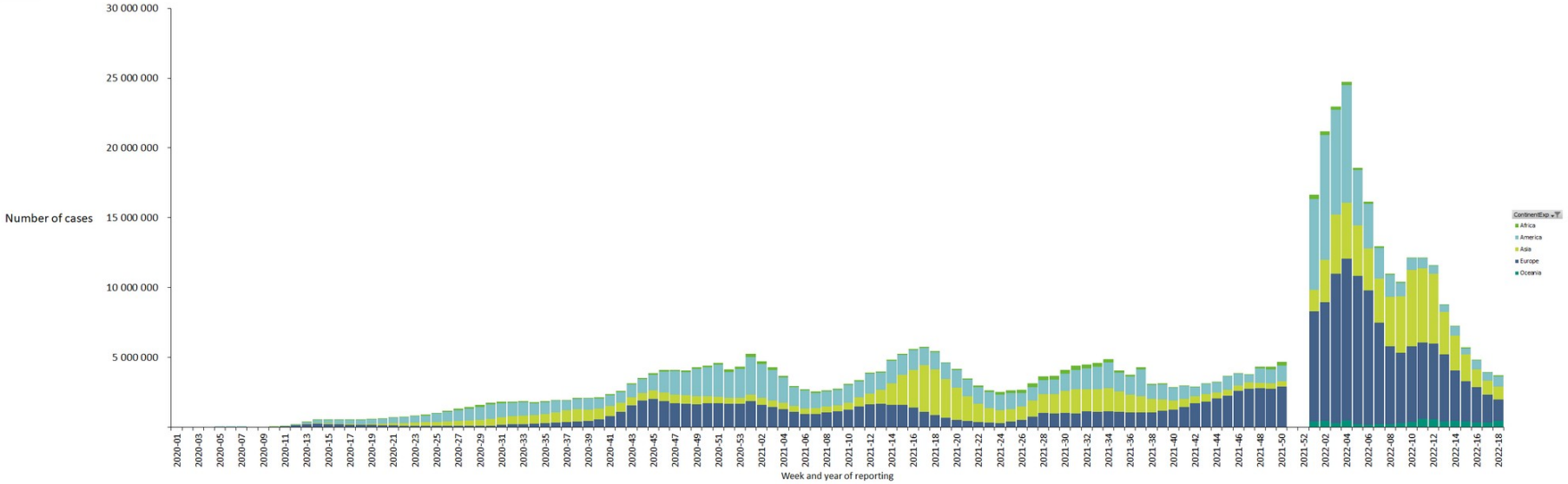
Natural and hybrid Immunity to SARS-COV-2

Ajibola Omokanye, ECDC

European COVID-19 Modelling Hub, 19 May 2022

Increasing population natural immunity

- Since 31 December 2019 and as of week 2022-18, **517 044 187 cases** of COVID-19 (in accordance with the applied case definitions and testing strategies in the affected countries) have been reported
- We know this is a **gross underestimate**, nonetheless the cumulative number of individuals that have recovered from at least 1 prior infection is increasing



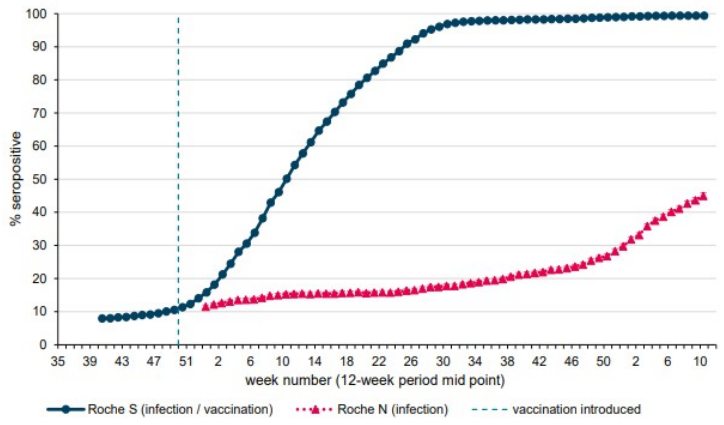
https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases

Increasing population natural immunity – seroprevalence data

UK HSA Surveillance Report 28/04

- Healthy adult blood donors aged 17 years and older, supplied by the NHS Blood w35 2020 - w12 2022 Approx. 250 samples from each geographic NHS region tested each week
- Age 17 - 49 now >50% seropositivity for prior infection following Omicron wave

Figure 11. Overall 12-weekly rolling SARS-CoV-2 antibody seroprevalence (% seropositive) in blood donors



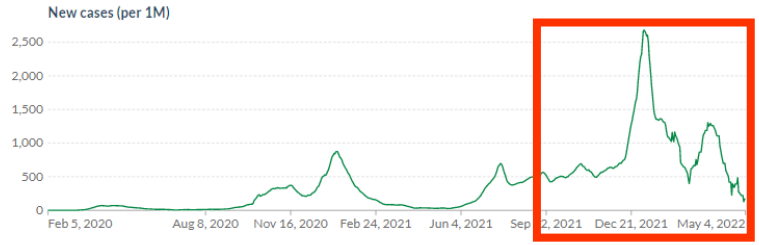


Figure 13. Population weighted 12-weekly rolling SARS-CoV-2 antibody seroprevalence (% seropositive) in blood donors from the Roche N assay by age group

