INSTITUTE OF HUMAN VIROLOGY

UNIVERSITY of MARYLAND
SCHOOL OF MEDICINE

What is new in COVID-19 research?

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COVID-19 in 2022

- Viral evolution
- Treatment update
- Vaccination update
- Natural history of COVID-19
- Lesson learned for future

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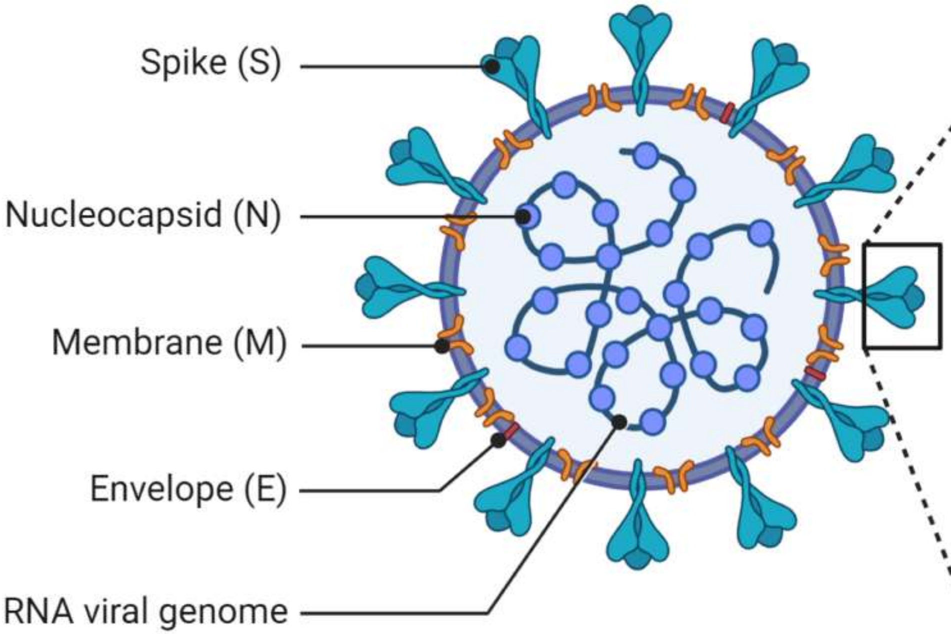
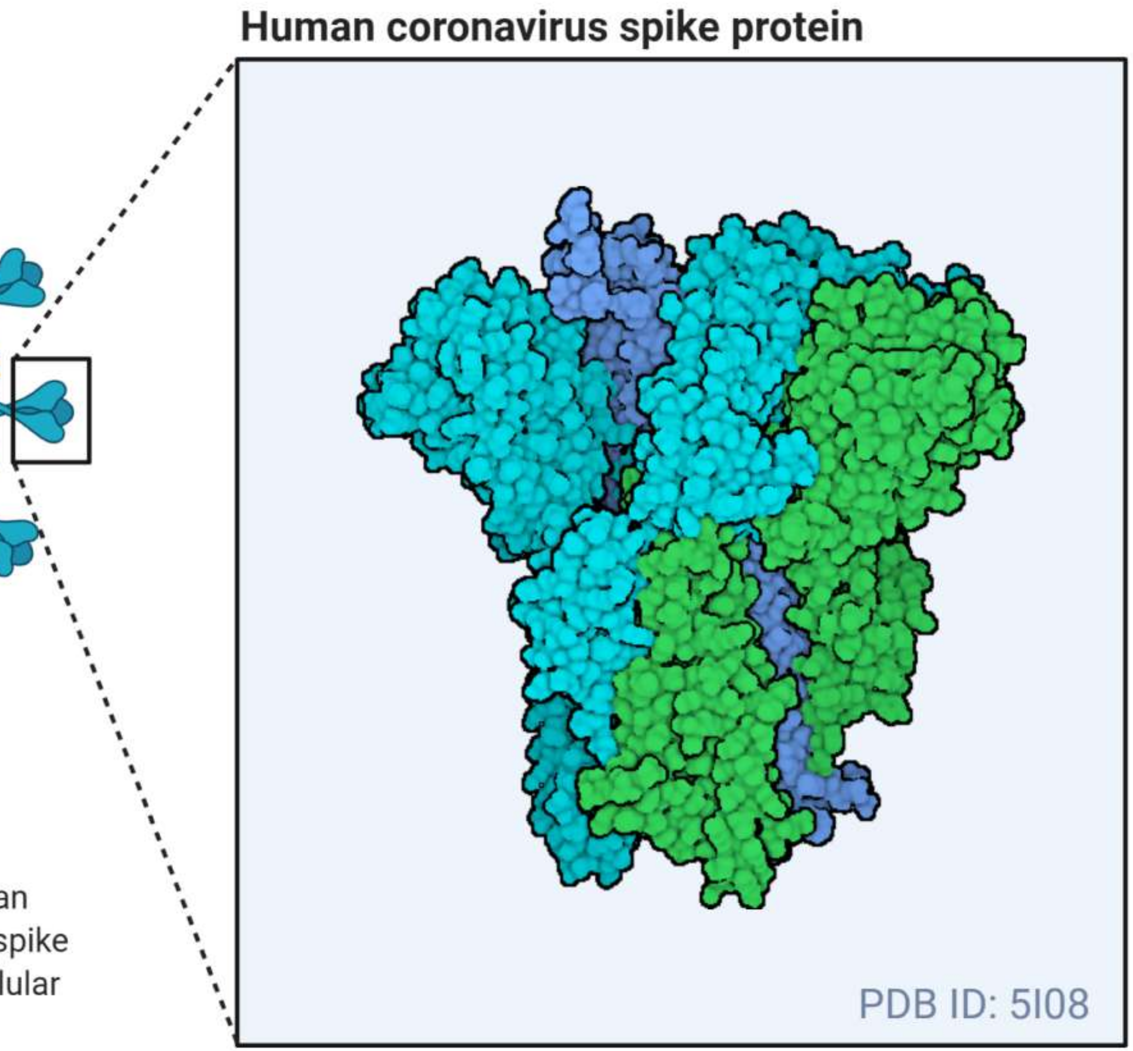
SARS-CoV-2 Virion and Structural Proteins



Coronaviruses belong in the family *Coronaviridae* and can cause disease in mammals and birds. The coronavirus spike (S) protein mediates membrane fusion by binding to cellular receptors.



Evolution of SARS-CoV-2 Variants

Table 1 | SARS-CoV-2 variants and related spike protein mutations

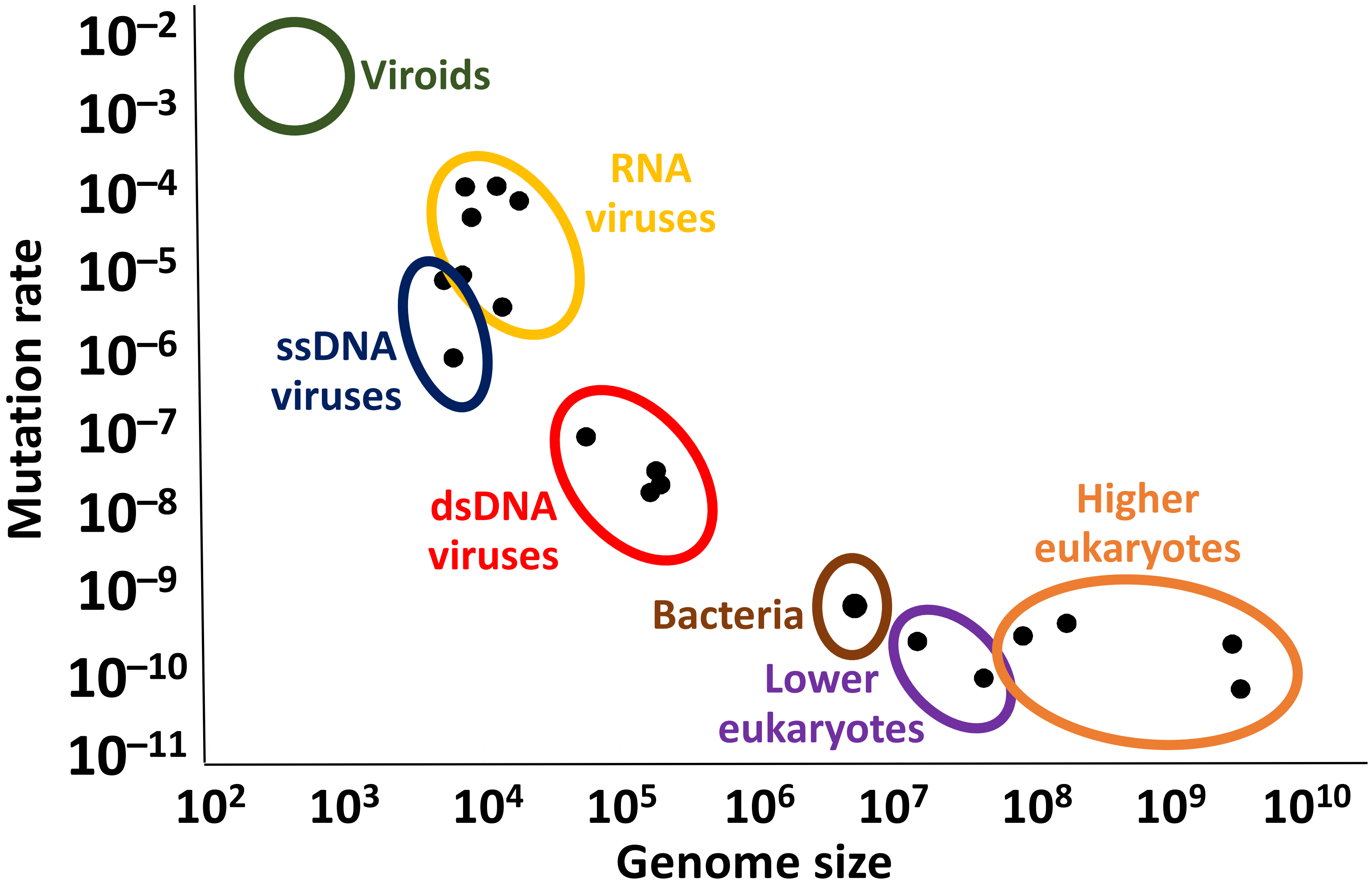
WHO nomenclature or designation	Pango lineage	Spike protein mutations of interest	First detected samples*
Variants of concern			
Alpha	B.1.1.7	N501Y. D614G, P681H	UK, September 2020
Beta	B.1.351	N501Y. D614G, E484K, K417N, A701V	South Africa, May 2020
Gamma	P.1	N501Y, D614G, E484K, K417T, H655Y	Brazil, November 2020
Delta	B.1.617.2	L452R, D614G, P681R, T478K	India, October 2020
Omicron	B.1.1.529	N501Y, D614G, E484A, P681H, K417N, H655Y, A67V, Δ69-70, T95I, G142D, Δ143-145, N211I, Δ212, ins215EPE, G339D, S371L, S373P, S375F, N440K, G446S, S477N, T478K, Q493R, G496S, Q498R, Y505H, T547K, N679K, N764K, D796Y, N856K, Q954H, N969K, L981F	South Africa and Botswana, November 2021
Variants of interest			
Lambda	C.37	L452Q, D614G, F490S	Peru, December 2020
Mu	B.1.621	N501Y, D614G, P681H, R346K, E484K	Columbia, January 2021
Variants under monitoring			
Not assigned	B.1.1.318	D614G, P681H, E484K	Multiple countries, January 2021
Not assigned	C.1.2	N501Y, D614G, E484K, H655Y, N679K, Y449H	South Africa, May 2021
Not assigned	B.1.640	N501Y, D614G, P681H, F490R, N394S, R346S, Y449N, 137-145del	Multiple countries, September 2021

Information correct as of 24 January 2022.

*First detection worldwide.

