# Overview of the day - COVID-19 appraisals

| Section | Data relevant to both appraisals | |
|---|---|---|
| 1.1 | SARS-CoV-2: variant tracking | Public |
| 1.2 | *In vitro* data | Public |
| 1.3 | Position of various organisations | Public |

| ID 4038 | MTA of COVID-19 treatments | ACM 2 |
|---|---|---|
| 2.1 | Community setting (mild COVID-19) – Part 1 | Public |
| 3.1 | Hospital setting (severe COVID-19) – Part 1 | Public |
| 2.2 | Community setting – Part 2 | Private |
| 3.2 | Hospital setting – Part 2 | Private |

| ID 6136 | STA of tixagevimab/cilgavimab (Evusheld) | ACM 1 |
|---|---|---|
| 4.1 | Prophylaxis in highly vulnerable people – Part 1 | Public |
| 4.2 | Prophylaxis – Part 2 | Private |

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# Section 1 Data relevant to both appraisals

- SARS-CoV-2 variant tracking
  - Evolution of variants
  - UK Health Security Agency (UKHSA) technical briefings
- *In vitro* data
  - The ***I**n **V**itro* data **A**ssessment **G**roup (IVAG)
  - BQ.1, BQ.1.1, XBB
- Position of various organisations

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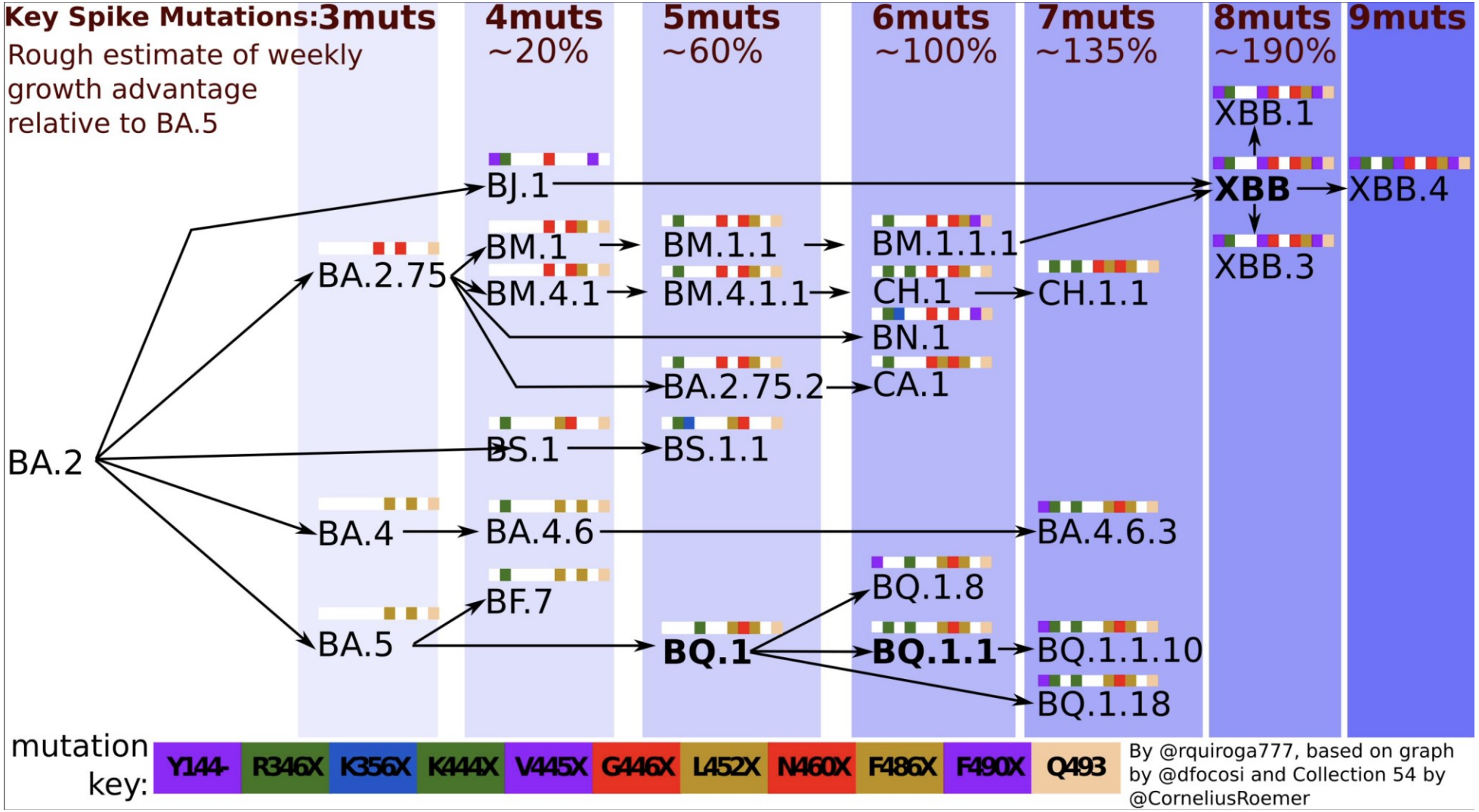
# Evolution of SARS-Cov-2 Omicron variants*

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* additional slide in appendix

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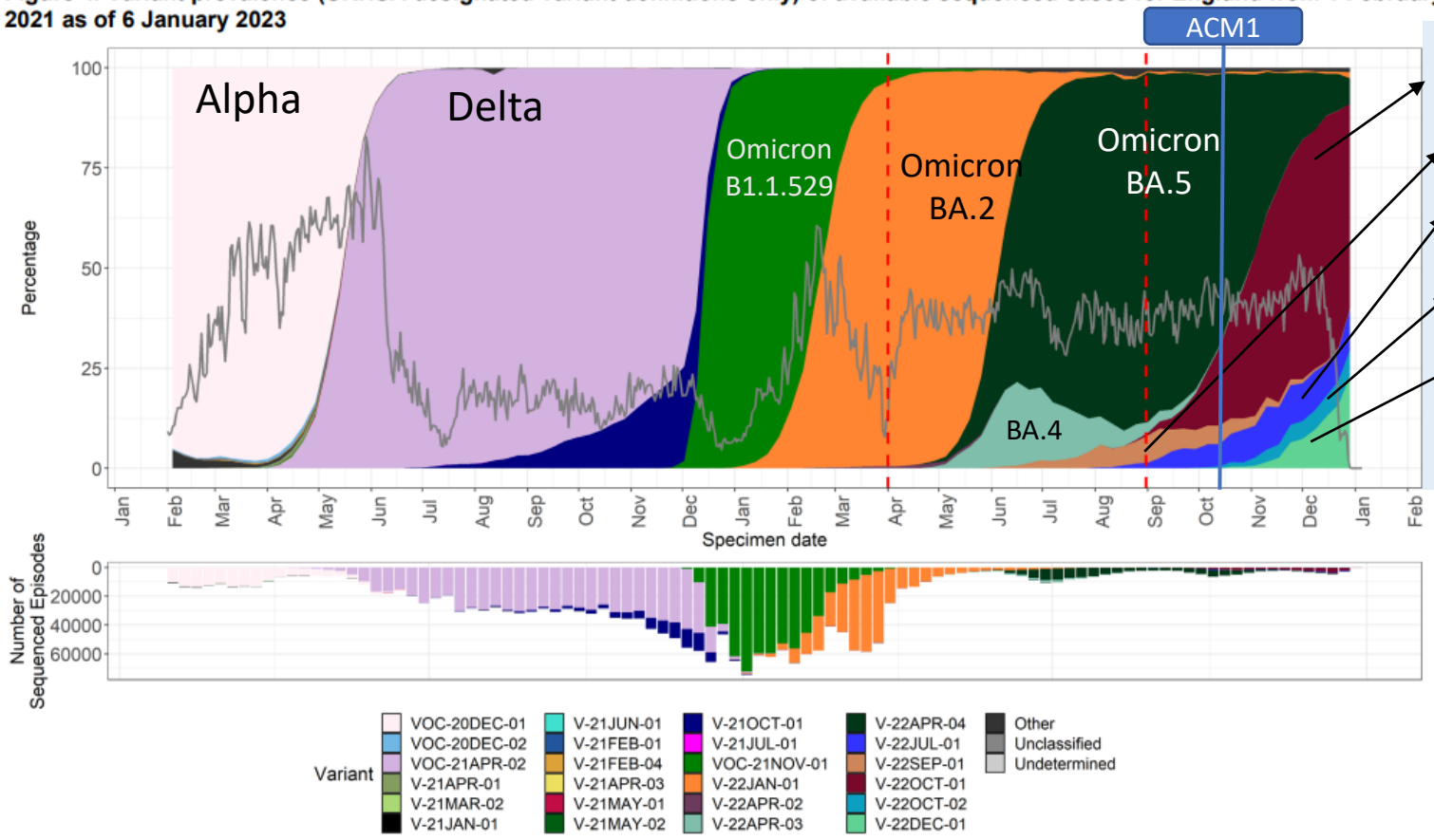
# Circulating variants change and difficult to predict

*Possible only to predict prevalence of variants from trajectories of **currently circulating** variants in the near future*

**Figure 4. Variant prevalence (UKHSA designated variant definitions only) of available sequenced cases for England from 1 February 2021 as of 6 January 2023**




- Omicron BQ.1 (51.3%)
- Omicron BA.4.6 (0.12%)
- Omicron BA.2.75 (4.9%)
- XBB recombinant (3.6%)
- Omicron CH.1.1 (19.5%)
- XBB.1.5 (V-23JAN-01) (4.5%)

Predicting change in currently circulating variants limited only to the ‘near future’ (1-2 months)

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Source: UKHSA Technical briefing 49 (11 January 2023). Weekly growth rates: Table 3 (Please note limitations of model methods in Technical briefing 49 and 48)

# UKHSA Technical Briefing 49. 11th Jan 2023

## Multinomial modelling, estimated prevalence

**Table 3. Growth rate (GR) of variants and signals under monitoring as of 25 December 2022^**

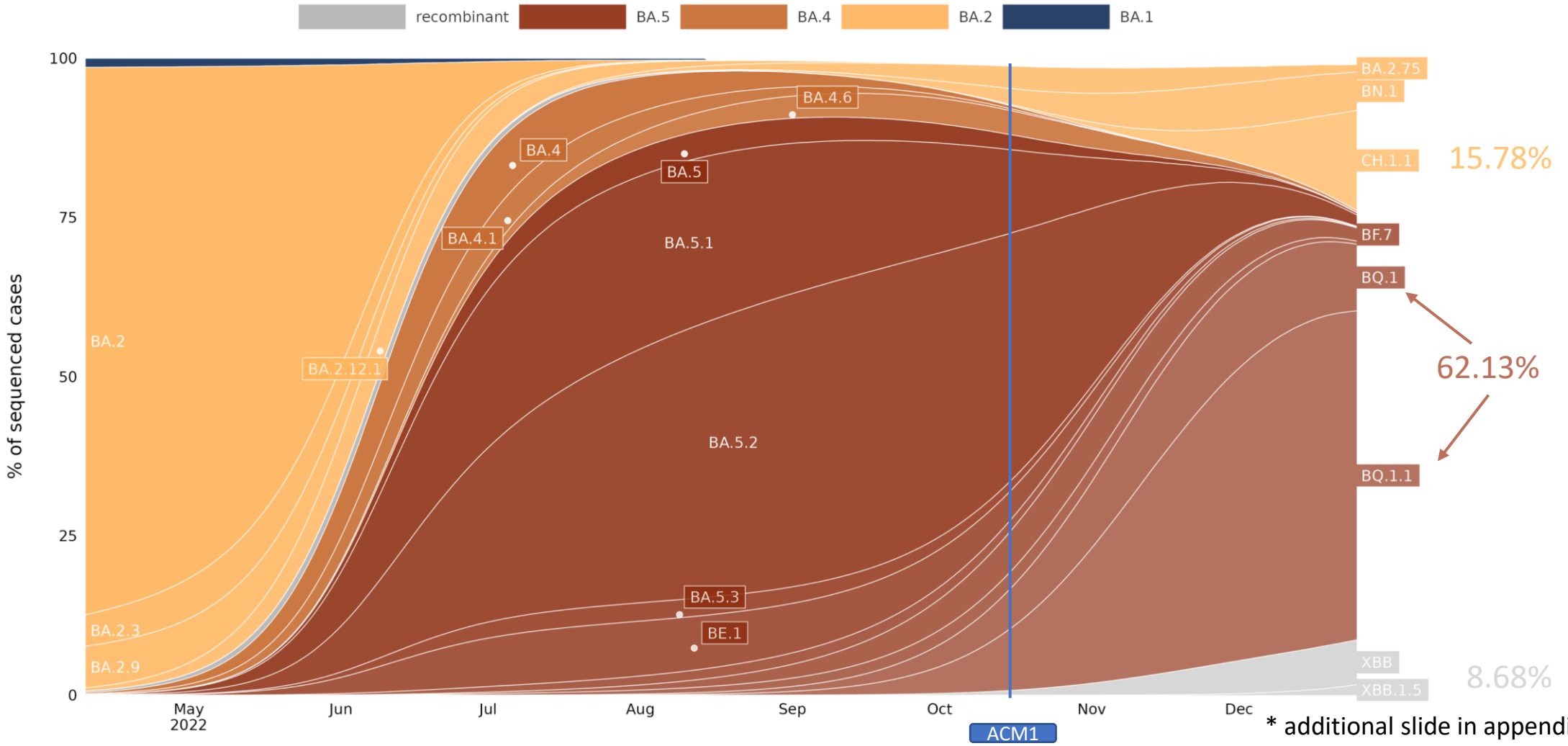
| Lineage | English sequences used in the multinomial model (MM) | MM England estimated prevalence | MM estimate for the weekly growth rate relative to BQ.1.1 lineages | English sequences counts used in the logistic regression and generalised additive model | Logistic regression GR (1/week) | Generalised additive model most recent GR (1/week) |
|---|---|---|---|---|---|---|
| BQ.1.1 | 1,4711 | 51.67% (95% CrI: 38.09 to 64.31) | - | 1,161 | 14% | -9% |
| CH.1.1 | 2,262 | 15.78% (95% CrI: 10.41 to 24.56) | 21.56% (95% CrI: 19.25 to 23.97) | 291 | 37% | 12% |
| BQ.1* | 5,963 | 10.46% (95% CrI: 6.71 to 16.06) | -8.85% (95% CrI: -10.09 to -7.42) | 2,053 | 16% | -18% |
| BN.1 | 2,410 | 6.01% (95% CrI: 3.35 to 10.21) | -6.12% (95% CrI: -7.69 to -4.39) | 71 | 3.6% | -55% |
| BA.2.75† | 2,016 | 1.16% (95% CrI: 0.67 to 1.97) | -21.52% (95% CrI: -22.93 to -19.95) | 1,153 | 13% | 4% |
| XBB** | 1,304 | 7.02% (95% CrI: 4.04 to 10.58) | 4.52% (95% CrI: 2.57 to 6.57) | 267 | 18% | 0% |
| XBB.1.5 | 124 | 1.66% (95% CrI: 0.89 to 2.74) | 38.87% (95% CrI: 32.2 to 45.63) | - | - | - |

* BQ.1 excludes BQ.1.1 which was modelled separately.
† BA.2.75 excludes BN.1 and CH.1.1 which were modelled separately.
** XBB excludes XBB.1.5 which was modelled separately.
^ Sampling range for both logistic regression and generalised additive models is from 12 October 2022 to 3 January 2023.

