



New antivirals and strategy to evaluate candidates for COVID 19 Treatment (AGILE)

Saye Khoo



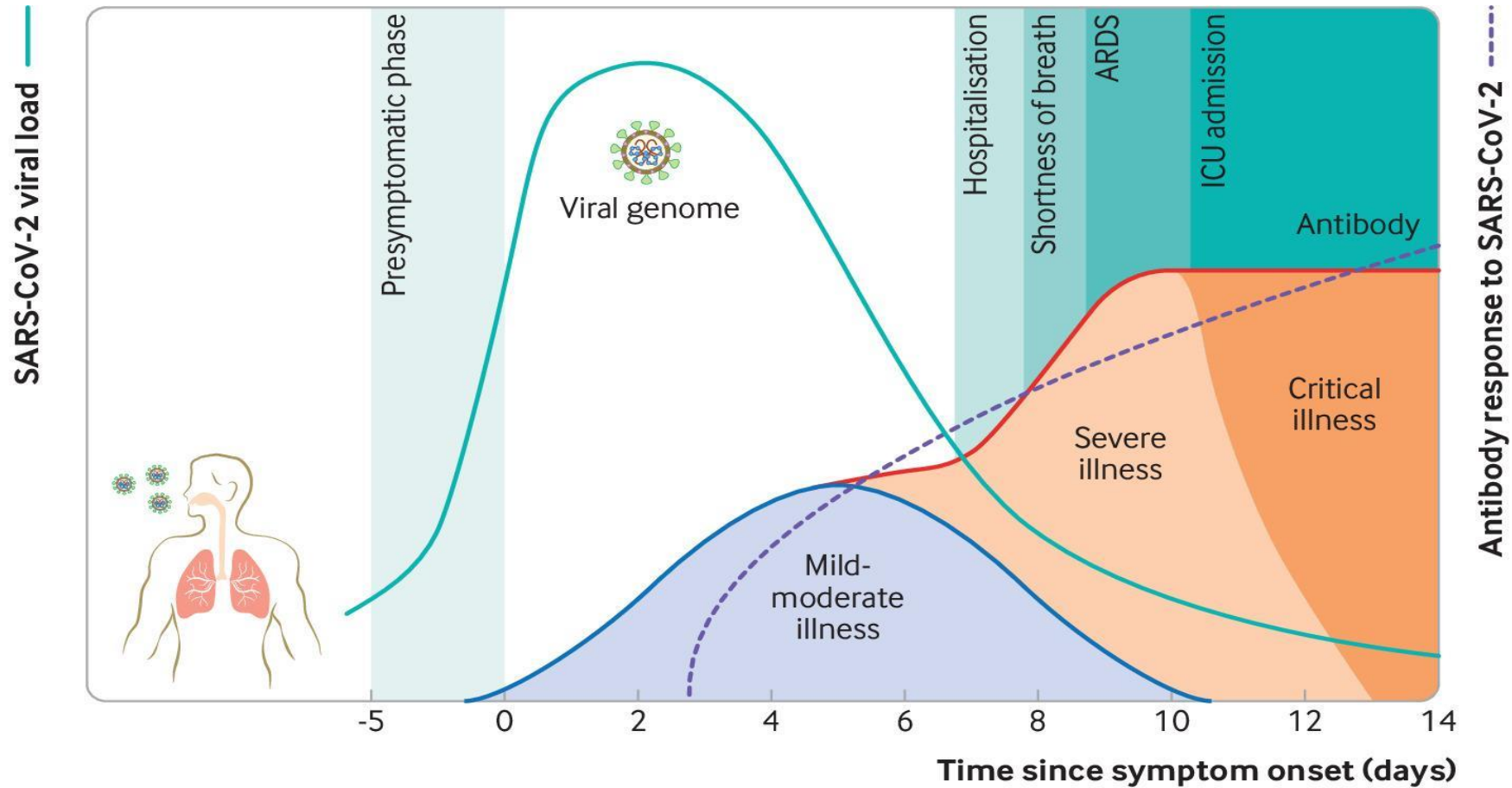
Disclosures and Funding

Disclosure & Funding Statement

- *The AGILE Platform is funded by the Wellcome Trust, the UK Medical Research Council, and UKRI*
- *AGILE trials have received support from Unitaid, Ridgeback Biotherapeutics, GSK and Vir Biotechnology*
- *Infrastructure support from NIHR, CRUK*
- *SK has received funding from ViiV, Gilead, Merck unrelated to this work*
- *A full transparency statement is available on www.agiletrial.net/*



COVID-19 : Clinical Progression of Disease



Vaccine

Antivirals

Prophylaxis

Host Directed Therapies

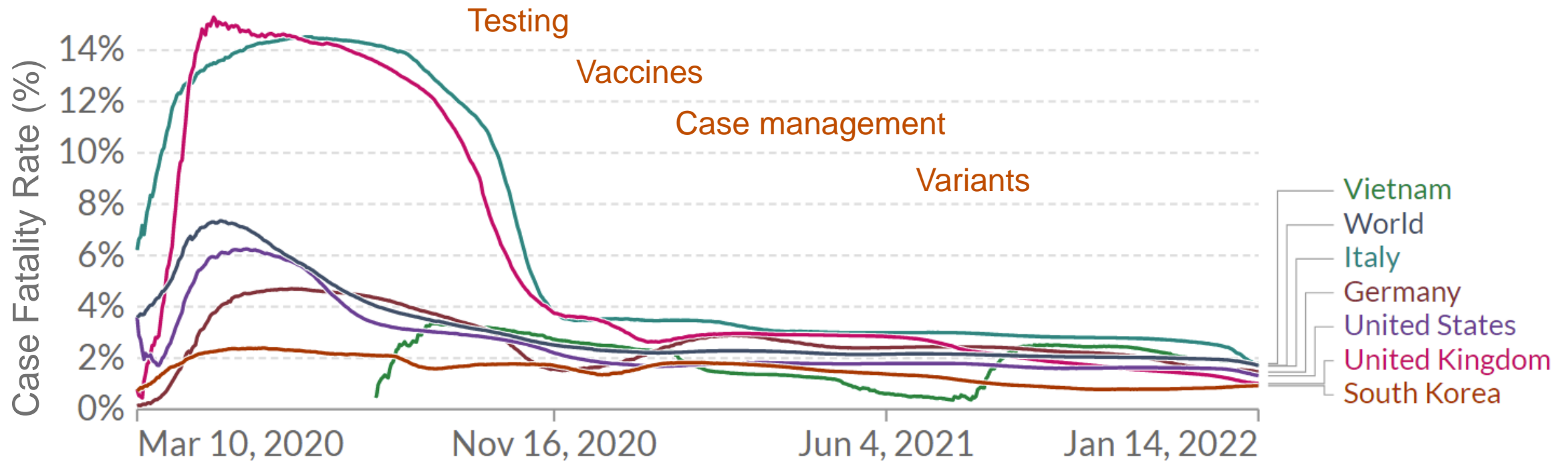


New Antiviral Treatments for COVID -19

The Problem:

- **‘Conventional’ drug development not designed for pandemic**
 - *too slow*
 - *not responsive to changes in clinical care, viral evolution, population immunity*
 - *initial candidates in Phase III without sufficient level of supportive evidence*
- **Need for new (antiviral) compounds**
 - *‘repurposing’ always going to be a stopgap*
- **Research in a very challenging environment**
 - *facilities, staff, environment, infection control, public health*
 - *each study carries opportunity costs*

