COVID education for SA GPs

Emerging COVID variants

Presented by:

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Learning outcomes

- Describe the differences between the various COVID-19 subtypes/variants.
- Explain the impacts of these variants on long COVID.

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CPD
CPD Activity
2020
22
2 points

2

SA GP COVID update

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Flu vaccine

Reimbursement information for free flu vaccines, when not NIP eligible

Information about how to claim reimbursement from SA Health for cost of private influenza vaccines at $21.95, administered in General Practice is now available on the SA Health website.

While we encourage all health providers to join the scheme, it is not mandatory and individual GPs may continue to charge for the vaccine. However, this should be communicated at the time of booking.

Children who need two doses, the doses can be set-aside in the fridge and claimed as part of the pre-June 30 dosing.

If you have any queries regarding the invoicing and reimbursement process, please contact: fluvaccination2022@health.sa.gov.au

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Expanded ATAGI criteria for winter COVID-19 booster vaccine dose

ATAGI has recently expanded the cohort definition for those expected to gain benefit from an extra booster of COVID-19 vaccination.

This winter dose should be given 4 months following the first booster.

The following groups are currently **not yet** recommended to receive an additional winter booster dose:

- healthy people aged 16 to 64 years of age who do not have any risk factors for severe COVID-19
- women who are pregnant without any other comorbidity that increases their risk of severe COVID-19
- people from occupational groups, such as healthcare workers, who do not have any other comorbidity that increases their risk of severe COVID-19.

As per previous advice, if an individual has had a recent confirmed SARS-CoV-2 infection, they should delay their winter booster dose until 3 months after their infection.

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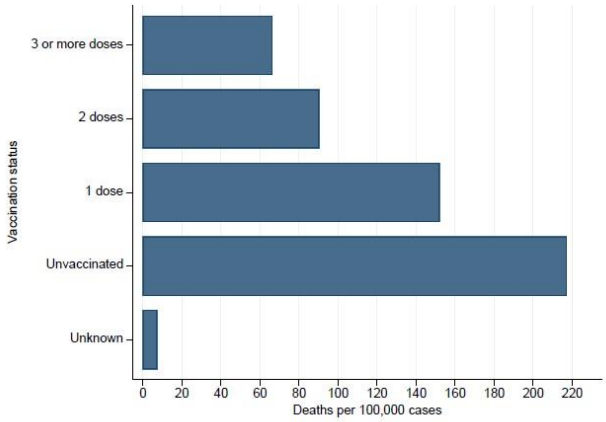
SA COVID vaccine rates



COVID-19 death rate* of confirmed and probable cases of COVID-19 reported in South Australia, by vaccination status, 23 November 2021 – 28 May 2022.
*Death rates are calculated as the number of deaths in each group, divided by the total number of cases in this group that are eligible for vaccination (excludes children under 5 years of age). This is given per 100,000 people.

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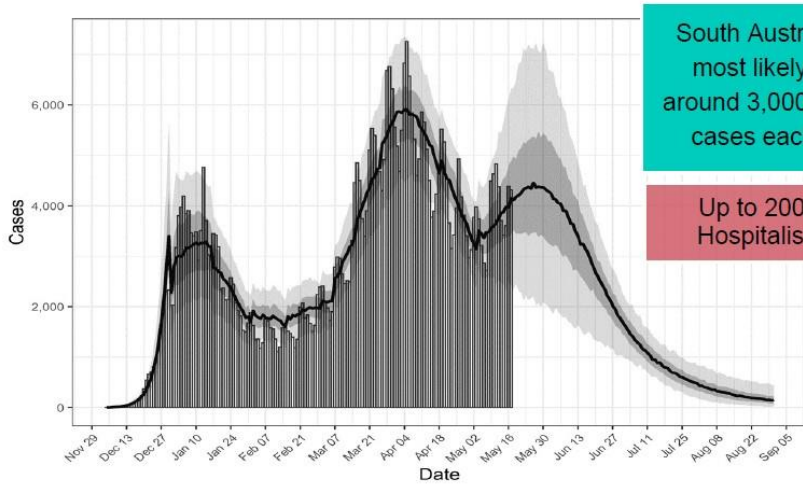
COVID-19 MODELLING



South Australia will most likely have around 3,000 – 4,000 cases each day.

Up to 200 Adult Hospitalisations

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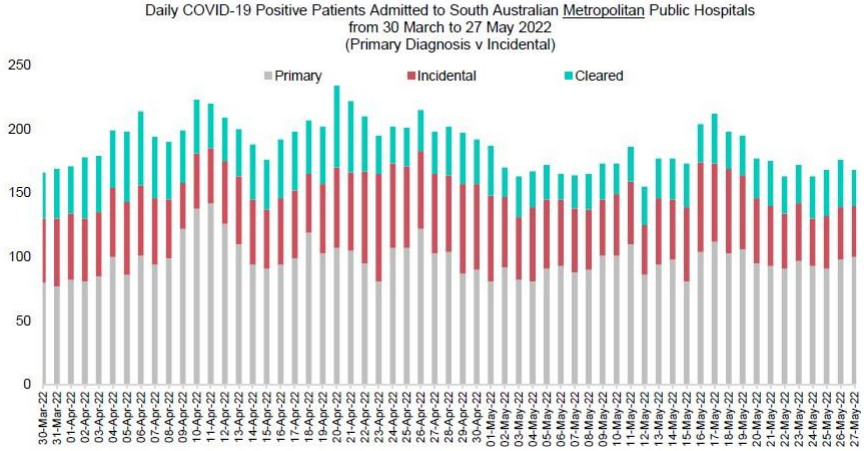
COVID-19 Hospital Occupancy

METRO COVID-19 HOSPITALISATIONS



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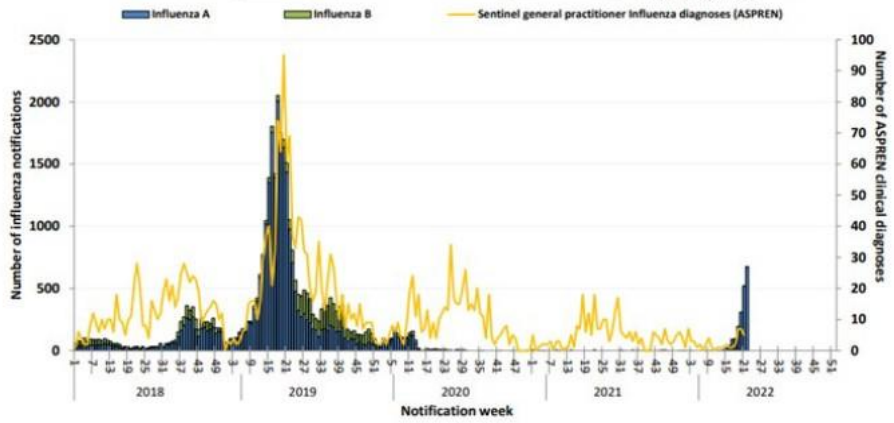
INFLUENZA SEASON

2022 1 JAN → 2022 6 JUNE

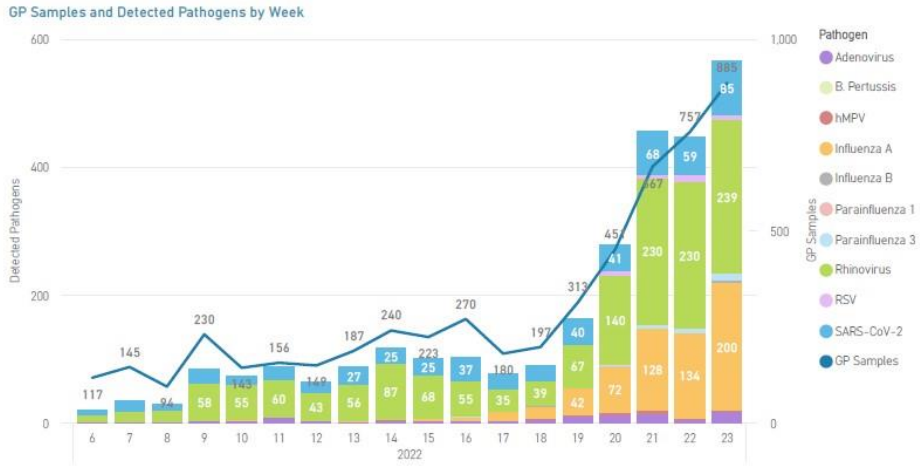
2,645 notifications of influenza virus infection reported to SA Health



