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Immunological Consequences of the COVID-19 Pandemic

Kingston Mills

Professor of Experimental Immunology

Academic Director Trinity Biomedical Sciences Institute

Lead PI on COVID-19 Research Hub at TCD

31/01/2025

Global Impact of COVID-19 pandemic (WHO data)

777,310,393

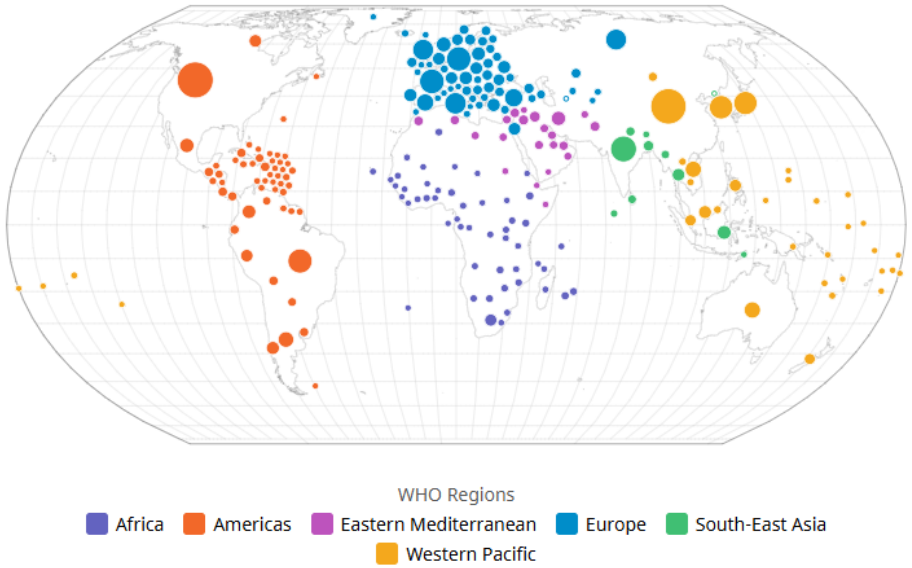
Reported COVID-19 cases

World, 7 days to 5 January 2025

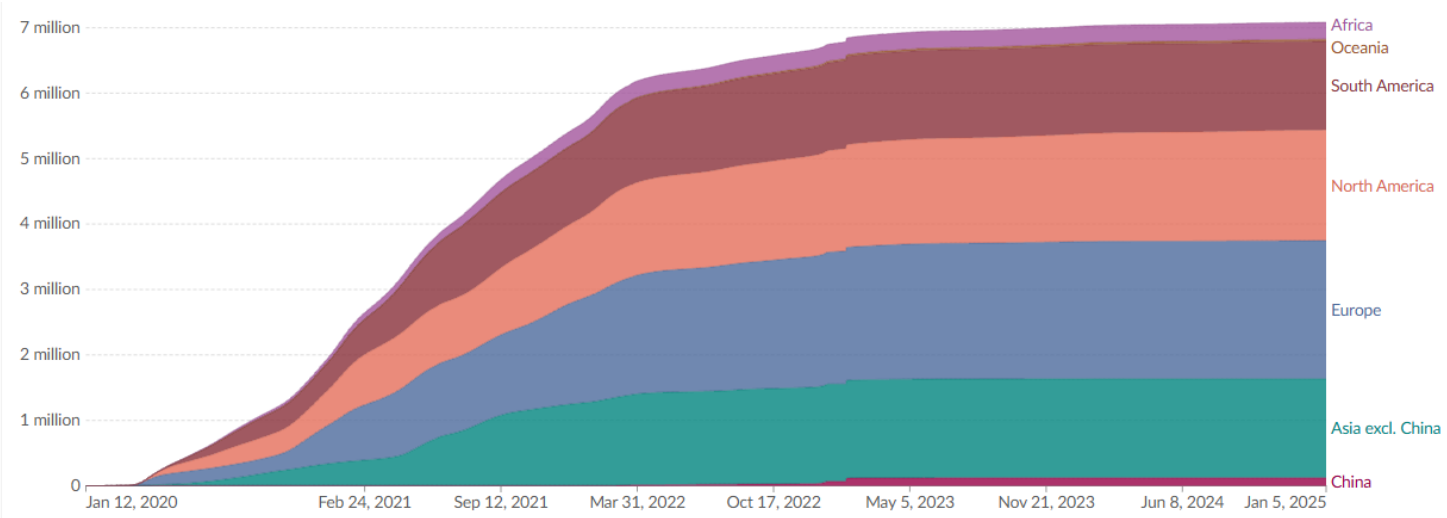
7,083,246

Reported COVID-19 deaths

World, 7 days to 5 January 2025



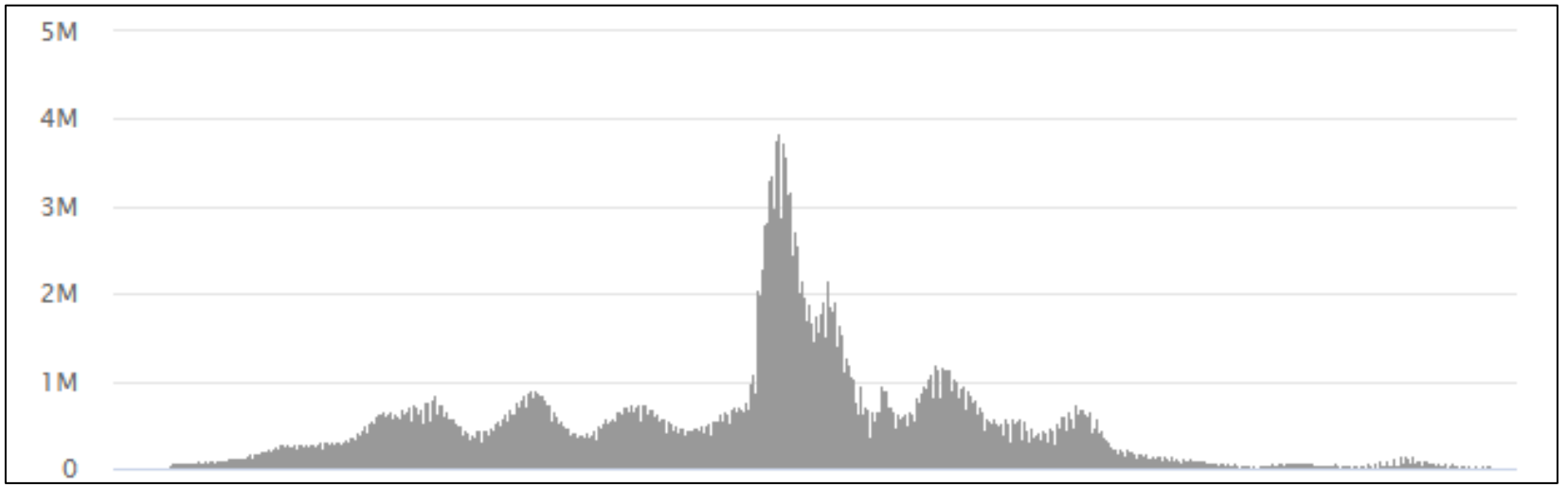
Cumulative confirmed deaths from COVID-19



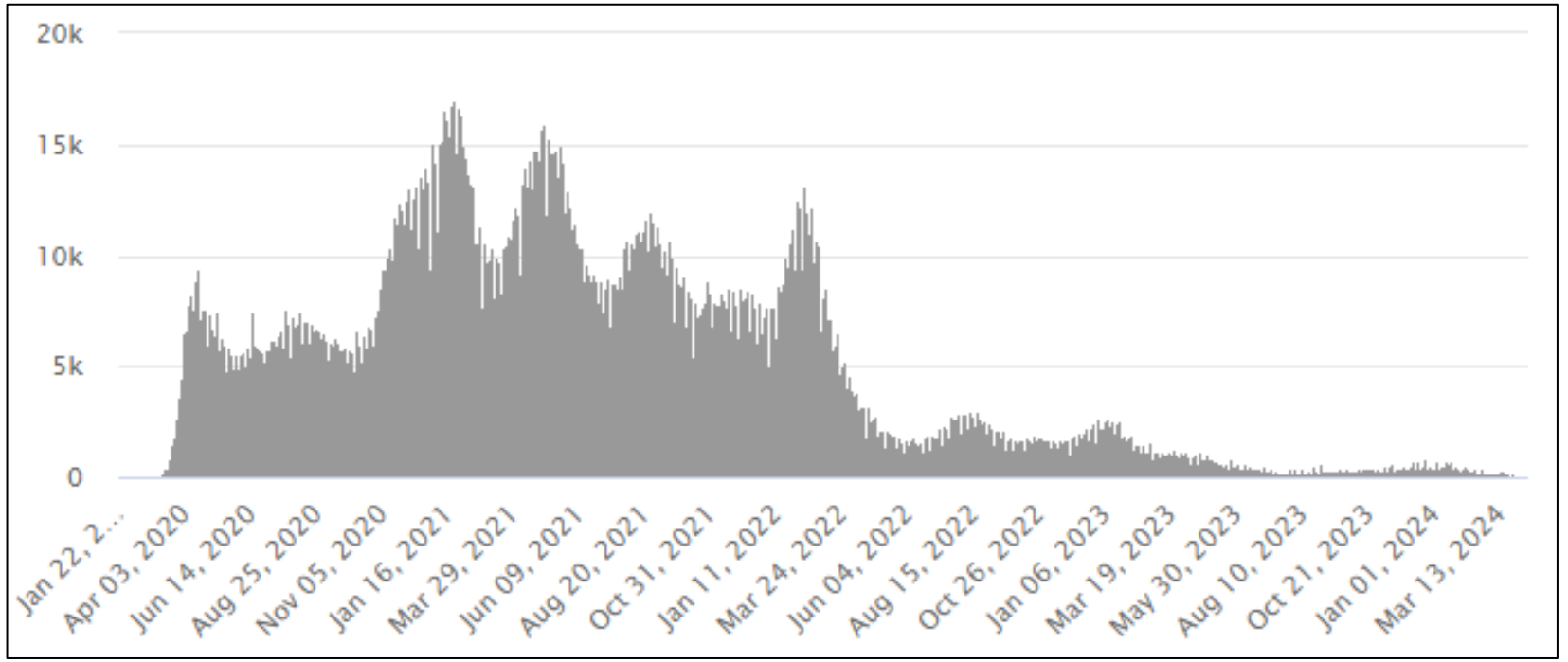
Changing dynamics of the COVID-19 pandemic (global)

impact of virus evolution, non-pharmaceutical interventions and vaccines

Daily New cases



Daily Deaths



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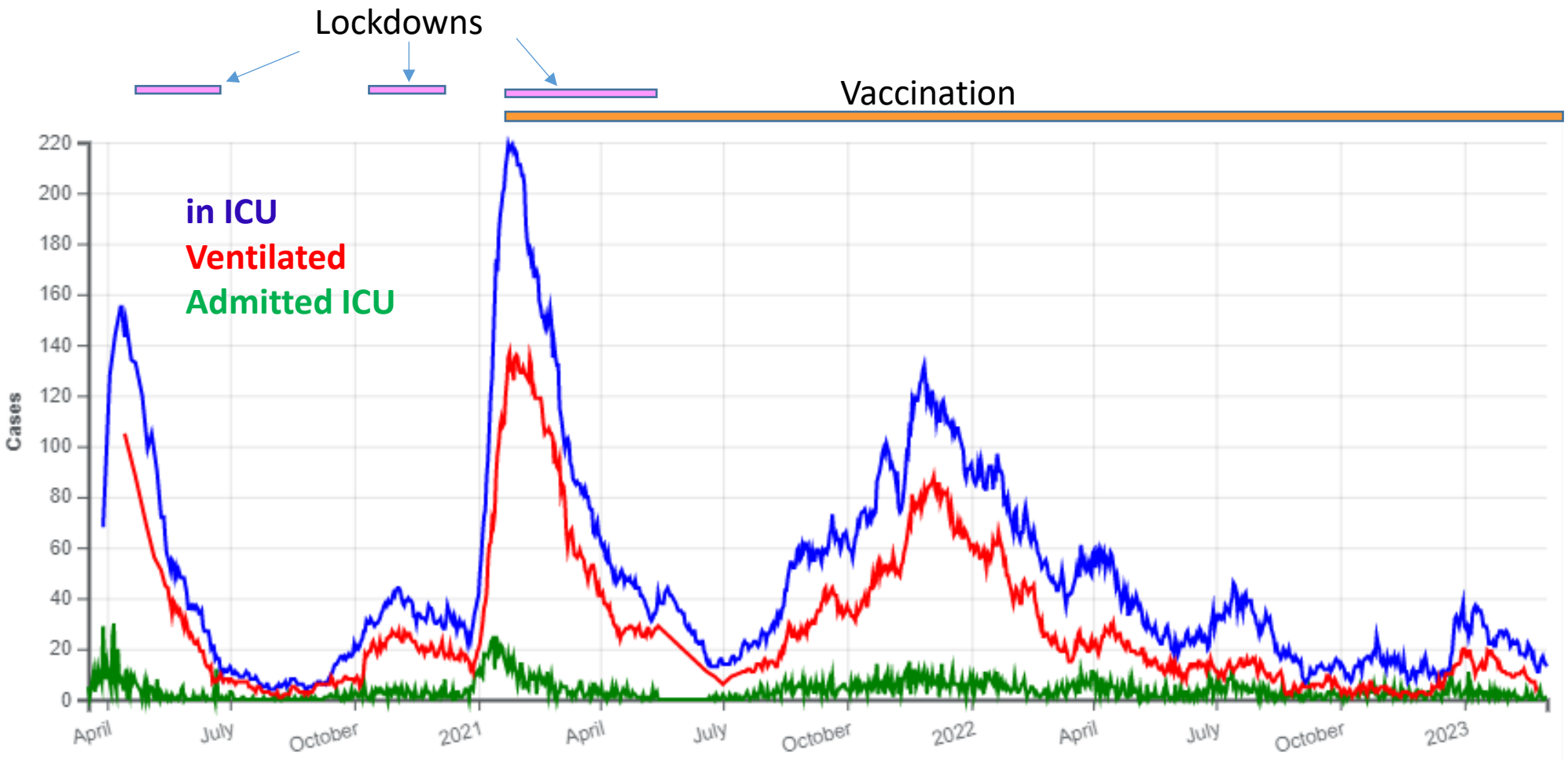
Ireland's response to COVID-19: Interventions to prevent severe COVID-19



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COVID-19 in Ireland (HSE/HPSC data)

Total cases

Age	Cases
0–4	72,443
5–14	199,753
15–24	262,202
25–34	291,714
35–44	319,346
45–54	244,622
55–64	160,400
65–74	85,504
75–84	50,608
85+	28,351

Hospitalized cases

Age	Number of cases
0–4	2,386
5–14	1,248
15–24	2,709
25–34	4,504
35–44	5,004
45–54	5,381
55–64	7,220
65–74	10,559
75–84	14,305
85+	9,620

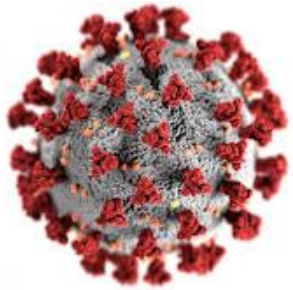
Deaths

Age	Deaths
0–24	17 (0.19%)
25–34	32 (0.35%)
35–44	93 (1.03%)
45–54	230 (2.55%)
55–64	566 (6.27%)
65–74	1,469 (16.26%)
75–84	2,946 (32.6%)
85+	3,678 (40.7%)

>1,750,000 cases >73,000 hospitalized 9,789 deaths (to 01/25)

