IMMUNISATION COALITION

2024 WEBINAR

COVID-19 UPDATE

TUESDAY 14 MAY 2024 | 6pm–7pm AEST

Presenter: Prof Gary Grohmann

Moderator: Andrew Minton, PhD

Presenter

Prof Gary Grohmann

Board Member/Director – Immunisation Coalition
Adjunct Professor – University of Sydney
Past Head of Immunology – TGA

Virologist
Consultant – WHO
Consultant – Environmental Pathogens P/L

Key Interest Areas:
Vaccine development, manufacturing and regulatory advice

Disclosures

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Recent advisory meetings:

- WHO IVB
- Seqirus
- MSD
- GPN
- Biocelect/Biointellect

The COVID-19 global health emergency is over

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3 years after WHO declared SARS-CoV-2 a PHEIC

(Public health emergency of international concern)

Drop in the death rate from 100,000/wk (Jan 2021) to 3500/wk (April 2023) (382 deaths in the last 7 days)

“Not to let down its guard, to dismantle the systems it has built, or to send the message to its people that Covid-19 is nothing to worry about"

World Health Organization

What are we dealing with now?

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- A steady state respiratory infection in the community
- The virus, SARS-CoV-2, has been mutating overtime towards less severity
  – Mostly Asymptomatic/Mild infections
- Omicron JN.1 lineage viruses are predominating globally. KP.2 in the USA now detected in Australia (FLiRT)
- There is no need to catastrophise every appearance of each new subvariant.
- Vaccines are available and important for those over 75 years and health compromised persons: can be rapidly updated
  – The rise of hybrid immunity.
- Antiviral Drugs are available
- Home testing kits available
- In Australia: approx. 1-3 thousand people are expected to die annually from COVID-19 but the death rate is declining

Challenges remain: Covid fallout…

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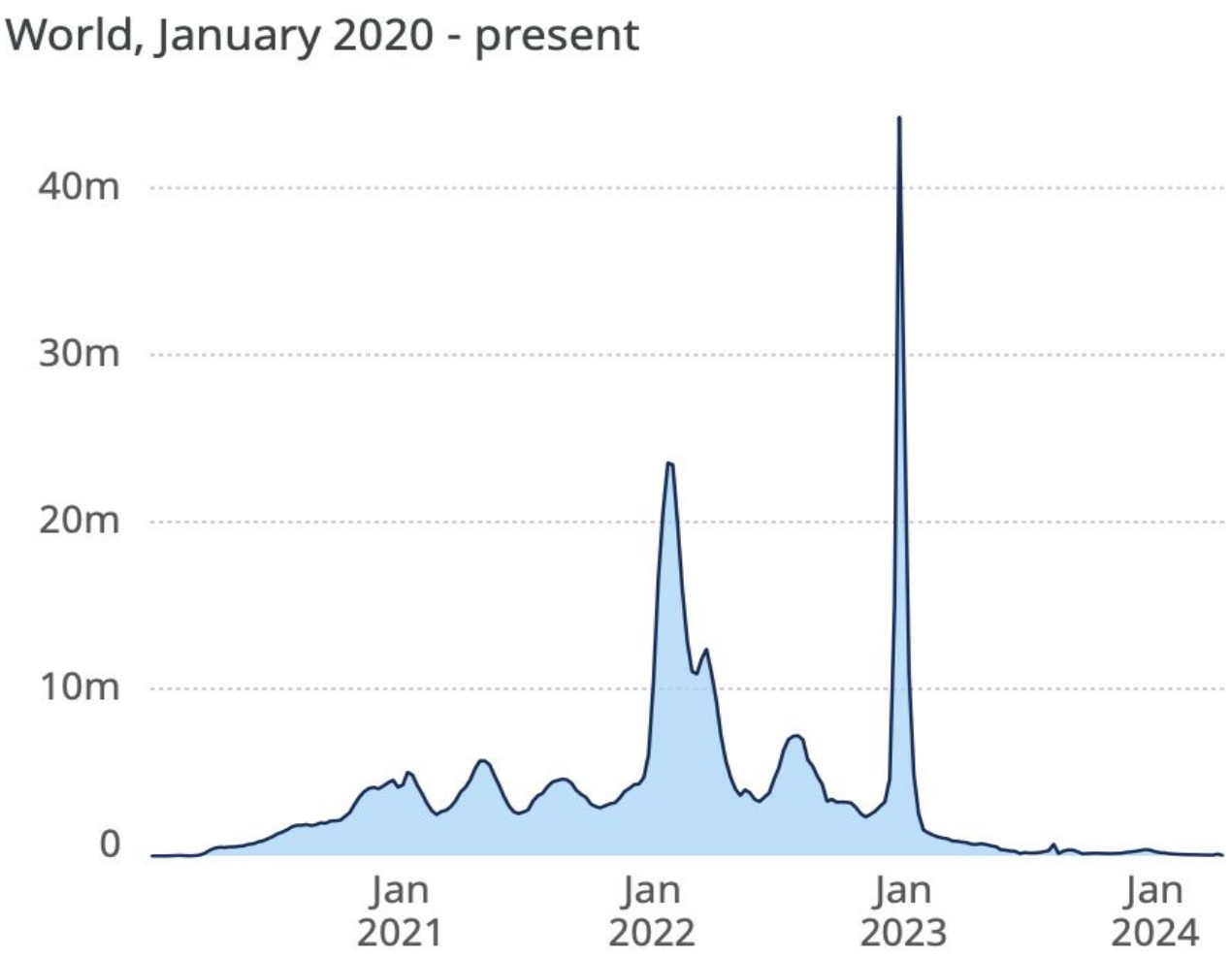
- Long Covid (10%)
- Community blasé attitude to booster vaccinations resulting in low vaccine uptake
- Covid rebound (after AVs)
- Damage to health & education programs, economies etc
- Vaccine injury, Mandates, job/income losses
  – class actions
- Vaccine fatigue, distrust, Fear and disinformation
- Need: Better Vaccines, Antivirals and other drugs

Reported SARS CoV 2 / COVID-19 cases

https://covid19.who.int

Total COVID-19 cases reported to WHO (weekly)