Case Fatality Rates have fallen

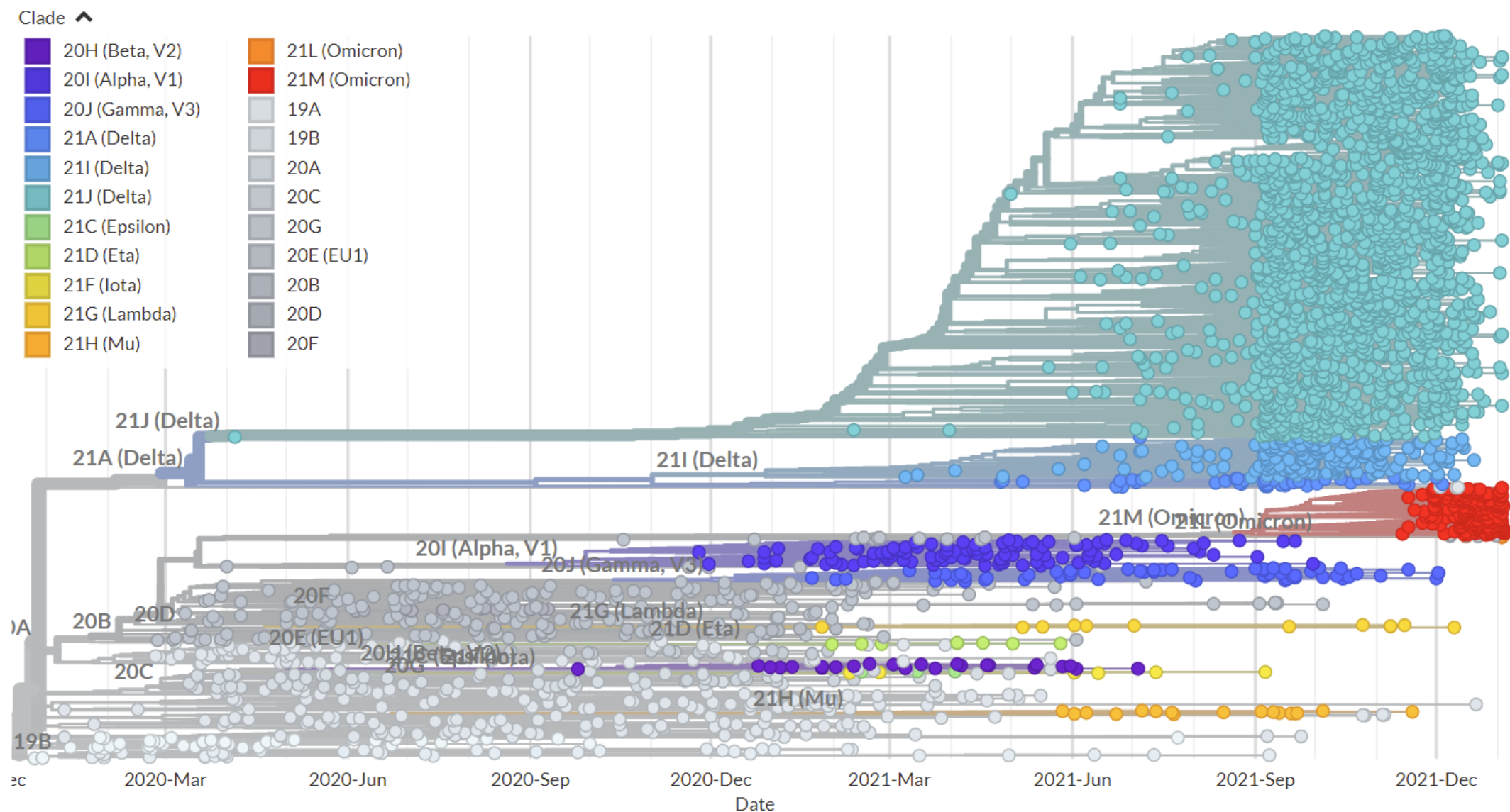


Source: Johns Hopkins University CSSE COVID-19 Data – Last updated 15 January, 09:05 (London time)

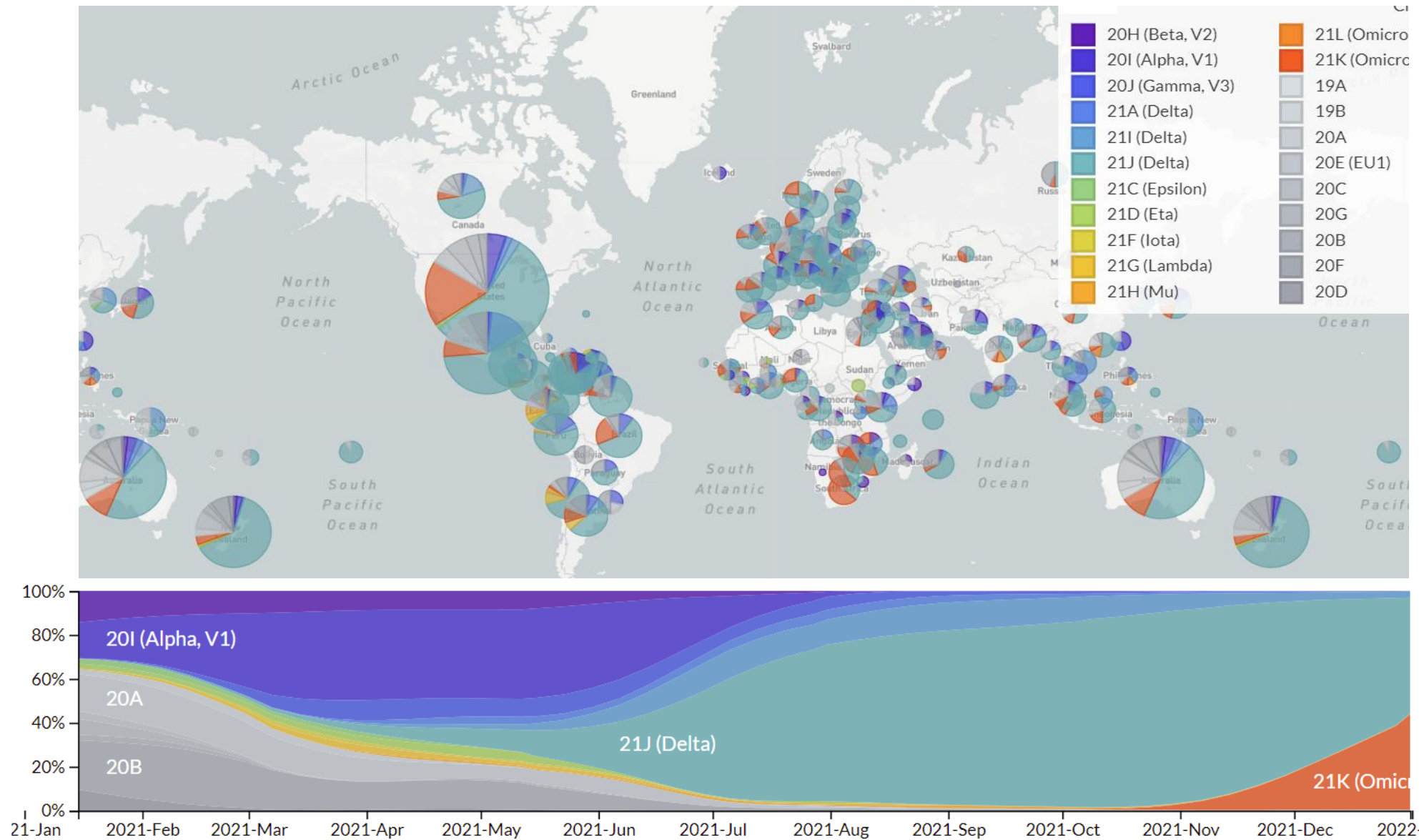
Note: Only countries with more than 100 confirmed cases are included. Only countries with more than 100 confirmed cases are included.

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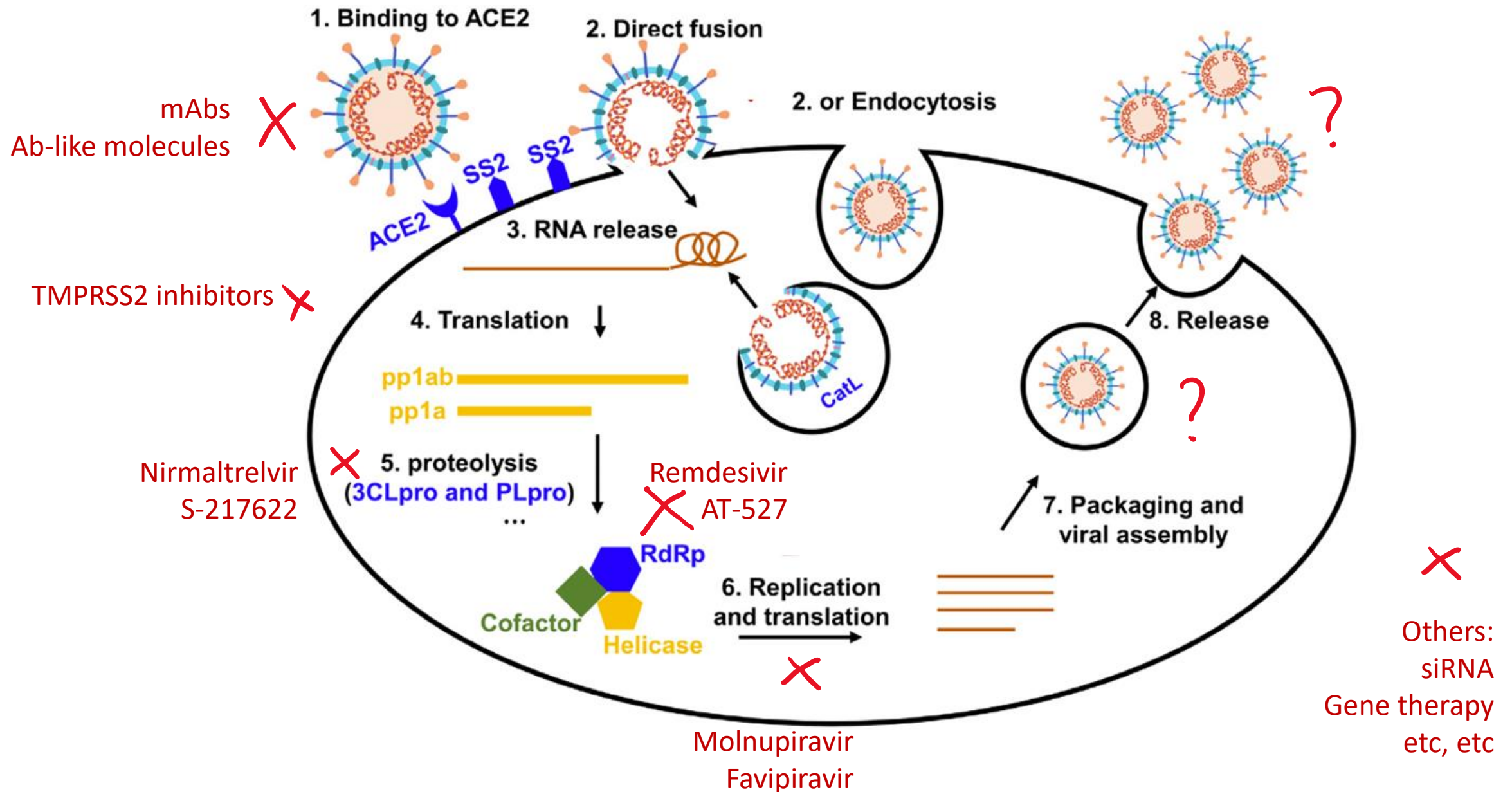
SARS CoV-2 Diversity and Evolution of the Pandemic



