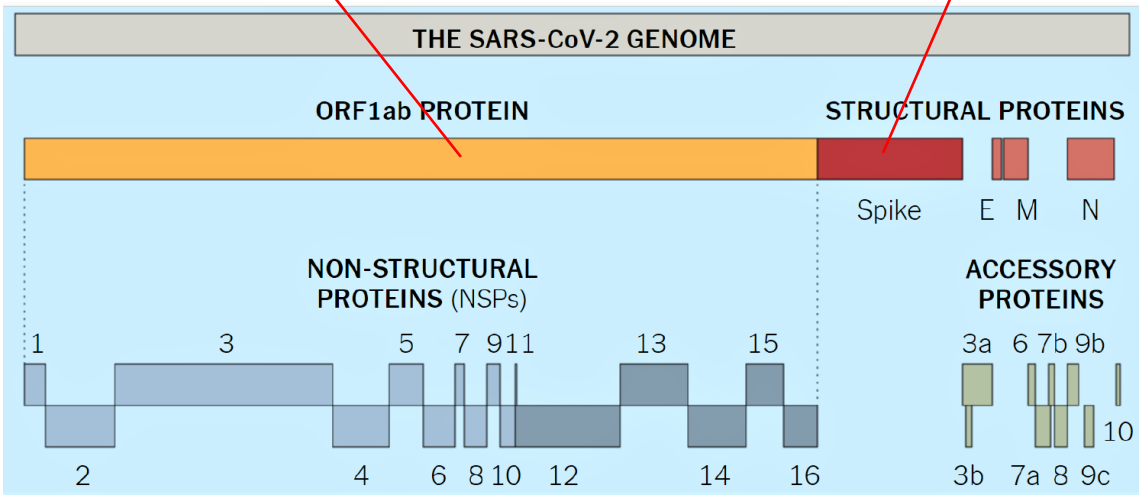




The maximum likelihood (ML) method available in RAxML (v8.2.11) with 1000 bootstrap replicates, employing the GTR nucleotide substitution model and a gamma distribution of rate variation among sites

