What recent evidence do we have that omicron is evading immunity and what are the implications?

William Dowling, Ph.D.
Chair, WHO COVID-19 Assays working Group
Co-Chair, WHO COVID-19 Models working Group
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Immune responses

- Neutralization data in the literature are limited, especially for certain vaccines. The percentage of responders is as important to assess as fold decrease. Pseudovirus assays correlated well with live virus neutralization assays.

- For neutralization, convalescent individuals have low titers against Omicron (no matter which is the infecting VOC), as do double vaccinated individuals; Triple vaccinated and convalescent vaccinated individuals have most residual neutralizing activity.

- There were high neutralizing antibody titers against all VOCs for vaccinated individuals or those previously infected following Omicron breakthrough infection; but samples from unvaccinated, previously uninfected individuals that were then infected with Omicron showed poor breadth of responses. These individuals neutralized Omicron well but other variants poorly.
Immune responses (2)

- Binding and neutralizing responses to 3rd doses of mRNA vaccines were higher than 2 doses and those responses also waned more slowly. The titers after third dose waned to low levels after 5 months but high titers were restored by a 4th dose.
- In breakthrough infection with Omicron in Israel, VE was low in boosted individuals but most cases were asymptomatic or very mild.
- The RBD dimer based vaccine ZF2001 used by itself or as a booster of inactivated vaccines boosted neutralization titers, and this boost was much better with longer intervals (4 months) between the primary series and the boost.
- Neutralization titers of BA.2 were similar to BA.1 for multiple vaccine sera- 2 or 3 doses Pfizer, Coronavac 3 doses or Coronavac 2 dose with Pfizer boost; Similar with hybrid immune individuals. This indicates BA.1 and BA.2 are similar in antigenic distance to the ancestral strain. In breakthrough BA.1 infections, antibody titers were similar to BA.1 and BA.2
Immune responses (3)

- Antibody binding – the reduction in binding to Omicron RBD, Spike or NTD was less pronounced than decreases in neutralization. Florian Krammer reported that the decrease in full Spike was greatest, while Galit Alter reported that binding to Spike was preserved, while there was a much greater loss of RBD binding.

- Fc Receptor binding and Spike specific NK cell activation were maintained against Omicron in individuals vaccinated with several vaccines indicating that these mechanisms can still control the infection and severe disease in the individual.

- The majority of T cell epitopes are not affected by Omicron mutations; even those epitopes that have minor amino acid changes are still able to bind HLA class 1 molecules.

- T cells from the majority of vaccinees are able to recognize Omicron, regardless of vaccine. CD4 and CD8 responses decrease slightly (up to 20%), although certain individuals lose CD8 responses, likely a specific HLA background.
Immune responses (4)

- Unvaccinated Omicron infected patients have similar T cell responses as individuals infected by previous variants.
- Omicron infection leads to higher Omicron immunity in vaccinated and unvaccinated people; Omicron also enhances Delta neutralizing immunity in the vaccinated and in some of the unvaccinated.
- There is reduced Omicron virus replication in interferon competent cells. Omicron is highly sensitive to interferon compared to other variants.
Animal Studies

- The disease caused by Omicron in mice, hamsters and NHPs is far milder than disease caused by ancestral strains or earlier variants.
- Primary infection with an ancestral strain protects animals from re-infection by Omicron. This is despite low neutralizing titers against Omicron prior to challenge.
- Transmission studies in hamsters demonstrated that Omicron is more transmissible than Delta in hamsters by contact and non-contact transmission. In competition experiments both in vitro and in vivo, Omicron is outcompeted by the Delta, however, it outcompetes Delta in the presence of immune pressure.
- Protection of mice against Omicron with mRNA-1273 is dose dependent, with low dose showing breakthrough and disease in the lungs of mice. A third dose results in good protection of the low dose animals.
Animal Studies (2)

- Boosting for Pfizer or JnJ (homologous or heterologous) in NHPs led to higher neutralizing antibody and T cell responses. All vaccinated groups had virus in the BAL but lower peak titers and duration. Lower levels in the nasal swabs and longer persistence with Omicron then seen with other variants.

- In vaccinated NHPs, control of viremia correlated with both antibody and T cell response; 4 animals were breakthroughs that had moderate neutralizing antibody levels but very low CD8+ T cells and did not control viral replication.
Animal Studies (3)

• An Omicron specific mRNA vaccine showed little advantage as a booster over prototype vaccines in NHPs

• Omicron specific vaccines protected against Omicron when used as a primary series, However, there was poor breadth of response against prototype strains or other variants.

• A third dose produced much higher responses with a boost and increased protection, with an Omicron boost better then current ancestral vaccine
Summary

- Neutralizing titers are severely impacted by Omicron
- Boosting clearly leads to better neutralization responses against Omicron
  - Both homologous and heterologous boosts lead to higher neutralization titers. Which is the optimal combination remains as an open question as well as the optimal interval
  - These responses wane, although more slowly than after 2 doses
- Binding and Fc functions are well maintained against Omicron, as are T cell responses, which should allow control of disease in the individual although not control of transmission
- Omicron causes a milder disease in all animal models tested
- Omicron is more transmissible than Delta and also out competes in the presence of immune pressure
- Infection with an ancestral strain or other variant protects form Omicron re challenge
- Omicron specific vaccines elicit neutralizing antibodies and protect against Omicron, but do not provide good neutralizing titers against other variants
- Omicron specific vaccines do not show a large advantage over current vaccines as a boost
Panel Discussion

- Strength and weakness of animal models
  - All of them suffer from not being matched to humans in term of interferon inhibiting properties
  - Goal should be to test for escape of neut ab (t cell responses are intact with Omicron)
  - Regulatory perspective – this evidence is critical, but some regulators may be reluctant to consider this strongly
  - Durability assessment needed; for boosters (esp. omicron specific)
  - Strength - Much in models replicates what is happening in humans; immune correlates for Wuhan-1; durability and waning
  - Increase in immunological diversity to reproduce in animals
  - Immunobridging – gap – mucosal immunity
  - Transmission data in hamsters and in vitro gave a great deal of useful information
  - Role of prior immunological history can be done in animals
Panel discussion

- Omicron specific vaccine
  - Ancestral vaccine works pretty well
  - Omicron is an outlier; are we likely to have other outliers? Or can we expect constraints?
  - Omicron specific vaccine could be counter productive – poor cross protection against other strains
  - Need more breadth than current vaccines are providing – multivalent, sequential immunization, etc. More research needed on this.
  - in a previously immune population, not a real benefit over current vaccines; unless an Omicron boost gives more durable protection; more studies needed
What data are still needed?

- Additional studies with more deployed vaccines, beyond mRNA;
  - Assessment of different regimens and intervals
- Omicron specific vaccines
  - Duration assessments against Omicron vaccines in animal models
  - Assessing breadth of responses across different VOCs with Omicron specific vaccines
- Additional animal studies on primary series vs boosters
- Development of broadly neutralizing vaccines
- Better assessment of mucosal immunity and development of vaccines that stimulate mucosal immunity