# UKHSA Technical Briefing 49. 11th Jan 2023*

Multinomial modelling, estimated prevalence

**Figure 7. Area plot showing the predicted representation of each lineage of the multinomial model of all sequenced cases in England**




* additional slide in appendix

# Section 1 Data relevant to both appraisals

- SARS-CoV-2 variant tracking
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    - The *In Vitro* data **A**ssessment **G**roup (IVAG)
    - BQ.1, BQ.1.1, XBB
- Position of various organisations

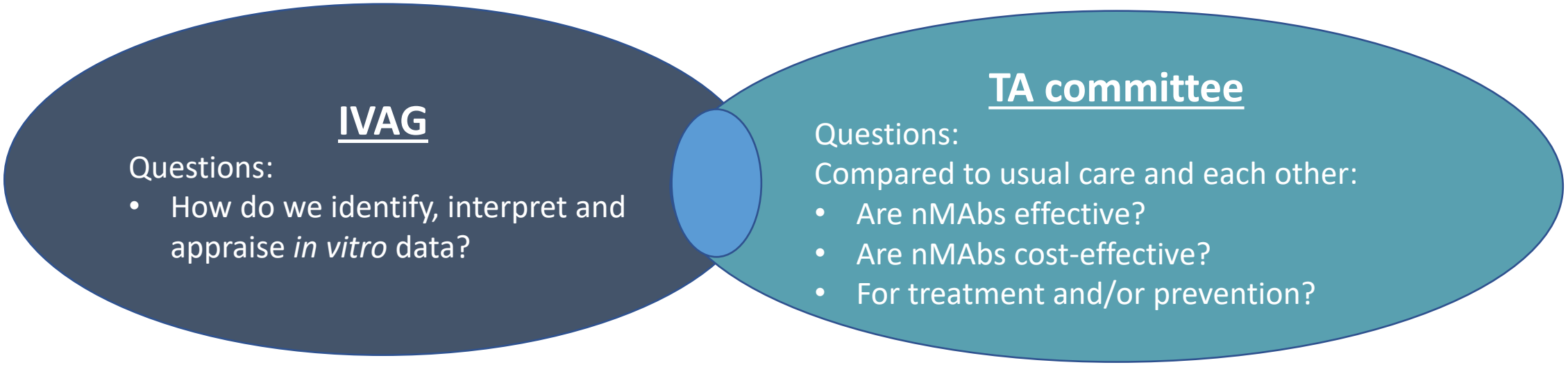
# About the IVAG

| | |
|---|---|
| Amanda Adler (Chair) | Director, Diabetes Trials Unit, University of Oxford |
| David Bauer | Group Leader & Head, RNA Virus Replication Laboratory. The Francis Crick Institute |
| Rupert Beale | Clinician Scientist Group Leader, Consultant Nephrologist, The Francis Crick Institute, UCL Division of Medicine |
| Sanjay Bhangani | Consultant Physician and Honorary Associate Professor, Royal Free Hospital and University College London |
| Neil Ferguson | Director, MRC Centre for Global Infectious Disease Analysis, Imperial College London |
| Neil Hawkins | Professor of Health Technology Assessment, University of Glasgow |
| Mark Jit | Professor of Vaccine Epidemiology, London School of Hygiene and Tropical Medicine |
| Saye Khoo | Professor in Pharmacology, Hon Consultant Physician in Infectious Diseases, University of Liverpool |
| David Lalloo | Director, Liverpool Tropical School of Medicine |
| Siraj Misbah | Consultant Clinical Immunologist, Oxford University NHS Foundation Trust |
| Andrew Owen | Professor of Pharmacology, University of Liverpool |
| Derek Smith | Professor of Infectious Disease Informatics, Zoology Department at Cambridge University |
| David Stuart | MRC Professor of Structural Biology, University of Oxford |
| Mark Sutton | Scientific Leader - Healthcare Biotechnology, and Professor for Antimicrobial Therapy, UKHSA and King's College London |
| Laurie Tomlinson | NIHR Research Professor, Honorary Consultant Nephrologist, London School of Hygiene and Tropical Medicine (Key author on OpenSAFELY data papers) |
| Erik Volz | Reader in Population Biology of Infectious Diseases, Faculty of Medicine, School of Public Health, Imperial College London |

- Four meetings in December chaired by Amanda Adler (previous TAC Chair)
- Expertise in using and understanding COVID-19 clinical, health economic and *in vitro* data
- Various schools of thought including Crick Institute, advisors to the WHO guideline and authors of the OpenSAFELY publications
- Output: interim framework and decision rules for assessing COVID-19 *in vitro* data

# Aim of *In Vitro* Advisory Group, IVAG

*To help technology appraisal committee make reimbursement decision when clinical trial evidence for a 'technology' - monoclonal antibody treatment for COVID – is based on variants no longer circulating*




**Output**

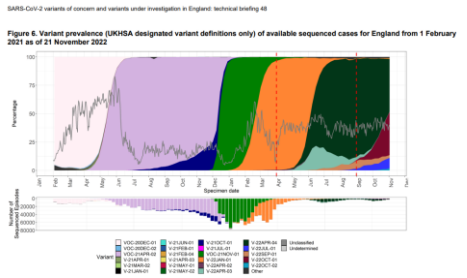
- Framework for linking data from *in vitro* studies of drug neutralisation of different coronavirus variants to clinical outcomes

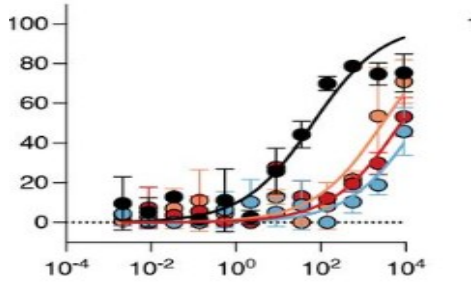
**Output**

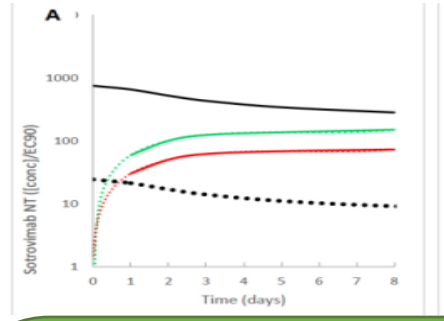
- Recommendations whether or not to recommend that the NHS reimburse nMAbs when clinical trials evidence is generated in a different variant era

nMAbs, neutralising monoclonal antibodies

# Conceptual framework for decision-making






IVAG

Epidemiology – currently circulating variants

*In vitro* neutralisation of drugs in reference variant from RCT vs. current variants

Yes

Data in people
Pharmacokinetic PK
Pharmacodynamic PD

No

*No neutralisation – likely no clinical effect*

NICE TA committee

Clinical outcome e.g. infection rate + hospitalisation

Cost-utility analysis QALY benefit, costs

Decision

◉ *trial data and observational data*

RCT, Randomised controlled trial

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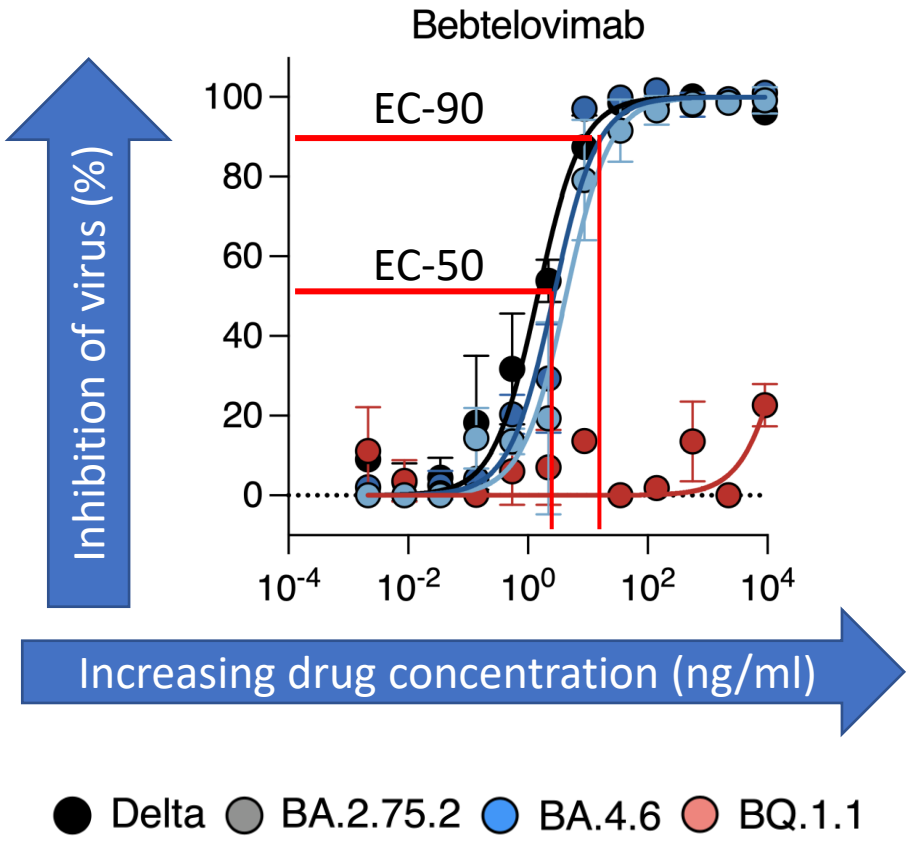
# How to interpret neutralisation curves*




- 1 graph per drug – monoclonal antibody or combinations
- X-axis: (exponential) increasing concentration of the antibody (in ng/ml) as would be expected in serum in people
- Y-axis: neutralising activity as a percentage of virus neutralised in the assay
- Colours reflect different viral variants. Black is reference - one on which clinical trial was conducted
    - For example bebtelovimab does not inhibit BQ.1.1 even at high concentrations
- EC-50 value is concentration needed to neutralise 50% of virus
    - EC-50 used to calculate the 'n-fold differences' between treatments as the most stable point in the dose-response curve
- EC-90 value is concentration needed to neutralise 90% of virus
    - EC-90 used to calculate threshold for efficacy because it represents most of the viral population being neutralised

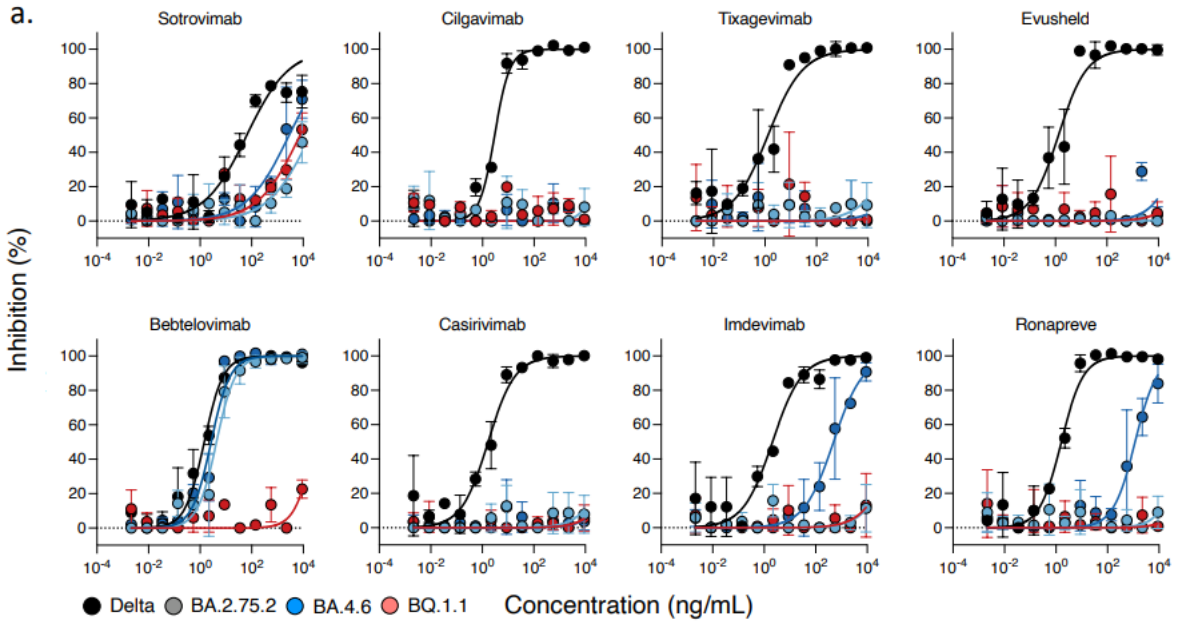
NICE

Planas et al. 2022

* additional slide in appendix

# *In vitro* neutralisation can indicate likely clinical effect

a.




b.

| mAb | D614G | BA.2* | BA.5* | BA.2.75.2 | BQ.1.1 | BA.4.6 |
|---|---|---|---|---|---|---|
| Bebtelovimab | 1.4 | 4.5 | 2 | 4,3 | - | 2,7 |
| Sotrovimab | 65 | 11,519 | 1,088 | 19,391 | 764 | 2,874 |
| Cilgavimab | 2.9 | 6.1 | 11 | - | - | - |
| Tixagevimab | 1.3 | - | - | - | - | - |
| Evusheld | 1,3 | 24.7 | 22.6 | - | - | - |
| Casirivimab | 1.7 | - | - | - | - | - |
| Imdevimab | 2.1 | 1,12 | 208 | - | - | 493 |
| Ronapreve | 1.6 | 1,985 | 700 | - | - | 1,181 |

IC50 (ng/mL)

