Antibody Testing for SARS-CoV-2 and use in VE Studies

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WHO EMRO COVID-19 Vaccine Effectiveness Study;
Status Update and Important Considerations
Capacity Building Workshop
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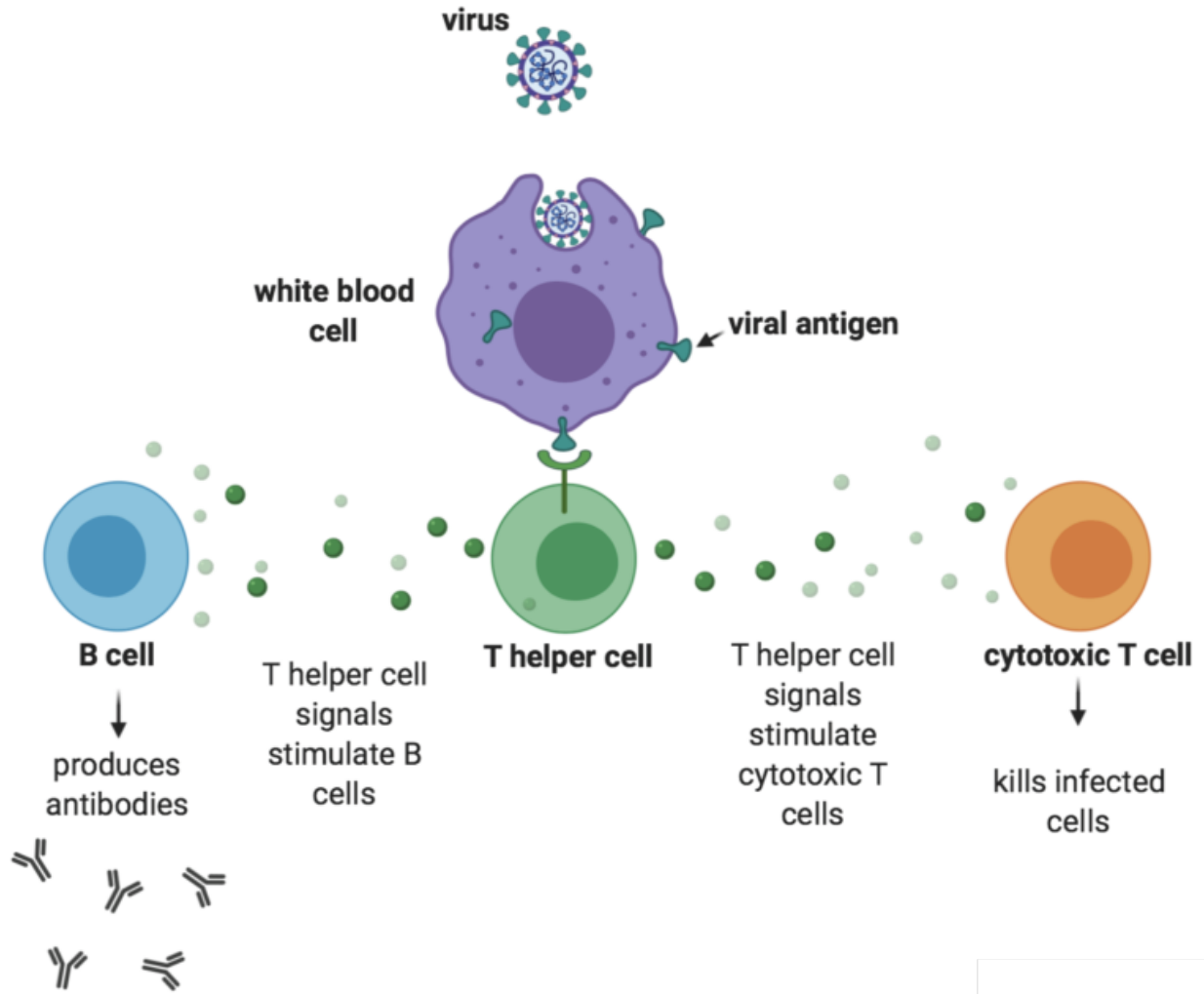
Outline

- Adaptive immunity and antibody tests
- Types of antibody tests
- SARS-CoV-2 humoral immunity
- Factors influencing test performance
- How can antibody tests be used in VE studies

Adaptive immune responses to viral infection



Antibodies are the targets of serological tests

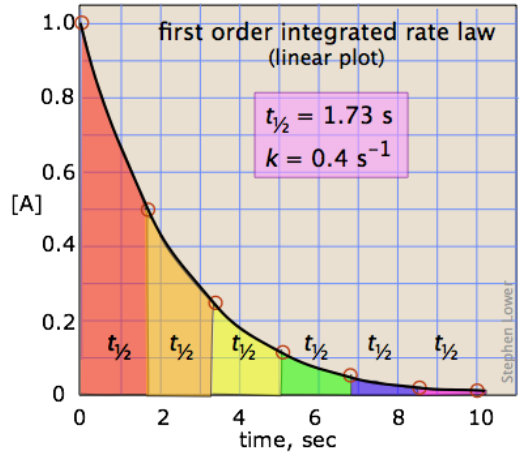
- The adaptive immune response includes **cellular responses** (T-cells, B-cells) and **humoral responses** (antibodies, produced by B cells)
- Both contribute to the defenses against SARS-CoV-2

https://www.virology.ws/2020/11/05/t-cell-responses-to-coronavirus-infection-are-complicated/

Adaptive immune responses to viral infection

- When foreign antigens are detected, the number of B and T cells will expand
- Once the acute event is resolved, the number of B and T cells will reduce. Virus-specific **memory** cells remain and can respond to a new challenge.
- Antibodies have a half-life: serum Ig is expected to decrease over time after the challenge

Immunoglobulin	Approximate half-life (days)
IgM	5-6
IgA	5-6
IgG	21



→ No antibodies detected ≠ no immunity!

