SARS-CoV-2 and Influenza
Lessons from Pandemic Respiratory Viruses

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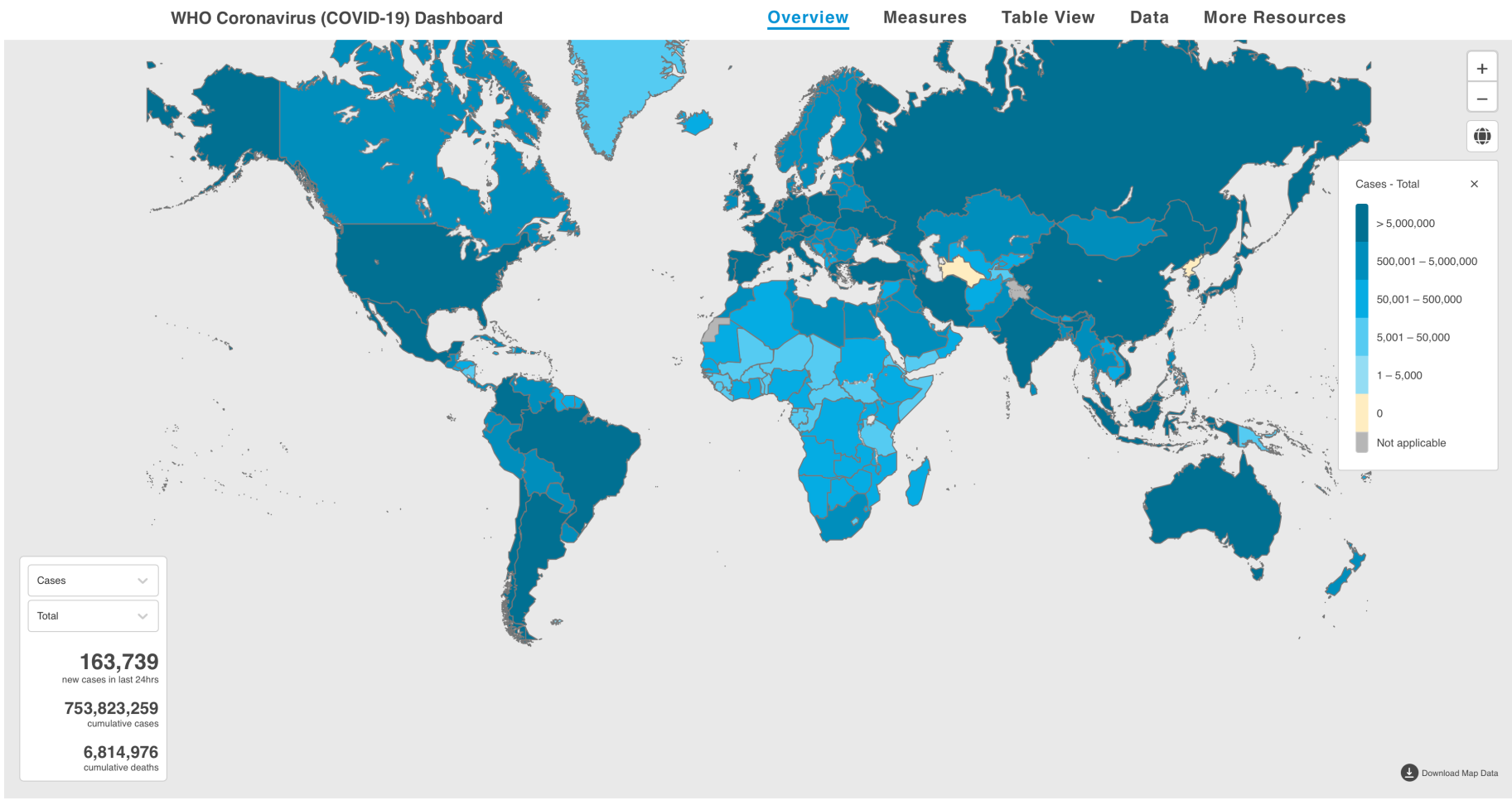
Current status



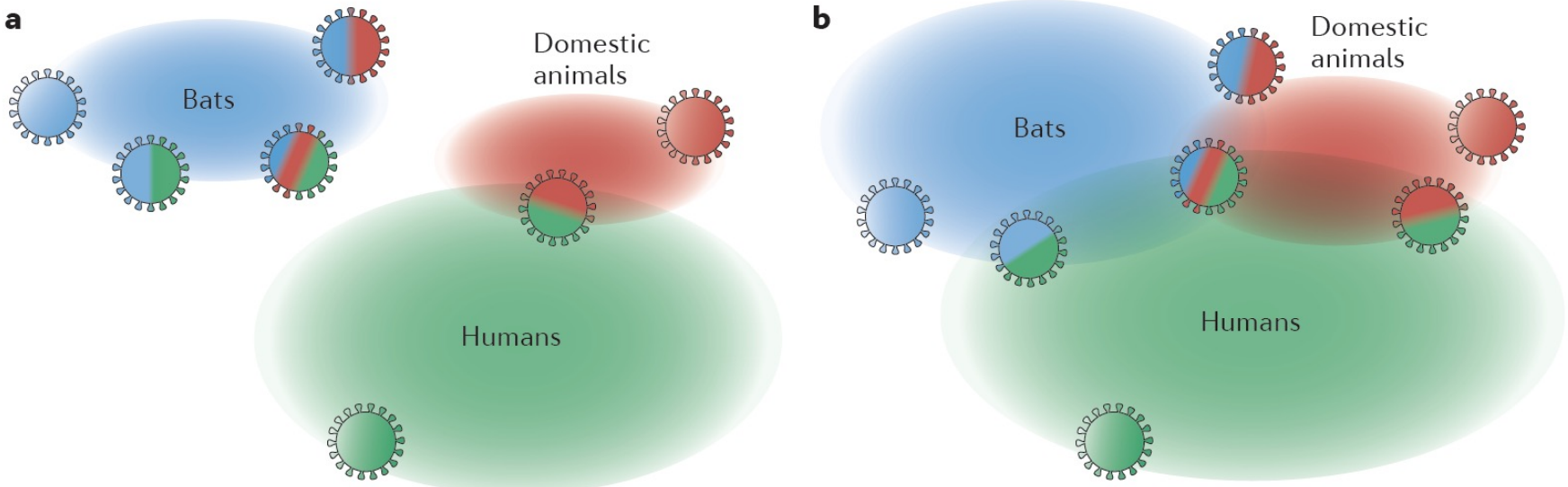
Globally, as of **4:58pm CET, 2 February 2023**, there have been **753,823,259 confirmed cases** of COVID-19, including **6,814,976 deaths**, reported to WHO. As of **30 January 2023**, a total of **13,168,935,724 vaccine doses** have been administered.

