Antibody responses to natural infection and vaccines

Miles Davenport

COVID-19 Vaccines meeting, 22 February 2022
Declaration of potential conflicts

Funding this work:
National Health and Medical Research Council (NHMRC) (Australia)
Medical Research Futures Fund (Australia)
University of New South Wales (UNSW Sydney)

Other research funding:
Australian Research Council
NHMRC + UNSW Sydney
National Institutes of Health (USA)
European Union Horizon 2020 funds

Other funding:
eLife Journal - stipend (as Senior Editor)
Outline

- Reconciling existing data on correlates
- Using correlates
- Correlates for severe disease
Reconciling correlates
Two current methods for detecting correlates

**Vaccine comparison method**

**Breakthrough infection method**

**Breakthrough infection studies:**

**Bergwerk (NEJM):** BNT162b2 Israeli healthcare.


**Feng et al (Nature Med):** ChAdOx1 trial.

https://www.nature.com/articles/s41591-021-01540-1

**Gilbert et al (Science):** mRNA1273 trial.

https://www.science.org/doi/10.1126/science.abm3425
**Protection for symptomatic:**

**Vaccine comparison:** (Khoury *et al*, Nature Med)

50% protective threshold = 54 IU/ml (95% CI=30-96)

**Breakthrough infection:** (Gilbert *et al*, Science)

70% protective threshold = 4 IU/ml
Protective threshold:

**Vaccine comparison:** (Khoury *et al*, Nature Med)

Geometric mean for mRNA-1273 = 1057 IU/ml

**Breakthrough infection:** (Gilbert *et al*, Science)

Geometric mean for mRNA-1273 = 247 IU/ml
Protective threshold:

**Vaccine comparison:** (Khoury et al, Nature Med)

Geometric mean for mRNA-1273 = 1057 IU/ml

Phase 2

**Breakthrough infection:** (Gilbert et al, Science)

Geometric mean for mRNA-1273 = 247 IU/ml

Phase 3
Protective threshold:

**Vaccine comparison:** (Khoury *et al*, Nature Med)
Geometric mean for mRNA-1273 = 1057 IU/ml

**Breakthrough infection:** (Gilbert *et al*, Science)
Geometric mean for mRNA-1273 = 247 IU/ml

Phase 2

Phase 3
Vaccine comparison

that these workers were less contagious than against infection. However, no secondary infection protected against symptomatic disease but not followed any minor known exposure. This factor detected without the rigorous screening that followed. Some who had been asymptomatic and thus infectious at some point. These workers included N gene Ct values that suggested they had been infected (>6 weeks).

Most of the infected health care workers had previously.

Figure 1. Titer and the function of subgroups defined by antibody levels.

The dotted lines indicate bootstrap point estimates of the reverse cumulative distribution function calibrated to the WHO International Standard.

Neutralizing antibody titers during the peri-infection period (within a week before SARS-CoV-2 detection) (Panel A) and the peak titers within 1 month after the second dose (Panel B), as compared with matched controls. Also shown are IgG titers during the peri-infection period (Panel C) and peak titers (Panel D) in the two groups. Each case of breakthrough infection was matched with 4 to 5 controls according to sex, age, immunosuppression status, and other factors.

Peri-infection timing of serologic testing after the second vaccine dose. In each panel, the horizontal bars indicate the mean geometric titers and the LOD (limit of detection).

Neutralizing antibody levels overlaid in green histograms are an estimate of the density of Day 57 cases. The g green shaded area is pointwise 95% confidence interval of the marker in baseline SARS-CoV-2 negatives per protocol vaccine recipients.

Copyright © 2021 Massachusetts Medical Society. All rights reserved.
Vaccine comparison

Among the 39 fully vaccinated health care workers who had breakthrough infection with SARS-CoV-2, shown are the neutralizing antibody titers during the peri-infection period (within a week before SARS-CoV-2 detection) (Panel A) and the peak titers within 1 month after the second dose (Panel B), as compared with matched controls. Also shown are IgG titers during the peri-infection period (Panel C) and peak titers (Panel D) in the two groups. Each case of breakthrough infection is represented by a red dot, with the blue dots representing the median value for each group. The green shaded area in Panel B indicates the distribution of the peak titers in the control group, with the dotted lines indicating the bootstrap point estimates of the reverse cumulative distribution function (CDF) among the control group.

Most of the infected health care workers had symptoms, yet 19% had long Covid-19 symptoms (>6 weeks).

Copyright © 2021 Massachusetts Medical Society. All rights reserved.

It is made available under a CC-BY-NC-ND 4.0 International license, which means that reuse is encouraged as long as proper attribution is given and the material is not used for commercial purposes.

