Healthed

COVID-19 In The Elderly

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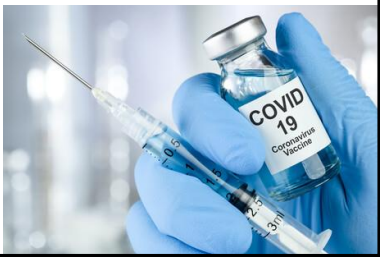
Immunisation Coalition Director and Scientific Advisory Board Member

Disclosures

- Principal Investigator on numerous vaccine clinical trials
  - including the following SARS-CoV-2 vaccines;
    - UQ
    - Novavax (including approved vaccine and Omicron specific booster)
    - Serum Institute of India
    - Symvivo
    - Tetherex
    - Sanofi (mRNA and protein)
  - And many Influenza and RSV vaccine and antibody studies
    - Including with Moderna, Novavax, Vaxxas, Vir, Visterra
- Immunisation Coalition Director and Scientific Advisory Board Member
- Speaker Honoraria includes Seqirus, Novartis, Gilead, Sanofi, MSD and Janssen
- Medical Advisory Board Memberships including AstraZeneca, GSK, MSD, Moderna, Biocelect/Novavax, Seqirus and Pfizer
- Content and opinions presented today are my own

Outline

- COVID-19 Basic Statistics/Epidemiology
  - Globally and Australia
- COVID-19 Virology
  - Particularly new variants and subvariants
- COVID-19 and the Elderly
  - Including Residential Aged Care Facilities (RACFs)
- COVID-19 Vaccination
  - Vaccination status and recommendations
- Updated Vaccines
  - Bivalent and most recent update
- COVID-19 Therapies
  - Including a discussion of evidence for Molnupiravir
- Summary



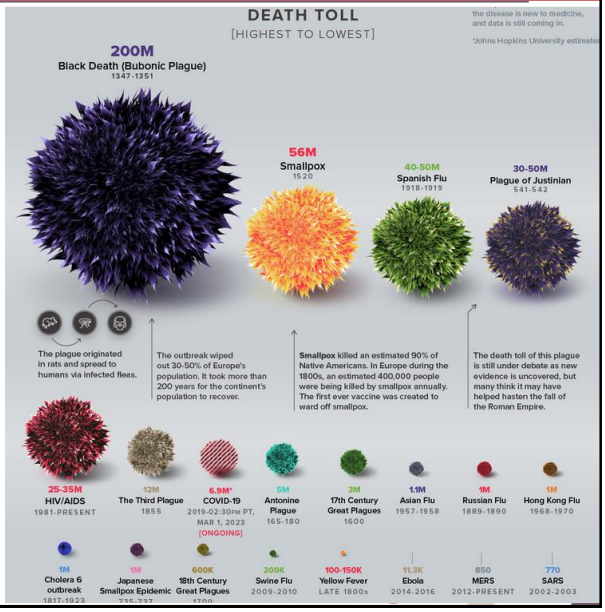
COVID-19 Basic Statistics/Epidemiology

Globally and Australia

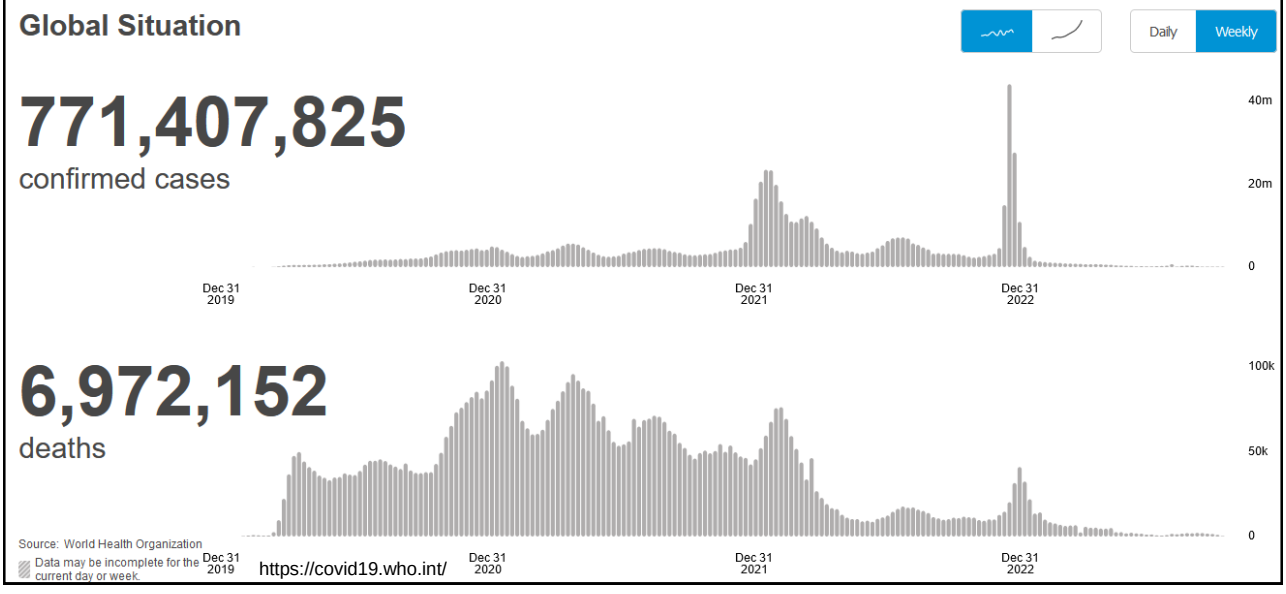
COVID-19 Basic Stats

- Discovered Wuhan China Dec 2019
- Pandemic declared 11th March 2020
- PHEIC terminated 5th May 2023
  - “ongoing and established”
- End of COVID-19 emergency response
  - AHPPC 20 October 2023
- Worldwide
  - Cases 771.4 million
  - Deaths 6.97 million
- Australia
  - Cases 11.8 million
  - Deaths 22 837

https://covid19.who.int/
https://www.visualcapitalist.com/history-of-pandemics-deadliest/