Comparative analysis of ORF1ab and Spike gene phylogenies



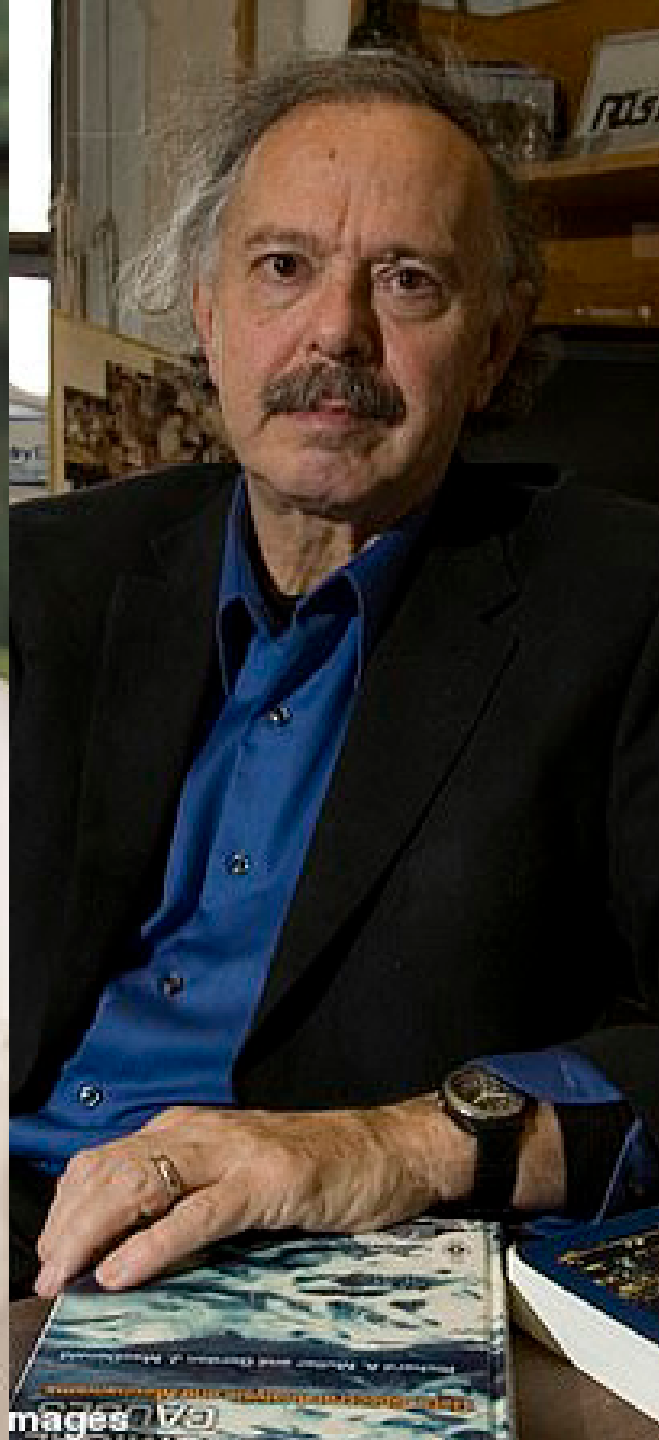


Covid was deliberately made in a Chinese lab? - 7 June 2021

- COVID-19 has the genome sequencing combination of 'CGG-CGG'
- Two US experts say that no naturally occurring coronavirus has ever had that combination
- The 'CGG-CGG' combination is extremely rare, except when it used by scientists doing 'gain-of-function' in laboratories
- The experts conclude that it is more likely than not that the virus was therefore created in a lab
- In recent weeks, many of the world's top scientists have pushed to determine whether the virus was leaked from the Wuhan Institute of Virology

Dr. Stephen Quay and Richard Muller

UC Berkeley



Covid was deliberately made in a Chinese lab? - 7 June 2021

- **Gain-of-function research** (GoF research or GoFR) is medical research that alters an organism or disease in a way that increases pathogenesis, transmissibility, or host range (the types of hosts that a microorganism can infect).
- Introducing a mutation that would allow influenza B to infect rabbits in a controlled laboratory situation would be considered a "gain of function" experiment as the virus did not previously have that function.
- The term "gain of function" is sometimes applied more narrowly to refer to "**research which could enable a pandemic-potential pathogen to replicate more quickly or cause more harm in humans or other closely-related mammals**."

Gain-of-Function

REPORT

Cell Cycle 13:16, 2600–2608; August 15, 2014; © 2014 Taylor & Francis Group, LLC

Induced expression of expanded CGG RNA causes mitochondrial dysfunction *in vivo*

Renate K Hukema[1,*], Ronald AM Buijsen[1], Chris Raske[2], Lies Anne Severijnen[1], Ingeborg Nieuwenhuizen-Bakker[1], Michelle Minneboo[1], Alex Maas[3], Rini de Crom[3], Johan M Kros[4], Paul J Hagerman[2], Robert F Berman[5,#], and Rob Willemsen[1,#]

[1]Department of Clinical Genetics; Erasmus MC; Rotterdam, The Netherlands; [2]Department of Biochemistry and Molecular Medicine; University of California Davis; Davis, CA USA; [3]Department of Cell Biology; Erasmus MC; Rotterdam, The Netherlands; [4]Department of Pathology; Erasmus MC; Rotterdam, The Netherlands; [5]Department of Neurological Surgery; University of California Davis; Davis, CA USA;

[#]These authors contributed equally to this work.
The first 2 authors are joint first authors and the last 2 authors are joint last authors.