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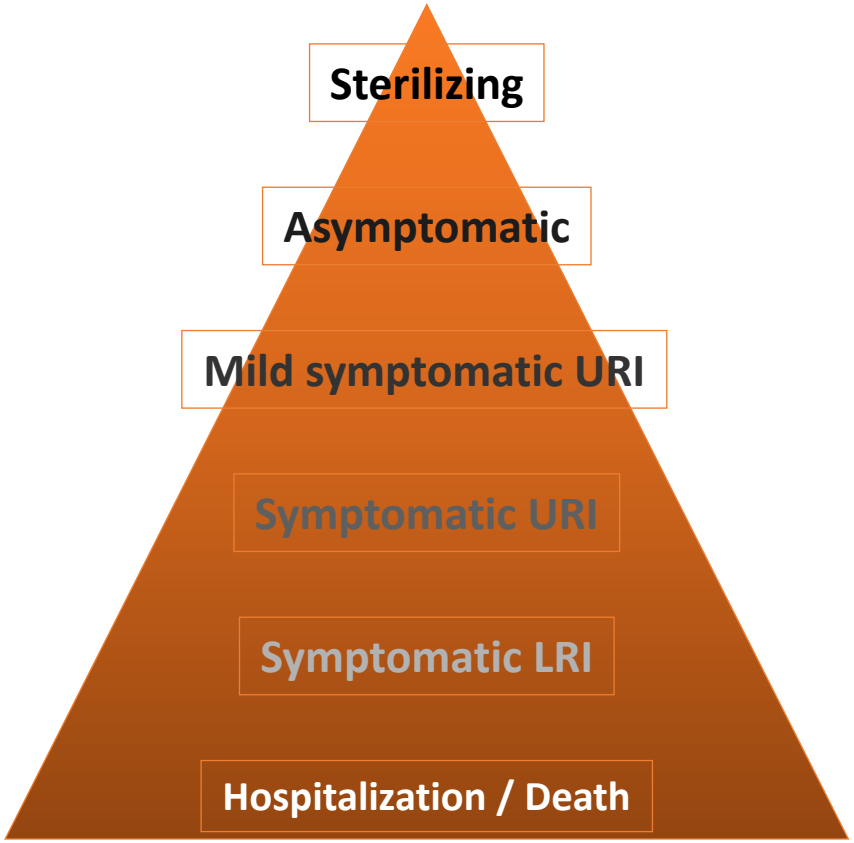
Immunity is a gradient

Levels of immunity



Contributors

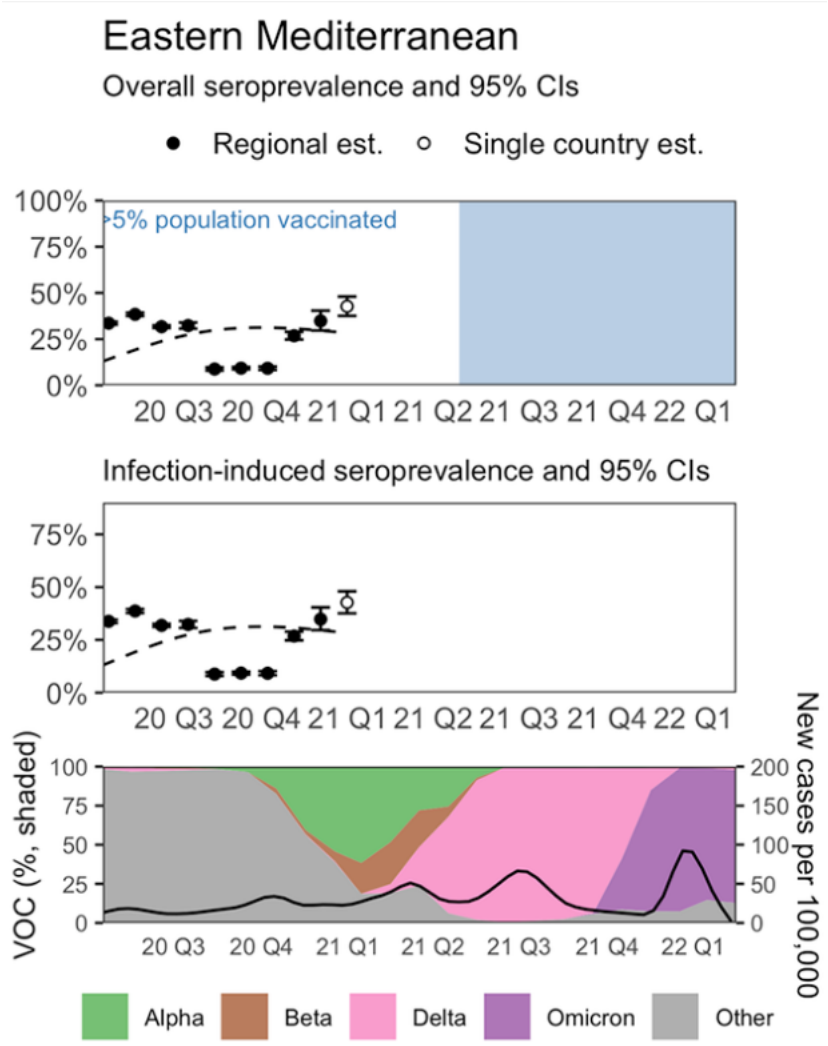
- Antibody levels
- Antibody isotypes
- Antibody functionality (neutralizing / epitopes / affinity)
- Antibody location
- Number and specificity T cells
- T cell ratios

URI – upper respiratory tract infection

LRI – lower respiratory tract infection

Advantages of antibody testing for SARS-CoV-2

- Infection with SARS-CoV-2 leads to a spectrum of diseases, from asymptomatic to severe disease and death
- Antibody tests can provide evidence of sub-clinical infections, and on humoral responses to infection and vaccination
- Contribute to models determining the true rate of infection in the population not captured by routine surveillance
- Ab tests have shown that population seroprevalence is rising due to vaccination and infection and has reached over 95% in Europe as of Dec 2021 [1]



[1] Global SARS-CoV-2 seroprevalence from January 2020 to April 2022: A systematic review and meta-analysis of standardized population-based studies. Bergeri et al. PloS Medicine 2022