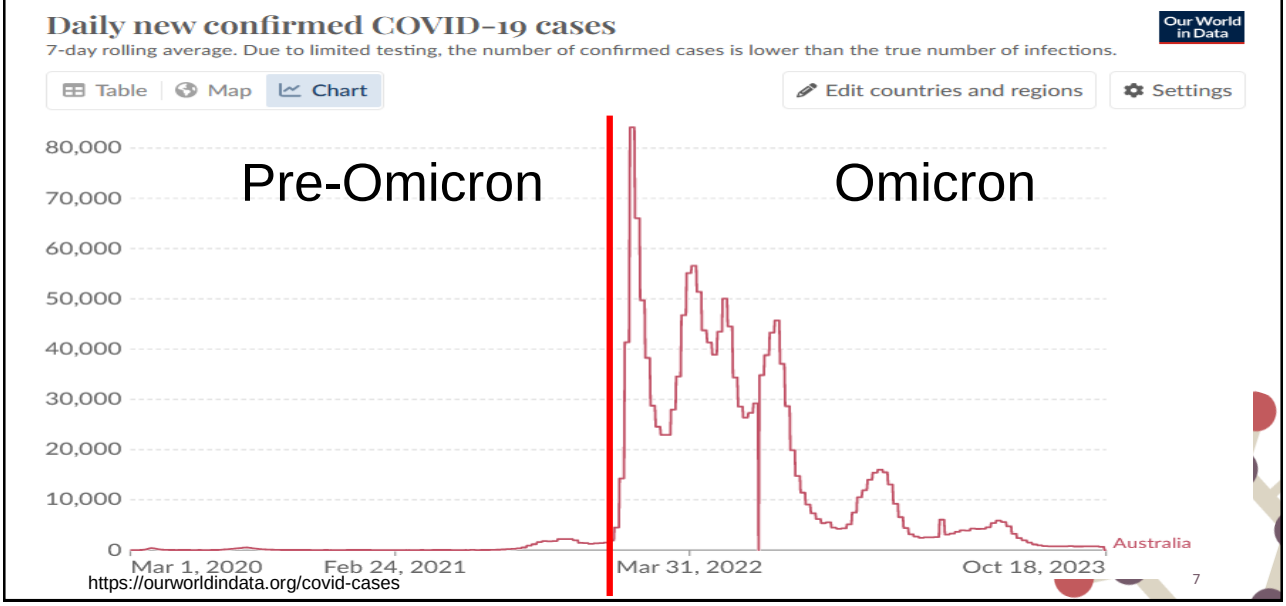


COVID-19 Global



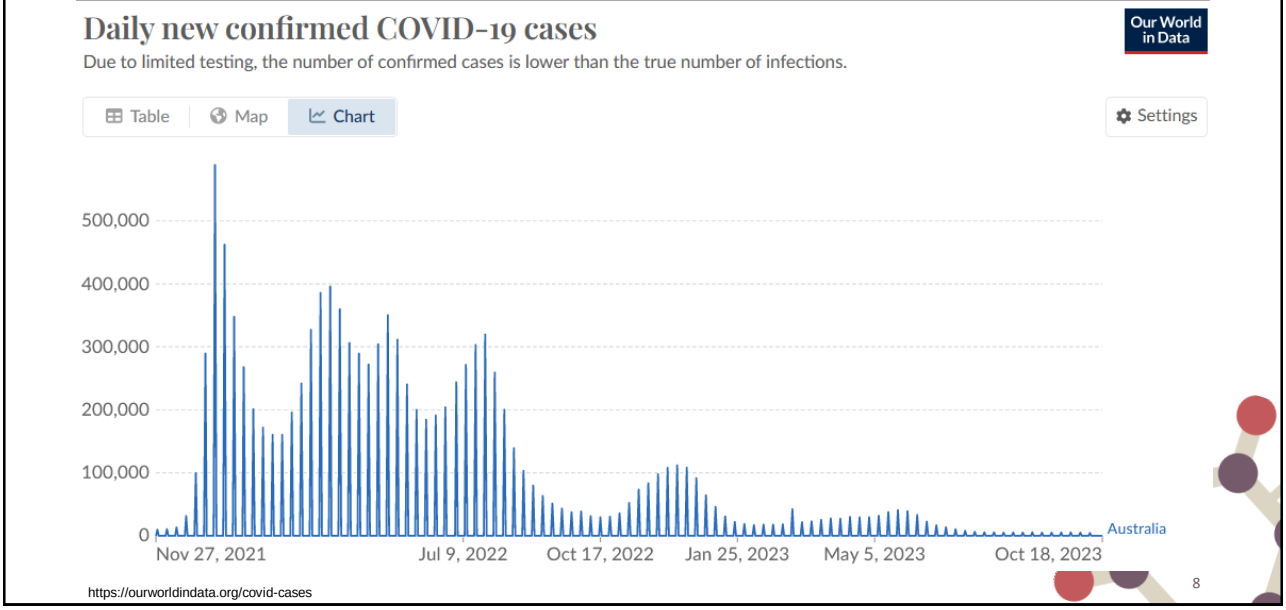
https://covid19.who.int/

COVID-19 Australia-Entire Pandemic



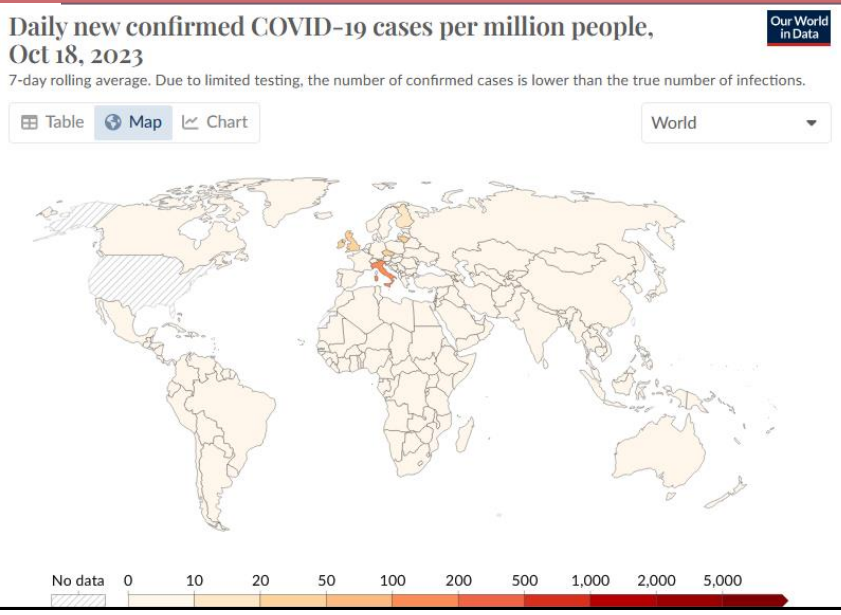
https://ourworldindata.org/covid-cases

COVID-19 Australia-Omicron



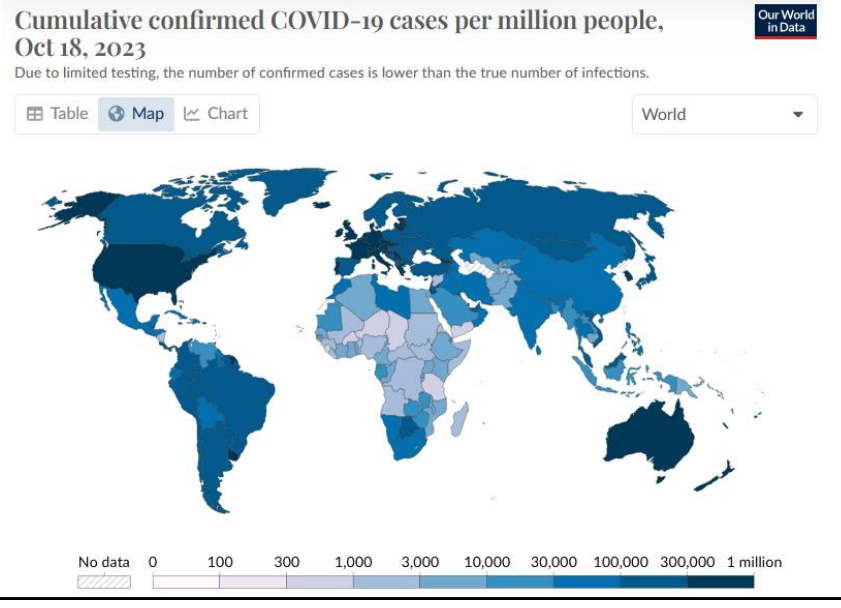
https://ourworldindata.org/covid-cases

How Do We Compare-New Cases



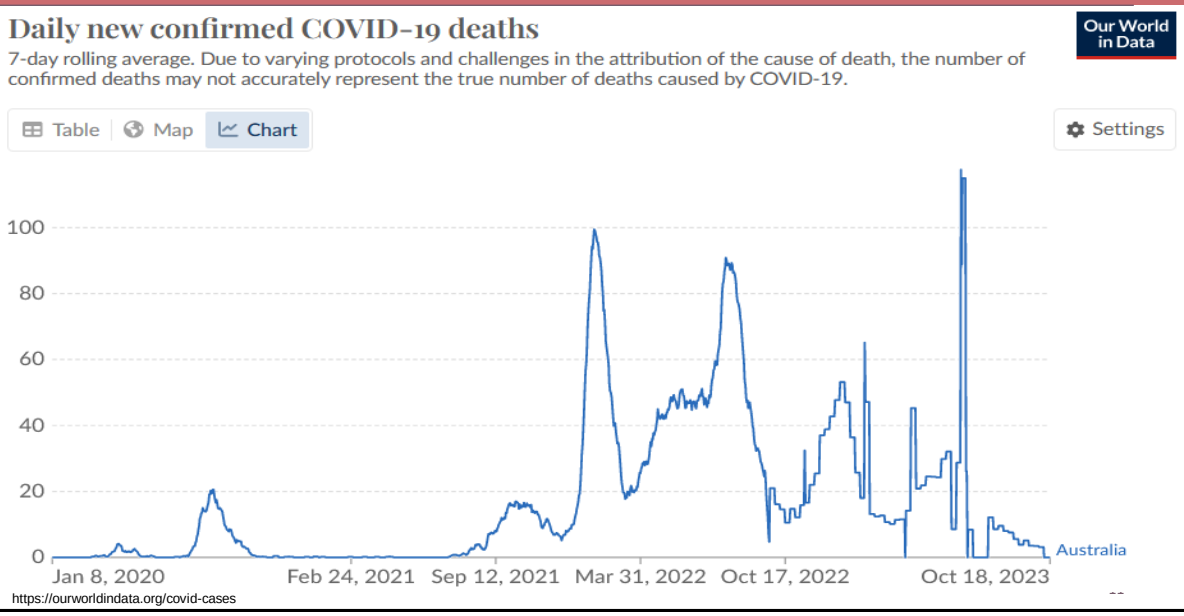
- Case numbers currently relatively Low
  - Rates of testing relevant here

How Do We Compare-Cumulative Cases



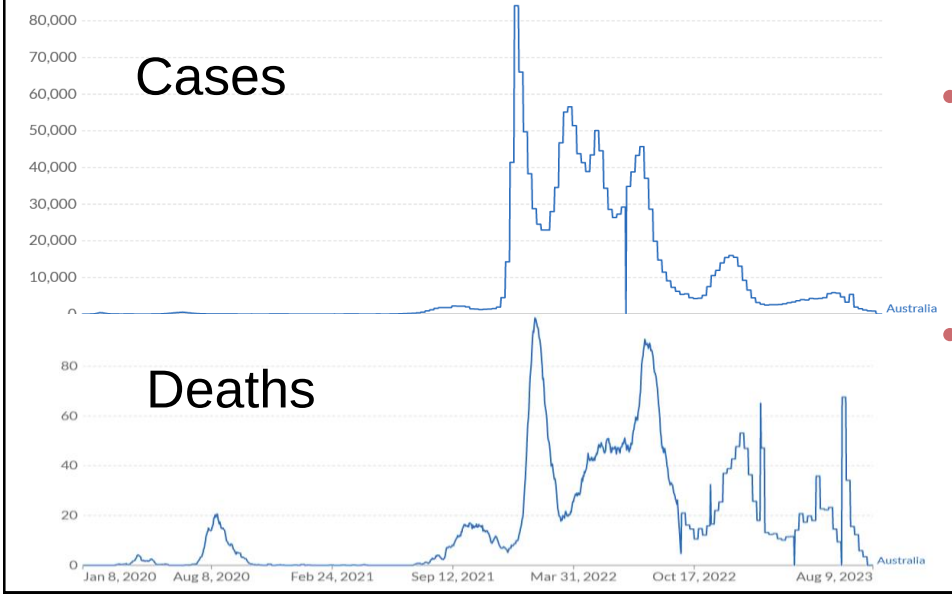
- Case numbers in Australia cumulatively relatively high
  - Access to testing relevant here