https://covid19.who.int

Shared Features of SARS-CoV-2 and Pandemic Influenza Viruses

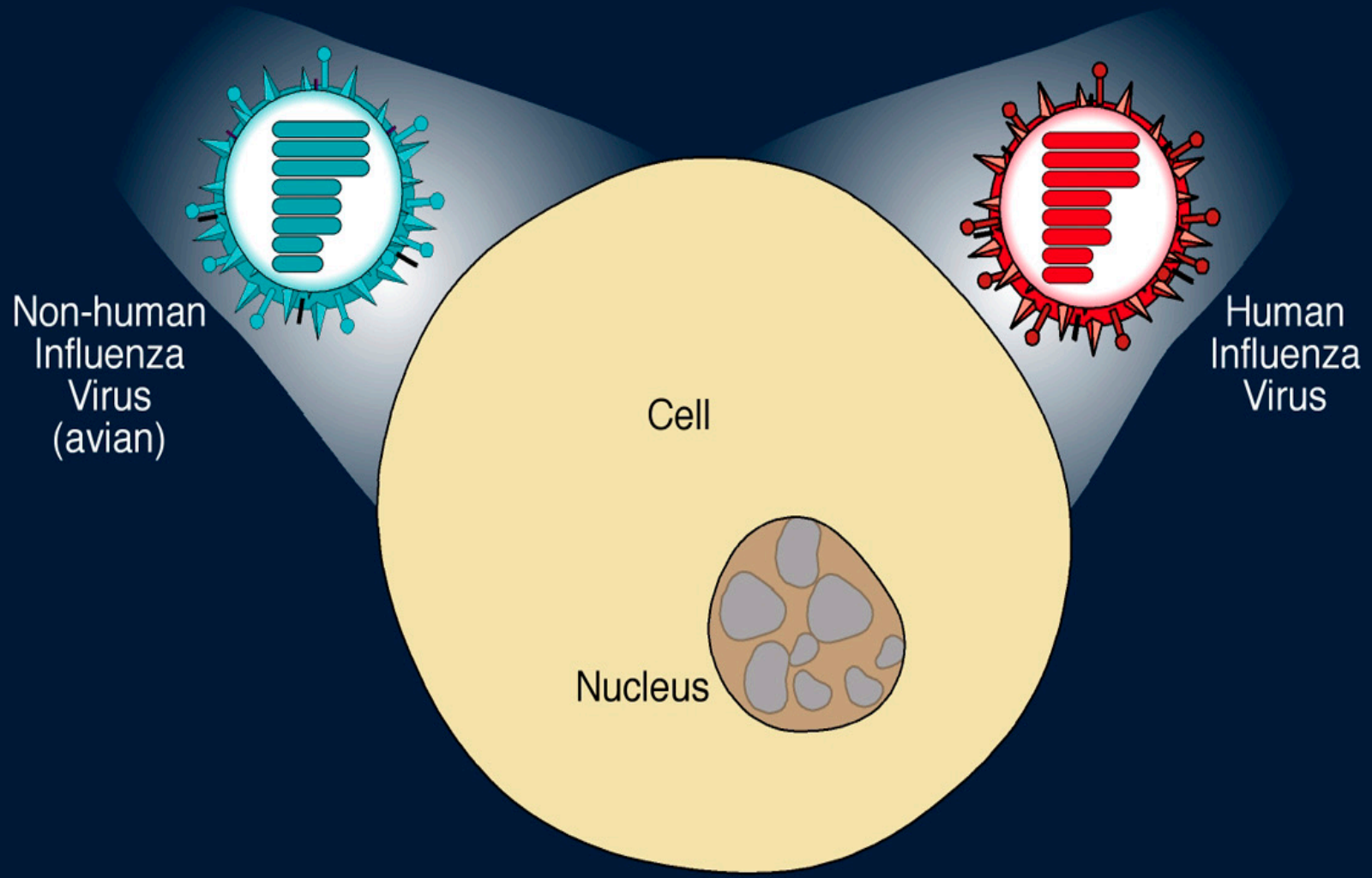
- Emergence from an animal source
- Genetic exchange: recombination (coronaviruses) vs reassortment (influenza)
- Airborne spread
- Genetic and antigenic drift
- Implications for vaccine strain composition

