Episode 301: First results on induction of neutralizing antibodies and vaccine effectiveness of bivalent vaccines

Dear colleagues,

Encouraged by your kind reactions after Ep 300 and, equally importantly, because new interesting data emerge, I present here the next episode. The format is unchanged, but, since the “urgency” is less, I will try to focus more and explain better the background and perspectives.

Two types of bivalent vaccines (from both Pfizer and Moderna) are being rolled out: the original wild-type (WT) + BA.1 in Europe and the WT + BA.5 in USA. In the meantime, however the omicron virus evolves further, with new sublineages such as BA.2.75(.2) and BQ.1(.1) as well as the recombinant XBB.

As a reminder:

Of all these variants, BQ.1(.1) seems to be spreading most in US and Europe
Neutralizing antibody induction by bivalent vaccines

Par 1: Neutralizing antibody induction by bivalent vaccines

Ep 301-1: Hitoshi Kawasuji medRxiv 18 Nov: Induction of neutralizing Ab by the wild-type/Omicron BA.1 bivalent vaccine as the second booster dose against Omicron BA.2 and BA.5

2wA3D, 2 weeks after the third dose; 3mA3D, 3 months after the third dose; 6mA3D, 6 months after the third dose; 2wA4D, 2 weeks after the fourth dose.

A) Serum concentration of anti-RBD (receptor binding domain) antibody at 2wA4D in the original WT group (n = 168) and the bivalent WT+BA.1 group (n = 23)

B) Pseudotype virus-based neutralizing activity against Omicron BA.2 and BA.5 at 2wA4D in the WT (n = 168) and the WT+BA.1 group (n = 23) The assay was performed using 100- or 1600-fold diluted serum. The numbers at the top indicate the median neutralizing values of each group. Hence: results are not expressed as neutralizing titer, but as % inhibition.
Therefore, bivalent (WT + BA.1) vaccine induces more neutralization than monovalent (WT) against both BA.2 and BA.5, but, overall both mono- and bivalent vaccines induce less neutralization against BA.5 < BA.2 << WT virus

Ep 301-2: Davis Gartner bioRxiv 1 Nov 2022: Bivalent BA.5 mRNA booster enhances neutralization against new omicron subvariants BA.2.75 and BQ.1.1

Bivalent booster is superior, but still low neut titers against BA.5 > BA.2.75.2 > BQ.1.1

Ep 301-3: Chaitanya Kurhade Nat Med 6 Dec: Induction of neut Ab by BA.5 bivalent Pfizer or Moderna mRNA booster without or with previous infection.

1) 4 X WT: low neutralization against all Omicron variants
2) BA.5-bivalent booster after 3rd dose: high neutralizing titer against BA.4/5 measured but not against the new variants BA.2.75.2, BQ.1.1, or XBB.1.
3) Previous infection significantly enhanced the magnitude and breadth of BA.5-bivalent-booster-elicited neutralization
Remark: the trends in the two studies is similar, but Davis Gartner admits that in their study the impact of prior SARS-CoV-2 infection is unknown. So, it is not excluded that some of the subjects with higher neut titers after BA.5 bivalent vaccine actually have been infected, hence take advantage of “hybrid immunity”.

Ep 301-4: Markus Hoffmann Lancet Infect Dis 5 Dec 2022: Effect of hybrid immunity and bivalent booster vaccination on omicron sublineage neutralisation

1) Effect of monovalent or BA.5 bivalent booster (without infection):
   - Monovalent booster has NO significant effect on neut titers (even not against B.1 = D614G Wuhan),
   - Bivalent booster increases neut versus BA.4/5 and BJ.1, but NOT versus BQ.1.1 or BA.2.75.2

2) A very complex picture with various combinations of vaccinations and breakthrough infection (BTI):
   BTI enhance the neut titers against most variants, but have very little effect on neutralization of BQ.1.1 and BA.2.75, which remain neutralization resistant
Ep 301-5: David Sullivan bioRxiv 16 Dec reviews virus neutralization data from 920 individual patient samples from 43 separate cohorts defined by boosted vaccinations with or without recent Omicron COVID-19, as well as infection without vaccination.