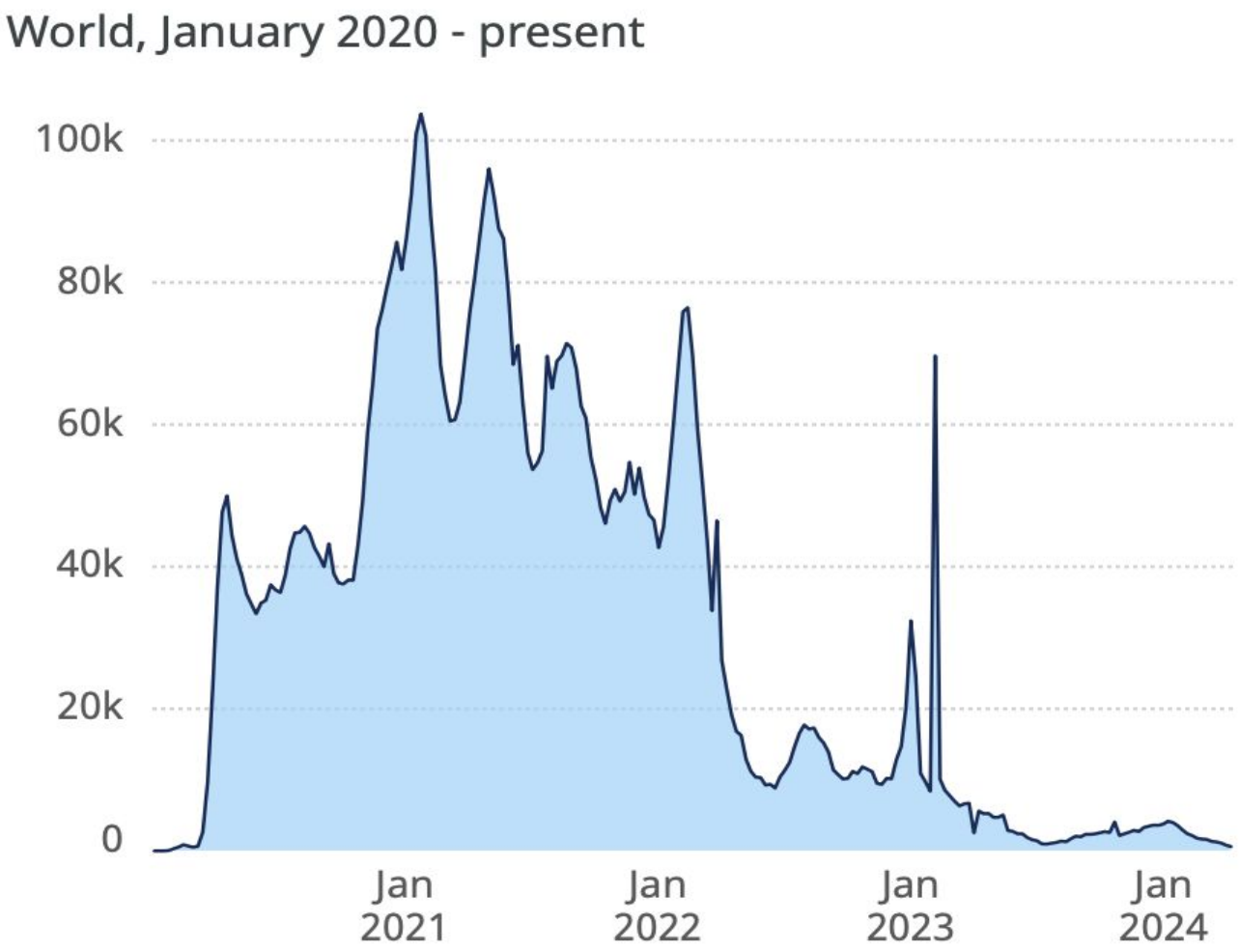
775,364,261 Cases

7 May 2024

Reported SARS CoV 2 / COVID-19 Deaths

https://covid19.who.int

Total COVID-19 deaths reported to WHO (weekly)



7,046,320 Deaths

21 April 2024

CFR 0.91

Daily new confirmed COVID-19 deaths per million people

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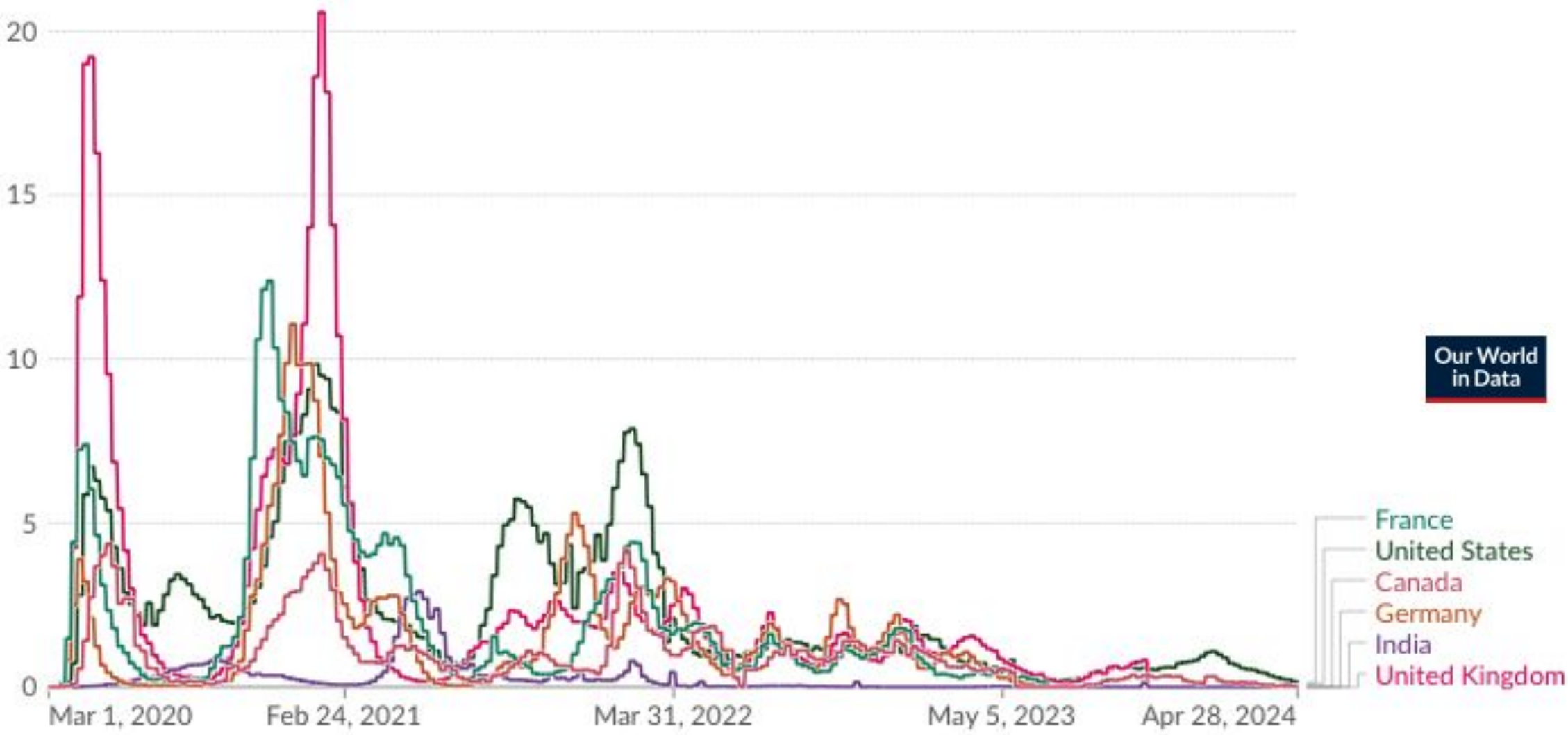