Changing viral ecology in animal and human populations

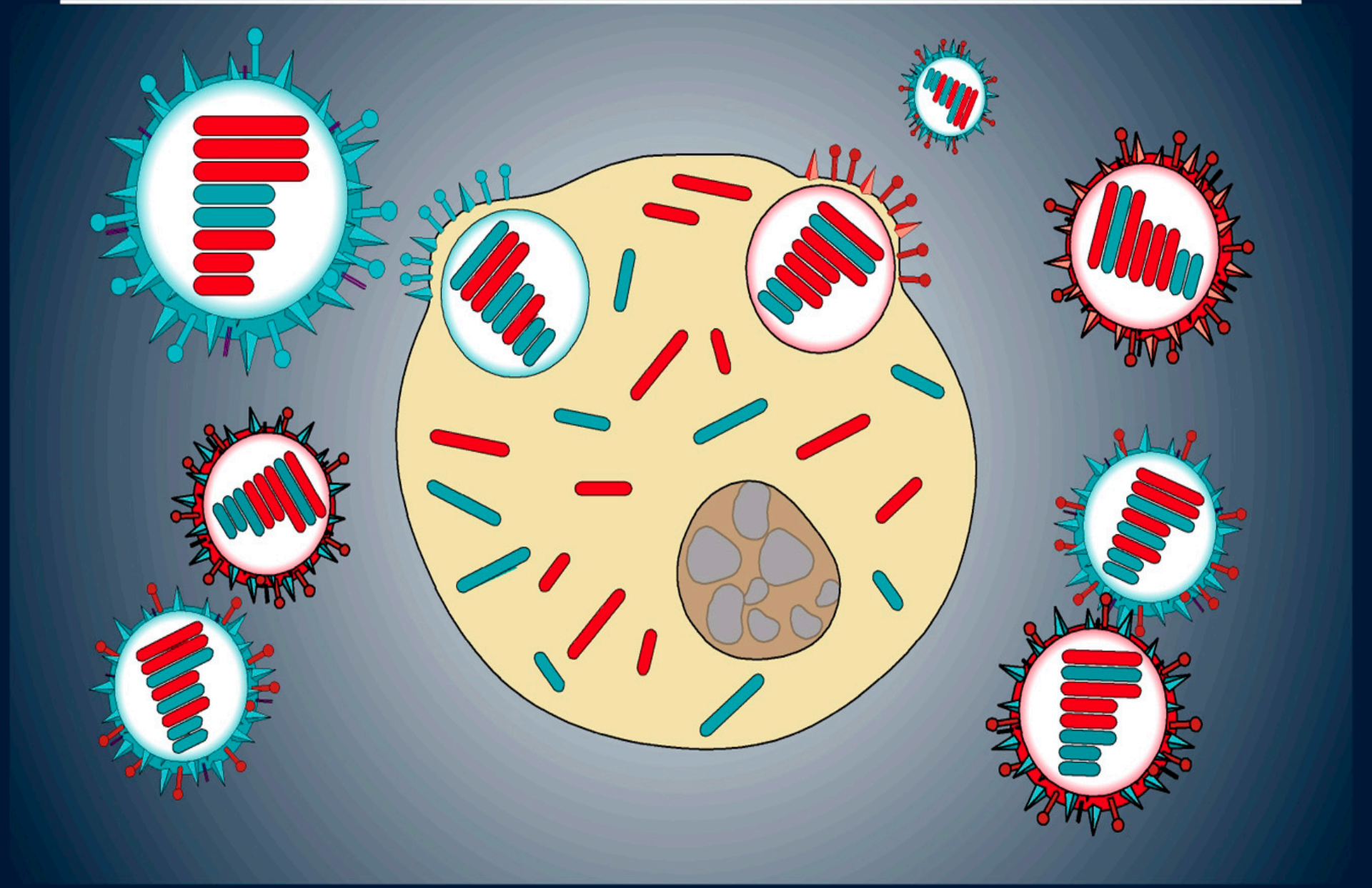


Graham Nat Rev Microbiol 2013

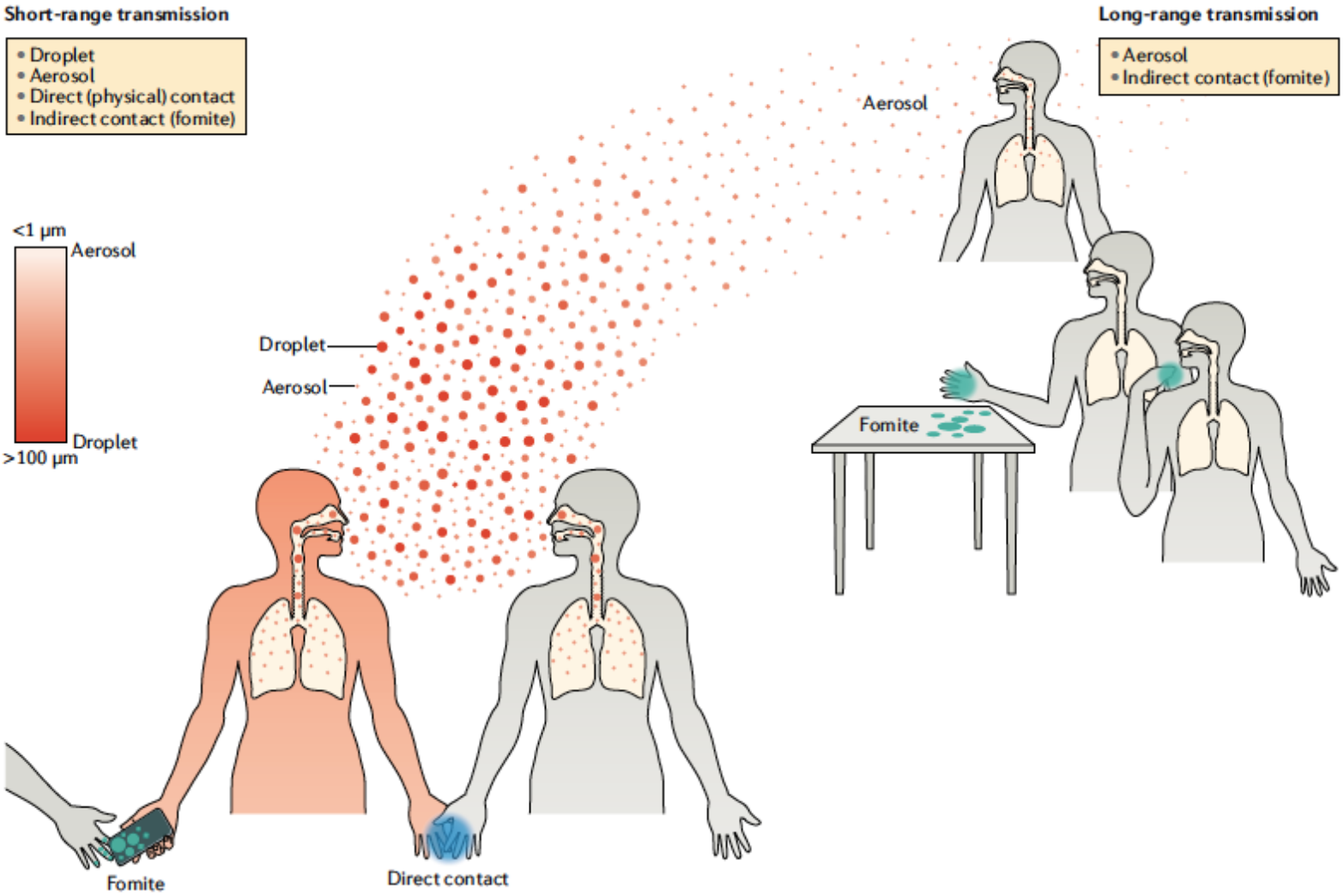
Generation of New Pandemic Virus by Gene Exchange: Antigenic Shift