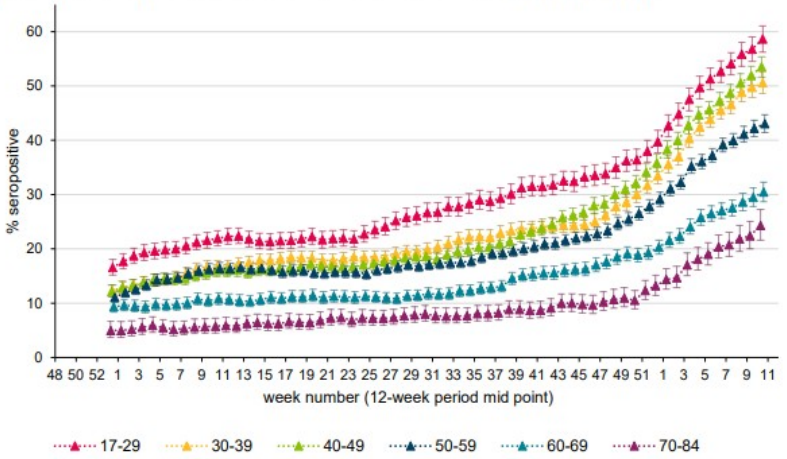
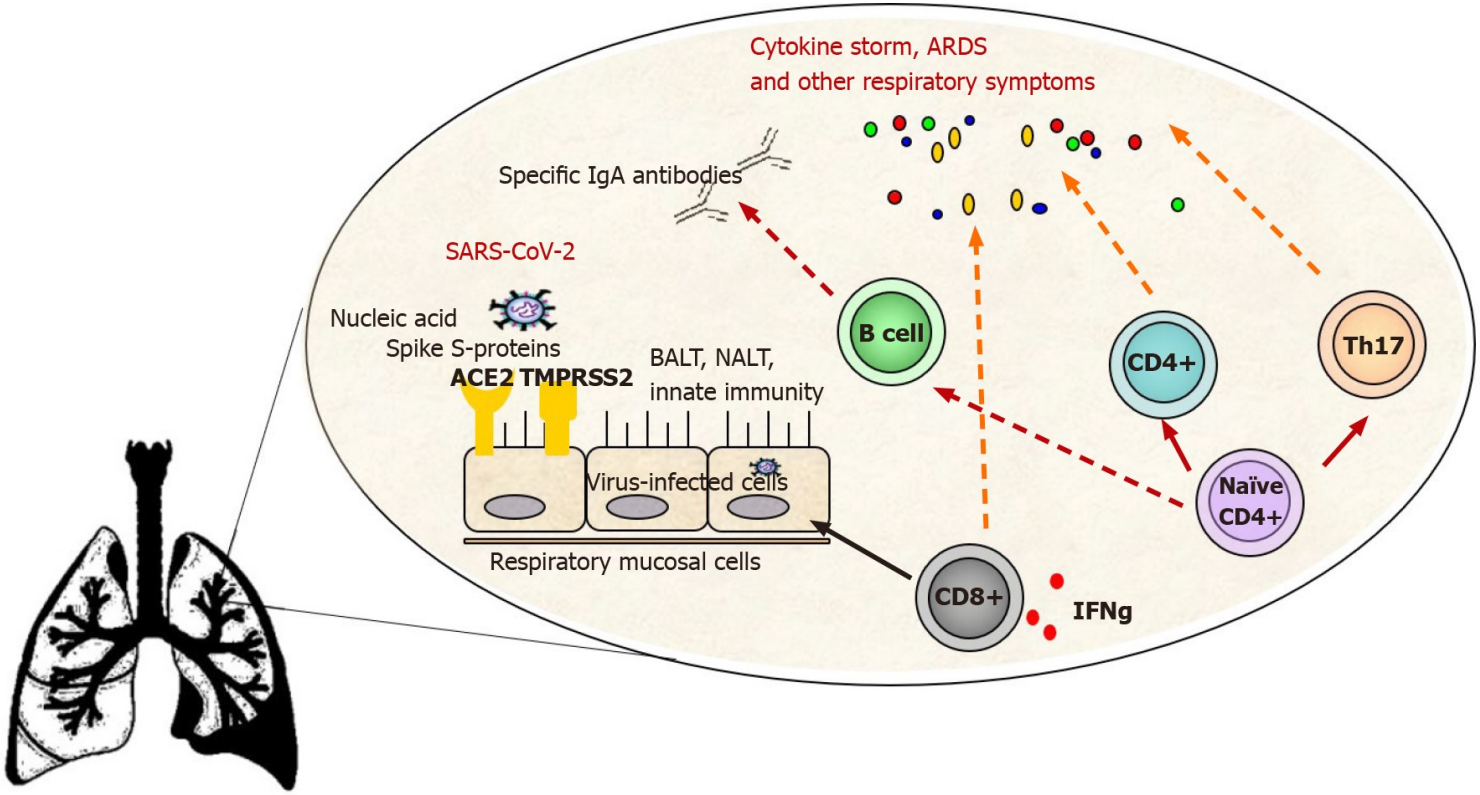