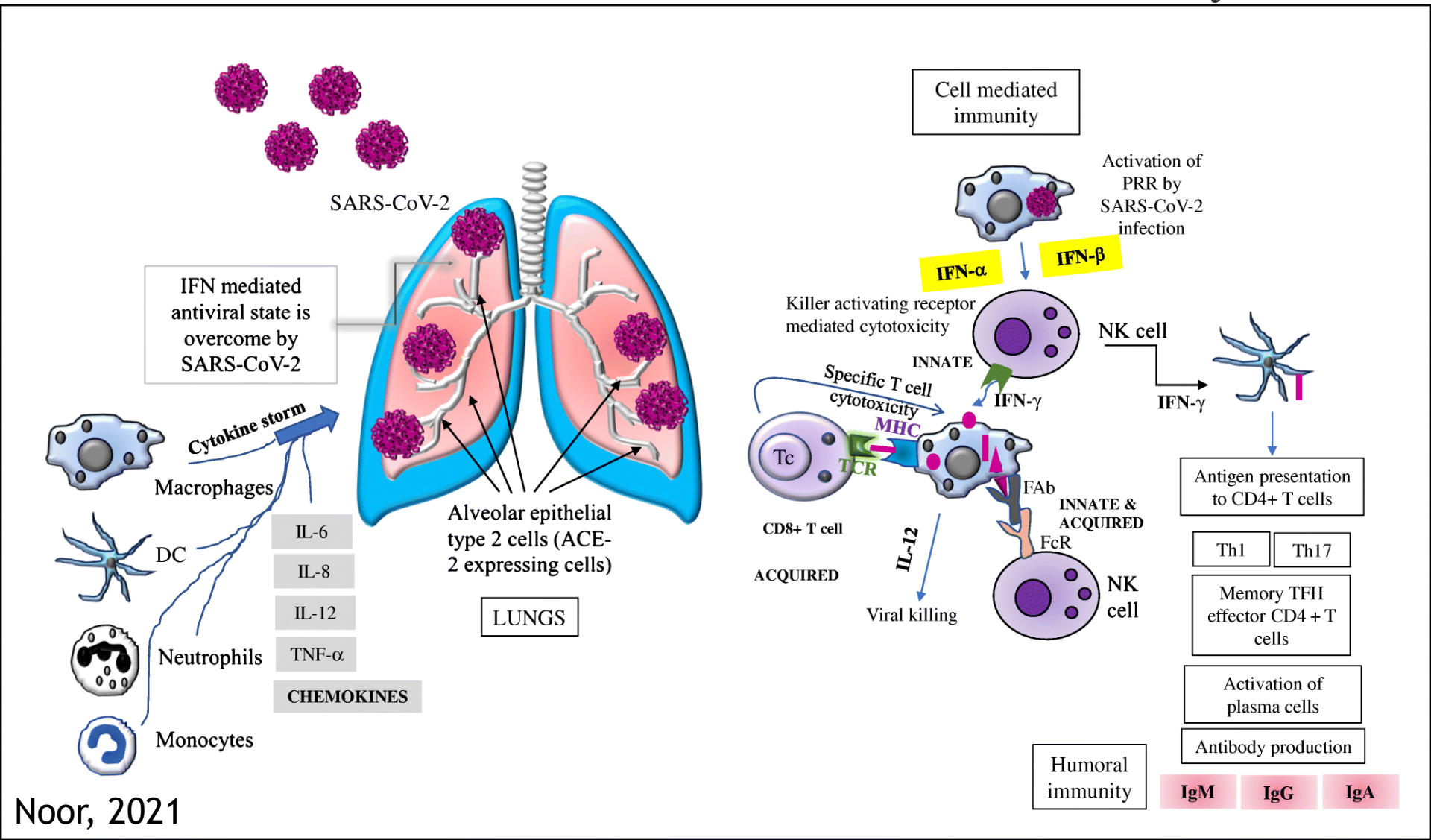
Keywords: apoptosis, caspase 3, CGG repeat, cytochrome C, FXTAS, gpx-1, inducible mouse model, mitochondria, RNA gain-of-function, Tet-On

Abbreviations: dox, doxycycline; eGFP, enhanced green fluorescent protein; FXTAS, Fragile X-associated tremor/ataxia syndrome; gpx, gluthation peroxidase; rtTA, reverse tetracycline transactivator; TRE, Tet Responsive Element

Fragile X-associated tremor/ataxia syndrome (FXTAS) is a late-onset neurodegenerative disorder affecting carriers of premutation forms of the *FMR1* gene, resulting in a progressive development of tremor, ataxia and neuropsychological problems. The disease is caused by an expanded CGG repeat in the *FMR1* gene, leading to an RNA gain-of-function toxicity mechanism. In order to study the pathogenesis of FXTAS, new inducible transgenic mouse models have been developed that expresses either 11CGGs or 90CGGs at the RNA level under control of a Tet-On promoter. When bred to an hnRNP-rtTA driver line, doxycycline (dox) induced expression of the transgene could be found in almost all tissues. Dox exposure resulted in loss of weight and death within 5 d for the 90CGG RNA expressing mice. Immunohistochemical examination of tissues of these mice revealed steatosis and apoptosis in the liver. Decreased expression of GPX1 and increased expression of cytochrome C is found. These effects were not seen in mice expressing a normal sized 11CGG repeat. In conclusion, we were able to show *in vivo* that expression of an expanded CGG-repeat rather than overexpression of a normal CGG-repeat causes pathology. In addition, we have shown that expanded CGG RNA expression can cause mitochondrial dysfunction by regulating expression levels of several markers. Although FTXAS patients do not display liver abnormalities, our findings contribute to understanding of the molecular mechanisms underlying toxicity of CGG repeat RNA expression in an animal model. In addition, the dox inducible mouse lines offer new opportunities to study therapeutic interventions for FXTAS.