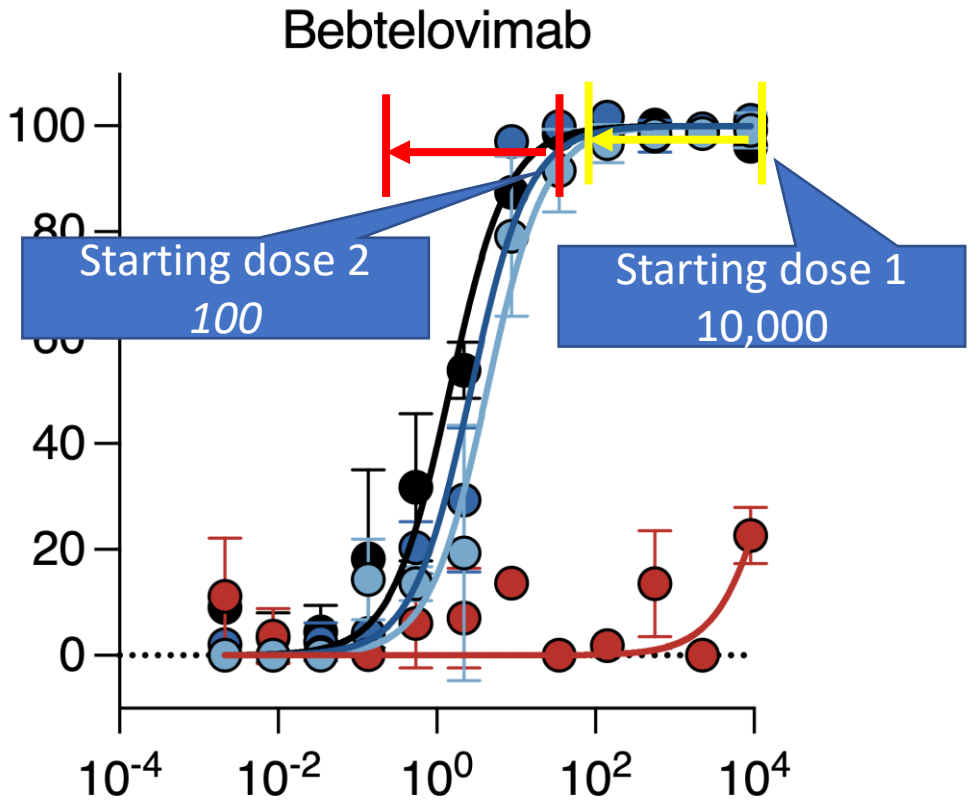
- Neutralisation used to identify promising treatments
- For each new variant, neutralisation assays of existing drugs can inform clinical effect
- A complete loss of neutralisation activity against a variant (no inhibition, even at supraphysiological doses) likely means no clinical effect
- NMAbs are dose-linear; if dose doubled then serum concentration doubled
- Reduced neutralisation: increased dose may maintain neutralisation
  - Requires PK/PD data in humans to understand the relationship to clinical efficacy
- Effector functions of nMAbs – effects beyond neutralisation- are hypothesised to have an additional effect, but little known about mechanism of action.

PK, Pharmacokinetic; PD, Pharmacodynamic

Planas *et al*. 2022

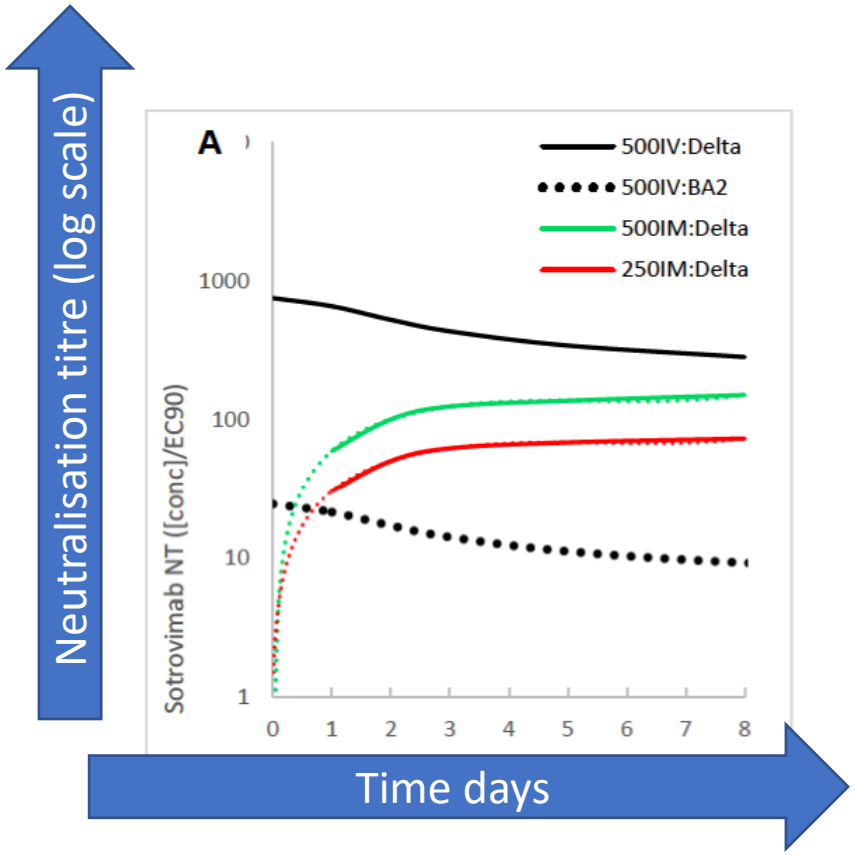
# PK/PD data needed to understand drug concentration in people

- *Dose available in the appropriate tissue (for example lung) unknown but is necessary to understand if there will be a change in efficacy*




- It is not possible to estimate neutralisation in people from *in vitro* neutralisation curves – this requires pharmacokinetic studies of licensed doses
- N-fold change alone cannot determine effectiveness. Consider a 100-fold change in neutralisation:
  - If licensed dose from RCT were dose 1, this would likely have minimal impact on clinical outcomes as there is still neutralisation activity
  - If licensed dose from RCT were dose 2, this would likely mean no clinical benefit
- There are 2 methods for this:
  - Dose-failure benchmarks - IVAG prefers
  - Adjusting serum drug concentrations to tissue

# How to interpret neutralising titres in people*



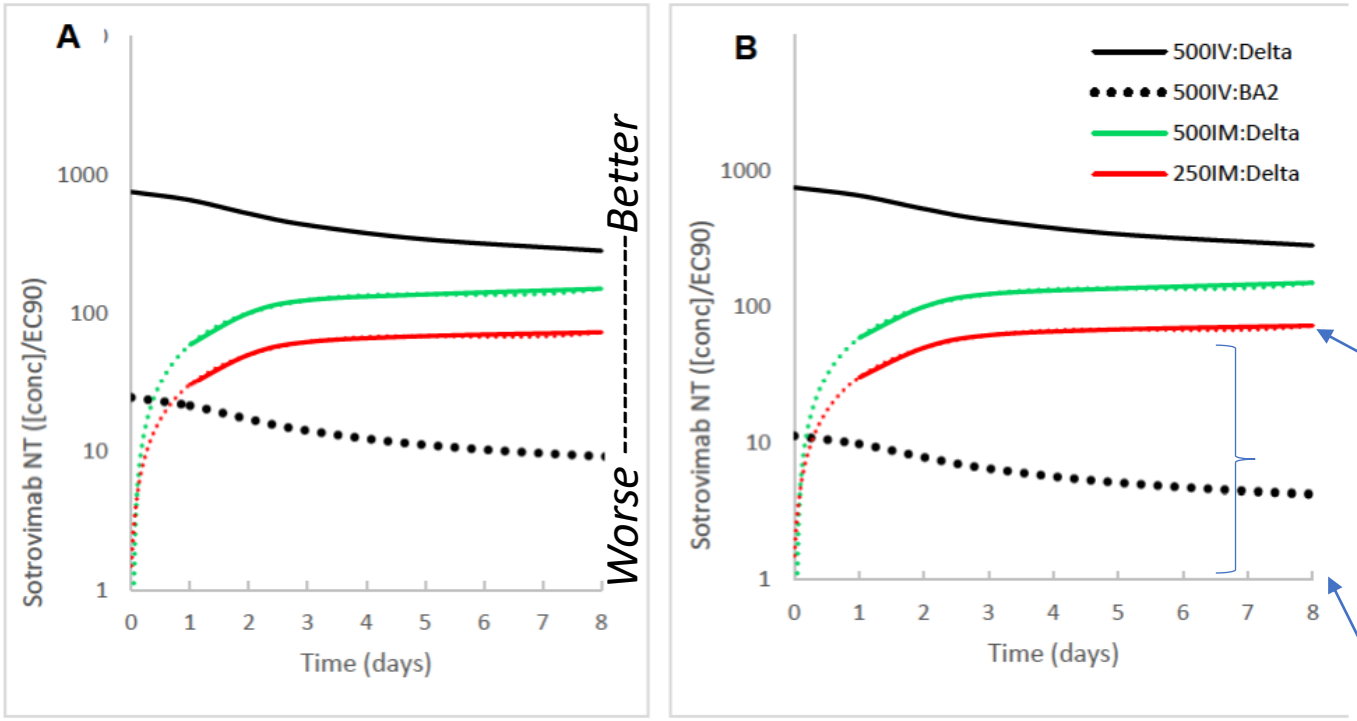

- Antibody titres - a test that determines the presence and level (titre) of antibodies in blood
- Example:  sotrovimab
- Curves are 3 different dosages of drug for delta variant(solid) and 1 dose for omicron BA.2 (dotted)
- X-axis is time
- Y-axis is neutralisation titre
  - defined as concentration of sotrovimab ÷ by concentration needed to neutralise 90% of virus
- Interpretation i.e. 500 mg IV treatment (black) shows higher number of antibodies in serum from administration, whereas 500 mg IM (green) takes longer to reach a steady level
- May need different neutralisation titres for treating or preventing COVID
- An n-fold reduction in neutralisation activity would result in the same reduction in neutralisation titre

*Source: https://www.fda.gov/media/157556/download*

# Identifying when a reduced dose worsens clinical outcomes*

*FDA has used trial to identify 'benchmarks'*

**Figure 3. Sotrovimab Neutralization Titers (NT) Based on Various Sotrovimab IV and IM Doses Normalized to $EC_{90}$ Values for Delta Variant and BA.2 Subvariant**




Note: Sotrovimab NT = sotrovimab concentration/(sub)variant EC90. Sotrovimab median PK exposures were generated from the values provided from various studies provided by the Sponsor (500 mg IV: BLAZE-4, COMET-PEAK, Japan-PK; 250 mg and 500 mg IM: COMET-TAIL); 250 mg IM (red) and 500 mg IM (green) dotted lines on Days 0-1 are projected median exposures. **Figure A** includes the BA.2 $EC_{90}$ value of ~6,800 ng/mL, and **Figure B** includes the BA.2 $EC_{90}$ value of 14,800 ng/mL. Delta $EC_{90}$ value is ~220 ng/mL (provided by the Sponsor).

*Source: https://www.fda.gov/media/157556/download*

- COMET-TAIL trial compared sotrovimab 500 mg IM vs 500 mg IV during Delta wave;
  the 250 mg IM cohort was terminated because of a higher rate of hospitalisation and death

Therefore, FDA assumed that 250 mg IM against Delta variant as a benchmark of suboptimal clinical efficacy

FDA assumed suboptimal clinical efficacy against BA.2 because n-fold adjusted neutralisation titre values of 500 mg IV for BA.2 (black dotted line) even lower that the 250 mg IM values against delta (lower than benchmarked dose failure)

# Summary of IVAG discussions

- Difficult to predict viral evolution and likely prevalence of future new variants that cause COVID
- Circulating variants in near future likely related to currently circulating variants with the same mutations that may reduce effectiveness
- In general, reduced effectiveness over time as new variants evolve
- It is possible to determine an association between *in vitro* neutralisation data and clinical outcomes
    - Clear when no neutralisation, no clinical benefit
    - If there is reduced neutralisation of a new variant compared to variant prevalent during a randomised trial for which evidence is available, neutralisation data alone is not enough to conclude that effect estimates seen in the trial is generalisable to new variant– this requires PK/PD data
    - Most appropriate method of estimating clinical effect is identifying when a dose fails to provide benefit and matching this to an expected reduction in neutralisation

# Section 1 Data relevant to both appraisals

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    - BQ.1, BQ.1.1, XBB (earlier BA.5)
- Position of various organisations

# Efficacy of Antibodies and Antiviral Drugs against Omicron BA.2.12.1, BA.4, and BA.5 Subvariants

**Table 1. Efficacy of Monoclonal Antibodies and Antiviral Drugs against Omicron Subvariants in Vitro.***

| Subvariant | Mean Neutralization Activity of Monoclonal Antibody† | | | | | | | | Susceptibility to Antiviral Drug‡ | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Imdevimab | Casirivimab | Tixagevimab | Cilgavimab | Sotrovimab Precursor | Bebtelovimab | Imdevimab+ Casirivimab | Tixagevimab+ Cilgavimab | Remdesivir | Molnupiravir | Nirmatrelvir |
| | *ng per milliliter* | | | | | | | | | *μmol* | |
| Reference§ | 7.4 | 6.1 | 6.1 | 7.0 | 95.1 | 2.5 | 3.4 | 6.3 | 1.7 | 2.8 | 2.7 |
| BA.1 | >50,000 | >50,000 | 1552.7 | 2916.9 | 40727.1 | 5.8 | >10,000 | 351.1 | 1.9 | 7.5 | 4.8 |
| BA.1.1 | >50,000 | >50,000 | 603.5 | >50,000 | 3769.2 | 3.9 | >10,000 | 1296.8 | 2.0 | 6.0 | 3.9 |
| BA.2 | 329.0 | >50,000 | 2756.6 | 16.9 | >50,000 | 3.3 | 835.1 | 34.6 | 5.9 | 8.7 | 6.9 |
| BA.2.12.1 | 238.1 | >50,000 | 335.2 | 21.0 | >50,000 | 4.0 | 452.7 | 38.1 | 0.5 | 3.2 | 1.8 |
| BA.4 | 132.6 | >50,000 | >50,000 | 53.6 | >50,000 | 2.9 | 459.1 | 37.8 | 1.2 | 3.3 | 2.9 |
| BA.5 | 583.4 | >50,000 | >50,000 | 56.8 | >50,000 | 3.3 | 1093.1 | 192.5 | 2.0 | 4.1 | 4.4 |

* The antibodies that were used in this analysis are listed by their commercial names for readability although they were produced in the authors' laboratories in their generic formulations. Omicron subvariants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are listed according to the World Health Organization labels for the Pango lineage.
† Individual monoclonal antibodies were tested at a starting concentration of 50,000 ng per milliliter on 50% focus reduction neutralization testing. The monoclonal antibody combinations were tested at a starting concentration of 10,000 ng per milliliter for each antibody.
‡ The susceptibility to antiviral drugs was measured as the 50% inhibitory concentration of the mean micromole value of triplicate reactions. GS-441524 is the main metabolite of remdesivir and EIDD-1931 is the active form of molnupiravir, both of which are RNA-dependent RNA polymerase inhibitors. Nirmatrelvir (PF-07321332) is a protease inhibitor.
§ The reference strain was SARS-CoV-2/UT-NC002–1T/Human/2020/Tokyo.

