Episode 215 : Omicron clinical, structural and functional aspects

Dear colleagues,

Information on omicron is rapidly evolving. Here I summarize some recent clinical data, confirming lower pathogenicity and structure-function relationships that underpin the high transmissibility, the lower pathogenicity and the immune escape.

CLINICAL ASPECTS

Ep 215-1: Retrospective cohort study in Canada, comparing > 12,000 omicron with delta cases, based on Ontario's Public Health Case and Contact Management Solution (CCM), a database containing all diagnosed SARS-CoV-2 infections.
Patients matched for gender, age, vaccination status, date of symptoms onset….

Parameter	Omicron	Delta
Hospitalization	0.51 %	1.6 %
Death	0.03 %	0.12 %

Hospitalization = 65 % lower; ICU 80 % lower; death 75 % lower with omicron compared to delta

Ep 215-2: Study on patients in Houston Methodist facilities (e.g., hospitals and urgent care centers), and institutions in the Houston metropolitan region that use our laboratory services. Comparing 862 omicron with 3159 alpha and over 15,000 delta.

Not really matched: omicron patients were younge r, more women, lower BMI and more vaccine breakthrough. Clearly much less hospital admissions, hospital stay and death with omicron

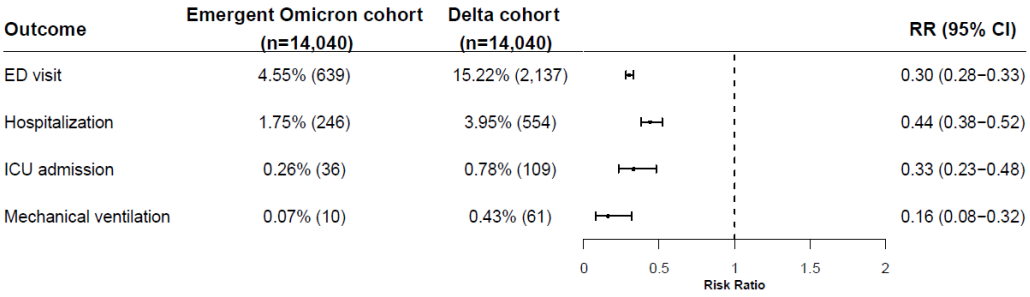
Parameter	Omicron	Alpha	Delta
Age	38.9	50	48
BMI	28.7	30.5	29.5
Full vaccination	49 %	3.2 %	24.2 %
Hospital admission	15.5 %	54.5 %	43 %
Death	0.9 %	5.4 %	5.3 %
Days in hospital	2.8	5.1	5.4

Thus omicron vs delta hospitalization risk reduced by 65 % and death by 83 %

Ep 215-3: Researchers from Cleveland analyzed a US database of over 577,000 first time infected subjects comparing over 14,000 in the period of "omicron emergence with over 560,000 in the "Delta period", narrowing down to 14,040 "omicron" and "delta" (propensity) matched individuals (see Table 1).

As can be seen in the graph, omicron patients displayed a significantly less severe disease course.

Comparison of 3−day acute outcomes
in matched patients with SARS−CoV−2 infections
Emergent Omicron cohort (12/15−12/24) vs. Delta cohort (9/1−11/15)



Reduction of hospitalization risk 55 %; ICU admission: 66 %

The lower severity was found in every age stratum (see Fig 2 p.8).

Ep 215-4: Peter Hall et al conducted a rather small study in subjects with previous delta infection versus non-infected controls. Using a standard questionnaire on "executive function" (impulsive behavior) they found a significant increase of dysfunction in previously infected subjects, correlated with disease severity. This study provides some evidence of **post-COVID cognitive dysfunction.**

Ep 215-5: COVID update in Washington Post 4 Jan:

- Approval of booster for 12-15 yrs old
- Omicron peak in South-Africa already over.
- Concerns over shortening isolation and quarantine rules

Conclusion:

Clear evidence that omicron is less severe than delta and alpha infections.

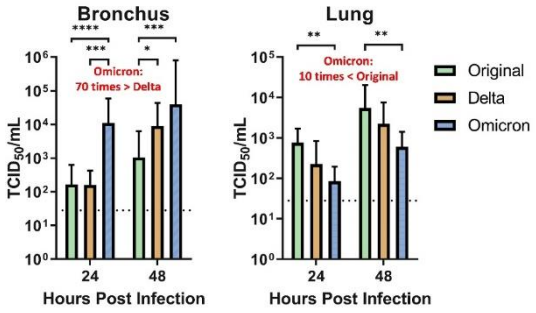
Although the different populations had a very different risk of severity overall (depending on the different selection?), **the relative risk reduction of hospitalization was consistent at 55-65%; ICU admission at 66-80 % and of death at 75-83 % for omicron versus delta**!