Young et al. BMJ Med 2022

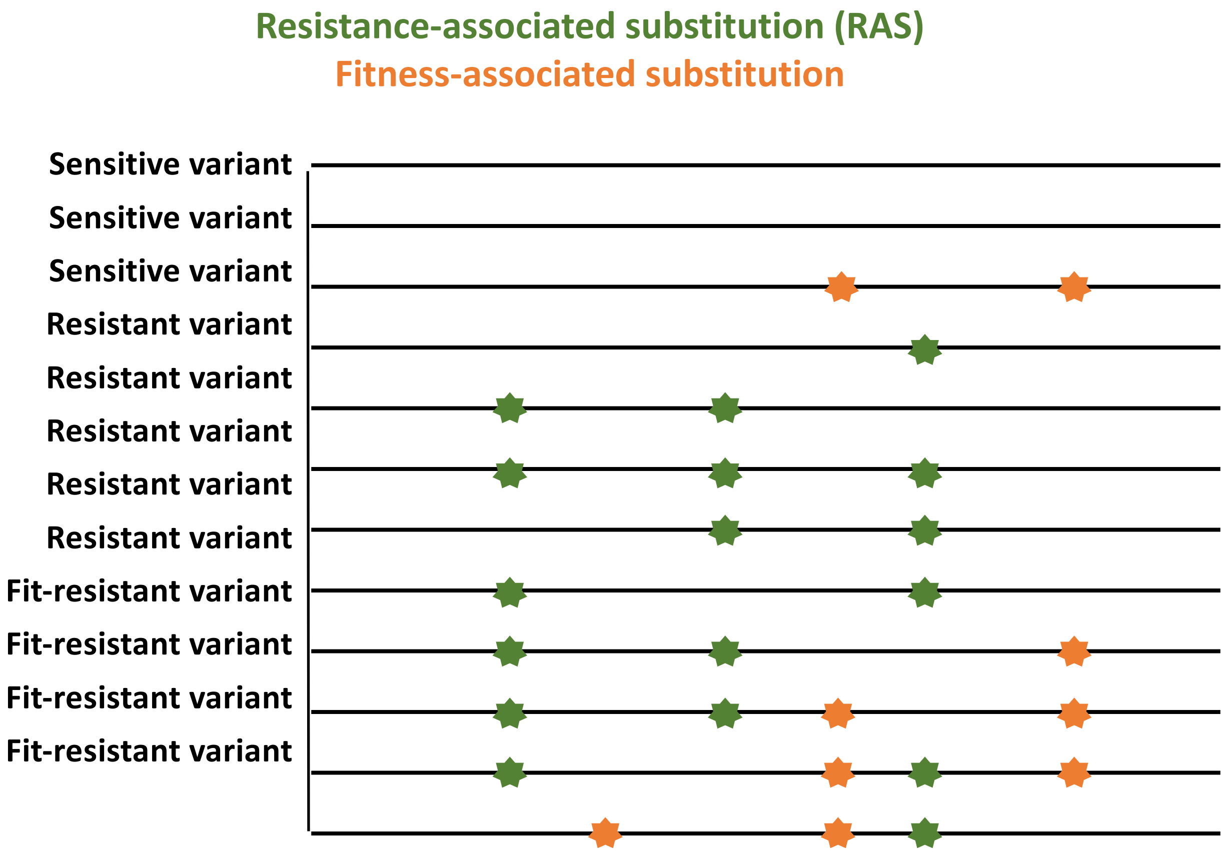
Mutational Capability of RNA Viruses



RNA = ribonucleic acid; DNA = deoxyribonucleic acid; ssDNA = single-stranded DNA; dsDNA = double-stranded DNA.

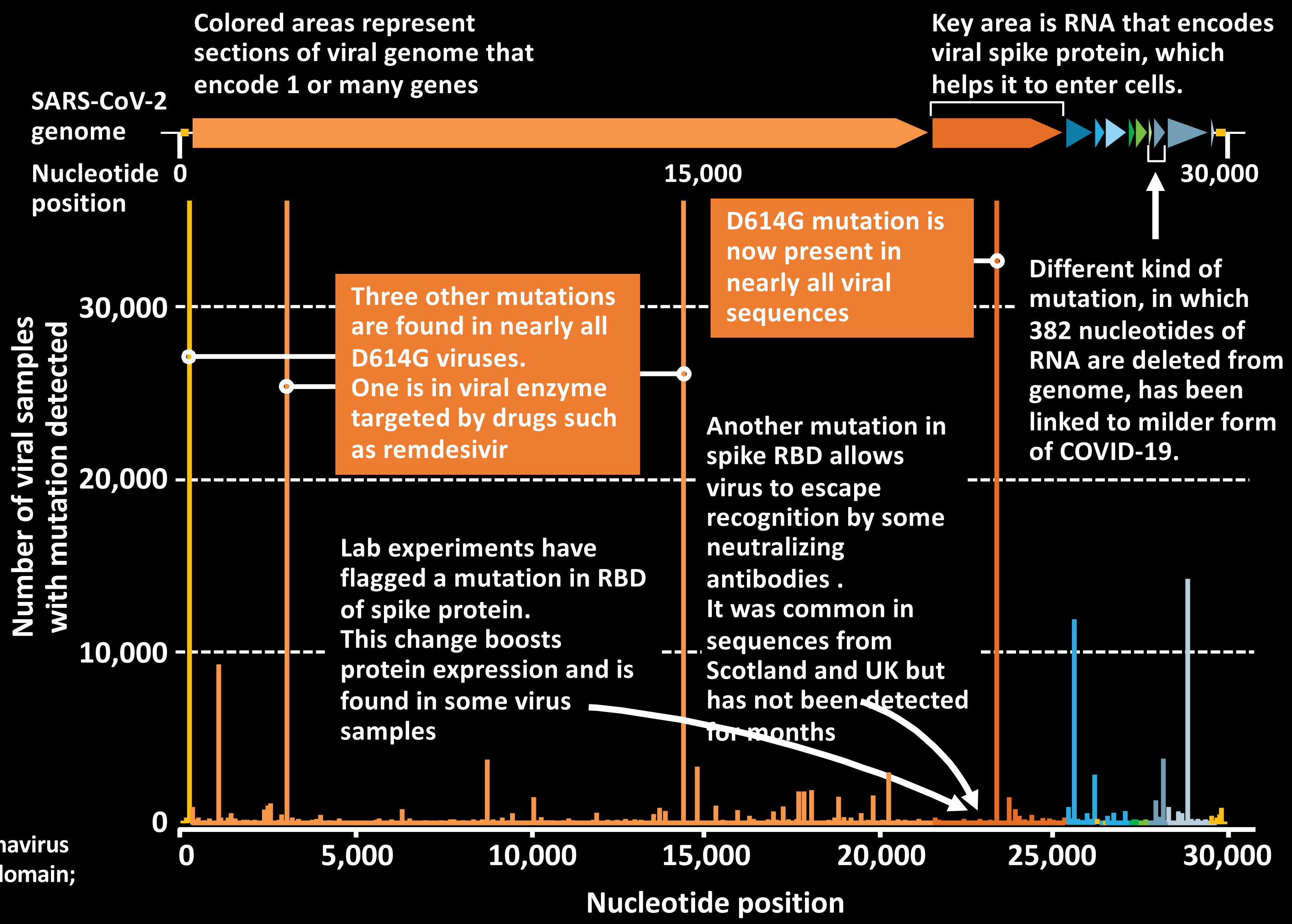
Holmes EC. *Proc Natl Acad Sci USA*. 2010;107(suppl 1):1742-1746.

Viral Mutations and Emergence of Resistance



Pawlotsky J-M. *Gastroenterology*. 2016;151:70-86.

Catalogue of SARS-CoV-2 Mutations

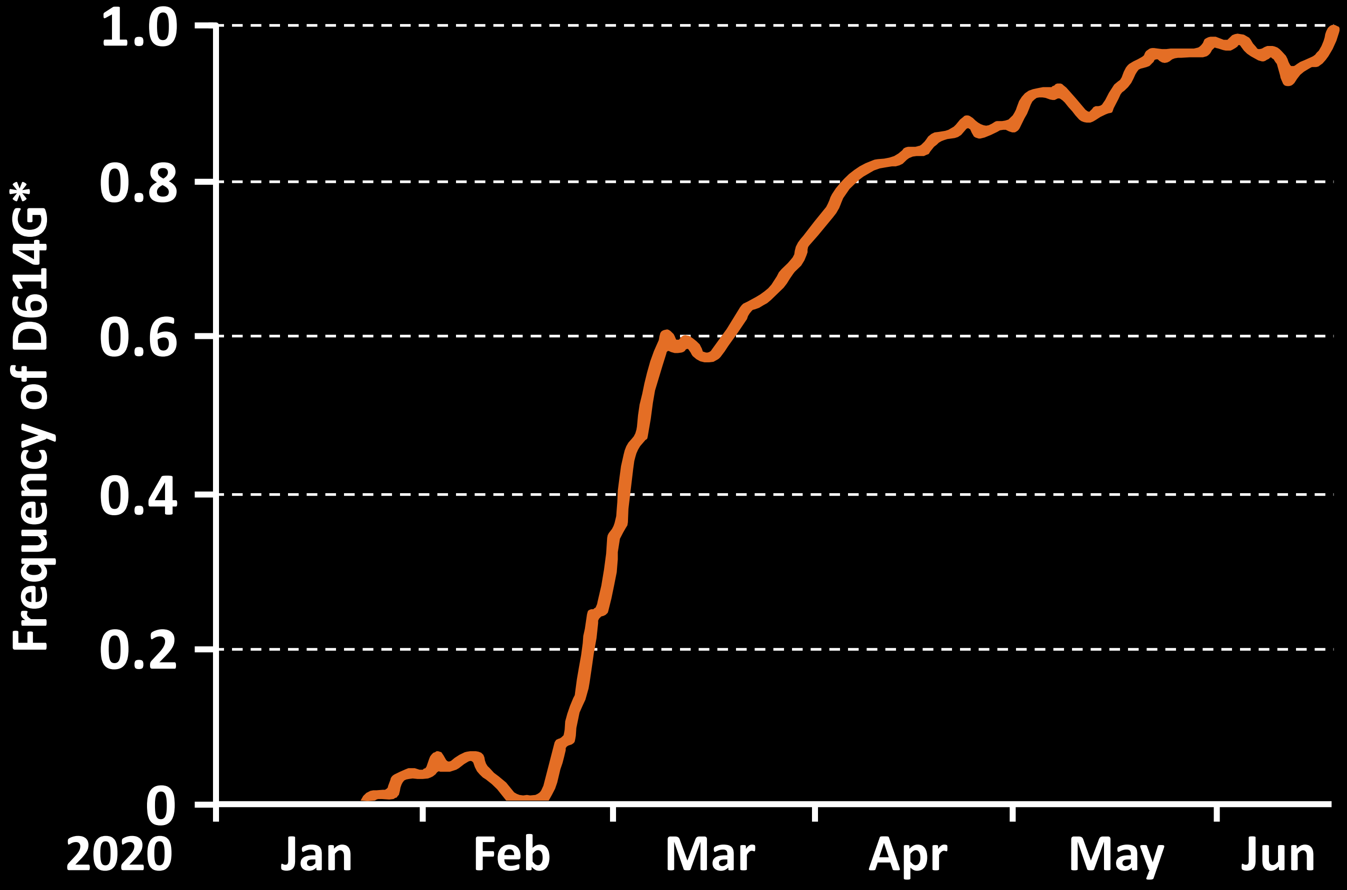


SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; RBD = receptor-binding domain; UK = United Kingdom.

Callaway E. *Nature.* 2020;585:174-177.

Rapid Spread of D614G Mutation

By the end of June 2020, D614G mutation was found in almost all SARS-CoV-2 samples worldwide



*Number of samples = 52,292

Callaway E. *Nature.* 2020;585:174-177.

