Episode 273: Immune escape and breakthrough infections in the delta, Omicron BA.1, BA.2 and BA.5 era.

Dear colleagues,

In this episode, I will reiterate the evolution of protection or breakthrough infection (BTI) by previous infection and/or vaccination over the delta and omicron waves, taking into account “waning immunity” and come back on the significance of “immune imprinting” as well. There is a definite trend of increasing BTI over time, but protection against severe disease remains rather high, explaining the discrepancy between numbers of infection vs hospitalizations and deaths, which is not necessarily linked to lower intrinsic pathogenicity of new variants, as we know. Despite this -at first view – reassuring trend, the impact of the present BA.4/5 wave is not yet very clear.

See

Par 1 DELTA

Ep 273-1: Goldberg NEJM 25 May 2022 on Aug-Sept 2021 nationwide in Israel
- Previous infection protects better than 2 dose vaccination.
- Hybrid immunity (with 1 dose) clearly superior to either 2 dose vaccination of previous infection alone.
- Effect of 3 dose difficult to judge, bc limited follow-up.

Ep 273-2: Seekircher medRxiv April 2022 looks for immunological correlates of protection against breakthrough infection after 2 doses of the Pfizer vaccine during median 6 months FU in Austria
Incidence of BTI = 68/2760 = 2.5 %. Seems high, but active FU for infection with Ag and Ab test (hence both ASY and SYMP BTI counted)

Baseline correlates of (later) protection against BTI =
- Prior SARS-CoV-2 infection (and anti-Nucleoprotein IgG) → hybrid immunity
- Anti-S IgG and surrogate virus neutralization (= inhibition of binding of S protein to ACE-2)
- NO significant difference with pseudovirus neutralization nor with CD4 or CD8 T cell responses to peptides, derived from Spike.

Ep 273-3: Lamacchia medRxiv Feb 2022 on Clinical and Immunological features amongst vaccinated and unvaccinated individuals requiring hospitalization Nov-mid Dec 2021 in Italy

Clinical
Comorbidity index (A), serum titers of ferritin (B), lactate dehydrogenase (C), C-reactive protein (D), interleukin-6 (E), and D-dimer (F) and WHO COVID-19 severity index of 36 vaccinated (blue box) and 29 unvaccinated (red box) hospitalized COVID-19 patients. (G). (H) Percentages of vaccinated and unvaccinated COVID-19 hospitalized patients who developed pneumonia, on a total of 65 patients. (I) Percentages of vaccinated and unvaccinated COVID-19 hospitalized patients who deceased, on a total of 65 patients. Medians and 25th and 75th percentile are shown in boxes. Minimum and maximum values are shown as whiskers. *P<0.05 calculated with Mann-Whitney U test and χ² test.

Vaccinated individuals were older (73 vs 67 yrs) showed more co-morbidity (= higher risk for severe disease). Nevertheless, unvaccinated subjects higher ferritin and LDH (but not other infl markers), more severe disease (including pneumonia) and higher mortality

Immunological

1) Vaccinated vs non-vaccinated

Vaccinated have higher anti-S and neut IgG, more Spike-specific B cells, but similar CD4 T cells
2) **Survivors vs non-survivors**

Survivors have higher anti-S and neut Ab, higher S-specific B cells AND CD4 T cells

3) **Anti-IFN-alpha**

Similar frequency of anti-IFN-alpha in vacc and unvaccinated, but the unvaccinated with anti-IFN all died and the vaccinated all survived!

**Par 2 OMICRON BA.1 and BA.2**

Ep 273-4: Altarawneh NEJM 15 June 2022 Effects of Previous Infection and Vaccination on Symptomatic Omicron BA.1 and BA.2 Infections in Qatar 23 Dec 2021 – 21 Feb 2022
Effects are quite similar on BA.1 vs BA.2:
- Previous infection: moderate protection against symptomatic infection, but strong against severe disease.
- Two doses of vaccine: no protection against infection, but strong against severe disease.
- 3rd dose and/or hybrid immunity increase level of protection.

*Ep 273-5: Carazo medRxiv 27 June 2022: Protection against Omicron BA.2 reinfection conferred by primary Omicron or pre-Omicron infection with and without mRNA vaccination in Canada (March-June 2022)*
Prior vaccination alone: weak to moderate protection depending (increasing with no of doses)

Prior pre-omicron infection: moderate protection, but much stronger after vaccination (hybrid)

Prior BA.1 infection: strong protection, further enhanced by vaccination.