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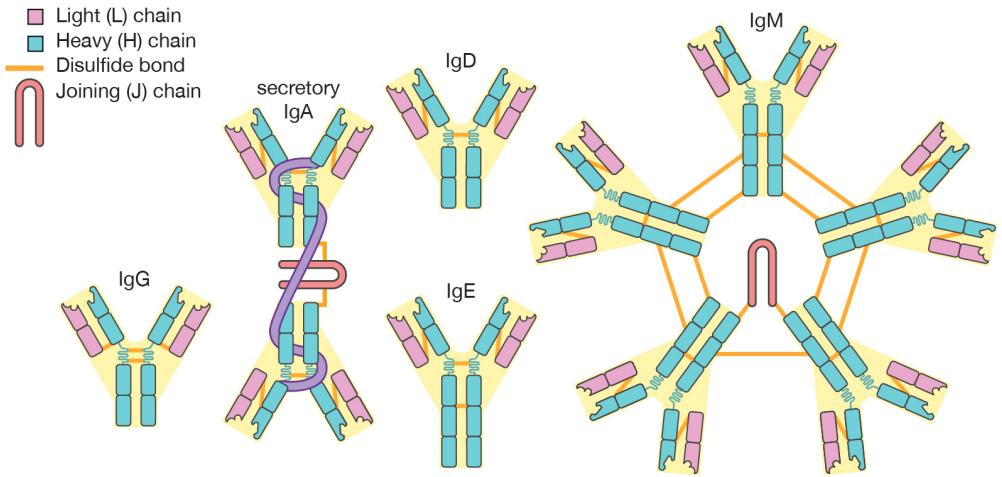
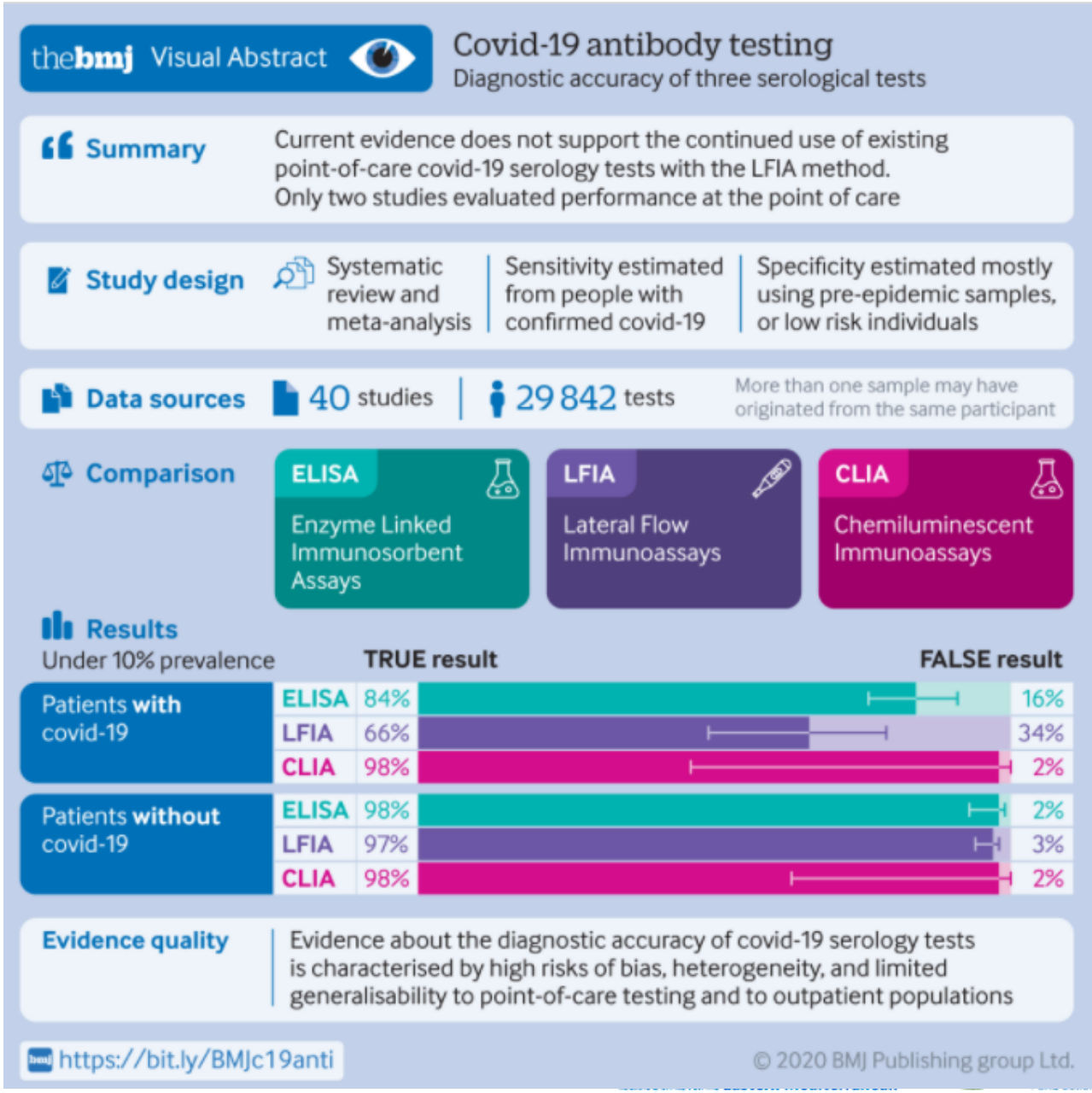
Types of antibody tests

- Method:
  - enzyme linked immunosorbent assays (ELISAs)
  - lateral flow immunoassays (LFIAs)
  - chemiluminescent immunoassays (CLIAs)
- Antigen (S, S1, RBD, N…)
- Antibody class (IgG, IgM, IgA)
- Quantitative vs qualitative tests





Antigen targets of SARS-CoV-2 serological assays

Main immunogens and indirect targets:

- **Spike protein**
  - Target of most vaccines
    (NB: variant and conformation matters!)
- S1 subunit of spike
  - Most **specific** to given hCoV
- **RBD (spike)**
  - Most common target of protective antibodies.
  - RBD genome is the most subject to evolutionary pressures
  - Evolution limited by ACE2 binding affinity
- Nucleocapsid (NCP or N)
  - Most abundant protein (mRNA and protein) in coronaviruses, highly immunogenic
  - Conserved (intra and inter species)
  - Not a target for current vaccines but under investigation for pan-sarbecovirus vaccines