Australian situation: SARS CoV 2 / COVID-19 11,836,372 cases and 25,165 deaths. CFR 0.22 : 22 April 2024

https://covid19.who.int

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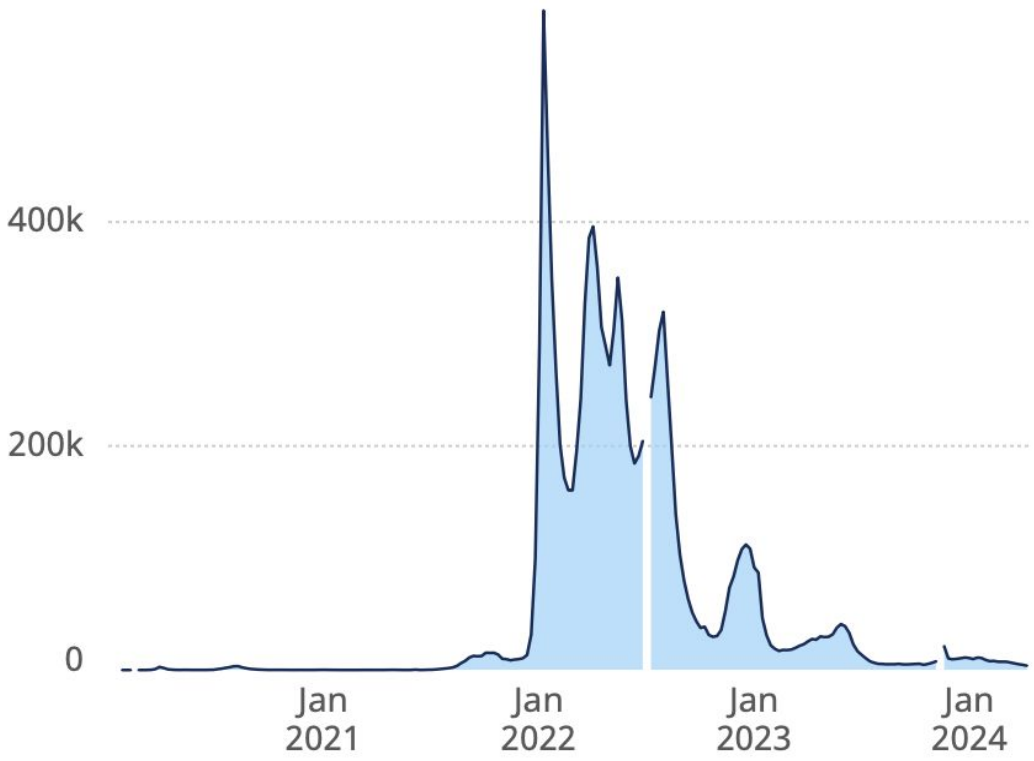
Australian situation: Influenza 0.09%

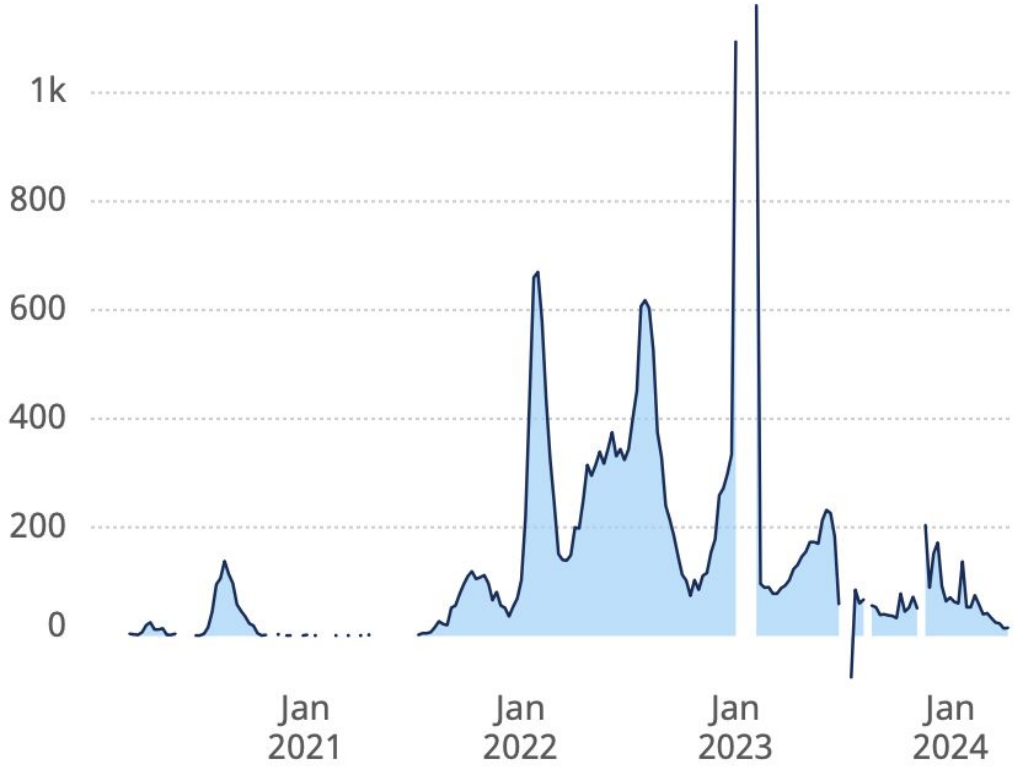
Total COVID-19 cases reported to WHO (weekly)

Australia, January 2020 - present



Total COVID-19 deaths reported to WHO (weekly)

Australia, January 2020 - present



Deaths from and with COVID-19 in Aboriginal and Torres Strait Islander people, age-specific death rates per 100,000 persons

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	Indigenous			Non-Indigenous people		
Age at death	Males	Females	Persons	Males	Females	Persons
0-44	2.7	2.0	2.4	1.0	0.6	0.8
45-54	21.1	18.1	19.5	5.4	3.7	4.5
55-64	54.1	37.5	45.3	14.2	7.9	11.0
65-74	101.5	97.2	99.2	55.2	28.0	41.2
75+	433.6	479.7	459.7	376.1	277.7	322.3

https://www.abs.gov.au/articles/covid-19-mortality-australia-deaths-registered-until-31-january-2024

Australian Bureau of Statistics

Excess Deaths per 100,000 during Covid-19

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Russia:	1125.13
India:	510.52
USA:	405.81
UK:	389.91
Sweden:	226.03
Australia:	131.91

https://ourworldindata.org/mortality-risk-covid

Epidemiology

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- Spread by respiratory droplets
- Hand/mouth/eyes/nose/fomites
- R = 5-6
- Virus is easily destroyed
- Masks - effective if used properly!
- **Sweden** was less affected than most comparable countries that implemented stricter lockdown measures
- **Hygiene measures and isolation effective**