COVID-19 Australia-Deaths



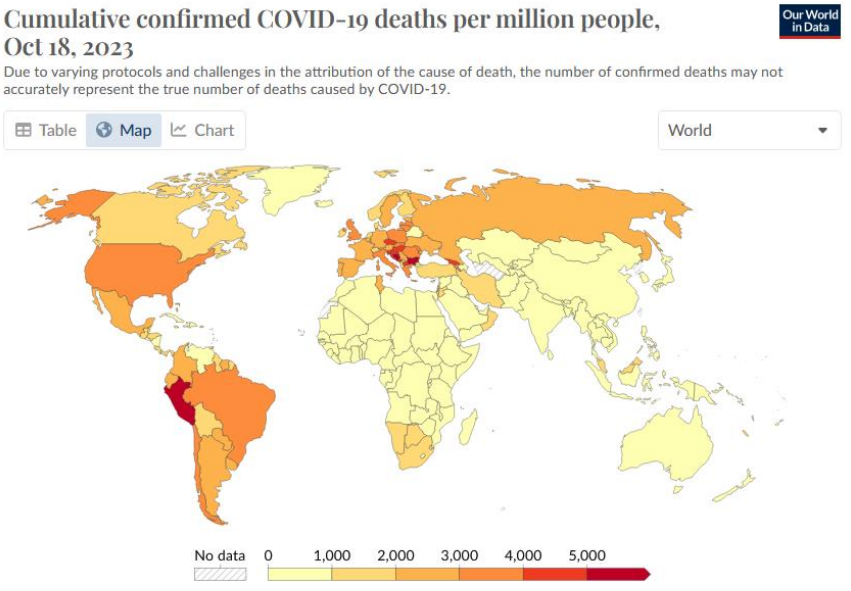
https://ourworldindata.org/covid-cases

COVID-19 Australia-Cases v. Deaths



- Relatively very few deaths prior to large Omicron waves commencing December 2021
- Waves successively smaller subsequently
  - Case finding relevant

How do we compare-cumulative deaths



Perhaps the most important

- Deaths cumulatively relatively **LOW**

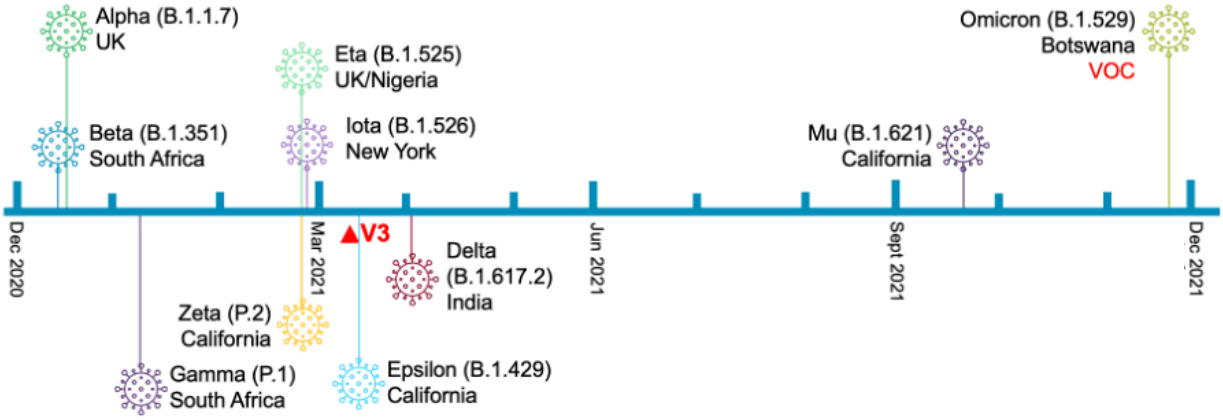
Many factors likely contributed, including

- High vaccination rate, prior to widespread community transmission
- First widespread community transmission was with Omicron variant
- Excellent health care system
  - Antivirals
  - High standards of supportive care

COVID-19 Virology

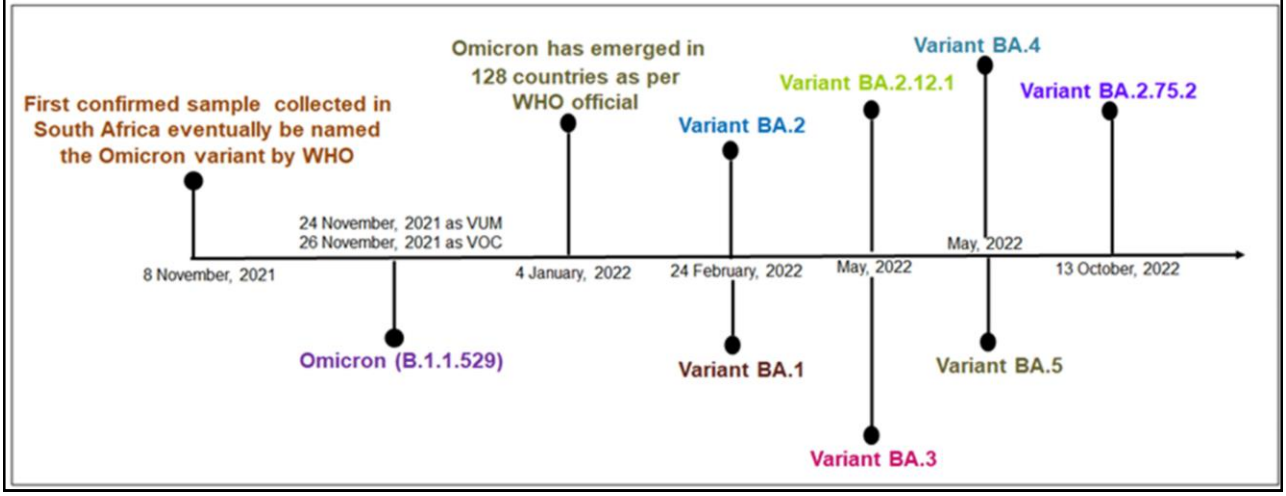
Particularly new variants and subvariants

Major Variants of SARS-CoV-2 Over Time

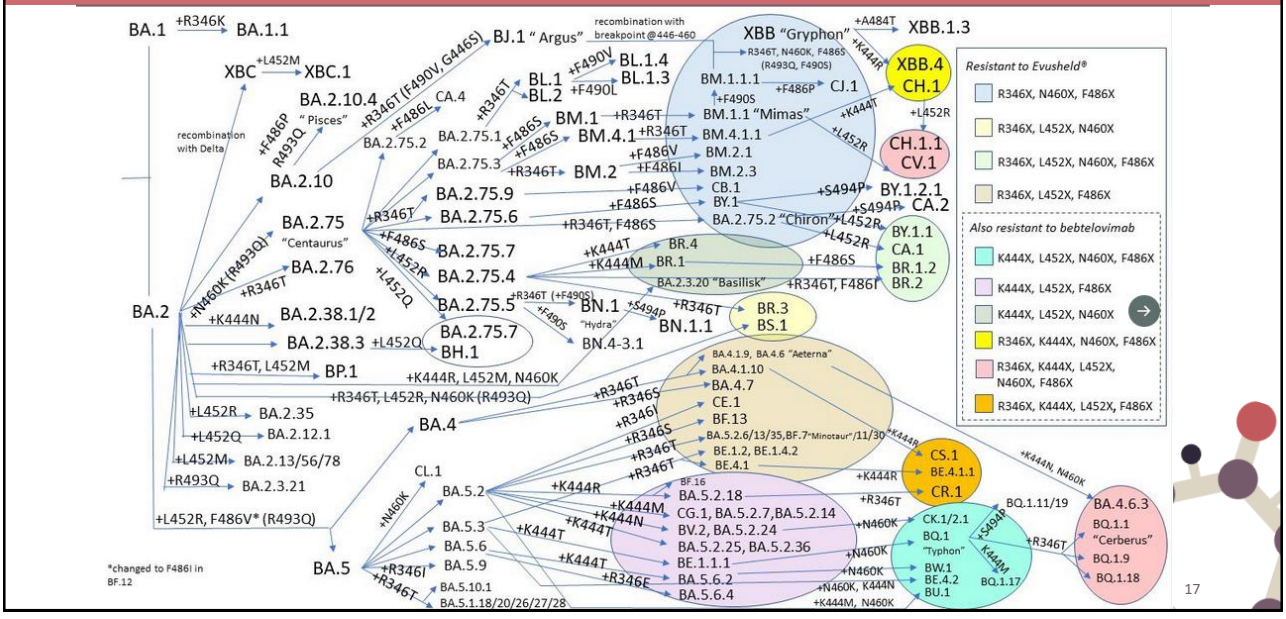


https://www.cdc.gov/coronavirus/2019-ncov/variants/variantinfo.html#anchor_1632154493691
https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/

Omicron and its Subvariants

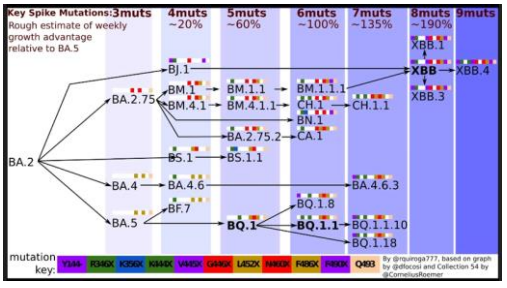


Omicron and its Subvariants

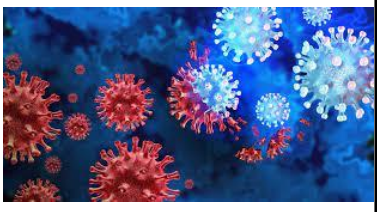


Omicron and its Subvariants

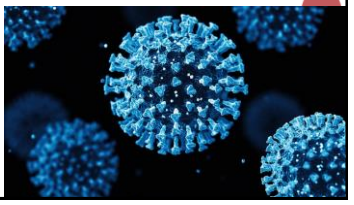
- Over 600 Omicron subvariants
  - Arisen via mutation and recombination
- Omicron waves driven by
  - BA.1
  - BA.2
  - BA.4/5
  - BA.2.75 (Centaurus)
  - XBB.1.5→XBB.1.9.1→XBB.1.9.2→XBB1.16
    - XBB.1.16 also known as Arcturus
      - Likely ~ 1.2 times as transmissible
      - no more severe
      - possibly higher incidence of conjunctivitis