Table 14. Roche N seropositivity (95%CI) estimates by age group

Age group	Weeks 45 2021 to 4 2022	Weeks 5 to 12 2022
17 to 29	36.4% (34.5% to 38.4%)	58.7% (56.2% to 61.1%)
30 to 39	30.0% (28.5% to 31.5%)	50.6% (48.6% to 52.5%)
40 to 49	32.1% (30.6% to 33.6%)	53.5% (51.7% to 55.4%)
50 to 59	26.5% (25.3% to 27.8%)	43.1% (41.4% to 44.7%)
60 to 69	18.8% (17.6% to 20.2%)	30.5% (28.7% to 32.3%)
70 to 84	10.5% (9.0% to 12.3%)	24.3% (21.6% to 27.2%)

UK cases Our World in Data

Infection-induced immunity critically differs from vaccine-induced immunity



https://www.wjgnet.com/1007-9327/full/v27/i30/WJG-27-5047-g001.htm

Infection-induced immunity critically differs from vaccine-induced immunity

- Mucosal immune system is by far the largest component of the entire immune system
- SARS-CoV-2 primarily infects the upper respiratory tract mucosa
- **Natural infection** induces site-specific mucosal immunity:

  - **mucosal, secretory IgA**; *binds to virus/virus expressing host cells*

  - **tissue-resident (TR) CD4 and CD8 T cells**; *lyse infected host cells*

  in addition to

  - systemic IgG and T cells

- **Intramuscular vaccination** does not induce site-specific mucosal immunity

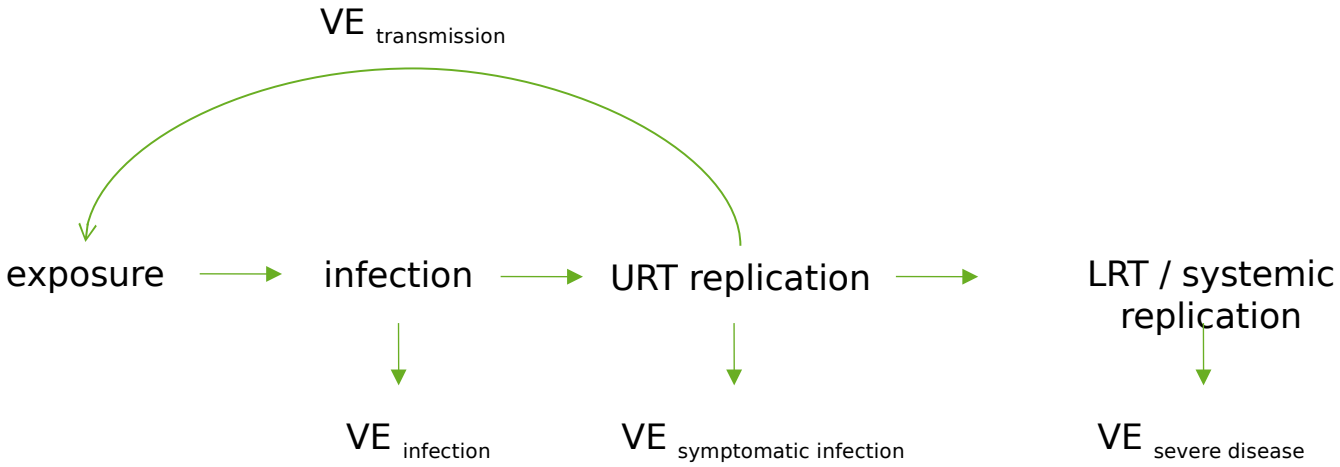
  - systemic IgG (transduced to tissues e.g. lung, but not mucosal surface)

  - systemic IgA (not transported into secretions)