Hygiene measures and isolation effective

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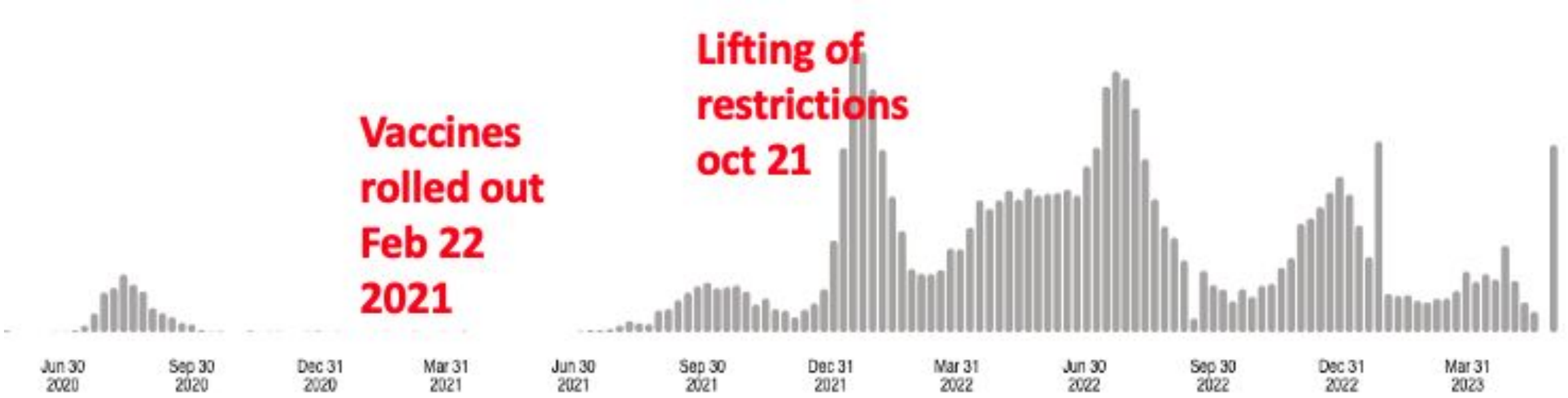
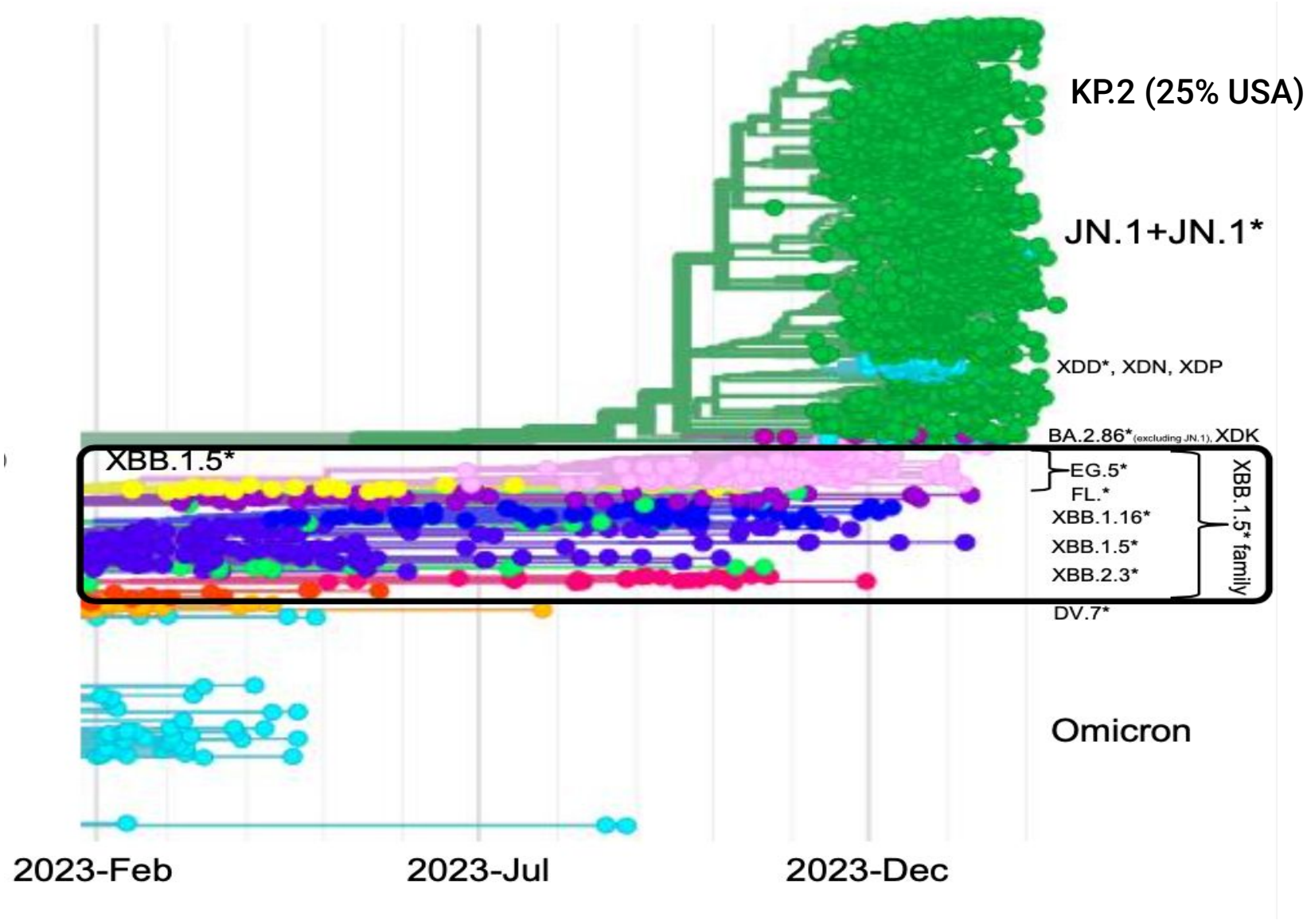
Covid Deaths in Australia




KP.2 (25% USA)
JN.1+JN.1*
XDD*, XDN, XDP
BA.2.86* (excluding JN.1), XDK
XBB.1.5*
EG.5*
FL.*
XBB.1.16*
XBB.1.5*
XBB.2.3*
XBB.1.5* family
DV.7*
Omicron
2023-Feb
2023-Jul
2023-Dec

COVID-19 Vaccine Coverage

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Australia 71.1M doses

- 85% primary series completed
- 56% at least one booster dose
- 44.3% at least two booster doses

Globally 13.59BN

- 67% primary series completed
- 32% at least one booster dose

World Health Organization

Australia: COVID-19 Booster Coverage last 6 months

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Australia - wide

- >75 years: 39.9%
- 65-74 years: 25.0%
- 18-64 years: 3.9%

Aged Care Residents

43%

Aboriginal and Torres Strait Islanders

11.6%

NDIS

26.1%

https://www.health.gov.au/sites/default/files/2024-05/covid-19-vaccine-rollout-update-10-may-2024.pdf

Seroprevalence studies

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- Globally: seroprevalence from infection or vaccination was 59.2%, (95% CI [56.1% to 62.2%]).
- **True infections of COVID-19 around the world far exceed reported cases.**
- 77.7% in England
- 79.5% in Wales
- 74.5% in Northern Ireland
- 79.8% in Scotland
- >85% in Italy
- **98% Australia**
- **Australia:** At least 64% of 0–19 year-olds have been infected with COVID-19 (nucleocapsid antibodies, signifying past infection)

Seroprevalence in Australia

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- Blood Donor study (Kirby Institute 2022)
- Anti-spike antibodies very high (98%) across all jurisdictions
- Anti-nucleocapsid seroprevalence was highest among donors aged 18–29 years at 27%, declining with increasing age
  – highest in Queensland (26%)
- Children and Adolescents (NCIRS 2022)
- At least 65% of 0–19-year-olds have been infected with COVID-19
- spike antibodies universally detected in vaccinated individuals
  – 65% of vaccinated individuals also had nucleocapsid antibodies, signifying past infection

Vaccination platforms

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- **mRNA vaccines**, **viral vectored vaccines**, and **recombinant protein vaccines** have demonstrated impressive efficacy and safety (Phase 3 trials)
- **WHO:** The necessity and risk-benefit balance of administering continuous booster doses of mRNA vaccines to healthy individuals under 50 years old are uncertain
  - that, "data to support an additional dose for healthy younger populations are limited; preliminary data suggest that in younger people, the benefit is uncertain."
  - “Tipping point” as people become infected and vaccinated together with favourable viral mutation leading to less severity. Covid-19 becomes less important to non risk groups in the community.

