Development Approach for Anti-Spike Monoclonal Antibodies to Keep Pace with SARS-CoV-2 Variants

EMA-FDA Workshop: Efficacy of monoclonal antibodies in the context of rapidly evolving SARS-CoV-2 variants

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There is significant unmet medical need for therapeutic options to prevent and treat COVID-19

- Advances in worldwide vaccination efforts and increased levels of population immunity have reduced SARS-CoV-2 associated disease and mortality

- However, there is still significant unmet medical need:
  - Persons who cannot respond to vaccines (e.g. immuno-compromised) remain vulnerable to infection and would benefit from effective immunoprophylaxis

  - People with reduced antibody titers over time and/or against novel variants need therapeutic interventions, especially those at higher risk of hospitalization and death (e.g. over 65)

  - Multiple antiviral modalities (direct antivirals and monoclonal antibodies) are needed to meet patient needs

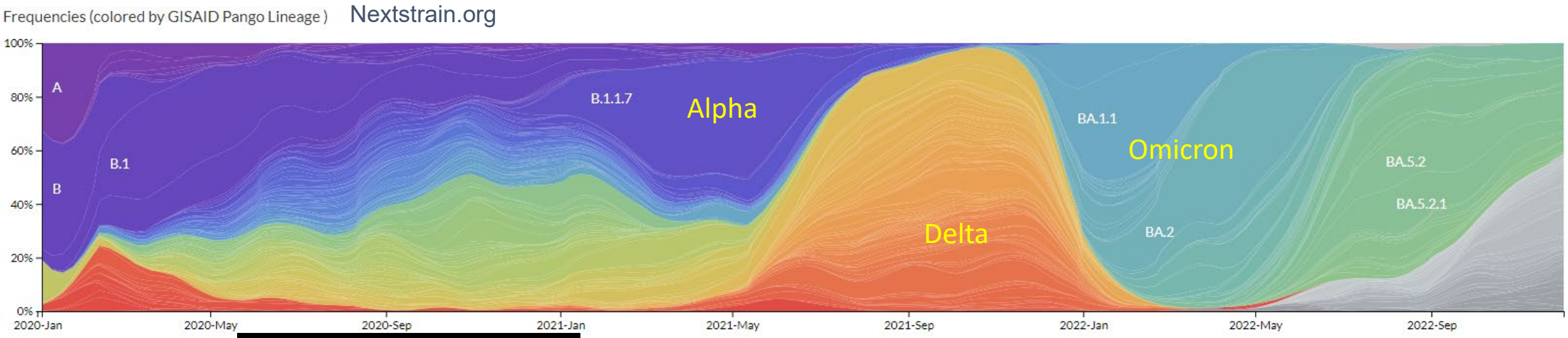
Although mAbs have shown efficacy in both the treatment and prevention of COVID-19, current development timelines are not consistent with rate of virus evolution

- Spike targeting neutralizing mAbs have shown efficacy for both prophylaxis and treatment of SARS-CoV-2 infection and are well-tolerated
  - Consistent experience with multiple neutralizing mAbs and formats from multiple sponsors
  - Safety profile consistent with fully human and *in vivo* selected mAbs against exogenous targets

- However, SARS-CoV-2 rapid evolution and variant dissemination are a challenge to current development paradigm
  - Emergence and global spread of novel variants is as quick as every 2-3 months

- A scientifically sound, data driven policy change to shorten development timelines is needed to keep pace with the rapid development of variants in order to meet patient needs
  - Expedited mAb manufacturing activities and scale up are also required

Global variant dominance – mAb development/authorization timeline



Phase 2/3

bamlanivimab — US EUA Nov 2020 — EUA Revoked April 2021

bamlanivimab/etesevimab — Phase 2/3 — US EUA Feb 2021 — Paused — FDA lifts Pause On US EUA Sept 2021 — Paused

bebtelovimab — Phase 2 — US EUA Feb 2022 — Paused

casirivimab/imdevimab — Phase 2/3 — US EUA Nov 2020 — Paused

sotrovimab — Phase 2/3 — US EUA May 2021 — Paused

tixagevimab/cilgavimab — Phase 3 — US EUA (PrEP) Dec 2021

Evidence to support establishment of serum neutralization titers as a correlate of protection for anti-Spike mAb therapeutics