SARS CoV-2 Diversity and Evolution of the Pandemic



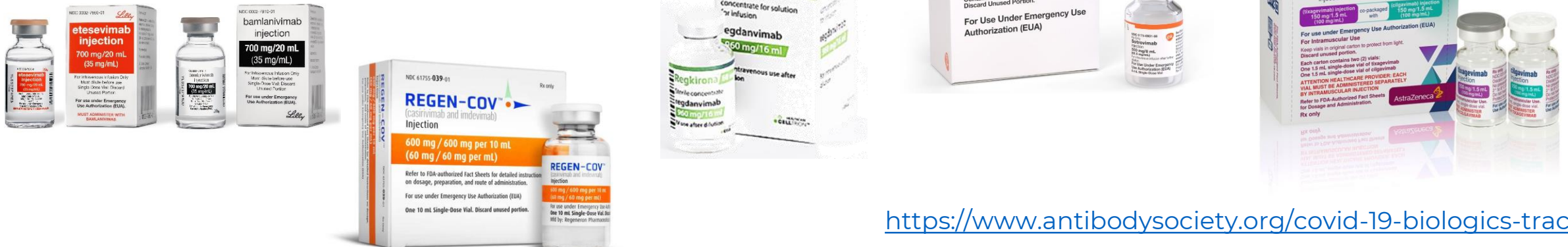
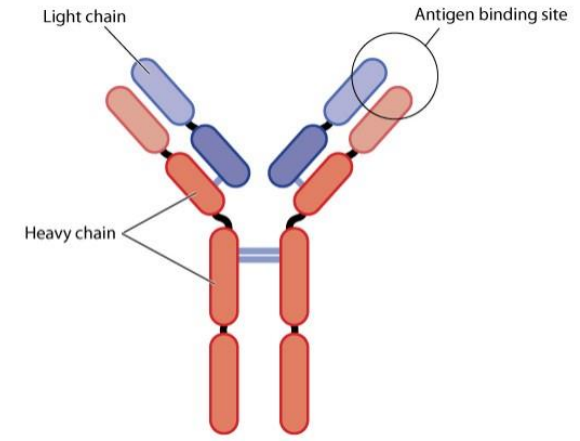
Antiviral Therapy – potential targets



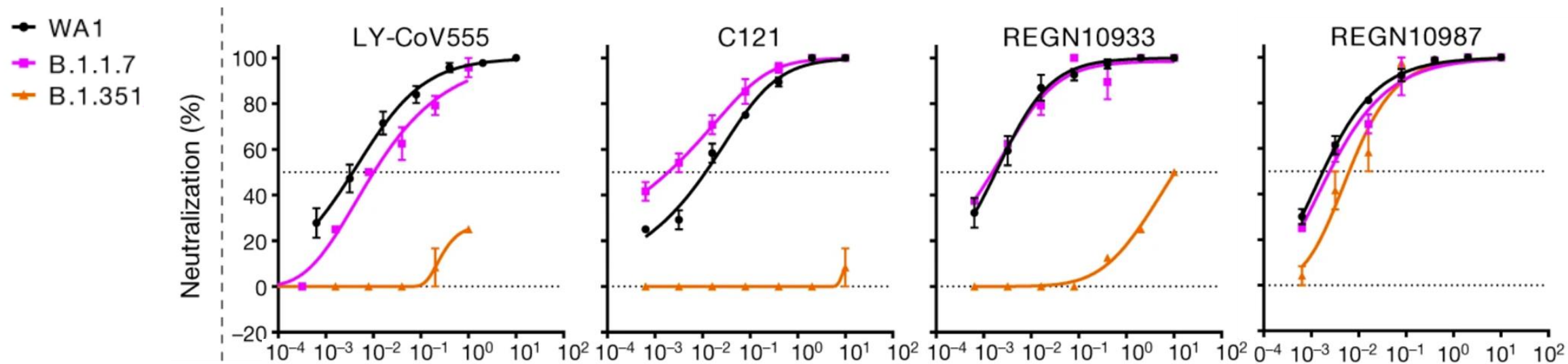
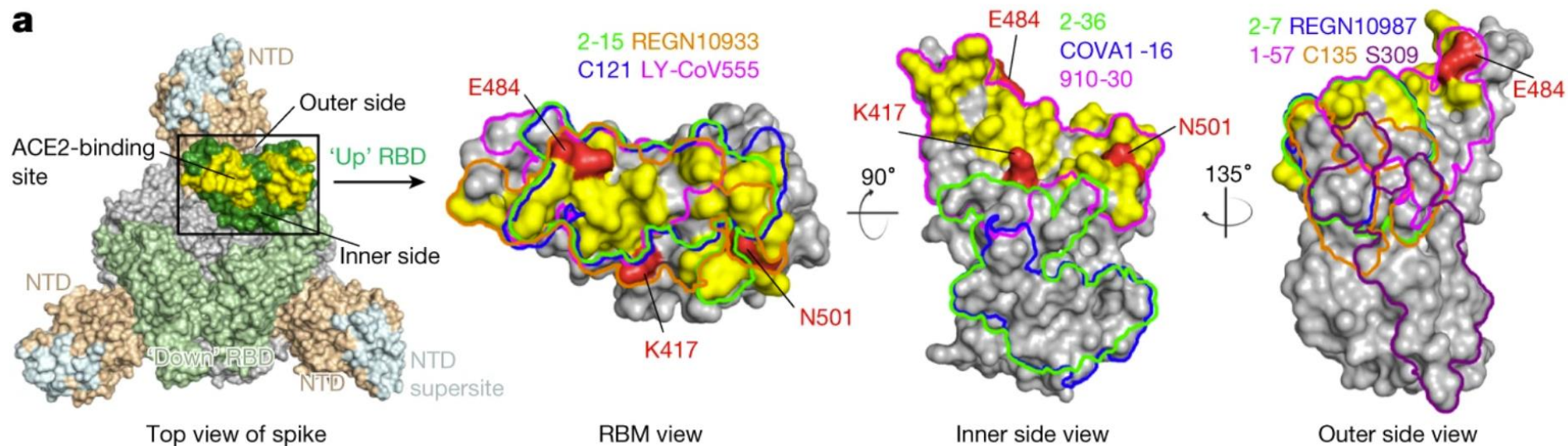
mAbs and Ab-like molecules

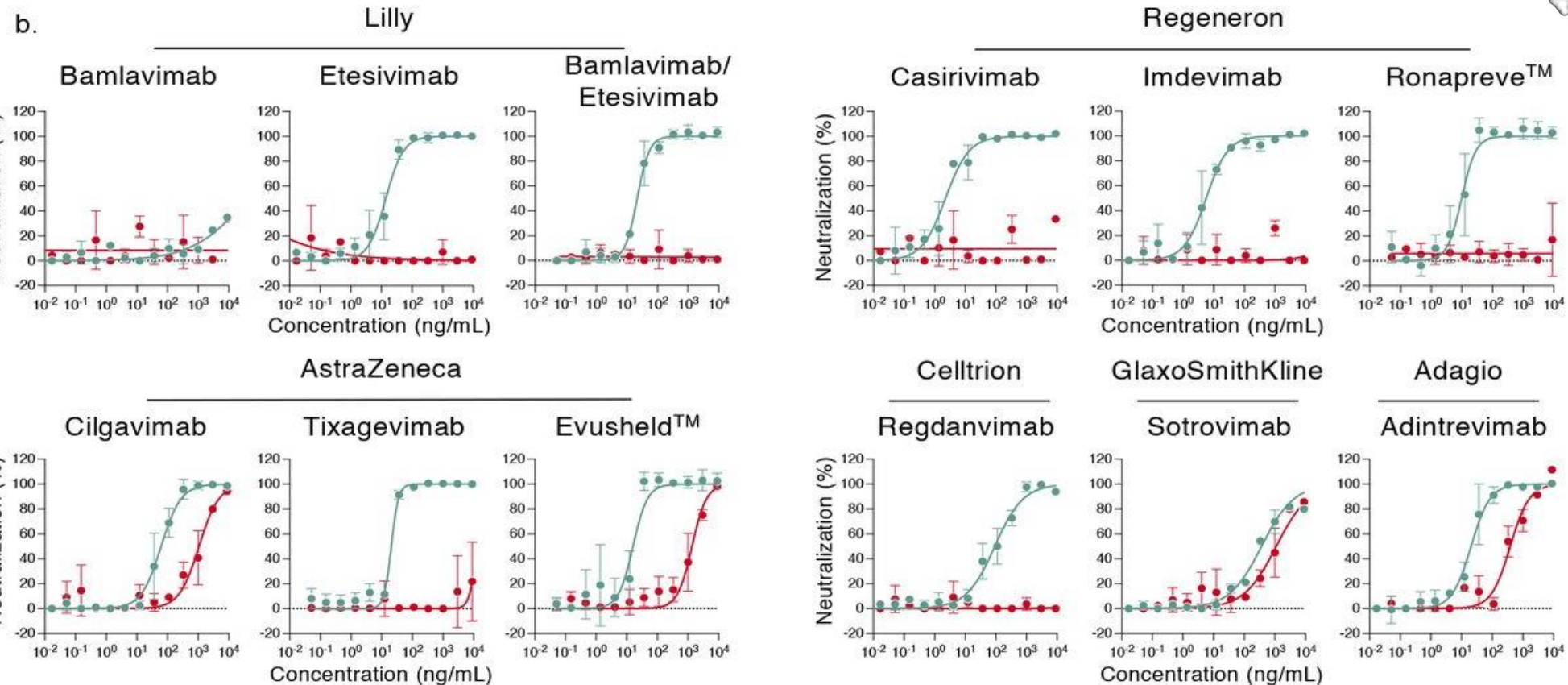
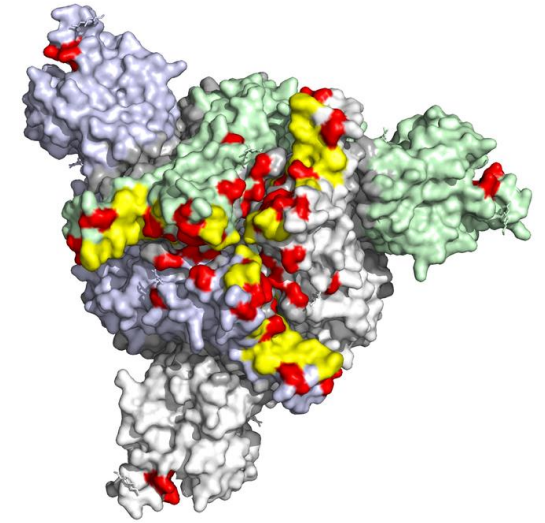
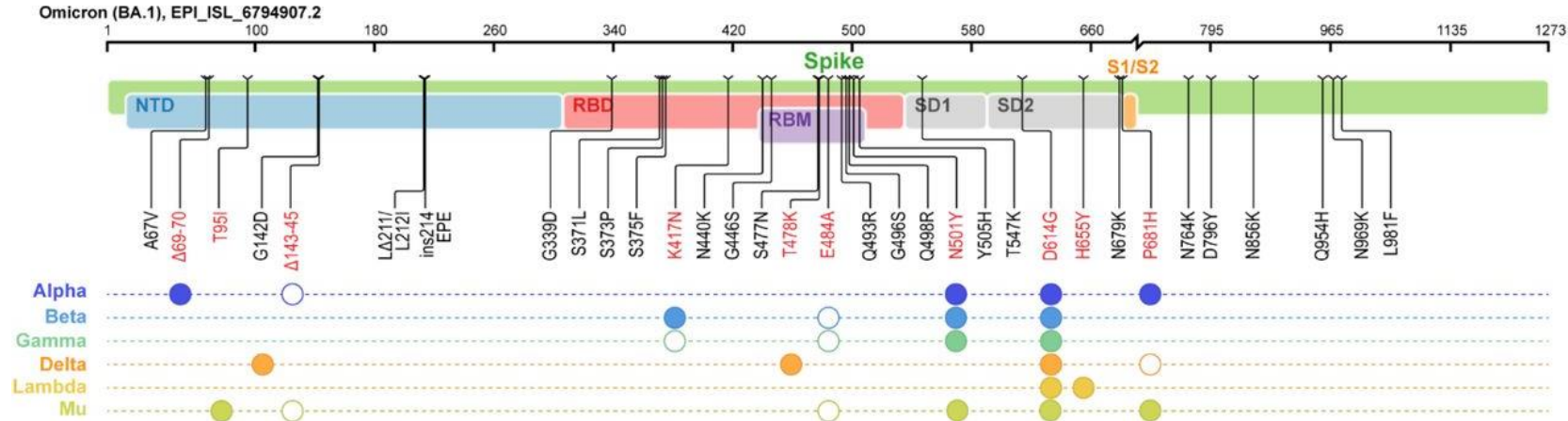
Monoclonal Antibodies – not all the same