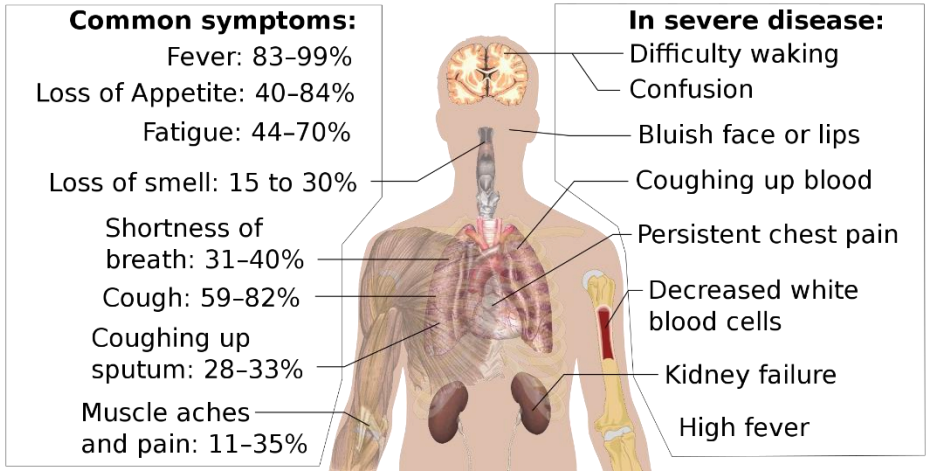
COVID-19 disease

Caused by infection with SARS-CoV-2



SARS-CoV-2 Infection

COVID-19 Disease (pre-omricon)



>50% infections are asymptomatic

Can transmit the virus to others - who may get COVID-19 disease

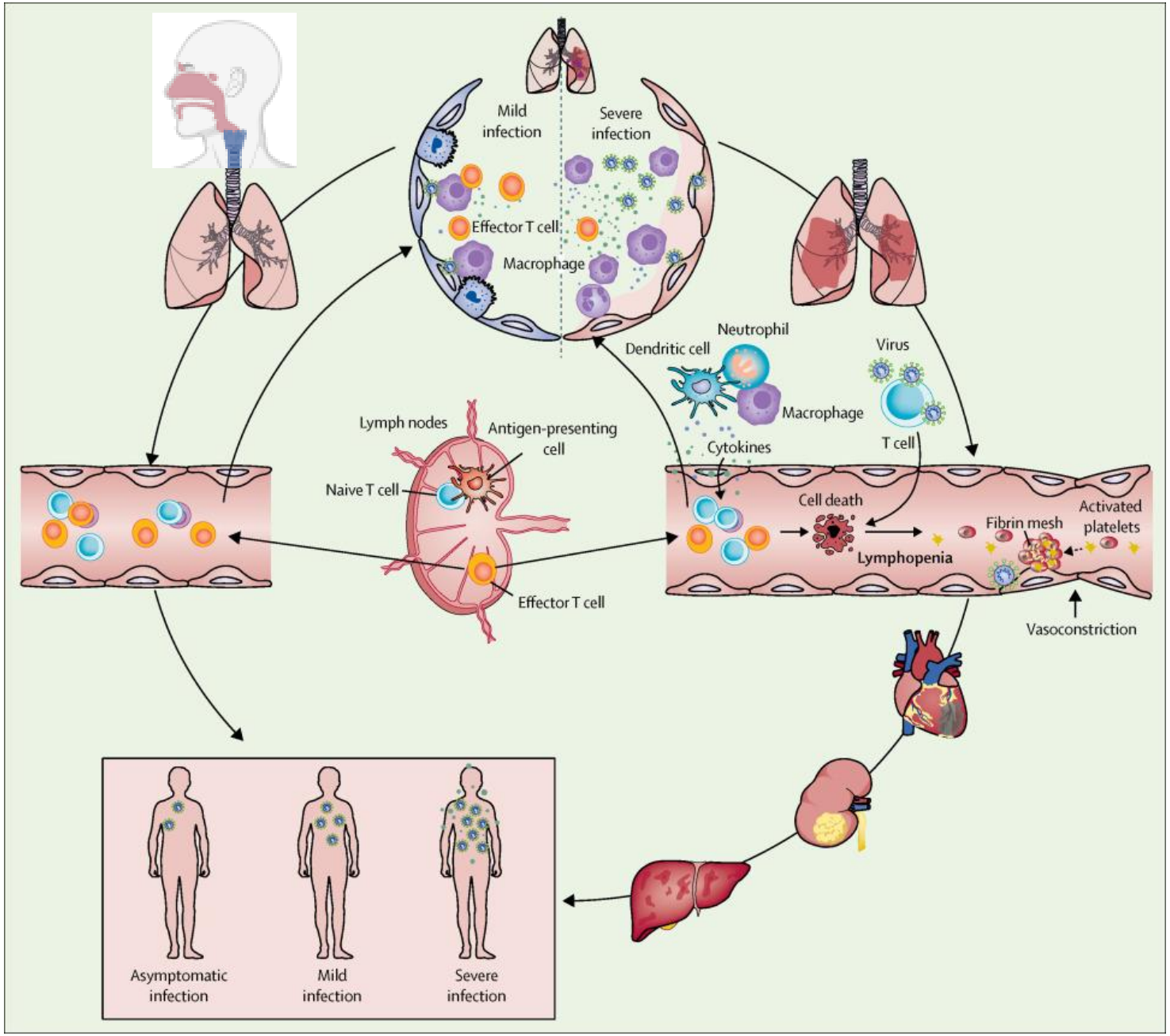
- **Early variants: 20% Hospitalized: 2% ICU, 0.5-1% deaths**
- **Omricon: 1% Hospitalized: <0.2% ICU, 0.06% deaths**
- **Risks factors: >70 yrs and underlying medical conditions**
  - **obesity, type 2 diabetes, cardiovascular disease**

Immune / inflammatory response to SARS-CoV2 infection

Mild/asymptomatic infection

Mainly upper respiratory tract Limited damage to lungs

Antibodies ↓ infection; Immune cells (NK and T cells) clear the infection



Severe infection

High virus load

Over-active immune responses

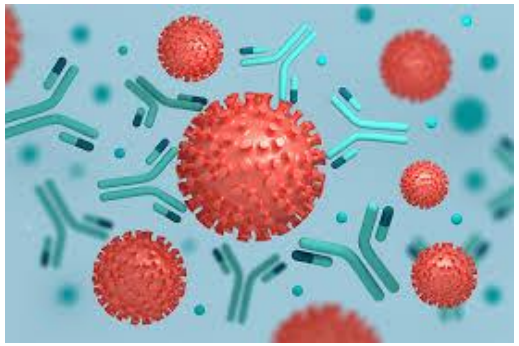
Lung and systemic inflammation and cytokine storms

Thrombosis & pulmonary embolisms

Organ damage

Neurological complications can occur, including: encephalopathy/ encephalitis, neurocognitive issues.

Immunology-based and other treatments for COVID-19



Monoclonal antibody therapy:

- Can prevents infection or reduce viral load early in infection
- Xevudy (Sotrovimab; GSK) REGEN-COV (Casirivimab + Imdevimab; Regeneron)
- Variants escape the effects of most of commercial antibodies

Anti-viral drugs:

- Pfizer's Paxlovid, Merck's Molnupiravir and Gilead's Remdesivir reduces viral load early in infection, less effective against advanced disease,
- Only for high-risk individuals, available in Ireland from April 2022

Anti-inflammatory drugs:

X Chloroquine, Anti-IL-6 (e.g. tocilizumab), IL-1 blockers (e.g. anakinra)

√ Dexamethasone, can reduce lethal inflammation

Anticoagulant/antithrombotic drugs

e.g. heparin, can prevent thromboembolic events

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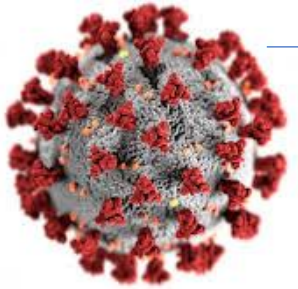
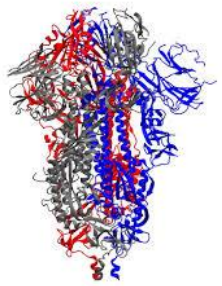
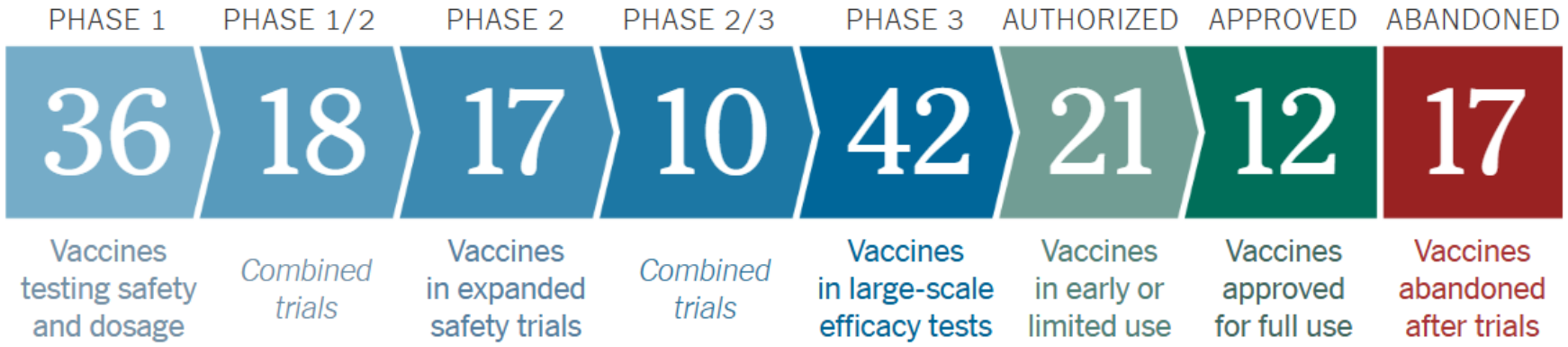
COVID-19 Vaccines

SARS-CoV-2   Spike (S) protein

- Helped to control COVID-19 pandemic
- Ideally should <u>prevent</u> SARS-CoV-2 infection and COVID-19 disease



New York Times Coronavirus Vaccine tracker, Aug 2022

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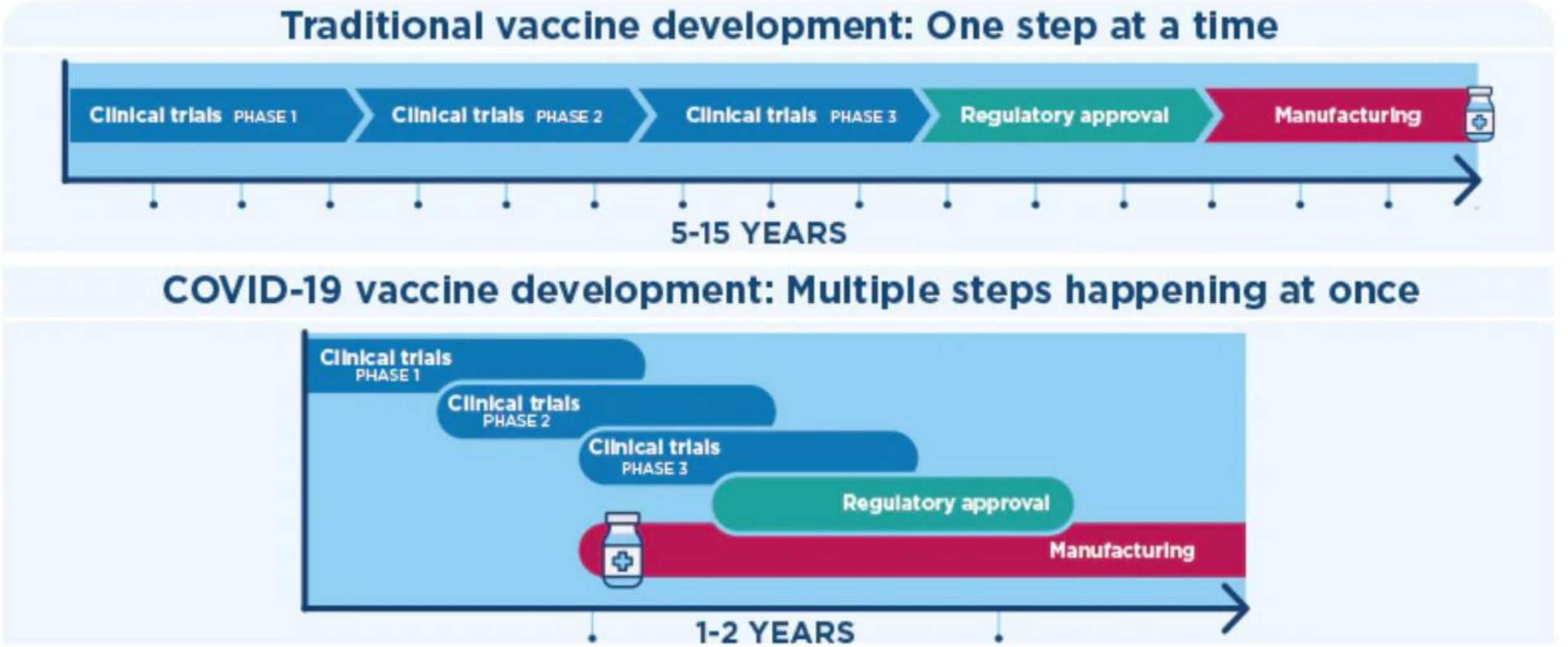
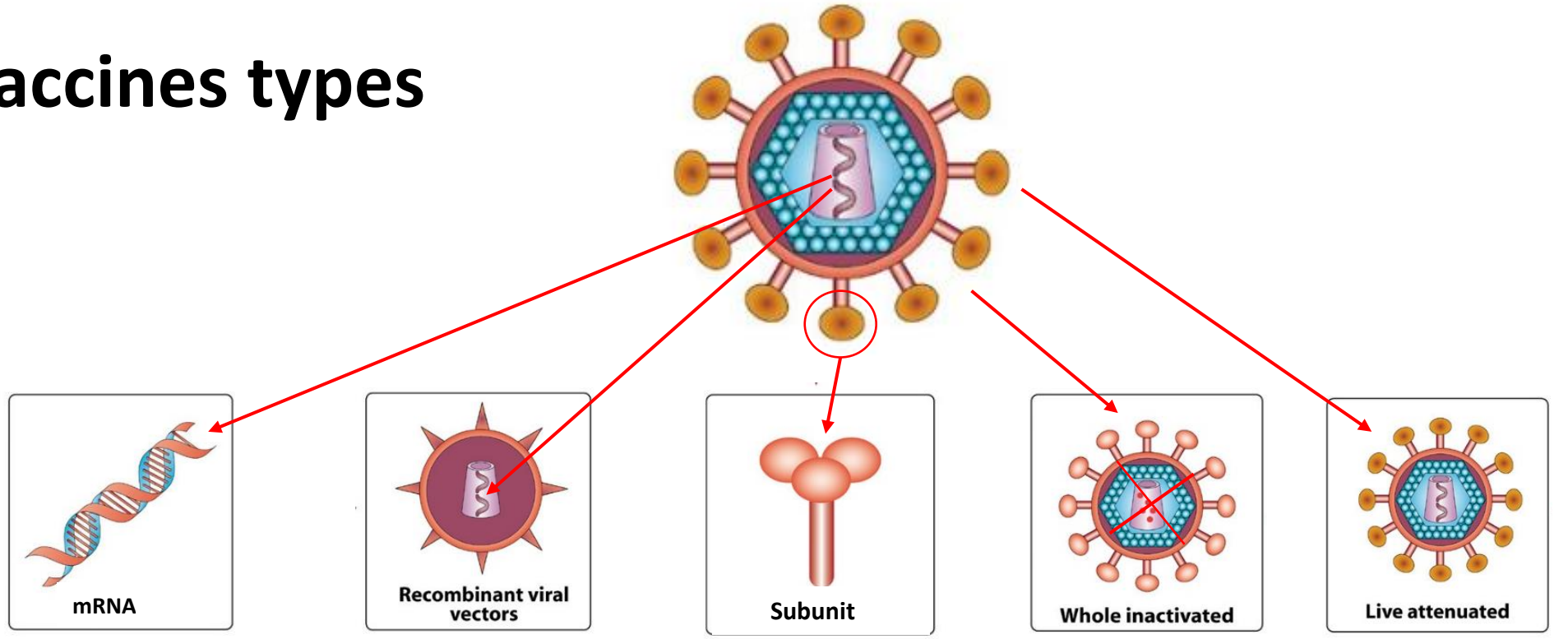
COVID-19 vaccines developed in 1/10 time of a typical vaccine