SARS-CoV-2
IMMUNITY

SAR-CoV-2 infection and host immune responses. The network between the innate and adaptive immunity as well as the humoral- and cell-mediated immunity

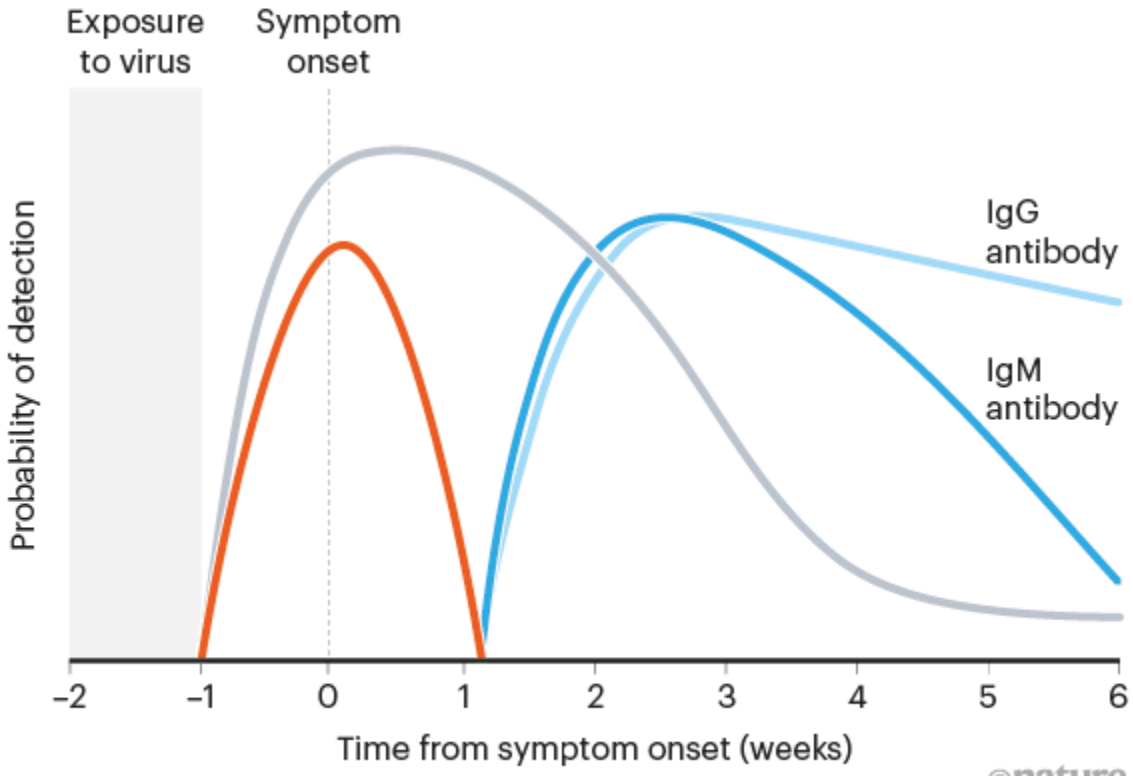


Noor, 2021

CATCHING COVID-19

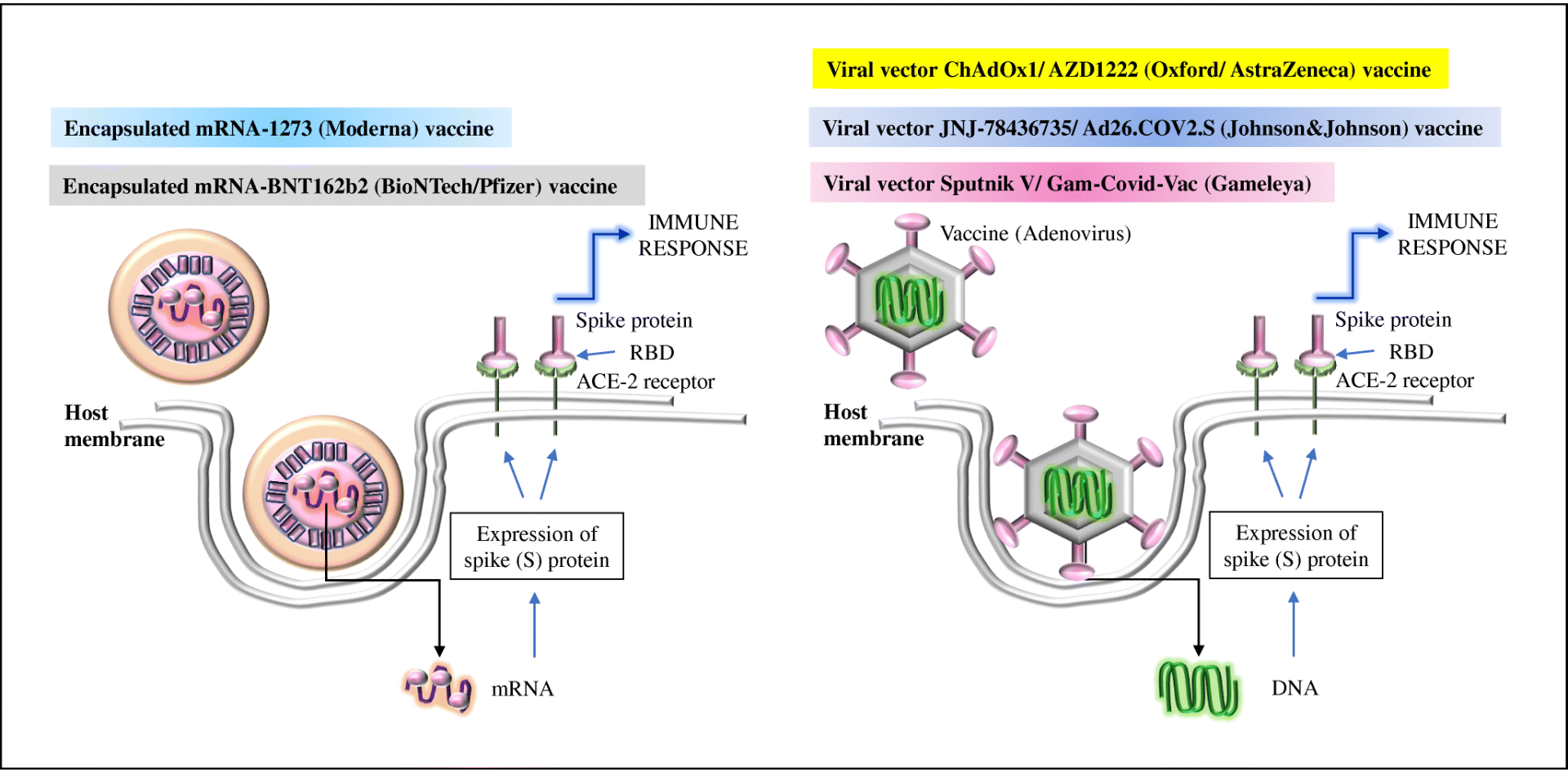
Different types of COVID-19 test can detect the presence of the SARS-CoV-2 virus or the body's response to infection. The probability of a positive result varies with each test before and after symptoms appear.

- **PCR-based tests** can detect small amounts of viral genetic material, so a test can be positive long after a person stops being infectious.
- **Rapid antigen tests** detect the presence of viral proteins and can return positive results when a person is most infectious.
- **Antibody tests** detect the body's immune response to the virus and are not effective at the earliest phase of infection.