N Engl J Med 2022; 387:468-470. DOI: 10.1056/NEJMc2207519

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# Wu (Crick group), 6th Oct 2022
# WHO's Therapeutics and COVID-19 Living Guideline on mAbs needs to be reassessed

- "At present there is an unrealistically high threshold to enter a therapeutic agent into clinical practice. The threshold to withhold or withdraw the same agent is much lower when based on *in vitro* evidence for loss of potency alone.

- Such a situation disproportionately affects vulnerable patients whose other essential medications or comorbidities exclude COVID-19 therapeutics other than a neutralising mAb.

- This situation also strongly disincentivises development of novel antivirals that are needed to continue to offer protection to highly vulnerable populations."

No BQs or XBBs in this paper

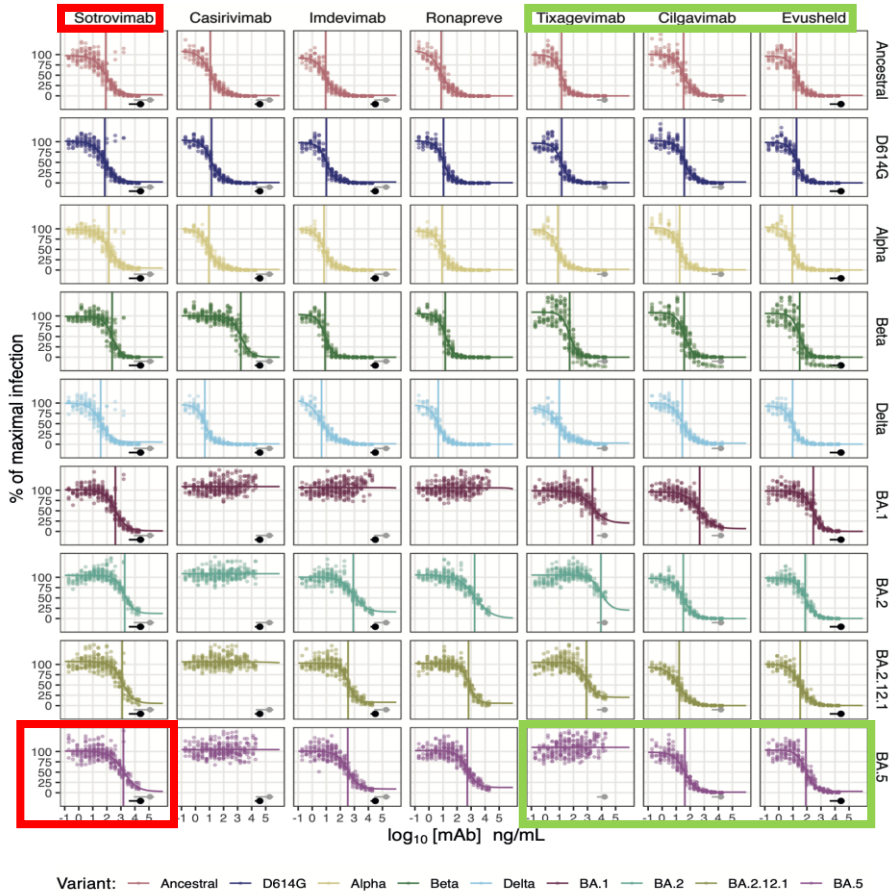


**Figure 1. Neutralisation of SARS-CoV-2 variants by monoclonal antibodies (mAbs).** For each combination of mAb and SARS-CoV-2 variant, 288 independent data points are shown, which were generated from 3 independent repeats of 12 independent titrations, each consisting of 2 technical replicates of a 4-point dilution series against live SARS-CoV-2 virus. **$EC_{50}$** values (solid vertical lines) by were calculated fitting a 4-parameter dose-response curve (solid curves) to this data. For each mAb, the mean serum concentration at maximum (grey point) and twice its standard deviation (grey error line), and at 28 days post-administration (black points) and twice its standard deviation (black error line) was obtained from its Summary of Product Characteristics (see Table 3) and plotted here for reference.



www.thelancet.com Published online October 6, 2022 https://doi.org/10.1016/S0140-6736(22)01938-9

# Recent papers on BQ.1, BQ.1.1, XBB

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

## Efficacy of Antiviral Agents against Omicron Subvariants BQ.1.1 and XBB



## Resistance of Omicron subvariants BA.2.75.2, BA.4.6 and BQ.1.1 to neutralizing antibodies

Delphine Planas[1,2#], Timothée Bruel[1,2], Isabelle Staropoli[1], Florence Guivel-Benhassine[1], Françoise Porrot[1], Piet Maes[3], Ludivine Grzelak[1], Matthieu Prot[4], Said Mougari[4], Cyril Planchais[5], Julien Puech[6], Madelina Saliba[6], Riwan Sahraoui[6], Florent Fémy[7], Nathalie Morel[8], Jérémy Dufloo[9], Rafael Sanjuán[9,10], Hugo Mouquet[5], Emmanuel André[11,12], Laurent Hocqueloux[13], Etienne Simon-Loriere[4], David Veyer[6,14], Thierry Prazuck [13*], Hélène Péré[6,14**] & Olivier Schwartz[1,2#*]

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[2]Vaccine Research Institute, Créteil, France.
[3]KU Leuven, Department of Microbiology, Immunology and Transplantation, Laboratory of Clinical and Epidemiological Virology, Leuven, Belgium.
[4]G5 Evolutionary Genomics of RNA Viruses, Institut Pasteur, Université Paris Cité, Paris, France.
[5]Humoral Immunology Laboratory, Institut Pasteur, Université Paris Cité, INSERM U1222, Paris, France.
[6]Laboratoire de Virologie, Service de Microbiologie, Hôpital Européen Georges Pompidou, Paris, France.
[7]Service d'accueil des urgences, Hôpital Européen Georges Pompidou, Paris, France.
[8]Service de Pharmacologie et Immunoanalyse (SPI), CEA, INRA, Université Paris-Saclay, F-91191 Gif-sur Yvette, France
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[10]Department of Genetics, Universitat de València, València, Spain.
[11]University Hospitals Leuven, Department of Laboratory Medicine, National Reference Centre for Respiratory Pathogens, Leuven, Belgium.
[12]KU Leuven, Department of Microbiology, Immunology and Transplantation, Laboratory of Clinical Microbiology, Leuven, Belgium.
[13]CHR d'Orléans, Service de Maladies Infectieuses, Orléans, France.
[14]Functional Genomics of Solid Tumors (FunGeST), Centre de Recherche des Cordeliers, INSERM, Université de Paris, Sorbonne Université, Paris, France.



### Omicron sublineage BQ.1.1 resistance to monoclonal antibodies

Vaccination represents the key strategy to control the COVID-19 pandemic through induction of neutralising antibody responses and T cell-associated immunity that substantially decrease the risk of developing severe disease.[1,2] However, individuals who are immunocompromised (eg, because of comorbidities, high age, or immunosuppressive treatment) might not mount a full adaptive immune response and thus remain susceptible.

For individuals at high risk, individual monoclonal antibodies (mAbs) or cocktails of mAbs are administered as prophylaxis or therapy.[3,4] All mAbs currently approved by the US Food and Drug Administration (FDA) or European Medicines Agency (EMA) target the spike (S) protein (appendix pp 1–2).[5] During the course of the COVID-19 pandemic, several SARS-CoV-2 lineages evolved mutations that confer partial or full resistance against some mAbs.[6–9] Consequently, only few mAbs remain suitable for treatment of individuals at high risk, and only bebtelovimab shows high efficacy against multiple omicron sublineages.[8]

However, novel omicron sublineages have been detected, harbouring additional S protein mutations within the epitopes of bebtelovimab and other mAbs (figure A; appendix p 11). Novel sublineages include BA.4.6 (with increasing incidence in several countries worldwide), BA.2.75.2 (with increasing incidence in India), BJ.1 (mainly observed in India and Bangladesh; notably BJ.1 is one parental lineage of the currently increasing XBB recombinant), and BQ.1.1 (with increasing incidence in the USA and Europe).

We compared neutralisation of omicron sublineages BA.1, BA.4–5

Lancet Infect Dis 2022
Published Online November 18, 2022 https://doi.org/10.1016/S1473-3099(22)00733-2

See Online for appendix

nature
https://doi.org/10.1038/s41586-022-05644-7
Accelerated Article Preview

## Imprinted SARS-CoV-2 humoral immunity induces convergent Omicron RBD evolution

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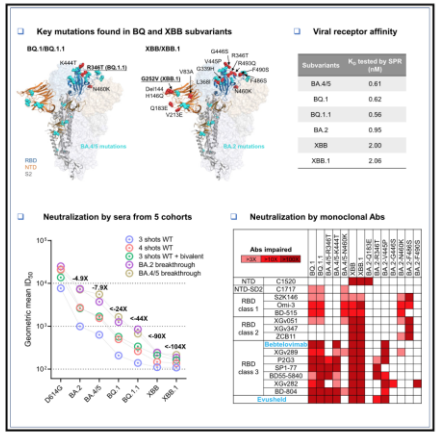
Yunlong Cao, Fanchong Jian, Jing Wang, Yuanling Yu, Weiliang Song, Ayijiang Yisimayi, Jing Wang, Ran An, Xiaosu Chen, Na Zhang, Yao Wang, Peng Wang, Lijuan Zhao, Haiyan Sun, Lingling Yu, Sijie Yang, Xiao Niu, Tianhe Xiao, Qingqing Gu, Fei Shao, Xiaohua Hao, Yanli Xu, Ronghua Jin, Zhongyang Shen, Youchun Wang & Xiaoliang Sunney Xie



Cell
Article

## Alarming antibody evasion properties of rising SARS-CoV-2 BQ and XBB subvariants

### Graphical abstract

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### In brief

Recent BQ and XBB subvariants of SARS-CoV-2 demonstrate dramatically increased ability to evade neutralizing antibodies, even those from people who received the bivalent mRNA booster or who are immunized and had previous breakthrough Omicron infection. Additionally, both BQ and XBB are completely resistant to bebtelovimab, meaning there are now no clinically authorized therapeutic antibodies effective against these circulating variants.

# Recent papers on BQ.1, BQ.1.1 or XBB*

| Lead | Title | Date | Journal | Origin | Link |
|---|---|---|---|---|---|
| Planas | Resistance of Omicron subvariants BA.2.75.2, BA.4.6 and BQ.1.1 to neutralizing antibodies | 17th November 2022 | bioRχiv (preprint) | Paris | https://pubmed.ncbi.nlm.nih.gov/36415455/ |
| Arora | Omicron sublineage BQ.1.1 resistance to monoclonal antibodies | 18th November 2022 | Lancet Infect Dis | Göttingen | https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(22)00733-2/fulltext |
| Wang | Alarming antibody evasion properties of rising SARS- CoV-2 BQ and XBB subvariants | 14th December 2022 | Cell | New York | https://www.sciencedirect.com/science/article/pii/S0092867422015318 |
| Cao | Imprinted SARS-CoV-2 humoral immunity induces convergent Omicron RBD evolution | 19th December 2022 | Nature | Beijing | https://www.nature.com/articles/s41586-022-05644-7 |
| Imai | Efficacy of Antiviral Agents against Omicron Subvariants BQ.1.1 and XBB | 5th January 2023 | NEJM | Tokyo | https://www.nejm.org/doi/full/10.1056/NEJMc2214302 |

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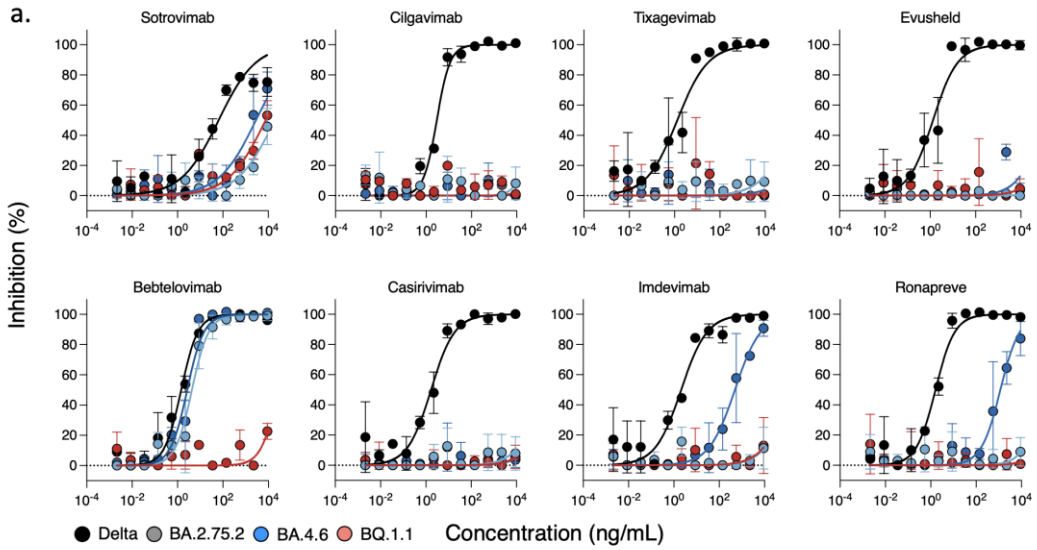
* additional slide in appendix

# 1/5 **Planas**. Resistance of Omicron subvariants BA.2.75.2, BA.4.6 and BQ.1.1 to neutralizing antibodies

a.




b.

| mAb | D614G | BA.2* | BA.5* | BA.2.75.2 | BQ.1.1 | BA.4.6 |
|---|---|---|---|---|---|---|
| Bebtelovimab | 1.4 | 4.5 | 2 | 4,3 | - | 2,7 |
| Sotrovimab | 65 | 11,519 | 1,088 | 19,391 | 764 | 2,874 |
| Cilgavimab | 2.9 | 6.1 | 11 | - | - | - |
| Tixagevimab | 1.3 | - | - | - | - | - |
| Evusheld | 1,3 | 24.7 | 22.6 | - | - | - |
| Casirivimab | 1.7 | - | - | - | - | - |
| Imdevimab | 2.1 | 1,12 | 208 | - | - | 493 |
| Ronapreve | 1.6 | 1,985 | 700 | - | - | 1,181 |
| | | | | | | IC50 (ng/mL) |

**Figure 3. Neutralization activity of therapeutic monoclonal antibodies against BQ.1.1, BA.2.75.2 and BA.4.6. a.** Neutralization curves of monoclonal antibodies. Dose–response analysis of the neutralization by the indicated antibodies or their clinical combinations. Evusheld: Cilgavimab and Tixagevimab. Ronapreve: Casirivimab and Imdevimab. Data are mean ± s.d. of 2 independent experiments. **b**. IC50 values in ng/ mL for each antibody against the indicated viral strains. *ED50 against BA.2 and BA.5 are from [47].