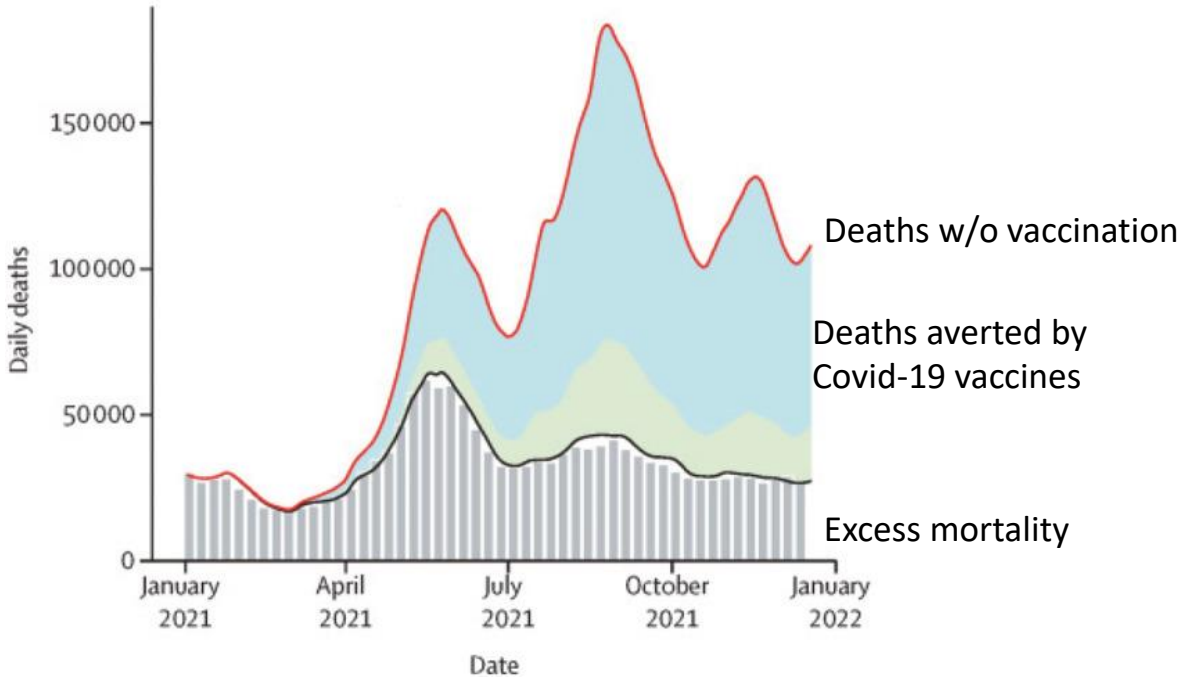
Vaccines types



Licensed Vaccines 2020:	**None (novel)**	**Ebola (limited)**	**DTaP, HepB, HiB Men-B, C, Pneumo HPV, Flu**	**Polio, Flu Rabies**	**MMR, Polio, TB, Flu, Rotavirus, Herpes**
COVID-19 vaccines	**Moderna** **BioNTech / Pfizer** CureVac, Germany Cadila, India (DNA) AnGes / Osaka Univ Arcturus / Duke Univ	**Oxford / Astra Zeneca** **Janssen/J&J** CanSino Bio, China Gamaleya Res Inst Russia	**Novavax, US** Sanofi/GSK Clover Bio, China Medicago, Canada Anhui Zhifei Longcom Vaxine, Australia CSL, Australia	Sinopharm/Wuhan Sinovac Biotech Sinopharm/Beijing Bharat, India Chinese Acad. Med Sci Valneva, France/UK	

Image adapted from Gorry et al *Retrovirology* **4**, 66 (2007)

COVID-19 vaccines prevented an estimated 14.4 million deaths from COVID-19 (19m including excess deaths) in first year of use.



J Paediatr Child Health. 2022 Sep 20 : 10.1111/jpc.16213.

Nobel Prize goes to scientists behind mRNA Covid vaccines

2 days ago

Nobel Prize

Professors Drew Weissman (left) and Katalin Kariko

By James Gallagher

Health and science correspondent

The Nobel Prize in Physiology or Medicine has been awarded to a pair of scientists who developed the technology that led to the mRNA Covid vaccines.

Professors Katalin Kariko and Drew Weissman will share the prize.

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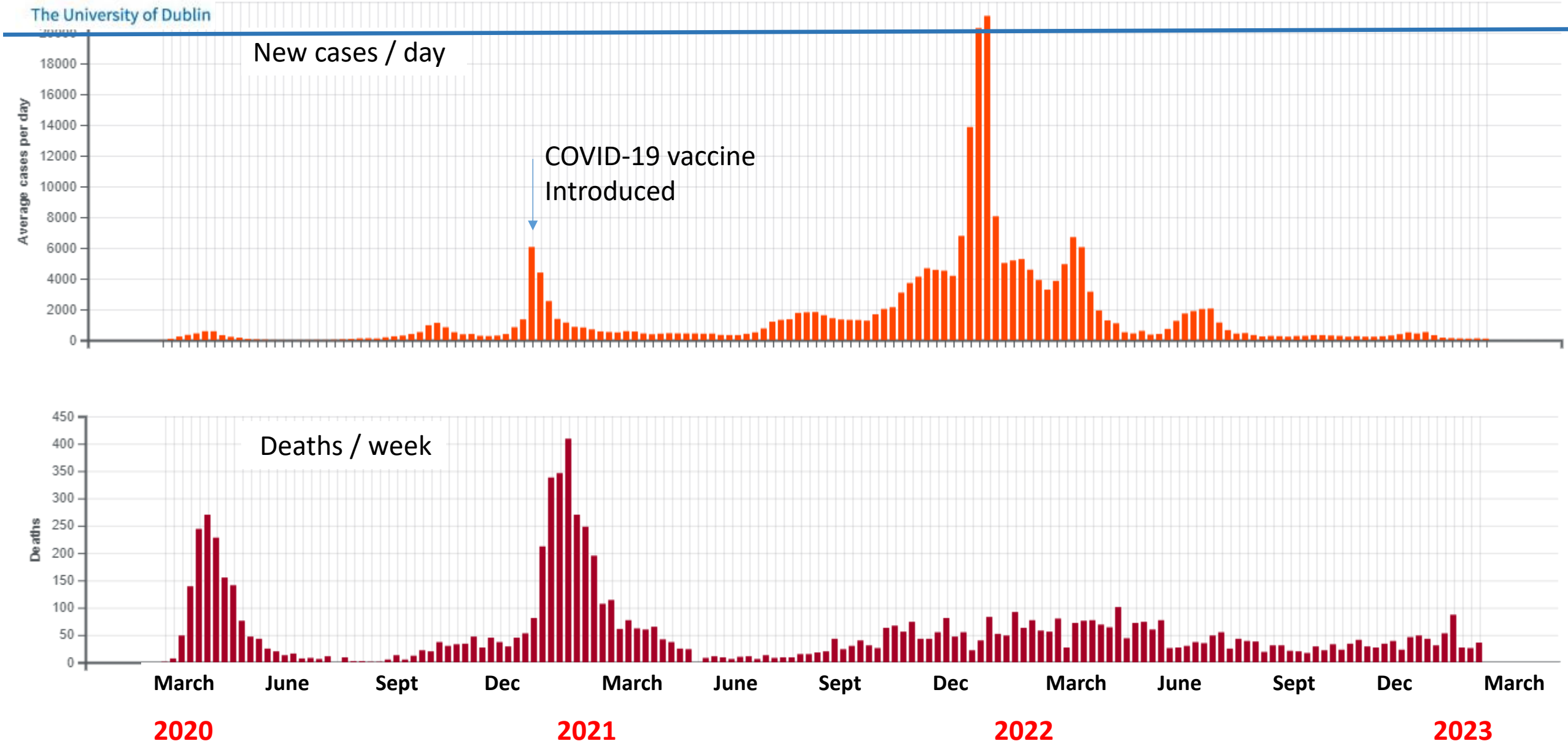
COVID-19 Cases and deaths in Ireland – impact of vaccination



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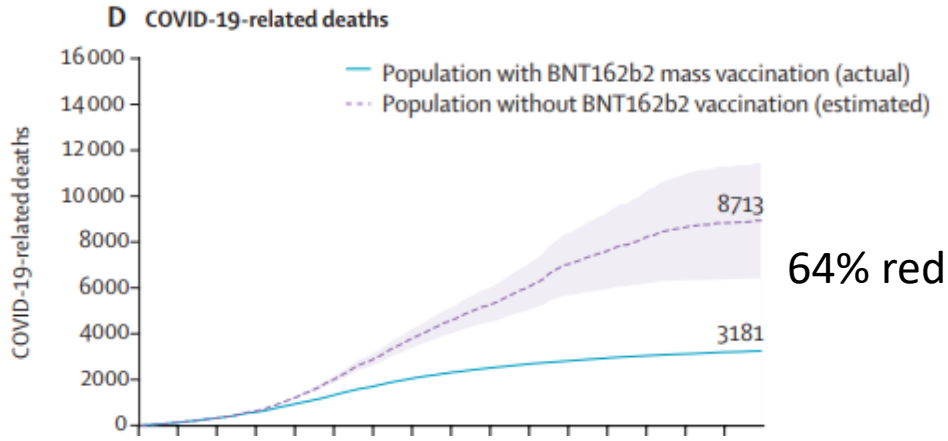
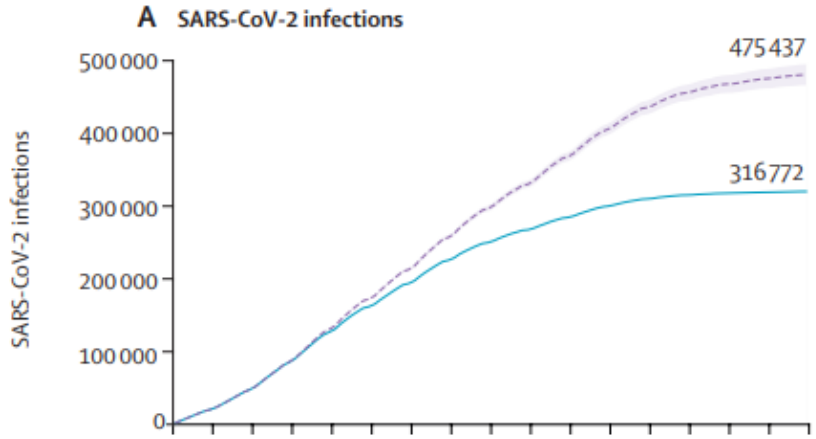
COVID-19 vaccines prevent severe disease but not infection with SARS-CoV-2