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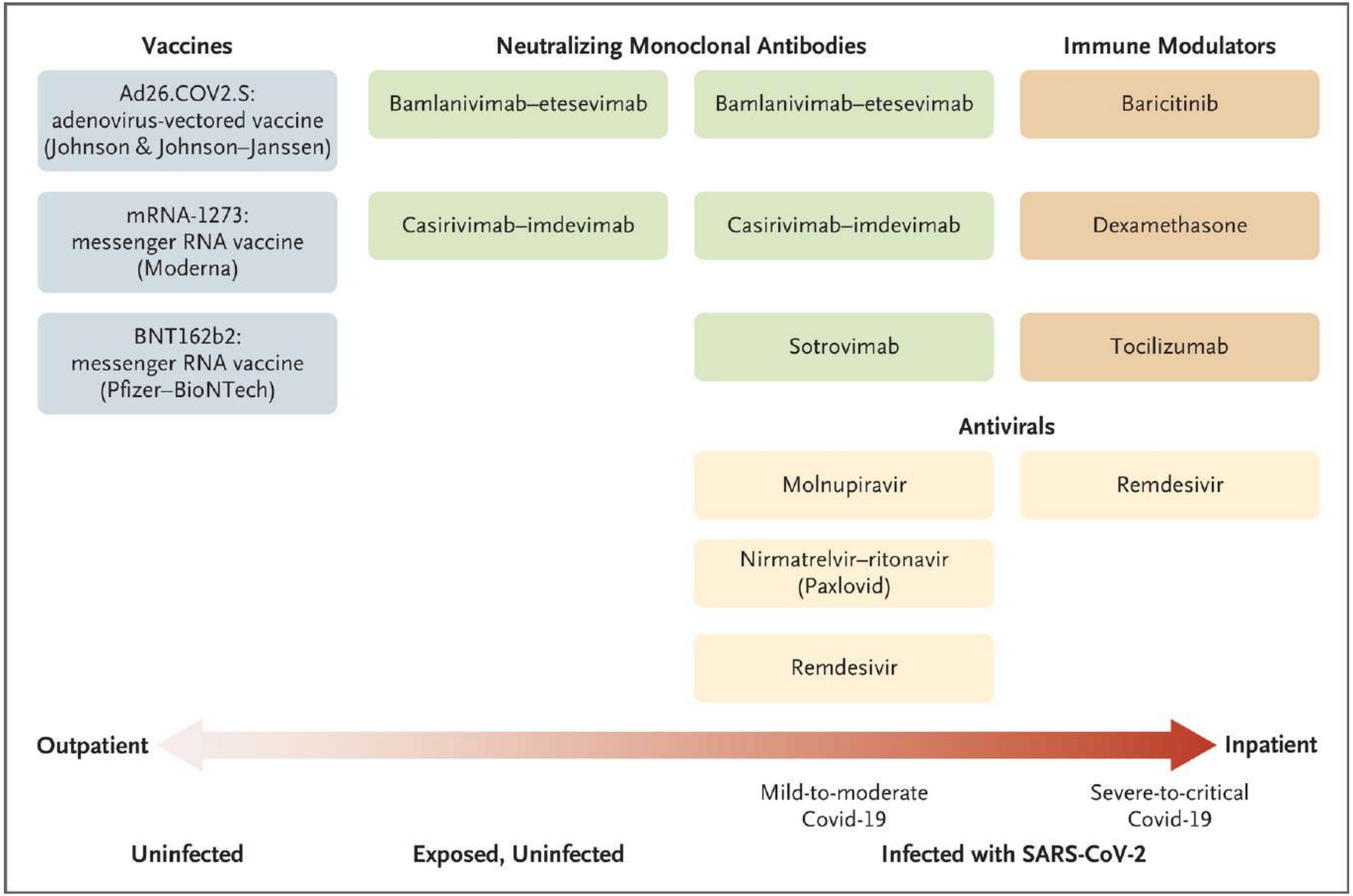
Therapy for COVID-19

	Asymptomatic or presymptomatic	Mild illness	Moderate illness	Severe illness	Critical illness
Features	Positive SARS-CoV-2 test; no symptoms	Mild symptoms (eg, fever, cough, or change in taste or smell); no dyspnea	Clinical or radiographic evidence of lower respiratory tract disease; oxygen saturation ≥94%	Oxygen saturation <94% respiratory rate ≥30 breaths/min; lung infiltrates >50%	Respiratory failure, shock, and multiorgan dysfunction or failure
Testing	Screening testing; if patient has known exposure, diagnostic testing	Diagnostic testing	Diagnostic testing	Diagnostic testing	Diagnostic testing
Isolation	Yes	Yes	Yes	Yes	Yes
Proposed disease pathogenesis			Viral replication	Inflammation	
Potential treatment		Antiviral therapy Antibody therapy		Antiinflammatory therapy	
Management considerations	Monitoring for symptoms	Clinical monitoring and supportive care	Clinical monitoring; if patient hospitalized and at high risk for deterioration, possibly remdesivir	Hospitalization, oxygen therapy, and specific therapy (remdesivir, dexamethasone)	Critical care and specific therapy (dexamethasone, possibly remdesivir)

Adapted from Gandhi RT, et al. *N Engl J Med.* 2020;383:1757-1766

Treatment Paradigm for COVID-19



Heil E and Kottilil S. NEJM 2022

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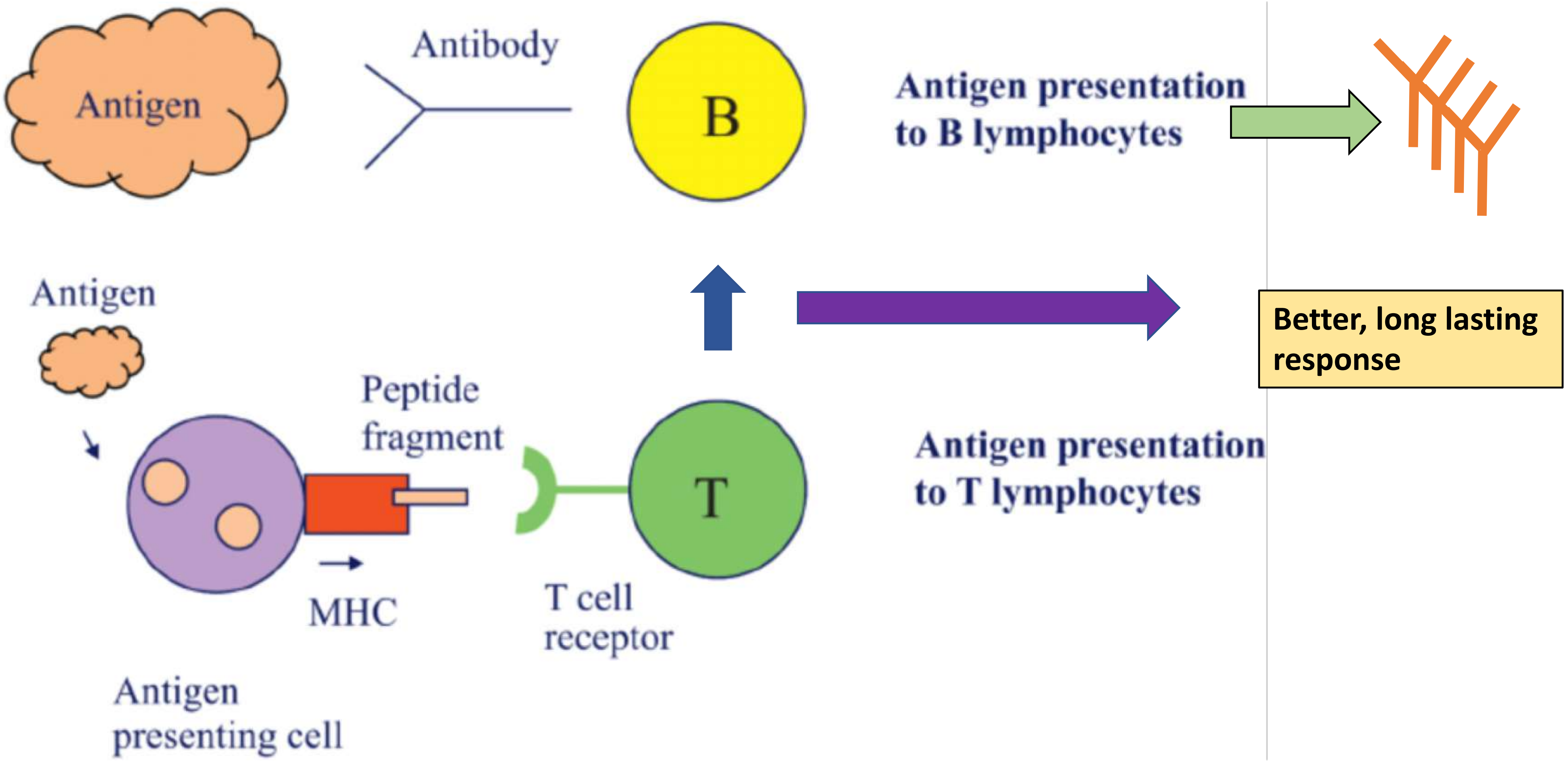
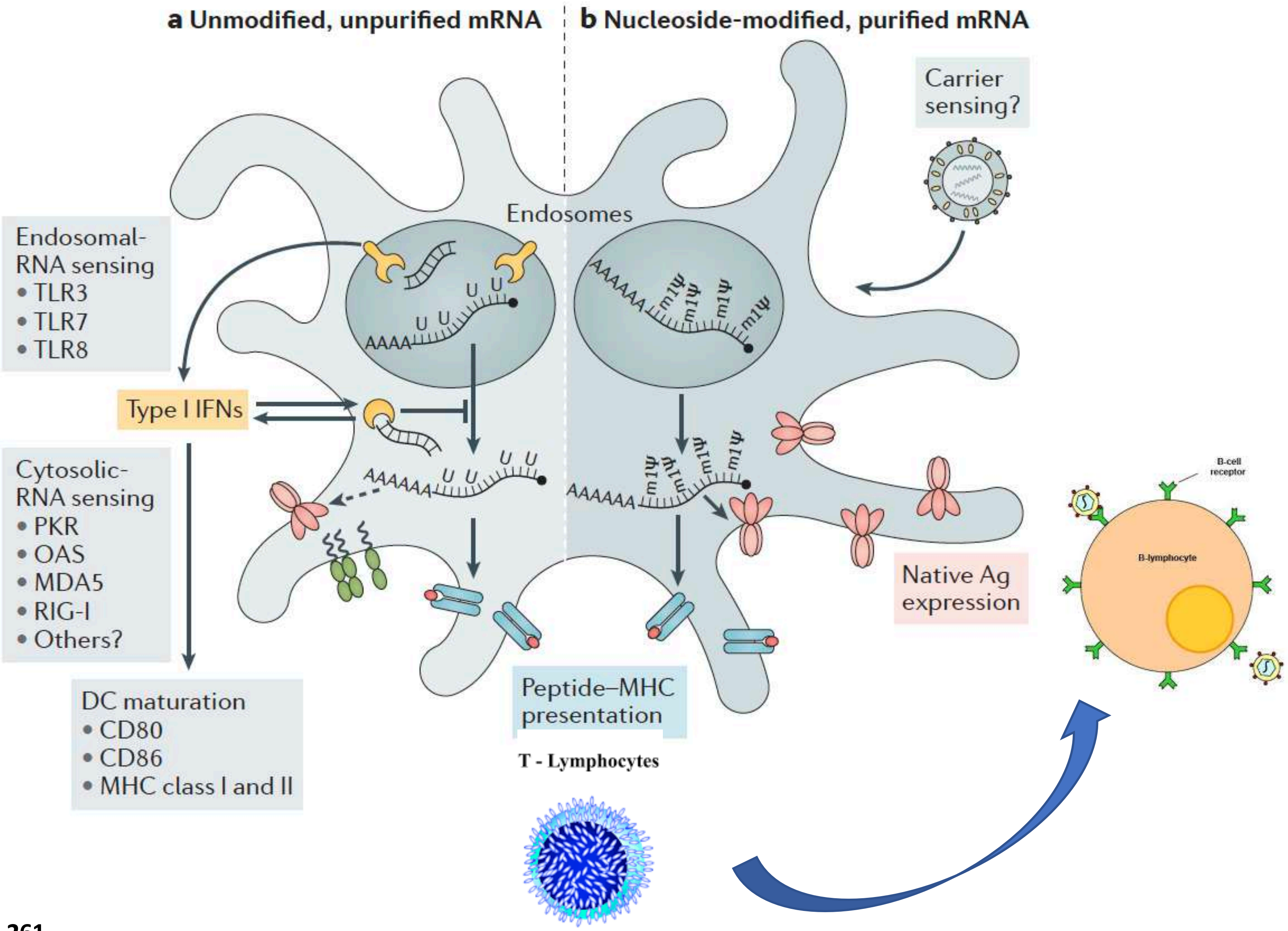
Vaccine Development