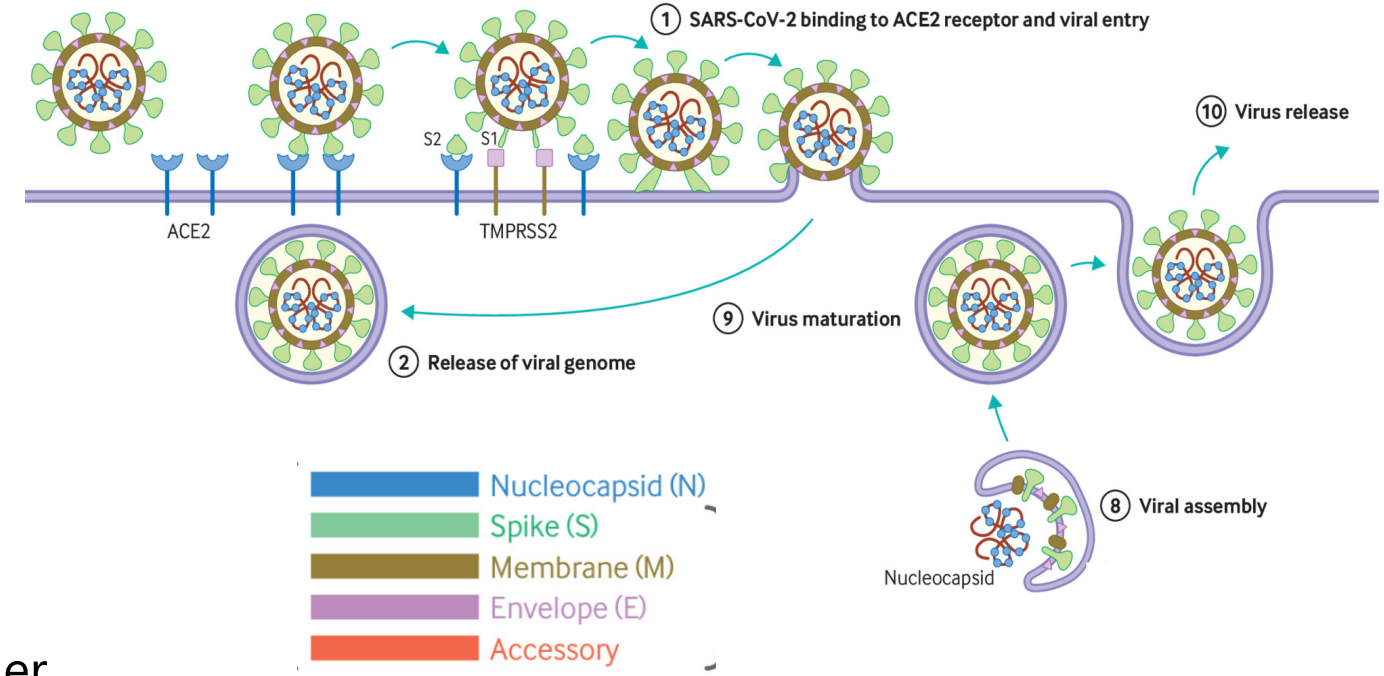


Figure: Adapted from *BMJ* 2020;371:m3862

→ Anti-S (RBD) antibodies play major role in vaccine-induced and natural immunity to SARS-CoV-2

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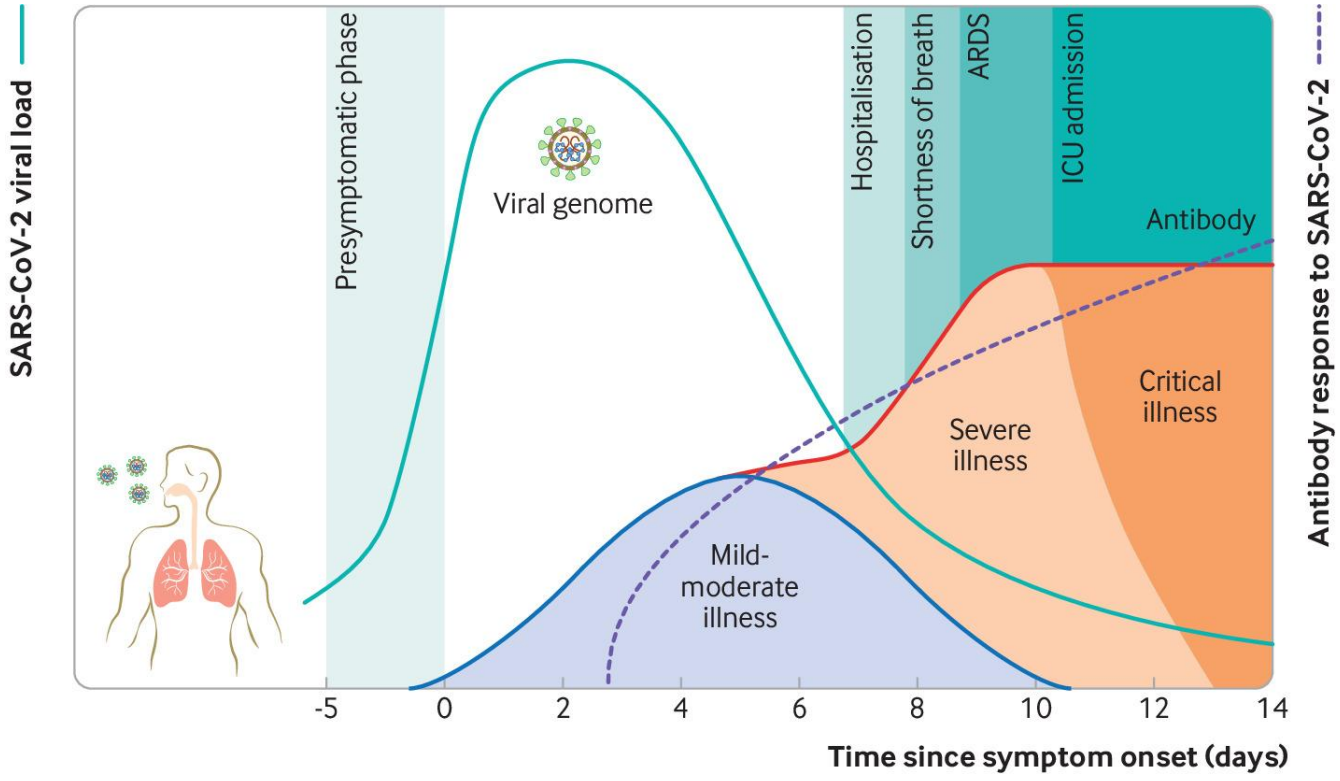
Severe COVID-19 produces a more robust humoral response