Omicron Subvariants Now

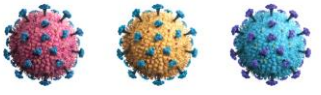


- New subvariant… EG.5 and EG.5.1
  - Nickname Eris (Greek god of strife and discord??)
  - First described from Indonesia in May
  - Many isolates in Australia from as far back as late May
  - No more severe but is more transmissible
  - Dominant in many countries, including the USA
    - Now most states of Australia too inc NSW, QLD, WA!
  - Variant of interest according to CDC
  - Speculation of lower rates of fever and more upper resp symptoms including rhinorrhea, sneezing and sore throat
- And then….BA.2.86
  - Nickname Pirola (an asteroid?)
  - More than 30 amino acid changes to the spike protein compared to closest ancestor BA.2
    - Similar in magnitude to what we saw with emergence of Omicron
    - Unusual to change so significantly
  - Variant being monitored (below variant of interest) as of Aug 17
  - Now over 640 cases in 30 countries
    - Highest in UK, USA, Sweden, Canada, South Africa and France
  - Likely XBB boosters will still provide good protection



The Implications

- Ongoing viral evolution leads to immune evasion
  - Protection both from vaccination as well as previous infection is reduced
    - Can contribute (with other factors) to “waves”
  - Also impacts antibodies for prevention or treatment
  - May also impact testing and antiviral therapies
    - Although less so to date



- Given the situation is going to continue to change, our response needs to be able to adapt accordingly
  - Vaccination: XBB.1.5 adapted nearly available
    - Fortunately, expectation of high levels of protection against EG.5/EG.5.1
    - Recommendations for use of this (and other) vaccines will depend on many factors, particularly the epidemiology
      - Needs to be agile
- Not correct to simply assume each successive variant/subvariant milder and of less concern
  - Changes are random
  - May be the case long term, but each significant subvariant needs to be assessed on its merits (and this takes some time)

COVID-19 and the Elderly

Including Residential Aged Care Facilities (RACFs)

Australian COVID-19 Deaths by Age

COVID-19 registered deaths by age and sex (a)(b)(c)(d)(e)

	Number of deaths		Age-specific rates	
Age (years)	Males	Females	Males	Females
0-19	13	9	0.1	0.1
20-29	15	13	0.3	0.2
30-39	43	27	0.7	0.4
40-49	92	55	1.6	1.0
50-59	270	158	5.1	2.9
60-69	688	405	15.0	8.3
70-79	1,886	1,053	57.7	29.9
80-89	3,327	2,502	248.8	150.1
90+	2,143	2,761	858.4	586.1

Age-specific death rates reflect deaths per 100,000 of the estimated resident populationhttps://www.abs.gov.au/articles/covid-19-mortality-australia-deaths-registered-until-31-july-2023

COVID-19 Fatality Rate by Age

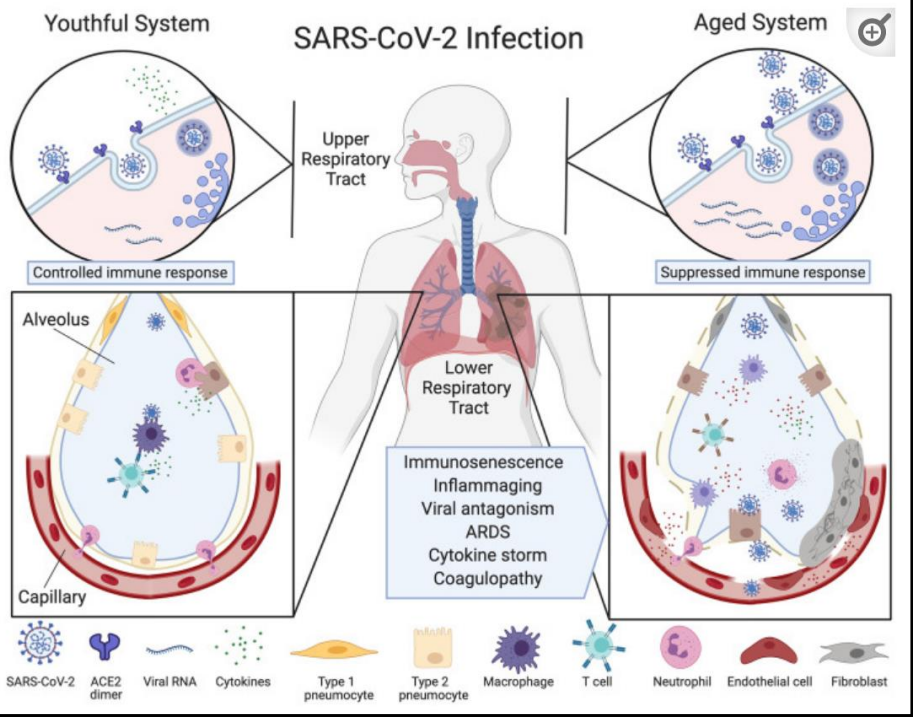
- Early data out of China in the early days of the pandemic
  - ~130 000 cases

AGE	DEATH RATE confirmed cases	DEATH RATE all cases
80+ years old	**21.9%**	**14.8%**
70-79 years old		**8.0%**
60-69 years old		**3.6%**
50-59 years old		**1.3%**
40-49 years old		**0.4%**
30-39 years old		**0.2%**
20-29 years old		**0.2%**
10-19 years old		**0.2%**
0-9 years old		**no fatalities**

https://www.worldometers.info/coronavirus/coronavirus-age-sex-demographics/

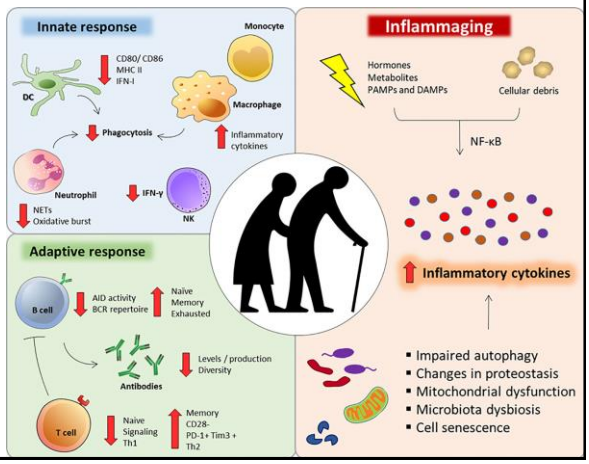
Pathology

- Virus binds ACE2 in upper respiratory tract
  - Endocytosis and replication
  - Travel to alveoli and infect type 2 pneumocytes
- Youthful system
  - Alveolar macrophages or dendritic cells recognise
  - Immune response including
    - Cytokine release
    - Antigen presentation
- Aged
  - Initial signals are slower
    - Greater viral replication
  - Antigen presentation less effective
  - More cells infected
  - Higher cytokine signalling
    - storm
  - Increased endothelial inflammation
  - Microvascular clotting and coagulopathy
    - Organ failure



Why is age such a risk

- Shown in many studies to be an independent risk factor in its own right
  - One study adults over 65 years comprised 80% of hospitalisations and 23 times risk of death v under 65 y.o.a.
- Direct effects include
  - During aging the immune system changes
    - Immunosenescence
      - Reduced pathogen recognition, alert signalling and clearance
    - Inflammaging
      - Increase in chronic systemic inflammation
- Indirect impacts
  - Lower immune response to vaccination
    - and past infection
  - Accumulation of comorbidities
  - Frailty
  - Residential aged care facilities



COVID-19 Severe Disease Risk Factors

Pre-existing chronic conditions certified with COVID-19 deaths (a)(b)(c)(d)(e)

Chronic conditions	Percent (%)
Chronic cardiac conditions	39.5
Dementia	30.0
Chronic respiratory conditions	17.9
Cancer	17.0
Diabetes	15.3
Chronic kidney diseases	13.0
Hypertension	12.6
Musculoskeletal disorders	6.3
Chronic cerebrovascular diseases	3.9
Parkinsons Disease	3.7
Obesity	1.7

a. Includes COVID-19 death registrations only. Numbers will differ to disease surveillance systems.
b. Includes all COVID-19 deaths (both doctor and coroner certified) that occurred and were registered by 31 July 2023.
c. All deaths due to COVID-19 in this report have been coded to ICD-10 code U07.1 COVID-19, virus identified; U07.2 COVID-19, virus not identified as the underlying cause of death; or U10.9 Multisystem inflammatory syndrome associated with COVID-19.
d. Data is provisional and subject to change.
e. Refer to the methodology for more information regarding the data in this graph.

https://www.abs.gov.au/articles/covid-19-mortality-australia-deaths-registered-until-31-july-2023

Residential Aged Care Facilities

COVID-19 outbreaks in Australian residential aged care facilities

National snapshot

As at 8:00 am 19 October 2023 there are 1,371 active COVID-19 cases in 185 active outbreaks in residential aged care facilities across Australia. There have been 92 new outbreaks, 13 new resident deaths and 1294 combined new resident and staff cases reported since 12 October 2023.