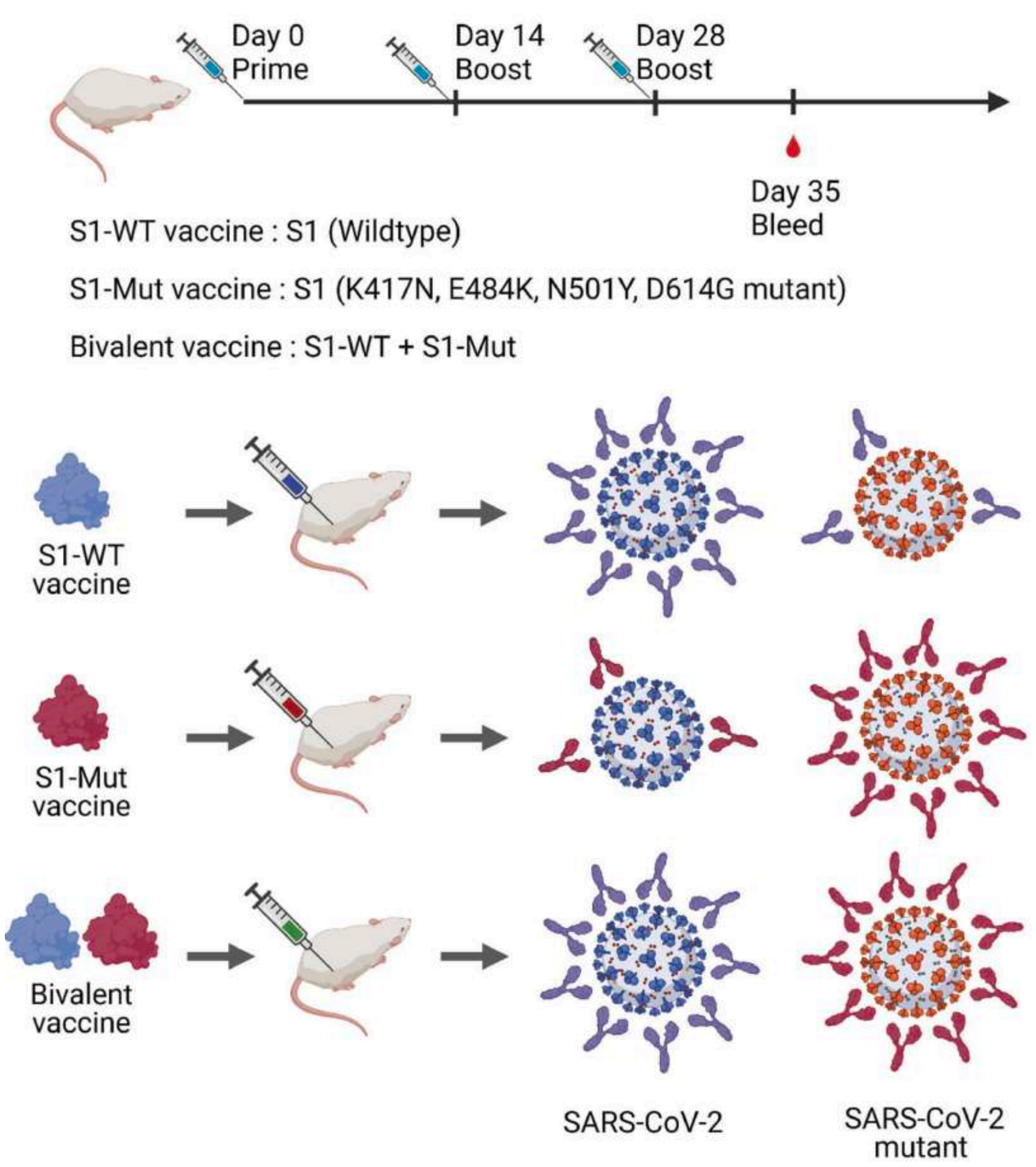


mRNA Vaccine



Pardi N et al. Nature Drug Discovery, 2018, 17: 261

Bivalent mRNA vaccines



Wang J. Nature 2021

Vaccines Do Work

- US CDC study evaluated 192,509 hospitalizations in 250 hospitals (Jan 2021 to April 2022)
- Risk of hospitalization over vaccinated and boosted
  - Unvaccinated 10.5 times more
  - Vaccinated, but not boosted 2.5 X more
- Older (70+, 3 or more underlying factors, nursing home residents)

Havers F et al. *JAMA Intern Med* 2022

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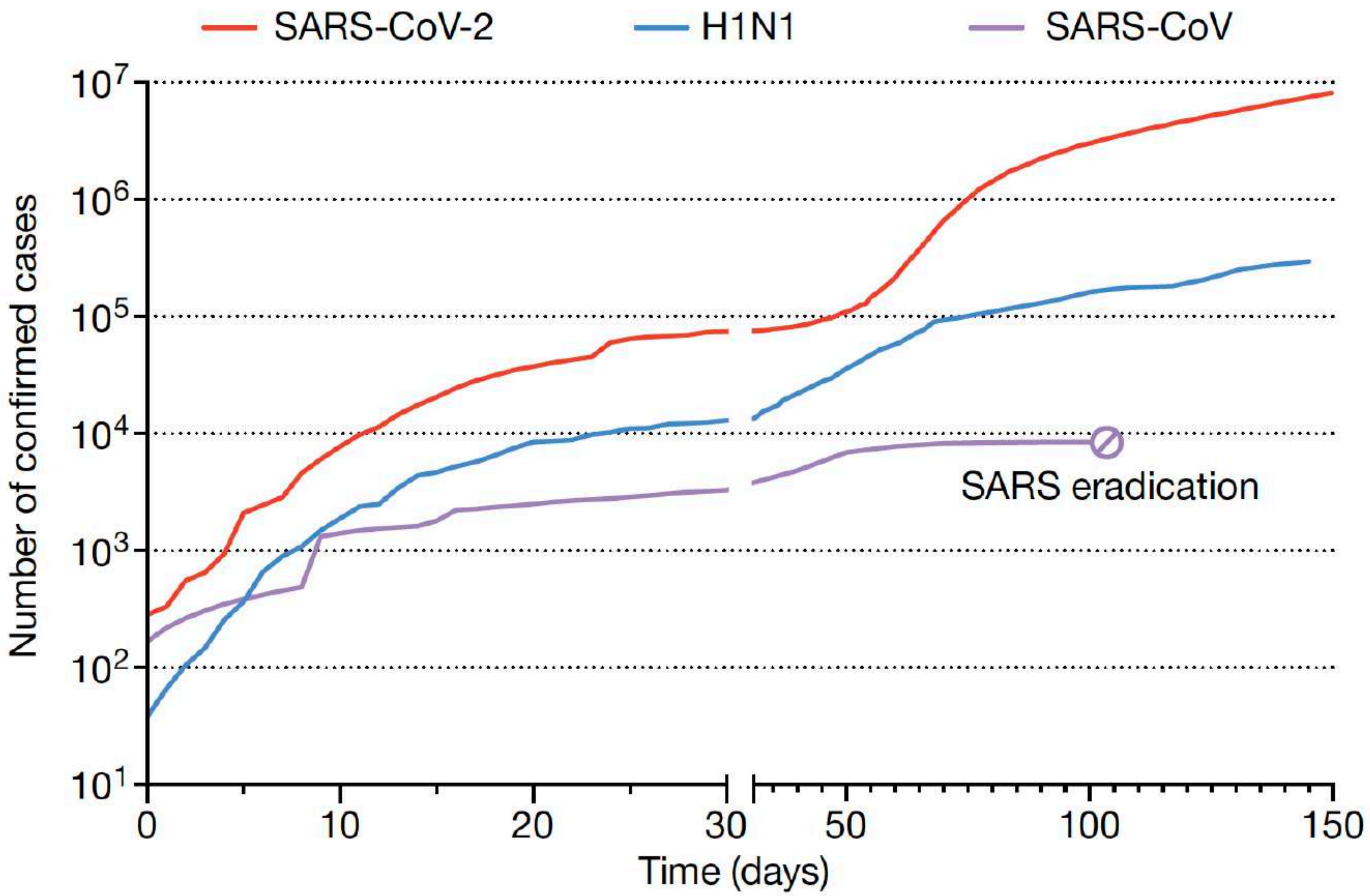
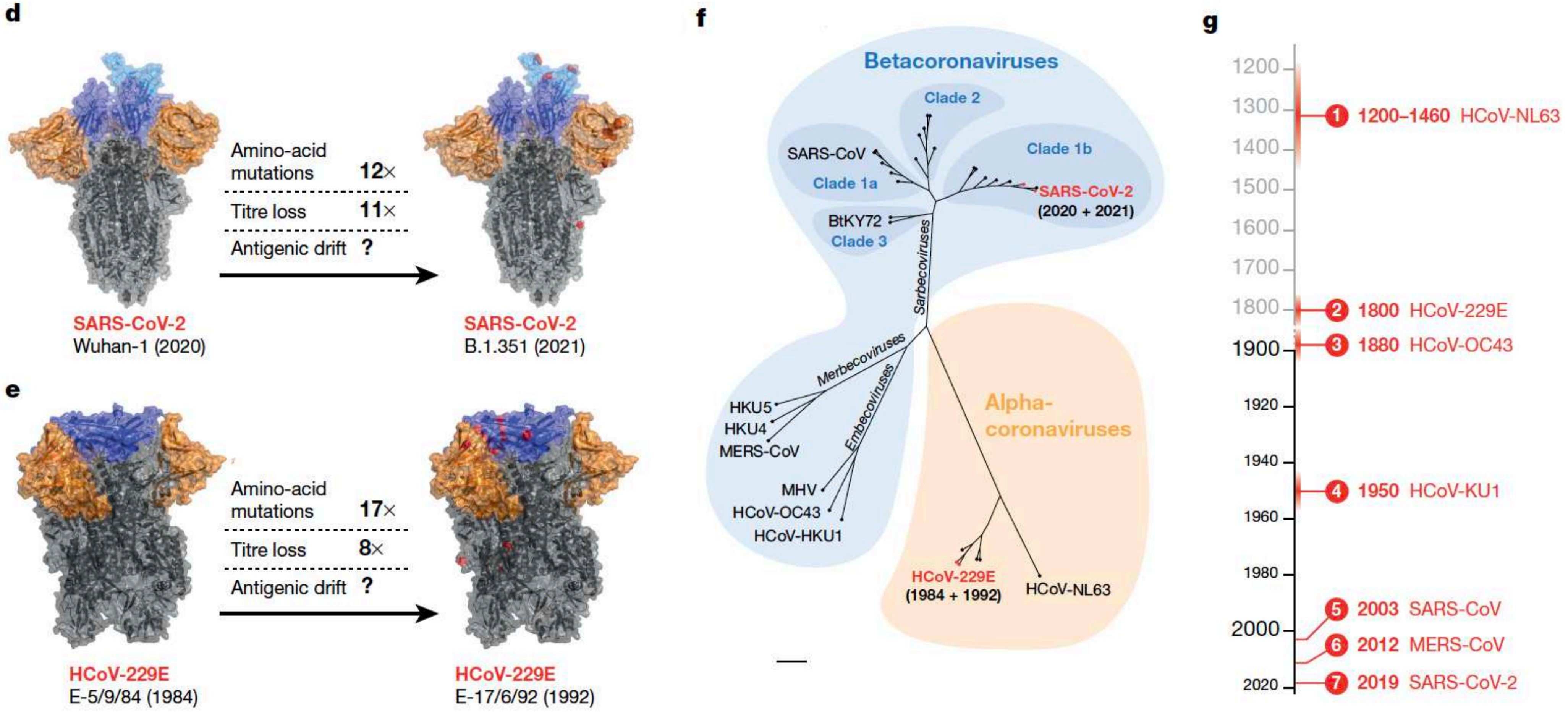
Natural History of Recent Pandemics