Replication Followed by Reassortment



Major modes of transmission of respiratory viruses



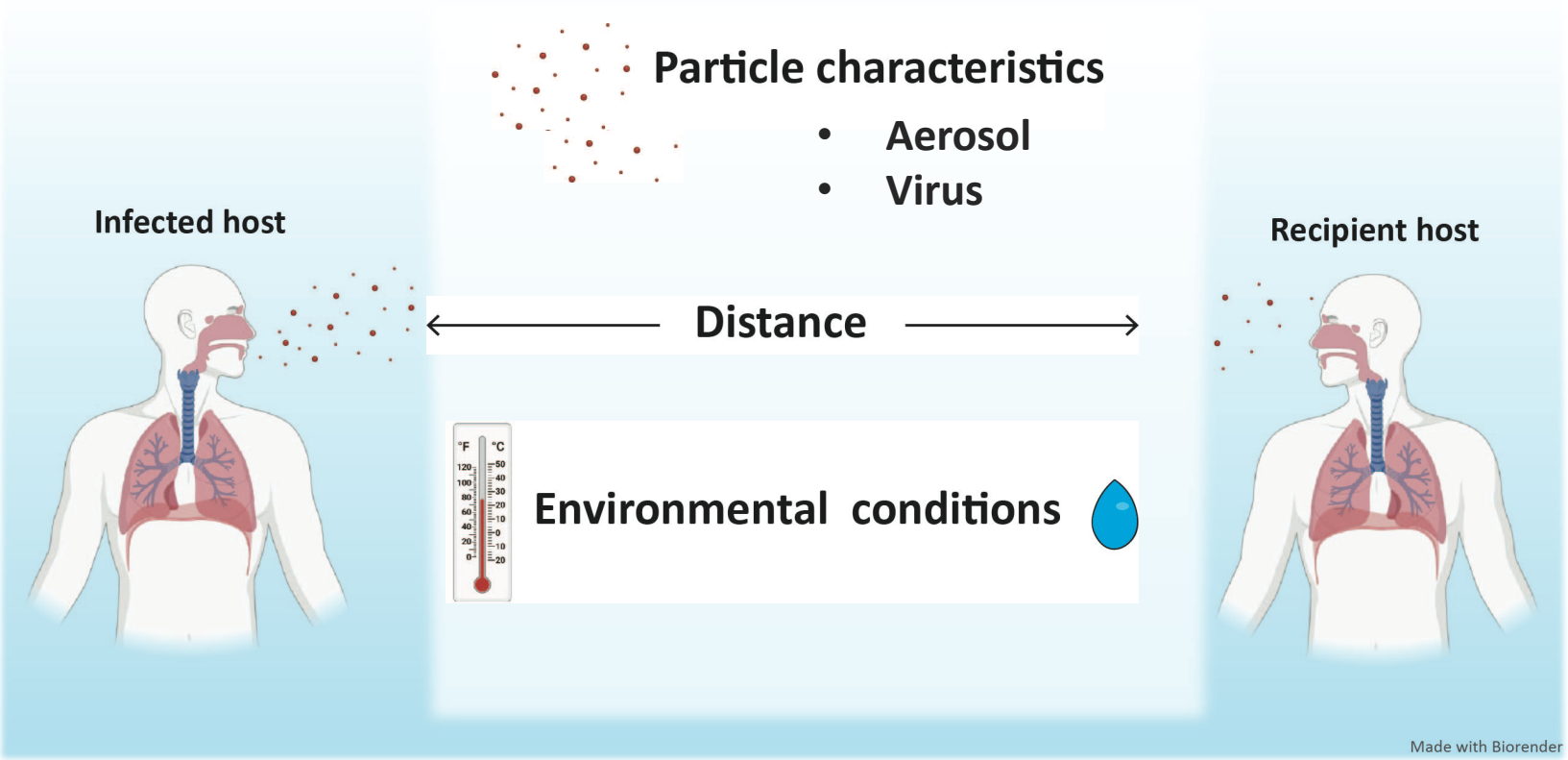
Leung *Nat Rev Microbiol* 2021

Updating traditional definitions

Terms	Traditional thinking	Updated descriptions informed by aerosol science		
		Description & typical size	Behaviour in Air	Exposure pathways
Aerosol	Particle<5µm	• Stable suspension of solid and/or liquid particles • <100 µm	• Can remain airborne for extended periods • Conc. highest near source and decreases with distance • Can travel >2 m (6ft) and build up in a room	Inhaled into respiratory tract
Droplet	Particle>5µm	• Liquid particle • >100µm	• Settles quickly to ground or surface • Travels <2m except when propelled eg cough/sneeze	Eyes, nose or mouth at close range

Adapted from US National Academies Workshop 2020

Factors affecting airborne transmission



Key points from SARS-CoV-2 research

- Droplet transmission dominates within 0.2 m with talking and 0.5 m with coughing
- Viruses are enriched in aerosols but there is great interpersonal variability
- Aerosols are the main mode of long range transmission but can also occur at a short range
- Only aerosols (not droplets and fomites) are affected by ventilation
- Transmission is favoured at low humidity
- Superspreading events