9

Multiplex Respiratory Panel - General Practitioner Results

885 GP referred tests in week 23



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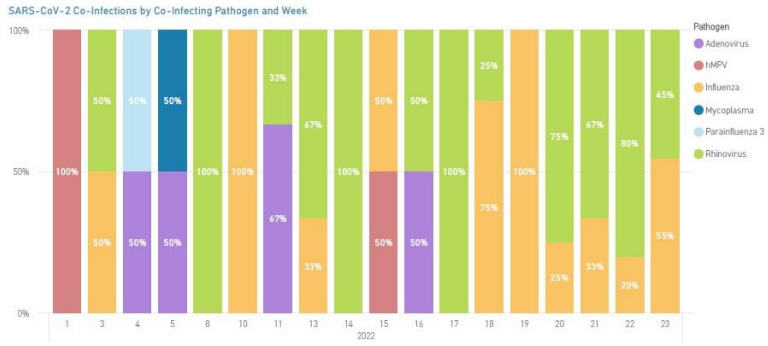
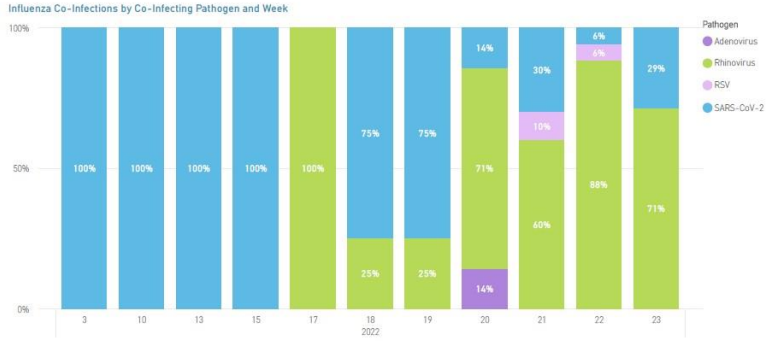
13 years and above





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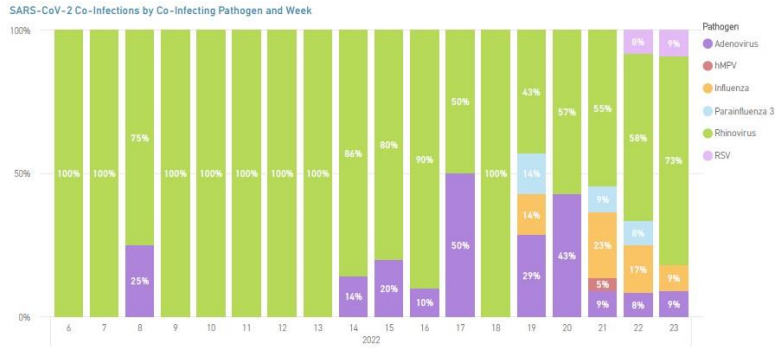
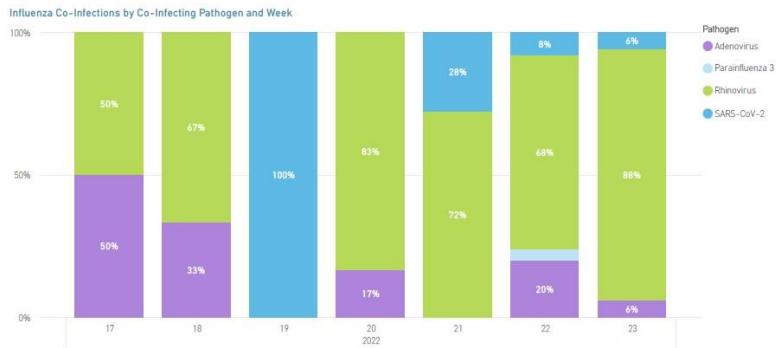
12 years and under





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Winter demand

HISTORICAL WINTER DEMAND

Analysis of emergency department and inpatient activity suggests hospital demand is consistent throughout the year, with minimal increase in the overall number of presentations to emergency departments in winter. However, the type of demand experienced in winter is different, with a clear increase in complexity resulting in more admissions and occupied beds.

2011 → 2020

- Respiratory presentations increase by **39%** — **30** more per day
- Paediatric presentations increase by **8%** — **21** more per day
- Hospital admissions increase by **3%** — **10** more per day

Jul 2015 → Dec 2019

- Average Occupied Beds increase by **3%** — **78** more per day

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Current strategies

24% of daily **000 CALLS WERE SAFELY DIVERTED** to an alternate care destination, avoiding an emergency department.
(1 January 2022 – 30 April 2022)

2,650 Adults seen by the **SA VIRTUAL CARE SERVICE**
With a **75% ED AVOIDANCE RATE**
(30 August 2021 – 4 April 2022)

→ Integrating with the **COVID-19 COMMUNITY HUB**
which will be available 8am to 8pm, 7 days a week, providing logistics and care coordination and strengthening partnerships with the primary healthcare network and community response.

3,647 Children and adolescents seen through the **CHILD AND ADOLESCENT VIRTUAL CARE SERVICE** at the Women's and Children's Hospital
(30 August 2021 – 4 April 2022)

1,420 Children and adolescents seen by **COVIDKIDS** at the Women's and Children's Hospital
(17 December 2021 – 27 March 2022)

→ Expanding to **VIRTUAL KIDS AT HOME SERVICE**
Available 24 hours, 7 days a week providing assessment and treatment for defined respiratory infections.

Linking patients with community services to avoid emergency departments and facilitate hospital discharge

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Community winter support

COMMUNITY STRATEGIES	
Residential Aged Care Community Pathway	Pilot commencing in June with support of Primary Health Networks to create a pathway between Residential Aged Care Facilities, the COVID-19 Community Hub and SA Virtual Care Service.
GP Advice Line	Continuing to support community healthcare practitioners to manage patients with respiratory symptoms.
National Coronavirus Helpline	Healthdirect continue to provide health advice and support for people who test positive to COVID-19.

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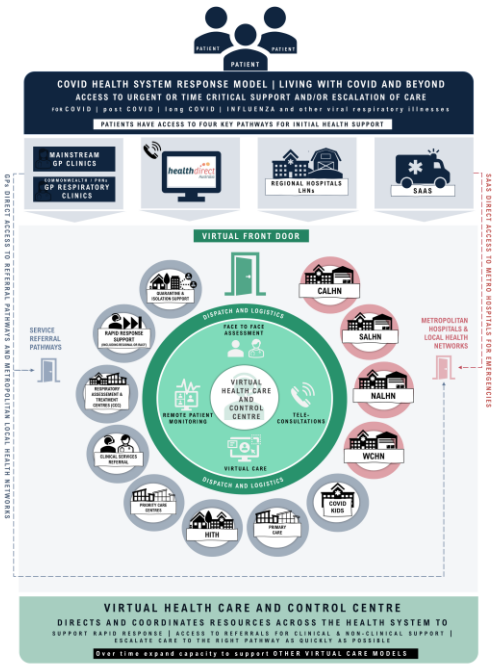
COVID Community Hub



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Emerging COVID variants

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- **Viruses like SARS-CoV-2 continuously evolve as changes in the genetic code (caused by genetic mutations or viral recombination) occur during replication of the genome**.
- **Mutation:** single change in a virus's genome (genetic code).
  - *Happen frequently, but only sometimes change the characteristics of the virus.*
- **Recombinant:** genomes of two SARS-CoV-2 variants (that have infected a person at the same time) combine during the viral replication process to form a new variant that is different from both parent lineages.

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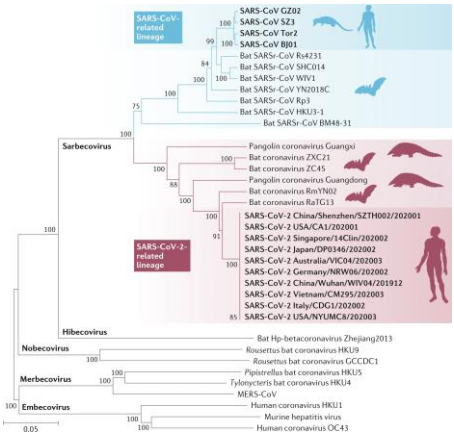
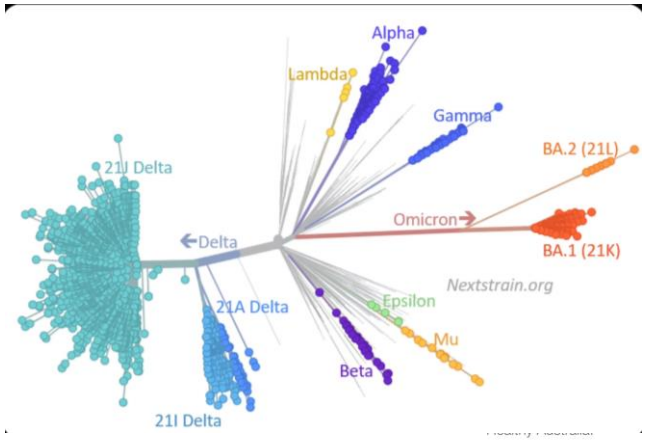
- A **lineage** is a genetically closely related group of virus variants derived from a common ancestor.





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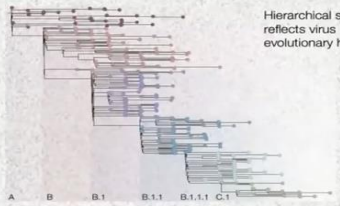
Unified Nomenclature

- PANGOLIN: Pango Lineages
- Next Strain: year of emergence and letter, e.g. 19A, 19B, 20A.
- GISAID: Letter with a lineage defining mutations: E.g: S, L, V, G,GH etc.
- WHO system Greek symbols –alpha, delta, omicron etc.