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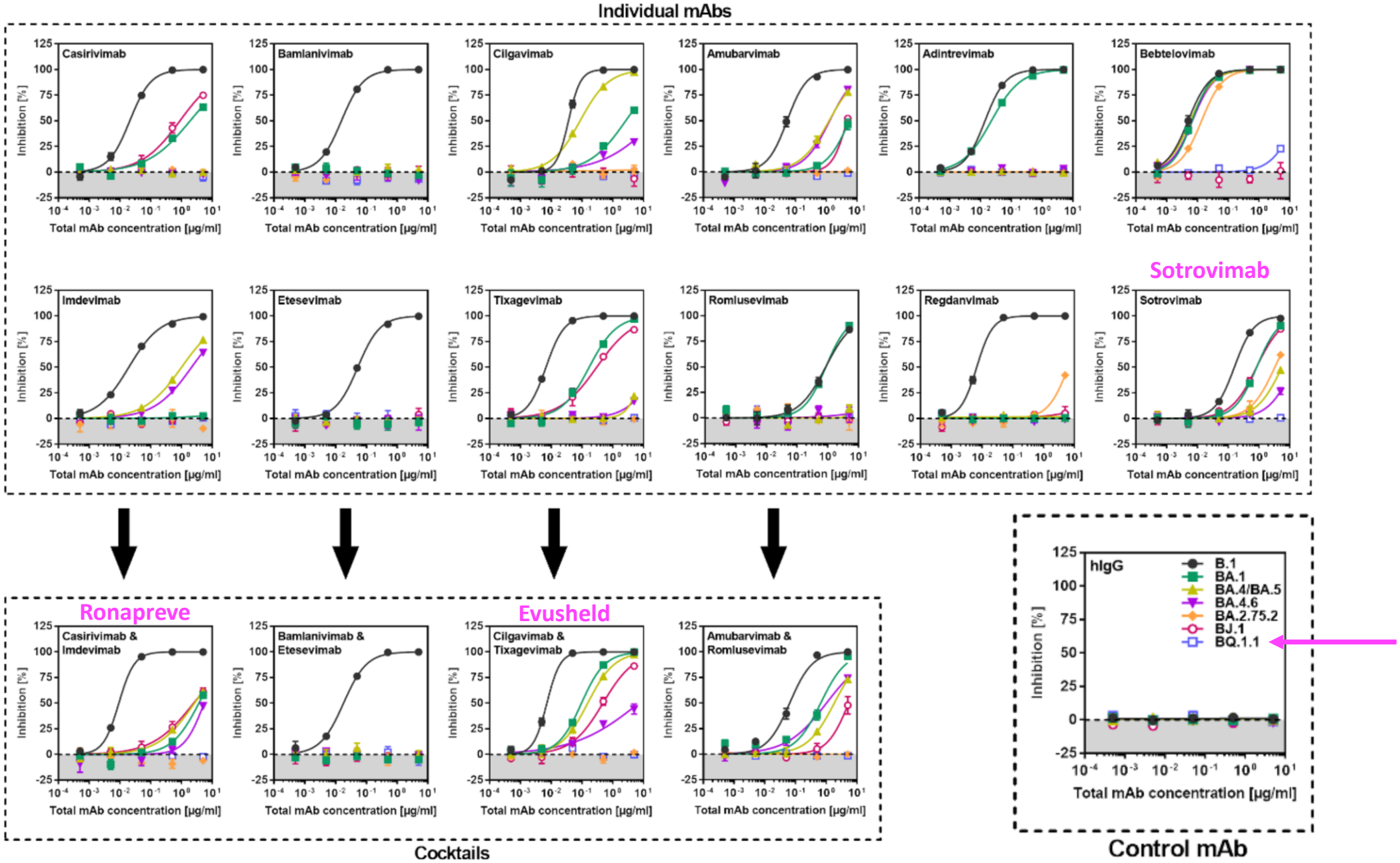
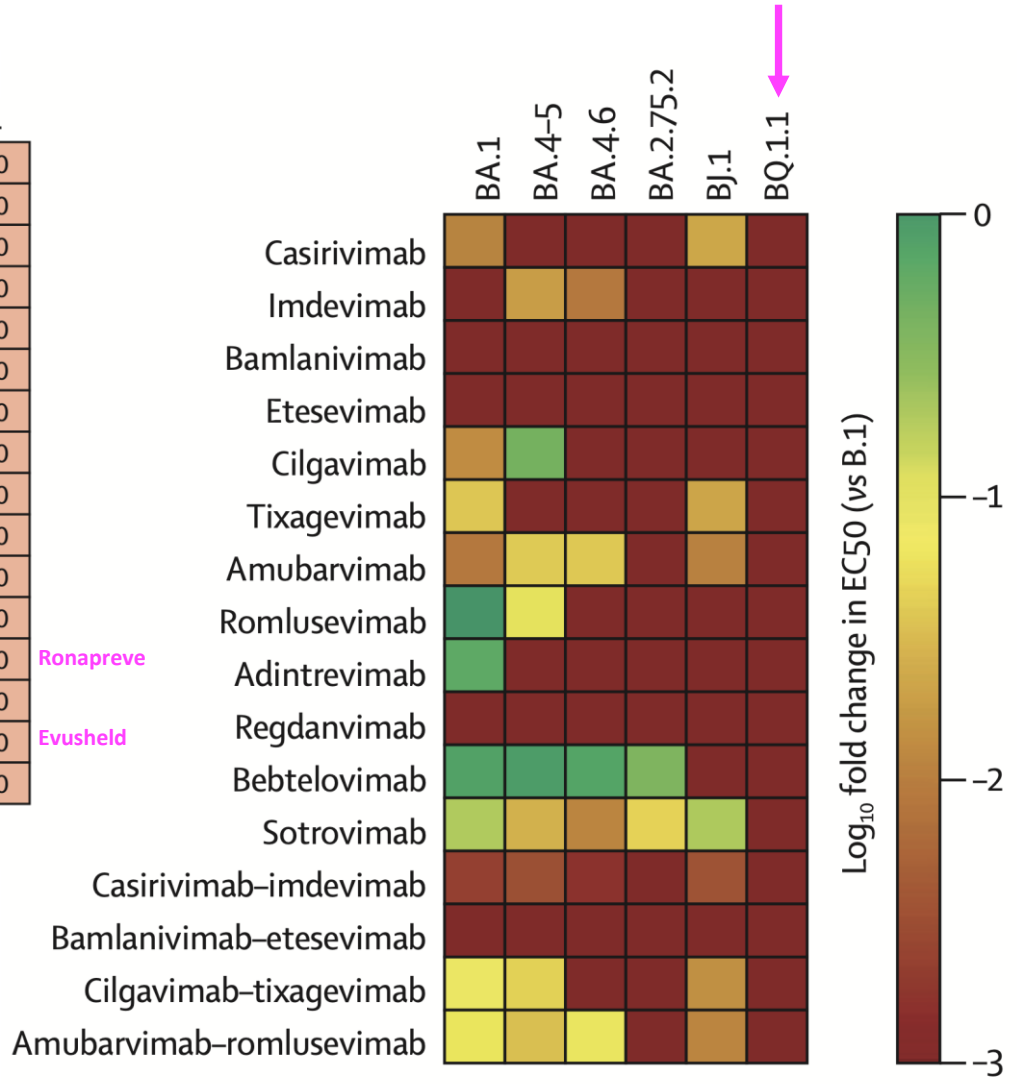
# 2/5 **Arora**. Omicron sublineage BQ.1.1 resistance to monoclonal antibodies



# 2/5 **Arora**. Omicron sublineage BQ.1.1 resistance to monoclonal antibodies

| | | B.1 | BA.1 | BA.4–5 | BA.4.6 | BA.2.75.2 | BJ.1 | BQ.1.1 | |
|---|---|---|---|---|---|---|---|---|---|
| Single mAbs | Casirivimab | 21 | 1890 | >50000 | >50000 | >50000 | 880 | >50000 | |
| | Imdevimab | 19 | >50000 | 994 | 2109 | >50000 | >50000 | >50000 | |
| | Bamlanivimab | 16 | >50000 | >50000 | >50000 | >50000 | >50000 | >50000 | |
| | Etesevimab | 53 | >50000 | >50000 | >50000 | >50000 | >50000 | >50000 | |
| | Cilgavimab | 37 | 2658 | 88 | 24200 | >50000 | >50000 | >50000 | |
| | Tixagevimab | 7 | 173 | 10090 | 27740 | >50000 | 304 | >50000 | |
| | Amubarvimab | 53 | 5641 | 1234 | 1290 | >50000 | 4762 | >50000 | |
| | Romlusevimab | 852 | 866 | 8279 | >50000 | >50000 | >50000 | >50000 | |
| | Adintrevimab | 14 | 23 | >50000 | >50000 | >50000 | >50000 | >50000 | |
| | Regdanvimab | 7 | >50000 | >50000 | >50000 | 6336 | >50000 | >50000 | |
| | Bebtelovimab | 5 | 7 | 6 | 7 | 14 | >50000 | >50000 | |
| | Sotrovimab | 157 | 833 | 5554 | 13000 | 3239 | 825 | >50000 | |
| Cocktails of mAbs | Casirivimab–imdevimab | 9 | 3642 | 2611 | 5395 | >50000 | 2456 | >50000 | Ronapreve |
| | Bamlanivimab–etesevimab | 18 | >50000 | >50000 | >50000 | >50000 | >50000 | >50000 | |
| | Cilgavimab–tixagevimab | 7 | 97 | 155 | 7131 | >50000 | 482 | >50000 | Evusheld |
| | Amubarvimab–romlusevimab | 64 | 657 | 1819 | 1015 | >50000 | 5359 | >50000 | |

EC50 (ng/ml)