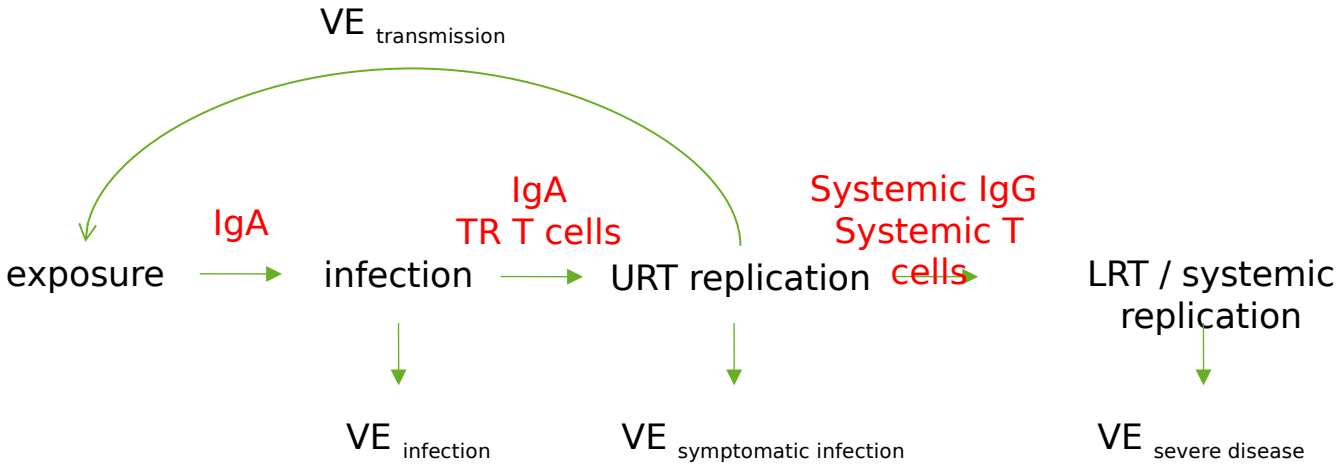
  - systemic CD4 and CD8 T cells

https://www.frontiersin.org/articles/10.3389/fimmu.2020.611337/full

How might mucosal immunity impact protection?



How might mucosal immunity impact protection?



VE studies do not typically report prior infection status

However, it does make a difference…

https://view-hub.org/sites/default/files/2022-05/COVID19_VEStudies_ForestPlots_Delta_Omicron.pdf

Czechia

- Evaluated individual-level data on all laboratory-confirmed SARS-CoV-2 infections in the Czech Republic to estimate the relative risk of infection, hospitalization, including severe states, for Delta and Omicron variants, adjusting for sex, age, previous infection, vaccine type and vaccination status.