- Binding sites
- Neutralising activity
- Breadth
- Resistance in VOCs
- Antibody-dependent cellular cytotoxicity
- Pharmacology



<https://www.antibodysociety.org/covid-19-biologics-tracker>





Planas et al
Nature: 23 December 2021

• Delta
• Omicron

mAbs and Ab-like molecules

Monoclonal Antibodies

Ab- like molecules

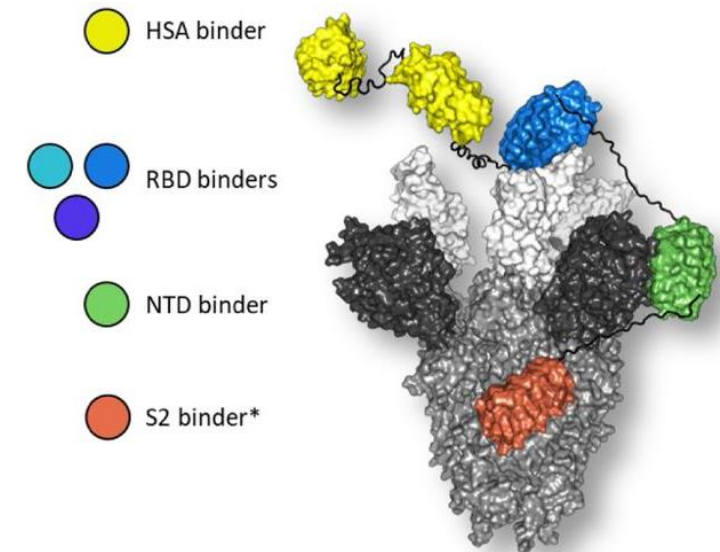
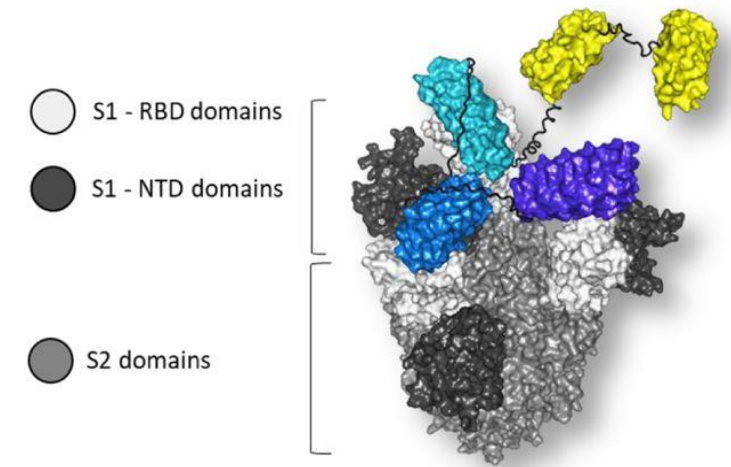
- IgY (egg-yolk immunoglobulin)
- Camelid antibodies /nanobodies (15-75k kDa)
- DARPins (designed ankyrin repeat protein)
- others

Ensovibep

- 'designed ankyrin repeat protein', or DARPin
- designed to bind to three different locations on spike protein
- prevent the virus from infecting human cells

EMPATHY (Phase 2/3)

- Phase 2 (N=407) - significant VL reduction over 8d at 75mg, 225mg and 600mg
- Hospitalisations/ER visits 6/99 (6%) controls vs 4/301 (1.3%) ensovibep
- Phase 3 in progress (75mg)



Small Molecules

Directly Acting Antivirals

- Remdesivir (iv) and GS-441524 (o)
- Molnupiravir
- Favipiravir
- Nirmatrelvir/r (Paxlovid)
- S-217622
- AT-527

www.covid19-druginteractions.org



COVID-19 Drug Interactions



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	Molnupiravir [Lagevrio]	Nirmatrelvir/ritonavir [Paxlovid] (Please read the interaction details as management of these interactions may be complex.)	Remdesivir [Veklury]	Sotrovimab [Xevudy]	Tixagevimab/ Cilgavimab [Evusheld]
Acenocoumarol	◆	■	◆	◆	◆
Apixaban	◆	●	◆	◆	◆
Argatroban	◆	◆	◆	◆	◆
Aspirin (Anti-platelet)	◆	◆	◆	◆	◆
Betrixaban	◆	■	◆	◆	◆
Clopidogrel	◆	●	◆	◆	◆
Dabigatran	◆	■	◆	◆	◆

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Olanzapine	◆	◆	◆	◆	◆
Paliperidone	◆	▲	◆	◆	◆
Perazine	◆	■	◆	◆	◆
Periciazine	◆	◆	◆	◆	◆
Perphenazine	◆	▲	◆	◆	◆
Pimozide	◆	●	◆	◆	◆
Pipotiazine	◆	◆	◆	◆	◆
Quetiapine	◆	●	◆	◆	◆
Risperidone	◆	■	◆	◆	◆