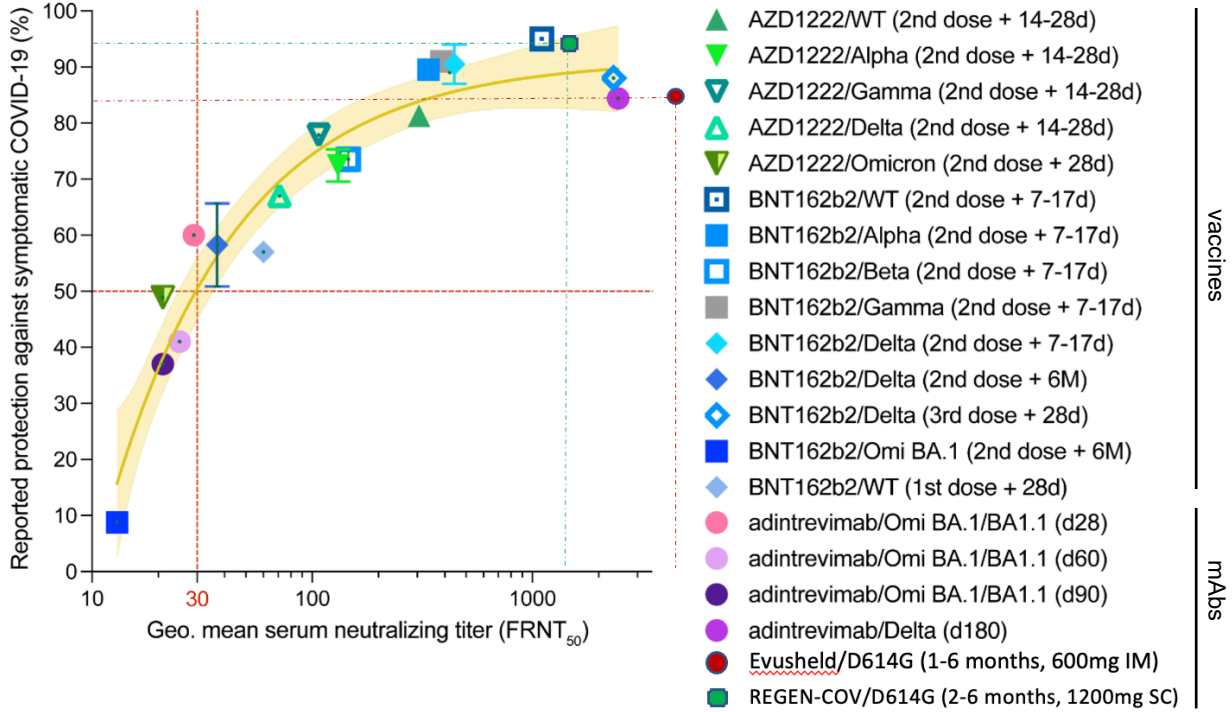
- Neutralization is an accepted correlate of protection for next generation SARS-CoV-2 vaccine development

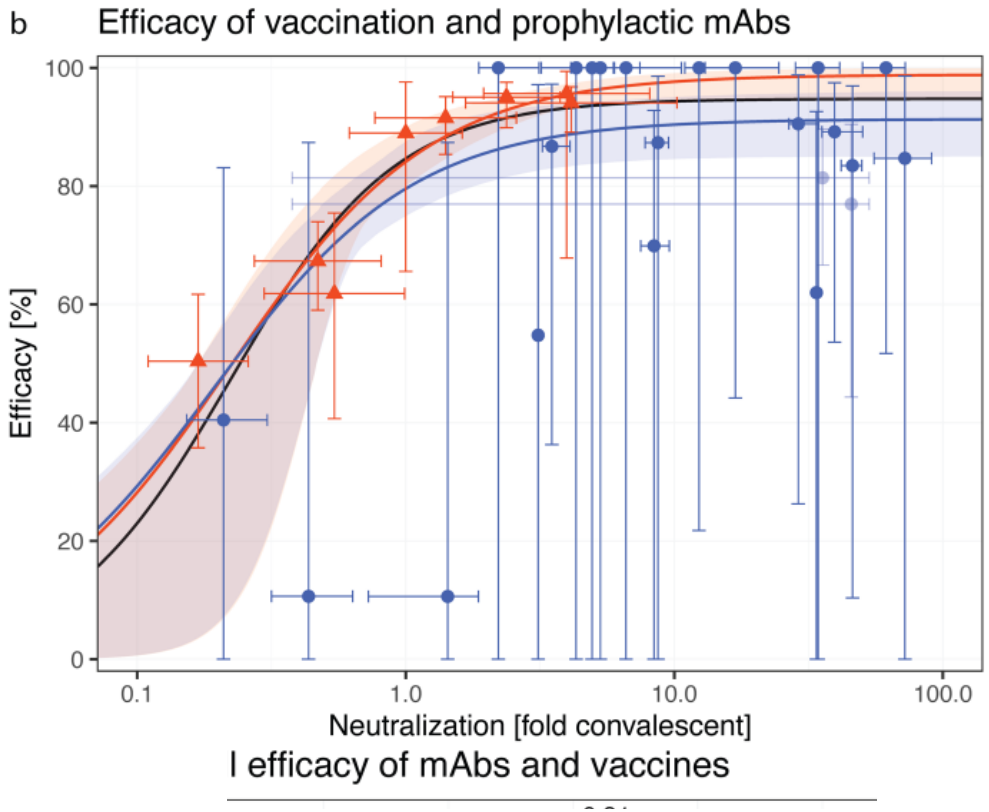
- Meta-analyses using clinical trial data support that neutralization potency against the circulating variant is correlated with efficacy in prevention
  - Association of monoclonal antibody serum titer with degree of protection
  - Similar accumulating evidence for efficacy in treatment settings for clinical benefit against COVID-19