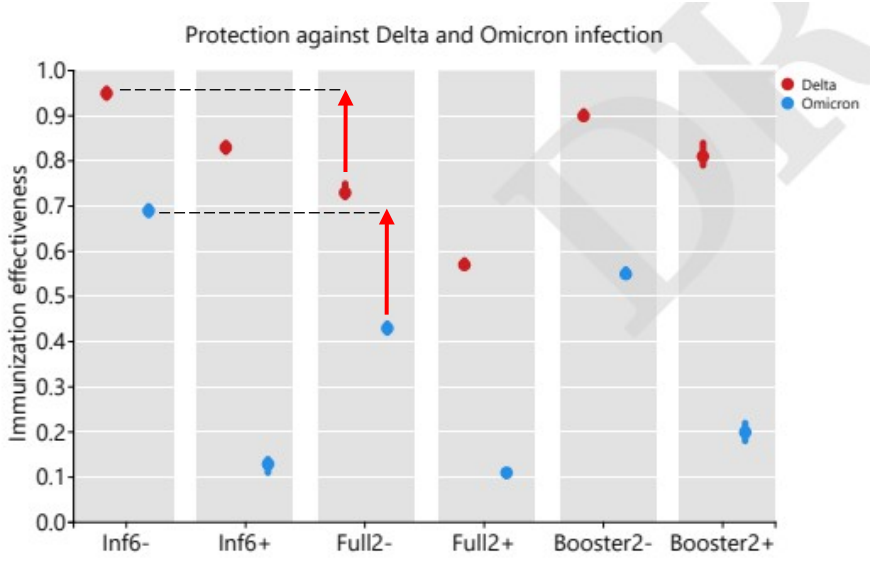


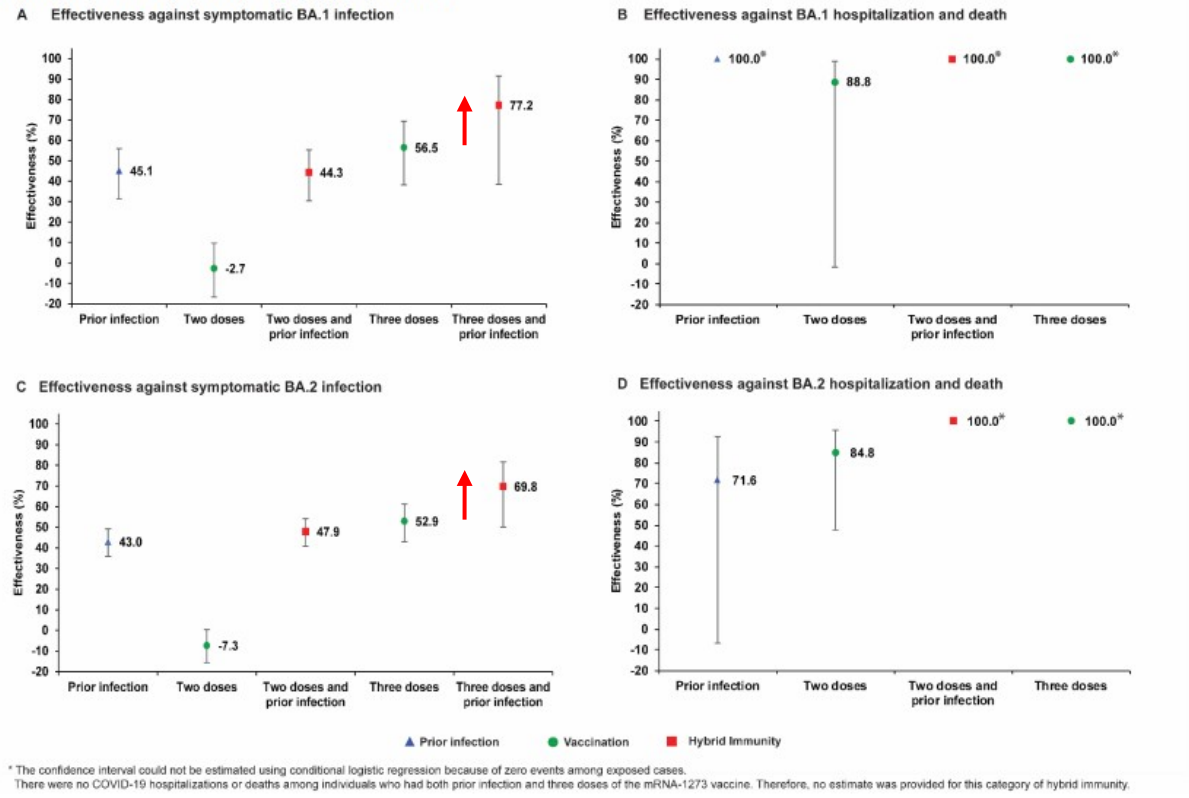
Fig. 2. Protection provided by vaccination or previous infection against infection by the Omicron and Delta variants of the SARS-CoV-2 virus. Inf6-, previous infection <6 months ago; Inf6+, previous infection >6 months ago; Full2-, complete vaccination <2 months ago; Full2+, complete vaccination >2 months ago; Booster2-, booster dose <2 months ago; Booster2+, booster dose >2 months ago. Shown are point estimates of protection with 95% CI.

https://www.medrxiv.org/content/10.1101/2022.02.24.22271396v1.full.pdf Feb 2022

Qatar

- Six national, matched, test-negative case-control studies conducted to estimate effectiveness of BNT162b2 (Pfizer-BioNTech) vaccine, mRNA-1273 (Moderna) vaccine, natural immunity due to prior infection with pre-Omicron variants, and hybrid immunity from prior infection and vaccination.

Figure 4. Effectiveness of prior infection, vaccination, and hybrid immunity against symptomatic Omicron infection and against severe, critical, or fatal COVID-19 for the BA.1 (panels A and B, respectively) and BA.2 (panels C and D, respectively) subvariants in the mRNA-1273-vaccine study.



* The confidence interval could not be estimated using conditional logistic regression because of zero events among exposed cases.
There were no COVID-19 hospitalizations or deaths among individuals who had both prior infection and three doses of the mRNA-1273 vaccine. Therefore, no estimate was provided for this category of hybrid immunity.

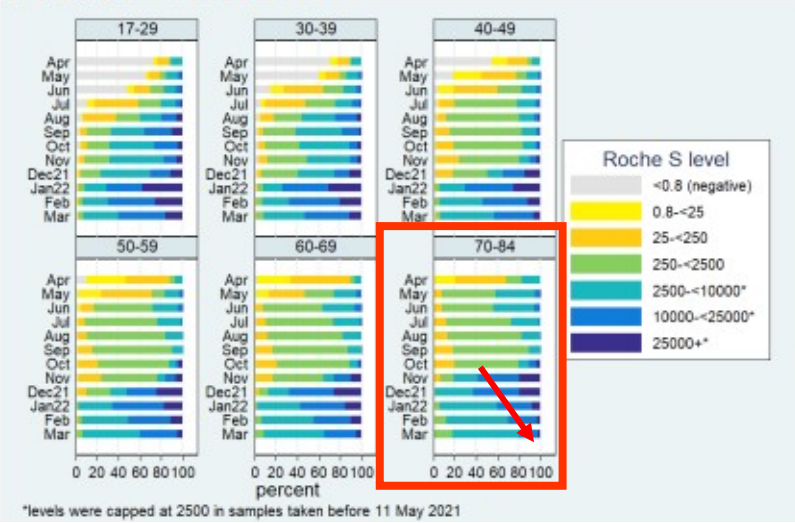
https://www.medrxiv.org/content/10.1101/2022.03.22.22272745v1.full.pdf - Mar 2022

Increasing population natural immunity – seroprevalence data; implications for waning