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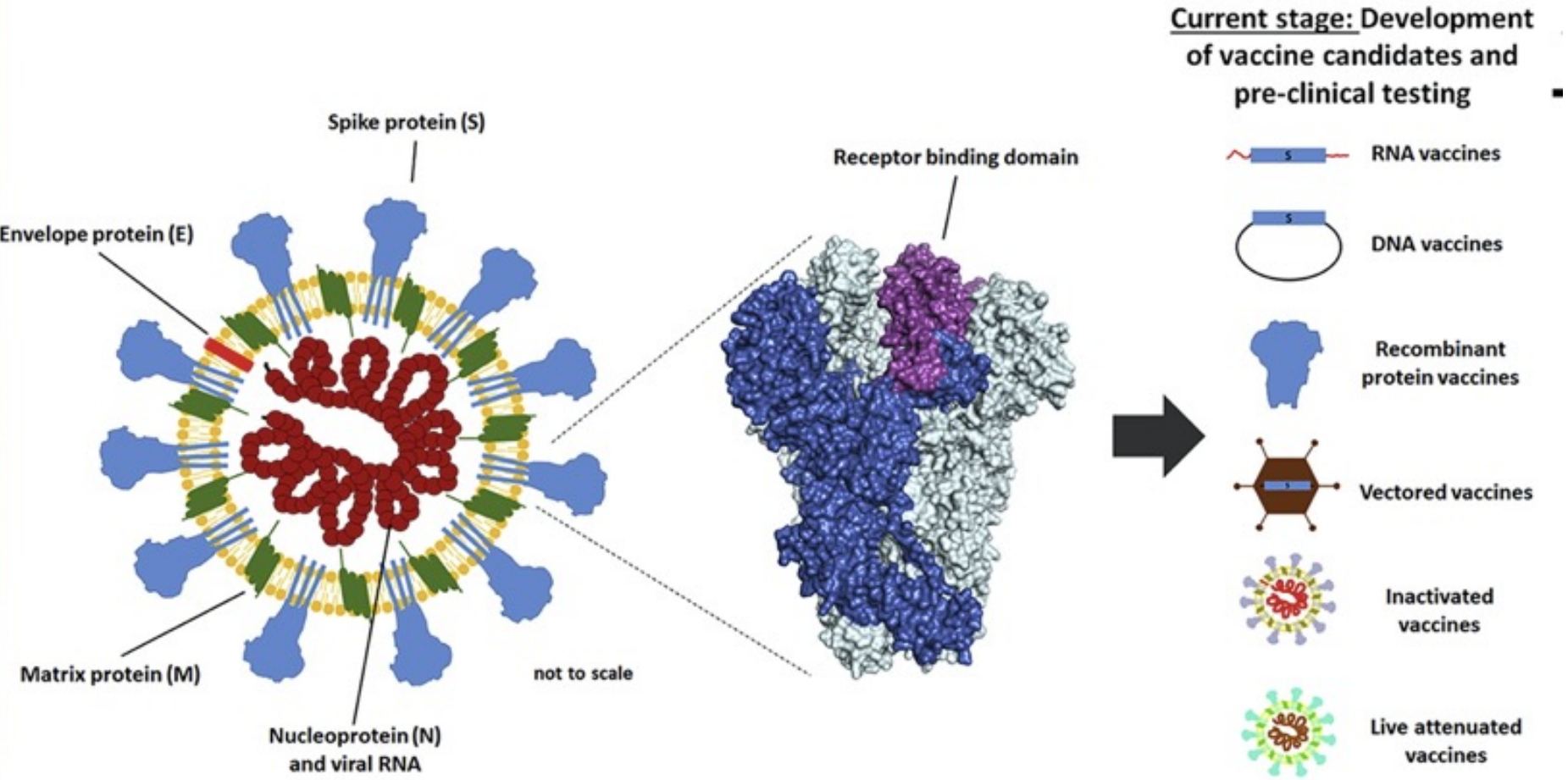
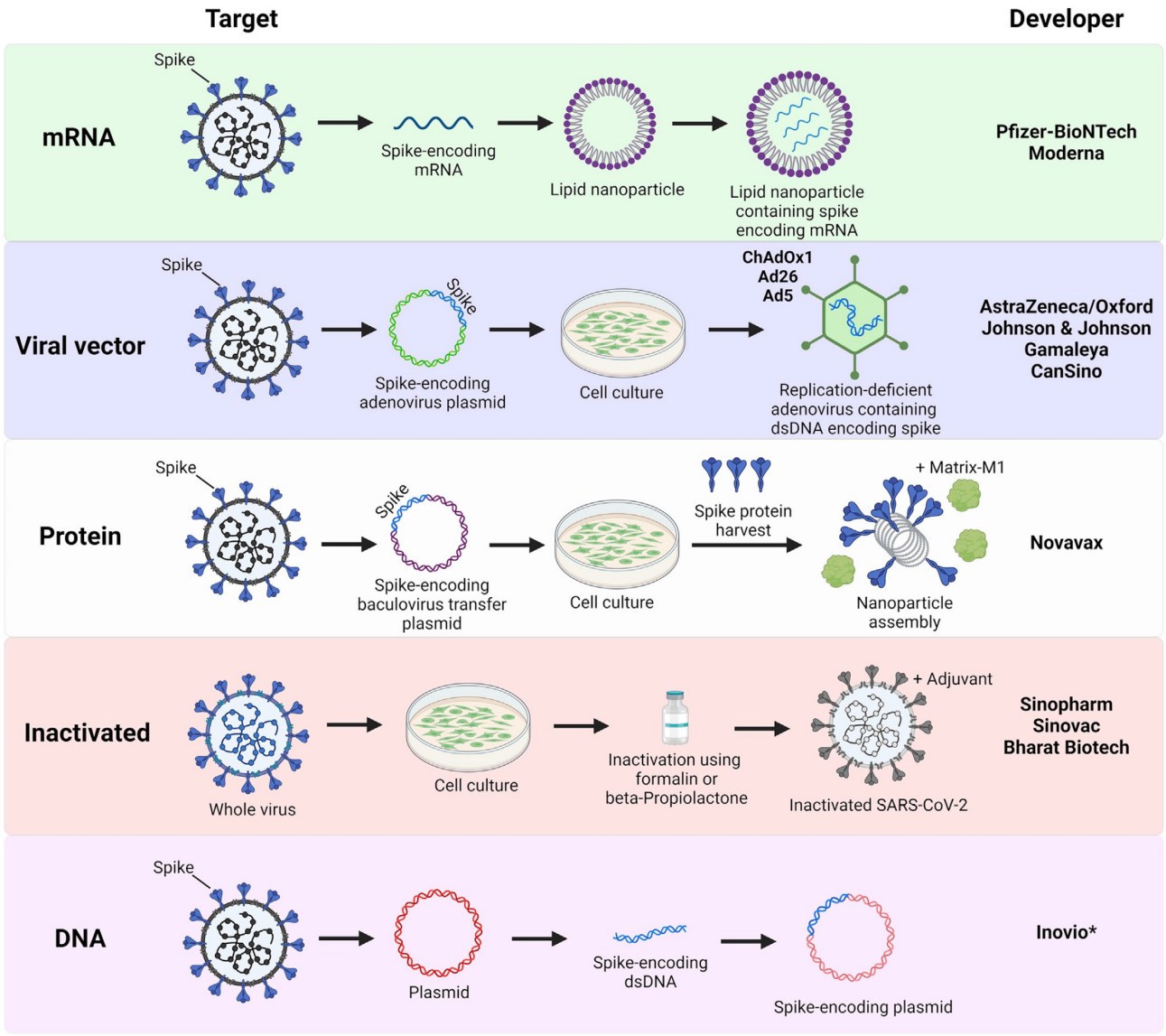
Airborne transmission of influenza and other respiratory viruses should be re-assessed