STRUCTURAL AND FUNCTIONAL CHARACTERISTICS

Ep 215-6: Short publication on site of Hong-Kong University found:

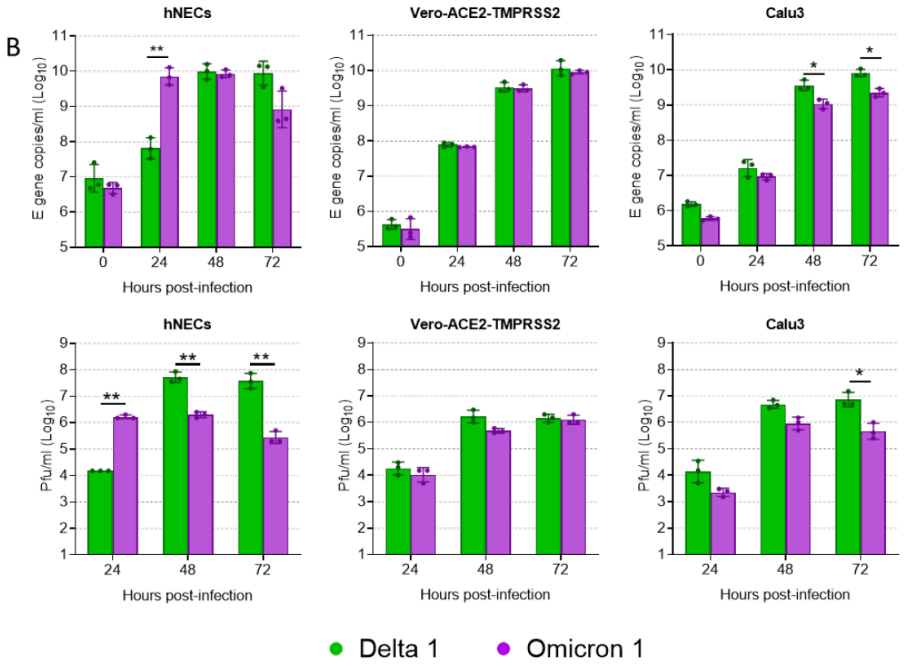
- Omicron infects and **multiplies 70 X faster** than the Delta variant and original SARS-CoV-2 in human bronchus: may explain why Omicron may transmit faster between humans.
- Omicron infection in the lung is **significantly lower** than the original SARS-CoV-2: may be an indicator of lower disease severity.

There is little experimental detail: ex vivo cultures of the respiratory tract, but nice graphs/pictures.



Ep 215-7: Thomas Peacock:

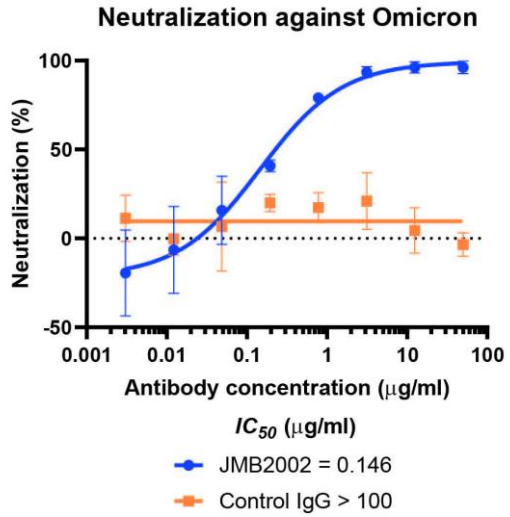
- **Omicron replicates more rapidly** in primary cultures of human nasal epithelial cells (hNEC) but is attenuated for entry in many cell lines. Thus omicron transmit rapidly (shorter interval)



Plaque forming units in nasal epithelium 100 times higher after 24 hours, then decreases due to cell death.