Α α Alpha	Β β Beta	Γ γ Gamma	Δ δ Delta	Ε ε Epsilon	Ζ ζ Zeta
Η η Eta	Θ θ Theta	Ι ι Iota	Κ κ Kappa	Λ λ Lambda	Μ μ Mu
Ν ν Nu	Ξ ξ Xi	Ο ο Omicron	Π π Pi	Ρ ρ Rho	Σ σ,ς Sigma
Τ τ Tau	Υ υ Upsilon	Φ φ Phi	Χ χ Chi	Ψ ψ Psi	Ω ω Omega

CMC: COVID PULSE https://covariants.org

Screenshot

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Classification

- Variants Being Monitored (VBM)
- Variant Of Interest (VOI)
- Variant Of Concern (VOC)
- Variant Of High Consequence (VOHC)

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- **Variants Being Monitored (VBM)**
  - Potential or clear impact on medical countermeasures or that have been associated with more severe disease or increased transmission but are no longer detected, or are circulating at very low levels
  - Do not pose a significant and imminent risk to public health
  - Currently - All variants but Omicron

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- **Variant of Interest (VOI)**
  - Specific genetic markers that are predicted to affect transmission, diagnostics, therapeutics, or immune escape.
  - Evidence that it is the cause of an increased proportion of cases or unique outbreak clusters.
  - *Enhanced sequence surveillance, enhanced laboratory characterization, or epidemiological investigations to assess how easily the virus spreads to others, the severity of disease, the efficacy of therapeutics and whether approved or authorized vaccines offer protection*

- Currently none

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Variant of Concern (VOC)

- Evidence of an increase in transmissibility
- More severe disease (for example, increased hospitalizations or deaths)
- Significant reduction in neutralization by antibodies generated during previous infection or vaccination
- Reduced effectiveness of treatments or vaccines
- *Notification to WHO under the International Health Regulations as well as local or regional bodies eg; CDC; local or regional efforts to control spread, increased testing, or research to determine the effectiveness of vaccines and treatments against the variant.*

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WHO Label: **Omicron**

Pango Lineage: **B.1.1.529, BA.1, BA.1.1, BA.2, BA.3, BA.4 and BA.5 lineages**

- Originally detected in South Africa
- Increased transmissibility
- Reduction in neutralization by some monoclonal antibody treatments
- Potential reduction in neutralization by post-vaccination sera
- Potential compromise in diagnostics - eg; S gene Target Failure(SGTF) (S gene drop out)

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Variant of High Consequence (VOHC)

- Clear evidence that prevention or medical countermeasures (MCMs) have significantly reduced effectiveness relative to previously circulating variants
- *In addition to the possible attributes of a VOC*
  - Demonstrated failure of diagnostic test targets
  - Evidence to suggest a significant reduction in vaccine effectiveness including against severe disease
  - Significantly reduced susceptibility to multiple approved therapeutics
  - More severe clinical disease and increased hospitalisations

- Currently none

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Mutant drivers

- Virus specific immunity – due to infection or vaccination (Grenfell, 2004)
- High viral load/prolonged viral shedding eg; *immunocompromised hosts*
- Intra-clade recombination (strand switching) (Lai, 1985; Samoilov, 2020)
- Site specific variation between upper and lower respiratory tract: compartmentalisation and evolve independently (Koel, 2021; Rueca, 2021)

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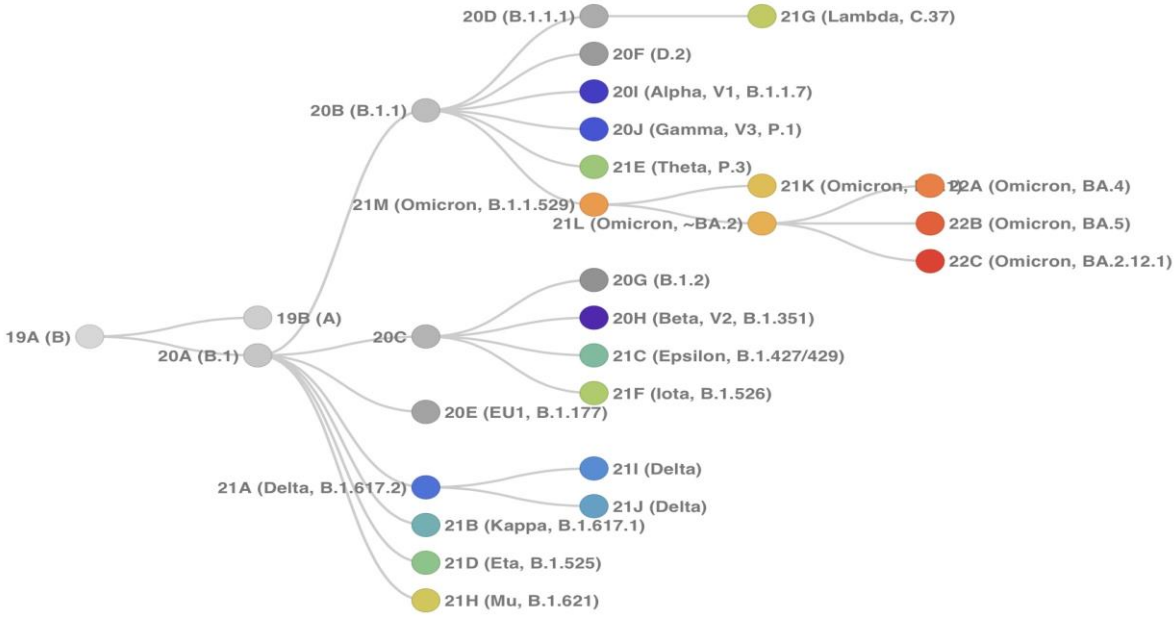

Phylogenetic relationships of Nextstrain SARS-CoV-2 clades. Please credit/link to Nextstrain if using this figure

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Nextstrain Clade	Pango Lineage	WHO Label	Other
20I (Alpha, V1)	B.1.1.7	α Alpha	VOC 202012/01
20H (Beta, V2)	B.1.351	β Beta	501Y.V2
20J (Gamma, V3)	P.1	γ Gamma	
21A (Delta)	B.1.617.2	δ Delta	
21I (Delta)		δ Delta	
21J (Delta)		δ Delta	
21B (Kappa)	B.1.617.1	κ Kappa	
21C (Epsilon)	B.1.427, B.1.429	ε Epsilon	CAL.20C
21D (Eta)	B.1.525	η Eta	
21F (Iota)	B.1.526	ι Iota	(Part of Pango lineage)
21G (Lambda)	C.37	λ Lambda	
21H (Mu)	B.1.621	μ Mu	
21K (Omicron)	BA.1	o Omicron	
21L (Omicron)	BA.2	o Omicron	
22A (Omicron)	BA.4	o Omicron	
22B (Omicron)	BA.5	o Omicron	
22C (Omicron)	BA.2.12.1	o Omicron	
20E (EU1)	B.1.177		EU1
20B/S:732A	B.1.1.519		
20A/S:126A	B.1.620		
20A.EU2	B.1.160		
20A/S:439K	B.1.258		
20A/S:98F	B.1.221		
20C/S:80Y	B.1.367		
20B/S:626S	B.1.1.277		
20B/S:1122L	B.1.1.302		

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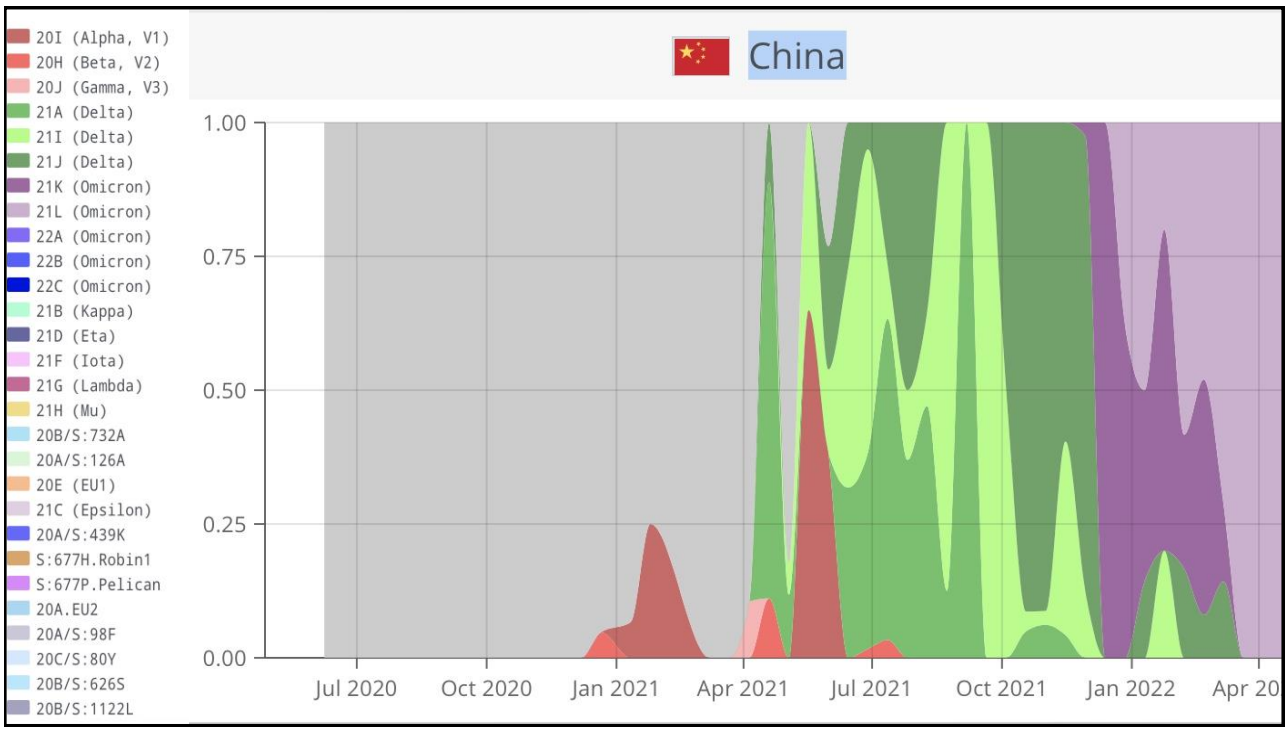