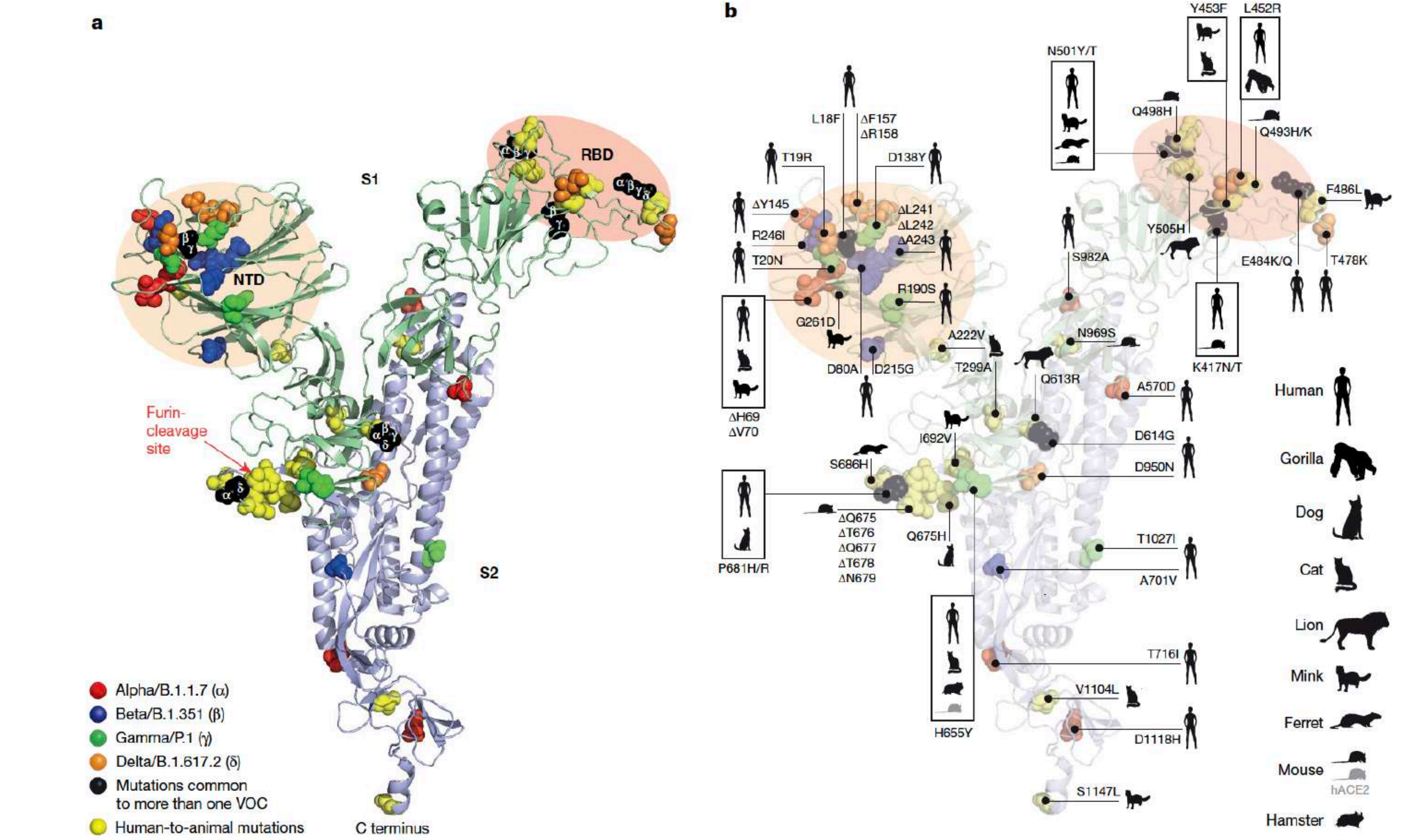
Telenti et al. Nature 2021

Antigenic Drift



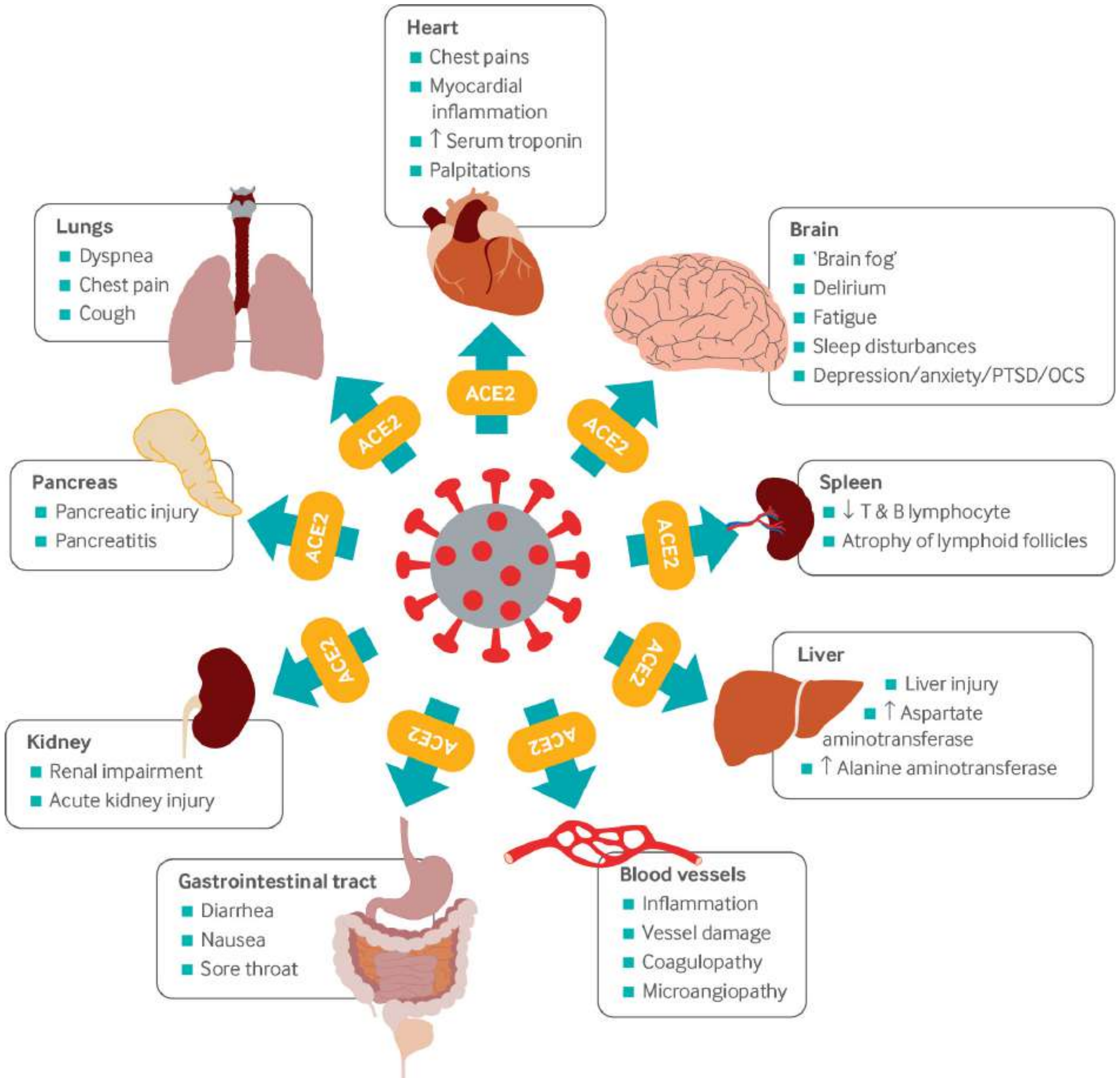
Telenti et al. Nature 2021

Adaption by Cross Species Transmission



Telenti et al. Nature 2021

Long COVID-19



Crook H et al. BMJ, 2021

Long COVID-19

- People with post-COVID conditions can have a wide range of symptoms that can last more than four weeks or even months after infection (13.3% and 2.5% after 3 months)
- Symptoms cannot be explained by tests or other causes
- Who gets it?
  - Severe COVID-19/ICU stay (30% at 6 months after discharge)
  - Unvaccinated who get COVID
  - Have Multisystem Inflammatory Syndrome with COVID

Long COVID-19 Symptoms

Symptoms

- Fatigue with exertion
- Fever
- SOB, Cough, Chest pain
- Brain fog
- Headaches
- Dizziness
- Change in taste and smell
- Anxiety/depression

Rare Symptoms

- Diarrhea
- Abdominal pain
- Myalgias
- Menstrual cycle changes

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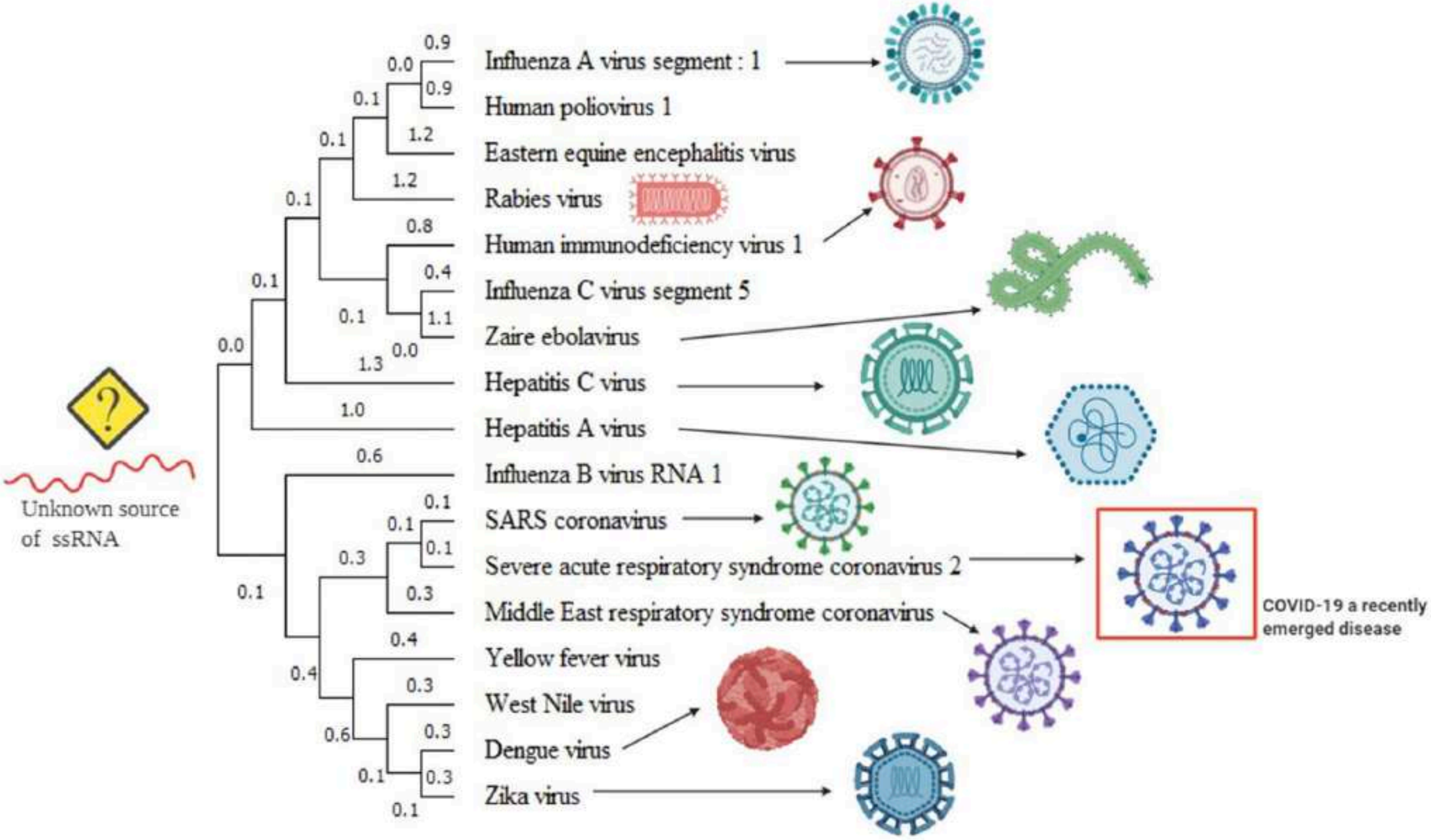
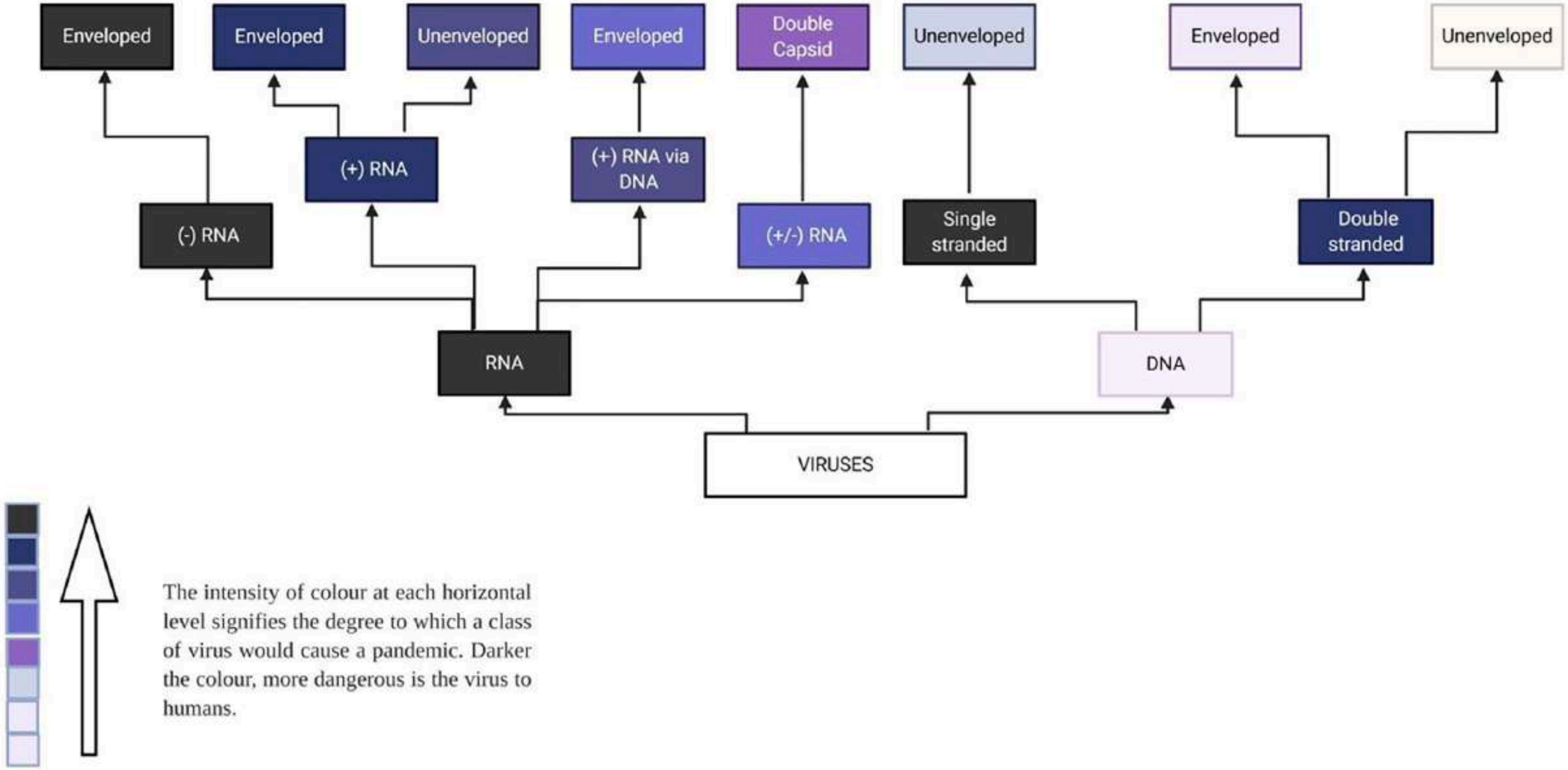
Closeness of Viruses that have Caused a Pandemic