Conclusion of the authors: Twice-vaccinated individuals who experienced BA.1 infection were subsequently well-protected for a prolonged period against BA.2 reinfection and derived no meaningful added benefit against BA.2 from a third dose of mRNA vaccine.
Par 3: Comparison delta vs BA.1 and BA.2


Vaccine effectiveness against symptomatic disease:

1) Delta > Omicron

2) BA.1 = BA.2

Effectiveness of 3 doses against hospitalization and mortality remains high against delta, BA.1, BA.2

<table>
<thead>
<tr>
<th>Dose</th>
<th>Interval (days)</th>
<th>Vaccine effectiveness (95% CI)</th>
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<tbody>
<tr>
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<td></td>
<td>BA.1</td>
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<tr>
<td></td>
<td></td>
<td>BA.2</td>
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<tr>
<td>Unvaccinated</td>
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<tr>
<td>1</td>
<td>0 to 27</td>
<td>24.2 (.12.5 to 48.9)</td>
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<td>28+</td>
<td>38.1 (.32.5 to 74.9)</td>
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<td>2</td>
<td>0 to 13</td>
<td>63.3 (.47.2 to 74.6)</td>
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<td>14 to 174</td>
<td>46.7 (.26.6 to 66.6)</td>
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<td>49.9 (.36.5 to 73.2)</td>
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<td>0 to 6</td>
<td>72.5 (.65.5 to 78.7)</td>
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<td>83.2 (.75.4 to 88.5)</td>
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<td>87.3 (.77.2 to 96.2)</td>
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<td></td>
<td>70+</td>
<td>70 (.49.3 to 82.2)</td>
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Estimation of hospitalizations averted in UK by vaccination.
Par 4: BA.2 subvariants: BA.2.12.1, BA.4 and BA.5

Two papers on antibody escape

Ep 273-7: Wang Nature 5 July: Escape from neutralization by sera from vaccinated + boosted subjects:

- BA 2.12.1 is only modestly (1.8-fold) more resistant than BA.2
- BA.4/5 substantially (4.2-fold) more resistant → more likely to lead to breakthrough infection

- a, Neutralization of pseudotyped D614G and Omicron subvariants by sera from 4 different clinical cohorts.
b. Fold change in geometric mean ID50 titers of boosted vaccinee sera relative to D614G and BA.2, with resistance colored red and sensitization 317 colored green:

→ Importance of delta 69/70; L452M/R/Q and F486V mutations for resistance.

d. Antigenic map based on the neutralization data of boosted vaccinee sera. SARS-CoV-2 variants are shown as colored circles and sera are shown as grey squares. The x-, y-, and z-axis represent antigenic units (AU) with one grid corresponding to a two-fold serum dilution of the neutralization titer.

Ep 273-8: Teukprahon Cell July 2022 gives a very similar message

SARS-CoV-2 Omicron BA.4 and BA.5 sublineages bear mutations that lead to their reduced neutralization by sera from triple-vaccinated individuals when compared with the more recent BA.1 and BA.2.

Importantly, sera from individuals with breakthrough BA.1 infections also show reduced neutralization, suggesting that repeat Omicron infections are likely in the population.

Ep 273-9: Eric Topol’s didactic explanation
The antigenic distance from BA.1 to BA.2 is far greater than the ancestral strain to Delta or Beta or Gamma. This is the basis for the immune escape of BA.5—our relatively poor recognition of and response to the spike protein.

BA.5 is fitter than BA.4 > BA2.12.1 >>> BA.2 > BA.1
Very poor cross-neutralization after either vaccination or BA.1/BA.2 infection

Do the current vaccines work against BA.4/5?
The new UKHSA report (= Ep 273-6) started to address this question, looking at symptomatic infections and severe disease, but it’s unclear: no clear excess BA.4 or BA.5 breakthrough infections as compared to BA.2 (odds ratio ≈1).

With the extent of BA.5’s immune evasion and the recent trends of lowered vaccine effectiveness vs severe disease (from 95% vs Delta with a booster to ~80% vs Omicron BA.1 or BA.2 with a booster) it would not be at all surprising to see further decline of protection against hospitalizations and deaths.

Ep 273-10: Johanna Chisholm in The Independent 8 July 2022 quotes various experts who fear that BA.4/5 could produce many more breakthrough infections. Hence the scary title “Stealthy’ new Covid variant can reinfect you every month” However this regular press article refers only to the publications that we have already discussed. So no final proof yet of the ominous scenario.

In the meantime, a new BA.2 subvariant BA.2.75 is spreading, but it remains unclear whether it has the potential to cause a next pandemic...

https://public.tableau.com/app/profile/raj.rajnarayanan/viz/TrackingBA_2_75LineageOverTime/BA_2_75

https://www.medpagetoday.com/special-reports/exclusives/99655

Sorry, no formal publications or preprints at this moment...

CONCLUSION

Ep 273-11: Clive Cookson in Financial Times 3 July explains “immune imprinting”. The point is that previous encounters with “antigens” (e.g. Spike protein, either by infection or vaccination) “shapes” our immune (memory) repertoire. The virus evolves by “immune escape” mutations, thus rendering some of the earlier responses ineffective.

- If our immune system focuses on “conserved” epitopes, from which the virus cannot escape, it will raise effective immune responses against the next variants (“broadening” of the immune response).
- However, if our immune system focuses the variable parts (that can easily mutate), recall immune responses may become ill-directed and less able to neutralize the virus. It is also called “immune deviation”.

The evolution we described in this Episode seems to indicate that Omicron and especially the most recent subvariants drive immune deviation rather than broadening.

This tendency to “broadening” or “immune deviation” is not only determined by the successive viral variants, but also by the genetically determined individual immune repertoire, which explains why different people react differently to a similar series of encounters with viral variants and vaccinations.

In addition, human behavior drives the speed of the successive waves: because of the perceived lesser pathogenicity of omicron and the “Corona fatigue, we are increasing our social contacts, hence chances to be infected, which may well offset our acquired immunity.