The copyright holder for this preprint is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
Protection level (raw data)

‘Protection curves’
Vaccine comparison
Moderna study
Astra-Zeneca study
Native virus
Pseudovirus

Khoury et al, submitted
Protection level (raw data)

‘Protection curves’
Vaccine comparison
Moderna study
Astra-Zeneca study
Native virus
Pseudovirus

Khoury et al, submitted
Protection level (raw data)

‘Protection curves’
Vaccine comparison
Moderna study
Astra-Zeneca study
Native virus
Pseudovirus

Khoury et al, submitted
Vaccine comparison and breakthrough infection approaches agree!
(where there is sufficient data in breakthrough)
Vaccine comparison and breakthrough infection approaches agree! (where there is sufficient data in breakthrough)

- Breakthrough analysis should be limited to where data is centred
- Vaccine comparison uses wider range of input

Khoury et al, submitted
Using correlates
Predicting efficacy against new variants

- Vaccine uses ancestral spike
- Drop in titre to VOC
Predicting efficacy against new variants

- Vaccine uses ancestral spike
- Drop in titre to VOC
Scaling existing model

Ancestral

Variant

Vaccine/Serum
- Ad26.COV2.S
- BNT162b2
- ChAdOx1 nCoV-19
- Convalescent
- CoronaVac
- Covaxin
- Gam–COVID–Vac
- mRNA–1273
- NVX–CoV2373

Variant
- Ancestral
- Alpha (B.1.1.7)
- Beta (B.1.351)
- Delta (B.1.617.2)

Study Design
- RCT
- TNCC

Cromer et al, Lancet Microbe
Scaling existing model

Ancestral

Variation

Vaccine/Serum
- Ad26.COV2.S
- BNT162b2
- ChAdOx1 nCoV-19
- Convalescent
- CoronaVac
- Covaxin
- Gam–COVID–Vac
- mRNA–1273
- NVX–CoV2373

Variant
- Ancestral
- Alpha (B.1.1.7)
- Beta (B.1.351)
- Delta (B.1.617.2)

Study Design
- RCT
- TNCC

Cromer et al, Lancet Microbe
Scaling existing model

Ancestral

Neutralisation level against ancestral (convalescent plasma)

Variant

Reported efficacy (%)

Vaccine/Serum
- Ad26.COV2.S
- BNT162b2
- ChAdOx1 nCoV-19
- CoronaVac
- Covaxin
- Gam-COVID-Vac
- mRNA-1273
- NVX-CoV2373

Variant
- Ancestral
- Alpha (B.1.1.7)
- Beta (B.1.351)
- Delta (B.1.617.2)

Study Design
- RCT
- TNCC

Cromer et al, Lancet Microbe
Omicron

If you know the vaccine (titre), the variant (drop in titre), and time since vaccination, can you predict efficacy?
Omicron

If you know the vaccine (titre), the variant (drop in titre), and time since vaccination, can you predict efficacy?

Khoury et al, MedRxiv 2021
https://www.medrxiv.org/content/10.1101/2021.12.13.21267748v2
Corelates for severe disease
“Any” symptomatic SARS-CoV-2 infection

Severe SARS-CoV-2 infection

Khoury, D., Cromer, D. Nature Medicine 2021
“Any” symptomatic SARS-CoV-2 infection

50% protection at 54 IU/ml
(20% convalescent)

Severe SARS-CoV-2 infection

50% protection at 8 IU/ml
(3% convalescent)

Khoury, D., Cromer, D. Nature Medicine 2021
Is 3% (8 IU/ml) mechanistic in protecting from severe infection?
Is 3% (8 IU/ml) mechanistic in protecting from severe infection?

Might it be a surrogate marker for antibody recall?
Kinetics of recall after infection

Recall of antibody response occurs around **5 days POS** (Delta infection) (8 days post-exposure)

Kinetics of recall after infection

Recall of antibody response occurs around 5 days POS (Delta infection) (8 days post-exposure)

**Does recall affect outcome?**

Recall of antibody response occurs around 5\_days\_POS (8 days post-exposure)

**COMET-ICE study**
- 0.5g Sotrovimab < 5 days POS
- 85% protection from hospitalization / death

Does recall affect outcome?

**COMET-ICE study**
- 0.5g Sotrovimab < 5 days POS
- 85% protection from hospitalization / death


**Antibodies affect outcome of severe disease!**

Acknowledgements

Infection Analytics (UNSW)
David Khoury
Deborah Cromer
Arnold Reynaldi
Tim Schlub
Sydney University
Jamie Triccas
Megan Steain

University of Melbourne
Stephen Kent
Jen Juno
Adam Wheatley
Marios Koutsakos

WHO Flu Centre (Melbourne)
Kanta Subbarao
Fred Hutchinson
Peter Gilbert

Funding:
NHMRC (Australia)
MRFF
Antibody responses to natural infection and vaccines

Miles Davenport COVID-19 Vaccines meeting, 22 February 2022