Behl A et al. Infection, Genetics and Evolution 2022

Pandemic Potential Based on Virology



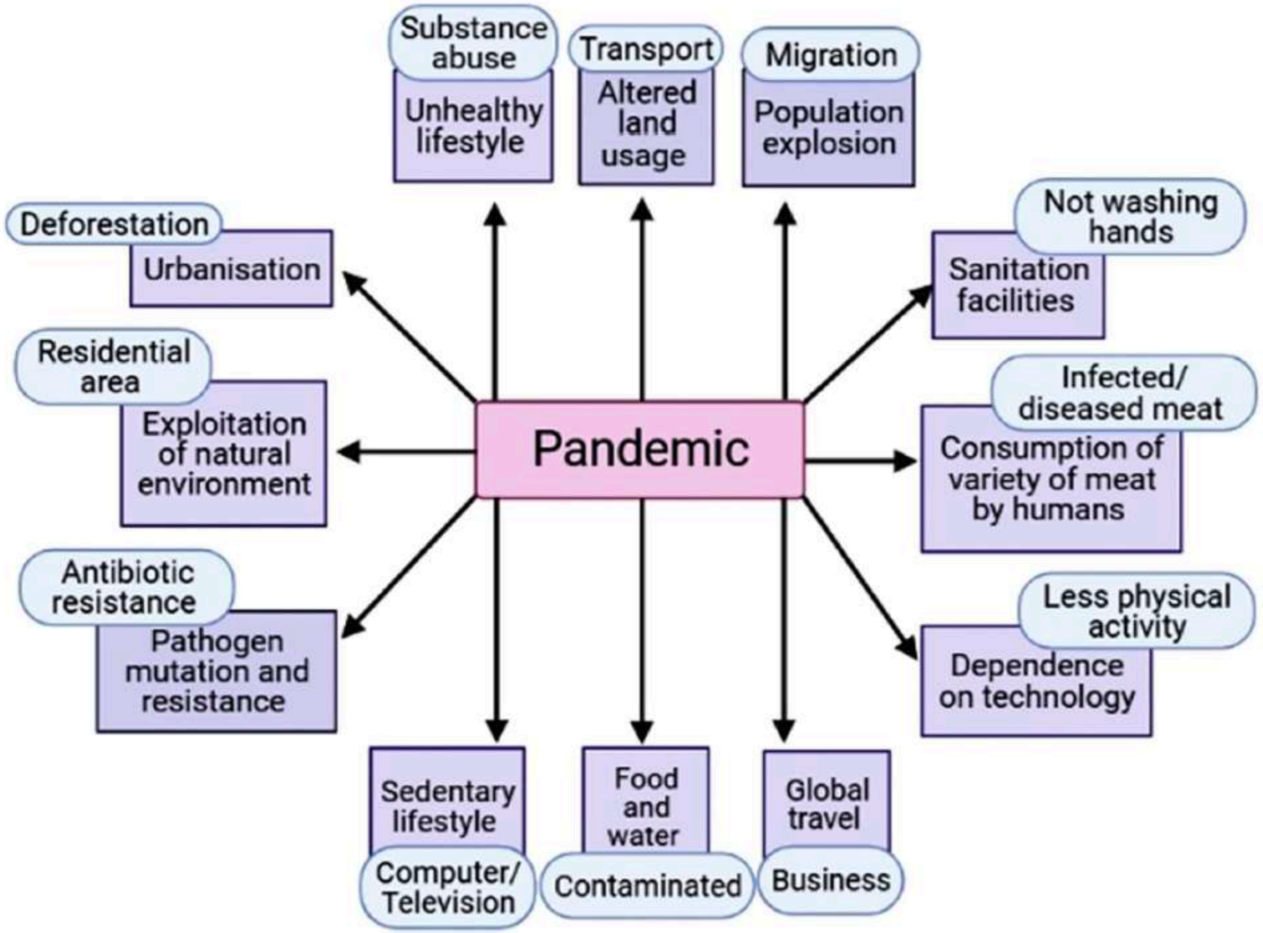
The intensity of colour at each horizontal level signifies the degree to which a class of virus would cause a pandemic. Darker the colour, more dangerous is the virus to humans.

Behl A et al. Infection, Genetics and Evolution 2022

What future holds?

- It will happen again
- Immediate measures
- Challenges

Factors Enhancing Risk of Pandemic



Behl A et al. Infection, Genetics and Evolution 2022

Non-specific Effects of Oral Polio Vaccine

- Oral Polio Vaccine developed by Albert Sabin (1955)
  - Large-scale clinical trials in USSR (1958-1959)
- 1959- Outbreak in Singapore caused by type 1 poliovirus was stopped by monovalent type 2 OPV
- OPV was used during 1975 outbreak of poliomyelitis-like disease in Bulgaria caused by Enterovirus 71
- Systematic studies of non-specific effects of OPV by Dr. Marina Voroshilova in Russia (1960s and 1970s)
- Recent studies in Denmark, Guinea-Bissau, Finland, Bangladesh (P. Aaby, C. Benn, W. Petri, and others)

Melnick JL (ed): Prog Med Virol. Basel, Karger, 1989, vol 36, pp 191–202

Potential Use of Nonpathogenic Enteroviruses for Control of Human Disease

Marina K. Voroshilova[1]

Institute of Poliomyelitis and Viral Encephalitides, Academy of Medical Science, Moscow, USSR

Журнал Микробиологии, Эпидемилогии, и Иммунологии 1992 (11-12) : 37-40.

М. П. Чумаков, М. К. Ворошилова. А. С. Анцупова, В. М. Бойко, М. И. Блинова, Л. С. Приймяги, В. И. Родин, В. Б. Сейбиль. К .М. Синяк, А. Ан. Смородинцев, В.А. Степанчук, С. Н. Терехов, Л. И. Трофимова, П. М. Чумаков

ЖИВЫЕ ЭНТЕРОВИРУСНЫЕ ВАКЦИНЫ ДЛЯ ЭКСТРЕННОЙ ПРОФИЛАКТИКИ МАССОВЫХ РЕСПИРАТОРНЫХ ЗАБОЛЕВАНИЙ ВО ВРЕМЯ ОСЕННЕ-ЗИМНЕЙ ЭПИДЕМИИ ГРИППА И ОСТРЫХ РЕСПИРАТОРНЫХ ЗАБОЛЕВАНИЙ

Институт полиомиелита и вирусных энцефалитов Российской АМН, Москва

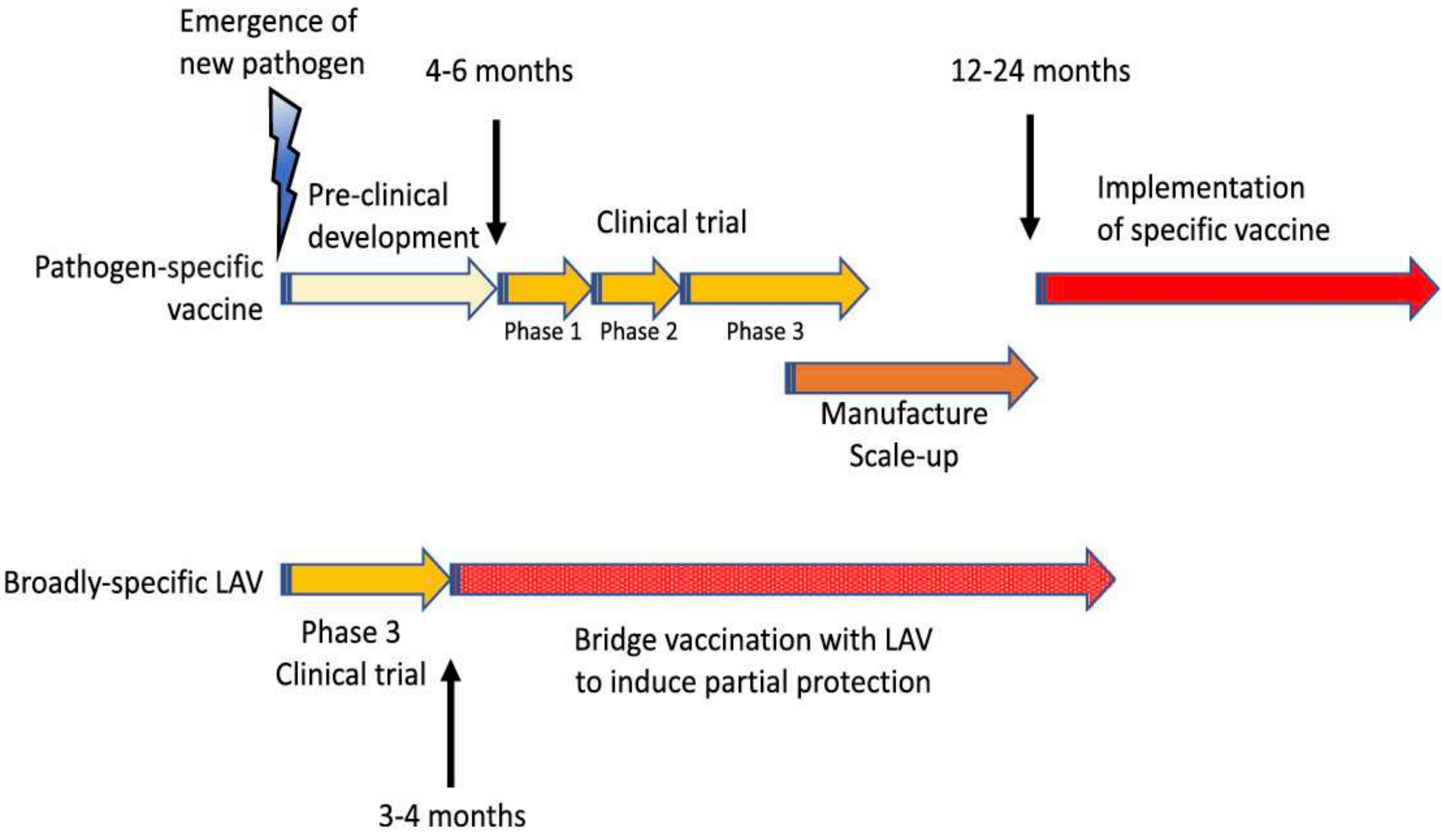
City, Year, Vaccine	Individuals under study			% of disease cases		Morbidity reduction, fold	Number of protected individuals
	Control	Vaccinated	All together	Control	Vaccinated		
Tallinn (1970) OPV1	2,984	7,560	10,544	26.41	5.81	4.5	1,558
Gorky (1970) mOPV1 + mOPV3	18,880	40,673	59,558	28.9	15.5	1.9	5,451
Balashikha (1970) mOPV1 + mOPV3	2,066	2,744	4,819	20.2	7	2.9	363
Vnukovo (1970) mOPV1 + mOPV3	1,994	9,083	11,077	64.9	11.2	5.8	4,878
Total:	25,924	60,965	85,989	-	-	3.8*	12,250