UK HSA Surveillance Report 28/04

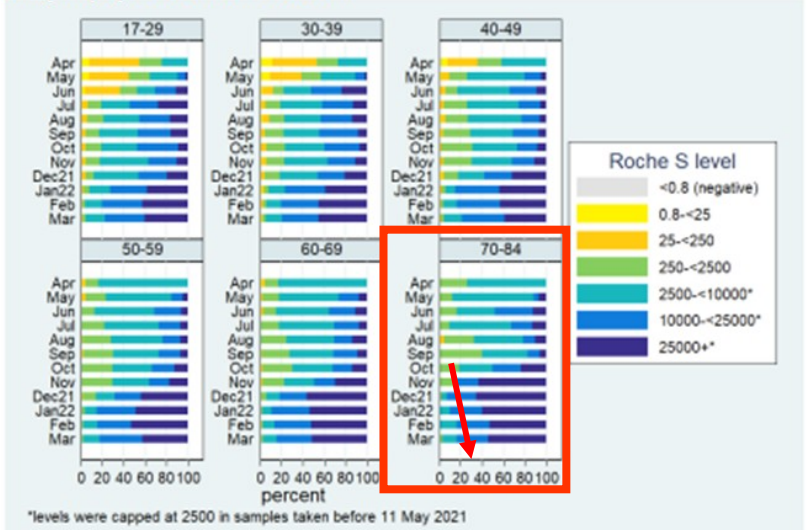
- Quantitative anti-S Ab assay facilitates exploration of waning
  When coupled with anti-N Ab assay, facilitates exploration of waning in the context of hybrid immunity
- Much higher titres, and less waning of anti-S Ab in those with hybrid immunity

Figure 14. Categorised Roche S antibody levels by age group and month in N negative samples, April 2021 to March 2022



*levels were capped at 2500 in samples taken before 11 May 2021

Figure 15. Categorised Roche S antibody levels by age group and month in N positive samples, April 2021 to March 2022



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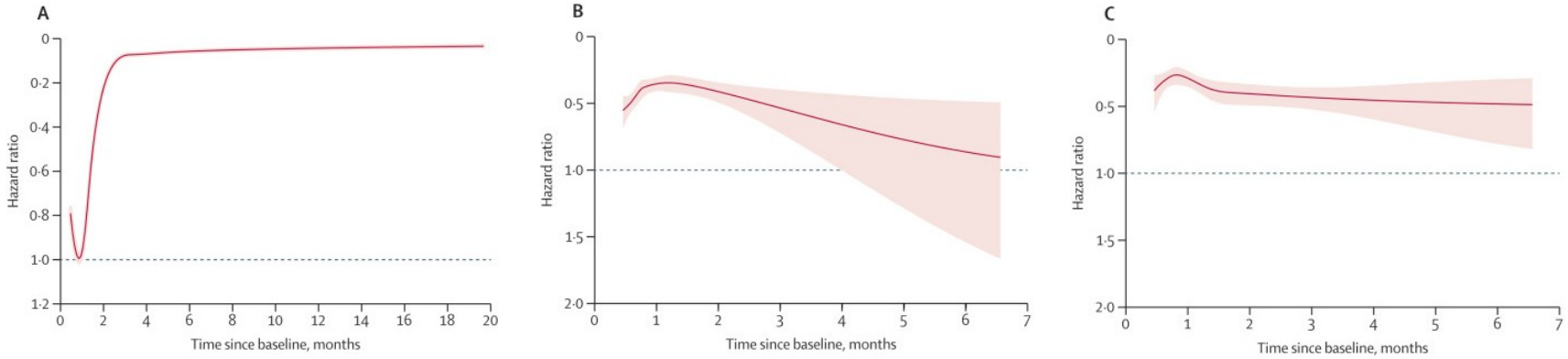
Sweden