Pfizer vaccine Israel 2021

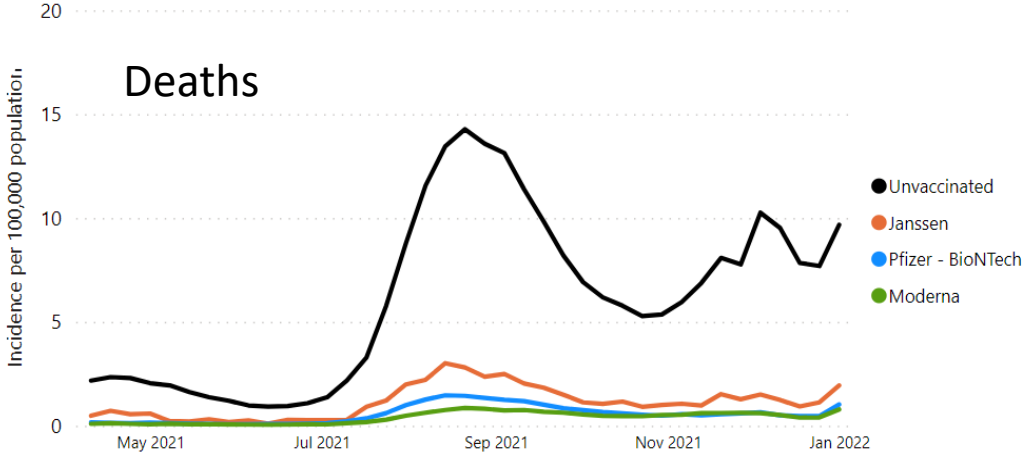


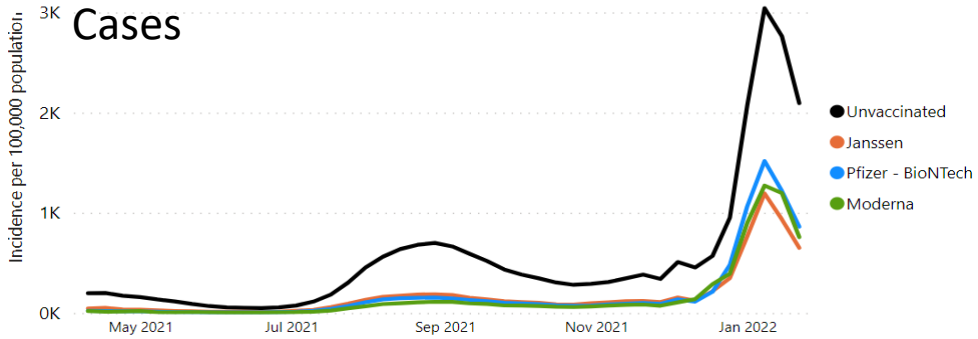
64% reduction



33% reduction

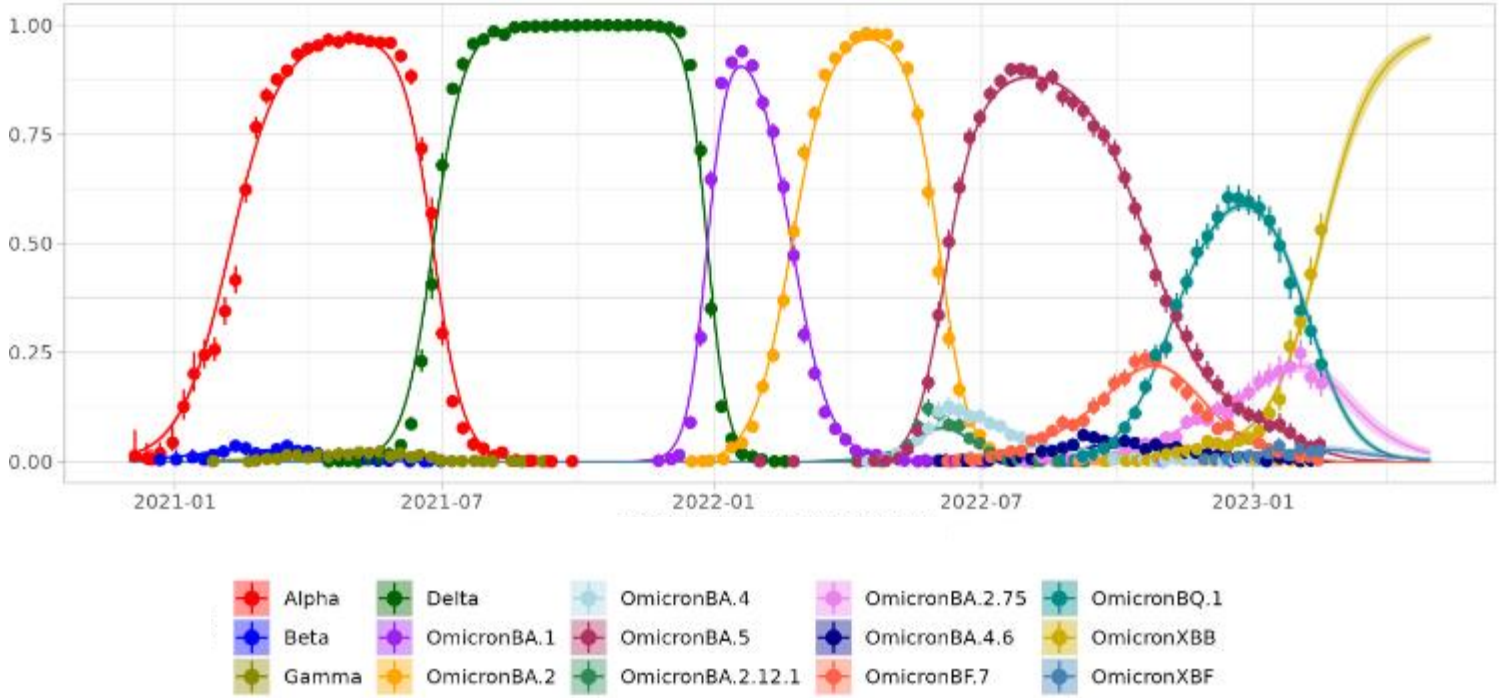
USA April 21 – Jan 22

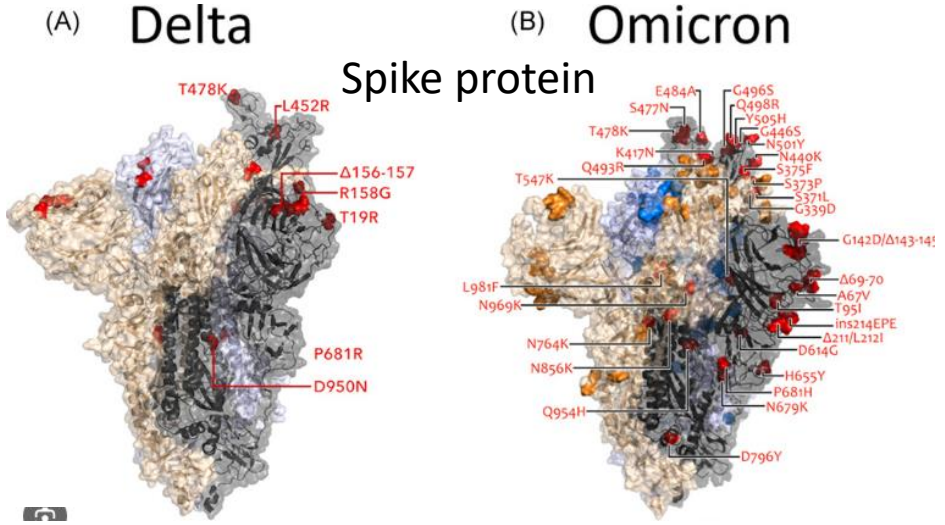




www.thelancet.com/infection Published online September 22, 2021 https://doi.org/10.1016/S1473-3099(21)00566-1

Emergence of SARS-CoV-2 variants





Omicron/Omicron variants

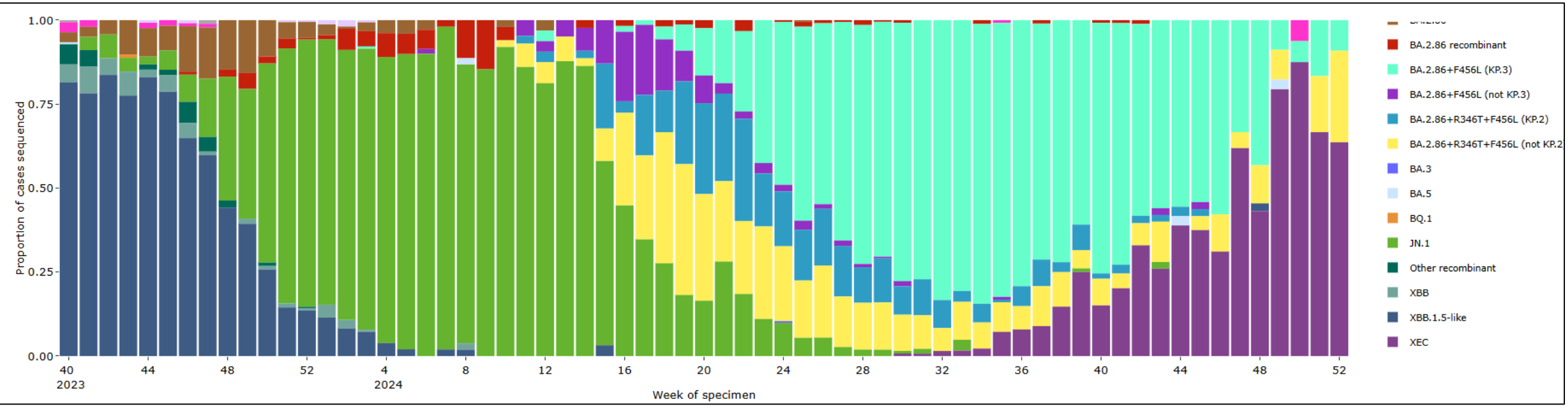
- Less pathogenic than delta or previous variants
- More transmissible
- Evades immunity induced by pre-omicron infections or vaccination

November 2023

Dominant circulating strain: EG.5 (Eris)

BA2.86 variant (Pirola), 30 new mutations.

Antigenic variation in SARS-CoV2 and impact on vaccine-induced neutralizing antibodies



Recent SARS-COV-2 evolution for Ireland (data from NDSC)

Article

Evolving antibody response to SARS-CoV-2 antigenic shift from XBB to JN.1

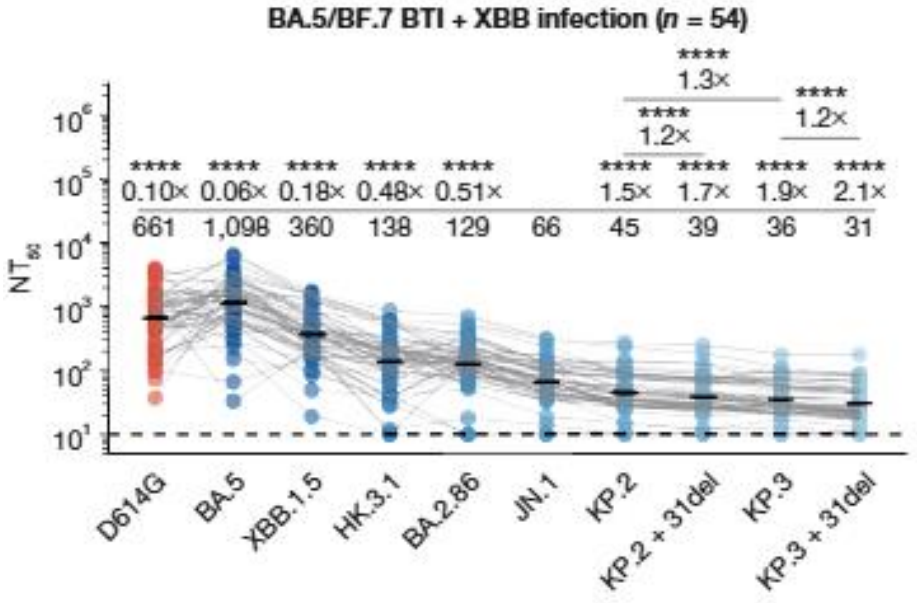
https://doi.org/10.1038/s41586-024-08315-x

Received: 18 June 2024

Accepted: 30 October 2024

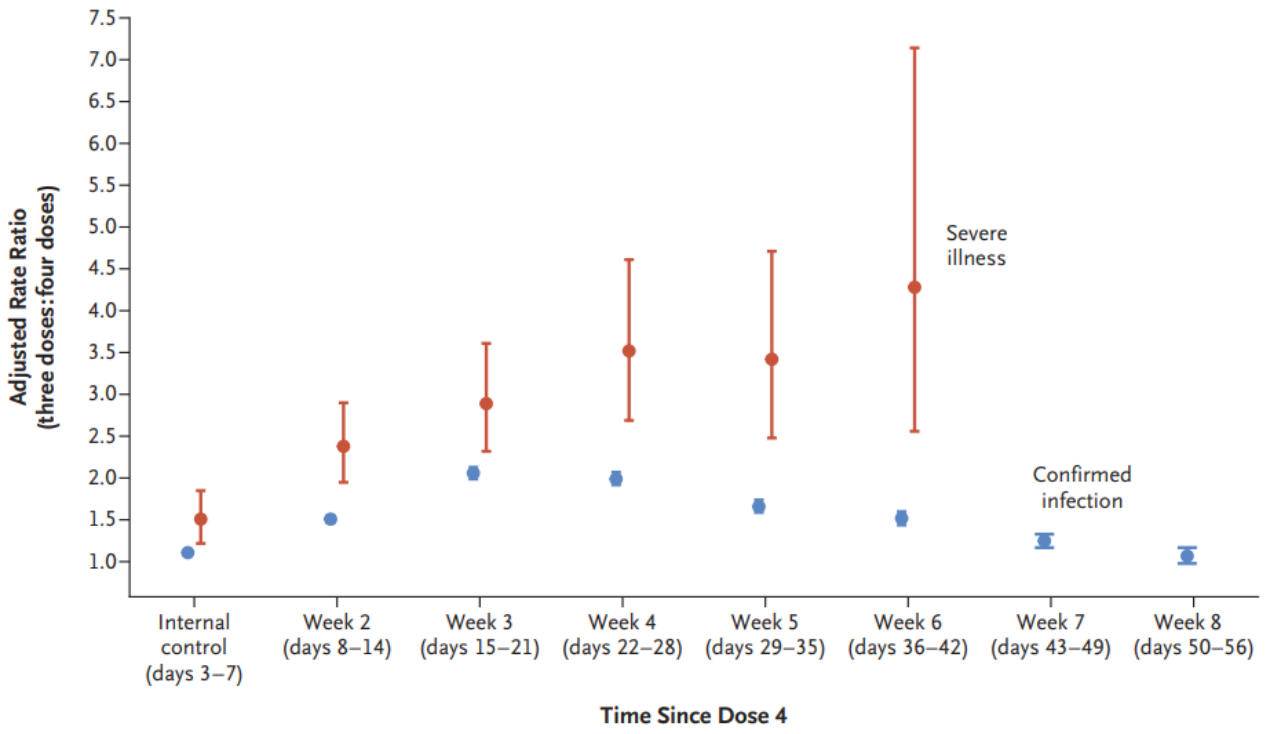
Published online: 7 November 2024

Fanchong Jian[1,2,3,11], Jing Wang[1,2,4,11], Ayijiang Yisimayi[1,2,4,11], Weiliang Song[1,2,4,11], Yanli Xu[5,11], Xiaosu Chen[6], Xiao Niu[1,3], Sijie Yang[1,7], Yuanling Yu[2], Peng Wang[2], Haiyan Sun[2], Lingling Yu[2], Jing Wang[2], Yao Wang[2], Ran An[2], Wenjing Wang[2], Miaomiao Ma[2], Tianhe Xiao[1,8], Qingqing Gu[2], Fei Shao[2], Youchun Wang[2,9], Zhongyang Shen[10], Ronghua Jin[5] & Yunlong Cao[1,2,7]✉

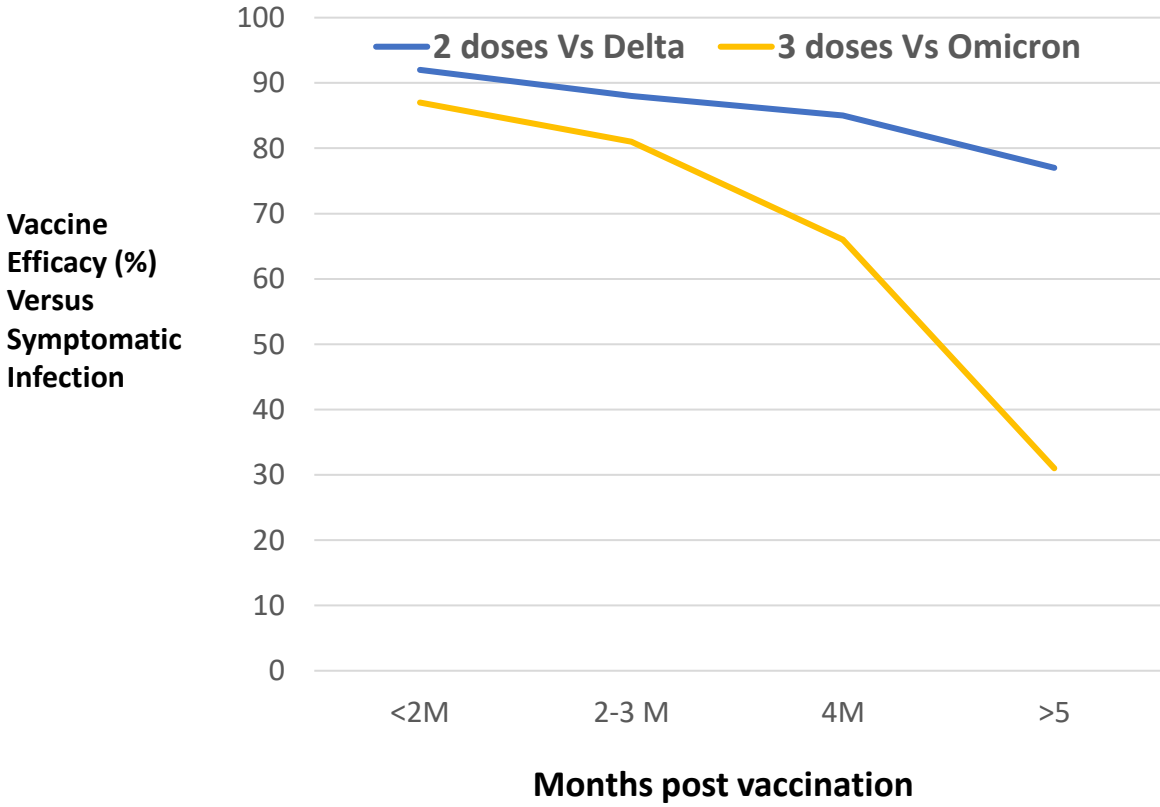


Waning immunity induced by vaccines, especially as new SARS-CoV-2 variants emerge

A fourth dose of Pfizer-BioNTech vaccine confers short-lived protection against infection with omicron, but more prolonged protection against severe disease



Bar-On et al NEJM April 6, 2022.