- **Omicron outcompetes Delta** in primary cultures of human nasal airway epithelial cells: correlates with rapid displacement of delta by omicron in the epidemic.
- **Omicron has higher affinity for human ACE-2 and binds a wide variety of animal ACE-2,** with even higher affinity in rat, mice, hamster, cat, dog and horseshoe bat: extensive zoonosis and reverse zoonosis capability. (see Fig 3).
- Despite containing mutations that enhance Spike S1/S2 cleavage (N679K andP681H), Omicron causes **reduced syncytia formation** compared to previous SARS-CoV-2 variants: less efficient use of cell surface TMPRSS2 by Omicron Spike protein has also resulted in a decrease in the propensity for syncytia formation, which may explain *reduced disease severity*
- Omicron is able to enter cells in both a TMPRSS2-dependent and –independent manner, having evolved the ability to **avoid endosomal restriction**. This allows Omicron to infect any ACE2-expressing cell in the airway instead of relying solely on double ACE_+ $TMPRSS2_+$ cells.

Ep 215-8: Wanchao Yin confirms a **10 X higher binding of omicron to ACE-2**, due to more tendency to an "open conformation" of the trimeric spike and an unusual interaction between the 3 receptor-binding domains of the trimer, unique to Omicron and extra interactions in the ACE2-RBD interface. Interestingly, while many therapeutic monoclonal Ab lost activity against omicron, **JMB2002 shows a nice neutralization with EC50 = 0.146 µg/ml.** This monoclonal Ab also blocks WT, alpha, beta and gamma, but not delta.



Ep 215-9: Bo Meng confirms that the "cleavability" of omicron Spike (S1/S2) is lower (despite theoretically favorable mutations) and therefore omicron has **lower "target cell- fusogenic capacity**" (which might imply a lower pathogenicity).

Moreover they show that omicron has a **lower infectivity in "lower airway organoids**" and Calu-3 lung cells, but similar to higher infectivity in H1299 lung epithelial cells. In contrast to delta, omicron infectivity could NOT be enhanced by TMPRSS2 overexpression.

The comparison of alveolar and airway epithelial cells revealed higher expression of TMPRSS2 in the alveolar AT1 and AT2 pneumocytes, and lower expression in the trachea.

These *in vitro* data indicate that **suboptimal Omicron S1/S2 cleavage reduces efficient infection of lower airway cells expressing TMPRSS2, but not TMPRSS2 negative cells such as those found in the upper airway.**

Ep 215-10 Lupala in BBRC provides molecular binding analysis, showing that the mutations on RBD of SARS-CoV-2 Omicron variant result in stronger binding to human ACE2 receptor.

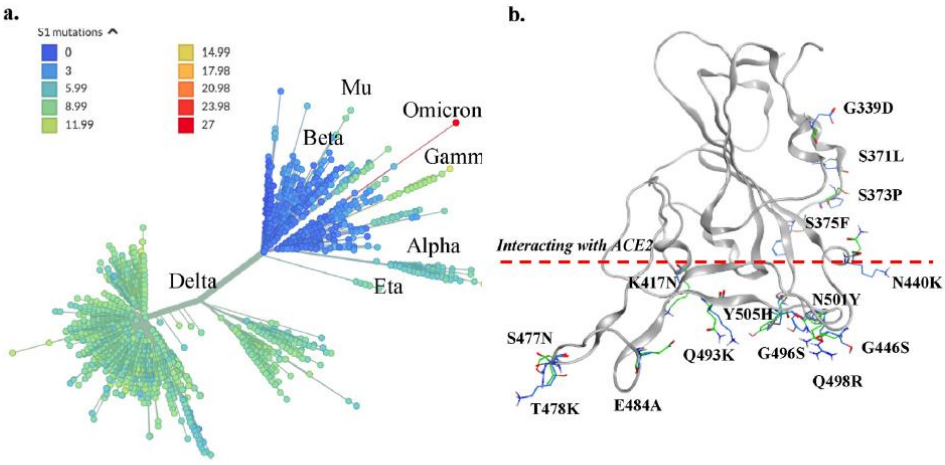


Fig. 1. Mutations and the diversity of SARS-CoV-2. (a) The phylogenetic tree of SARS-CoV-2. Major variants are labelled on the graph, and the color of clans is according to the

Ep 215-11: McCallum shows the loss of binding of most avaiable monoclonal Ab to the receptor-binding domain of omicron, because of the Spike mutations (in red).