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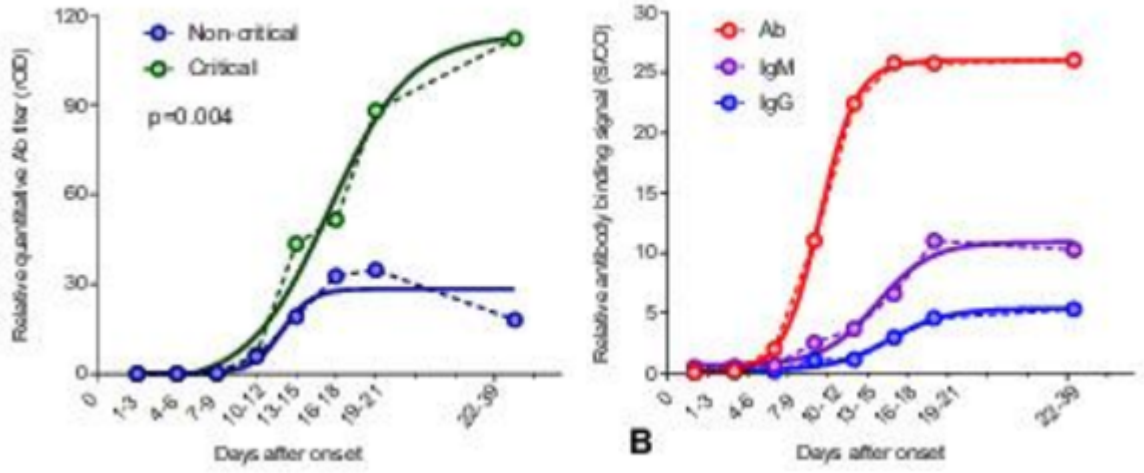
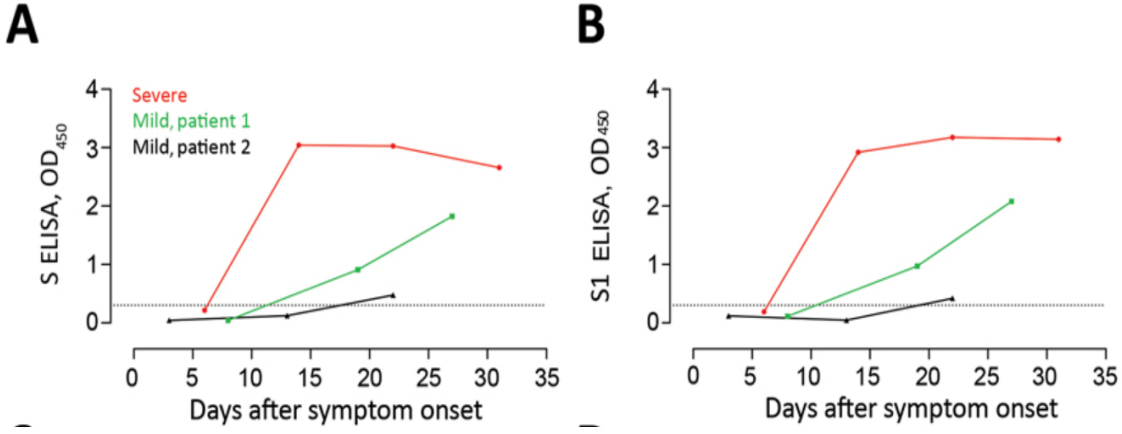


Above: Antibody responses observed in a cohort of 173 patients (Zhao et al.), by clinical severity (left panel) and by type of antibody (right panel)

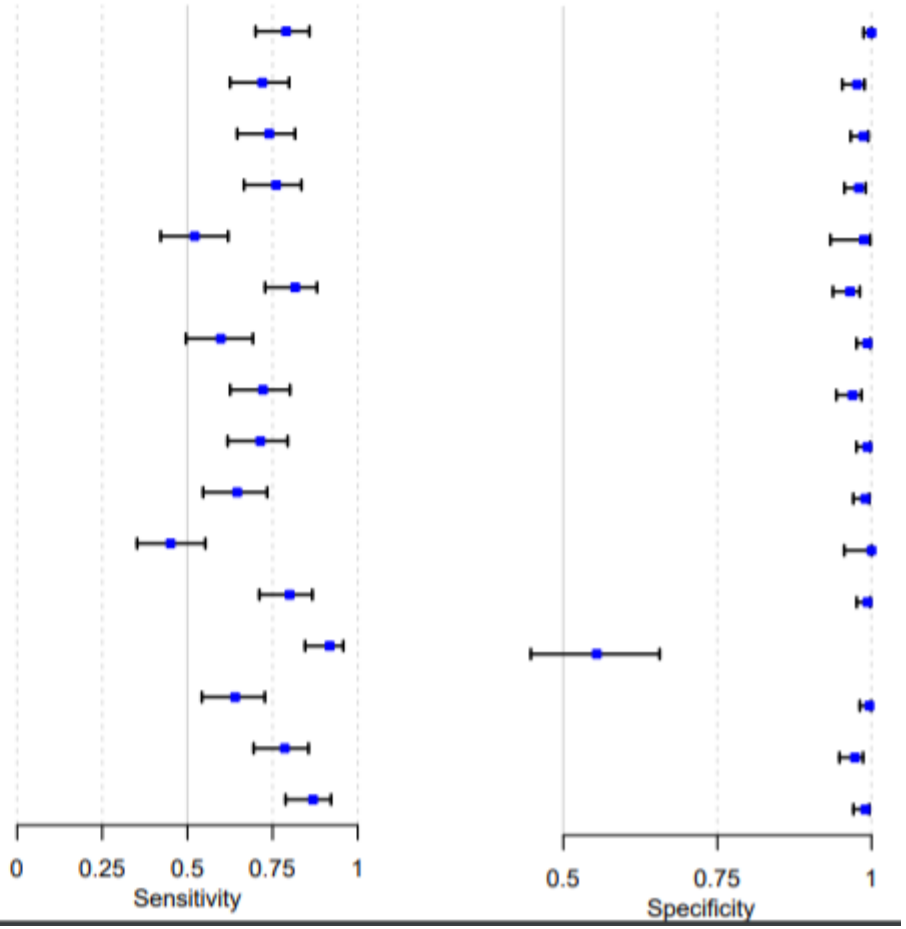
Below: Antibody kinetics (by ELISA) in three RT-PCR confirmed COVID-19 cases (Okba et al. EID 2020)