Table 1: Aged Care COVID-19 data as at 8.00am 19 October 2023[1]

Category	Active[2]	Previous 7 days	Cumulative Total	Previous 7 days
Outbreaks[3]	185	43	16,603	72
Residential Aged Care Facilities affected	185	43	2,844	1
Resident Cases[4]	983	270	161,588	939
Resident Deaths	N/A	N/A	5,908	13
Staff Cases	388	123	93,104	355

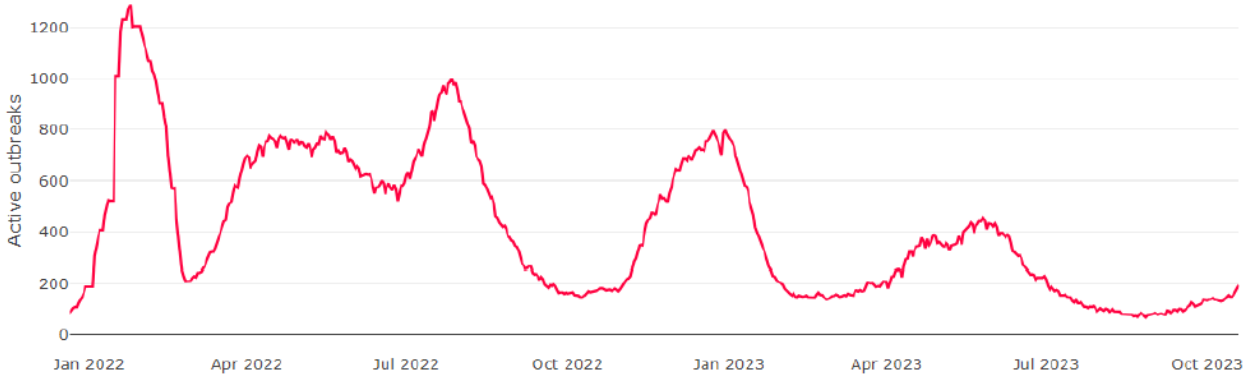
Active RACF Outbreaks

Table 2: Overview of Active Outbreaks in Australia

	ACT	NSW	NT	QLD	SA	TAS	VIC	WA	Total
Total Facilities with outbreaks	0	40	0	23	24	5	76	17	185
Total number of active resident cases	0	187	0	106	150	14	442	84	983
Total number of active staff cases	0	67	0	41	50	8	178	44	388
Total Outbreaks Opened in Previous 7 Days	0	23	0	14	12	2	30	11	92
Total Outbreaks Closed in Previous 7 Days	1	14	0	8	6	2	17	1	49

Outbreaks in Aged Care

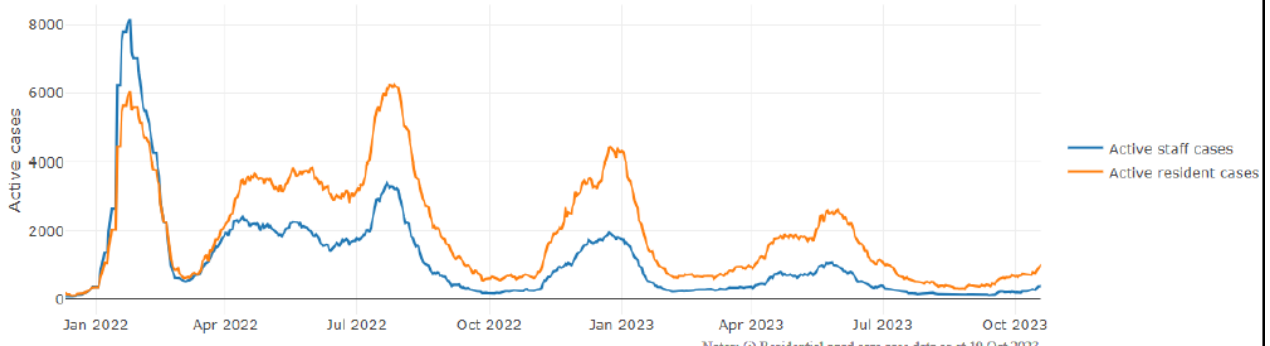
Figure 1: National Outbreak Trends in Aged Care



Notes: (i) Residential aged care case data as at 19 Oct 2023
(ii) The large increase in outbreaks on 16 January 2022 is driven by a reporting lag.

Cases in Staff and Residents

Figure 2: Trends in Aged Care Cases – December 2021 to Present

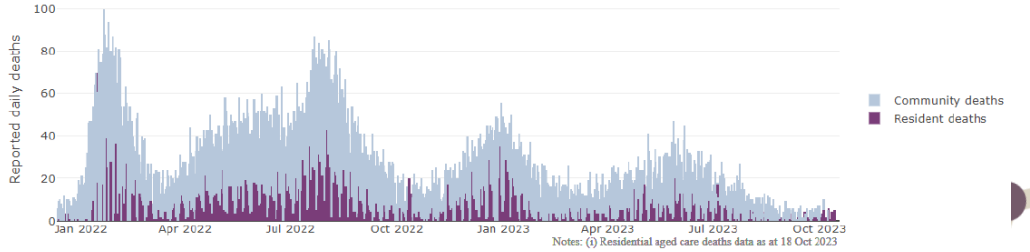


Notes: (i) Residential aged care case data as at 19 Oct 2023
(ii) The large increase in active cases on 16 January 2022 is driven by a reporting lag.
(iii) Cases are considered active for 14 days from the date they are reported.

Mortality in Australian RACF

- 1 July 2023 to 12 October 2023, COVID-19 recorded as cause of death in 1.2% of all deaths in permanent residents in aged care facilities
- Since the beginning of the Omicron outbreak in December 2021
  - 110 530 deaths in residential aged care from all causes
    - COVID-19 accounts for 4.5%

Figure 3: COVID-19 Deaths in Residential Aged Care Facilities overlaid with Community deaths



Notes: (i) Residential aged care deaths data as at 18 Oct 2023
(ii) COVID-19 deaths data from NNDSS as at 18 Oct 2023
(iii) The large increase in deaths on 16 January 2022 is driven by a reporting lag.
deaths have been adjusted to align with deaths reported in the NNDSS data. As a result, daily deaths may not align exactly with the raw residential aged care COVID-19 case data.
(v) Community deaths are total COVID-19 deaths reported in the NNDSS data less resident deaths.

Treatment and Vaccination

- Oral antivirals
  - Molnupiravir (Lagevrio) distribution commenced on February 6, 2022, to all RACF's with outbreak sites prioritised for delivery
    - National Medical Stockpile deployed 48 269 treatment courses of Molnupiravir (Lagevrio) to aged care facilities
  - Prescriptions for antivirals to residents in residential aged care facilities (22 Feb 2022 to 15 Oct 2023)
    - Molnupiravir (Lagevrio) 80 036
    - Nirmatrelvir + Ritonavir (Paxlovid) 6 763

- Vaccination
  - As at October 18
    - 82 000 or 48% of aged care residents received a booster dose in the last 6 months
      - 757 aged care residents received a booster dose in the last week

COVID-19 Vaccination

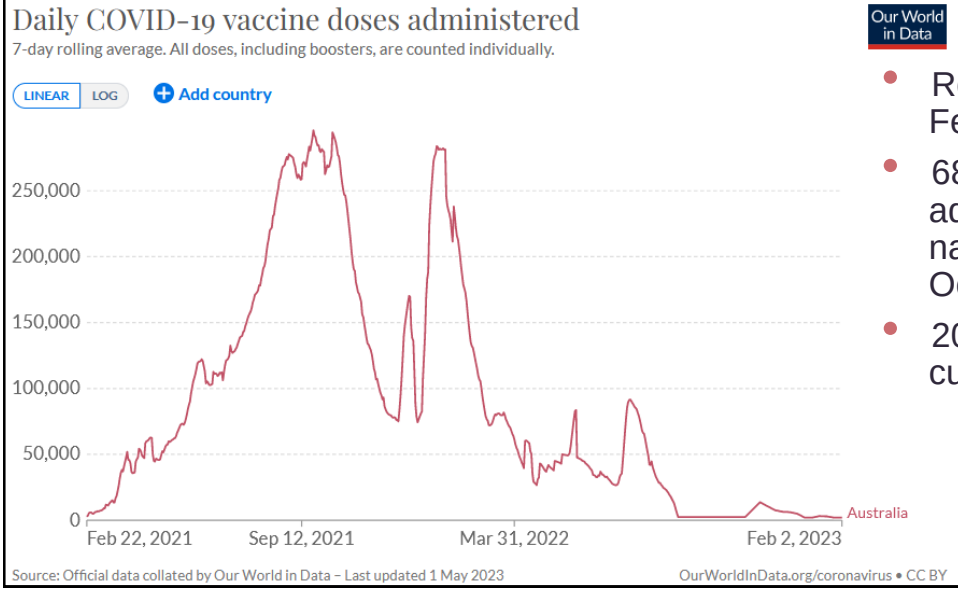
Vaccination status and recommendations

Australia-Vaccines Approved and In Clinical Trials

- 11 Vaccines Approved for Use (inc bivalent and newer boosters)
  - Nuvaxovid (Novavax)
  - Vaxzevria (Oxford/AstraZeneca)
  - Jcovden (J &J)
  - Pfizer (Original, BA.1 Bivalent, BA.4/5 Bivalent, XBB.1.5)
  - Moderna (Original, BA.1 Bivalent, BA.4/5 Bivalent, XBB.1.5)
- ~ 28 Vaccines in Clinical Trials Currently

RNA	Protein Subunit	DNA	Viral Vector	VLP
Moderna (3)	ACM Biolabs	**Symvivo**	EnGeneIC	**SpyTech**
Pfizer (2)	Intravacc B.V.	University of Sydney	**Tetherex** (Nasal)	
Chulalongkorn University	University of Melbourne			
EyeGene Inc	**Novavax** (7)			
GSK	Clover			
RVAC Medicines	**Sanofi/GSK**			
University of Melbourne				