Qatar study NEJM Feb 2022

npj | vaccines

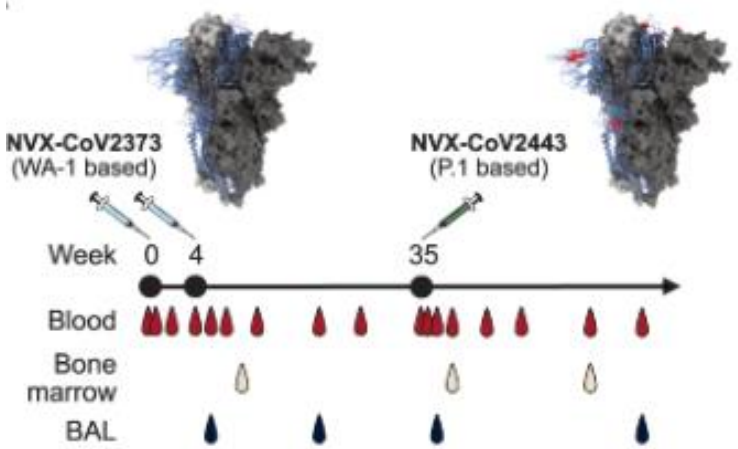
www.nature.com/npjvaccines

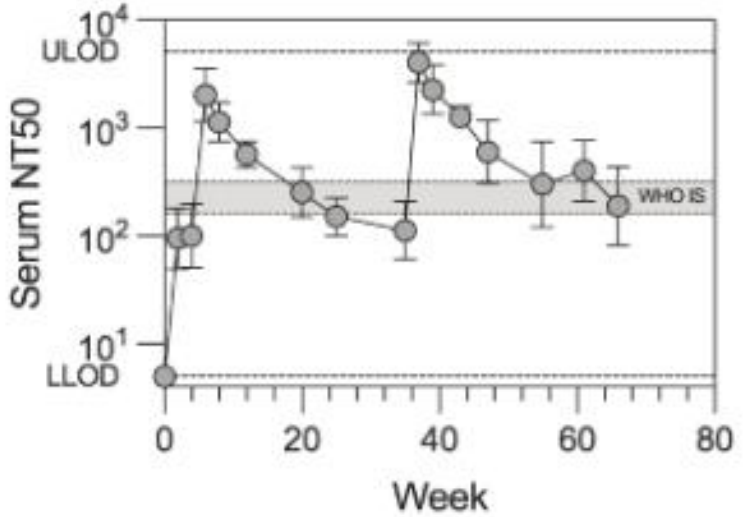
ARTICLE OPEN

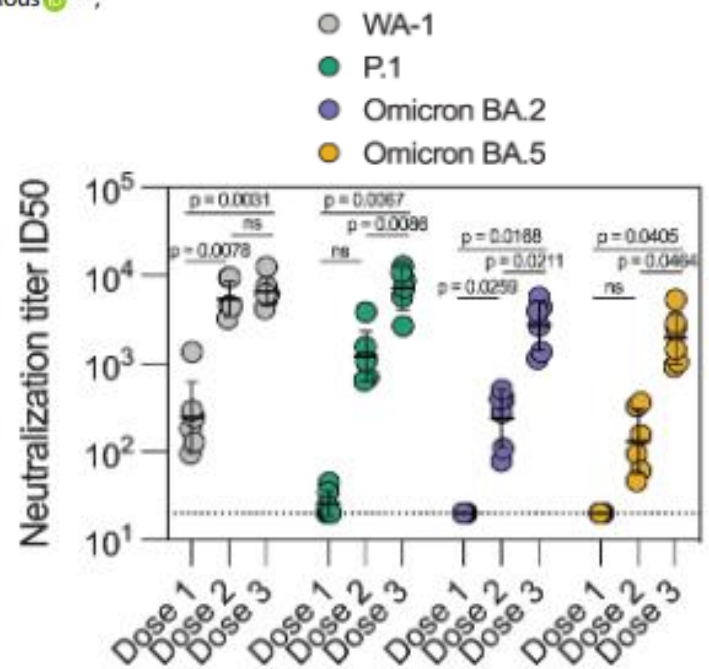
Check for updates

Three immunizations with Novavax's protein vaccines increase antibody breadth and provide durable protection from SARS-CoV-2

Klara Lenart[1,2,3], Rodrigo Arcoverde Cerveira[1,2,3,11], Fredrika Hellgren[1,2,3,11], Sebastian Ols[1,2,3], Daniel J. Sheward[4], Changil Kim[4], Alberto Cagigi[1,2,3], Matthew Gagne[5], Brandon Davis[6], Daritza Germosen[6], Vicky Roy[6], Galit Alter[6], Hélène Letscher[7], Jérôme Van Wassenhove[7], Wesley Gros[7], Anne-Sophie Gallouët[7], Roger Le Grand[7], Harry Kleanthous[8,10], Mimi Guebre-Xabier[9], Ben Murrell[4], Nita Patel[9], Gregory Glenn[9], Gale Smith[9] and Karin Loré[1,2,3]✉







"Novavax's COVID-19 protein vaccine, eliciting durable antibody titers, and may perform better than mRNA vaccines as yearly SARS-CoV-2 boosters."

THE LANCET

ARTICLES · Volume 405, Issue 10475, P314-328, January 25, 2025 · *Open Access* Download Full Issue

Impact of SARS-CoV-2 spike antibody positivity on infection and hospitalisation rates in immunosuppressed populations during the omicron period: the MELODY study

Lisa Mumford, MSc [a] · Rachel Hogg, MSc [a] · Adam Taylor, MEng [b] · Peter Lanyon, MD [b,c,d] · Mary Bythell, MSc [c] · Sean McPhail, PhD [c]

Table 3 Clinical characteristics of participants who had three or more vaccinations, with incidence and IRR of hospitalisation incidence within 14 days of a SARS-CoV-2 infection

		IRR	Anti-S Ab negative			Anti-S Ab positive		
			n	Cases	Incidence rate	n	Cases	Incidence rate
SOT								
Cohort total		0·34 (0·30–0·39)	1947	124	35·9	6519	147	12·4
Transplant type								
	Kidney only	0·38 (0·33–0·45)	1343	81	33·9	4278	97	12·5
	Liver only	0·31 (0·22–0·43)	278	16	32·5	1411	28	10·9
	Pancreas, islet, or simultaneous pancreas or islet and kidney	0·52 (0·22–1·19)	75	3	22·3	221	3	7·4
	Heart only	0·36 (0·22–0·58)	124	9	41·2	379	10	14·6
	Lung (including heart–lung)	0·19 (0·11–0·32)	107	14	77·1	180	7	21·8

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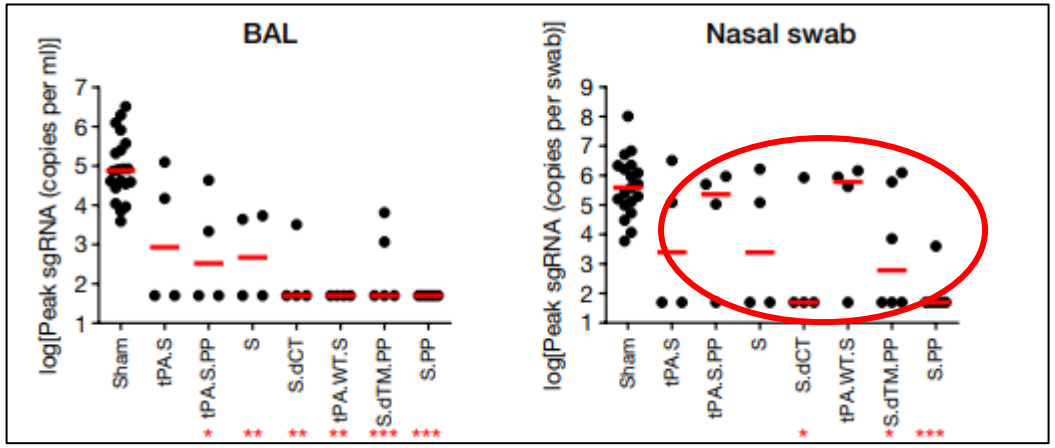
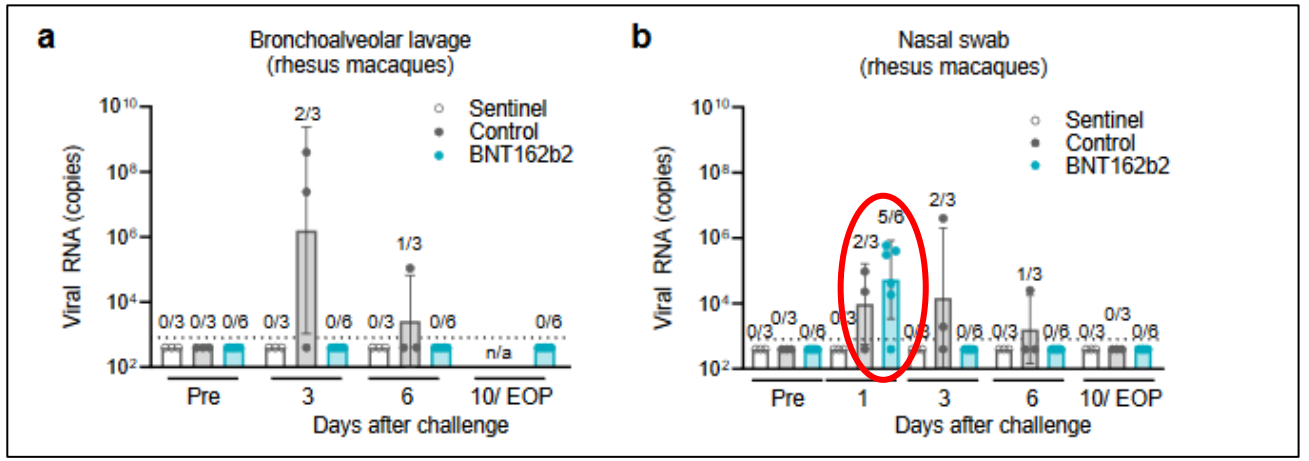
Current COVID-19 vaccine fail to induce sterilizing immunity in nasal mucosa – evidence from non-human primate studies

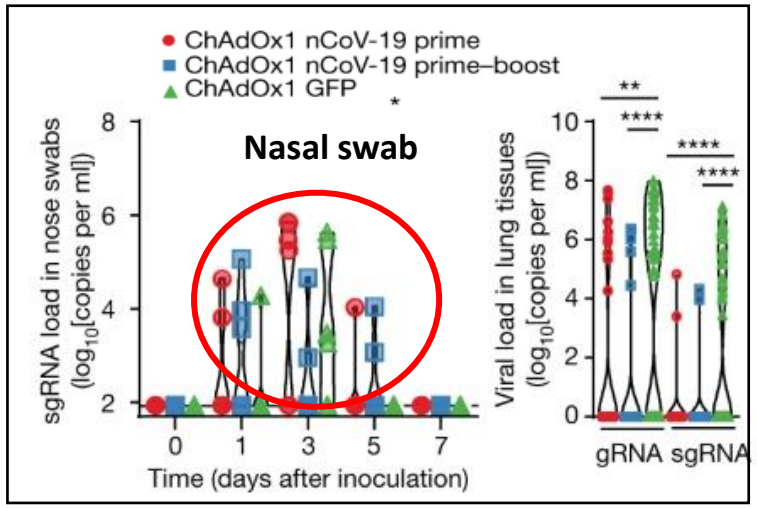
Janssen / J&J (Mercado et al Nature, 22 Oct 2020)



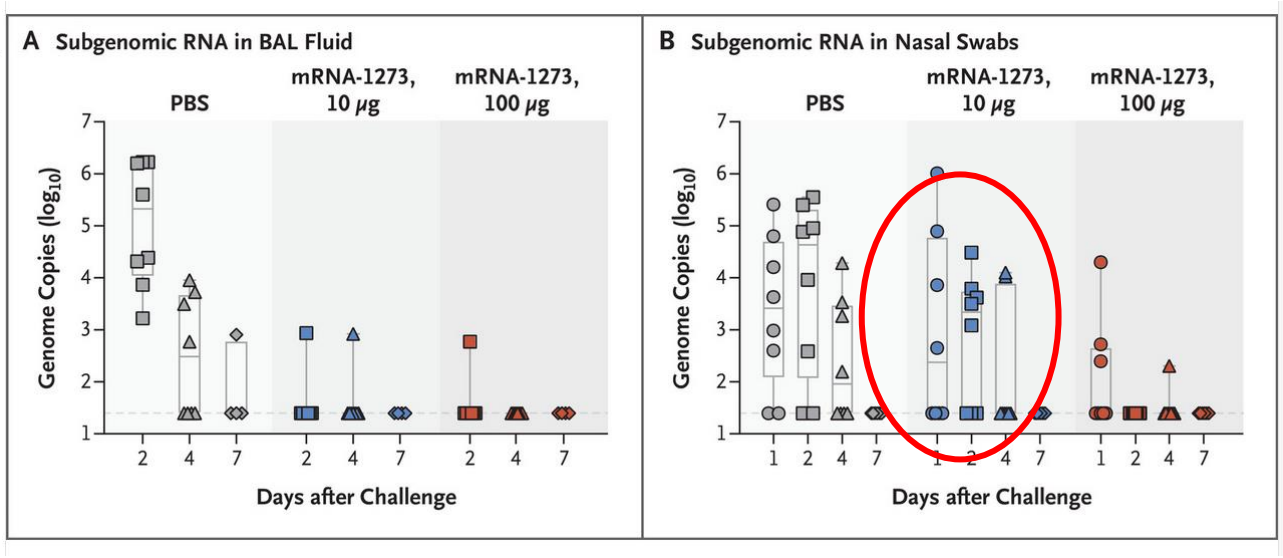
Pfizer – BioNtech (Vogel et al BioRxiv 8 Sept 2020)



Oxford –AstraZeneca (Van Doremalen et al Nature 586, 578 (2020)



Moderna (N Eng J Med 383, 16, Oct 2020)



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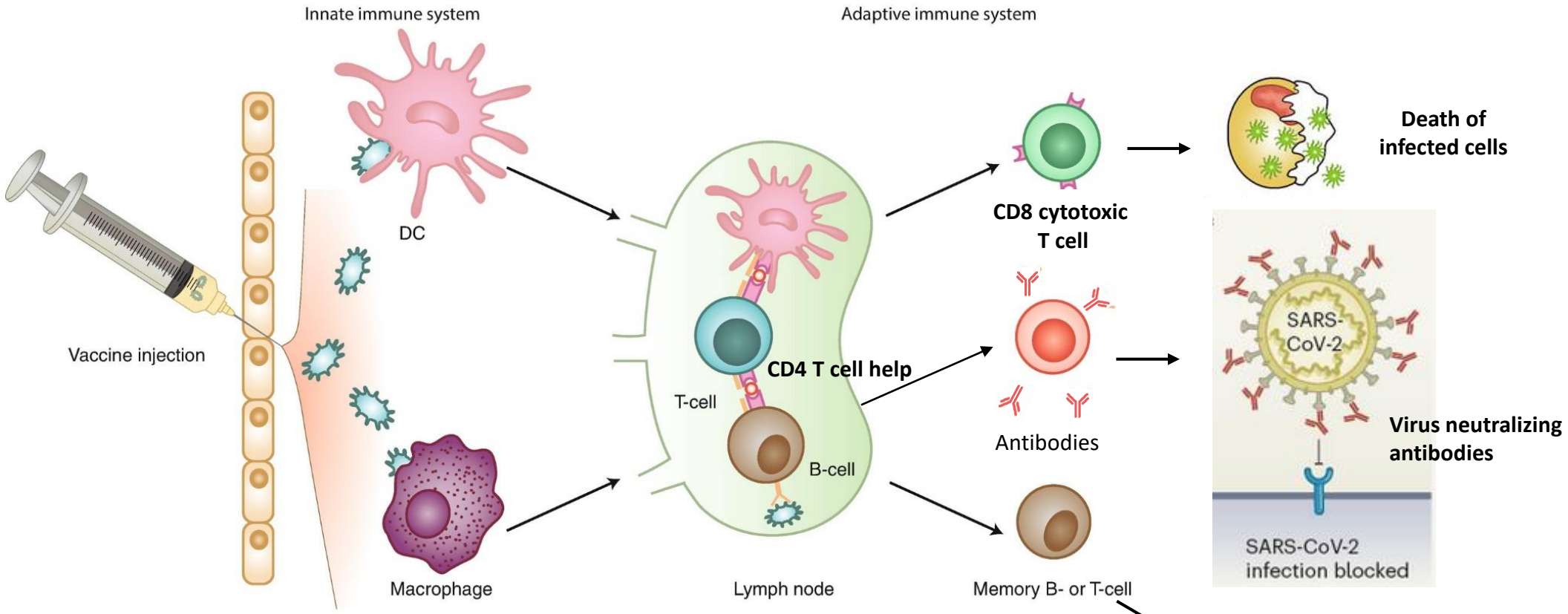
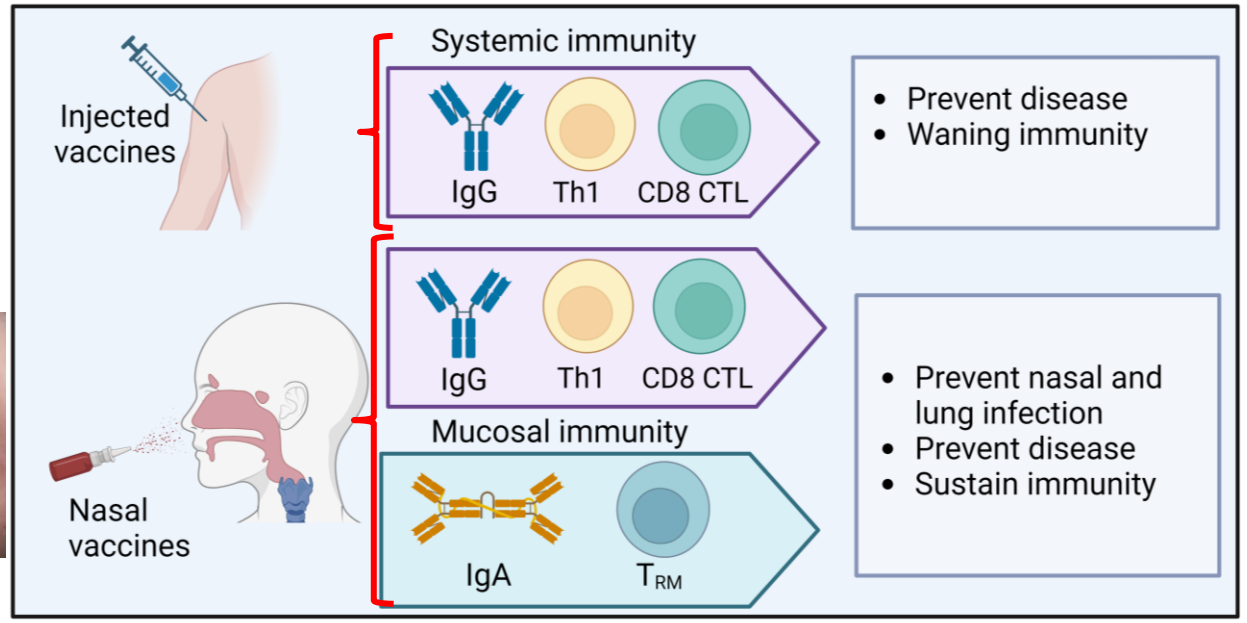
COVID-19 vaccines mediated immunity to SARS-CoV-2 via a combination of antibodies and T cells