# 3/5 **Wang**. Alarming antibody evasion properties of rising SARS- CoV-2 BQ and XBB subvariants

| IC50 (μg/ml) | NTD | NTD-SD2 | SD1 | RBD Class 1 | | | | RBD Class 2 | | | | RBD Class 3 | | | | | | | | | | | RBD Class 4 | Evusheld |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | C1520 | C1717 | S3H3 | S2K146 | Omi-3 | Omi-18 | BD-515 | XGv051 | XGv347 | ZCB11 | COV2-2196 | LY-CoV1404 | XGv289 | XGv264 | S309 | P2G3 | SP1-77 | BD55-5840 | XGv282 | BD-804 | 35B5 | COV2-2130 | 10-40 | |
| D614G | 0.002 | 0.125 | 0.022 | 0.004 | 0.004 | 0.012 | 0.010 | 0.001 | 0.002 | 0.002 | 0.002 | 0.002 | 0.002 | 0.001 | 0.023 | 0.001 | 0.003 | 0.002 | 0.001 | 0.011 | 0.014 | 0.007 | 0.049 | 0.003 |
| BA.4/5 | 0.001 | 0.209 | 0.014 | 0.090 | 0.023 | 0.013 | 0.010 | 0.050 | 3.450 | 4.868 | >10 | 0.001 | 0.038 | 0.002 | 0.514 | 0.002 | 0.005 | 0.009 | 0.001 | 0.019 | >10 | 0.021 | 2.414 | 0.035 |
| BQ.1 | 0.001 | 0.666 | 0.019 | 0.585 | 0.860 | 0.131 | 0.343 | 0.159 | 2.830 | >10 | >10 | >10 | 0.425 | 0.494 | 0.600 | 1.608 | >10 | 0.034 | 0.020 | >10 | >10 | >10 | >10 | >10 |
| BQ.1.1 | 0.003 | 1.117 | 0.025 | 0.527 | 0.804 | 0.170 | 0.377 | 0.191 | 3.311 | >10 | >10 | >10 | 1.013 | >10 | 2.140 | >10 | >10 | >10 | 0.098 | >10 | >10 | >10 | >10 | >10 |
| BA.4/5-R346T | 0.002 | 0.141 | 0.020 | 0.081 | 0.019 | 0.009 | 0.006 | 0.042 | 2.166 | 2.560 | >10 | 0.001 | 0.045 | 0.003 | 1.726 | 0.041 | >10 | 1.447 | 0.001 | >10 | >10 | >10 | 5.069 | >10 |
| BA.4/5-K444T | 0.002 | 0.116 | 0.009 | 0.104 | 0.016 | 0.010 | 0.006 | 0.040 | 4.766 | 3.731 | >10 | >10 | 0.161 | 0.273 | 0.552 | 1.245 | 4.007 | 0.038 | 0.006 | >10 | >10 | >10 | 6.976 | >10 |
| BA.4/5-N460K | 0.002 | 1.166 | 0.016 | 0.542 | 1.279 | 0.186 | 0.431 | 0.152 | 3.046 | >10 | >10 | 0.002 | 0.353 | 0.003 | 0.934 | 0.003 | 0.009 | 0.012 | 0.002 | 0.122 | >10 | 0.030 | >10 | 0.063 |
| BA.2 | 0.002 | 0.561 | 0.016 | 0.028 | 0.015 | 0.005 | 0.012 | 0.001 | 0.003 | 0.012 | 1.924 | 0.001 | 0.067 | 0.003 | 0.833 | 0.002 | 0.006 | 0.014 | 0.001 | 0.038 | 0.827 | 0.009 | 8.770 | 0.019 |
| XBB | >10 | 0.836 | 0.016 | 0.223 | 1.181 | 0.468 | 0.555 | >10 | >10 | >10 | >10 | >10 | >10 | >10 | 0.343 | >10 | >10 | >10 | >10 | >10 | >10 | >10 | >10 | >10 |
| XBB.1 | >10 | 0.693 | 0.019 | 0.190 | 1.705 | 0.605 | 0.803 | >10 | >10 | >10 | >10 | >10 | >10 | >10 | 0.405 | >10 | >10 | >10 | >10 | >10 | >10 | >10 | >10 | >10 |
| BA.2-V83A | 0.001 | 0.354 | 0.015 | 0.036 | 0.019 | 0.007 | 0.015 | 0.002 | 0.003 | 0.013 | 3.039 | 0.001 | 0.070 | 0.002 | 0.641 | 0.002 | 0.007 | 0.019 | 0.001 | 0.045 | 1.274 | 0.011 | >10 | 0.025 |
| BA.2-Del144 | 0.002 | 0.501 | 0.011 | 0.026 | 0.016 | 0.004 | 0.011 | 0.002 | 0.002 | 0.008 | 4.134 | 0.001 | 0.063 | 0.002 | 0.455 | 0.002 | 0.005 | 0.014 | 0.001 | 0.031 | 0.341 | 0.010 | 8.766 | 0.021 |
| BA.2-H146Q | 0.001 | 0.356 | 0.011 | 0.032 | 0.011 | 0.004 | 0.009 | 0.002 | 0.002 | 0.010 | 2.924 | 0.002 | 0.055 | 0.002 | 0.641 | 0.003 | 0.007 | 0.019 | 0.001 | 0.044 | 1.107 | 0.009 | 9.106 | 0.019 |
| BA.2-Q183E | 0.322 | 0.307 | 0.019 | 0.034 | 0.018 | 0.006 | 0.014 | 0.002 | 0.003 | 0.013 | 3.098 | 0.001 | 0.067 | 0.003 | 0.649 | 0.002 | 0.008 | 0.020 | 0.002 | 0.028 | 1.019 | 0.011 | 9.251 | 0.022 |
| BA.2-V213E | 0.002 | 0.406 | 0.013 | 0.030 | 0.014 | 0.004 | 0.010 | 0.002 | 0.002 | 0.006 | 2.177 | 0.001 | 0.047 | 0.003 | 0.720 | 0.002 | 0.006 | 0.014 | 0.001 | 0.026 | 1.247 | 0.009 | 8.198 | 0.018 |
| BA.2-G252V | 0.001 | 0.577 | 0.013 | 0.030 | 0.012 | 0.004 | 0.008 | 0.002 | 0.003 | 0.008 | 2.258 | 0.001 | 0.048 | 0.002 | 0.564 | 0.002 | 0.005 | 0.012 | 0.001 | 0.032 | 0.939 | 0.011 | >10 | 0.026 |
| BA.2-G339H | 0.001 | 0.485 | 0.017 | 0.034 | 0.020 | 0.006 | 0.012 | 0.002 | 0.002 | 0.010 | 3.876 | 0.002 | 0.114 | 0.002 | 0.302 | 0.002 | 0.007 | 0.040 | 0.002 | 0.050 | 0.661 | 0.012 | 8.575 | 0.023 |
| BA.2-R346T | 0.003 | 0.372 | 0.012 | 0.017 | 0.010 | 0.003 | 0.007 | 0.001 | 0.002 | 0.007 | 2.109 | 0.002 | 0.048 | 0.004 | 1.433 | 0.007 | >10 | 1.442 | 0.001 | 0.112 | >10 | >10 | 7.767 | 1.486 |
| BA.2-L368I | 0.003 | 0.453 | 0.019 | 0.027 | 0.010 | 0.004 | 0.010 | 0.002 | 0.001 | 0.006 | 2.603 | 0.001 | 0.030 | 0.002 | 0.605 | 0.002 | 0.005 | 0.021 | 0.001 | 0.026 | 0.324 | 0.008 | 3.202 | 0.018 |
| BA.2-V445P | 0.001 | 0.433 | 0.019 | 0.026 | 0.009 | 0.004 | 0.009 | 0.002 | 0.002 | 0.008 | 2.313 | >10 | >10 | 1.141 | 0.428 | >10 | 0.007 | 0.144 | >10 | 1.582 | 0.486 | >10 | 6.311 | 3.135 |
| BA.2-G446S | 0.002 | 0.367 | 0.012 | 0.021 | 0.009 | 0.004 | 0.009 | 0.001 | 0.003 | 0.008 | 2.614 | 0.002 | 0.026 | 0.004 | 0.686 | 0.002 | 0.004 | 0.014 | 0.022 | 0.026 | 0.965 | 0.017 | 5.774 | 0.029 |
| BA.2-N460K | 0.002 | 1.323 | 0.012 | 0.132 | 0.784 | 0.013 | 0.358 | 0.007 | 0.004 | 0.073 | 1.756 | 0.001 | 0.355 | 0.003 | 0.878 | 0.002 | 0.011 | 0.017 | 0.001 | 0.058 | 1.957 | 0.013 | >10 | 0.025 |
| BA.2-F486S | 0.002 | 0.677 | 0.008 | >10 | 0.583 | 0.011 | 0.017 | >10 | >10 | >10 | >10 | 0.001 | 0.049 | 0.003 | 0.581 | 0.002 | 0.006 | 0.009 | 0.002 | 0.060 | 2.264 | 0.011 | >10 | 0.023 |
| BA.2-F490S | 0.001 | 0.428 | 0.014 | 0.022 | 0.033 | 0.004 | 0.008 | 0.001 | 0.004 | 0.012 | 1.105 | 0.001 | 0.030 | 0.002 | 0.564 | 0.002 | 0.006 | 0.011 | >10 | 0.048 | >10 | 0.013 | 5.337 | 0.016 |
| BA.2-R493Q | 0.003 | 0.338 | 0.024 | 0.005 | 0.006 | 0.006 | 0.006 | 0.001 | 0.001 | 0.002 | 0.034 | 0.001 | 0.045 | 0.002 | 1.109 | 0.002 | 0.007 | 0.022 | 0.000 | 0.010 | 1.175 | 0.010 | 3.419 | 0.008 |

| >10 | 1-10 | 0.1-1 | 0.01-0.1 | <0.01 |
|---|---|---|---|---|

**Figure S2. Pseudovirus neutralization $IC_{50}$ values for mAbs against BQ and XBB subvariants and point mutants, related to Figure 3**

Pseudovirus neutralization $IC_{50}$ values for mAbs against D614G, Omicron subvariants, and point mutants of BQ.1, BQ.1.1, XBB, and XBB.1 in the background of BA.4/5 or BA.2.

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# 4/5 **Cao**. Imprinted SARS-CoV-2 humoral immunity induces convergent Omicron RBD evolution

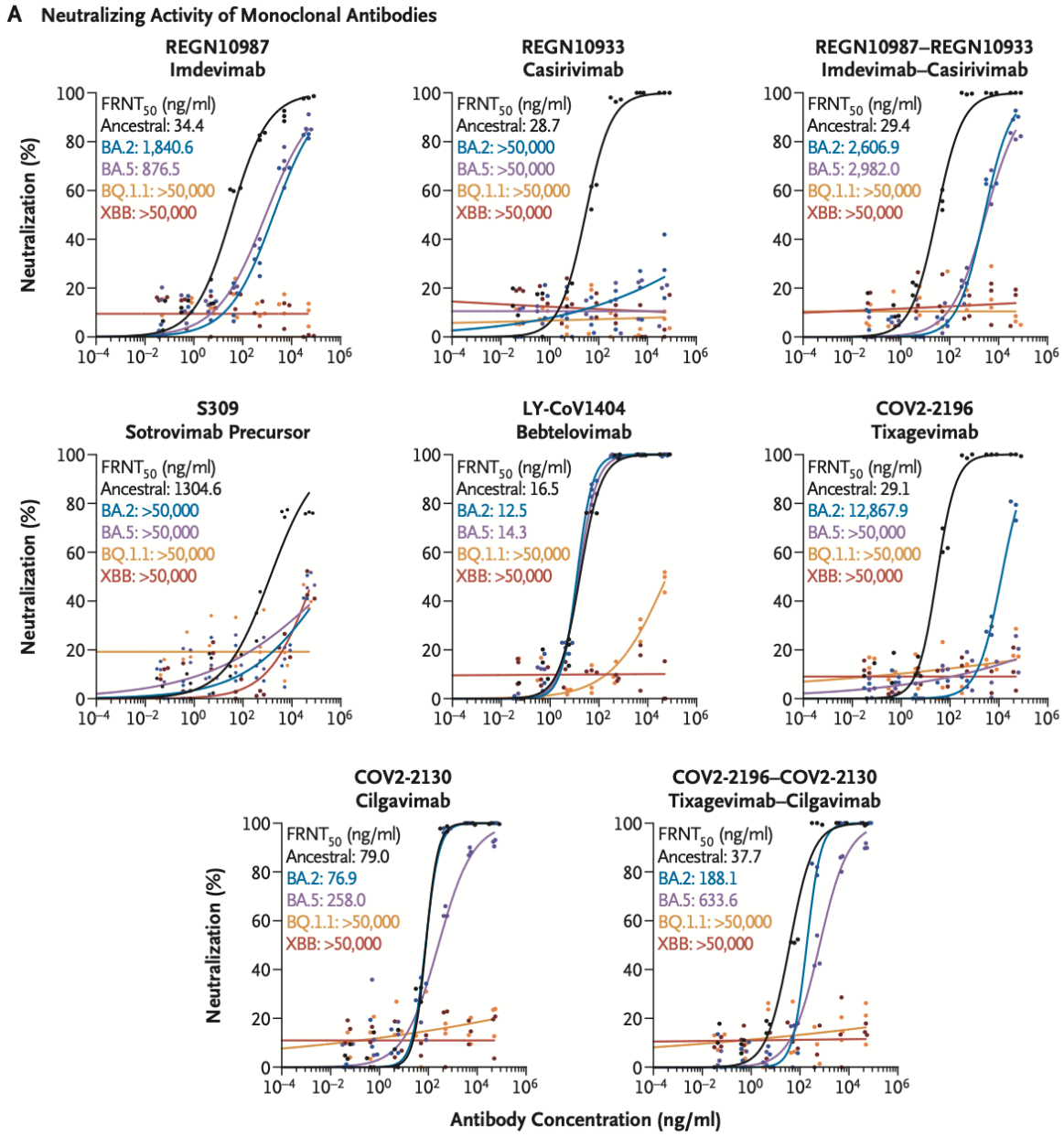
| | | | | Tixagev | Cilgav | Evusheld | | | | Sotrov | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pango lineages | REGN 10933 | REGN 10987 | REGN10933 +10987 | COV2-2196 | COV2-2130 | COV2-2196+2130 | BRII-196 | BRII-198 | BRII-196+198 | S309 | DXP-604 | LY-CoV 1404 | SA58 | SA55 | SA55+ SA58 | Additional RBD mutations |
| BA.2 | * | 590 | 821 | 4312 | 6.3 | 8.2 | 8530 | 8990 | 8610 | 852 | 219 | 0.9 | 5.1 | 7.2 | 7.8 | |
| BA.2.3.20 | 121 | * | 199 | 15 | * | 26 | 14 | * | 24 | 897 | 181 | 9.7 | 20 | 4.6 | 7.8 | K444R+N450D+L452M +N460K+R493Q |
| BA.2.10.4 | * | * | * | * | 289 | 501 | 2109 | 7990 | 3984 | 706 | 6348 | 1.3 | 4.3 | 4.9 | 5.0 | G446S+F486P+R493Q +S494P |
| BJ.1 | * | * | * | 3076 | * | 5985 | 7609 | * | * | 709 | 166 | * | 8163 | 3.7 | 8.6 | D339H+R346T+L368I+ V445P+G446S+V483A +F490V |
| XBB | * | * | * | * | * | * | * | * | * | 963 | * | * | 8805 | 5.3 | 9.8 | D339H+R346T+L368I+ V445P+G446S+N460K +F486S+F490S+R493Q |
| BA.2.75 | 278 | * | 410 | 119 | 352 | 121 | 1730 | 6622 | 3861 | 672 | 5920 | 2.2 | 246 | 4.3 | 9.6 | |
| BL.1 | 260 | * | 511 | 93 | * | 174 | 1251 | * | 3075 | 508 | 7193 | 2.8 | 7975 | 6.3 | 10 | R346T |
| BR.1 | 319 | * | 679 | 117 | * | 170 | 1992 | * | 3160 | 564 | 6689 | * | 1616 | 5.9 | 9.7 | L452R+K444M |
| BN.2.1 | 390 | * | 701 | 59 | 303 | 109 | 4101 | * | 8444 | 6979 | 8901 | 1.7 | 4960 | 5.7 | 9.4 | K356T+F490S |
| BN.1 | 344 | * | 599 | 70 | * | 166 | 3683 | * | 7791 | * | 6012 | 3.3 | 8295 | 4.9 | 9.0 | R346T+K356T+F490S |
| BA.2.75.2 | * | * | * | * | * | * | * | * | * | 852 | * | 3.0 | 6922 | 5.9 | 9.7 | R346T+F486S |
| BM.1.1 | * | * | * | * | * | * | * | * | * | 879 | * | 2.3 | 8823 | 5.2 | 8.9 | R346T+F486S |
| BM.1.1.1 | * | * | * | * | * | * | * | * | * | 956 | * | 1.9 | 8082 | 4.8 | 10.5 | R346T+F486S+F490S |
| BR.2 | * | * | * | * | * | * | * | * | * | 921 | * | 2.6 | 7263 | 4.7 | 10.5 | R346T+L452R+F486I |
| CA.1 | * | * | * | * | * | * | * | * | * | 897 | * | 3.2 | 6927 | 6.0 | 11.5 | R346T+L452R+F486S |
| BA.4/5 | * | 520 | 709 | * | 23 | 40 | 7124 | * | * | 1055 | 6264 | 0.8 | 3.9 | 5.0 | 4.5 | |
| BA.4.6.1 | * | 2338 | 5402 | * | * | * | 4763 | * | 7809 | 4456 | 4634 | 1.2 | 50 | 4.8 | 9.9 | R346T |
| BA.5.6.2 | * | * | * | * | * | * | 4636 | * | 7883 | 1408 | 5892 | 1662 | 58 | 5.1 | 8.9 | K444T |
| BQ.1 | * | * | * | * | * | * | * | * | * | 1709 | * | 1905 | 44 | 6.6 | 9.2 | K444T+N460K |
| BU.1 | * | * | * | * | * | * | * | * | * | 1082 | * | 26 | 56 | 5.3 | 10.5 | K444M+N460K |
| BQ.1.1 | * | * | * | * | * | * | * | * | * | 5581 | * | * | 900 | 5.9 | 10.3 | R346T+K444T+N460K |