COVID-19 Vaccination in Australia



Our World in Data

- Rollout commenced Feb 22, 21
- 68.8 doses administered nationally as of 18 October 2023
- 2023 Booster doses currently ~5 million

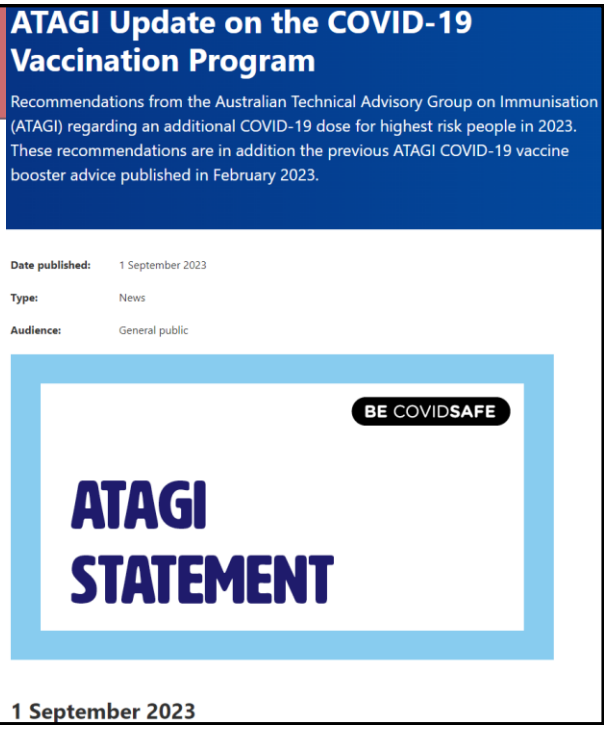
Current Vaccine Recommendations

- Booster eligibility expanded-from Feb 20th, 2023
  - Booster if ≥ 6 months since last dose/infection
    - Recommended if ≥ 65 y.o.a or 18 to 64 with comorbidities
    - Consider otherwise based on individual risk assessment/discussion with provider, 18 to 64 years without risk factors and Children 5-17 years with comorbidities
    - Not recommended < 18 years without comorbidities
  - Choice
    - Bivalent recommended

ATAGI 2023 Booster Advice		
Age	**At risk**	**No risk factors**
	Not recommended	
5-17 years	**Consider**	**Not recommended**
18-64 years	**Recommended**	**Consider**
≥ 65 years	**Recommended**	

And then…

- ATAGI updated advice 1st September 2023
  - Recommend for over 75 years of age if 6 months since last dose
  - Consider if
    - 65 to 74
    - 18 to 64 severe immunocompromise
  - Most benefit if
    - No history infection
    - Medical comorbidities or complex health needs
    - Reside in aged care facility
- *ATAGI notes that XBB.1.5-based vaccines have been developed, but these are not yet approved for use by any country and updates will be provided as information is available.*



ATAGI Update on the COVID-19 Vaccination Program

Recommendations from the Australian Technical Advisory Group on Immunisation (ATAGI) regarding an additional COVID-19 dose for highest risk people in 2023. These recommendations are in addition the previous ATAGI COVID-19 vaccine booster advice published in February 2023.

Date published: 1 September 2023

Type: News

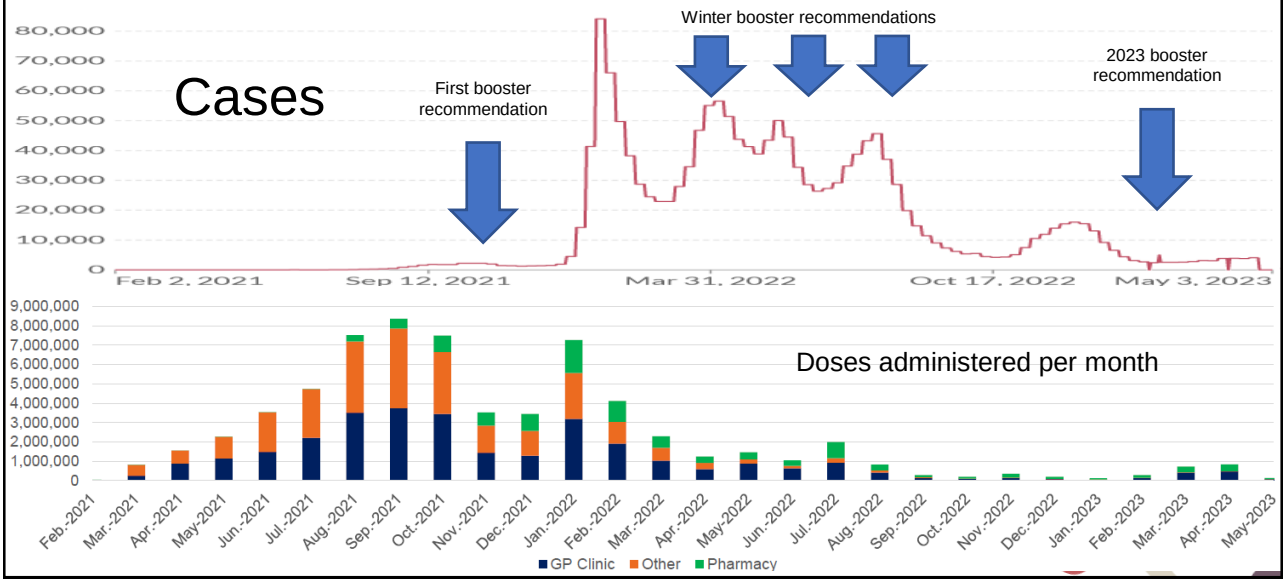
Audience: General public

BE COVIDSAFE

ATAGI
STATEMENT

1 September 2023

Australia Doses Administered By Week



2023 Booster Doses

COVID-19 2023 Booster Doses

Australia's COVID-19 Vaccine Program

Data as at: 18 Oct 2023

4.0m
Total 2023 Booster Doses administered to **all ages** (18 years and over)

666.6k (35.3%#)
individuals aged **75 years and over** have received a 2023 Booster Dose in the last six months##

654.0k (26.9%#)
individuals aged **65 to 74 years** have received a 2023 Booster Dose in the last six months##

1.1m (6.9%#)
individuals aged **18 to 64 years** have received a 2023 Booster Dose in the last six months##

Total 2023 Booster Doses administered by age group (years)

75+	65-74	18-64
1.2m	1.1m	1.7m

Number of 2023 Booster Doses administered by provider state###

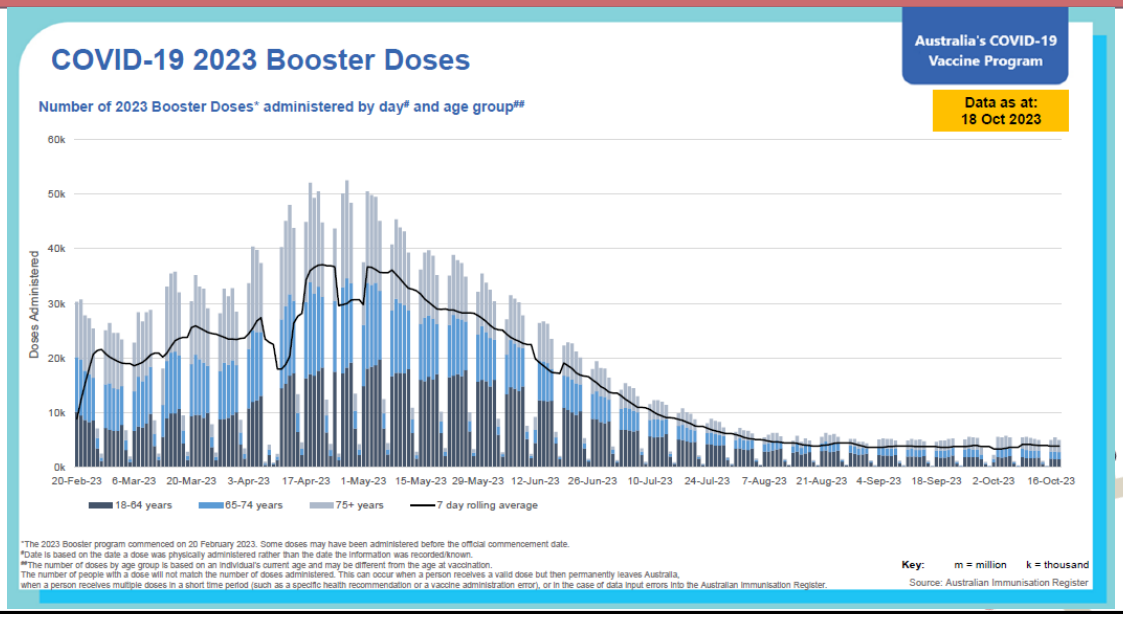
Provider state	2023 Booster Doses (18+ years)	Weekly increase
National	**4.0m**	**+28.2k**
ACT	122.2k	+1.3k
NSW	1.3m	+9.6k
NT	18.1k	+131
QLD	729.6k	+4.0k
SA	314.7k	+2.3k
TAS	132.6k	+944
VIC	1.1m	+8.0k
WA	394.4k	+2.0k

#Coverage uses the Australian Bureau of Statistics June 2021 Estimated Resident Population (ERP) as denominator.
##The number of people with a dose will not match the number of doses administered. This can occur when a person receives a valid dose but then permanently leaves Australia, when a person receives multiple doses in a short time period (such as a specific health recommendation or a vaccine administration error), or in the case of data input errors into the Australian Immunisation Register.
###State breakdown is based on the state in which a vaccine was physically administered and may differ from a person's residential address.