Vaccines available in Australia (Updated XBB lineage; Monovalent)

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Paediatric formulations

Comirnaty Omicron XBB.1.5
5 to <12 years

Adolescent and adult formulations

Comirnaty Omicron XBB.1.5

>12 years

Spikevax Omicron XBB.1.5

≥12 years

(Nuvaxoid XBB.1.5 vaccine still undergoing registration process)

ATAGI COVID-19 Vaccine Recommendations

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VE against mortality 70-78%. Wanes after 8-12 weeks.

Age	With severe immunocompromise	Without severe immunocompromise
≥ 75 years	Recommended every 6 months	Recommended every 6 months
65-74 years	Recommended every 12 months and can consider a dose every 6 months	Recommended every 12 months and can consider a dose every 6 months
18-64 years	Recommended every 12 months and can consider a dose every 6 months	Can consider a dose every 12 months
5-17 years	Can consider every 12 months	Not recommended
<5 years	Not recommended	Not recommended

https://immunisationhandbook.health.gov.au/contents/vaccine-preventable-diseases/covid-19

Australia's vaccination program

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- It’s important that everyone over 75 and those in high-risk groups get vaccinated and take boosters around every 6 months, and that vulnerable people and those with complex needs, take sensible precautions, especially in closed or poorly ventilated spaces.
  – High-risk groups will gain the most from receiving a COVID-19 booster.

- Vaccines for the vulnerable, masks, sensible social distancing, hygiene measures, as well as continuing education programs, are still important in our post-pandemic response.

- People in high-risk groups including older adults and people with immune problems should get regular booster vaccines every 6 months.

Medical Conditions where COVID-19 vaccines are recommended

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- Any immunocompromising condition
- Cardiac disease
- Chronic respiratory condition
- Chronic neurological condition
- Chronic metabolic condition
- Chronic kidney disease stage 4 and 5
- Haematological disorders
- Chromosomal abnormality
- Obesity

Pregnancy

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- Unvaccinated pregnant women are at increased risk of severe disease from COVID-19.
- …are recommended to receive a primary course of COVID-19 vaccine.
- …the latest (monovalent XBB)
- mRNA COVID-19 vaccines have not been formally studied in pregnant women, ATAGI considers them suitable and safe for use.
- Women who are breastfeeding can receive COVID-19 vaccine at any time

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Total adverse event reports following immunisation to 29 October 2023

2.0	139,654	68,864,839
Reporting rate per 1,000 doses	Total adverse event reports	Total doses administered
48,857	81,913	7,628
Total reports for Vaxzevria	Total reports for Comirnaty	Total reports for Spikevax
1,025	781	
Total reports for Nuvaxovid	Total reports for brand not specified	

Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Adverse Events

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Comirnaty and Spikevax (mRNA)

Irritability, drowsiness, injection site tenderness, fatigue and fever. Headache, loss of appetite and muscle pain

Anaphylaxis

around 10 per million doses

Myocarditis and/or pericarditis

Very rare. The highest incidence has been reported in adolescent males after a second dose of an mRNA vaccine (Comirnaty or Spikevax)

Nuvaxovid (r Protein)

Injection site tenderness (75%), injection site pain (53%), muscle pain (51%), headache (50%), malaise (41%), joint pain (24%) and nausea or vomiting (15%). Adverse events occurred at a similar frequency in adolescents aged 12-17 years and in adults aged ≥18 years.

Anaphylaxis R

Rate undetermined <10 per million doses.

Myocarditis and/or pericarditis

Very rare. Low incidence of myocarditis. Pericarditis

Anaphylaxis

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- Anaphylaxis after one mRNA COVID-19 vaccine is a contraindication to all other mRNA COVID-19 vaccines
- Comirnaty and Spikevax vaccines would be contraindicated in someone with Anaphylaxis to **polyethylene glycol (PEG)**,
- Nuvaxovid would be contraindicated in someone with Anaphylaxis to **polysorbate 80**

Vaccines

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- We need at least 3 doses of vaccine
  - **Current vaccines do not stop transmission (ameliorate severity)**
  - Heterologous vaccination gives better protection (e.g. mRNA followed by protein)
  - Hybrid gives the best (vaccine plus natural infection)
- Adverse events do occur and severe adverse events are rare affecting around 1/50,000-100,000 persons, but that people (especially men) under 30 have a higher risk of myocarditis from mRNA vaccines
- AZ vaccine: TTS - increased GBS signal? Withdrawn
- Protein vaccine (e.g.Novavax) has a lower risk of myocarditis

https://www.scientificamerican.com/article/is-the-novavax-covid-vaccine-better-than-mrna-vaccines-what-we-know-so-far/#:~:text=Compared%20with%20mRNA%20vaccines%2C%20the,does%20not%20have%20zero%20risk.