1) Effect of infection or vaccination (2 doses without booster) on neutralization of omicron subvariants: low titers BA.4/5 > BA.2.75 > B.Q.1 > XBB

2) Effect of vaccination + infection (A) or boosted vaccination (B):
   - Same order BA.4/5 > BA.2.75 > B.Q.1.1 > XBB
   - All (but one B.7) higher in patients with “hybrid immunity” (= vaccine + infection) > boosted
CONCLUSION:

It is very evident from all the studies that the new variants, including BA.2.75, XBB and certainly also BQ.1.1, are rather “neutralization resistant”. Clearly also “hybrid immunity” is superior to bivalent boosters (either BA.1 or BA.5 containing), which is superior to monovalent booster.

Par 2: “Real life” Effectiveness of monovalent versus bivalent (BA.5) boosters

Ep 301-6: Diya Surie MMWR Oct 2022: Waning Effectiveness of Monovalent mRNA Vaccines Against COVID-19–Associated Hospitalization Among Immunocompetent Adults During BA.1/BA.2 and BA.4/BA.5

Three-dose VE during the BA.1/BA.2 and BA.4/BA.5 periods was 79% and 60%, respectively, during the initial 120 days after the third dose and decreased to 41% and 29%, respectively, after 120 days from vaccination.

<table>
<thead>
<tr>
<th>Group/No.</th>
<th>Interval from last vaccine dose to illness onset, days</th>
<th>Median interval (IQR) from last vaccine dose to illness, days</th>
<th>VE 7 days</th>
<th>VE &gt;3 months</th>
<th>VE &gt;3 months</th>
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<tbody>
<tr>
<td>BA/1/BA.2 period</td>
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<tr>
<td>≥14</td>
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<td></td>
<td>277 (210–341)</td>
<td>533/1,242 (43)</td>
<td>485/9,18 (53)</td>
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<td>111 (87–130)</td>
<td>62771 (8)</td>
<td>79/5,14 (15)</td>
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<td>295 (213–213)</td>
<td>471/1,365 (40)</td>
<td>400/8,198 (48)</td>
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<td>145 (82–190)</td>
<td>432/1,414 (30)</td>
<td>694/1,229 (61)</td>
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<td>80 (55–100)</td>
<td>167/84 (19)</td>
<td>399/8,28 (47)</td>
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<td>100/754 (24)</td>
<td>265/7,34 (27)</td>
<td>307/7,35 (41)</td>
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<td>80 (60–100)</td>
<td>261/7,28 (36)</td>
<td>294/7,26 (40)</td>
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<td>20 (16–35)</td>
<td>25/7,03 (9)</td>
<td>43/7,46 (9)</td>
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<td>20 (16–35)</td>
<td>25/7,03 (9)</td>
<td>43/7,46 (9)</td>
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<tr>
<td>BA/4/BA.5 period</td>
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<td>≥14</td>
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<td>428 (324–466)</td>
<td>131/917 (14)</td>
<td>183/7,34 (64)</td>
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<td>126/828 (42)</td>
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<td>74 (53–110)</td>
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<td>307/7,19 (41)</td>
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<td>237 (204–269)</td>
<td>219/465 (54)</td>
<td>206/363 (57)</td>
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<td>69 (54–120)</td>
<td>102/277 (40)</td>
<td>60 (20–53)</td>
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<td>66 (51–85)</td>
<td>56/242 (21)</td>
<td>95/250 (38)</td>
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<tr>
<td>240</td>
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<td></td>
<td>133 (126–137)</td>
<td>21/83 (4)</td>
<td>31/240 (4)</td>
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</table>

Abbreviation: VE = vaccine effectiveness.