Key: m = million k = thousand

Source: Australian Immunisation Register

2023 Booster Doses



Why has booster uptake plateaued

- High rates of COVID-19 infection
  - Survivorship bias
  - Genuine misunderstanding (some driven by misinformation) that vaccination not required after infection
  - Perception that high case numbers demonstrates vaccines ineffective
  - Waiting for the 6 months to be up
- Perception of risk fallen dramatically
  - Above plus,
  - Overstating reduced severity of Omicron
    - Whilst not appreciating the vaccine is likely largely responsible
  - Reassuring messages to support withdrawal of mitigation strategies
    - Many feel intervention no longer required
  - Reduced focus on public messaging for COVID-19
- Fatigue and frustration
- Many others

Has Vaccination Made an Impact

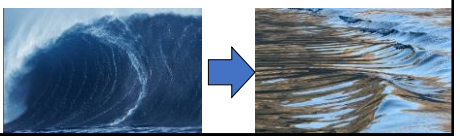
- Global impact of first year of vaccination, (Watson et al)
  - **14.4 million deaths prevented** in 185 countries (Dec 8, 2020, to Dec 8, 2021)
- Another global study through Sep 2021, vaccines prevented an estimated, (Yang et al)
  - Median of **151.7 million cases**
  - **620.5 thousand deaths**
  - Estimated direct outpatient cost savings were $21.2 billion, indirect savings of $135.1 billion
    - Total cost saving of $155 billion

- USA: compared with no vaccination scenario Dec 12, 2020, to June 30, 2021, (Vilches et al)
  - Estimated **240 797 lives saved**
  - Hospitalisations prevented 1 133 617
  - Cases averted projected to exceed **14 million**

- European Union December 2020 to November 2021 in 33 countries, (Mesle et al)
  - Deaths averted in people 60 years and older was **469 186**

COVID-19 Ongoing Challenges - Vaccination

- Ongoing viral evolution
  - Applies to immunity derived from vaccination, past infection and administered antibodies
    - Immune evasion
  - While Omicron may well be milder than previous variants, not necessarily the case that each successive variant will be of reduced severity
  - While reporting has declined, COVID-19 isn't going to simply go away (ripples)
- Fatigue, frustration and reduced perception of risk
  - Unable to maintain a sense of emergency indefinitely, PHEIC now ceased
  - Whilst newer subvariants may have reduced severity, perception COVID-19 is now "mild" makes intervention more challenging
  - Generally declining rates of boosters,
    - As well as testing, surveillance and non-pharmaceutical intervention
- Limitations of existing vaccination strategy include
  - Immune evasion
  - Relatively short duration of protection regardless meaning repeat doses required
  - Limited protection against infection
  - The most vulnerable, unable to respond
    - Significant proportion of the population, perhaps 2%
- First step to addressing is to update vaccines…

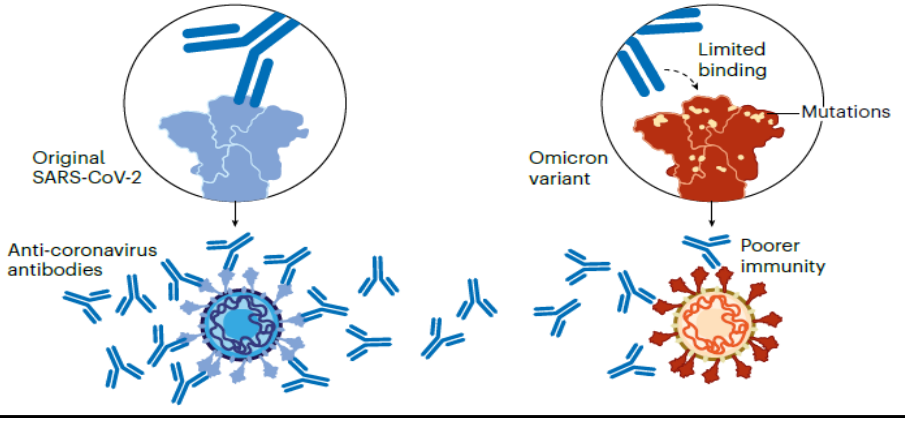


Updated Vaccines

Bivalent and most recent update

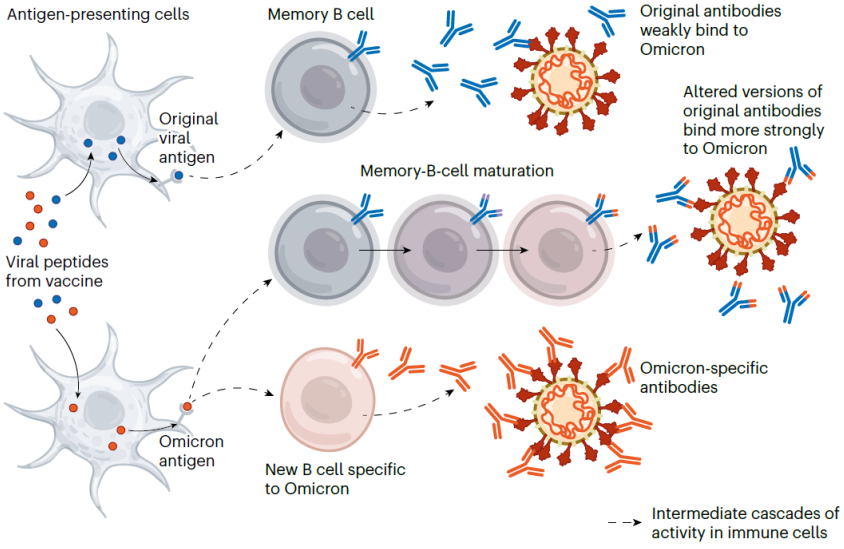
Updated Vaccines

- Antibodies generated by the original SARS-CoV-2 vaccine are less adept at binding mutated variants such as Omicron
  - Immune evasion



Updated Vaccines: BA.4/5 Bivalent

- Bivalent vaccines
  - Some existing memory B cells produce more antibodies
  - Some memory B cells mature to produce altered versions of the original antibodies capable of binding more strongly
  - Some new B cells make Omicron specific antibodies



Updated Vaccines: BA.4/5 Bivalent

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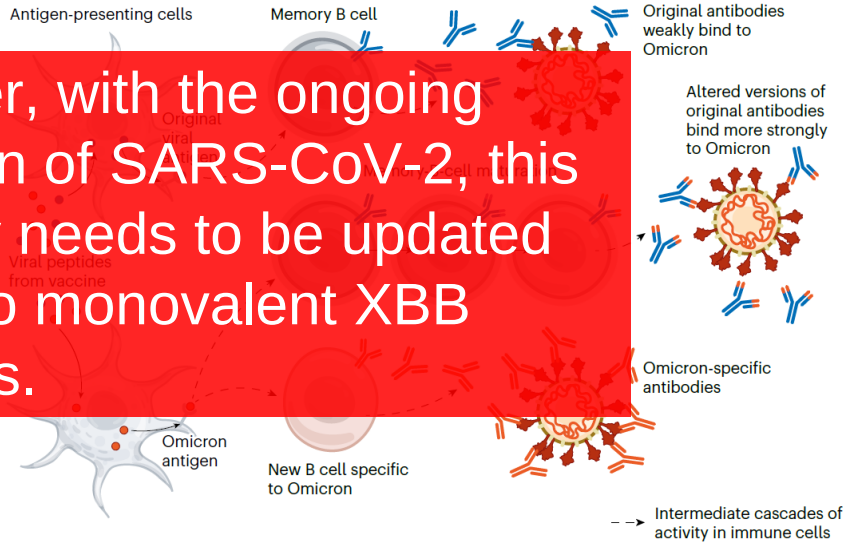
However, with the ongoing evolution of SARS-CoV-2, this strategy needs to be updated again, to monovalent XBB vaccines.



Updated Vaccines XBB

- XBB.1.5 mRNA vaccines by Moderna and Pfizer approved in the USA in mid-September
  - Novavax approved early October
- Thought to provide good protection even for EG.5 and BA.2.86
- Australia;

Moderna Australia Pty Ltd	SPIKEVAX XBB.1.5 (andusomeran)	mRNA	For individuals aged 6 years and older	Full registration granted 06 October 2023 for individuals 12 years and older.
Pfizer Australia Pty Ltd	COMIRNATY OMICRON XBB.1.5 (raxtozinameran)	mRNA	For individuals aged 6 months and older	a. Full registration granted 06 October 2023 for individuals 5 years and older. b. Under evaluation for full registration for individuals 6 months to less than 5 years.