www.covid19-druginteractions.org

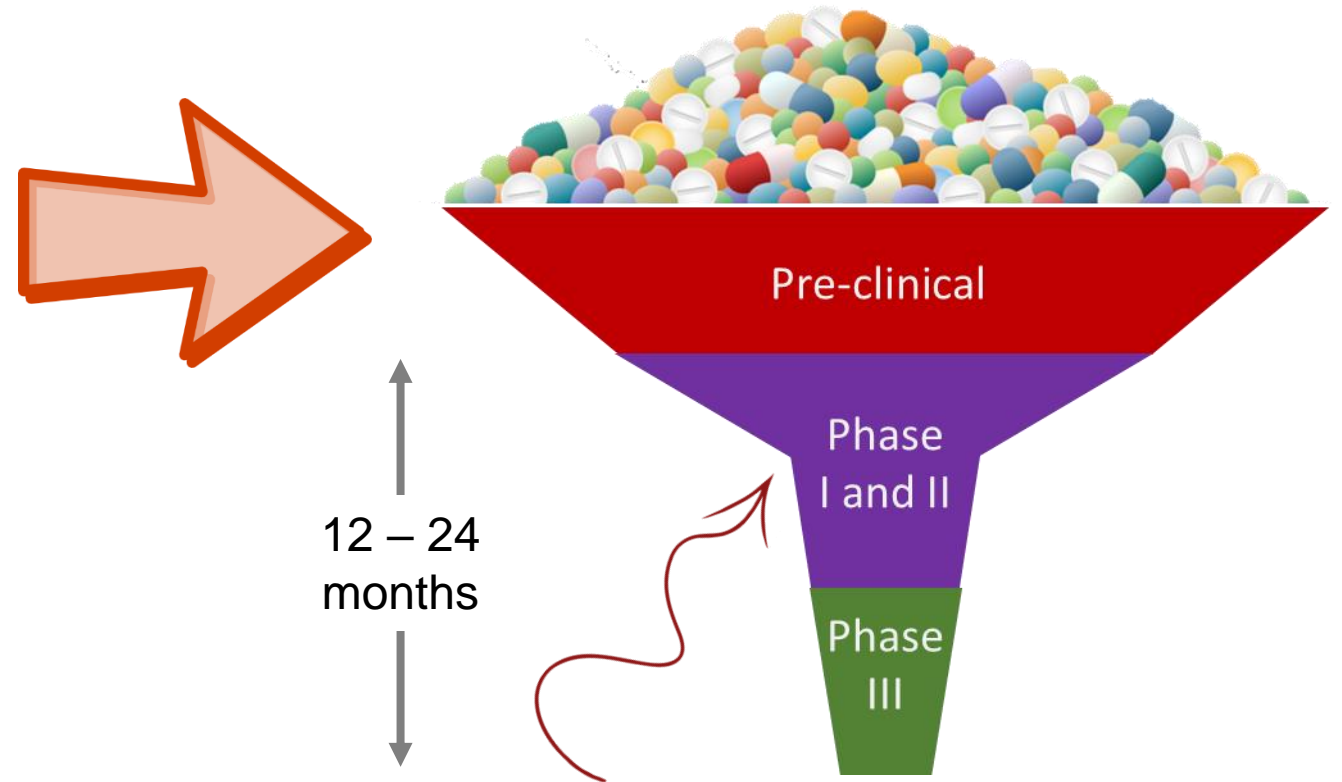
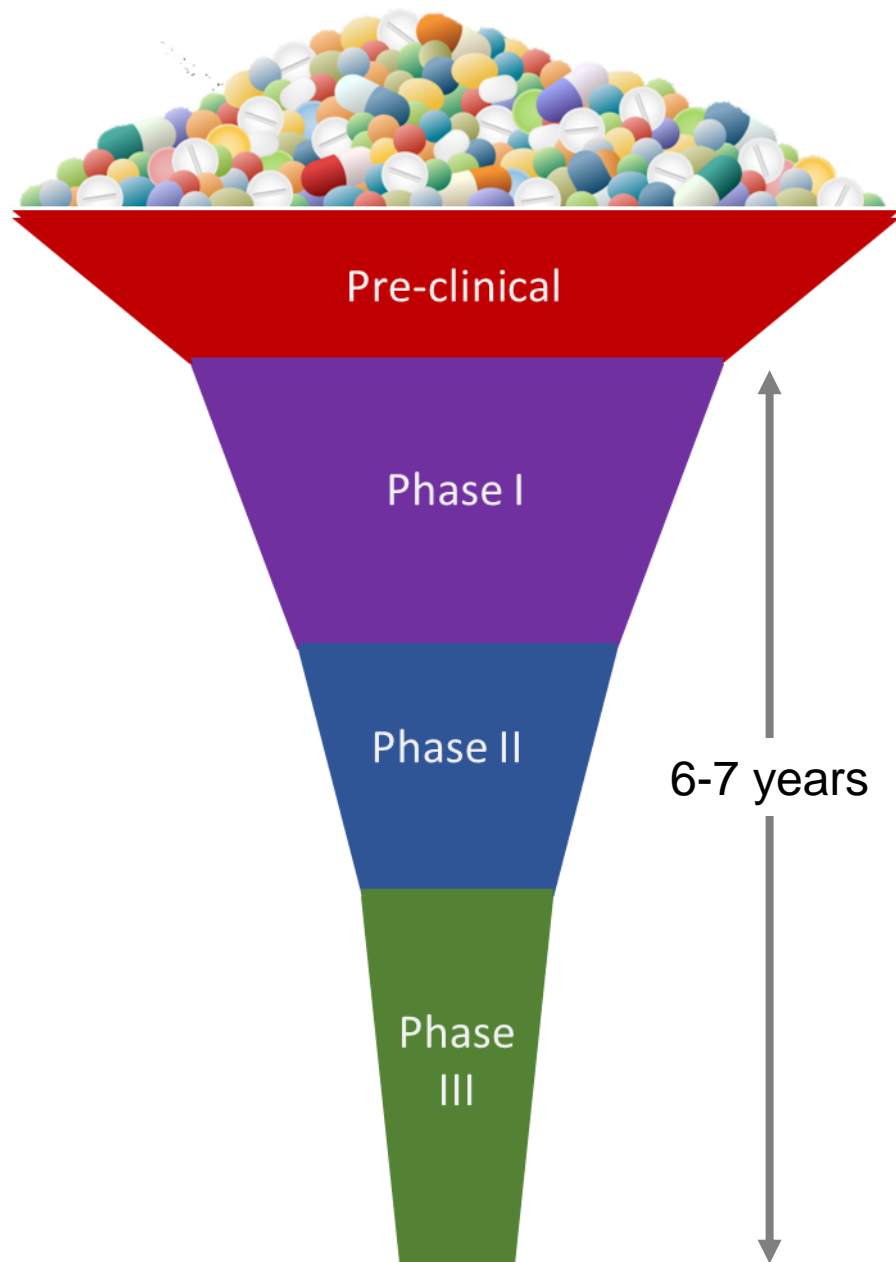


COVID-19 Drug Interactions



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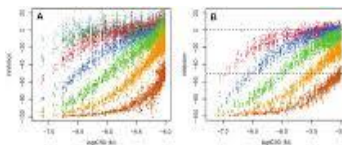
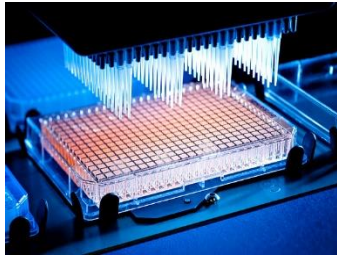
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Amiodarone	◆	●	◆	◆	◆
Bepridil	◆	●	◆	◆	◆
Digoxin	◆	■	◆	◆	◆
Disopyramide	◆	●	◆	◆	◆
Dofetilide	◆	●	◆	◆	◆
Flecainide	◆	●	◆	◆	◆
Lidocaine (Lignocaine)	◆	■	◆	◆	◆
Mexiletine	◆	■	◆	◆	◆
Propafenone	◆	●	◆	◆	◆
Quinidine	◆	●	◆	◆	◆



Early-phase drug development:

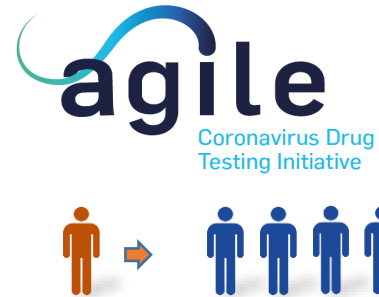
- **Fast-track** promising candidates
- **Screen-out** compounds with limited potential
- **Accelerate** decision-making
- Seamlessly **transition** between phases
- Test **multiple** candidates at once

Late preclinical



FIH – Ib

IIa

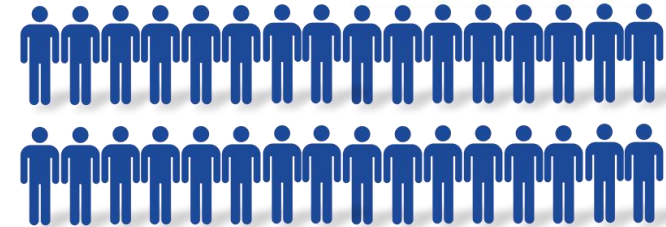


IIb

III

RECOVERY
Randomised Evaluation of COVID-19 Therapy

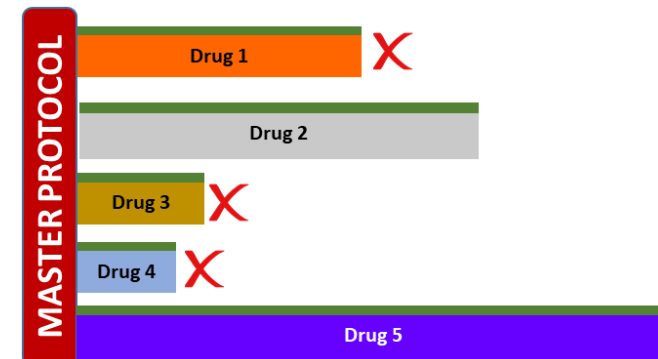
PRINCIPLE
Platform Randomised trial of Interventions
against COVID-19 in older people



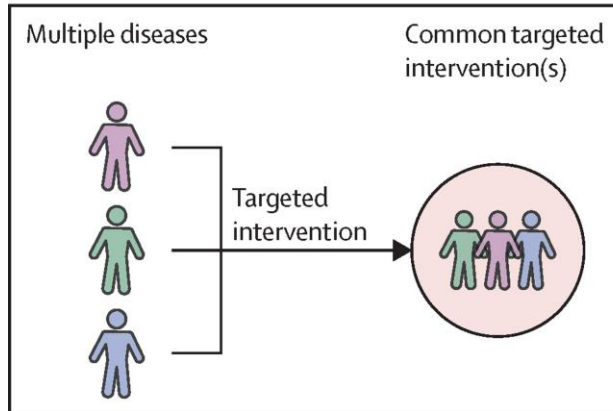
Multi-arm, multi-stage, adaptive Bayesian platform trial
Community or hospital
Antiviral or host targets