SARS-CoV-2 Vaccine Strategies



Amanat and Krammer Immunity 2020

COVID-19 vaccine platforms



Subbarao *Cell Host & Microbe* 2021; figure made by Matthew Gartner

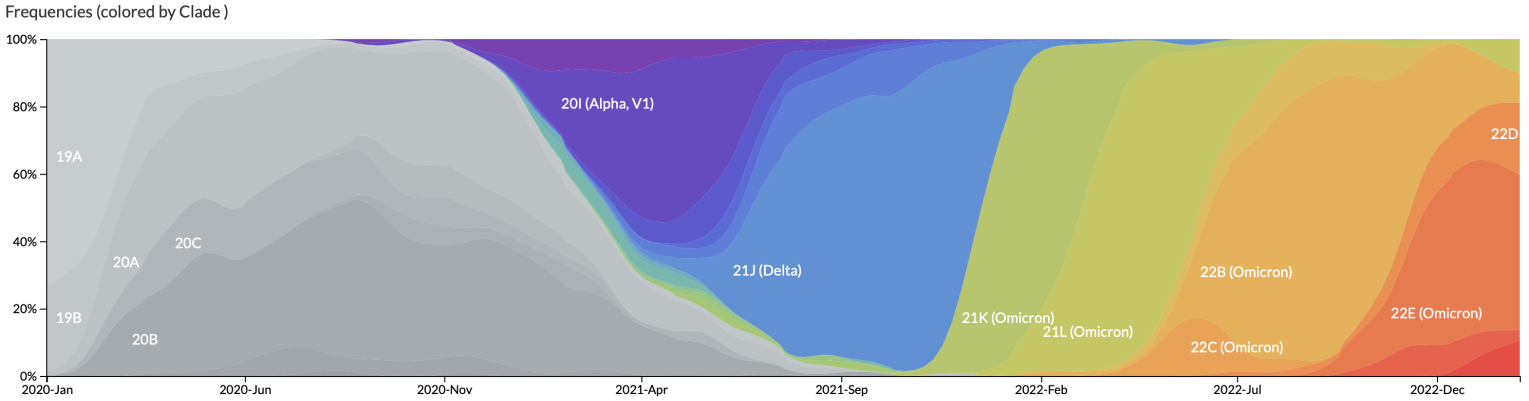
Variants of concern

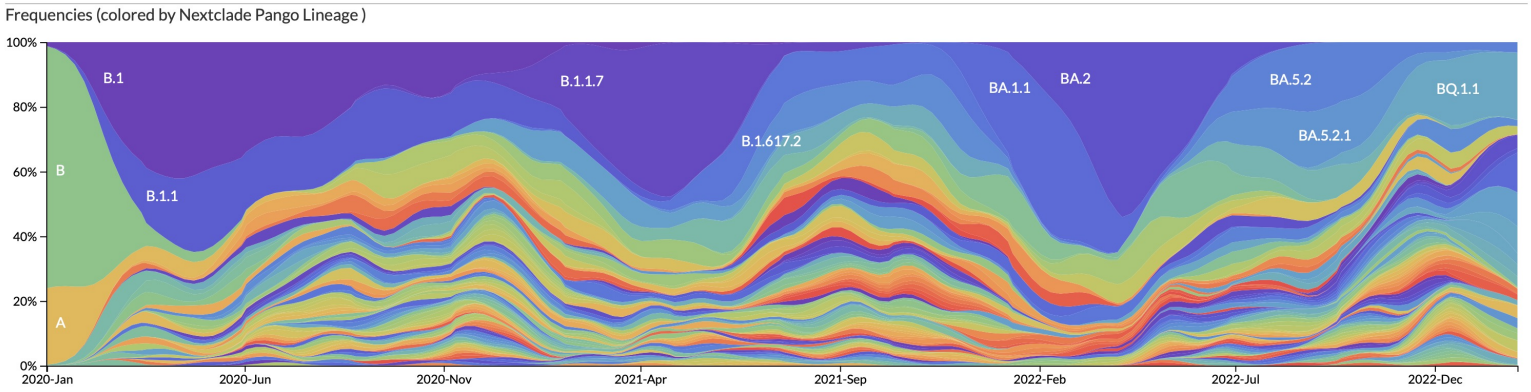
				
May 2020 UK	**August 2020** South Africa	**November 2020** Brazil	**October 2020** India	**November 2021** Multiple countries
Spreads more easily	Spreads more easily and some vaccines may be less effective against it	Spreads more easily and some vaccines may be less effective against it	Spreads more easily Symptoms may present differently May reduce vaccine efficacy Still protects against severe disease	Early studies show that it spreads more easily