- Pre-Omicron
- Risk of SARS-CoV-2 infection in

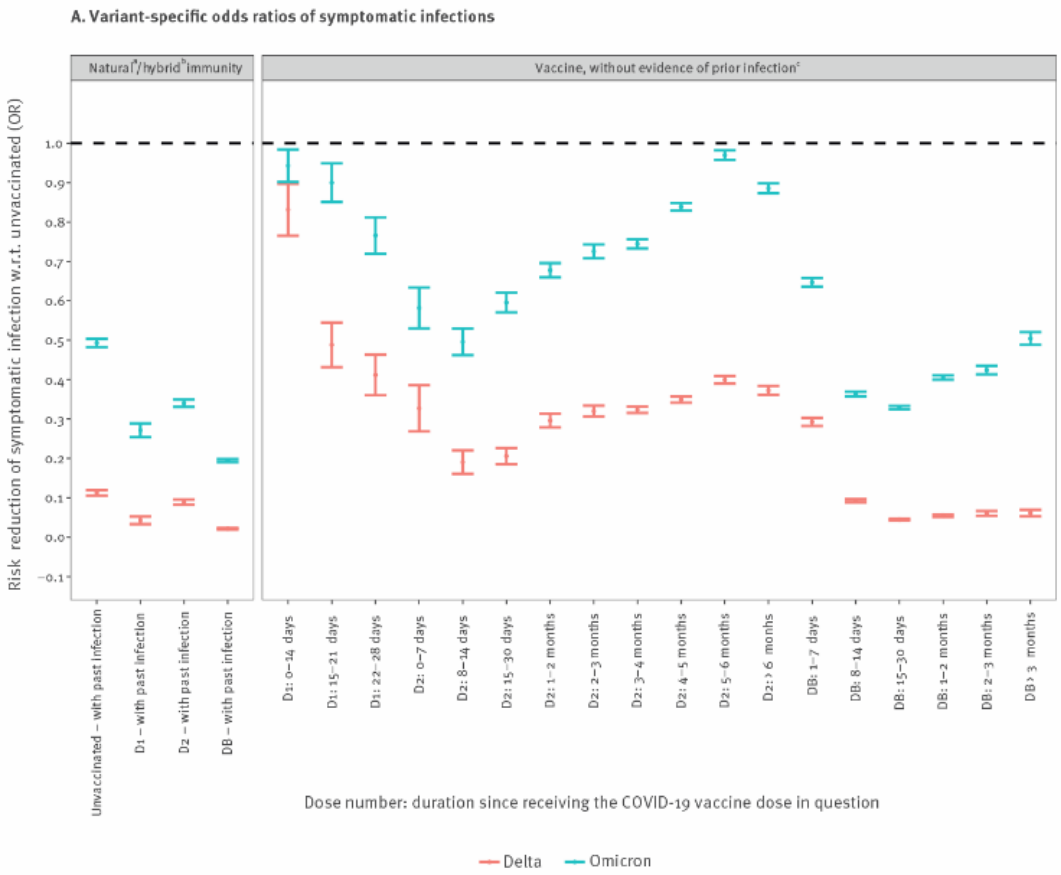
  A - individuals with natural immunity vs individuals without immunity
  B - individuals with one-dose hybrid immunity vs individuals with natural immunity
  C - individuals with two-dose hybrid immunity vs individuals with natural immunity



https://www.sciencedirect.com/science/article/pii/S1473309922001438?via%3Dihub Apr 2022