- Previously authorized neutralizing mAbs have shown efficacy in clinical trials independent of ACE-2 blockade, effector function and/or half-life extending modifications
  - Neutralization is the correlate of efficacy

- Serum titers achieved with passive administration of mAbs and active immunization with vaccines result in similar levels of protection
  - Neutralization, independent of epitope and effector function, is the drivers of efficacy

Serum neutralizing titers (either mAb or vaccine) correlate with protection against symptomatic SARS-CoV-2 infection across multiple variants





doi: https://doi.org/10.1101/2022.10.18.22281172
N England J Med Journal (2022)
Lancet Infect Dis (2022)

Stadler (Khoury and Devenport) et al. MedRxiv 2022

There is a sound scientific basis for relying on evidence from first generation mAbs to support development of new mAbs

- Previously authorized neutralizing mAbs have shown efficacy in well-controlled and powered clinical trials and are well-tolerated
  - Real World Evidence studies confirmed findings of clinical trials

- Next generation mAbs should be discovered and manufactured using technologies and processes used to produce previously approved and/or authorized mAb products

- Nonclinical characterization should demonstrate similarity of the new mAb to the first generation mAb on key characteristics, thereby bridging to the body of evidence that initially supports(ed) use
  - Neutralization potency of new mAb as assessed by IC50 against circulating variants is a key parameter

- *In vivo* selected, naturally occurring, mAbs against exogenous targets have demonstrated a consistent, well tolerated safety profile
  - Limited safety data should support authorization and use

Establishing protective titer threshold for anti-Spike mAb therapeutics

Proposed Approach in Prevention Setting:

- Use standardized neutralization assays to determine correlation of neutralization titers (measured or estimated from *in vitro* potency and drug concentration) and protection against the development of symptomatic SARS-CoV-2 infection in historical clinical trials → establish minimum efficacious titer
- Use *in vitro* neutralization assays to measure potency and calculate titers for any next generation or existing antibody against new/emerging variants at certain serum mAb concentrations
- Select dose based on calculated neutralization titers and PK modeling

Proposed Approach in Treatment Setting:

- Use standardized neutralization assays to determine neutralization titers (measured or estimated from *in vitro* potency and drug concentration) at which protection from hospitalization and death were observed in clinical studies → titer above which therapeutic benefit is expected
- Use *in vitro* neutralization assays to measure potency and calculate titers for any next generation or existing antibody against new/emerging variants at certain serum mAb concentrations
- Select dose based on calculated neutralization titers and PK modeling

Summary

- There is continuous unmet medical need for SARS-CoV-2 infection prophylaxis and treatment
- Current development paradigm for next generation SARS-CoV-2 mAbs is not consistent with the rate of virus evolution
- Next generation mAbs with potent neutralization activity against novel SARS-CoV-2 variants can be discovered and manufactured using platforms and well-established processes that were used for the first generation mAbs
  - Approaches have been established for development of next generation vaccines against SARS-CoV-2 and seasonal influenza
- Combining *in vitro* evaluation of neutralization potency, PK modeling and meta-analyses of existing clinical trial data can provide the basis for a scientifically sound approach to develop next generation SARS-CoV-2 mAbs