SARS-CoV-2
VACCINES

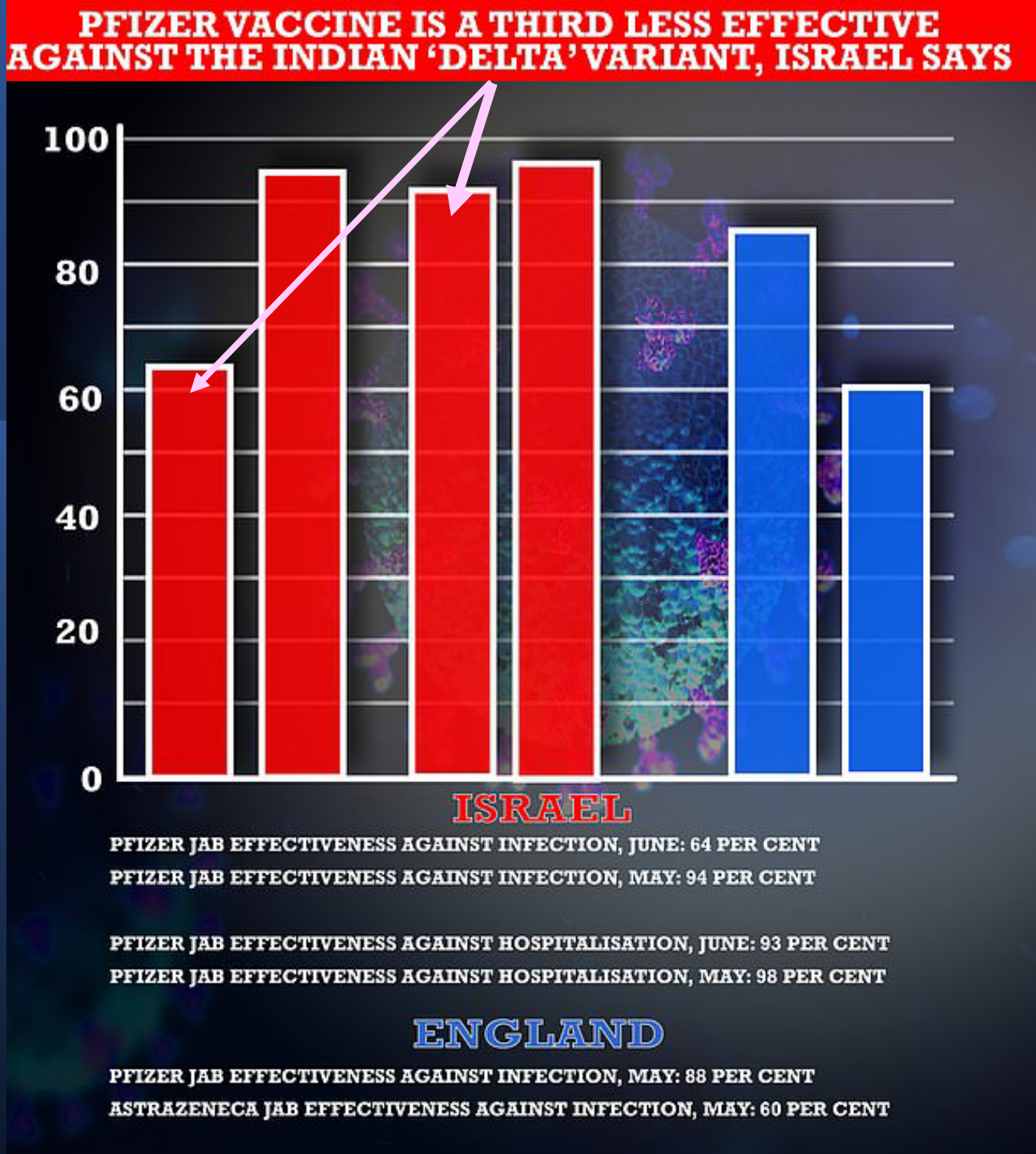
Schematic presentation of the mode of actions of mRNA and viral vector vaccines



Noor, 2021

Vaccines vs corona variants

DELTA



By LUKE ANDREWS HEALTH REPORTER FOR MAILONLINE
PUBLISHED: 19:44 BST, **5 July 2021** | **UPDATED:** 19:44 BST, 5 July 2021


India
Name: B.1617
In UK? 77
Key mutations: E484Q
which help it spread and
L452R can 'escape' some
antibodies from vaccines

КовиВак

Федерального научного центра исследований и разработки иммунобиологических препаратов имени М. П. Чумакова РАН

КовиВак

- В март-апрель 2020
- Биоматериал первых пациентов "Коммунарки"
- РНК коронавируса SARS-CoV-2 – сравнение с уханьскими образцами
- Культивирование отобранных вирусов в клеточной линии Vero → штамм AYDAR-1
- Производство вакцины - культивирование клеточной линии Vero, наработку в ней штамма AYDAR-1, химическое уничтожение оболочки вируса, инактивацию РНК и очистка

КовиВак

- Неактивные цельновирионные частицы и фрагменты вирусных белков.
  - Сохраняются поверхностные белки-шипы, необходимые для формирования защитных антител.
- Действующее вещество "КовиВака" находится в буферном растворе вместе с вспомогательными молекулами, включая гидроксид алюминия, усиливающий иммунный ответ.
- Хранение при температуре 2-6 оС.
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