**Pseudovirus IC50 (ng/mL)**

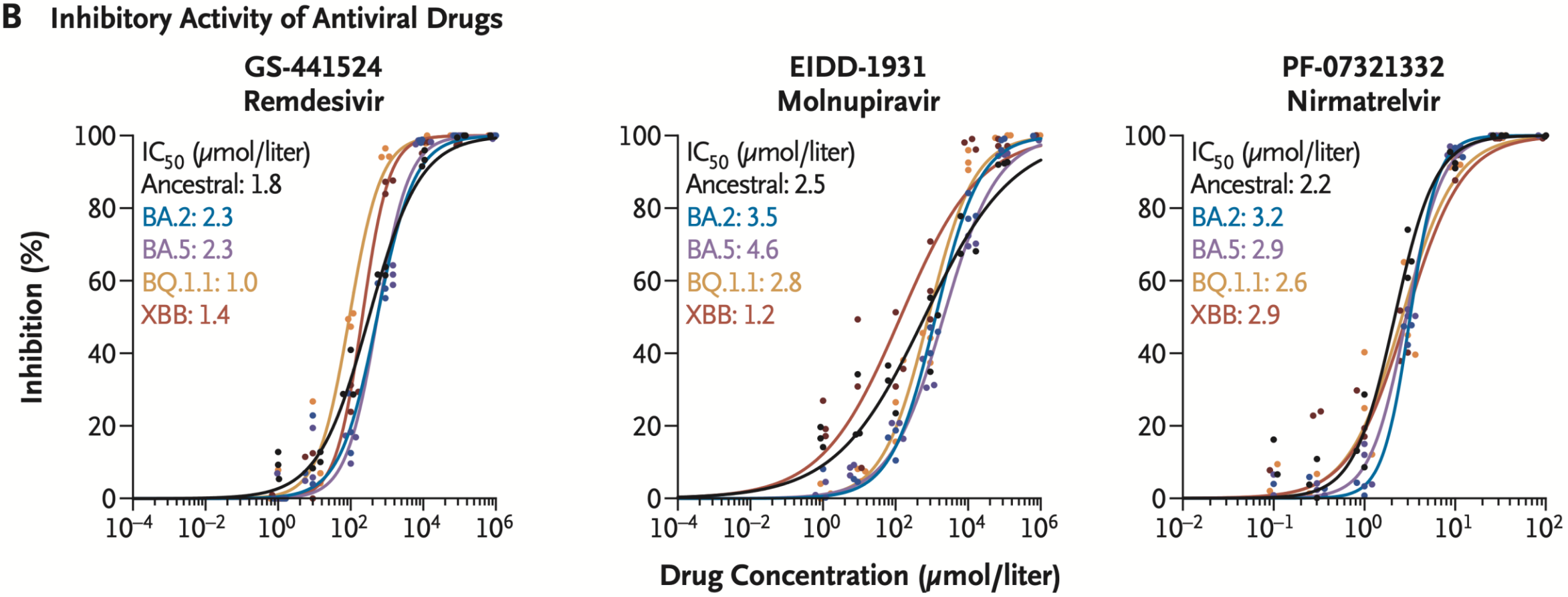
| <100 | 100~1,000 | >1,000 | * >10,000 |
|---|---|---|---|

RBD, Receptor binding domain

# 5/5 **Imai**. Efficacy of Antiviral Agents against Omicron Subvariants BQ.1.1 and XBB



# 5/5 **Imai**. Efficacy of Antiviral Agents against Omicron Subvariants BQ.1.1 and XBB



# Recent papers on BQ.1, BQ.1.1 or XBB*

| Lead | Title | Date | Journal | Origin | Link |
|---|---|---|---|---|---|
| Planas | Resistance of Omicron subvariants BA.2.75.2, BA.4.6 and BQ.1.1 to neutralizing antibodies | 17th November 2022 | bioRχiv (preprint) | Paris | https://pubmed.ncbi.nlm.nih.gov/36415455/ |
| Arora | Omicron sublineage BQ.1.1 resistance to monoclonal antibodies | 18th November 2022 | Lancet Infect Dis | Göttingen | https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(22)00733-2/fulltext |
| Wang | Alarming antibody evasion properties of rising SARS- CoV-2 BQ and XBB subvariants | 14th December 2022 | Cell | New York | https://www.sciencedirect.com/science/article/pii/S0092867422015318 |
| Cao | Imprinted SARS-CoV-2 humoral immunity induces convergent Omicron RBD evolution | 19th December 2022 | Nature | Beijing | https://www.nature.com/articles/s41586-022-05644-7 |
| Imai | Efficacy of Antiviral Agents against Omicron Subvariants BQ.1.1 and XBB | 5th January 2023 | NEJM | Tokyo | https://www.nejm.org/doi/full/10.1056/NEJMc2214302 |

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* additional slide in appendix

# Summary of *in vitro* papers investigating BQ.1, BQ.1.1, XBB.

| | | **Sotrovimab** | **Casirivimab** | **Imdevimab** | **Ronapreve** Cas + Imdev | **Tixagevimab** | **Cilgavimab** | **Evusheld** Tixa + Cilga | **Remdesivir** | **Molnupiravir** | **Paxlovid** Nirmatrelvir Ritonavir |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Planas** | BQ.1.1 | | | | | | | | | | |
| | ~~XBB~~ | | | | | | | | | | |
| **Arora** | BQ.1.1 | | | | | | | | | | |
| | ~~XBB~~ | | | | | | | | | | |
| **Wang** | BQ.1.1 | S309 (precursor) | | | | | | | | | |
| | XBB | | | | | | | | | | |
| **Cao** | BQ.1.1 | S309 (precursor) | | | | | | | | | |
| | ~~XBB~~ | | | | | | | | | | |
| **Imai** | BQ.1.1 | S309 (precursor) | | | | | | | | | |
| | XBB | ? | | | | | | | | | |

Not evaluated | No neutralisation | Reduced neutralisation | Unaffected neutralisation

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# Susceptibility summaries

Search database • Suggest new study • report error

SEARCH DATABASE

Last updated on Jan 11, 2023, 10:18 PM

## Table 1: Virus variants and spike mutations vs monoclonal antibodies

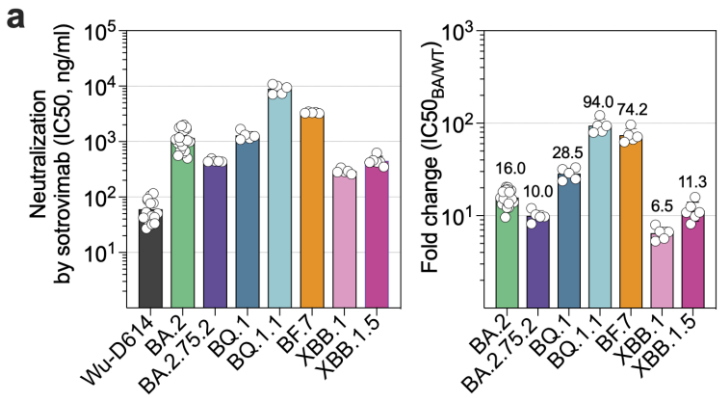
https://covdb.stanford.edu/susceptibility-data/table-mab-susc/

### Fold reduced neutralizing susceptibility to monoclonal antibodies under Emergency Use Authorization (EUA)

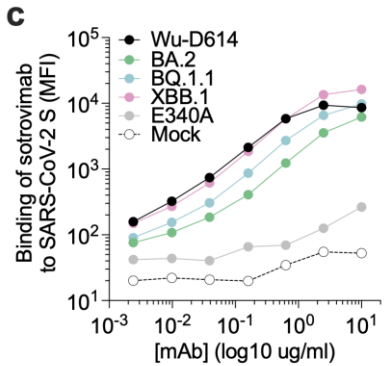
Copy to clipboard

| Test\mAb | BAM | ETE | BAM/ETE | CAS | IMD | CAS/IMD Ronapreve | CIL | TIX | CIL/TIX Evusheld | SOT Sotrovimab | BEB | ADI |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Alpha | $1_{23}$ | $13_{20}$ | $1.3_{9}$ | $1_{32}$ | $0.6_{33}$ | $0.9_{14}$ | $0.6_{15}$ | $1.5_{14}$ | $0.8_{14}$ | $1.6_{29}$ | $0.9_{6}$ | $1.3_{6}$ |
| Beta | $>1000_{29}$ | $516_{25}$ | $990_{12}$ | $91_{38}$ | $0.6_{38}$ | $1.6_{19}$ | $1.1_{16}$ | $5.8_{17}$ | $1.7_{16}$ | $1.0_{30}$ | $1_{8}$ | $2.8_{6}$ |
| Gamma | $>1000_{16}$ | $348_{16}$ | $404_{4}$ | $124_{24}$ | $0.4_{24}$ | $1_{9}$ | $0.5_{12}$ | $3.7_{11}$ | $0.9_{10}$ | $1_{23}$ | $1_{5}$ | $2.2_{6}$ |
| Delta | $>1000_{24}$ | $0.4_{24}$ | $1_{9}$ | $0.7_{32}$ | $1.5_{33}$ | $1.3_{14}$ | $2.7_{14}$ | $1_{15}$ | $1_{17}$ | $1.1_{29}$ | $1_{11}$ | $1.5_{7}$ |
| Omicron/BA.1 | $>1000_{41}$ | $432_{41}$ | $980_{17}$ | $>1000_{49}$ | $>1000_{50}$ | $>1000_{23}$ | $263_{46}$ | $264_{48}$ | $60_{34}$ | $3.8_{61}$ | $1_{25}$ | $110_{19}$ |
| Omicron/BA.2 | $>1000_{22}$ | $504_{22}$ | $744_{15}$ | $>1000_{30}$ | $220_{29}$ | $387_{21}$ | $2.1_{33}$ | $893_{32}$ | $8_{31}$ | $23_{45}$ | $1_{27}$ | $>1000_{14}$ |
| Omicron/BA.2.12.1 | $>1000_{10}$ | $468_{10}$ | $794_{8}$ | $>1000_{11}$ | $88_{11}$ | $250_{9}$ | $3_{12}$ | $382_{12}$ | $9.5_{9}$ | $19_{15}$ | $1_{11}$ | $>1000_{5}$ |
| Omicron/BA.2.75 | $705_{7}$ | $383_{7}$ | $554_{5}$ | $233_{9}$ | $>1000_{9}$ | $>1000_{7}$ | $19_{10}$ | $30_{10}$ | $25_{8}$ | $9.6_{10}$ | $3.8_{10}$ | $673_{6}$ |
| Omicron/BA.2.75.2 | $556_{2}$ | $489_{2}$ | $>1000_{1}$ | $589_{4}$ | $588_{4}$ | $>1000_{3}$ | $700_{4}$ | $819_{4}$ | $738_{4}$ | $17_{4}$ | $3.0_{4}$ | $509_{2}$ |
| Omicron/XBB | - | - | - | $177_{1}$ | $175_{1}$ | $200_{1}$ | $700_{2}$ | $819_{2}$ | $738_{2}$ | $14_{2}$ | $>1000_{2}$ | - |
| Omicron/BA.4/5 | $>1000_{17}$ | $432_{17}$ | $588_{11}$ | $>1000_{23}$ | $143_{23}$ | $379_{16}$ | $8.1_{27}$ | $>1000_{27}$ | $22_{23}$ | $22_{33}$ | $1_{23}$ | $968_{12}$ |
| Omicron/BA.4.6 | $556_{2}$ | $489_{2}$ | $>1000_{1}$ | $589_{4}$ | $173_{4}$ | $738_{3}$ | $527_{6}$ | $819_{6}$ | $738_{6}$ | $44_{5}$ | $1.1_{6}$ | $509_{2}$ |
| Omicron/BQ.1 | - | - | - | $177_{1}$ | $175_{1}$ | $200_{1}$ | $700_{2}$ | $819_{2}$ | $738_{2}$ | $25_{2}$ | $>1000_{2}$ | - |
| Omicron/BQ.1.1 | $>1000_{1}$ | $943_{1}$ | $>1000_{1}$ | $>1000_{3}$ | $>1000_{3}$ | $>1000_{3}$ | $>1000_{4}$ | $>1000_{4}$ | $>1000_{4}$ | $106_{4}$ | $>1000_{4}$ | $>1000_{1}$ |
| Omicron/BF.7 | - | - | - | - | - | - | $>1000_{1}$ | $>1000_{1}$ | $>1000_{1}$ | $49_{1}$ | $1_{1}$ | - |

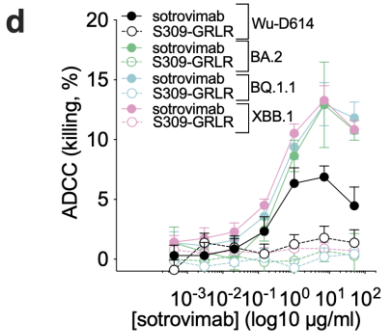
# Late breaking (17th Jan 2023): *Therapeutic and vaccine-induced cross-reactive antibodies with effector function against emerging Omicron variants*



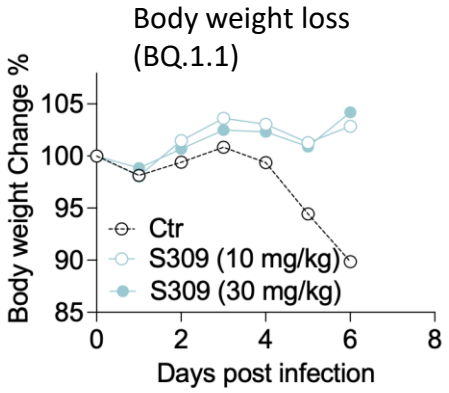

1) Neutralisation activity reduced

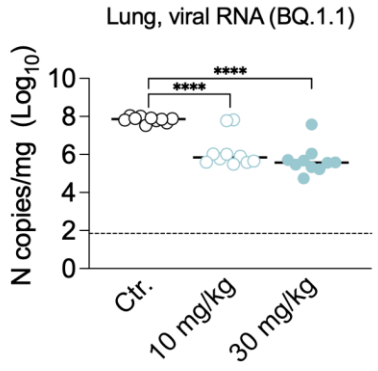


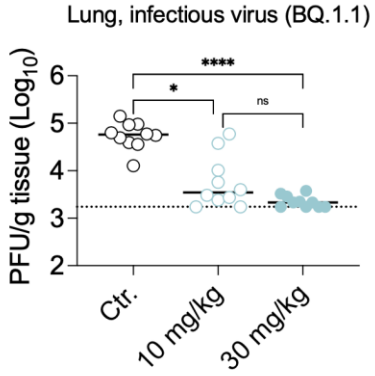

2) Sotrovimab still binds to virus




3) Virus-infected cells still killed




4) Still works in mice with BQ.1.1

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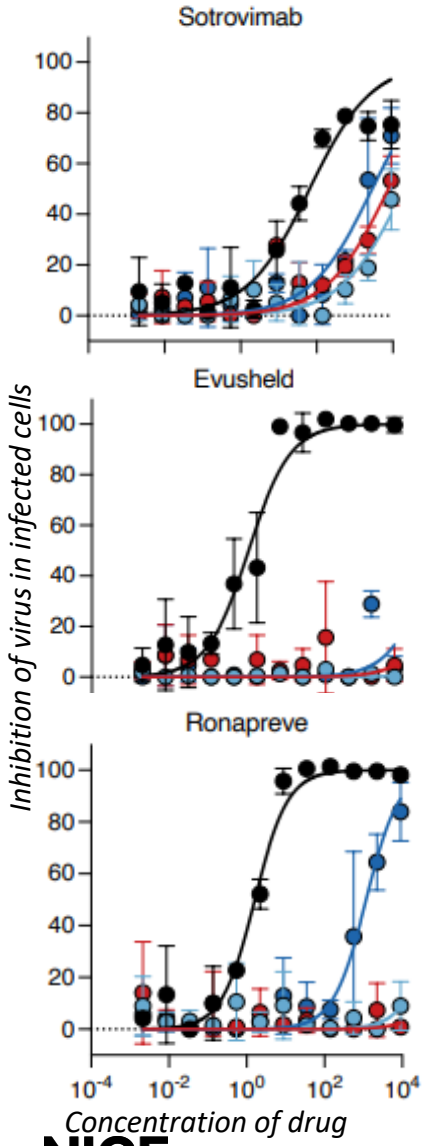
ADCC: antibody-dependent cell cytotoxicity