Vaccine platforms

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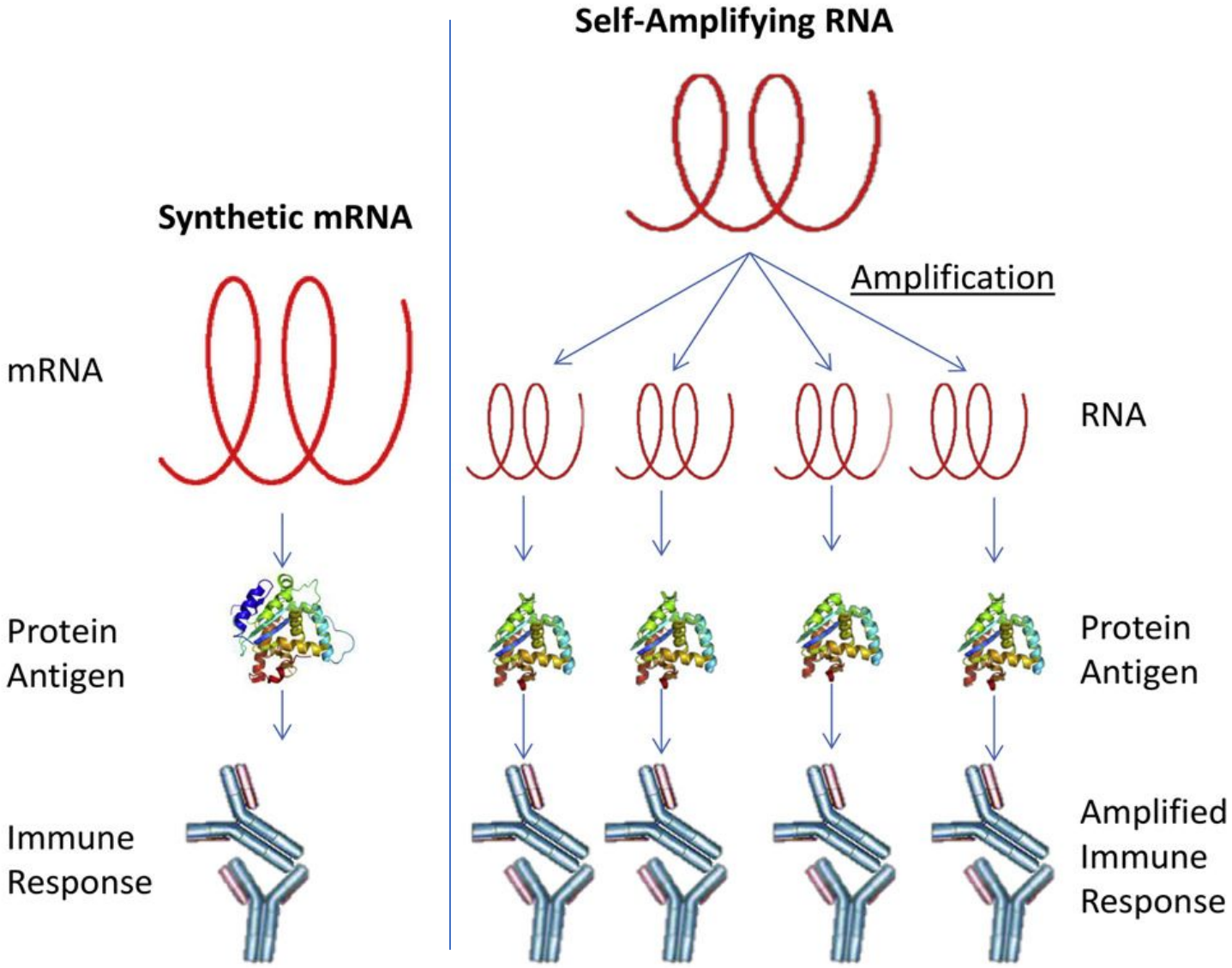
- mRNA vaccines, viral vectored vaccines, and recombinant protein vaccines have demonstrated impressive efficacy and safety
- Protein-based vaccines options offer advantages and can be used as a booster if preferred by the patient. (More vaccine providers guarantee supply)
- Self Amplified RNA (SA-RNA) vaccines – coming? ARTC-154 Arcturus/CSL
  APPROVED in JAPAN



Vogel et al 2017 https://doi.org/10.1016/j.ymthe.2017.11.017

COVID-19 Vaccine candidates in clinical trials

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Platform		Number	Percent %
PS	Protein subunit	59	32
VVnr	Viral Vector (non-replicating)	25	14
DNA	DNA	17	9
IV	Inactivated virus	22	12
RNA	RNA	43	24
VVr	Viral Vector (replicating)	4	2
VLP	Virus like particle	7	4
VVr+APC	VVr + Antigen presenting cell	2	1
LAV	Live attenuated virus	2	1
VVnr=APC	VVnr + Antigen presenting cell	1	1
BacAg-SpV	Bacterial antigen-spore expression vector	1	1

Symptoms

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Symptoms may appear 2-14 days after exposure to the virus. Anyone can have mild to severe symptoms.

Possible symptoms include:

- Fever or chills
- Cough
- Shortness of breath or difficulty breathing
- Fatigue
- Muscle or body aches
- Headache
- New loss of taste or smell
- Sore throat
- Congestion or runny nose
- Nausea or vomiting or diarrhoea

Symptoms

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Emergency warning signs for COVID 19:

- Trouble breathing
- Persistent pain or pressure in the chest
- New confusion
- Inability to wake or stay awake
- Pale, Gray, or blue-coloured skin, lips, or nail beds, depending on skin tone

Children

MIS-C (multisystem inflammatory disease)

An unusual presentation in children, similar to Kawasaki Disease (rare):

- Hypotension
- Non-purulent conjunctivitis
- Polymorphic rash
- Mucosal changes
- Swollen extremities

SARS CoV 2 is a neurotropic virus

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- 10%-15% of patients develop acute neurologic symptoms.
- is associated with specific neurologic syndromes in the form of stroke or acute neuroinflammatory disorders, such as meningitis or encephalitis.
- Less frequently, peripheral nerve involvement, such as muscle weakness or Guillain-Barre syndrome.

Clinical symptoms

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- **Multifocal pathogenesis**

  – sometimes instigating destruction to blood vessel endothelial cells leading to blood clots, strokes, heart failure, heart attack, as well as potential kidney and neurological problems (Sardu et al., 2020)

- **Cytokine storm**

  – Lymphocytopenia,
  – elevation of inflammatory markers like C-reactive protein (CRP)
  – elevation of cytokine interleukin 6 (IL-6) (Chen G. et al., 2020)