Source: www.who.int/en/activities/tracking-SARS-CoV-2-variants/

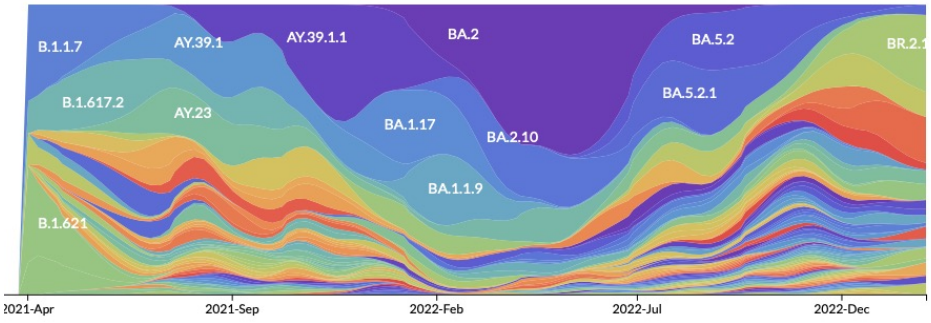
wellcome

Emergence and dominance of SARS-CoV-2 variants globally

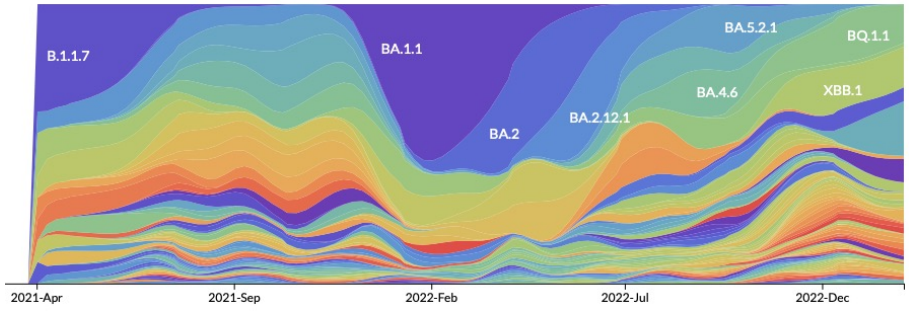




Oceania

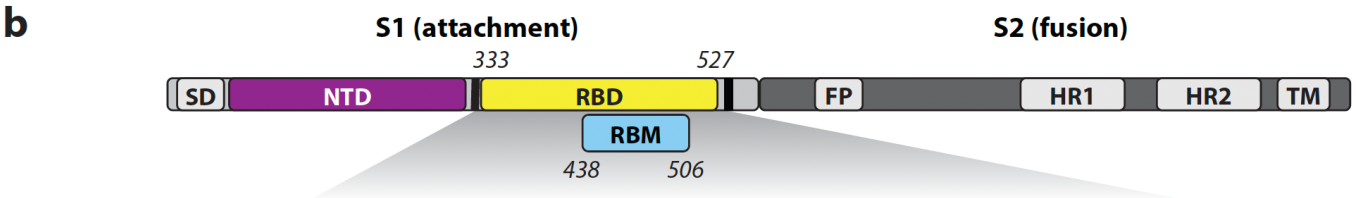


North America



https://nextstrain.org/ncov/gisaid/global

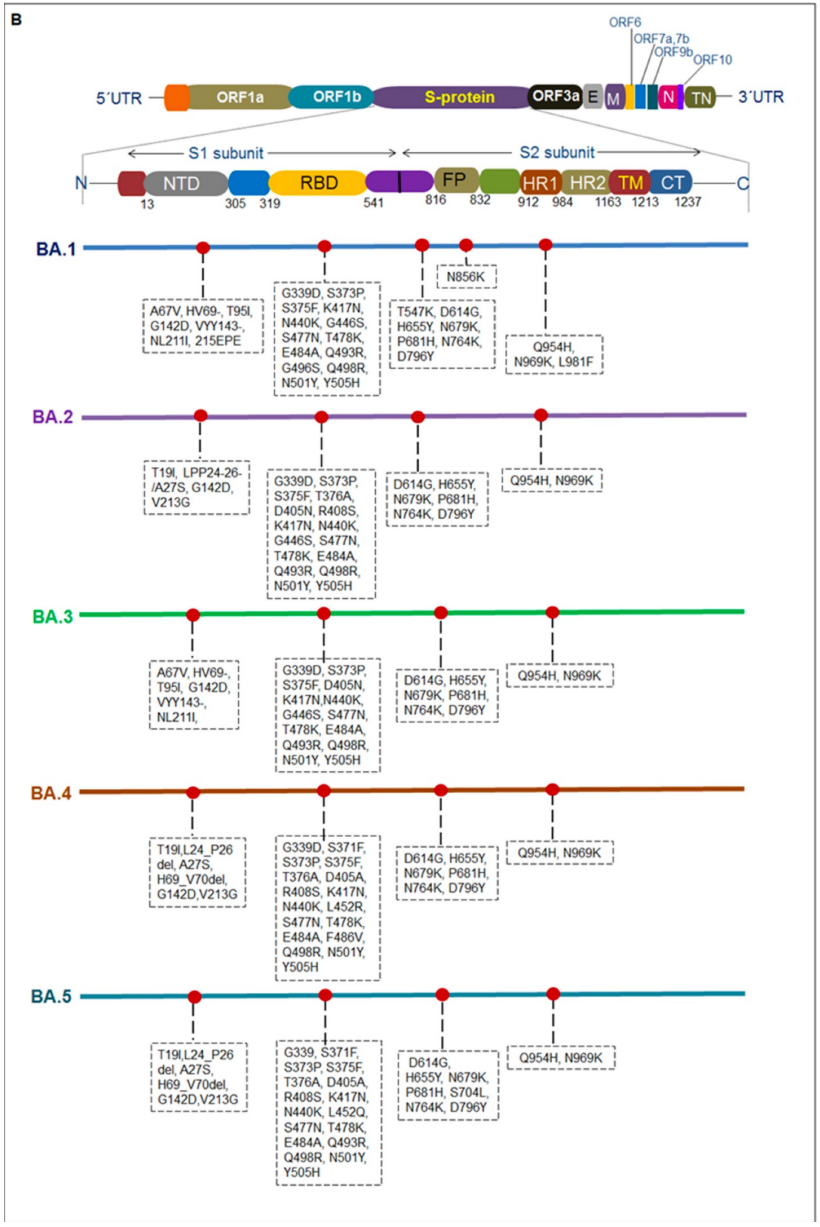
Key S glycoprotein mutations in VOCs



	RBD																	
Alpha																	N501Y	
Beta								K417N						E484K			N501Y	
Gamma								K417N						E484K			N501Y	
Delta											L452R		T478K					
Omicron BA.1	G339D	S371L	S373P	S375F				K417N	N440K	G446S		S477N	T478K	E484A	Q493R	Q496S	Q498R	N501Y	Y505H
Omicron BA.2	G339D	S371F	S373P	S375F	T376A	D405N	R408S	K417N	N440K			S477N	T478K	E484A	Q493R		Q498R	N501Y	Y505H

Jacobs et al. *Ann Rev Med* 2023; 74: 31-53

S glycoprotein mutations in Omicron subvariants



Chatterjee et al. *Viruses* 2023; 15: 167

WHO COVID-19 advisory group landscape

Aim: Monitor & assess SARS-CoV-2 variants and evaluate their impact on countermeasures, including vaccines, therapeutics, diagnostics or effectiveness of public health and social measures.

TAG-VE

- Determines which variants warrant further investigations
- Assesses whether variants alter
  - transmission or disease characteristics or
  - impact vaccines, therapeutics, diagnostics or
  - effectiveness of public health and social measures

R&D Blueprint for epidemics

- COVID-19 Vaccines Research Expert Group

TAG-CO-VAC

- Assesses the impact of Variants of Concern on current COVID-19 vaccines
- Determines whether changes to vaccine composition are needed

SAGE

- Advises on vaccine use and implementation

TAG-CO-VAC

An advisory body to WHO

- make recommendations to WHO on the methods to assess the impact of VOCs on vaccines
- provide interpretation of available evidence on the effect of VOCs on vaccines, including but not limited to vaccine effectiveness
- recommend to WHO, for each COVID-19 vaccine platform, adaptations (if any) needed so that vaccines continue to safely provide WHO-recommended levels of protection against VOCs.

https://www.who.int/groups/technical-advisory-group-on-covid-19-vaccine-composition-(tag-co-vac)

Chair

Professor Kanta Subbarao

Director of the WHO Collaborating Centre for Reference and Research on Influenza and Professor, Department of Microbiology and Immunology

Learn more >

Vice-Chair

Dr David Wentworth

Chief of the Virology, Surveillance, and Diagnosis Branch (VSDB) of the Influenza Division at the U.S. Centers for Disease Control and Prevention (CDC)

Learn more >

Dr Supamit Chunsuttiwat >
Advisor, Department of Disease Control, Ministry of Public Health THAILAND

Professor Cheryl Cohen >
Professor in epidemiology at the University of the Witwatersrand and Head of the Centre for Respiratory Disease and Meningitis at the National Institute for Communicable Diseases

Professor John Peter Figueroa >
Professor of Public Health, Epidemiology and HIV/AIDS at the University of the West Indies

Professor Thomas Fleming >
Professor, member of the Scientific Steering Committee for the WHO Solidarity COVID-19 Vaccines Trial.