Assay performance in independent evaluations

Group	Test	N	TP	FP	TN	FN	Sensitivity [95% CI]	Specificity [95% CI]
All								
	Bio−Rad Total Ab	398	79	0	298	21	0.79 [0.70−0.86]	1.00 [0.99−1.00]
	Darui IgG	400	72	7	293	28	0.72 [0.63−0.80]	0.98 [0.95−0.99]
	Darui IgM	400	74	4	296	26	0.74 [0.65−0.82]	0.99 [0.97−0.99]
	Epitope Dx IgG	389	73	6	287	23	0.76 [0.67−0.83]	0.98 [0.96−0.99]
	Epitope Dx IgM*	175	49	1	80	45	0.52 [0.42−0.62]	0.99 [0.93−1.00]
	EuroImmun IgA−S	387	80	10	279	18	0.82 [0.73−0.88]	0.97 [0.94−0.98]
	EuroImmun IgG−S	388	55	2	294	37	0.60 [0.50−0.69]	0.99 [0.98−1.00]
	EuroImmun IgG−N	392	70	9	286	27	0.72 [0.63−0.80]	0.97 [0.94−0.98]
	NovaTec IgA	393	70	2	293	28	0.71 [0.62−0.79]	0.99 [0.98−1.00]
	NovaTec IgG	392	62	3	293	34	0.65 [0.55−0.73]	0.99 [0.97−1.00]
	NovaTec IgM*	174	41	0	83	50	0.45 [0.35−0.55]	1.00 [0.96−1.00]
	SD Bio Total Ab	400	80	2	298	20	0.80 [0.71−0.87]	0.99 [0.98−1.00]
	Teco IgG*	180	89	37	46	8	0.92 [0.85−0.96]	0.55 [0.45−0.66]
	Teco IgM	396	64	1	295	36	0.64 [0.54−0.73]	1.00 [0.98−1.00]
	Wantai IgM	397	77	8	291	21	0.79 [0.69−0.86]	0.97 [0.95−0.99]
	Wantai Total Ab	397	86	3	295	13	0.87 [0.79−0.92]	0.99 [0.97−1.00]

d not pass to full panel.



FIND Independent Evaluations https://www.finddx.org/wp-content/uploads/2021/04/forestplot_All_ELISAS.pdf

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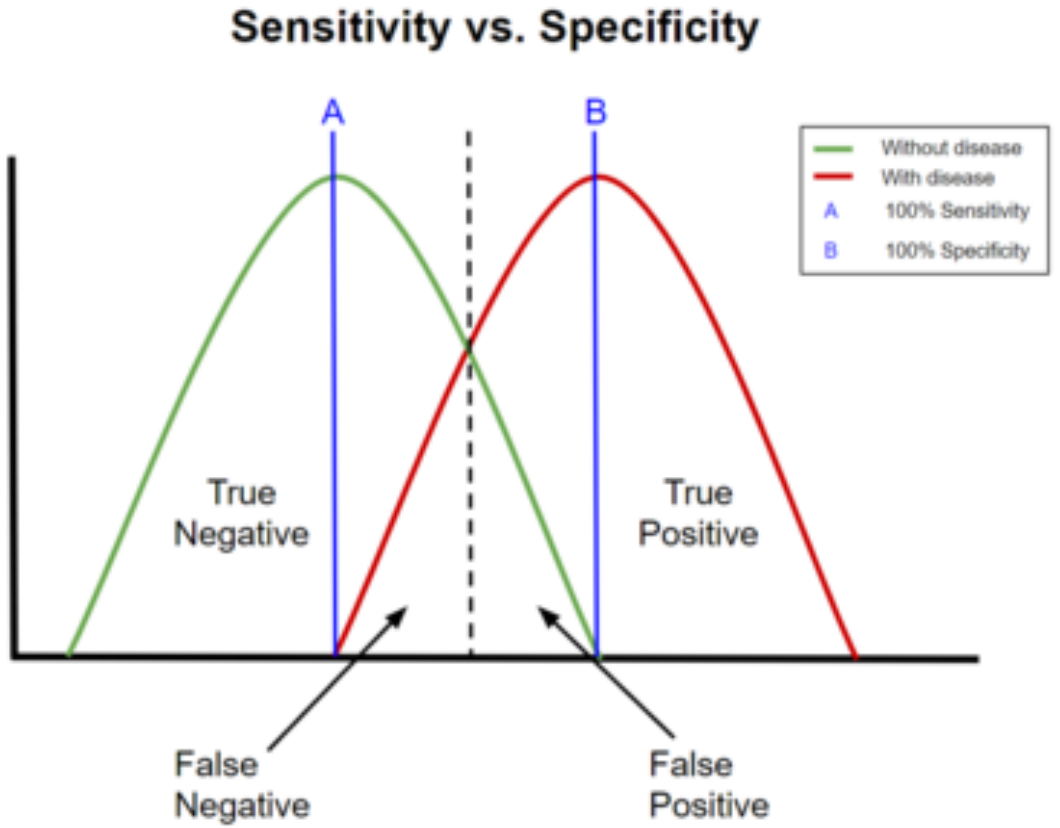
Factors that can influence assay performance

- Product and method
- Type of antibody
- Time since infection or vaccination
- Disease severity (if infection)
- Other circulating hCoVs
- Other population factors



Antibody tests in vaccine effectiveness (VE) studies

Serology as an endpoint in VE studies

- Laboratory confirmation of SARS-CoV-2 infection in the endpoint strengthens design of a vaccine effectiveness study
- **Molecular testing** (RT-PCR, sequencing) is the gold standard to confirm infection
- Serological tests are not recommended as a diagnostic tool for SARS-COV-2 infection