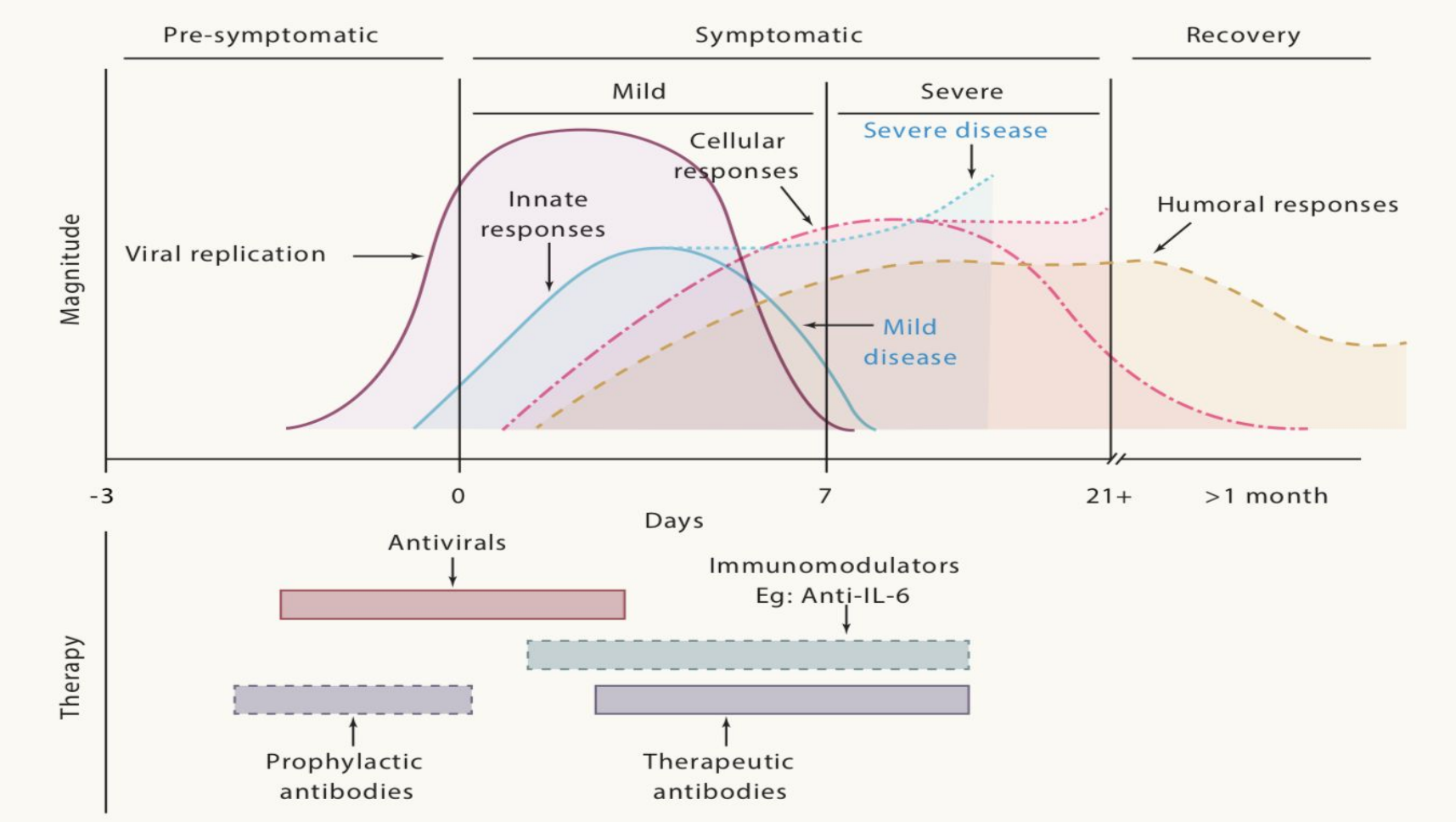
- **Patients with Pre-existing Neuromuscular Conditions**

  – Exacerbation of Neuromuscular Degenerative Conditions
  – Autoimmune conditions, GBS.
  – Virus reactivation – Herpes group, enteroviruses, HTLVs
  (Jacob et al., Front Neurol. 2022. doi: 10.3389/fneur.2022.914411)

COVID-19: Clinical course

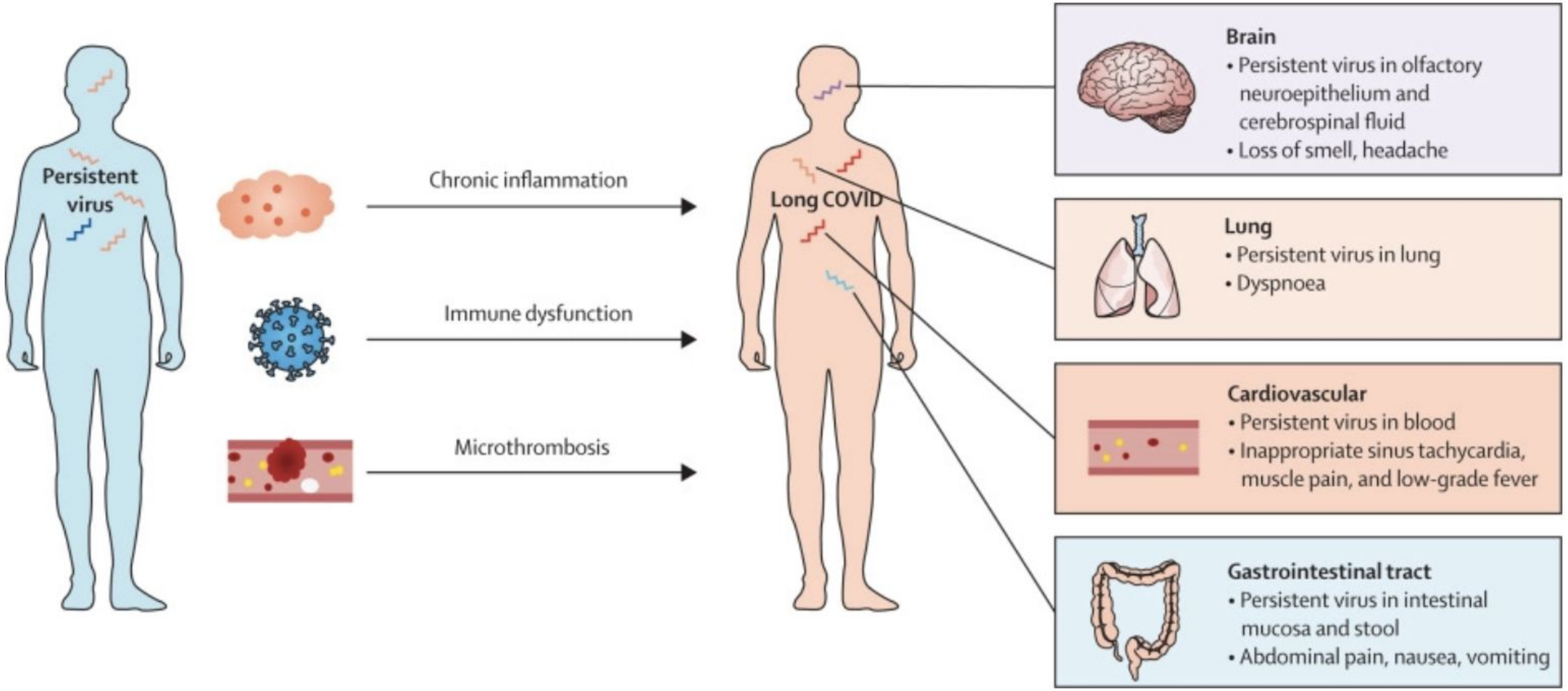
PCR TEST

RAT TEST



- Some have significant sequalae
- Many have poor neutralizing antibody.
- Antibody wanes leading to reinfection
- Post-COVID19 syndrome

Long Covid (Post-Covid syndrome)



Post-COVID-19 syndrome (Long COVID)

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Definition

The continuation or development of new symptoms 3 months…..

Numbers affected

- 10–20% of people
- It is believed that more than 50 million people across the WHO European Region have experienced Long Covid during the first three years of the pandemic and over 20 million in the USA

WHO

https://www.who.int/europe/news-room/fact-sheets/item/post-covid-19-condition

Post-COVID-19 syndrome (Long COVID)

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https://www.aihw.gov.au/reports/covid-19/long-covid-in-australia-a-review-of-the-literature/summary

COVID-19: Long term effects: Post-COVID-19 syndrome

Post-COVID conditions, long COVID-19, post acute sequelae of SARS COV-2 infection (PASC).

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Anyone who gets COVID-19 can have long-term effects, including people with no symptoms or mild illness with COVID-19.