* Morbidity reduction, mean

City, Year, Vaccine	Individuals under study			% of disease cases		Morbidity reduction, fold	Number of protected individuals
	Control	vaccinated	All together	control	vaccinated		
Tallinn (1970) mOPV1 + ECHO12	1,344	649	1,993	7.6	3.8	2	76
Khabarovsk (1969) ECHO1	12,179	16,454	28,624	6.33	1.45	4.4	802
Khabarovsk (1970) ECHO1 + ECHO12	716	2,733	3,449	50.98	18.23	2.8	892
Khabarovsk (1971) ECHO1 + ECHO12	1,006	942	1,948	17.59	8.7	2	105
Khabarovsk (1971) ECHO1 + ECHO12	343	1,243	1,586	18.37	9.89	1.9	105
Total:	15,579	22,021	37,600	-	-	2.62*	2,059

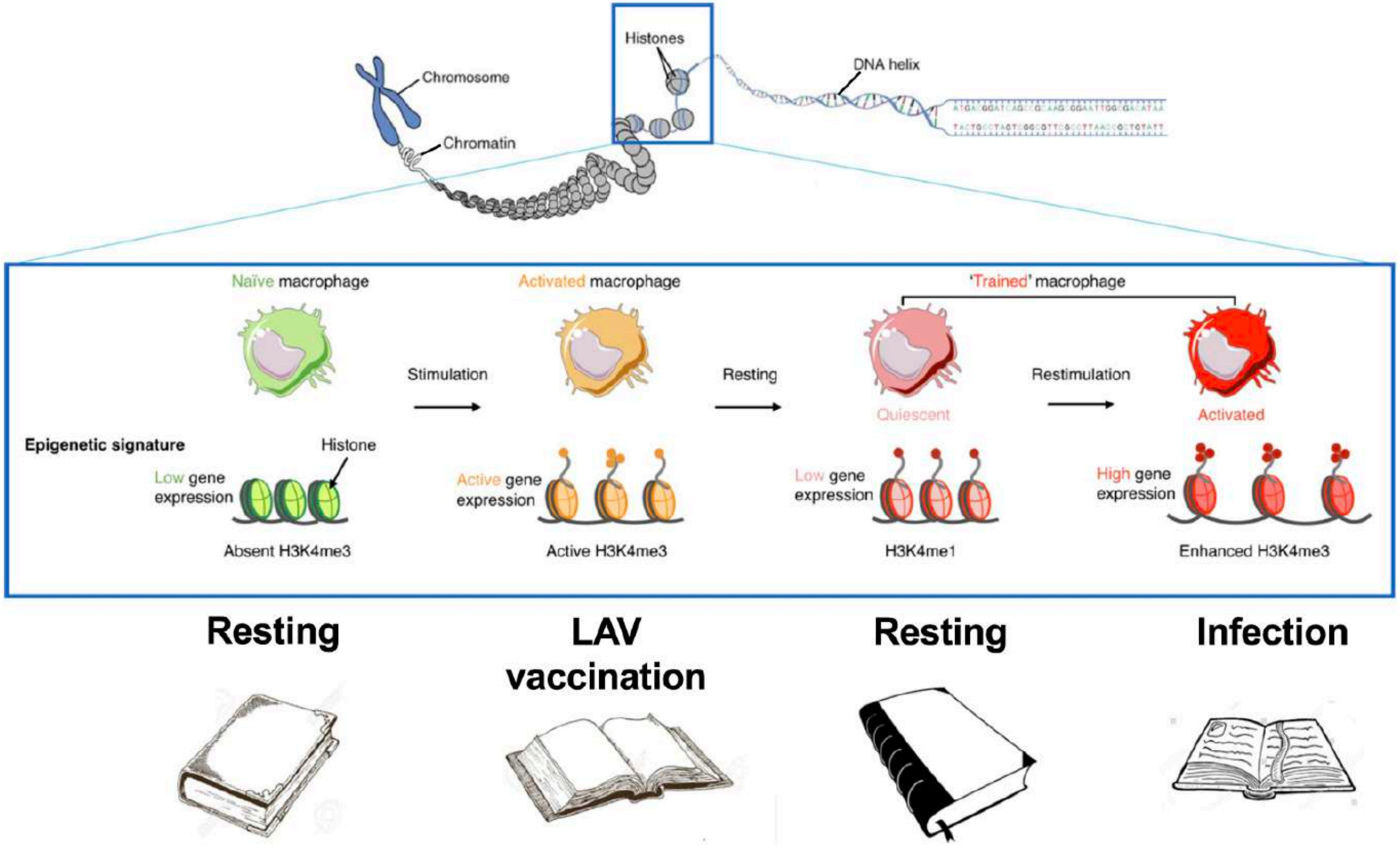
* Morbidity reduction, mean

Potential for Prevention of Future Pandemics



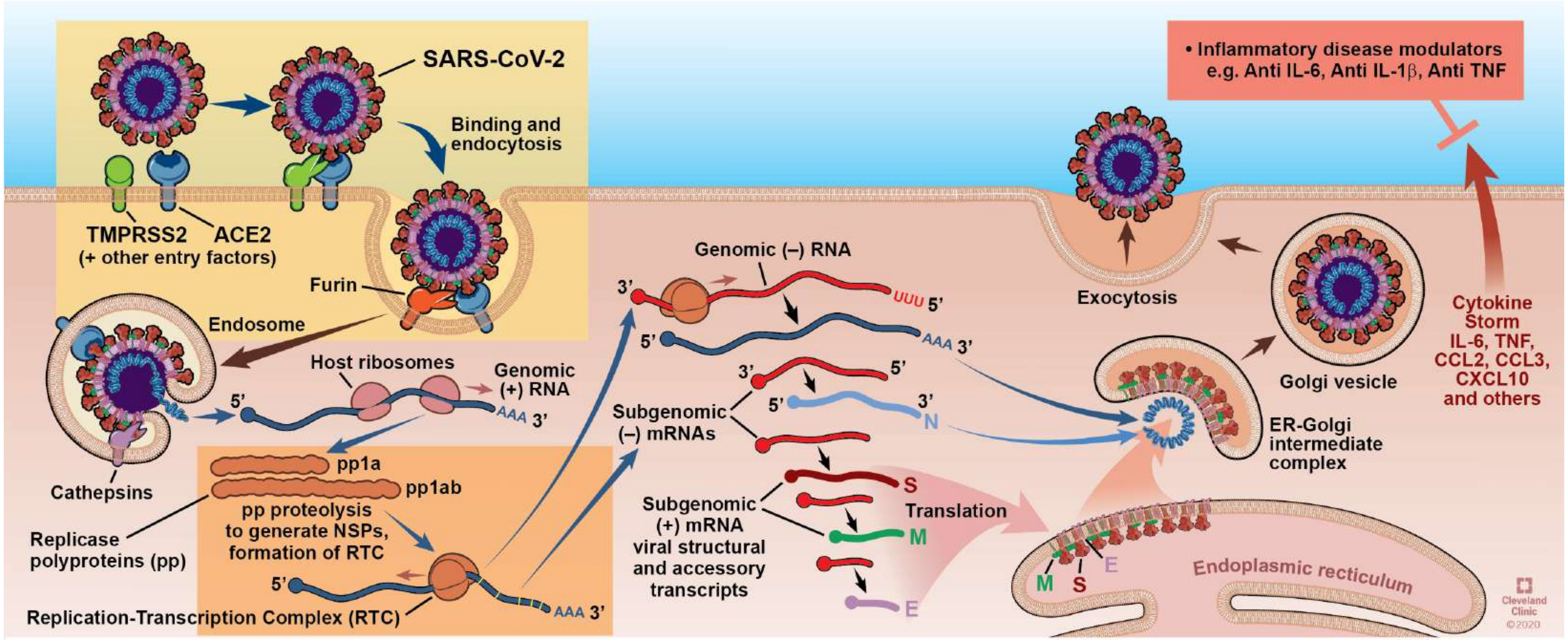
Chumakov K….Kottilil S. PNAS 2021

Potential for Prevention of Future Pandemics



Chumakov K….Kottilil S. PNAS 2021

Viral Targets



Blockade of Entry

- Anti-spike Ab
  - convalescent serum
  - vaccine expressing spike
- Inhibition of S1/S2 cleavage
  - e.g. TMPRSS2
- Endocytosis inhibitor
  - chloroquine
  - hydroxychloroquine

Blockade of Replication

- Interference with RdRP (Replicase)
  - Remdesivir (GS-5734)
  - EIDD-1931
- Viral protease inhibitor
- Ribavirin

Innate Immune Response

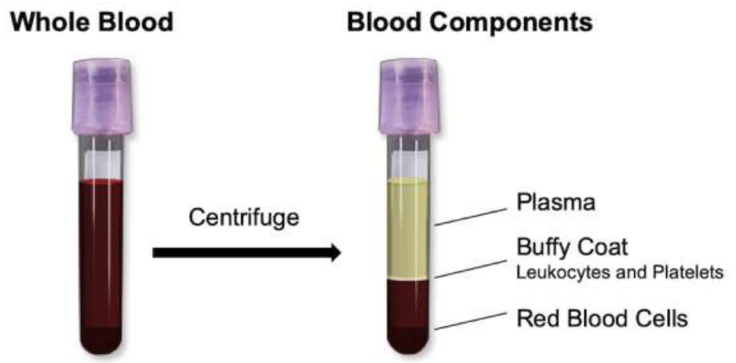
- MDA5
- IFN-I, IFN-III
- ISG effectors
  - OAS, PKR, ...

Enhancers of Antiviral Innate Immunity

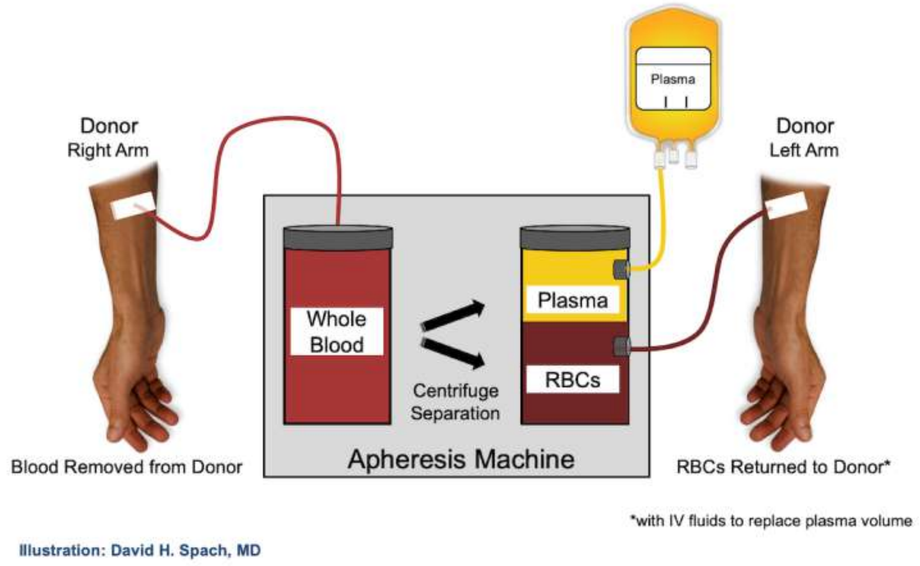
- Early treatment with IFN or IFN inducers
- Blockade of IFN antagonists

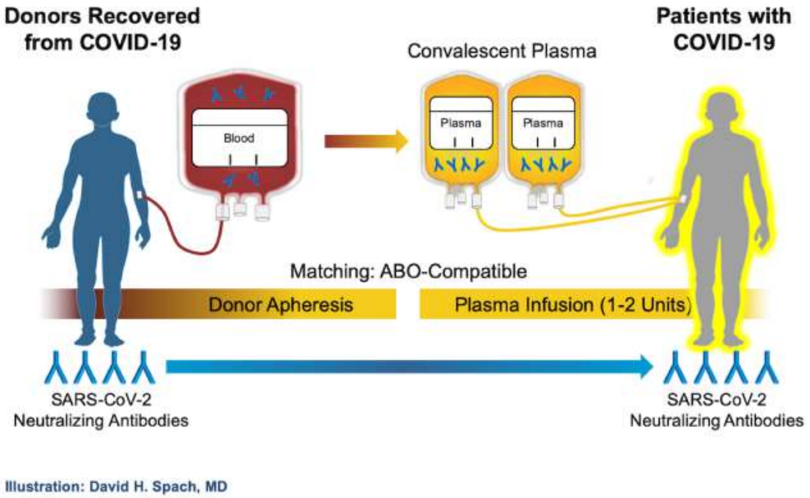
Bergmann, C. and Silverman, R.H. Cleveland Clinic Journal of Medicine (2020)