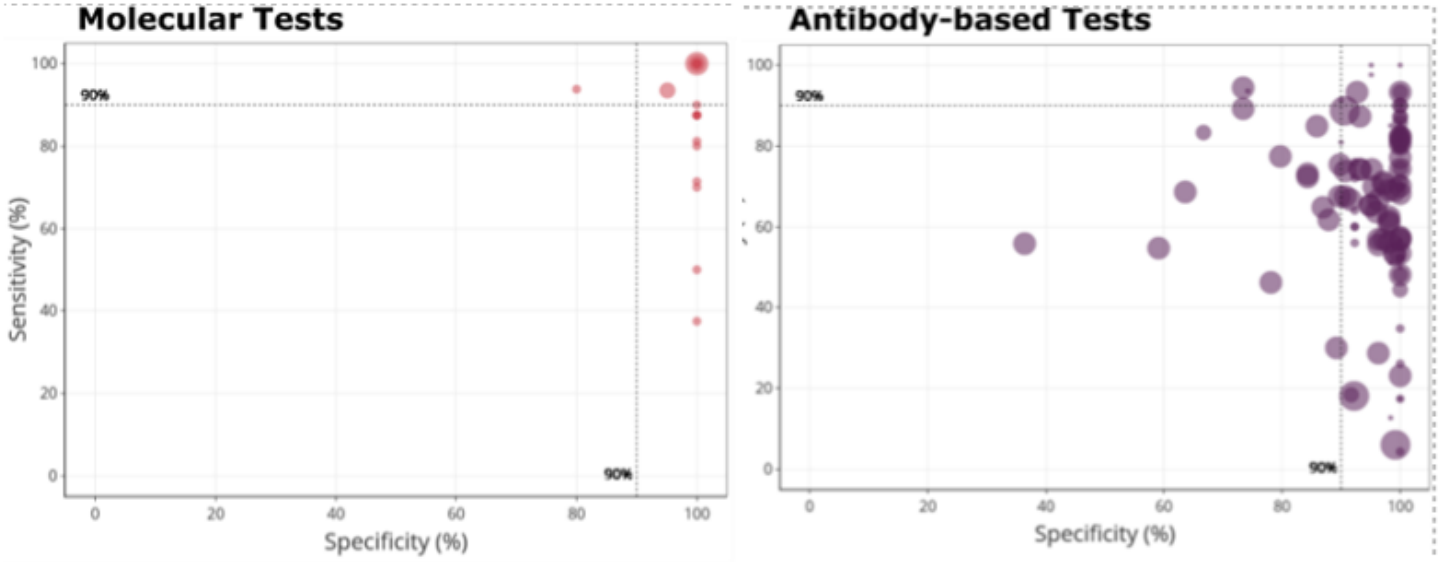


Figure: FIND Diagnostics tracking and evaluations finddx.org

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Serology as an endpoint in VE studies

At this time, SARS-CoV-2 antibody tests cannot be used to infer:

- Current infection status
- Protection from disease or infection
- Whether re-vaccination is required
- Vaccine success or failure

Q: Can positive serology be used as an endpoint for VE studies? A: Yes… and no…

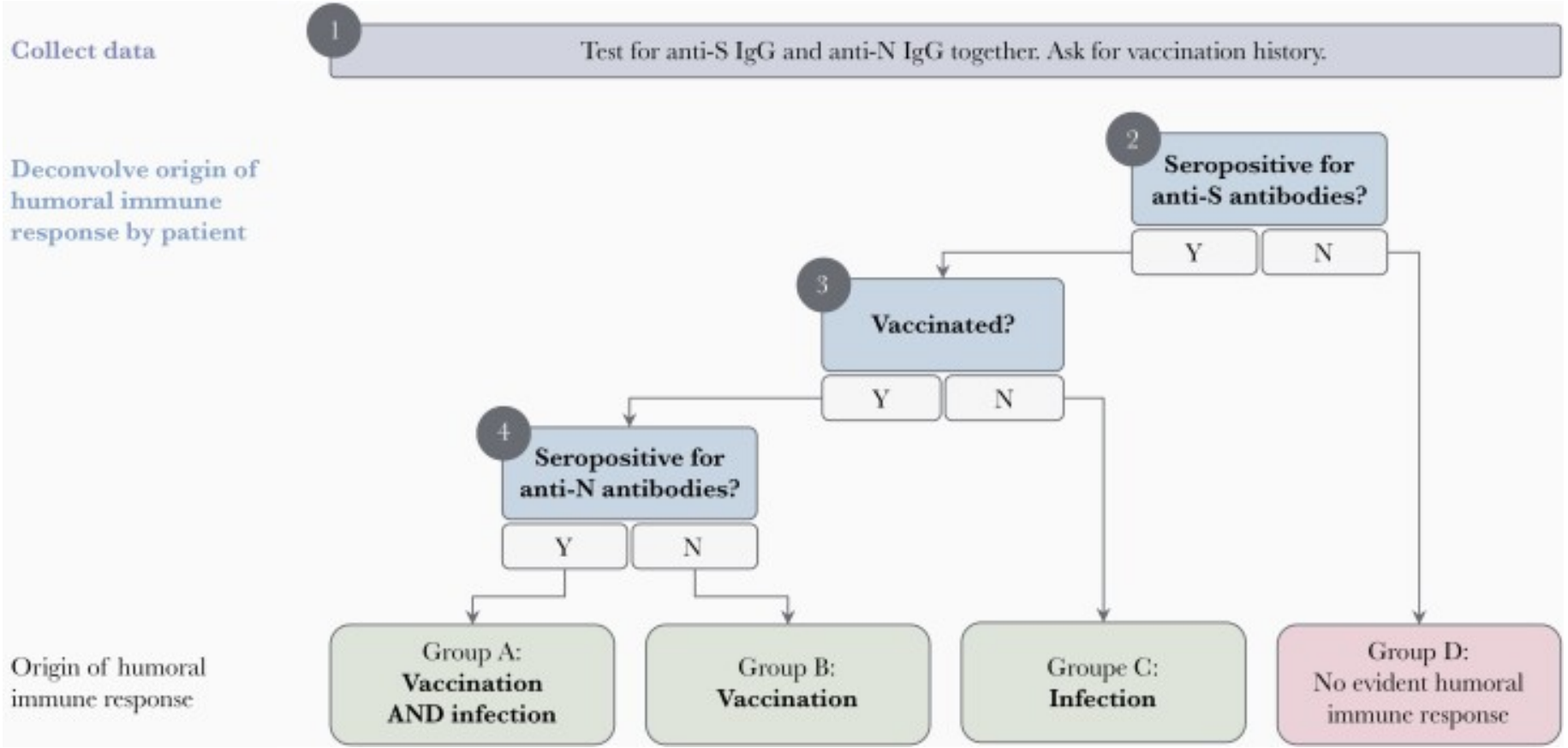
- Yes = serology can be used to evaluate the probability of **prior infection** in participants IF vaccines are S-antigen based only