Three dose: VE 7 days – 3 months after 3rd dose is 79 % (BA.1/2), down to 60 % (BA.4/5)
VE > 3 months after 3rd dose monovalent is 41 % in BA.1/2 period and 29 % in BA.4/5 period

Fourth dose: VE 7 days – 3 months after 4th dose is 61 % (BA.1/2), 61 % (BA.4/5)

Among immunocompromised adults hospitalized with a COVID-like illness, 2-dose monovalent mRNA COVID-19 vaccine VE against COVID-19–associated hospitalization during Omicron predominance was 36%.

The monovalent 3rd dose (1st booster)
- VE was 67% ≥7 days after a third dose during BA.1 predominance
- VE declined during BA.2/BA.2.12.1 and BA.4/BA.5 predominance to 32% ≥90 days after dose 3

Monovalent 4th dose
- VE 43% ≥7 days after dose 4 (= BA.4/5 period).

Ep 301-8: Ruth Link-Gelles MMWR 2 Dec 2022: Effectiveness of Bivalent mRNA Vaccines in Preventing Symptomatic SARS-CoV-2 Infection in Immunocompetent adults.

- BA.5 bivalent vaccine provided significant additional protection against symptomatic SARS-CoV-2 infection in immunocompetent persons who had previously received 2, 3, or 4 monovalent vaccine.
- Due to waning immunity of monovalent doses, the benefit of the bivalent booster increased with time since receipt of the most recent monovalent vaccine dose.
Remarkable:

1) Protection seems low as compared to Ep 301-6, but in this paper (Ep 301-8) it is about protection against symptomatic disease, while 301-6 it is about hospitalization.

2) Results ((of 301-8) limited to the period of BA.4/BA.5 predominance were not meaningfully different from the period when BA.4/BA.5 sublineages (including BA.4.6, BA.5.2.6, BF.7, BQ.1, and BQ.1.1) predominated

Ep 301-9: Surie Diya MMWR 16 Dec 2022 : Estimates of Effectiveness of bivalent vaccine against hospitalization

In immunocompetent adults aged 265 years in the multistate IVY Network, a bivalent booster dose provided > 70% additional protection against COVID-19 hospitalization compared with past monovalent mRNA vaccination only.

The absolute effectiveness (as compared to no vaccine) was > 80 % and relative effectiveness (as compared to monovalent only) increased with increasing time since the last booster.

This was a relatively small study on 798 hospital admission in 22 hospitals and limited to older subjects.

Study from Sept-Nov, covering the transition from BA.5 to BQ.1.1, but variant-specific VE could not be evaluated.
In a larger group, similar, but less pronounced trends were seen. Bivalent booster dose recipients were older (median age = 68 years) than were those who had not received a bivalent booster dose (median age = 55 years).

VE of a bivalent booster dose (after 2, 3, or 4 monovalent doses) against Emergency Department/Urgent Care encounters for COVID-19–associated illness was:
- 56% (95% CI = 49%–62%) compared with no vaccination,
- 31% (95% CI = 19%–41%) compared with receipt of last monovalent dose 2–4 months earlier,
- 50% (95% CI = 43%–57%) compared with receipt of last monovalent dose ≥11 months earlier (Table 2).

This was a large study on over 78,000 ED/IC admissions in adults (> 18 years), but also in this study the variant-specific VE could not be evaluated.

**Ep 310-10:** Marc Tenforde MMWR 16 Dec 2022: In a larger group, similar, but less pronounced trends were seen.

**Ep 301-11:** UK Health Security Agency: COVID-19 vaccine surveillance report Week 48 1 December 2022 p. 11-12

*VE of the bivalent (WT + BA.1) boosters was estimated against hospitalisation in the period following 5 September 2022 against all Omicron sub-lineages in circulation at the time amongst aged 50+: ...it is incremental effectiveness on top of at least 6 months waned protection.*
In the study period, there were 176 cases (those testing positive) and 621 controls (those testing negative) amongst those who received a bivalent booster at least 14 days prior and there were 1,975 cases and 3,844 controls amongst those who had received no bivalent valent vaccine. The incremental protection conferred by the bivalent vaccines relative to those with waned immunity was 57% (95% C.I.: 48-65%).