Most commonly reported symptoms

- Fatigue/dizziness
- Symptoms that get worse after physical or mental effort
- Recurrent Fever
- Difficulty breathing or shortness of breath and cough

More rarely

Neurological symptoms, difficulty thinking or concentrating, headache, sleep problems, dizziness, pins-and-needles, loss of smell or taste, and depression

- Joint or muscle pain
- Heart symptoms
- Digestive symptoms
- Blood clots and (vascular) issues
- Rash
- Changes in the menstrual cycle
- Reactivation of Herpes viruses – Shingles, GBS, Bell's palsy

Post-COVID-19 syndrome

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Long term effects:

- Organ damage: People who had severe illness with COVID-19 might experience organ damage affecting the heart, kidneys, skin and brain.
- Inflammation - leading to the development of new conditions, such as diabetes or a heart or nervous system condition.
- Multisystem inflammatory syndrome.

Recent research:

- COVID-19 causes brain "abnormalities" 6 months after symptoms are gone
- Changes to the brainstem and front lobe in areas of the brain associated with fatigue, insomnia, anxiety, depression, headaches, and cognitive issues.
- Special MRI to detect and monitor neurological conditions such as microbleeds, vascular malformations, brain tumours, and stroke. (CDC 2022)

Long COVID and elevated inflammatory biomarkers

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- Long COVID patients present elevated inflammatory biomarkers
  – eg interleukin-6, C-reactive protein, tumour necrosis factor-α,
  – function as a core set of blood biomarkers that can be used to diagnose and manage long COVID patients in clinical practice.

- Evidence, including from murine studies on the related Middle East respiratory syndrome and severe acute respiratory syndrome, identified the role of coronaviruses in complement activation, which could be a key contributor to COVID-19 pathogenesis

Lai YJ, Liu SH, Manachevakul S, Lee TA, Kuo CT, Bello D. Biomarkers in long COVID-19: A systematic review. doi: 10.3389/fmed.2023.1085988.
Phetsouphanh C, Darley DR, Wilson DB, et al. Immunological dysfunction persists for 8 months following initial mild-to-moderate SARS-CoV-2 infection. Nat Immunol 2022;23(2):210–16. doi: 10.1038/s41590-021-01113-x.

Long COVID and elevated inflammatory biomarkers
Complement

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- Dysregulation of immune responses, as well as complement and coagulation pathways, leads to inflammation and is implicated in the tissue damage
- Patients with COVID-19 demonstrated activation of the complement pathway, which was related to disease severity a generalized thrombotic microvascular injury [and decreased levels of C3 plus high sC5b-9 levels, which were associated with poor prognosis and respiratory failure, respectively
- Blockade of specific complement pathway components may be a potential therapeutic strategy for COVID-19
- Recent therapeutic options in hospitalized patients with COVID-19 have included blocking complement pathway components targeted include C5 inhibitors (e.g., eculizumab and pozelimab), C3 inhibitors (e.g., AMY-101), and LP inhibitors (e.g., narsoplimab)

Fang S., Wang H., Lu L., Jia Y., Xia Z. Decreased complement C3 levels are associated with poor prognosis in patients with COVID-19: a retrospective cohort study. *Int Immunopharm.* 2020;89 Holter J.C., Pischke S.E., de Boer E., Lind A., Jenum S., Holten A.R., et al. Systemic complement activation is associated with respiratory failure in COVID-19 hospitalized patients. *Proc Natl Acad Sci U S A.* 2020;117:25018–25025
Risitano A.M., Mastellos D.C., Huber-Lang M., Yancopoulou D., Garlanda C., Ciceri F., et al. Complement as a target in COVID-19? *Nat Rev Immunol.* 2020;20:343–344

Treatments

https://www.health.gov.au/health-alerts/covid-19/treatments/about

Molnupiravir and Paxlovid (nirmatrelvir/ritonavir)

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Both antivirals were associated with lower all-cause mortality risk—a 39% reduction for molnupiravir, 75% for paxlovid compared with no antiviral use.

Also, while Paxlovid is authorized for use in children as young as 12 years old, molnupiravir isn't authorised for use in children younger than 18 years because it may affect bone and cartilage growth.

Molnupiravir, is not recommended for pregnant individuals because animal studies suggest it could cause foetal harm.

https://doi.org/10.1016/j.ymthe.2017.11.017

Covid Rebound

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COVID-19 rebound in people who’ve taken nirmatrelvir/ritonavir appears to be mild and short-lived, resolving, on average, in 3 days without additional anti-COVID-19 treatment.

https://jamanetwork.com/journals/jama/fullarticle/2793357?guestAccessKey=59a25017-a249-4c12-8cbf-dfd3df7e90a1&utm_source=silverchair&utm_medium=email&utm_campaign=article_alert-jama&utm_term=mostread&utm_content=olf-widget_01272024&adv=000004400667

COVID-19 Fallout

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Vaccine Mandates

- Vaccine Mandates Landmark Case 28/2/24
- Queensland public servants who were stood down or sacked after refusing to comply with Covid-19 vaccine mandates will likely be back to work and seek compensation following a landmark legal win by a group of police officers and paramedics.

Vaccine injury

- Class actions
- Federal Government has implemented a claims scheme for people who suffer a moderate to severe impact following an adverse reaction to a TGA-approved COVID-19 vaccine.

https://www.health.gov.au/our-work/covid-19-vaccine-claims-scheme

Long covid and CFS

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- Both conditions exhibit overlapping symptoms:
- For Long Covid a myriad of symptoms that can persist for weeks or months commonly include fatigue, dyspnea, cognitive impairment (brain fog), muscle weakness, joint pain, and headaches gastrointestinal issues, chest pain, palpitations, and mood disturbances
- Chronic Fatigue Syndrome predominantly manifests as profound fatigue lasting for at least six months, often exacerbated by physical or mental exertion,
- Other hallmark symptoms include unrefreshing sleep, cognitive dysfunction, orthostatic intolerance, and flu-like symptoms after exertion.
- CFS: Excess levels of serotonin and its metabolites in the central system are also thought to be key
- Excess serotonin leads to reduced motor activity which appears to be a leading contributor to the fatigue

Yamashita M, Yamamoto T. Tryptophan circuit in fatigue: From blood to brain and cognition. Brain Res. 2017 Nov 15;1675:116-126.

Cotel F, Exley R, Cragg SJ, Perrier JF. Serotonin spillover onto the axon initial segment of motoneurons induces central fatigue by inhibiting action potential initiation. Proc Natl Acad Sci U S A. 2013 Mar 19;110(12):4774-9

Concluding remarks

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- 2nd generation vaccines are needed
- **Ideally Vaccines must stop transmission**
- mRNA, and recombinant proteins vaccines are currently the most successful platforms
  – Mild to severe adverse reactions
  –Those under 30 should know the risks of myocarditis
  –Self amplifying RNA?
- **COVID vaccines must gain acceptance**
  – Annual vaccination
  – Biannual vaccination for those at high risk

Next challenges

- Continuous pandemic preparedness
- Avoidance of the cycle of neglect
- Long Covid
- Vaccine injury
- Use of MoAbs
- Better AV drugs
- Threat of multiple respiratory agents. e.g. Influenza, Covid-19 hMPV and RSV

Acknowledgements