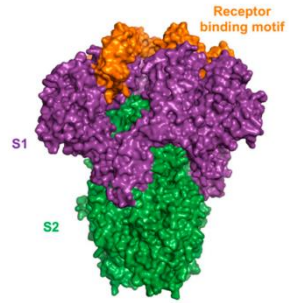
Long-term immunity:
mediated by tissue-resident memory T (T_{RM}) cells and memory B cells

Next generation Vaccines against respiratory pathogens

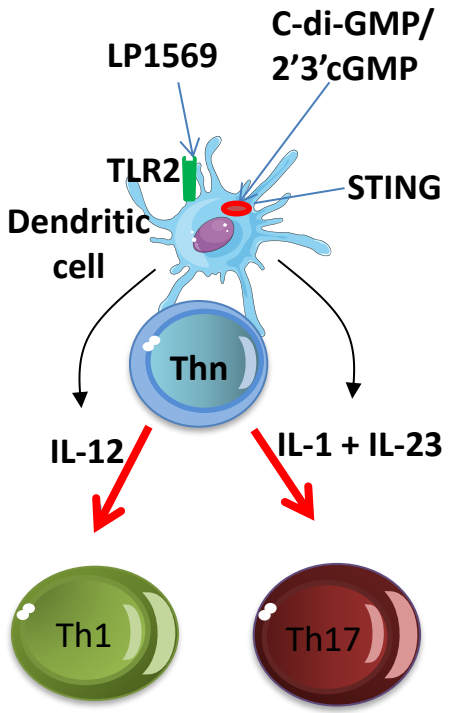


Schmitt --- Mills. Current Opinion in Immunology 2023, Oct:84:102355.

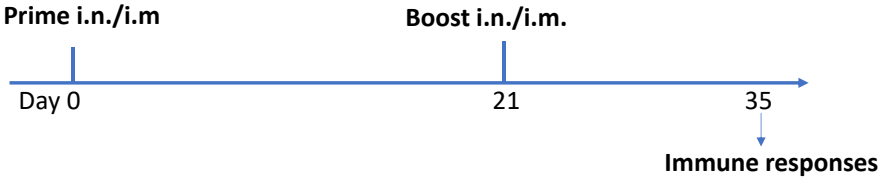
Candidate nasal COVID-19 vaccine



SARS-CoV-2 Spike
Recombinant protein
+LP-GMP

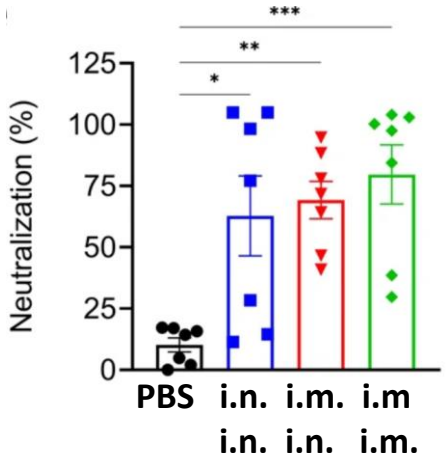


Immunization with S trimer + LP-GMP by i.n. or i.m/i.n. route induces S-specific neutralizing IgG and respiratory IgA

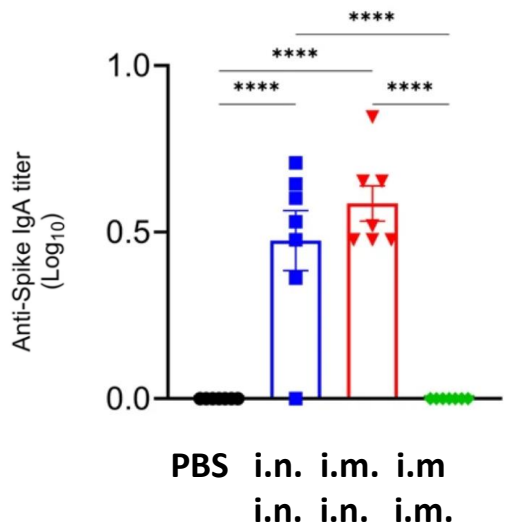


1. PBS
2. S + LP-GMP i.n. + i.n.
3. S + LP-GMP i.n. + i.m.
4. S + LP-GMP i.m. + i.m.

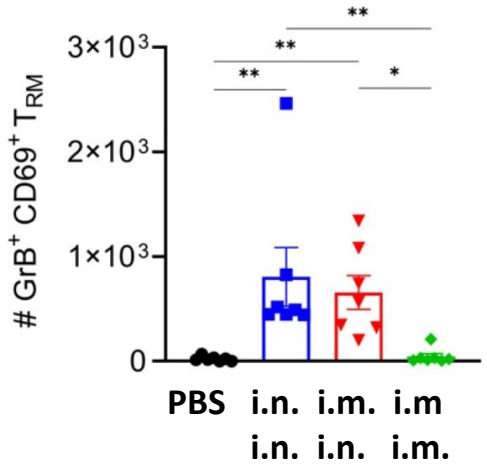
Serum Neut Abs



Nasal IgA



Nasal tissue T_{RM} cells



npj | vaccines

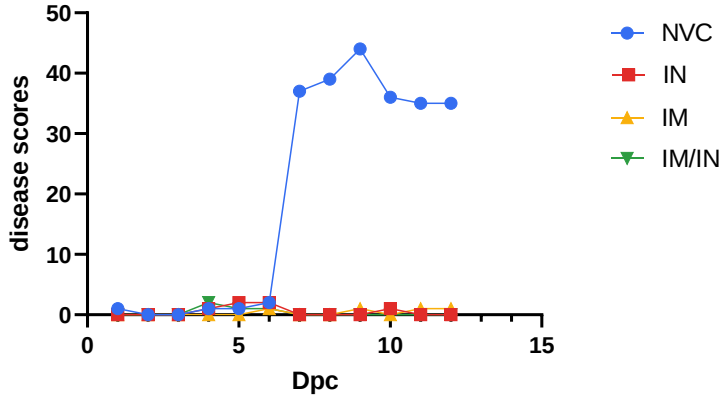
www.nature.com/npjvaccines

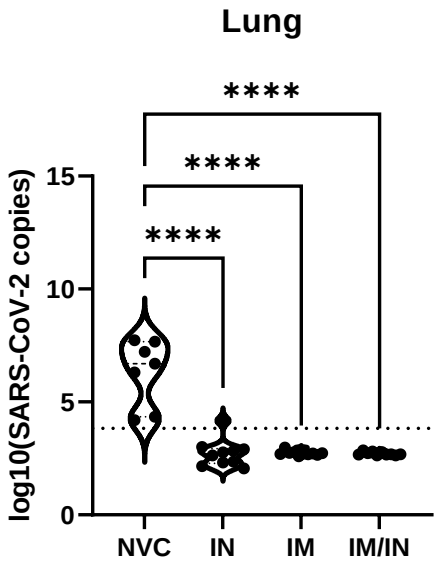
ARTICLE OPEN

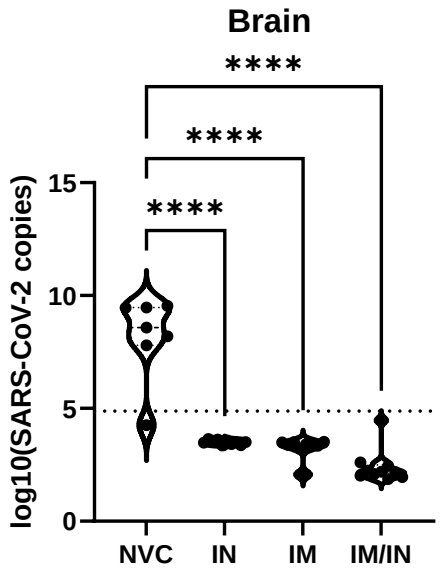
Check for updates

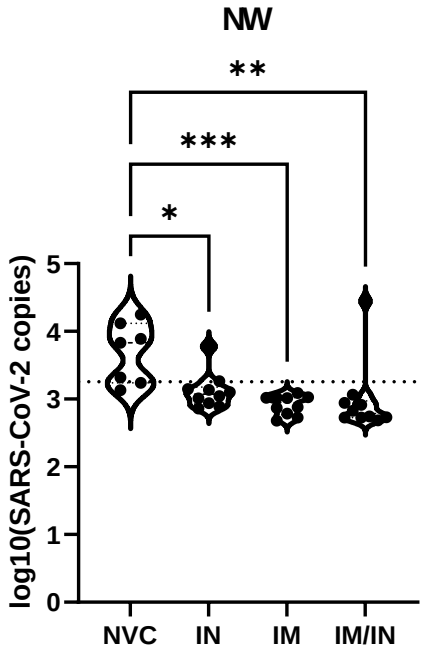
Intranasal COVID-19 vaccine induces respiratory memory T cells and protects K18-hACE mice against SARS-CoV-2 infection

Béré K. Diallo[1,3], Caitlín Ní Chasaide[1,3], Ting Y. Wong[2,3], Pauline Schmitt[1], Katherine S. Lee[2], Kelly Weaver[2], Olivia Miller[2], Melissa Cooper[2], Seyed D. Jazayeri[1], F. Heath Damron[2] and Kingston H. G. Mills[1]✉









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Impact of mRNA technology on vaccine/treatments for other diseases

nature

NEWS EXPLAINER | 03 October 2023

mRNA COVID vaccines saved lives and won a Nobel – what's next for the technology?

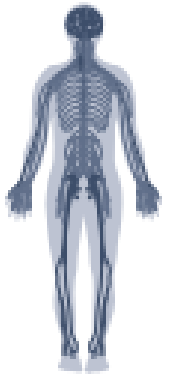
Nature **talks to experts about how messenger RNA is transforming medicine.**

Elie Dolgin & Heidi Ledford

- Rapid vaccine development against "new" pathogens
- Tackling tough pathogens
  - ➢ MRSA, HIV, CMV, TB, universal flu mRNA vaccines
- mRNA vaccine against cancer
- Genome editing: long lasting mRNA to correct rare diseases
  - ➢ Cystic fibrosis, Muscular dystrophy, Huntington's disease, Haemophilia, Cancers

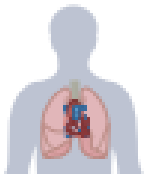
Long COVID

Signs and Symptoms

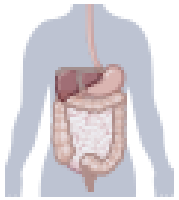


Fever
Fatigue
'Brain fog'
Headache
Neuropathy
Sleep problems
Loss of smell/taste
Memory disturbances

Autonomic dysregulation

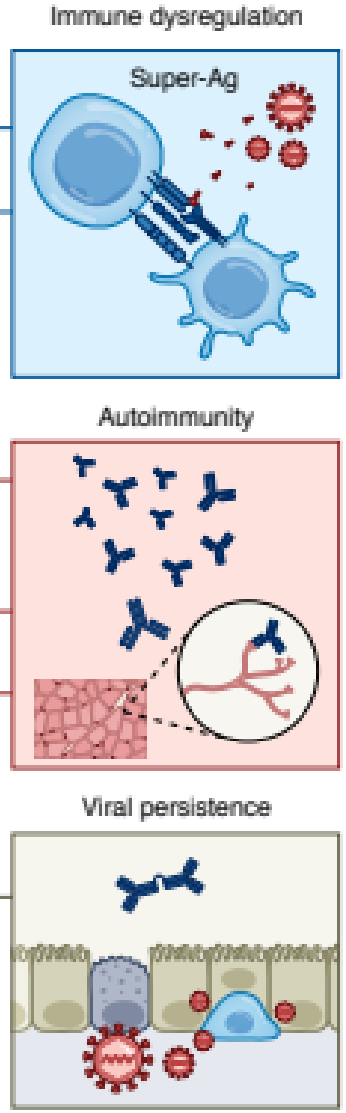


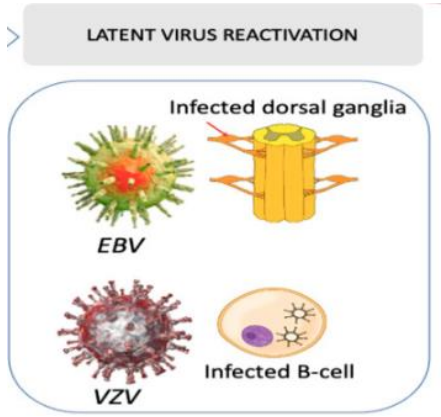
Chest pain
Heart palpitations
Shortness of breath



Dysmotility
Loss of appetite
Difficulty in swallowing

Possible mechanisms





Brodin *Nature Medicine* **28**, 879–882 (2022)

Serapide J Clin Med 2024,13(23):7124.