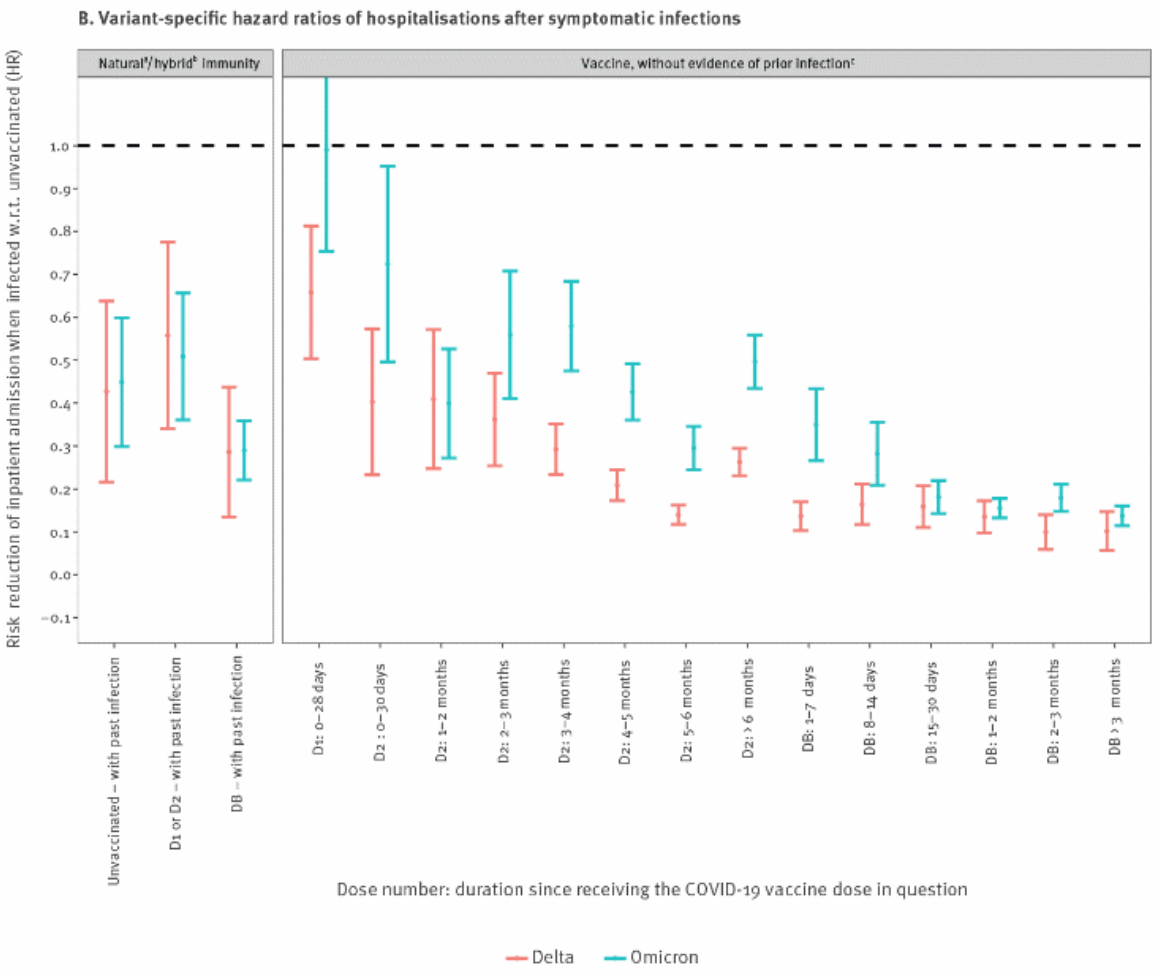
France

- Large, nationwide study to investigate the impact of vaccination and/or previous SARS-CoV-2 infection on the risk of symptomatic infections, hospital admissions, intensive care unit (ICU) admissions and deaths attributable to the Omicron and Delta variants.



https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2022.27.16.2200250?emailalert=true Apr 2022

France



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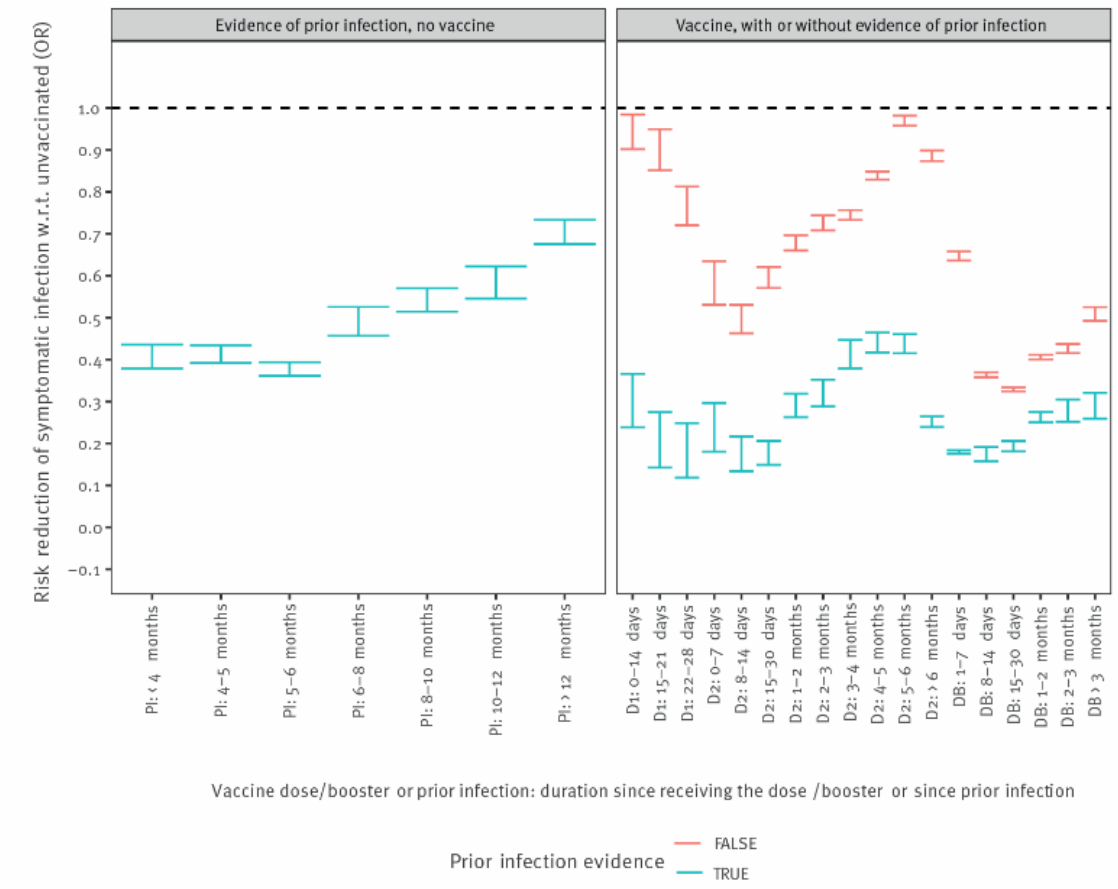

https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2022.27.16.2200250?emailalert=true

Summary

- The cumulative number of individuals that have recovered from at least 1 prior infection is increasing
- Natural infection induces site-specific mucosal immunity:

  - **mucosal, secretory IgA**; *binds to virus/virus expressing host cells*

  - **tissue-resident (TR) CD4 and CD8 T cells**; *lyse infected host cells*

  in addition to

  - systemic IgG and T cells

- This has implications, primarily for $VE_{infection}$ and $VE_{symptomatic\ infection}$ but also $VE_{severe\ disease}$
- However, VE studies rarely report prior infection status
- Where studies disaggregate by prior infection status, hybrid immunity confers substantial additional protection
- When studied over time, hybrid immunity appears to confer protection that is more resistant to waning
- **As we encounter more transmissible variants, hybrid immunity will play an increasingly important role and should be accounted for in modelling estimates**

https://www.sciencedirect.com/science/article/pii/S1473309922001438?via%3Dihub