COVID-19 Vaccination Summary

- Very fortunate to be able to develop numerous safe and effective vaccines for COVID-19 in a relatively short timeframe
- No question the benefits of vaccination for COVID-19 have been tremendous
- Both in Australia and globally, the uptake of vaccines recently has declined
- There are many limitations of the current vaccine options, including immune evasion, waning and limited protection against infection
  - Note immune evasion has also applied to antibodies as therapy
- Updating vaccines helps
  - To a degree, for a period of time
    - Hence not sustainable
- Next generation vaccines are likely to address some of these challenges, at least to a degree, but are likely still some time away
- Hence, other strategies, to complement our existing vaccination strategy, such as oral antiviral therapy, remains vitally important

COVID-19 Therapies

Including a discussion of evidence for Molnupiravir

Oral Antivirals in Australia

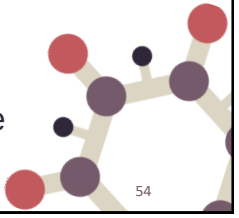
- 2 oral antivirals were approved by TGA on 20 January 2022
  - Nirmatrelvir plus ritonavir “Paxlovid”
    - 500 000 doses secured initially
  - Molnupiravir “Lagevrio”
    - 300 000 doses secured initially
- Initially provided via a national medicines stockpile, i.e., funded by Federal Government
- Eligibility initially very narrow
  - Confirmed positive test
  - Within 5 days of symptom onset
  - Unvaccinated or immunocompromised
  - Not on oxygen
  - Risk factors for progression

Oral Antivirals in Australia

- Available on Pharmaceutical benefits scheme, a more conventional way of funding medications
  - molnupiravir 1 March 2022, nirmatrelvir and ritonavir was 1 May 2022
- Eligibility sequentially expanded
  - Under 6 months from initial approval (11 July 2022), eligibility expanded, then again
    - 1 November 2022
    - 1 January 2023
    - 1 April 2023 and 1 July 2023 (Paxlovid only)
      - April 1 was 1 risk factor instead of 2 for 60 to 69 years
- Current eligibility
  - 70 years or older regardless of risk or symptoms
  - 50 years and older with risk factor(s)
    - i.e., 1 is enough
  - 30 years and older if first nations and with one risk factor
  - 18 years and older
    - Moderately to severely immunocompromised
    - Previously hospitalised with COVID-19

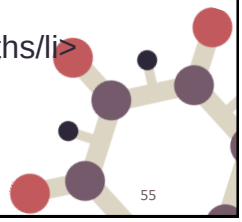
Risk Factors for Eligibility

- An expected list…
  - living in residential aged care
  - living with disability with multiple conditions and/or frailty (but not limited to living in supported accommodation)
  - neurological conditions like stroke or dementia and demyelinating conditions, for example, multiple sclerosis, Guillain-Barre Syndrome
  - chronic respiratory conditions including COPD, moderate or severe asthma
  - obesity or diabetes (type I or II requiring medication)
  - heart failure, coronary artery disease, cardiomyopathies
  - kidney failure or cirrhosis
  - living remotely with reduced access to higher level healthcare
  - past COVID-19 infection episode resulting in hospitalisation.



Moderately to Severely Immunocompromised

- For the purpose of oral antiviral eligibility, conditions include:
  - blood cancer or some red blood cell disorders (thalassemia, sickle cell disease)
  - transplant recipient
  - primary or acquired (HIV) immunodeficiency
  - chemotherapy or whole-body radiotherapy in the last 3 months
  - high dose corticosteroids or pulse corticosteroid therapy in the last 3 months
  - immunosuppressive treatments in the last 3 months
  - anti-CD20 monoclonal antibody treatment in the last 12 months/li>
  - cerebral palsy or Down Syndrome
  - congenital heart disease
  - living with disability with multiple conditions and/or frailty.



Oral Antivirals

Oral Antiviral	Indication	Important Considerations
PAXLOVID **(Nirmatrelvir/ritonavir)**[1]	Treatment of adults with a current diagnosis of mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death	• **Not recommended in severe renal or severe hepatic impairment** • **Multiple potential drug-drug (DDIs)** interactions with concomitant medications which **may limit utilization**
LAGEVRIO **(molnupiravir)**[2]	Treatment of adults with a current diagnosis of mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death, and *for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate*	• **Not recommended for use in pregnancy or breastfeeding** • No dose adjustments or limitations of use for patients with moderate or severe renal or hepatic impairment • No drug interactions have been identified

- Information from FDA therefore relevant for USA
- Consult local sources such as PBS and health.gov.au for relevant information

1.US FDA Fact Sheet for Healthcare Providers: Emergency Use Authorization for Paxlovid. Accessible from: https://www.fda.gov/media/155050/download
2.US FDA Fact Sheet for Healthcare Providers: Emergency Use Authorization for Lagevrio. Accessible from: https://www.fda.gov/media/155054/download

Evidence for Efficacy - Molnupiravir

- Has been challenging for many to follow
  - MOVe-OUT trial published in NEJM, Feb 2022
    - Phase 3 double blind, randomised, placebo-controlled trial, n = 1433
      - Non hospitalised adults with mild to mod COVID-19, unvaccinated
        - Lab confirmed no more than 5 days earlier and at least 1 risk factor for severe disease (inc age > 60)
      - Interim analysis (50% target enrolment)
        - Hospitalisation through day 29 reduced 7.3% v 14.1%
        - Hospitalisation and death through day 29 reduced 6.8% v 9.7%
          - Study recruitment stopped early on DSMC recommendation


ORIGINAL ARTICLE

Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients

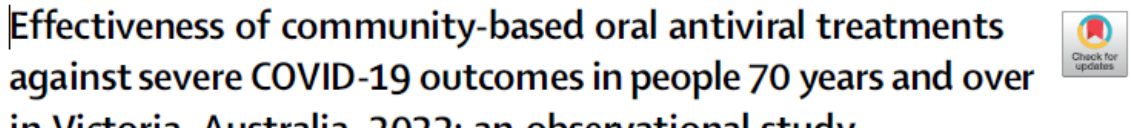
Angélica Jayk Bernal, M.D., Monica M. Gomes da Silva, M.D., Dany B. Musungaie, M.D., Evgeniy Kovalchuk, M.D., Antonio Gonzalez, M.D., Virginia Delos Reyes, M.D., Alejandro Martín-Quirós, M.D., Ph.D., Yoseph Caraco, M.D., Angela Williams-Diaz, B.S., Michelle L. Brown, B.S., Jiejun Du, Ph.D., Alison Pedley, Ph.D., et al., for the MOVe-OUT Study Group*


Molnupiravir plus usual care versus usual care alone as early treatment for adults with COVID-19 at increased risk of adverse outcomes (PANORAMIC): an open-label, platform-adaptive randomised controlled trial

Prof Christopher C Butler, FMedSci • Prof F D Richard Hobbs, FMedSci • Oghenekome A Gbinigie, DPhil • Prof Najib M Rahman, DPhil • Gail Hayward, DPhil • Prof Duncan B Richards, DM • et al. Show all authors

  - PANORAMIC, Lancet Dec 2022
    - UK-based, national, multi-centre, open-label, multigroup, prospective, platform adaptive randomised controlled trial.
      - Unwell with confirmed COVID-19 for 5 days or fewer in the community
        - 50 years or older, or 18 with relevant comorbidities
        - n=26 411, mean age 56.6 years, 94% had at least 3 doses of vaccine
      - Primary outcome: hospitalization or death, 1% in both groups
      - Other outcomes in molnupiravir group included: recovered 4 days earlier, more often reported early sustained recovery, higher self rated wellness, reduced time to sustained recovery, reduced time to alleviation of all symptoms, reduced time to sustained alleviation of all symptoms, fewer moderate or severe symptoms at days 7, 14 and 28 and less contact with general practitioners
      - Also reduced rates of viral detection and viral loads at day 7

Evidence for Efficacy - Molnupiravir


Effectiveness of community-based oral antiviral treatments against severe COVID-19 outcomes in people 70 years and over in Victoria, Australia, 2022: an observational study

Christina Van Heer,[a,b,g] Suman S. Majumdar,[a,b,c,d,g,*] Indra Parta,[a] Marcellin Martinie,[a] Rebecca Dawson,[a] Daniel West,[a] Laura Hewett,[a] David Lister,[a] Brett Sutton,[a,d] Daniel P. O'Brien,[e,f] and Benjamin C. Cowie[a,f]

- Retrospective study of 2 vaccinated cohorts of COVID-19 cases aged ≥ 70 years
  - Diagnosed during BA.4/5 Omicron wave, Victoria
  - n = 38 933 in the mortality study population
    - 13.5 % nirmatrelvir-ritonavir, 51.3% molnupiravir (35.2% untreated)
      - Both reduced odds of death: 73% nirmatrelvir-ritonavir, 55% molnupiravir
        - Impact linked to time to initiation
      - Both reduced odds of hospitalisation: 40% nirmatrelvir-ritonavir, 29% molnupiravir

Treatment-Some Important Points

- Eligibility for oral antivirals includes per previous slide
  - Also includes a positive test for COVID-19 (PCR or RAT)
  - Give on basis of risk, counterintuitive to wait for progression
- Given complexities of accessing testing and then oral antivirals
  - Recommend plan in advance, particularly for high-risk patients
- Both oral antivirals contraindicated in pregnancy
- Conflicting evidence relating to oral antiviral efficacy
  - Clearly of benefit if used in appropriate risk patients AND commenced early
    - The reason eligibility not expanded further is that benefit less likely
    - Also probably change probability of post COVID sequelae
- Main consideration when deciding on which to prescribe
  - Efficacy versus organ dysfunction and drug-drug interaction considerations
- Guidelines likely to become increasingly challenging
  - NCET not likely to be able to update moving forward
- IV treatment available for hospitalised patients
- Adjunctive therapy particularly Dexamethasone continues to make a significant difference
- Antibody therapy to date rendered ineffective by immune evasion
  - New monoclonals close, particularly for pre-exposure prophylaxis
- More antivirals to come

Summary

Summary

- Predictions for COVID-19 moving forward
  - Only certainty is it is impossible to predict with any certainty
  - Repeated waves inevitable
    - Impossible to predict when/which subvariant, but inevitable
    - Driven by many factors
      - New variants/subvariants→ immune evasion
      - Waning immunity
  - With significant ongoing transmission between waves
  - Cannot assume going to evolve to lower pathogenicity
    - May happen in the long term but properties of new variants are entirely random
  - As essentially all other mitigating strategies ceased, reliance on vaccination even greater but
    - Challenges increasing, including fatigue, complacency, misinformation, immune evasion
  - Fortunately, real world evidence continues to support the use of oral antivirals
- The impact of COVID-19 is perhaps greatest in the elderly and particularly those in RACFs
  - Need to prioritise this population for infection prevention, vaccination and early treatment
- While COVID-19 not going to go away, given the tools we have, including vaccines and oral antivirals, and those that continue to be developed
  - Reasonable to expect high levels of control
    - Utilisation however going to be one of the key determinants

END

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