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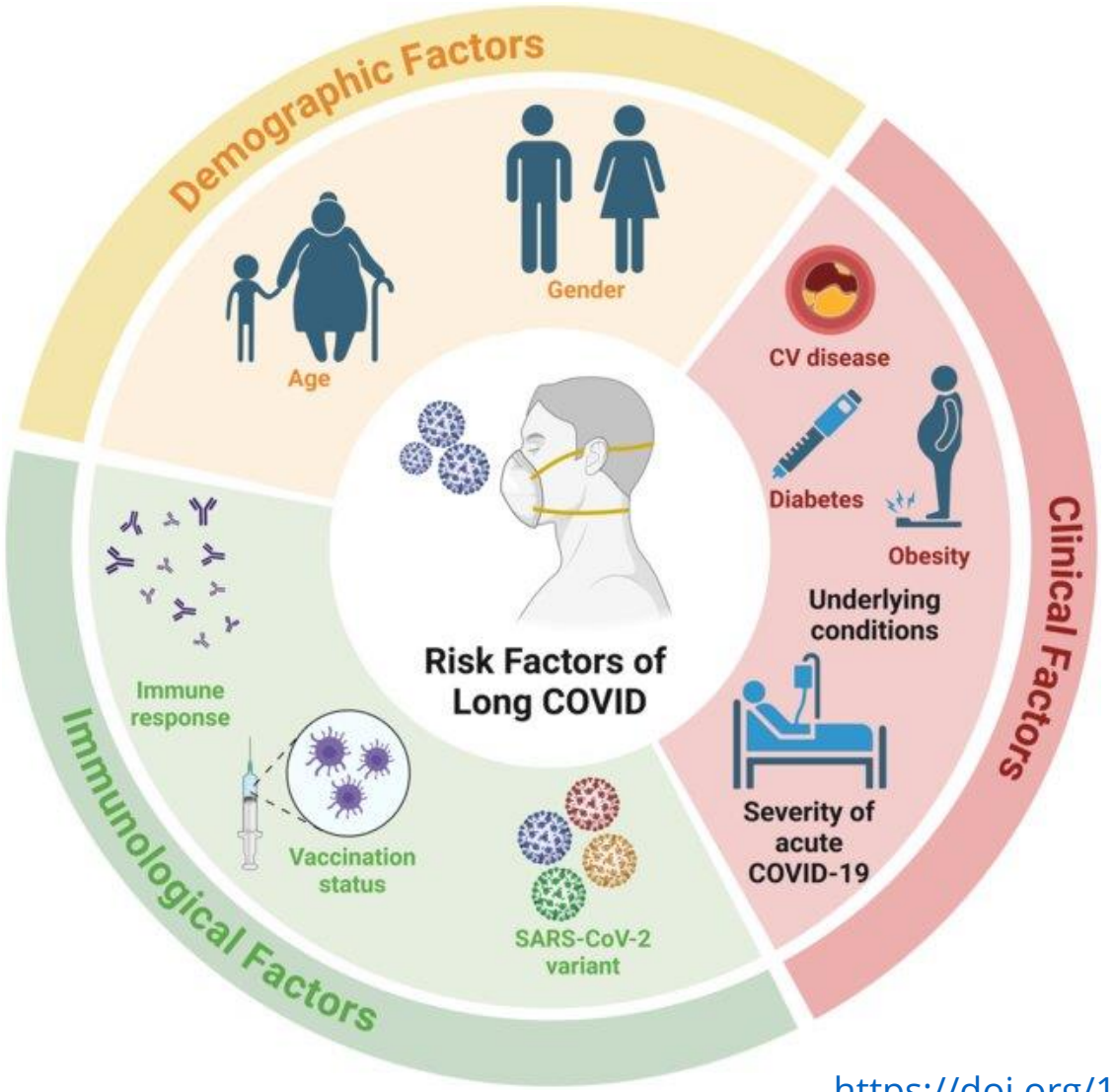
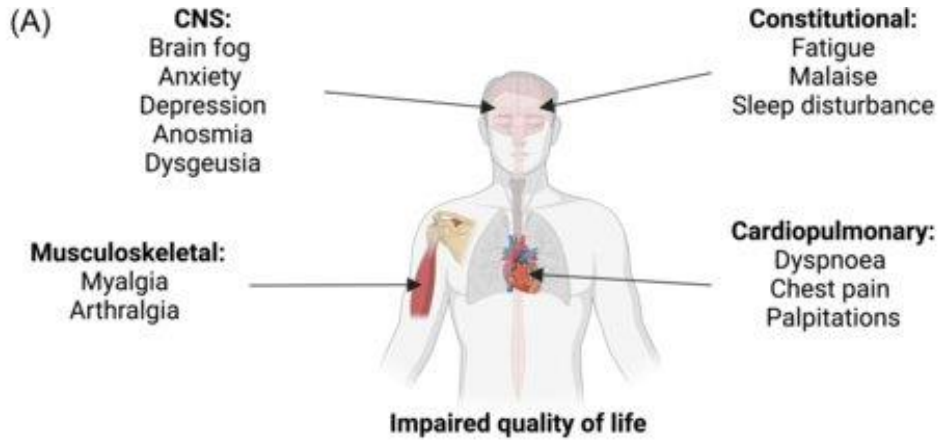
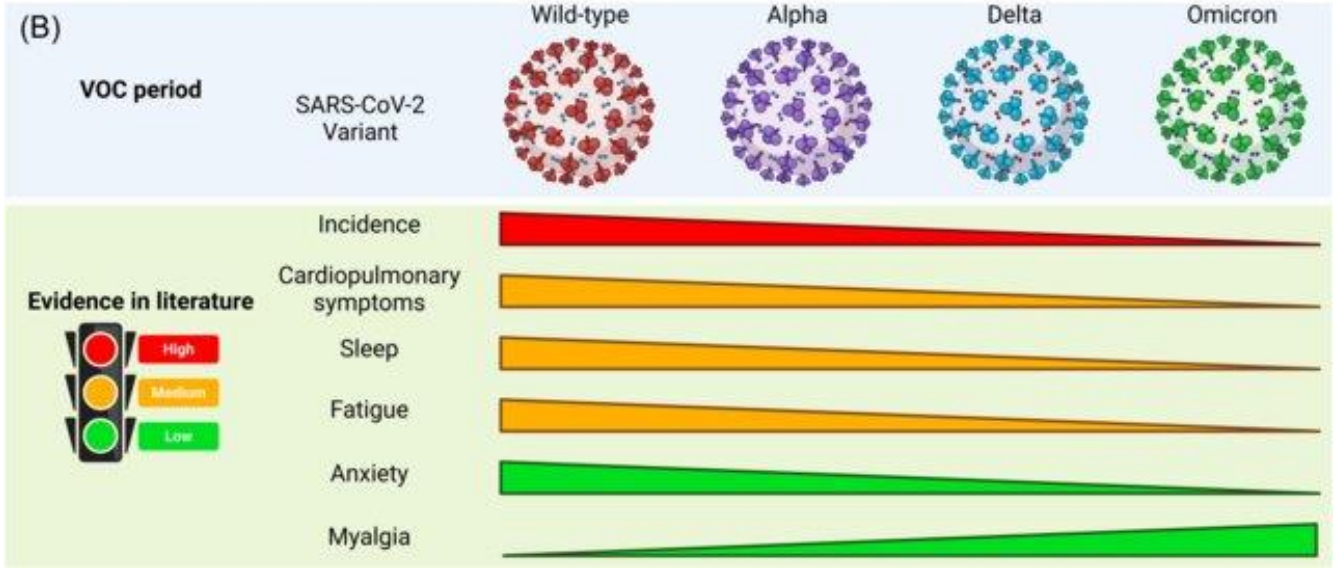
LONG COVID – Risk factors







https://doi.org/10.1002/mef2.70004

Large scale phenotyping of long COVID inflammation reveals mechanistic subtypes of disease

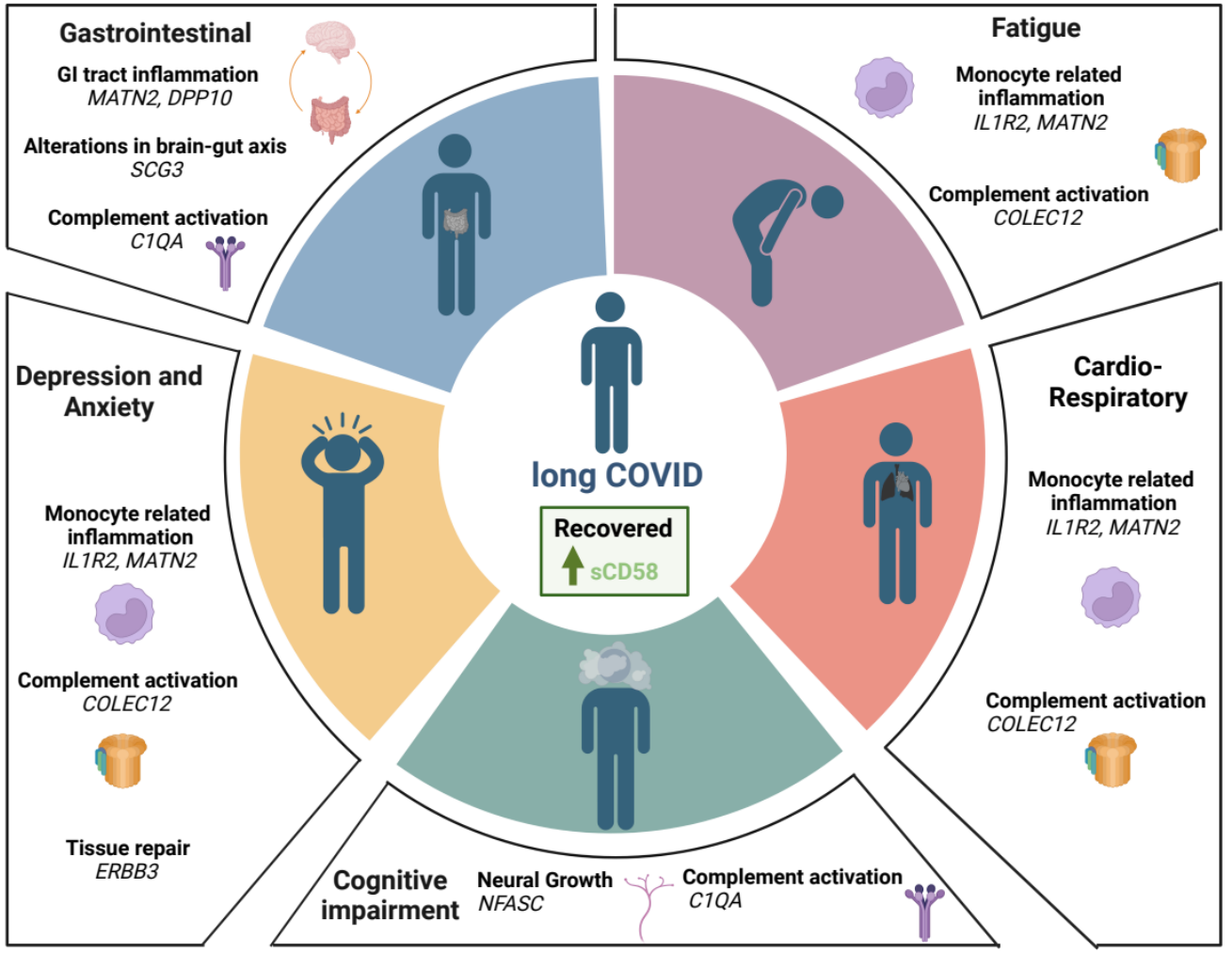
Felicity Liew, Claudia Efstathiou, Sara Fontanella, Matthew Richardson, Ruth Saunders, Dawid Swieboda,
---
Louise V. Wain, Christopher Brightling, Lance Turtle, Ryan S. Thwaites, Peter J.M. Openshaw,
ISARIC4C Investigators and the PHOSP-COVID collaborative group

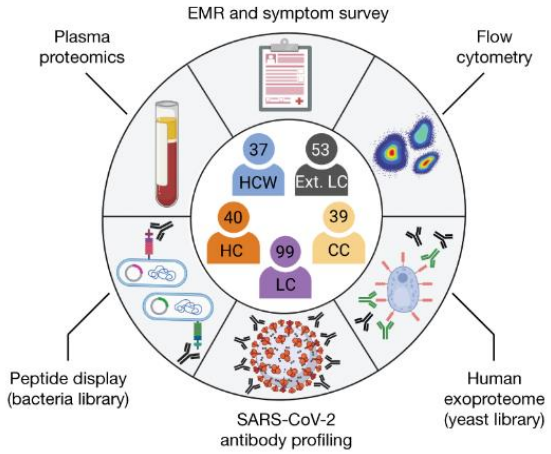
doi: https://doi.org/10.1101/2023.06.07.23291077

Study on large hospitalised cohort found:

- Monocytic inflammation and complement activation in those with continued symptoms 6 mo after COVID-19
- Distinctive inflammatory patterns in those with cognitive impairment and GI symptoms.
- Prolonged symptoms arise from different causes
- Therapeutic trials need to take this diversity into account.

Distinct proteome of long COVID subtypes





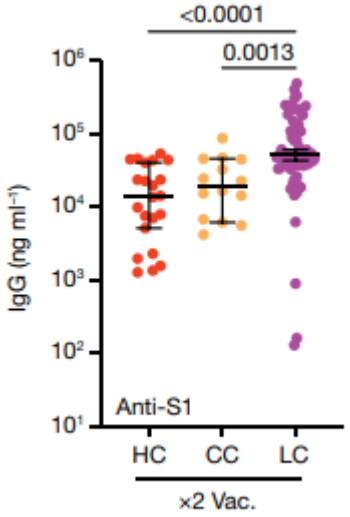
Distinguishing features of long COVID identified through immune profiling

Jon Klein, Jamie Wood, Jillian R. Jaycox, Rahul M. Dhodapkar, Peiwen Lu, Jeff R. Gehlhausen, Alexandra Tabachnikova, Kerrie Greene, Laura Tabacof, Amyn A. Malik, Valter Silva Monteiro, Julio Silva, Kathy Kamath, Minlu Zhang, Abhilash Dhal, Isabel M. Ott, Gabrielee Valle, Mario Peña-Hernández, Tianyang Mao, Bornali Bhattacharjee, Takehiro Takahashi, Carolina Lucas, Eric Song, Dayna McCarthy, ... Akiko Iwasaki + Show authors

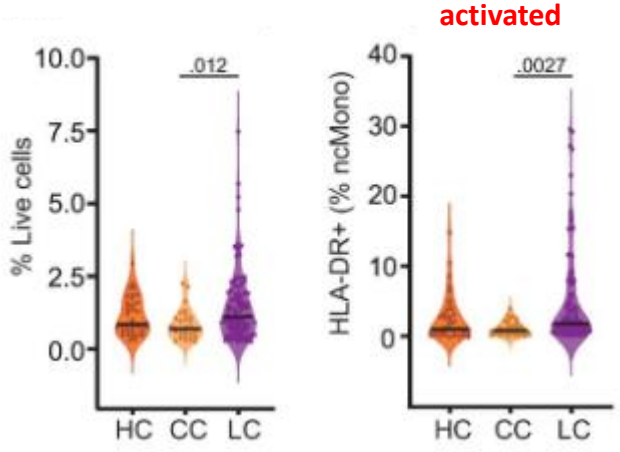
Nature **623**, 139–148 (2023) | Cite this article