Convalescent Plasma Therapy



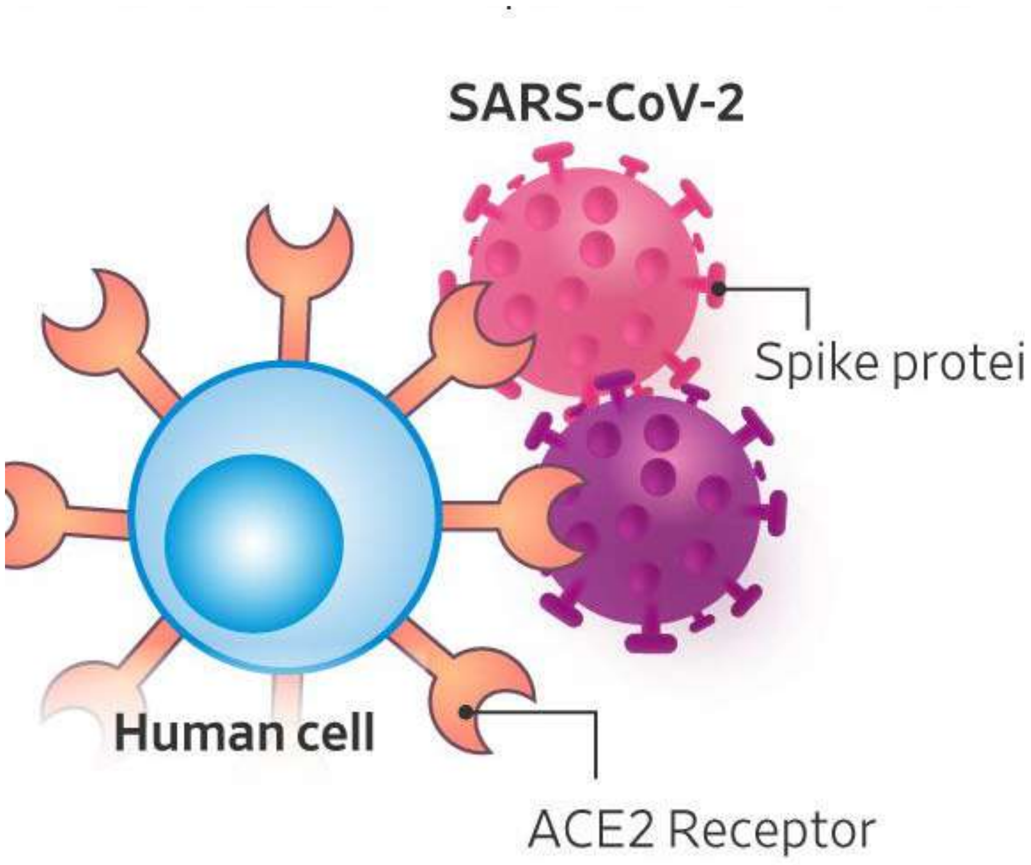
Plasma is the liquid portion of blood. Consists of water, proteins (antibodies, albumin, gamma globulin and coagulation factor), mineral salts, sugars, fats, and hormones.

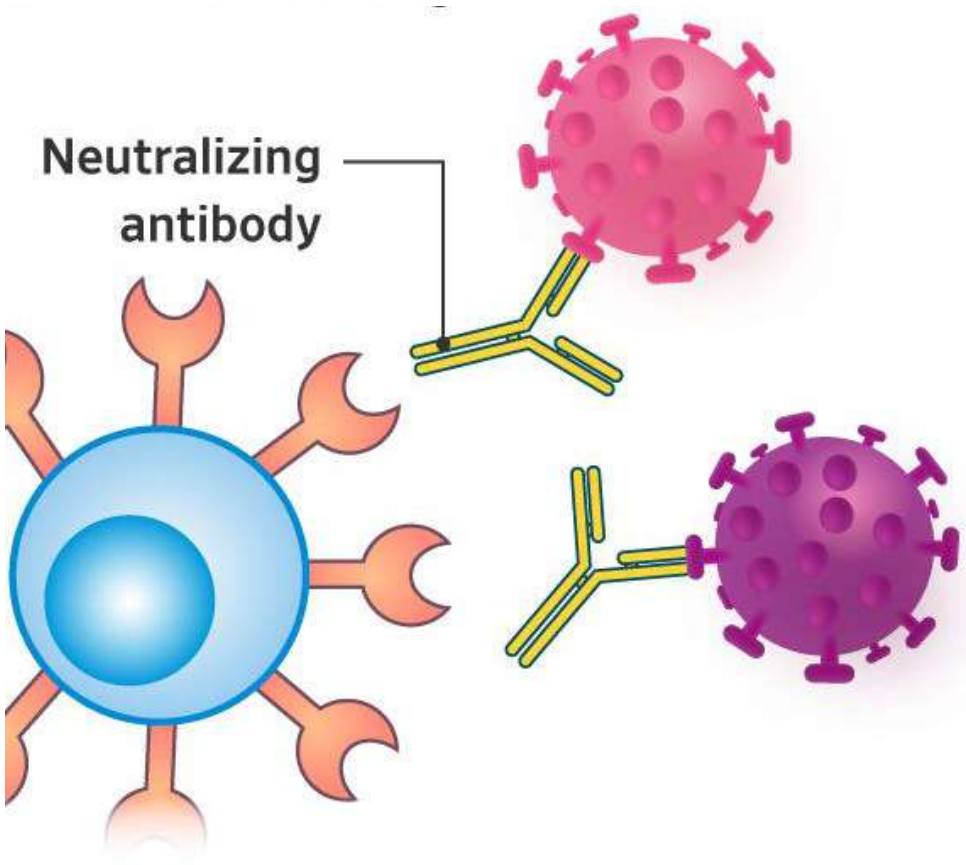




David Spach Univ of Washington

Neutralizing Monoclonal Antibodies



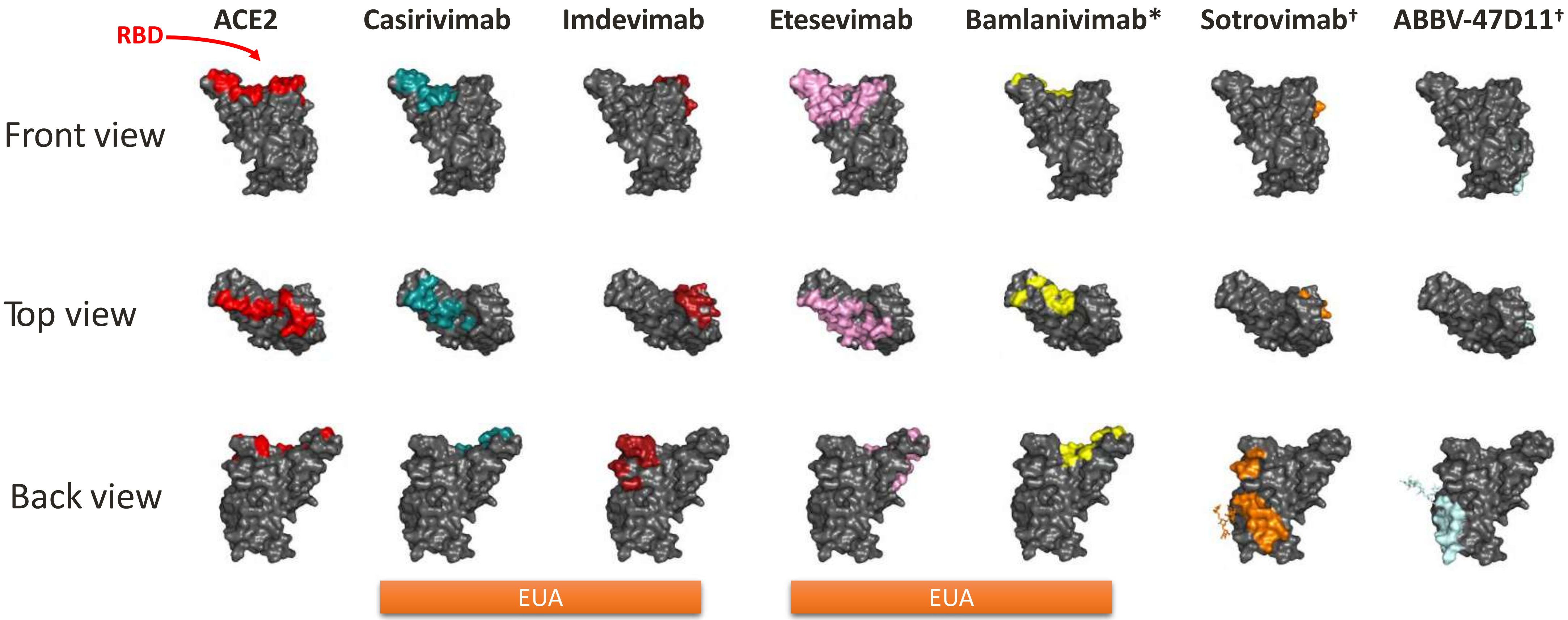


Advantages of Monoclonal over Polyclonal Therapies

- Small Changes in antigen: Single nucleotide polymorphisms/variants (too small to generate a robust antibody response using convalescent plasma)
- Post translational modifications of target (phosphorylation, methylation, etc)
- Since polyclonal response in individuals vary significantly, this approach raises regulatory concerns due to batch to batch variability and variations in performance/outcomes
- Cross-reactivity and adverse events such as hypersensitivity reactions and rarely target organ damage

Fundamental immunology 7th Edition, 2012 Ed. William Paul

Yin and Yang of Antibody Therapy



* Structure is solved but not released; † Both sotrovimab and ABBV-47D11 bind to the N-glycan on Asn343, which adopts different conformations and is shown as sticks.
ACE2, human angiotensin converting enzyme 2; mAb, monoclonal antibody; RBD, receptor binding domain (BRIGHT RED).

Illustration adopted from AbbVie Inc.
Confidential Data

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Summary Points

- It is likely that another pandemic will emerge in the future, although when and where is unpredictable
- Early time is the most critical time
- Dissemination of “fake news” is rampant. Research into public behavior is critical
- Small studies are not generalizable
- Guidance can change over time
- It is a time for us to be humble not play heroes

SCIENCE

Friday, May 30, 1919

CONTENTS

THE LESSONS OF THE PANDEMIC

The pandemic which has just swept round the earth has been without precedent. There have been more deadly epidemics, but they have been more circumscribed; there have been epidemics almost as widespread, but they have been less deadly. Floods, famines, earthquakes and volcanic eruptions have all written their stories in terms of human destruction almost too terrible for comprehension, yet never before has there been a catastrophe at once so sudden, so devastating and so universal.

The most astonishing thing about the pandemic was the complete mystery which surrounded it. Nobody seemed to know what

GA Soper *Science* 1919

Quotable Quotes

vention: First, public indifference. People do not appreciate the risks they run. The great

The measures which were introduced for the control of the pandemic were based upon the slenderest of theories. It was assumed

the present time. Nobody can now speak authoritatively upon this subject. When all

The second factor which stands in the way of prevention is the personal character of the measures which must be employed. Th

scarlet fever. Influenza is in this class. The symptoms at the beginning may be identical with those of the common cold and the true nature of the disease escape notice until the patient shows unmistakable and alarming symptoms. By that time other persons may be infected.

It does not lie in human nature for a man who thinks he has only a slight cold to shut himself up in rigid isolation as a means of protecting others on the bare chance that his cold may turn out to be a really dangerous infection.

Third, the highly infectious nature of the respiratory infections adds to the difficulty of their control. The period of incubation varies

GA Soper *Science* 1919

What future holds?

Will there be another visitation? Nobody can positively answer this question. Influenza commonly sweeps in more than one wave over a country. America experienced an unmistakable, but mild, wave before the great one of September and October and since then there have been local disturbances corresponding to fresh outbreaks in many places. In England a new and alarming prevalence has been reported. It would not be surprising if there should be another pandemic in the United States.

GA Soper *Science* 1919