Addetia *et al*. https://www.biorxiv.org/content/10.1101/2023.01.17.523798v1

# Interpretating neutralisation curves – IVAG conclusions




| | |
|---|---|
| Unclear | **Sotrovimab**<br>• Sotrovimab neutralises all variants tested, but needs higher concentrations to achieve the same effect as when used to neutralise Delta ~100 n-fold difference measured at EC50<br>• ∴ need to consider PK/PD to understand the effect on clinical outcomes |
| No neutralising activity | **Tixagevimab + cilgavimab**<br>• No evidence of neutralisation activity against any new variants tested at concentrations likely to be achieved in the body<br>• ∴ likely no clinical effect of the treatment for these variants |
| Variant - dependent | **Casirivimab/ + imdevimab**<br>• No evidence of neutralisation activity against BA.2.75.2 or BQ.1.1.<br>• Reduced neutralisation against BA.4.6<br>  • ~1000 n-fold more drug required to achieve EC50<br>• ∴ need to consider PK/PD to understand effect on clinical outcomes<br>• NICE can appraise drugs only within licensed dosages |

● Delta ● BA.2.75.2 ● BA.4.6 ● BQ.1.1

Planas et al. 2022

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# Section 1 Data relevant to both appraisals

- SARS-CoV-2 variant tracking
  - Evolution of variants
  - UK Health Security Agency (UKHSA) technical briefings
- *In vitro* data
  - The ***In Vitro*** data **A**ssessment **G**roup (IVAG)
  - BQ.1, BQ.1.1, XBB
- Position of various organisations

# Position of various organisations

| | Sotrovimab | Casirivimab plus imdevimab | Tixagevimab plus cilgavimab |
|---|---|---|---|
| World Health Organization | Strong recommendation against use (13 January 2023, first published 14 January 2022) | Strong recommendation against use (13 January 2023, first published 24 September 2021) | NA (prevention only) |
| U.S. FOOD & DRUG ADMINISTRATION | Emergency Use Authorisation (EUA) withdrawn 5 April 2022 | EUA withdrawn 24 January 2022 | NA (prevention only) |
| EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH | As of 9th December 2022, EMA's Emergency Task Force (ETF) has cautioned that monoclonal antibodies currently authorised for COVID-19 (including sotrovimab, casirivimab plus imdevimab and tixagevimab plus cilgavimab) are unlikely to be effective against emerging strains of SARS-CoV-2. | | |

# Overview of the day

| Section | Data relevant to both appraisals | |
|---|---|---|
| 1.1 | SARS-CoV-2: variant tracking | Public |
| 1.2 | *In vitro* data | Public |
| 1.3 | Position of various organisations | Public |

| ID 4038 | MTA of COVID-19 treatments | ACM 2 |
|---|---|---|
| 2.1 | Community setting (mild COVID-19) – Part 1 | Public |
| 3.1 | Hospital setting (severe COVID-19) – Part 1 | Public |
| 2.2 | Community setting – Part 2 | Private |
| 3.2 | Hospital setting – Part 2 | Private |

| ID 6136 | STA of tixagevimab/cilgavimab (Evusheld) | ACM 1 |
|---|---|---|
| 4.1 | Prophylaxis in highly vulnerable people – Part 1 | Public |
| 4.2 | Prophylaxis – Part 2 | Private |

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# *Appendix slides

# Variants can have ‘spike mutations’ which cause resistance to neutralising monoclonal antibody treatments


- Certain spike mutations are associated with more significant loss of neutralisation compared to drug’s activity against reference variant e.g. R346T
- Spike mutations can develop independently through different lineages
- Evolution of virus **in the near future** likely from currently circulating variants that may retain these mutations (e.g. BQ.1.1 from BQ.1)
- Neutralisation activity of drugs against historical variants (or their sublineages) may become relevant because mutations and recombinant strains can occur in immunocompromised patients

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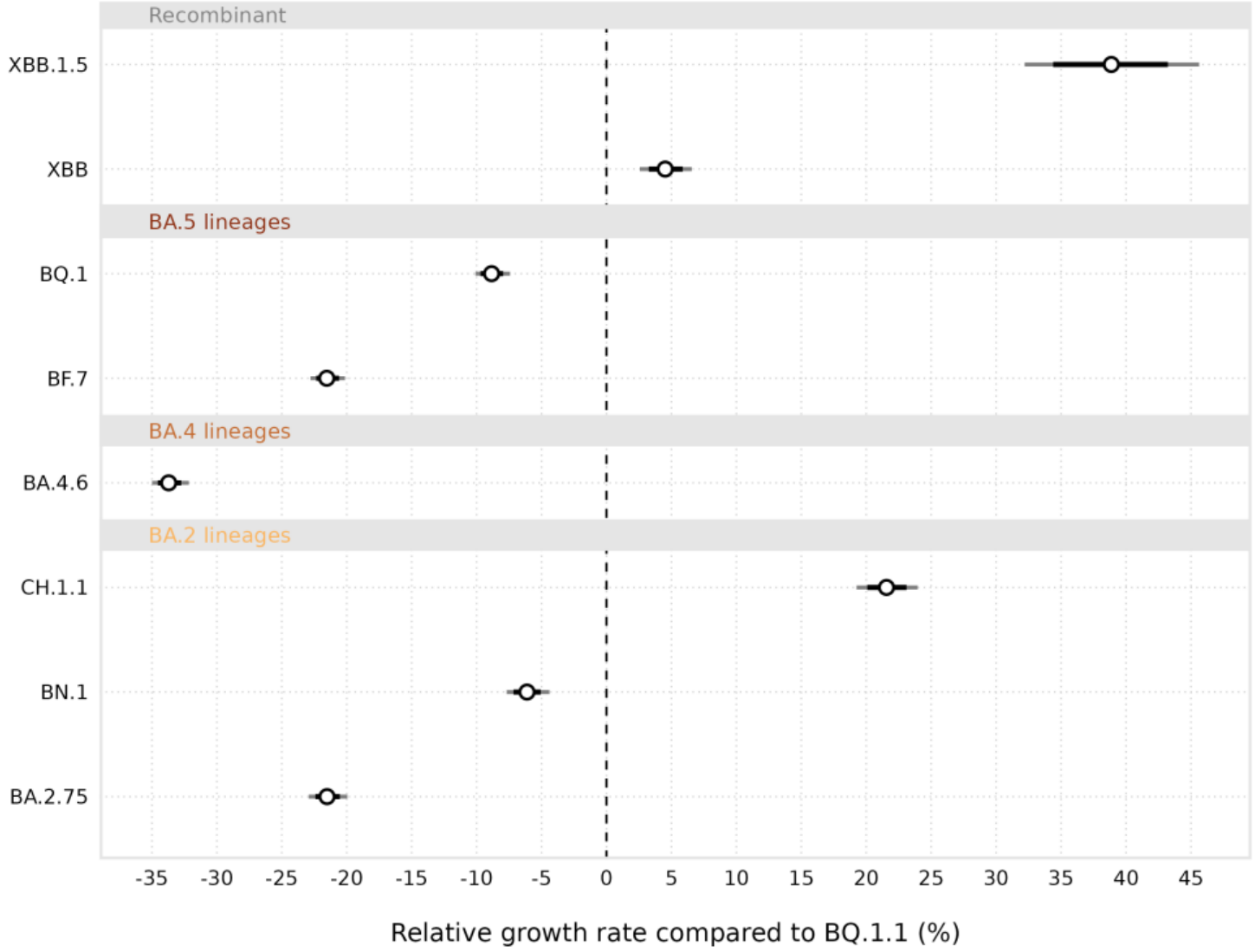
# Comparison of the estimated relative growth rates for emerging BA.5, BA.4, BA.2 and recombinant lineages versus that for specifically BQ.1.1 lineages

Omicron BQ.1 - relative growth rate vs BA.5.2 ~x39 (Tech briefing 48)

| Relative growth rate compared with Omicron BQ.1.1 |
|---|
| XBB.1.5: ~ x39% |
| CH.1.1 ~ x22% |
| XBB~ x4 |




Source: UKHSA Technical briefing 49 (11 January 2023).

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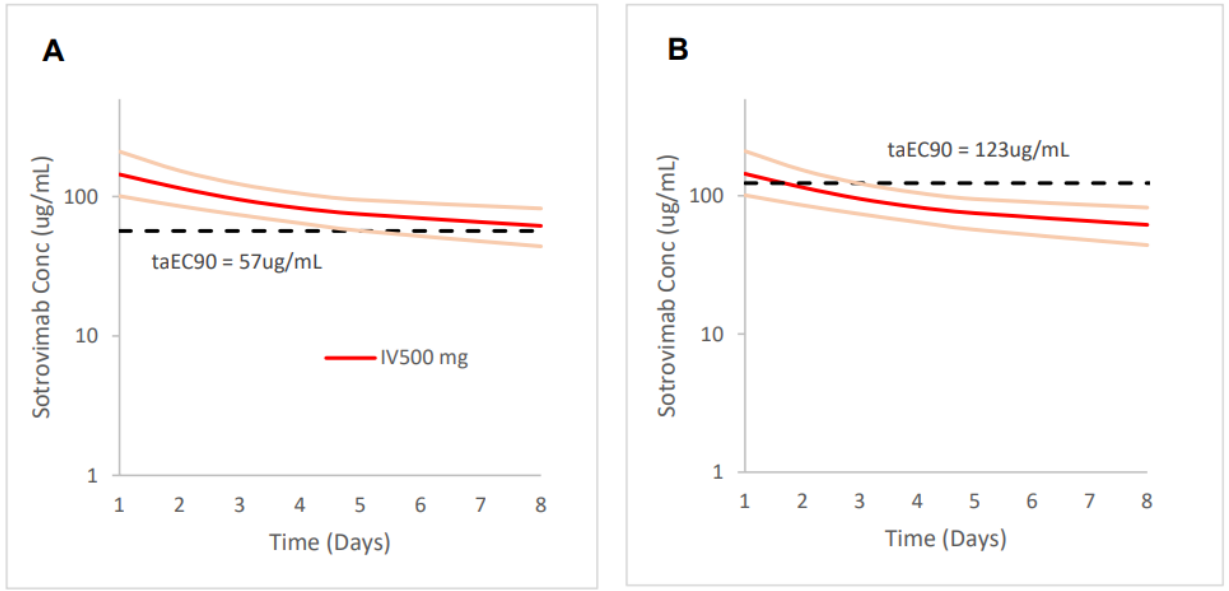
# How to determine the quality of in vitro evidence

- Cell-lines
- Pseudo-virus/live virus
- Reproducibility
- Good Clinical Practice-compliant high-throughput platform, calibrated to WHO International Standards (Wu et al 2022)
- MHRA in partnership with DHSC have created a variant framework (agreed with companies) for best practice

# Adjusting serum concentrations to reflect lung tissue

- An alternative approach is to simulate an EC-90 value for sotrovimab compared to reference variant generating  trial evidence
- Reduce this using a tissue-adjustment – to account for serum levels of sotrovimab being higher than where it would have effect (i.e. the lungs)
- FDA suggests lung tissue concentrations are 6.5% to 12% of serum
- IVAG concurs that this approach has limited use for quantifying likelihood of efficacy and is weaker than analysis of when a dose would fail

**Figure 2. Simulated Sotrovimab 500 mg IV Compared to Tissue Adjusted $EC_{90}$ Value for Live BA.2 Subvariants at Lung Penetration of 12%**




Note: The sotrovimab 500 mg IV concentration-time profile is based on data from BLAZE-4, Japan-PK, COMET-PEAK studies in relationship to the $taEC_{90}$ value (live virus Omicron BA.2 subvariant $EC_{90}$/ lung penetration at 12%.

# GSK submitted data on sotrovimab (VIR-7831), 13 Jan 2023

**Table 1 Activity of Sotrovimab Against Pseudotyped Virus Expressing SARS-CoV-2 Omicron Spike Variants**

| SARS-CoV-2 Variant Name | | Geometric Mean EC50 (ng/mL) | Average Fold Change in EC50 Compared to Wuhan-Hu-1 Wild-Type |
|---|---|---|---|
| WHO | Lineage | | |
| Omicron | BA.1 | 336.4 | 2.7 |
| | BA.1.1 | 201.85 | 3.3 |
| | BA.2 | 1139 | 16 |
| | BA.4 | 1711 | 21.3 |
| | BA.5 | 1556 | 22.6 |
| | BA.2.12.1 | 1120 | 16.6 |
| | BA.2.75 | 541.8 | 8.3 |
| | BA.4.6 | 3637 | 57.9 |
| | BQ.1 | 1277 | 28.5 |
| | BQ.1.1 | 8818 | 94 |
| | BF.7 | 3317 | 74.2 |
| | BA.2.75.2 | 447.6 | 10.0 |
| | XBB.1 | 289.5 | 6.5 |

Sources: Cathcart, 2022[1]; Park Y-J et al. Science. 2022;378(6620):619-627[2]; GSK data on file[3].

[1]Cathcart AL, Havenar-Daughton C, Lempp FA, et al. The dual function monoclonal antibodies VIR-7831 and VIR-7832 demonstrate potent in vitro and in vivo activity against SARS-CoV-2. bioRxiv [Preprint]. 01 April 2022. doi: 10.1101/2021.03.09.434607v12

[2]Park YJ, Pinto D, Walls AC, et al. Imprinted antibody responses against SARS-CoV-2 Omicron sublineages. Science. 2022 Nov 11;378(6620):619-627. doi: 10.1126/science.adc9127. Epub 2022 Oct 20.

[3] GSK data on file not public/peer reviewed