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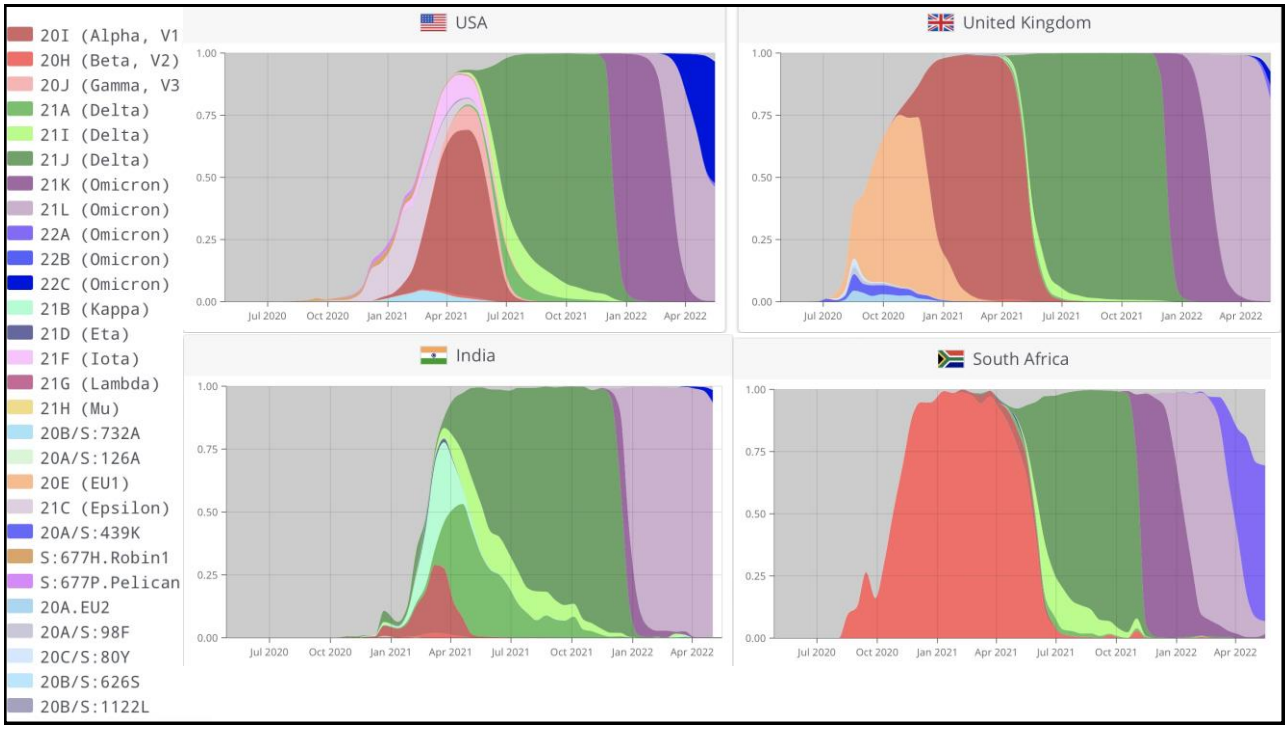
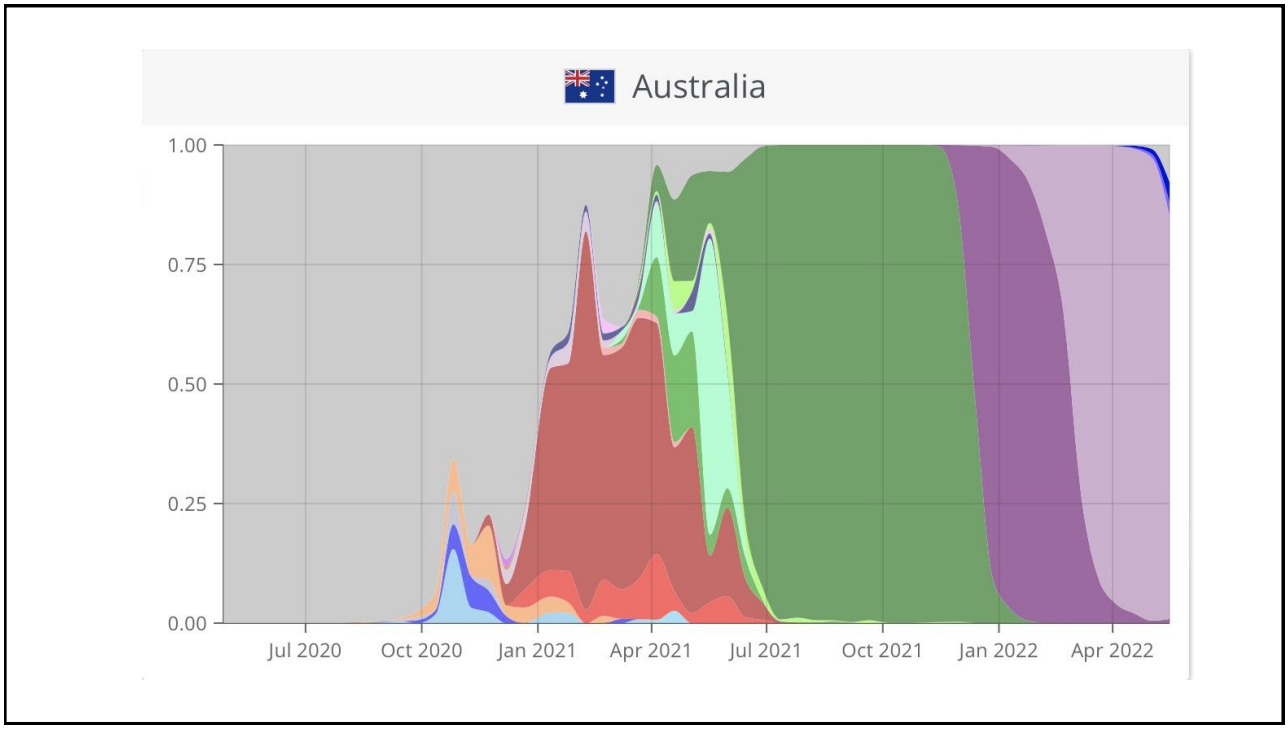

20I (Alpha, V1
20H (Beta, V2)
20J (Gamma, V3
21A (Delta)
21I (Delta)
21J (Delta)
21K (Omicron)
21L (Omicron)
22A (Omicron)
22B (Omicron)
22C (Omicron)
21B (Kappa)
21D (Eta)
21F (Iota)
21G (Lambda)
21H (Mu)
20B/S:732A
20A/S:126A
20E (EU1)
21C (Epsilon)
20A/S:439K
S:677H.Robin1
S:677P.Pelican
20A.EU2
20A/S:98F
20C/S:80Y
20B/S:626S
20B/S:1122L
USA
United Kingdom
India
South Africa
1.00
0.75
0.50
0.25
0.00
Jul 2020
Oct 2020
Jan 2021
Apr 2021
Jul 2021
Oct 2021
Jan 2022
Apr 2022

31


Australia
1.00
0.75
0.50
0.25
0.00
Jul 2020
Oct 2020
Jan 2021
Apr 2021
Jul 2021
Oct 2021
Jan 2022
Apr 2022