Par 3 Some more viro-immune info on BQ.1.1

Ep 301-12: Junpei Ito bioRxiv 5 Dec: Convergent evolution of Omicron subvariants leading to BQ.1.1

These author claim that 5 mutations of BQ.1.1 are crucial:
- R346T and N460K result in higher affinity to ACE2 and increased fusogenicity, independent from TMPRSS2
- R346T, K444T and F486V associate with escape from antibodies
- L452R compensates for the attenuated ACE2 binding affinity by F486V

BQ.1.1 shows increased infectivity and independency from TMPRSS2

BQ.1.1 shows a lower pathogenicity than Delta and even slightly lower than BA.5 in hamsters
BQ.1.1 induces no loss of body weight and only minimal changes in the parameters of lung function: Penh (= enhanced pause) and Rpef (= ratio of peak expiratory flow / total expiratory time)

Ep 301-13:

Neutralizing Ab investigated in the following groups:

- BNT162b2 = triple-vaccinated SARS-CoV-2-naïve individuals (n=18; age <55 years),
- BNT162b24 = quadruple-vaccinated SARS-CoV-2-naïve elderly (>60 years n=15),
- mRNA-Vax3 + BA.1 = triple mRNA vaccinated individuals with Omicron BA.1 breakthrough (n=14),
- mRNA-Vax3 + BA.2 = triple mRNA vaccinated individuals with Omicron BA.2 breakthrough (n=19),
- mRNA-Vax3 + BA.4/5 = triple mRNA vaccinated individuals with Omicron BA.4/5 breakthrough (n=17)

As expected neut against BQ.1.1 and XBB are very low, but increase with number of vaccinations and with breakthrough infection, where the order of higher neut for BQ.1.1 is BA.5 BTI > BA.2 BTI > BA.1 BTI.

T cell immunity: inferred from filtering experimentally confirmed Spike epitopes reported for HLA class I and II alleles from the IEDB database. → 260 unique HLA class I epitopes (for CD8 T cells) and 468 class II (for CD4 T cells):

90% of CD8+ and CD4+ T-cell epitopes of the wild-type S glycoprotein were fully conserved in the Alpha, Beta, and Delta variants and over 80% of CD8+ and ~70% CD4+ T-cell epitopes were fully conserved in Omicron sublineages including BA.2.75.2, BQ.1.1, and XBB
GENERAL CONCLUSIONS:

There is a clear additional protective effect of WT/BA.5 bivalent vaccines (as compared to monovalent WT only) against symptomatic disease and hospitalization in immunocompetent individuals, including the more vulnerable older subjects in US.

There was only one report on effectiveness of the “UK-European” bivalent (WT + BA.1) vaccine, which is in line with the US data, but cannot really directly be compared.

Nevertheless, the beneficial effects are less impressive than after primary vaccinations and booster with WT in 2021 and they wane rather rapidly. It seems very logical to attribute those phenomena to the viral evolution towards a “neutralization resistant” phenotype (such as BQ.1.1) as a consequence of multiple escape mutations and imprinting.

On the other hand, worse could have been expected, based on the very low sensitivity to vaccine-induced neutralization, enhanced infectivity and equal pathogenicity of BQ.1.1 as compared to previous Omicrons.

Therefore it is likely that the relatively conserved T cell immunity has a major role in protection against severe disease. However, besides Ep 310-13 (showing “inferred data”), I could not find published data on T cell function against BQ.1.1 Spike epitopes after monovalent or bivalent vaccination or after vaccination + breakthrough infection.

The question can be asked whether it is interesting and useful to develop a BQ.1.1 booster?
- In view of “imprinting”, it would certainly be preferable NOT to combine BQ.1.1 mRNA with WT mRNA (since the latter would skew the immunity towards already escaped WT epitopes), but rather use sub-lineage (e.g. BQ.1.1) mRNA only .
- It would then be important to not only monitor in vitro neutralization tests against all circulating sub-lineages, but also assess a T cell function against conserved and mutant Spike T cell epitopes, before deciding on a new mass vaccination campaign.

Looking forward to your thoughts on this matter.

Best wishes,

Guido