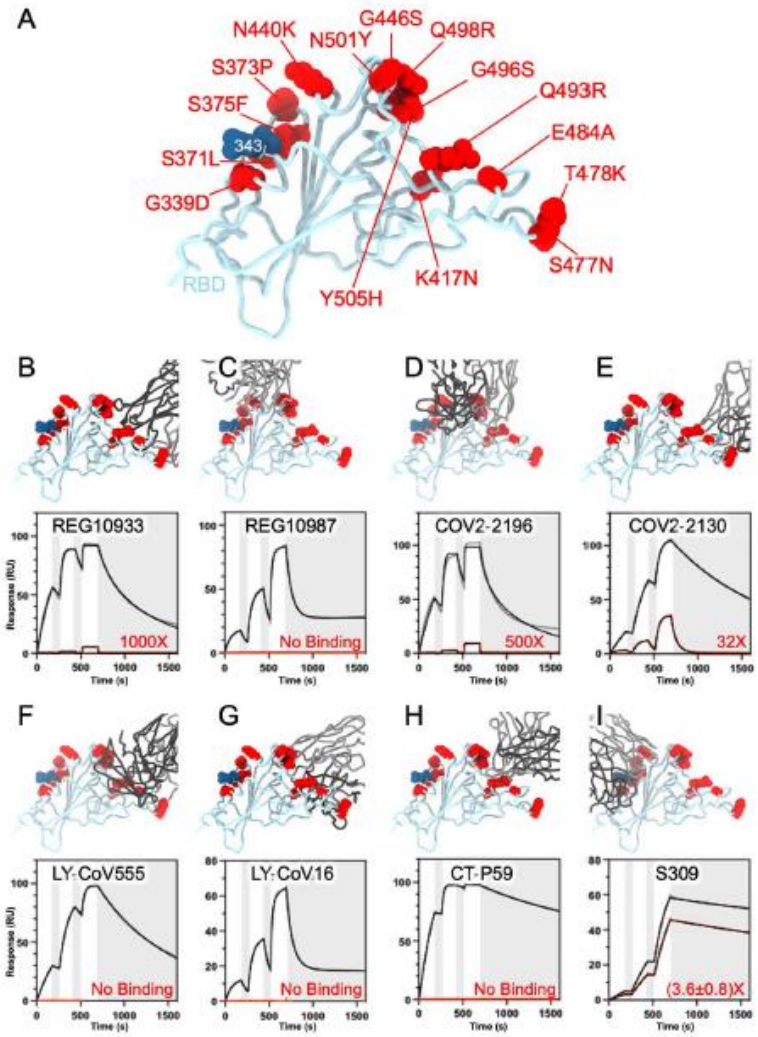


Fig. 3. SARS-CoV-2 Omicron RBD mutations promote escape from a panel of clinical mAbs. A, Ribbon diagram of the RBD with residue mutated relative to the Wuhan-Hu-1 RBD shown as red spheres. The N343 glycan is rendered as blue spheres. **B-I,** Zoomed-in view of the Omicron RBD superimposed to structures of the RBD bound to REGN10933 (B), REGN10987 (C), COV2-2196 (D), COV2-2130 (E), LY-CoV555 (F), LY-CoV16 (G), CT-P59 (H) or S309 (I). Binding of the Wuhan-Hu-1 (gray line) or Omicron (red line) RBD to the corresponding mAb was evaluated using surface plasmon resonance (single-cycle kinetics) and is shown at the bottom. The black line is a fit to a kinetic model. The decrease in affinity between Wuhan-Hu-1 and Omicron binding is indicated in red.

Ep 215-12: Further molecular analysis by reveals four groups of crcial residues in Spike:
1) Group I includes **six identical residues** such as G447, Y453, N487, Y489, T500 and G502,
2) Group II consists of **five homologous residues** like Y449/F/H, F456/L, Y473/F, F486/L and Y505H,

3) Group III five **conditionally altered residues** like G446/S/T, L455/S/Y, A475/P/S, G476/D, G496/S,
4) Group IV five highly diverse residues K417/V/N/R/T, E484/K/P/Q/V/A, Q493/N/E/R/Y, Q498/Y/H/R and N501/Y/T/D/S

Substitutions in the last two groups are tolerated or even enhance ACE2 binding, and are frequently observed in variant viruses

Mutations in the first two groups are strictly constrained, presumably because they act as molecular determinants in either retaining basic affinity for ACE2 or ensuring proper protein folding.

→ Broad neutralizing antibodies should target group I and II amino acids.

(this will be discussed in the next episode)

Summary on Omicron receptor-binding and spike domains

1) **RBD has a more "open confirmation and higher affinity for ACE-2**
2) **Entry not dependent on TMPRSS-2**
3) **Lower fusogenic capacity**
4) **Lower infectivity in lungs, higher in upper respiratory tract**
5) **Escapes from many monoclonal antibodies**

That's it for today!

Best wishes,

Guido