HC: Health controls
CC: Convalescent controls
LC: Long Covid

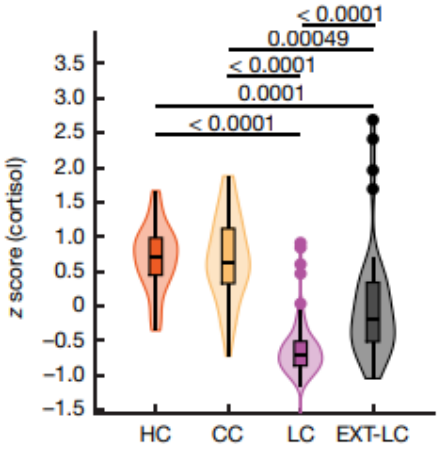
Anti-S1 Abs



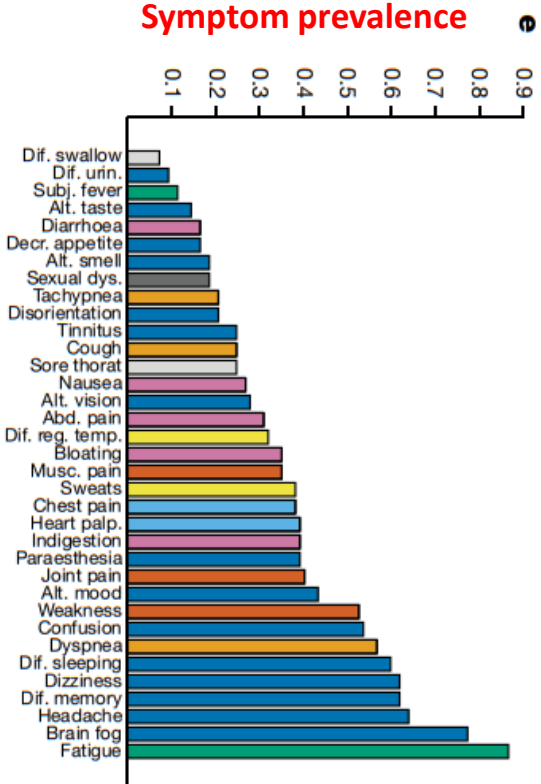
Non-conventional monocytes



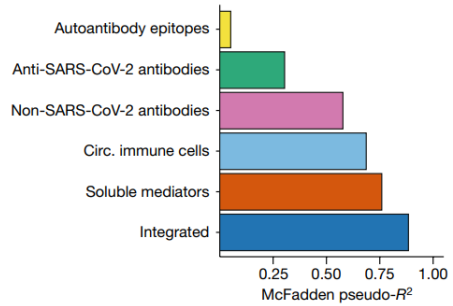
Cortisol



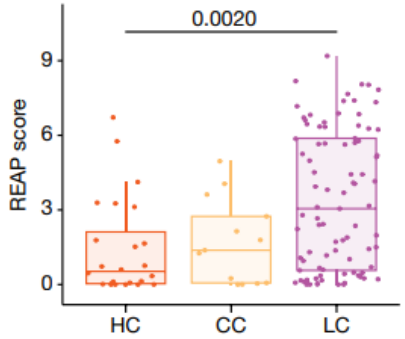
Symptom prevalence



Immunological features

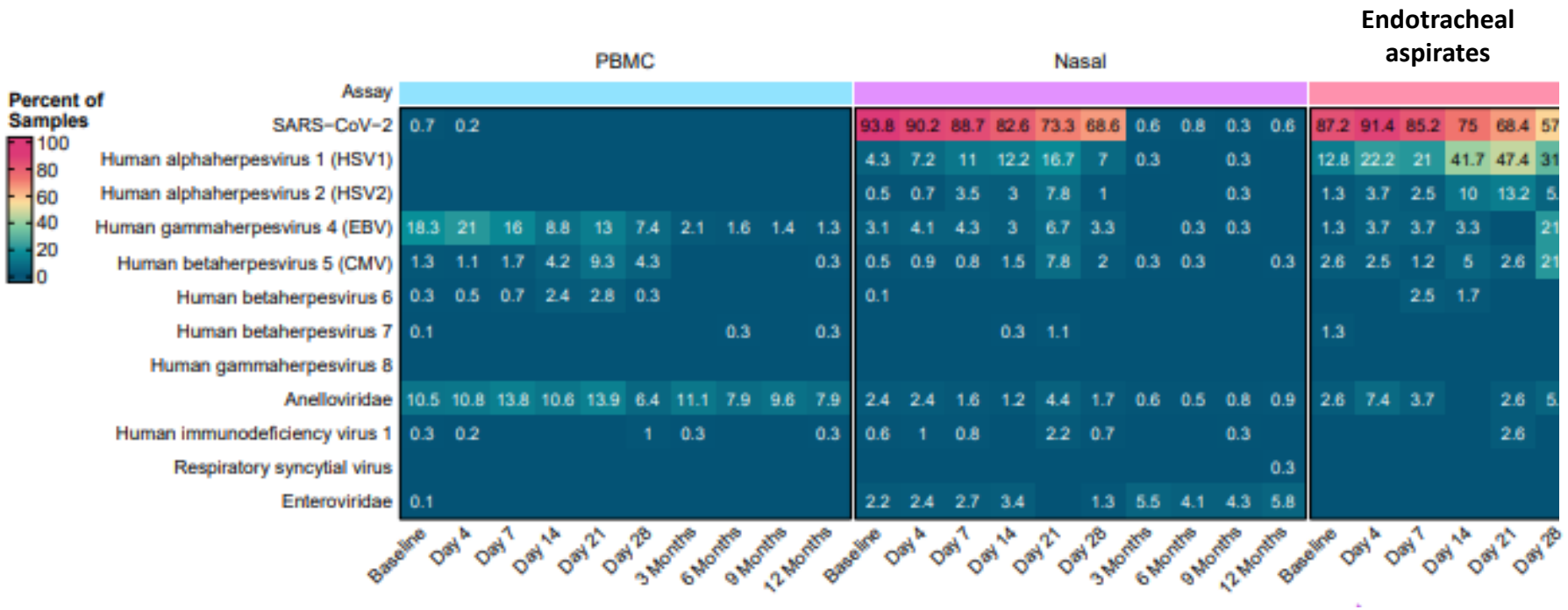


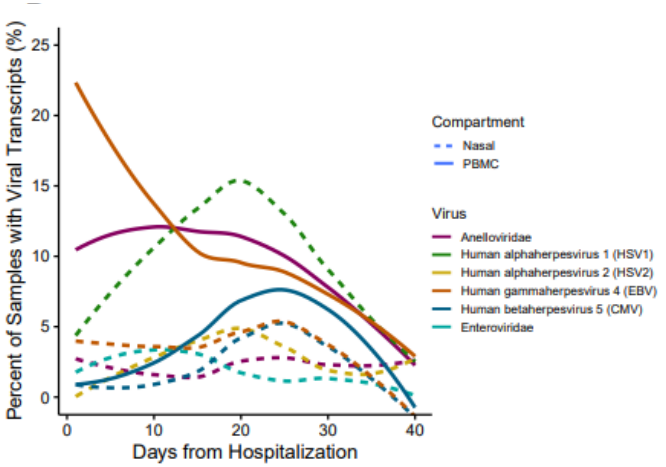
Anti-EBV p23 Abs



Chronic Viral Reactivation and Associated Host Immune Response and Clinical Outcomes in Acute COVID-19 and Post-Acute Sequelae of COVID-19

bioRxiv [Preprint]. 2024 Nov 16:2024.11.14.622799. doi: 10.1101/2024.11.14.622799.





Reactivation of the Human Virome Correlated with Changes in Inflammatory Cytokines and Chemokines

nature neuroscience

Article

https://doi.org/10.1038/s41593-024-01576-9

Blood–brain barrier disruption and sustained systemic inflammation in individuals with long COVID-associated cognitive impairment

Received: 16 November 2022

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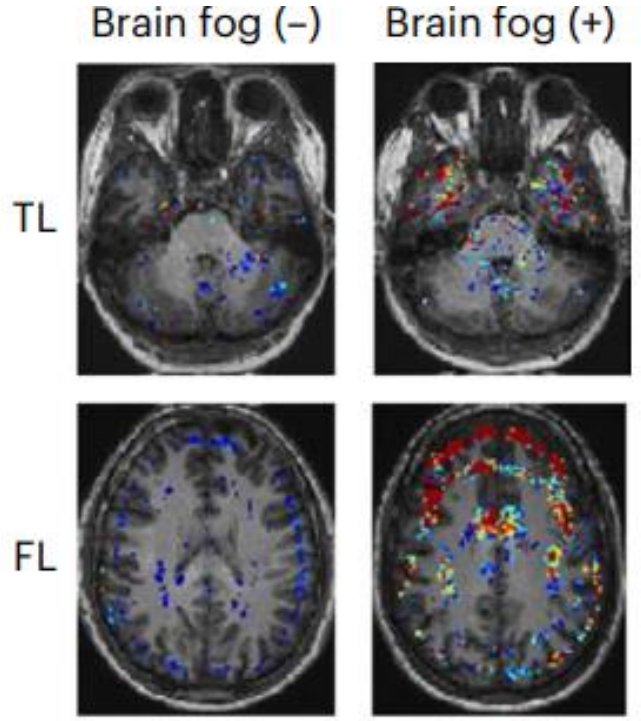
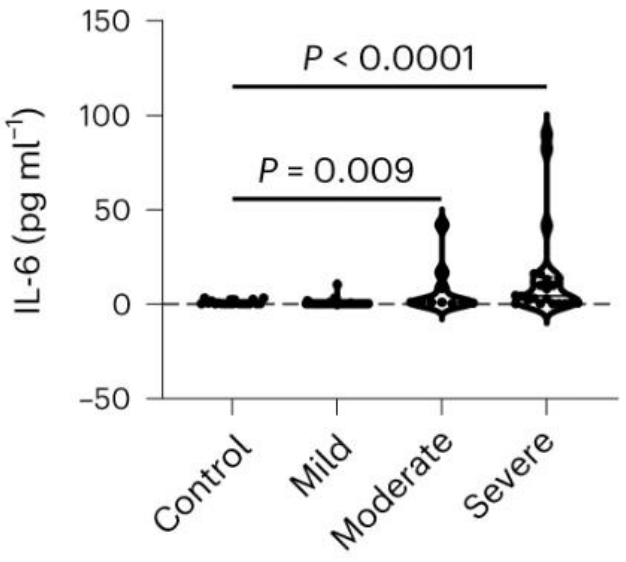
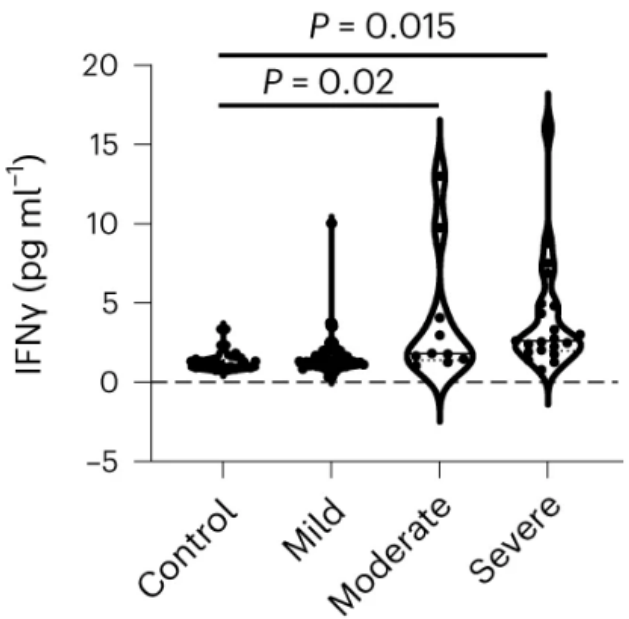
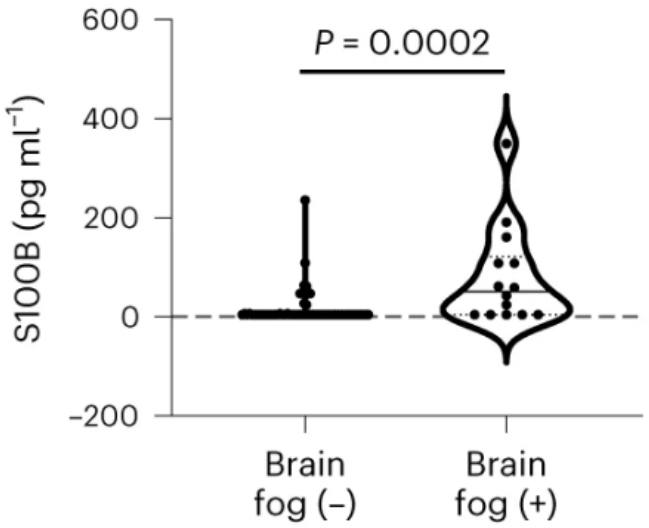
Chris Greene[1], Ruairi Connolly[2], Declan Brennan[2], Aoife Laffan[2], Eoin O'Keeffe[1], Lilia Zaporojan[2], Jeffrey O'Callaghan[1], Bennett Thomson[1], Emma Connolly[3], Ruth Argue[4], James F. M. Meaney[5], Ignacio Martin-Loeches[6], Aideen Long[7], Cliona Ni Cheallaigh[7,8], Niall Conlon[8,9], Colin P. Doherty[2,10,11] & Matthew Campbell[1,11]



Increased leakiness of blood vessels in temporal lobe region of brain







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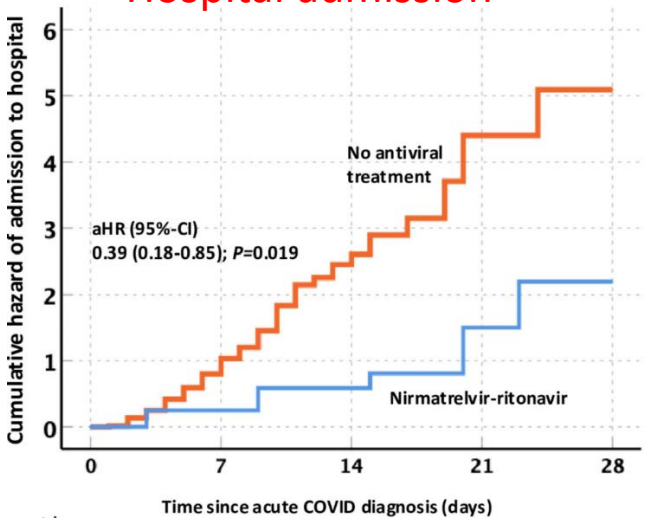
Treatments for Long Covid?

Nirmatrelvir plus ritonavir reduces COVID-19 hospitalization and prevents long COVID in adult outpatients

Fatemeh Saheb Sharif-Askari, Hawra Ali Hussain Alsayed, Narjes Saheb Sharif-Askari, Ali Al Sayed Hussain, Saleh Al-Muhsen & Rabih Halwani

Scientific Reports **14**, Article number: 25901 (2024) | Cite this article

Hospital admission

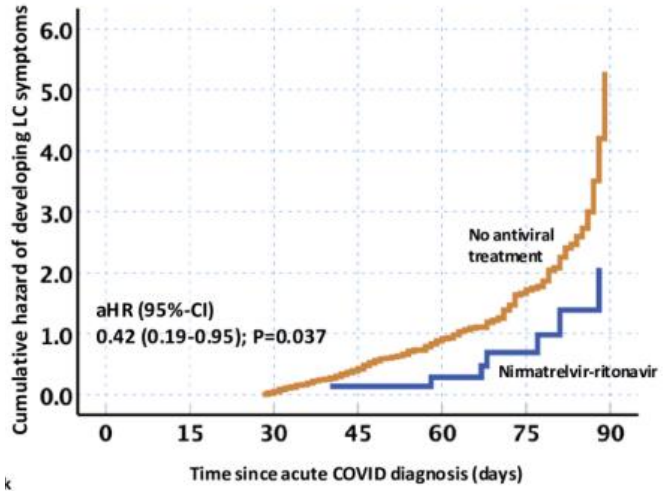


Impact of extended-course oral nirmatrelvir/ritonavir in established Long COVID: a case series

Alison K. Cohen, Toni Wall Jaudon, Eric M. Schurman, Lisa Kava, Julia Moore Vogel, Julia Haas-Godsil, Daniel Lewis, Samantha Crausman, Kate Leslie, Siobhan Christine Bligh, Gillian Lizars, JD Davids, Saniya Sran, Michael Peluso & Lisa McCorkell

Communications Medicine **4**, Article number: 261 (2024) | Cite this article

Long Covid



The New York Times

Symptoms and Treatment | Is It Covid or the Flu? | Can I Still Use Expired Tests? | Free Tests Are Back

Paxlovid Improved Long Covid Symptoms in Some Patients, Researchers Report

But the report, on the experiences of 13 patients, found that the drug had no benefit for some people and that some who benefited said the improvement didn't last.

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Lessons from the COVID-19 Pandemic: we need to be ready for disease-X

The Monetary cost of COVID-19 pandemic: >$16 trillion in lost output and public health expenditure

Mail Online

The next pandemic is already coming and it could kill millions more than Covid. We need to prepare for it now... writes experts KATE BINGHAM and TIM HAMES

By KATE BINGHAM and TIM HAMES
PUBLISHED: 23:07, 22 September 2023 | **UPDATED:** 02:57, 23 September 2023

Disease X Could Bring Next Pandemic, Kill 50 Million People, Says Expert

Kate Bingham further said that scientists have identified 25 virus families, but there could be more than one million undiscovered variants.

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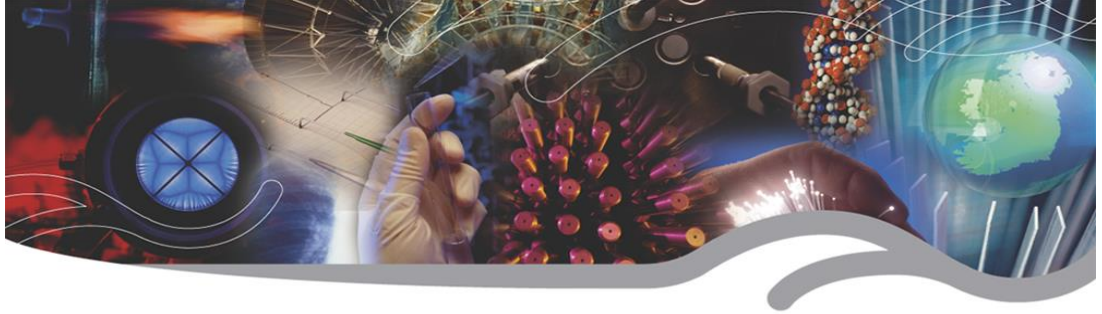

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Joe Keane,
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UniCoV project
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