Professor David Goldblatt >
Professor of Vaccinology and Immunology and Head of the Immunobiology Section at the Great Ormond Street Institute of Child Health

Dr Ziad Memish >
Senior Infectious Disease Consultant and Director, Research Centre, King Saud Medical City, Ministry of Health KINGDOM OF SAUDI ARABIA

Professor Priya Abraham >
Director of Indian Council of Medical Research

Professor Paul Fine >
Professor of Communicable Disease Epidemiology

Professor Elizabeth Miller >
Professor in Infectious Disease Epidemiology at the London School of Hygiene and a visiting professor at the Sackler School of Public Health at Tel Aviv University

Professor Samba Sow >
Professor of Medicine, Directeur général, Centre pour la mise au point de vaccins du Mali, Centre National d'Appui à la Lutte contre la Maladie, Djicoroni para Bamako, Mali

Dr Oyewale Tomori >
Member of the Global Virome Project Leadership Board

Dr Youchun Wang >
Chief scientist at the National Institute for Food and Drug Control (NIFDC) of China

Professor Raina MacIntyre >
Head of Biosecurity Research Program in Kirby Institute

Dr Sergio Nishioka >
Technical Adviser for Capacity Building and Clinical Evaluation of COVID-19 vaccines

Dr Amadou Alpha Sall >
Director of Institut Pasteur de Dakar and WHO Collaborating Center for Arboviruses and Viral Hemorrhagic Fevers, Senegal

Dr Hideki Hasegawa >
Director of the WHO Collaborating Centre for Reference and Research on Influenza, Japan

Vaccine updates for SARS-CoV-2?

- Questions:
  - Is an update in the composition of SARS-CoV-2 vaccines needed?
  - What is the threshold for doing so?

- Potential approaches
  - Build on a model of a vaccine that is updated regularly: Influenza
  - Develop a new approach de novo
  - Other models?

- Mechanism
  - New WHO technical advisory group: TAG-CO-VAC
  - Interface with WHO technical advisory group on Virus Evolution
  - Regulators
  - Developers

Data considered for influenza vaccine strain composition updates

- Virologic and disease surveillance data
- Genetic characterisation
- Antigenic characterisation including antigenic cartography
- Human serology: post vaccination sera from different age groups and geographic locations
- Predictive modeling
- Vaccine effectiveness data

Overview of TAG-CO-VAC evidence base

Since the designation of Omicron as a SARS-CoV-2 Variant of Concern in November 2021, the TAG-CO-VAC has reviewed published and unpublished data on the antigenicity and cross-protection of Omicron specific responses following vaccination or infection with prior VOCs, as well as following Omicron infection and/or Omicron-specific vaccine candidates.

The data highlighted in the following slides are not exhaustive, but were specifically reviewed and considered to inform the interim statement on COVID-19 vaccine composition.

Overview of evidence base

1. SARS-CoV-2 evolution and spread
2. Vaccine effectiveness against Omicron
3. Cross-neutralization and cross-protection data following infection with index virus or prior VOC or vaccination
4. Antigenic cartography
5. Preliminary data on Omicron infection
6. Preliminary data on candidate vaccines with updated composition

World Health Organization

TAG-CO-VAC evidence base summary

- To date, **Omicron is the most antigenically distinct** SARS-CoV-2 VOC to have emerged, with BA.1 appearing to be the most distant from the index virus.
- Antibody responses **in previously naïve (unprimed) individuals exposed to Omicron are strong, but not broad** (i.e. fairly high Omicron-specific neutralizing antibody titres are elicited, with limited neutralizing activity against other VOCs or the index virus), indicating that a stand-alone Omicron-specific vaccine product will not suit the objectives of an update to COVID-19 vaccine composition.
- In contrast, in individuals who have been previously primed by SARS-CoV-2 infection or COVID-19 vaccination, **a broad immune response is elicited following Omicron infection**.

- **These data support a preference for the inclusion of Omicron in an updated vaccine composition, administered as a booster dose.**

World Health Organization

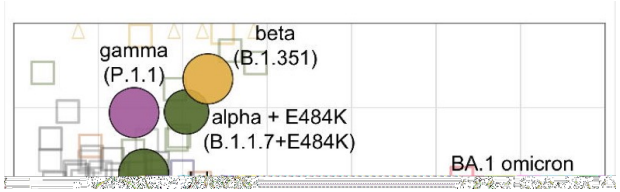
TAG-CO-VAC Statement – 17 June 2022

Summary of interim statement

- The continued use of **currently licensed vaccines** based on the index virus **confers high levels of protection against severe disease outcomes** for all variants, including Omicron with a booster dose, and is therefore appropriate to **achieve the primary goals of COVID-19 vaccination.**

- Given the uncertainties in the trajectory of SARS-CoV-2 evolution and the characteristics of future variants, it may be prudent to pursue an additional objective of COVID-19 vaccination of **achieving broader immunity** against circulating and emerging variants while **retaining protection against severe disease and death.**

- Available data indicate that the inclusion of **Omicron**, as the most antigenically distinct SARS-CoV-2 VOC, as part of an updated vaccine composition may be beneficial if administered as a booster dose to those who have already received a COVID-19 vaccination primary series.



Antigenic map of SARS-CoV-2 variants constructed from single exposure convalescent and double vaccinated sera.

Full statement available at: https://www.who.int/news/item/17-06-2022-interim-statement-on--the-composition-of-current-COVID-19-vaccines

World Health Organization

Further considerations in TAG-CO-VAC proposal

TAG-CO-VAC **does not advise the use of an Omicron-specific monovalent vaccine product as a standalone formulation for the primary series** because it is not yet known whether Omicron-specific vaccines will offer cross-reactive immunity and cross-protection from severe illness caused by other VOCs in naïve individuals as the index vaccines have done.

For the Omicron-specific vaccine product, the TAG-CO-VAC recognises **that viruses or viral genetic sequences very closely related to BA.1** are some of the most antigenically distant from the index virus to date and are likely to enhance the magnitude and breadth of the antibody response.

While the TAG-CO-VAC recommends an Omicron-containing vaccine product, this does not preclude the consideration of other variant-specific formulations and/or bi/multivalent products by regulatory authorities, and that data support the fulfillment of the additional objective of achieving breadth of cross-reactive immunity to previous, currently circulating and/or emerging variants .

Accompanying SAGE statement, available from: https://www.who.int/news/item/17-06-2022-interim-statement-on-decision-making-considerations-for-the-use-of-variant-updated-covid-19-vaccines

World Health Organization

What was done in 2022 and what does the future hold?

- mRNA vaccines were updated
  - Bivalent Ancestral + BA.1 vaccines were used in the UK, Europe and Australia
  - Bivalent Ancestral + BA.5 vaccines were used in the US and are now licensed in Europe as well
- TAG-CO-VAC will review data on the impact of Omicron containing vaccine boosters on breadth of immunity and vaccine effectiveness
- TAG-CO-VAC is discussing the timing and frequency of strain composition meetings
- The US FDA proposes an annual fall/winter revaccination campaign with strain selection in May/June