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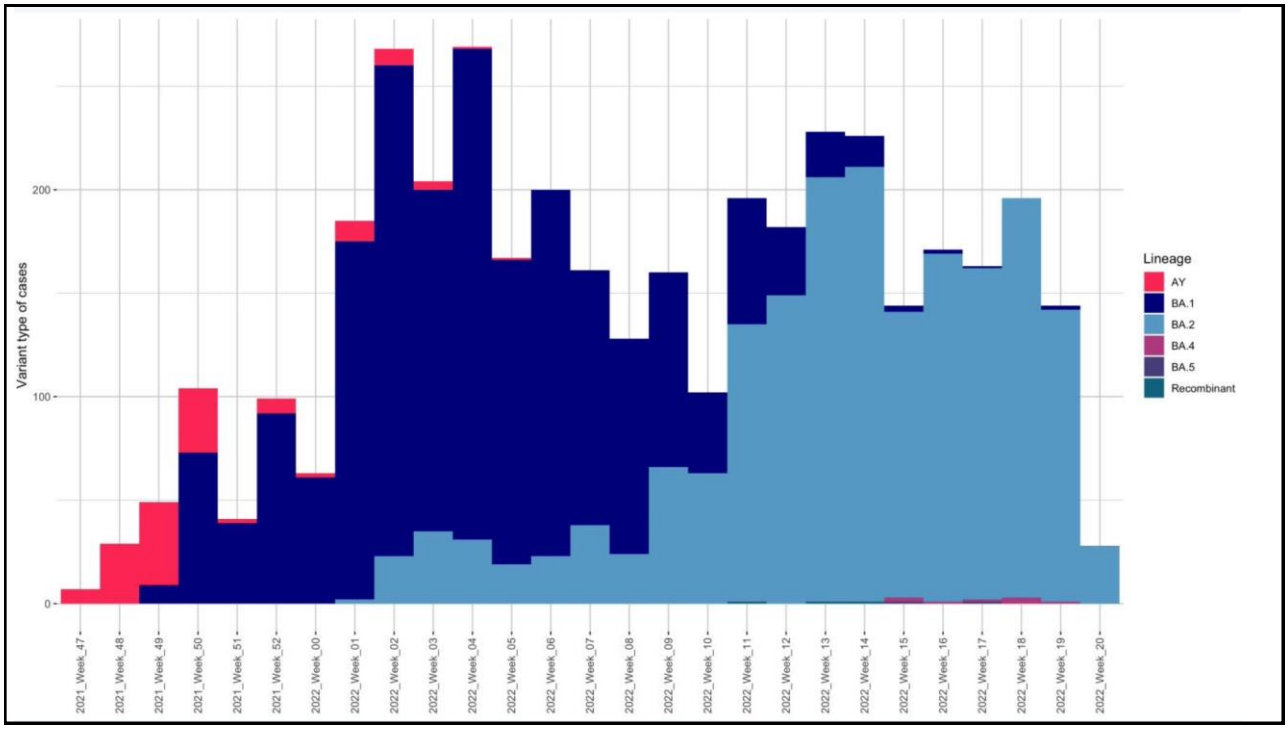
Variant type of cases
200
100
0
2021_Week_47
2021_Week_48
2021_Week_49
2021_Week_50
2021_Week_51
2021_Week_52
2022_Week_00
2022_Week_01
2022_Week_02
2022_Week_03
2022_Week_04
2022_Week_05
2022_Week_06
2022_Week_07
2022_Week_08
2022_Week_09
2022_Week_10
2022_Week_11
2022_Week_12
2022_Week_13
2022_Week_14
2022_Week_15
2022_Week_16
2022_Week_17
2022_Week_18
2022_Week_19
2022_Week_20
Lineage
AY
BA.1
BA.2
BA.4
BA.5
Recombinant

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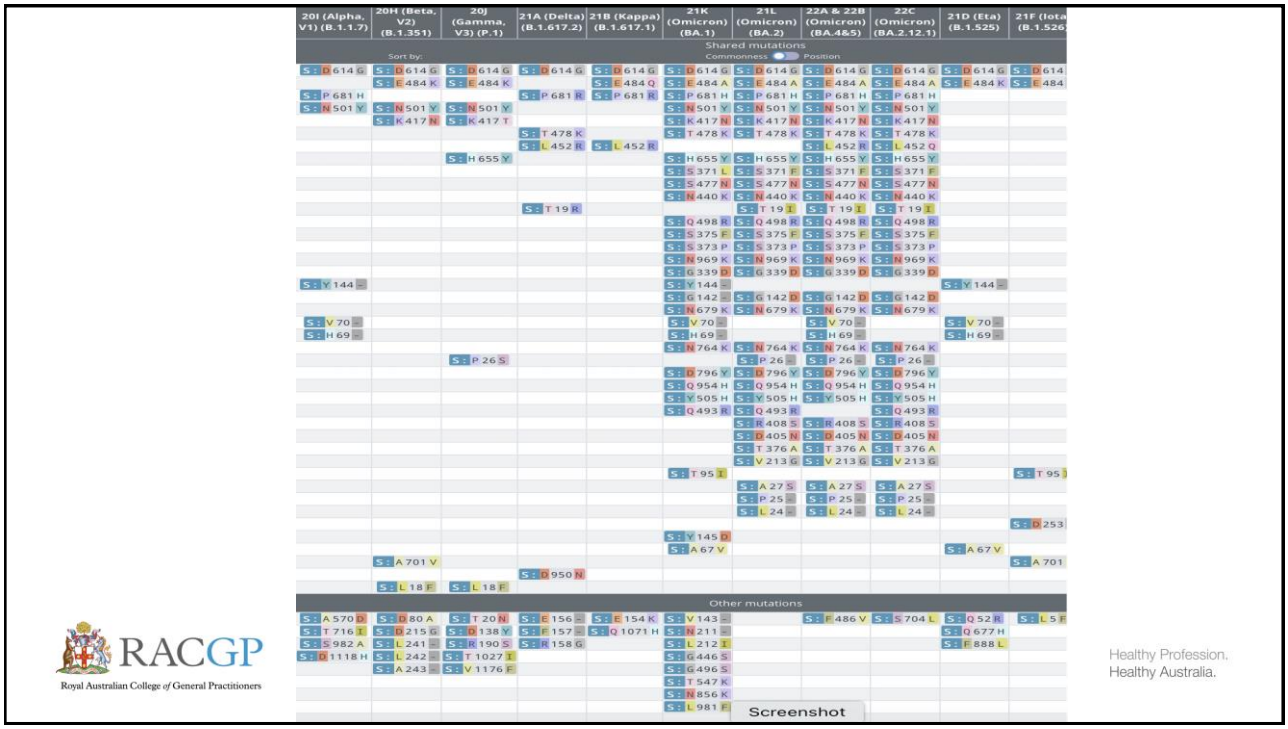
20I (Alpha, V1) (B.1.1.7)
20H (Beta, V2) (B.1.351)
20J (Gamma, V3) (P.1)
21A (Delta) (B.1.617.2)
21B (Kappa) (B.1.617.1)
21K (Omicron) (BA.1)
21L (Omicron) (BA.2)
22A & 22B (Omicron) (BA.4&5)
22C (Omicron) (BA.2.12.1)
21D (Eta) (B.1.525)
21F (Iota (B.1.526
Shared mutations
Sort by:
Commonness
Position
Other mutations
Screenshot
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Omicron

- Low quality data suggests possible recombination event (C.1.2 and B.1) with postulation of origin in HIV patient due to chronic infection
- 10 mutations within spike
- Many mutations within the nucleocapsids

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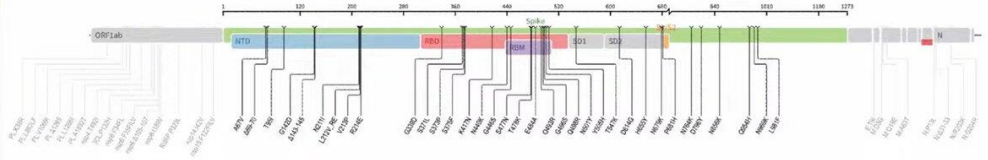
Impact

B.1.1.529 – potential impact of mutations



- Multiple RBD and NTD mutations associated **with resistance to neutralizing antibodies** (and therapeutic monoclonal antibodies)
- Cluster of mutations (H655Y + N679K + P681H) adjacent to S1/S2 furin cleavage site – **associated with more efficient cell entry → enhanced transmissibility**
- nsp6 deletion (Δ105-107) – similar to deletion to Alpha, Beta, Gamma, Lambda – may be associated with **evasion of innate immunity (interferon antagonism) → could also enhance transmissibility**
- R203K+G204R mutations in nucleocapsid - seen in Alpha, Gamma, Lambda – associated with **increased infectivity**

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Important questions about vaccine effectiveness (VE) and Omicron

- VE against infection of primary series and booster dose
- VE against severe disease of primary series and booster dose
- Duration of Protection
  - Against severe disease of primary series and booster dose
- VE against transmission
- Impact of interval between primary and booster doses
- Product-specific VE
- VE among those with and without prior infection

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Infectivity

(b) Probability of testing positive

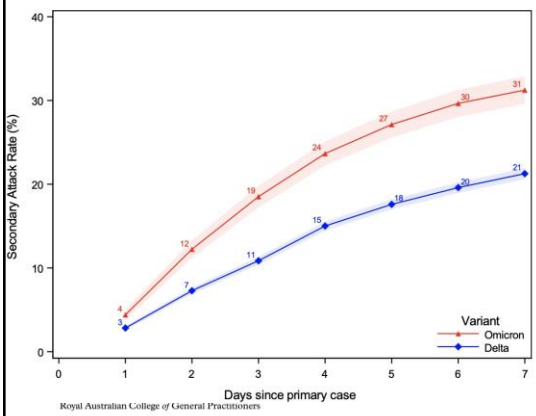

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Table 3: Relative effect of the Omicron VOC