- **Pragmatic**
- **Flexible**
- **Seamless**
- **Efficient**

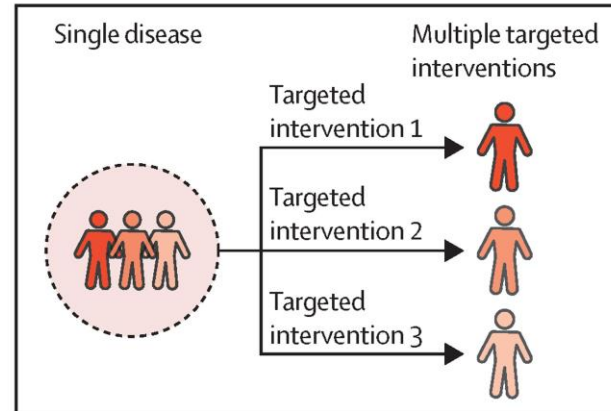
FIH in COVID patients
endpoints tailored to drug action
population tailored to expected deployment
phase I → II
Bayesian approach to decision-making



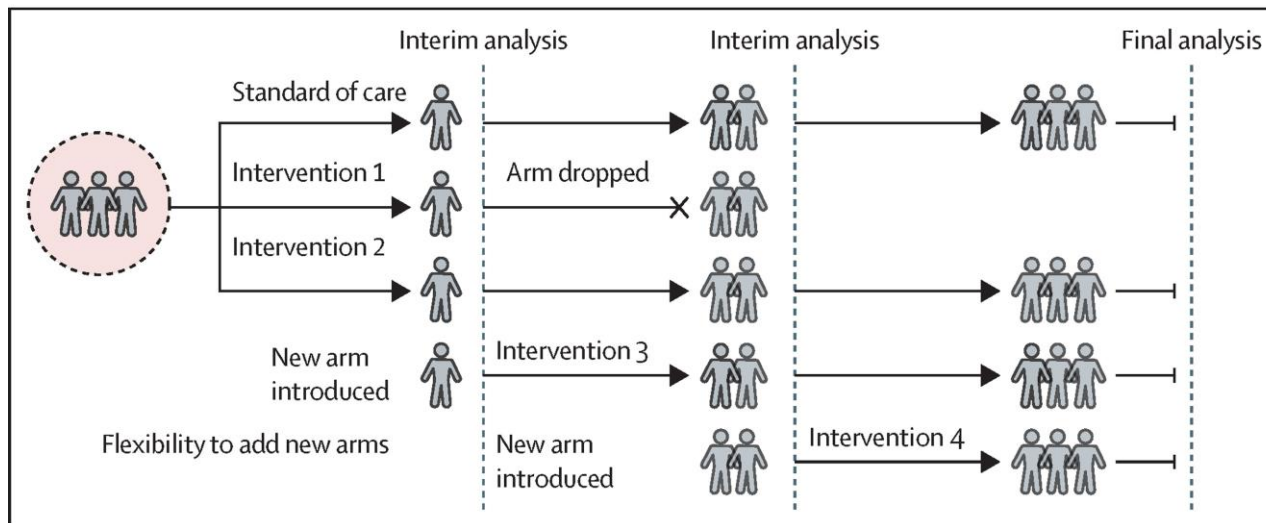
Basket trial



Umbrella trial



Platform trial



Flexibility to

- Drop arms
- Introduce new arms
- Re-estimate N within an arm
- Response adaptive randomization – adapt allocation ratio
- Share controls (with caveats)
- Enrich subgroups of particular interest
- etc

ANTICOV

RECOVERY
Randomised Evaluation of COVID-19 Therapy

COMBATCOVID

OTAC
INSIGHT012

ACTIV-4

ACTIV-6

ACTIV-1 IM
Randomized Master Protocol for
Immune Modulators for Treating COVID-19

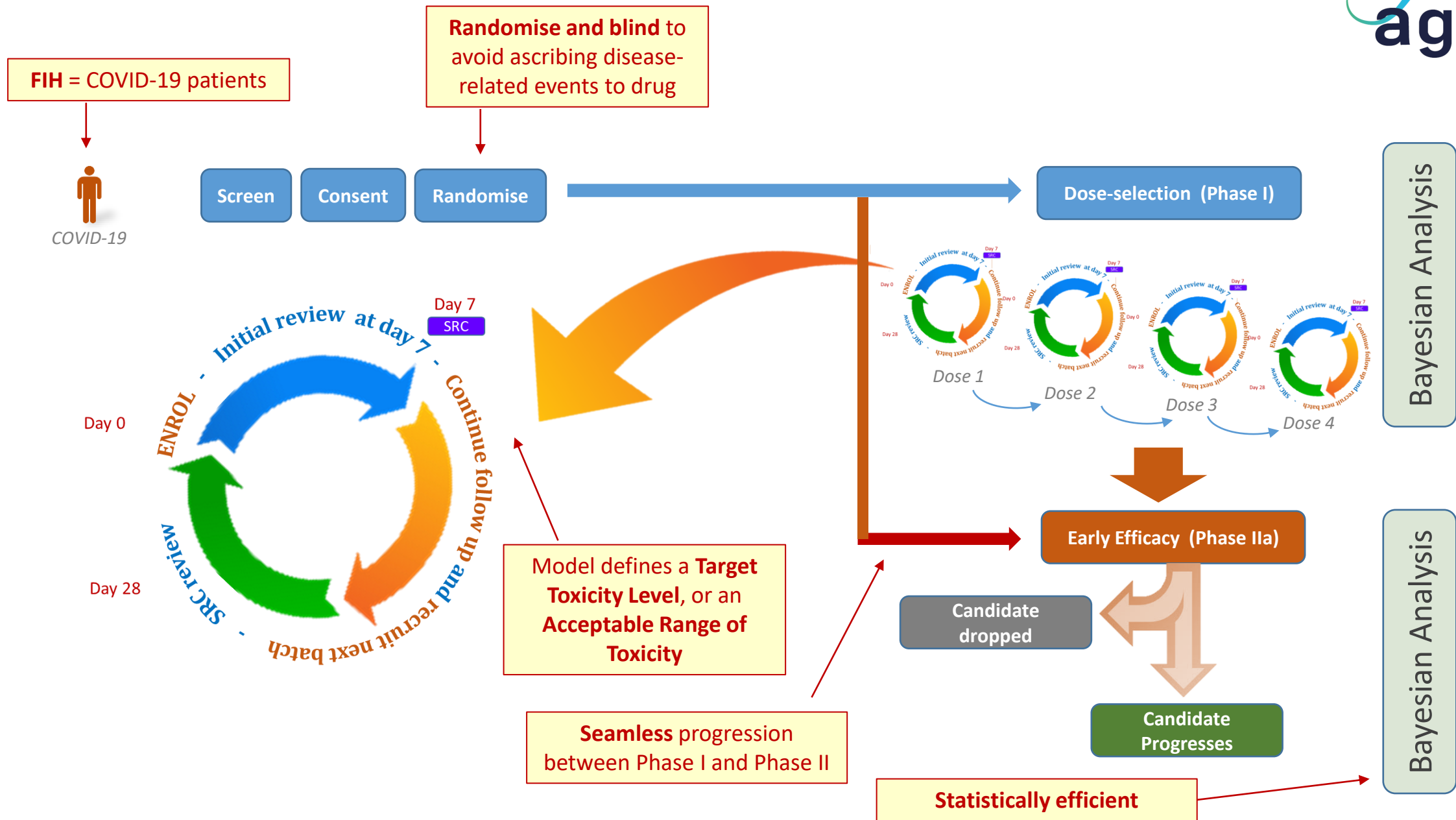
PRINCIPLE
Platform Randomised trial of Interventions
against COVID-19 In older peoPLE

REMAP-CAP

PANORAMIC
Platform Adaptive trial of NOvel
antivirals for eArly treatMent of
COVID-19 In the Community

together•COVID-19
clinical trials

SOLIDARITY TRIAL PLUS



How the Bayesian Model Works

- Efficient use of Information
- **Accelerates Decision-Making**

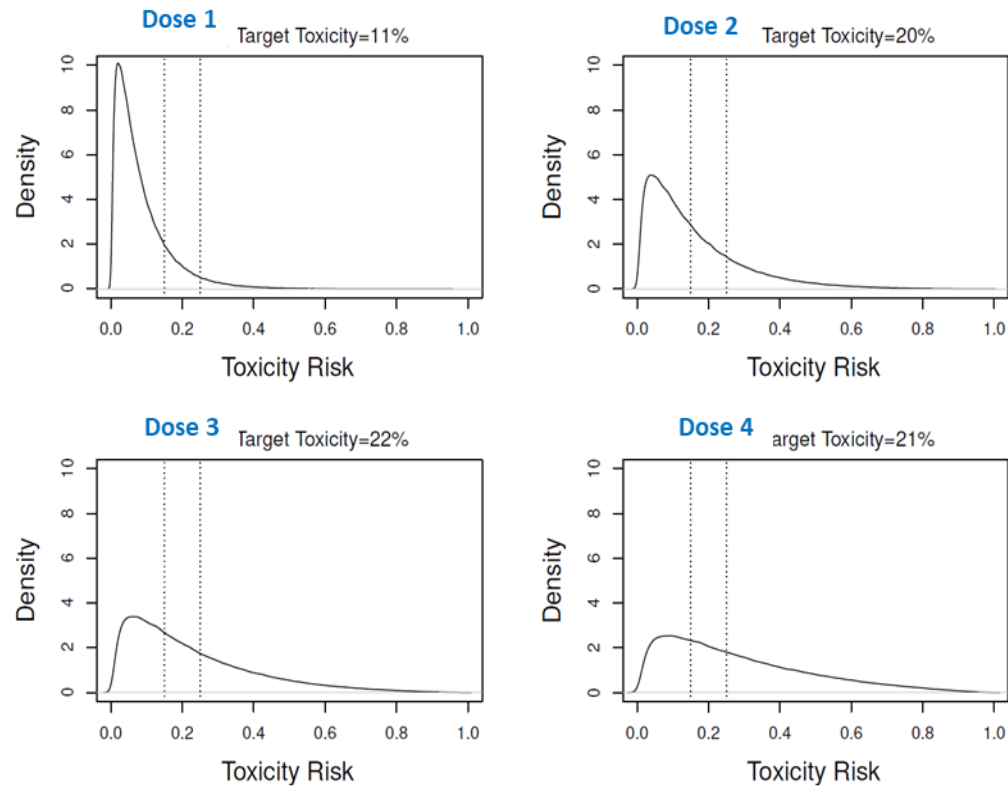


Establishing Safe Dose (Phase I)