- No = antibody tests are not a reliable method to confirm acute infection or disease

Feasibility needs to be determined by the context:

- Vaccine-products in use
- Expected baseline seroprevalence in the study population
- COVID-19 testing strategies

Algorithm for serological testing in context of spike antigen vaccination

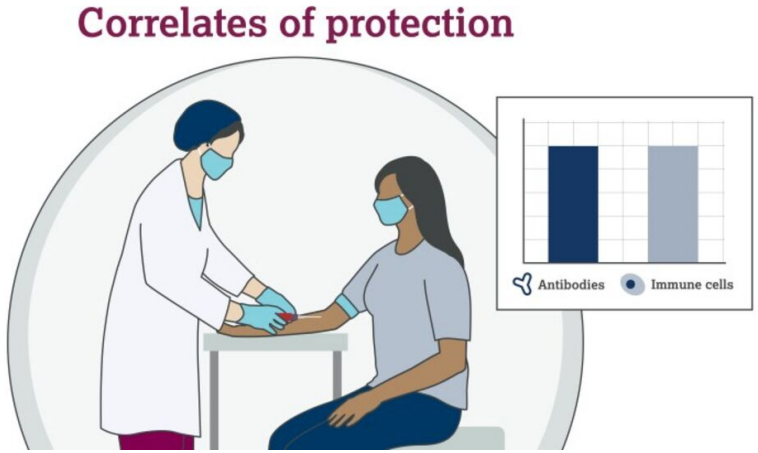


NB: This algorithm *cannot* be used if the vaccines used are inactivated virus products

Duarte N, et al. Adapting Serosurveys for the SARS-CoV-2 Vaccine Era. Open Forum Infect Dis. 2021 Dec 23;9(2):ofab632. doi: 10.1093/ofid/ofab632. PMID: 35103246; PMCID: PMC8755308.

Correlates of protection (CoP)

- CoP = an immune response that is statistically correlated with protection
- For some vaccines, serological tests can be used to test for the individual's response to vaccination (i.e. if immunization has been successful)
- Anti-SARS-CoV-2 neutralizing antibodies have been found to play an important role in protection from disease, however CoPs are still being investigated
- CoPs are still being investigated for Covid-19 vaccines: antibody tests *cannot* be used as a measure of protection at this time



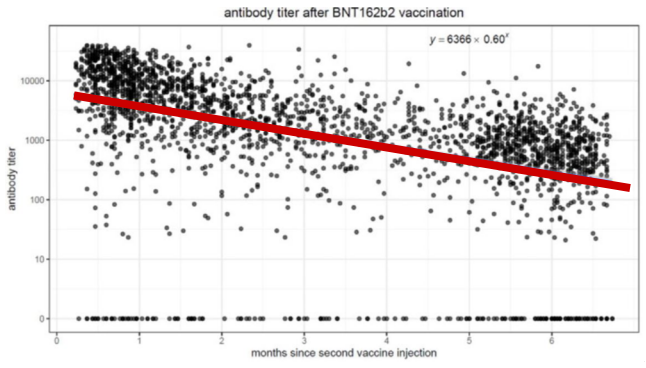
Figures: https://www.astrazeneca.com/what-science-can-do/topics/covid-19/covid-19-correlates-of-protection-explained

VE Studies to measure hybrid immunity

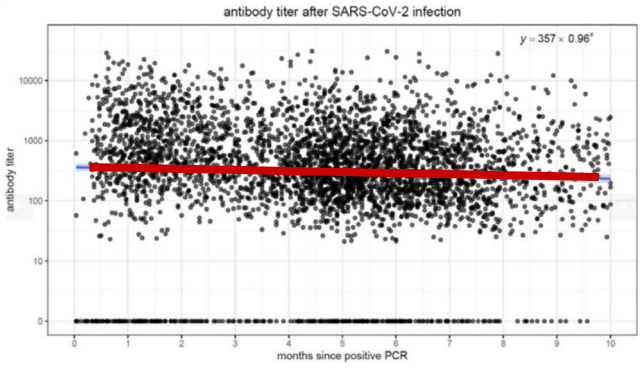
- Evidence suggests that hybrid immunity confers greater protection from disease than infection or vaccination alone
- Previous infection can be documented by:
  - RT-PCR-confirmed SARS-CoV-2 infection
  - Clinician-diagnosed COVID-19 (where testing unavailable)
  - Presence of **antibodies** suggesting natural infection (e.g. anti-S if no vaccination, anti-N)
- Challenges:
  - Sample sizes needed for antibody dynamic trends
  - Waning titres of serum Ig can act as a confounder
  - Large proportion of the population has been exposed and this is increasing over time (comparison to naïve subjects increasingly difficult)

Definitions

- **Infection-induced immunity**: Protection after SARS-CoV-2 infection
- **Vaccine-induced immunity**: Protection after vaccination (alone)
- **Hybrid immunity**: Protection afforded by vaccination +SARS-CoV-2 infection



n=2,653 **mRNA vaccinated individuals**



n=4,361 **naturally-infected unvaccinated** convalescent individuals

Refs: Altarawenah et al., Spensley et al., Israel, 2021 medrxiv

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Conclusions

- Serological tests for SARS-CoV-2 have multiple indirect antigen targets
- Immune responses to SARS-CoV-2 infection are heterogeneous
- Assay performance varies with products, populations, and timing of sample collection
- Correlates of protection for COVID-19 vaccines are still being investigated
- Serological tests can be used in VE studies to investigate hybrid immunity
- Feasibility needs to be assessed in light of vaccine products and population seroprevalence

THANK YOU