	Unvaccinated	Fully vaccinated	Booster-vaccinated
Omicron households	1.17	2.61	3.66
	(0.99-1.38)	(2.34-2.90)	(2.65-5.05)
Delta households	ref	ref	ref
	(.)	(.)	(.)
Number of observations	27,874	27,874	27,874
Number of households	11,937	11,937	11,937

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VE against transmission in Denmark

	Omicron	Delta
Number of cases	2225	
Secondary Attack Rate	31%	21%
Among unvaccinated	29%	28%
Among fully vaccinated with primary series/prior infection	32%	19%
Among boosted persons	25%	11%
aOR for secondary infection (ref fully vaccinated/prior infection)		
Unvaccinated	1.04 (0.87-1.24)	2.31 (2.09-2.55)
Boosted	0.54 (0.40-0.71)	0.38 (0.32-0.46)
aOR for transmission (ref fully vaccinated/prior infection)		
Unvaccinated primary	1.41 (CI: 1.27-1.57)	
Boosted primary	0.72 (.56-0.92)	

Lyngse, F. P., Mortensen, L. H., Denwood, M. J., Christiansen, L. E., Møller, C. H., Skov, R. L., Spiess, K., Fomsgaard, A., Lassauniere, R., Rasmussen, M., Stegger, M., Nielsen, C., Sieber, R. N., Cohen, A. S., Møller, F. T., Ethelberg, S., Overvad, M., Mølbak, K., Krause, T. G., & Kirkeby, C. T. (2021). SARS-CoV-2 Omicron VOC Transmission in Danish Households. *MedRxiv*, 2021.12.27.21268278. https://doi.org/10.1101/2021.12.27.21268278

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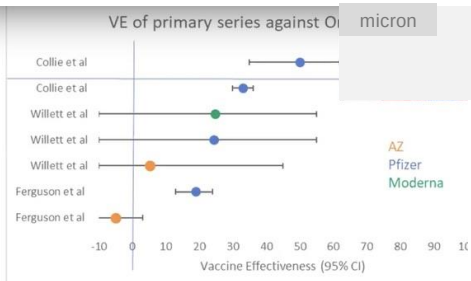
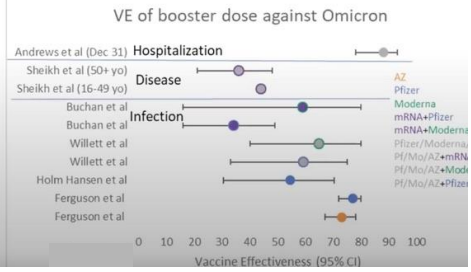
Primary series and booster VE

- Primary Series
  - 3 studies with VE estimates 2+ weeks after primary series
  - Only 1 looking at hospitalization
- Booster Dose
  - 6 studies with VE estimates 1-2 weeks post booster dose
  - Only 1 looking at hospitalization
- All studies compare Delta to Omicron→Omicron VE always lower than Delta





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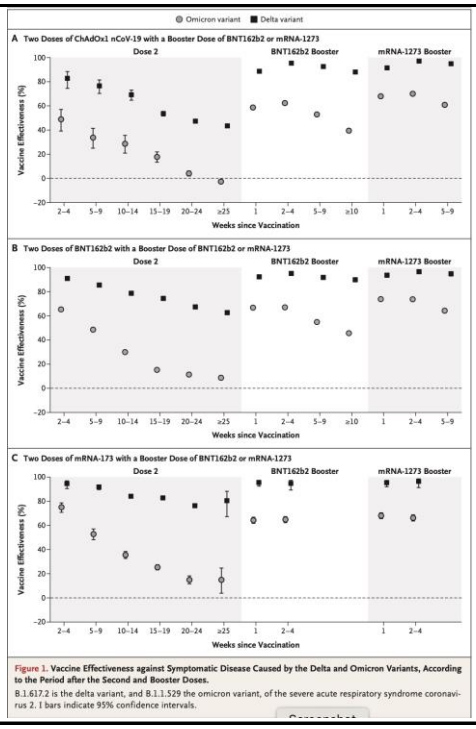

Figure 1. Vaccine Effectiveness against Symptomatic Disease Caused by the Delta and Omicron Variants, According to the Period after the Second and Booster Doses.

B.1.617.2 is the delta variant, and B.1.1.529 the omicron variant, of the severe acute respiratory syndrome coronavirus 2. I bars indicate 95% confidence intervals.

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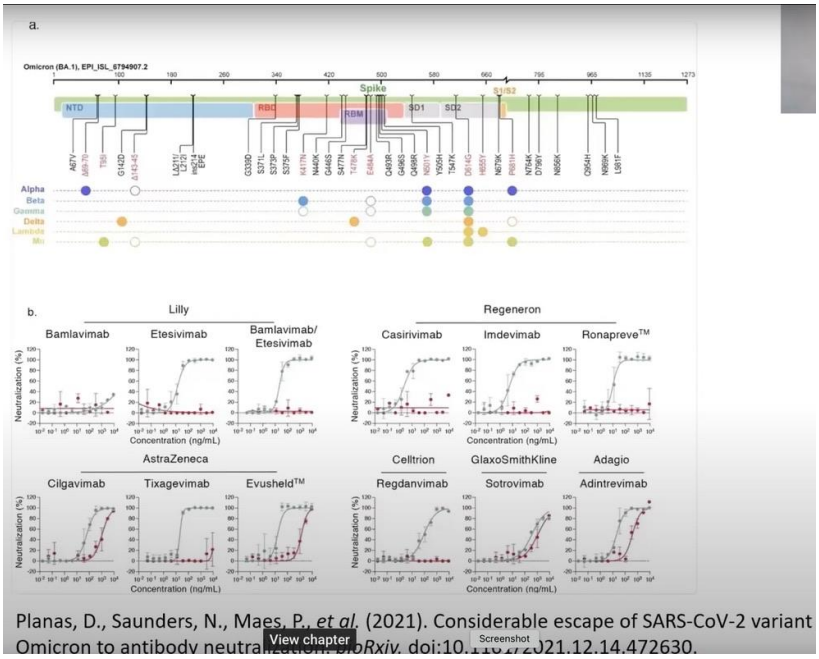

Planas, D., Saunders, N., Maes, P., *et al.* (2021). Considerable escape of SARS-CoV-2 variant Omicron to antibody neutralization. *bioRxiv.* doi:10.1101/2021.12.14.472630.

View chapter
Screenshot

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Re-infection

European Centre for Disease Prevention and Control

- *Laboratory confirmation of two infections by two different strains (minimum distance to be determined or supported by phylogenetic and epidemiological data) with timely separated illness/infection episodes*

The Centers for Disease Control and Prevention (CDC)

- *Detection of SARS-CoV-2 RNA (with Ct values < 33 if detected by RT-PCR) > 90 days after the first detection of viral RNA whether or not symptoms were present and paired respiratory specimens from each episode that belong to different clades of virus or have genomes with > 2 nucleotide differences per month*

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Differentiation between true reinfection and prolonged primary infection with SARS-CoV-2 is challenging

- Detection bias due to different testing frequencies among those previously infected and those not previously infected, and also between vaccinated and unvaccinated individuals.
- Misclassification due to unrecognized infections (both primary and reinfections). *Meta-analysis - even among patients with confirmed COVID-19, 40.5% were asymptomatic* (Ma et al., 2021)
- Misclassification due to imperfect sensitivity and specificity of molecular and antibody tests.
- Confounding factors e. g. degree of protection and extent of risk/exposures (because of different health consciousness and potential sense of protection given prior infection), different uptake of vaccines, differences in comorbidities, in demographics, occupation, socioeconomic status, living in institutionalised settings, etc

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- High-income countries with huge testing efforts – capable of detecting and reporting every second SARS-CoV-2 case
- Ratio between true cases and reported cases in low-income countries - about 62 to 1 (Bergeri et al., 2021). Probably decreased over time but ratios exceeding 10 still common.
- eg; India - national serosurvey in August 2021 showed a seroprevalence of almost 70% while the documented cases were only about 2% (Jahan et al., 2021

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Efficacy of natural infection

Population based cohort studies and National Health data

- First study - 0.02% (95% CI: 0.01%–0.02%) (95% protection) (Abu-R- addad et al., 2021e)

Protection against SARS-CoV-2 reinfections in population based studies.