- Prior is set to maximise probability of accurate dose selection for phase II
- Borrows information across doses
- Dose-limiting toxicities: Dose is **unsafe if $\geq 25\%$ chance that treatment gives $\geq 30\%$ higher DLTs** over controls
- **Next dosing tier set as closest to a 20% (tolerance 15-25%) increase in DLT**
- Next dosing tier no more than double last dosing tier

How the Bayesian Model Works

Prior Distribution on Each Dose

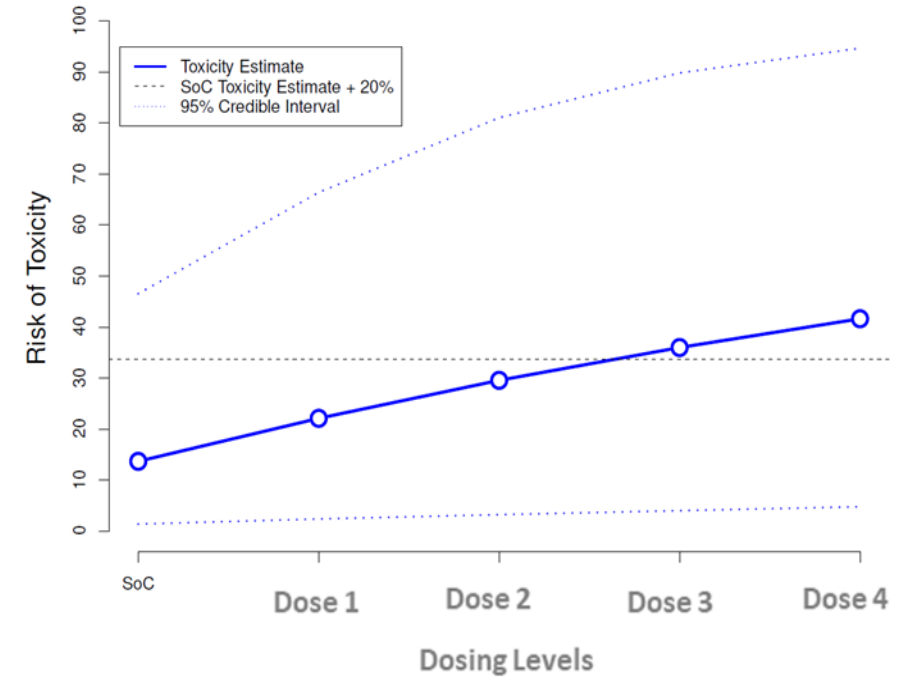


Dose-Toxicity Model

$$\text{logit} p_j = \theta_1 + \theta_2 \tilde{d}_j$$

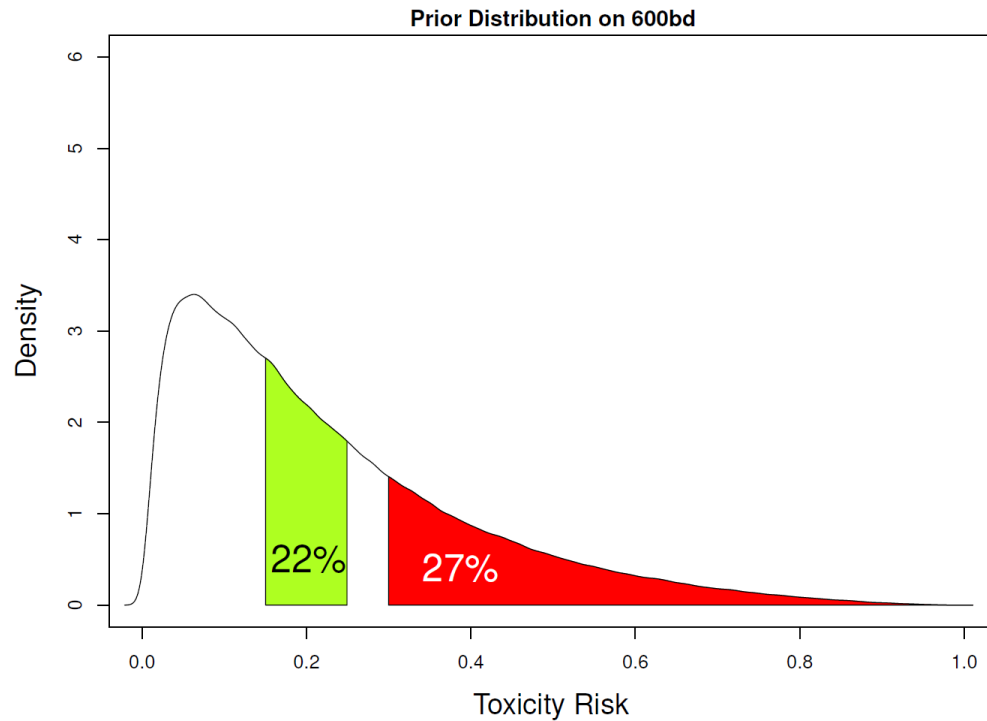
- \tilde{d}_j are the standardized dose levels
- θ_1 (intercept), θ_2 (slope) are (continuously updated) parameters;