Country (Ref.)	Participants (n)	Infected at baseline (n)	Reinfections (n)	Follow-up time (mean ± SD)	Period of first infection and reinfection follow-up	Protection against reinfection (95% CI)
Austria (Pilz et al., 2021)	8,901,064	14,840	40	212 ± 25 days	First infection from February to April 30, 2020; Follow-up from September 1 to November 30, 2020	91% (87% to 93%)
Denmark (Hansen et al., 2021)	525,339	11,068	72	A total of 1,346,920 person days	First infection from March to May 2020; Follow-up from September 1 to December 31, 2020	80.5% (75.4% to 84.5%)
Qatar (Chemaitelly et al., 2021a)	89,642	44,821	263	A total of 280,835.1 person weeks	First infection in June 2021 (median); Follow-up from March 8 to April 21, 2021	Beta variant: 92.3% (90.3% to 93.8%) Alpha variant: 97.6% (95.7% to 98.7%)
Qatar (Abu-Raddad et al., 2021a)	308,714	158,608	214	A total of 996,341.5 person weeks	First infection before November 1, 2020; Follow-up from January 18 to March 3, 2021	Alpha variant: 97.5% (95.7% to 98.6%) Unknown variant: 92.2% (90.6% to 93.5%)
United States (Kim et al., 2021)	325,157	50,327	40	300 ± 76 days	First infection March 9 to December 31, 2020; Follow-up from July 1 to September 9, 2021	85.4% (80.0% to 89.3%)
United States (Spicer et al., 2021)	550,168	41,647	593	90 to 300 days (minimum to maximum)	First infection from March 6 to August 31, 2020; Follow-up until December 31, 2020	77.3% (75.4% to 79.0%)
United States (Sheehan et al., 2021)	150,325	8845	62	139 ± 46 days	First infection from March 12 to August 30, 2020; Follow-up until February 24, 2021	81.8% (76.6% to 85.8%)
Italy (Vitale et al., 2021)	13,496	1579	5	280 ± 41 days	First infection from February to July 2020; Follow-up until February 28, 2021	94% (92% to 95%)
United Kingdom (Breathnach et al., 2021b)	66,001	10,727	8	Not indicated	First infection from February to July 2020; Follow-up from August to December 2020	94% (88% to 97%)

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- ***Omicron*** – reduced to **56.0%** (95% CI: 50.6%–60.9%)
- Protection **against hospitalization or death** - similarly high as for other variants with **87.8%** (95% CI: 47.5%–97.1%) (Altarawneh et al., 2022)
- Inconsistent and require cautious interpretation (Eggink et al., 2021; Pulliam et al., 2021)

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Omicron BA.2 infection after BA.1 infection

- Largely extrapolated from surveillance data from UK, South Africa, Denmark and Qatar and a couple of studies.

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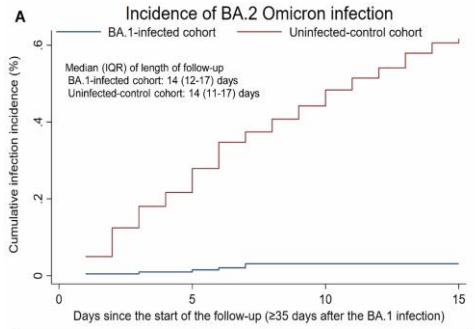
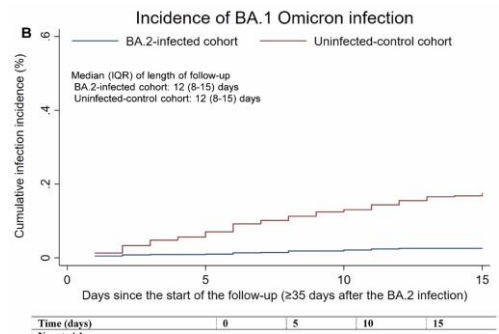


Time (days)	0	5	10	15
No. at risk				
BA.1-infected cohort	20,197	19,260	16,855	9,081
Uninfected-control cohort	20,197	19,210	16,762	8,995



Time (days)	0	5	10	15
No. at risk				
BA.2-infected cohort	100,925	91,825	70,976	28,912
Uninfected-control cohort	100,925	91,648	70,665	28,735

Table 2. Effectiveness against reinfection in the BA.1-against-BA.2 and BA.2-against-BA.1 studies.

Epidemiological measure	BA.1-against-BA.2 study: Effectiveness of BA.1 infection against reinfection with BA.2		BA.2-against-BA.1 study: Effectiveness of BA.2 infection against reinfection with BA.1	
	Estimate (95% CI)	Effectiveness in % (95% CI)	Estimate (95% CI)	Effectiveness in % (95% CI)
Main analysis				
Total follow-up time—BA.1/BA.2-infected cohort (person-weeks)	40,091	--	170,799	--
Total follow-up time—Uninfected-control cohort (person-weeks)	39,901	--	170,272	--
Incidence rate of infection— BA.1/BA.2-infected cohort (per 10,000 person-weeks)	1.5 (0.7 to 3.3)	--	1.3 (0.9 to 2.0)	--
Incidence rate of infection—Uninfected-control cohort (per 10,000 person-weeks)	29.3 (24.5 to 35.2)	--	8.4 (7.1 to 9.9)	--
Unadjusted hazard ratio for infection	0.05 (0.02 to 0.12)	94.9 (88.4 to 97.8)	0.15 (0.10 to 0.24)	84.7 (76.0 to 90.2)
Adjusted hazard ratio for infection*	0.05 (0.02 to 0.12)	94.9 (88.4 to 97.8)	0.14 (0.09 to 0.23)	85.6 (77.4 to 90.9)
Sensitivity analysis				
Total follow-up time—BA.1/BA.2-infected cohort (person-weeks)	40,091	--	170,799	--
Total follow-up time—Uninfected-control cohort (person-weeks)	39,901	--	170,272	--
Incidence rate of infection— BA.1/BA.2-infected cohort (per 10,000 person-weeks)	0.5 (0.1 to 2.0)	--	1.8 (1.2 to 2.5)	--
Incidence rate of infection—Uninfected-control cohort (per 10,000 person-weeks)	30.1 (25.2 to 36.0)	--	9.5 (8.2 to 11.1)	--
Unadjusted hazard ratio for infection	0.02 (0.004 to 0.07)	98.3 (93.3 to 99.6)	0.18 (0.13 to 0.27)	81.5 (72.7 to 87.5)
Adjusted hazard ratio for infection*	0.02 (0.004 to 0.07)	98.4 (93.3 to 99.6)	0.18 (0.12 to 0.26)	82.2 (73.7 to 88.0)

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Protection of Omicron sub-lineage infection against reinfection with another Omicron sub-lineage, Hiam Chemaitelly, Laith J. Abu-Raddad et al, medRxiv 2022.02.24.22271440

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Age groups	N (%)	Vaccination status: Not vaccinated (N= 95; 68%)	Started primary vaccination program (N=17; 12%)	Full effect after primary vaccination program (N=25; 18%)	Booster vaccinated (N=3; 2%)
0-5 years	9 (6%)	9	0	0	0
6-9 years	32 (23%)	25	7	0	0
10-14 years	27 (19%)	24	3	0	0
15-19 years	8 (6%)	6	1	1	0
20-29 years	18 (13%)	12	1	4	1
30-39 years	28 (20%)	15	5	8	0
40-49 years	14 (10%)	3	0	10	1
50-75 years	4 (3%)	1	0	2	1

First infection	Second infection			
	No symptoms	Mild Symptoms	Moderate Symptoms	Total
No symptoms	2	1	0	3
Mild Symptoms	2	13	2	17
Moderate Symptoms	1	9	3	13
Total	5	23	5	33

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Duration of natural infection

- *Epidemiological studies* – lasts for over one year with only moderate, if at all, decline over this period.
- Persistence of anti SARS-CoV-2 antibodies and cellular immunity over more than one year (Chellamuthu et al., 2021; Dehgani-Mobaraki et al., 2021; Gussarow et al., 2021; Lau et al., 2021; Rosati et al., 2021)

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Duration of natural infection

Protection against SARS-CoV-2 reinfections in population based studies stratified by follow-up time.

Country (Ref.)	Follow-up time	Protection against reinfection (%) (95% CI)
Denmark (Hansen et al., 2021)	3 to 6 months	79.3 (74.4 to 83.3)
	7 months and longer	77.7 (70.9 to 82.9)
United States (Kim et al., 2021)	90 to 150 days	63.9
	151 to 210 days	93.2
	211 to 270 days	93.9
	271 to 330 days	91.3
	331 to 390 days	90.8
	After 390 days	87.3
United States (Spicer et al., 2021)	90 to 120 days	70.1 (65.6 to 74.0)
	121 to 150 days	78.7 (75.1 to 81.7)
	151 to 180 days	81.4 (77.5 to 84.6)
	181 to 210 days	74.0 (67.2 to 79.4)
	211 to 240 days	70.4 (59.5 to 78.4)
	241 to 270 days	79.8 (65.0 to 88.4)
	271 to 300 days	Not indicated (no infection in 1335 participants with a prior infection and 77 infections in 10,382 without a prior infection)
United States (Sheehan et al., 2021)	90 to 150 days	60.0
	151 to 210 days	90.6
	After 210 days	93.9

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Pilz S, Theiler-Schwetz V, Trummer C, Krause R, Ioannidis JPA. SARS-CoV-2 reinfections: Overview of efficacy and duration of natural and hybrid immunity. Environ Res. 2022 Jun;209:112911

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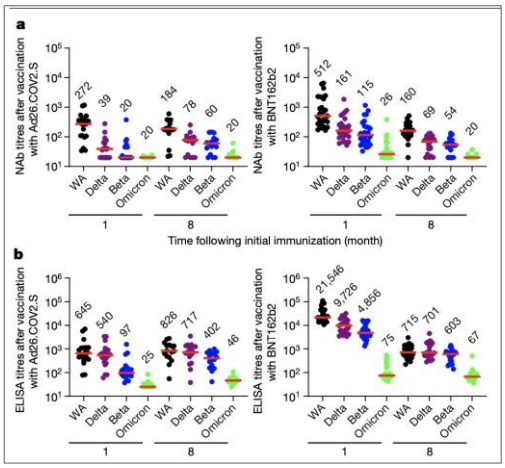
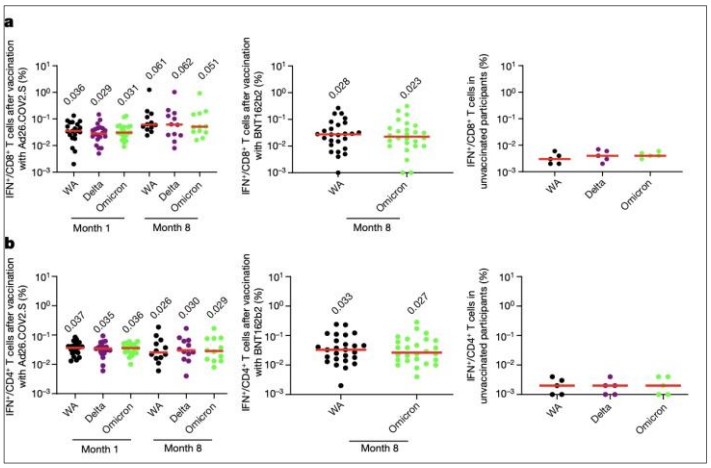
Invitro





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Risk factors for reinfection

Case reports and case series

- Certain comorbidities or exposure risk (e.g. health-care workers) may have higher rates of reinfections, but data remain inconsistent
- May be a function of exposure risk (more exposures as societies use less or no lockdown measures and citizens feel more safe to get exposed, higher rates of reinfections may ensue) (Ioannidis, 2021a)
- Reinfection risk not significantly different in patients with prior infection, when comparing groups with versus without detectable antibodies (Breathnach et al., 2021a)
- Severity of infection not associated with reinfection

Pilz S, Theiler-Schwetz V, Trummer C, Krause R, Ioannidis JPA. SARS-CoV-2 reinfections: Overview of efficacy and duration of natural and hybrid immunity. Environ Res. 2022 Jun;209:112911

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Clinical severity of reinfections

National databases and case reports and case series

- 90% lower odds (95% CI: 75%–97%) of resulting in hospitalisation or death when compared to primary infections (Abu-Raddad et al., 2021c).
- Huge implications for the COVID-19 pandemic and its evolution into an endemic phase.
- Primed immune system should be better prepared for a re-challenge with this virus (Boyton and Altmann, 2021; Castro Dopico et al., 2022; Cromer et al., 2021; Milne et al., 2021)
- Reinfections versus primary infections with SARS-CoV-2 - significantly lower viral load(RT-qPCR cycle threshold (Ct)) value, may be less infectious and may thus be associated with reduced transmission (Abu-Raddad et al., 2022)

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Comparison of natural immunity with vaccine induced and hybrid immunity

Vaccine induced immunity

- RCTs and real-world studies on vaccines particularly mRNA vaccines - very high short-term efficacy (less than 4 months) (Baden et al., 2021; Chemaitelly et al., 2021b; Polack et al., 2020; Rosenberg et al., 2022)
- Significantly waning protection (e.g. only approximately 20% after about 6 months) (Chemaitelly et al., 2021b; Goldberg et al., 2021b; Rosenberg et al., 2022).
- Protection against severe disease was either sustained or showed only a moderate decline (Chemaitelly et al., 2021b; Goldberg et al., 2021b; Rosenberg et al., 2022)
- Booster restored and probably exceeded the initial short-term efficacy after the initial vaccination (Arbel et al., 2021; Bar-On et al., 2021a)

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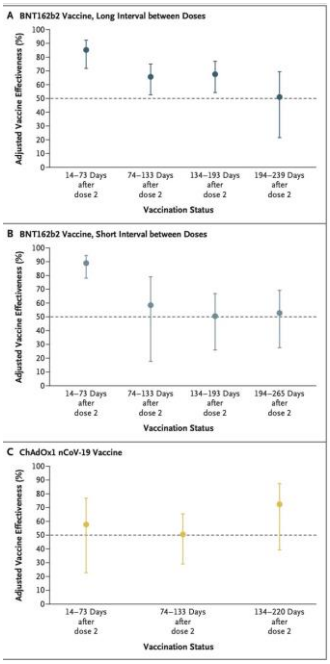
Efficacy of vaccine and natural infection



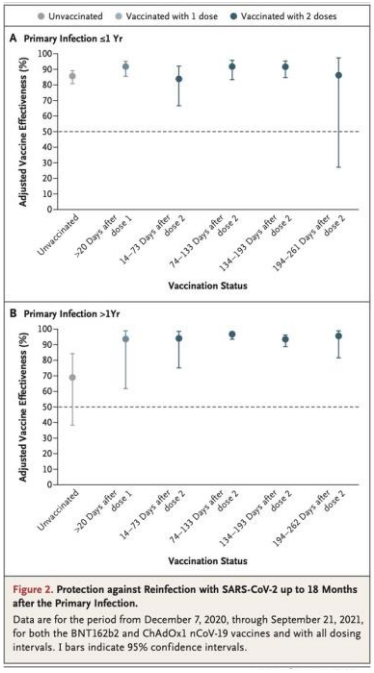


Figure 2. Protection against Reinfection with SARS-CoV-2 up to 18 Months after the Primary Infection.

Data are for the period from December 7, 2020, through September 21, 2021, for both the BNT162b2 and ChAdOx1 nCoV-19 vaccines and with all dosing intervals. I bars indicate 95% confidence intervals.

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Protection against SARS-CoV-2 after Covid-19 Vaccination and Previous Infection V. Hall et al for SIREN study group, NEJM 386;13 March 31, 20

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Observational studies, Nationwide surveys

- Equal or greater immunity from past infection over vaccination X 2 doses
- Booster dose reduces the difference
- Omicron - far lower ability to restore protection from infection and vaccination (Altarawneh et al., 2022; Buchan et al., 2022; Lyngse et al., 2021; Pulliam et al., 2021).
- Fatalities and hospitalisations remain distinctively low (Christie, 2021; Kupferschmidt and Vogel, 2021; Ulloa et al., 2022)

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Hybrid immunity

National surveys

- **Israel (nearly 6 million people)** –
  - (a) previous infection and no vaccination,
  - (b) an infection and then vaccinated with a single dose after at least 3 months
  - (c) vaccinated (two doses) and then infected (Goldberg et al., 2021a).
  - (d) received two vaccine doses

  4 to 6 months after the last immunity-conferring event, the adjusted rates of

SARS-CoV-2 infections	Severe infection and death (95% CI)/100,000 days
(a) **10.5** (8.8 to 12.4)	(a) 0.6
(b) **10.3** (9.4 to 11.4)	(b) 0.5
(c) **12.8** (9.9 to 16.6)	(c) 1.1. (0.4 for those who received booster dose)
(d) **69.2** (95% CI: 68.8 to 69.8)	(d) 4.6

- Similar results from Qatar and USA

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Summary

- Seroprevalence surveys suggest that more than a third and possibly more than half of the global population has been infected with SARS-CoV-2 by early 2022 (Bergeri et al., 2021; Hotez et al., 2021; McIntyre et al., 2022)
- National surveys covering 2020–2021 documented that a previous SARS-CoV-2 infection is associated with a significantly reduced risk of reinfections with efficacy lasting for at least one year and only relatively moderate waning immunity (Pre-Omicron)
- Natural immunity showed roughly similar effect sizes regarding protection against reinfection across different SARS-CoV-2 variants
  - SARS-CoV-2 infection with earlier variants elicits **>85% (~92%)** protection against reinfection with the **Alpha2 (B.1.1.7), Beta2 (B.1.351), and Delta2 (B.1.617.2) variants**,
  - Protection against reinfection with the **Omicron BA.1** sub-lineage is inferior at **<60%.**
  - Effectiveness of **Omicron BA.1 infection against reinfection with BA.2** is around **95%**
  - Risk of hospitalisations and deaths was also reduced in SARS-CoV-2 reinfections versus primary infections

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- Vaccine effectiveness
  - **2 doses >80%** against **severe disease by Delta after 5 months** and **40-80%** against **symptomatic disease after 5 months**. **Booster dose** - **>90%** protection against symptomatic disease **2 weeks after vaccine**
  - **2 doses >70% against severe disease by Omicron after 6 months** and **<25%** against **symptomatic disease after 6 months**. **Booster dose - >80%** protection against **severe disease** and **40-70%** against **symptomatic disease (wanes over time)**
- Combination of a previous SARS-CoV-2 infection & vaccination (hybrid immunity), seems to confer the greatest protection against SARS-CoV-2 infections
- Background/community vaccination rates influence generation of variants

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- Risk factors and frailty can contribute to hospitalisation and death (Omicron)
- Consider early treatment in patients with risk factors – PBS for >65 years and online referral for <65 years who are eligible
- Continue to test for COVID and other RVPs including Influenza
- Promote influenza vaccination
- Individuals, regardless of history of prior infection, should continue to participate in mitigating the spread of infection by practicing social distancing and mask-wearing.
- Consider Evusheld in immunocompromised patients and patients who cant legitimately vaccinate

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