Dose-Toxicity Model

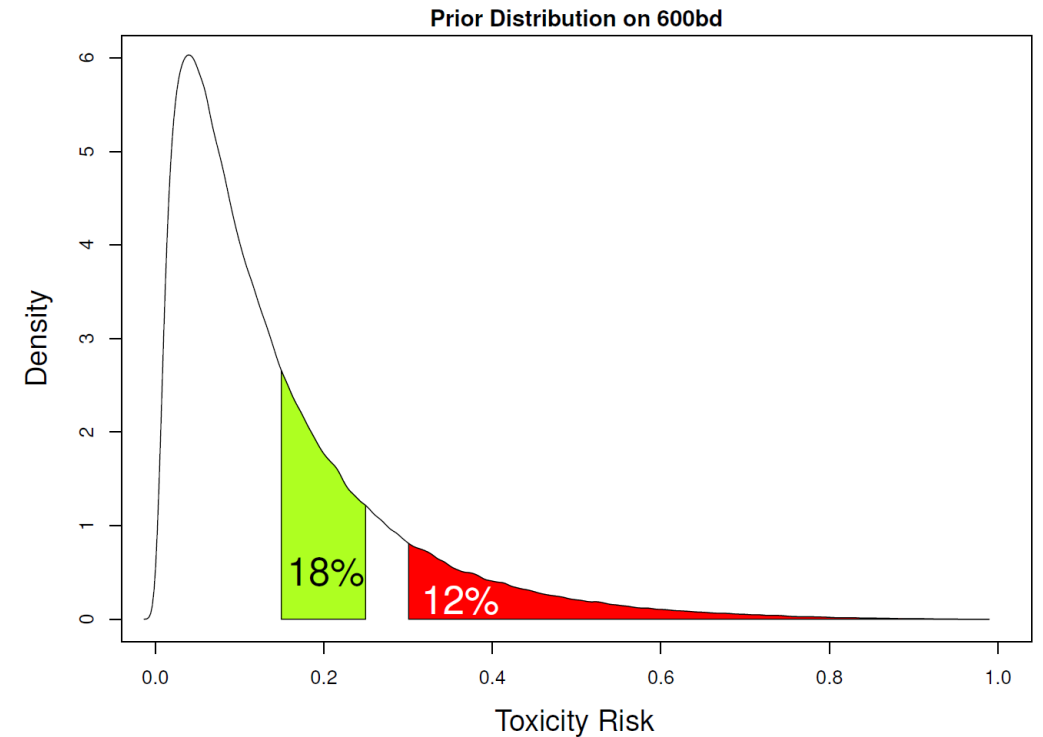


How the Bayesian Model Works

Prior Distribution on 600bd



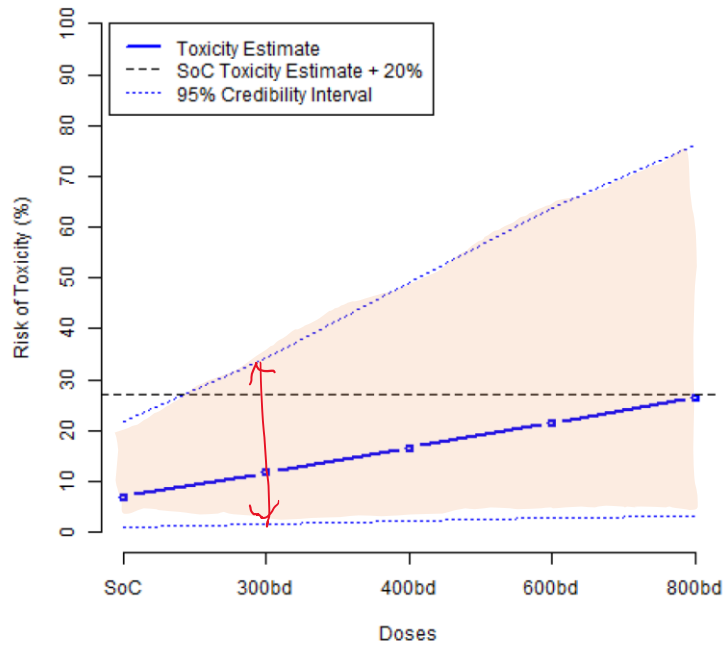
Posterior Distribution on 600bd



Case Study - Molnupiravir

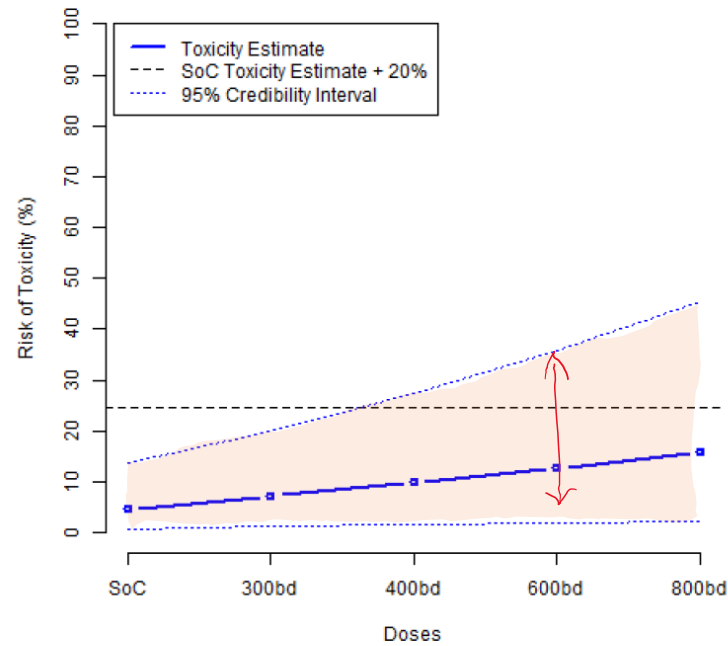
Cohort 1 – 300mg bd

Dose-Toxicity Plot (7 day data only)



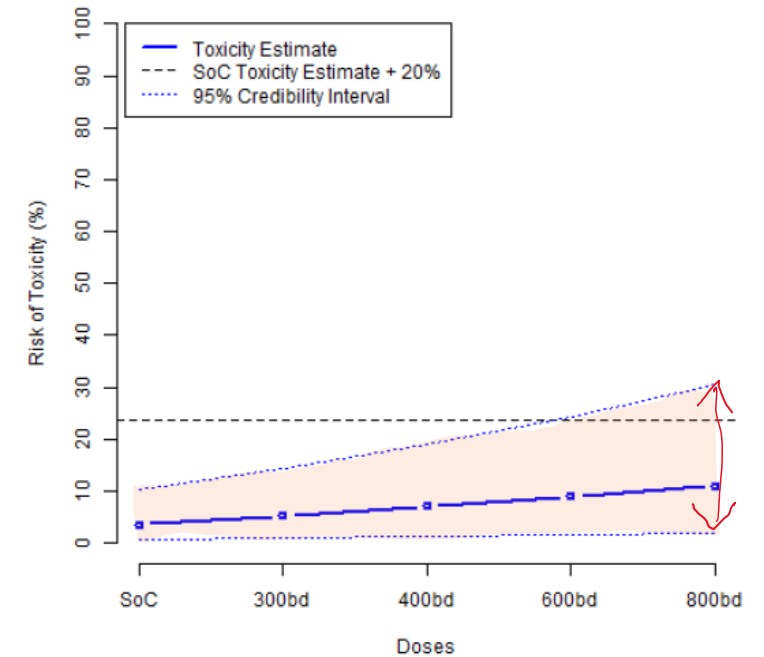
Cohort 2 – 600 mg bd

Dose-Toxicity Plot (7 day data only)



Cohort 3 800mg bd

Dose-Toxicity Plot (7 day data only)



How the Bayesian Model Works

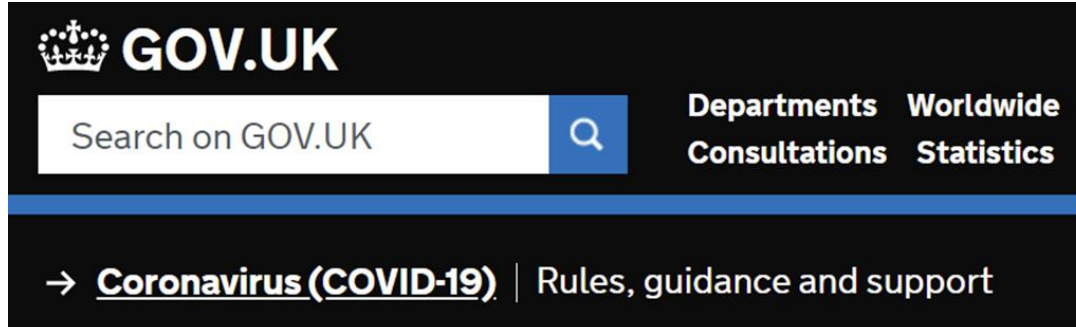
- Efficient use of Information
- Accelerates Decision-Making



Establishing Early Efficacy (Phase IIa)

- HR over control or placebo (e.g. virological response)
- **FUTILITY** if probability of HR >1 is <33%
- **EFFICACY** if probability HR >1 is >80%
- Interim evaluation

AGILE - Portfolio



Press release

Groundbreaking COVID-19 treatments to be fast-tracked through clinical trials

The world's most innovative treatments for COVID-19 will soon be fast-tracked through the UK's clinical trial system, as the government announces funding for the most promising treatments.

From: [Department of Health and Social Care](#)

Published 13 February 2021

AGILE CST-2 (molnupiravir)

- Phase Ib completed – dose optimized
- Phase IIa recruiting

AGILE CST-3 (high-dose nitazoxanide)

- Phase Ia completed – dose optimized
- Phase Ib/IIa under regulatory assessment (S Africa)

AGILE CST-5 (GSK/Vir 7832 monoclonal antibody)

- Phase I recruiting (FIH cycle 3)

IN DEVELOPMENT

Conclusions

- **COVID has accelerated use of Master Protocols and Platform Trials**
- **Coupled with statistically efficient methods to offer flexibility, responsiveness, and accelerated decision making**
- **Could be applied to LMIC settings**
- **A vital tool for medical countermeasures during PH emergencies**



Saye Khoo
 Andrew Owen
 Helen Reynolds
 Bill Greenhalf
 Julian Hiscox
 Tori Shaw
 Laura Else
 Justin Chiong
 Michelle Tetlow



Liverpool CRF

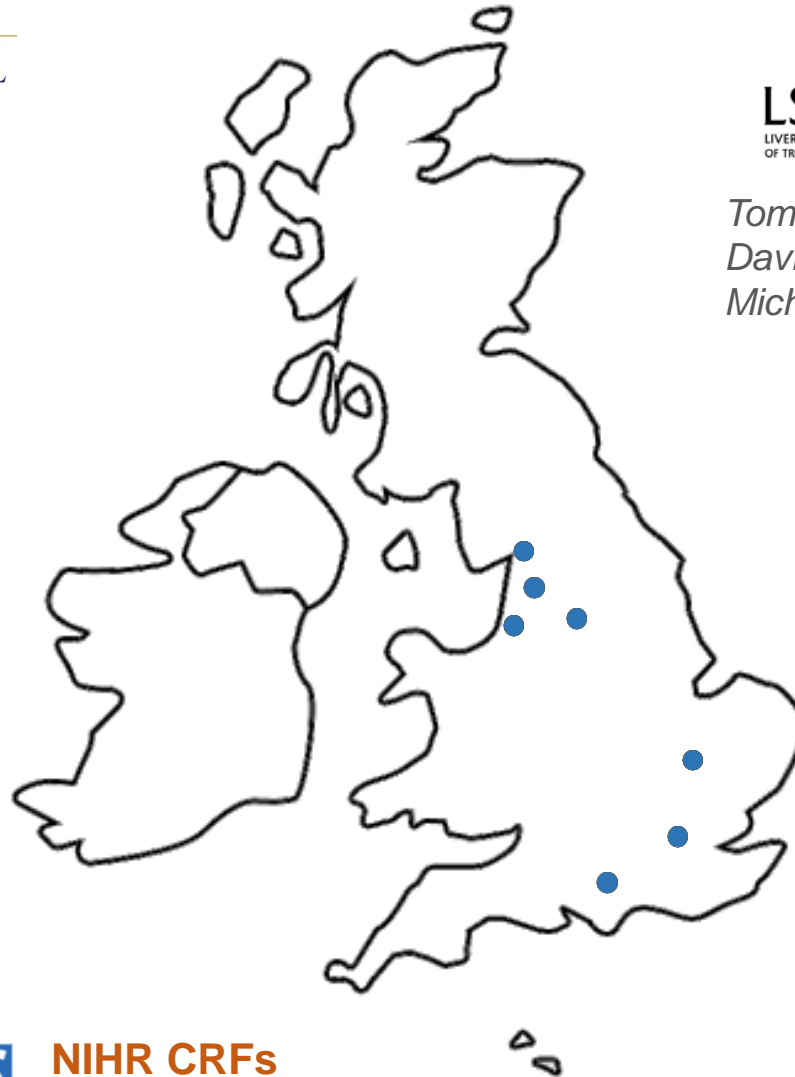
Richard Fitzgerald
 Lauren Walker
 Rebecca Lyon
 Christie Woods
 Marcin Bula



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NIHR CRFs

Manchester
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 London



Tom Fletcher
 David Laloo
 Michael Jacobs



Southampton Clinical Trials Unit

Gareth Griffith
 Sean Ewings
 Geoff Saunders
 Andrea Corkhill
 Nicky Downs
 Emma Knox
 Anna Song
 et al



Thomas Jaki
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Infectious Diseases Institute

Shevin Jacob
 Mohamed Lamorde



University of Cape Town

Catherine Orrell



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