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Fast clinical assessment of antivirals in a crisis response: AGILE

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agile
Coronavirus Drug Testing Initiative

COVID-19 Drug Interactions

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Disclosure Statement

agile Coronavirus Drug Testing Initiative

- *Core funding from Wellcome, MRC, and UKRI*
- *Trial funding from Unitaid, Ridgeback Biotherapeutics, GSK and Vir Biotechnology*
- *Infrastructure support from NIHR*

COVID-19 Drug Interactions

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- *Funding from UKRI, European AIDS Clinical Society, British HIV Association*
- *Additional funding from Merck, Pfizer, Novartis, Gilead, Abbvie, Sobi*

Other

- *Research grants from ViiV, Gilead, Merck*
- *Speaker's honoraria from ViiV, Merck, Pfizer*

See also :
https://www.liverpool.ac.uk/systems-molecular-and-integrative-biology/staff/saye-khoo/external-engagement/

New Antiviral Treatments for COVID -19

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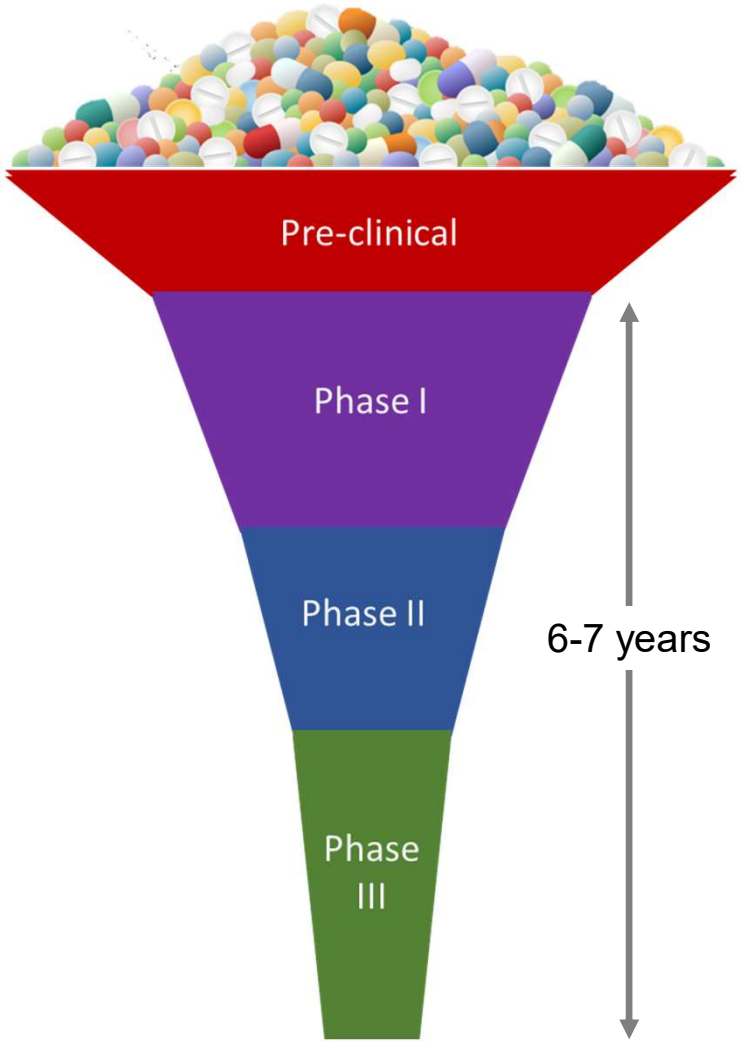
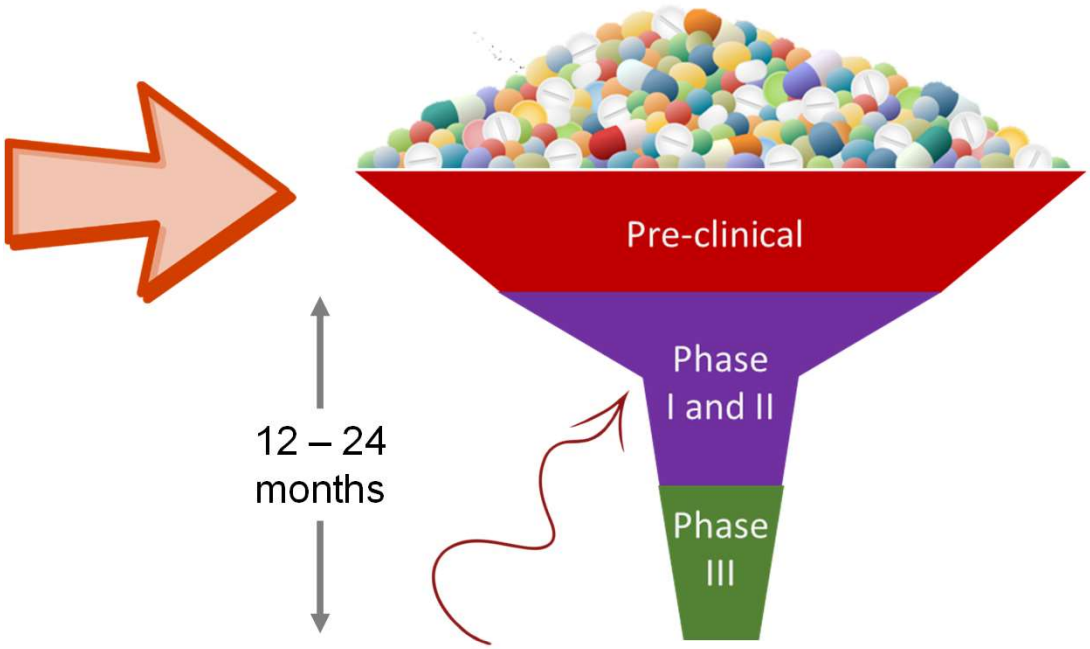
The Problem:

- **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 (directly-acting antiviral) small molecules**
  - *'repurposing' was always a stopgap, not the destination*
  - *mAbs not a globally scalable health solution*

- **Research in a very challenging environment**
  - *facilities, staff, environment, infection control, public health*
  - *opportunity costs: bad trials costs lives*

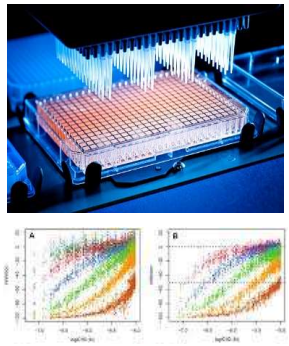




Early-phase drug development:

- **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



Meet drug wherever it is

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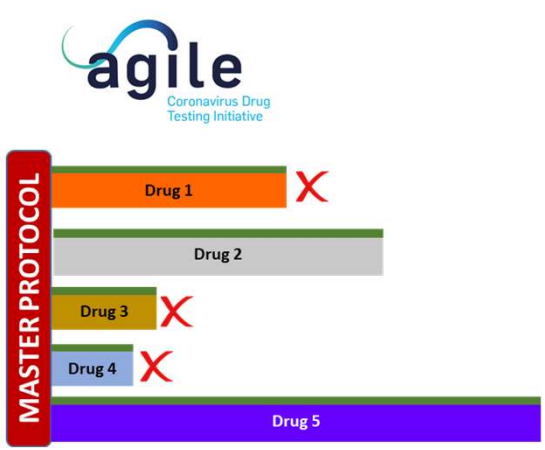
Pass drug on with enough evidence

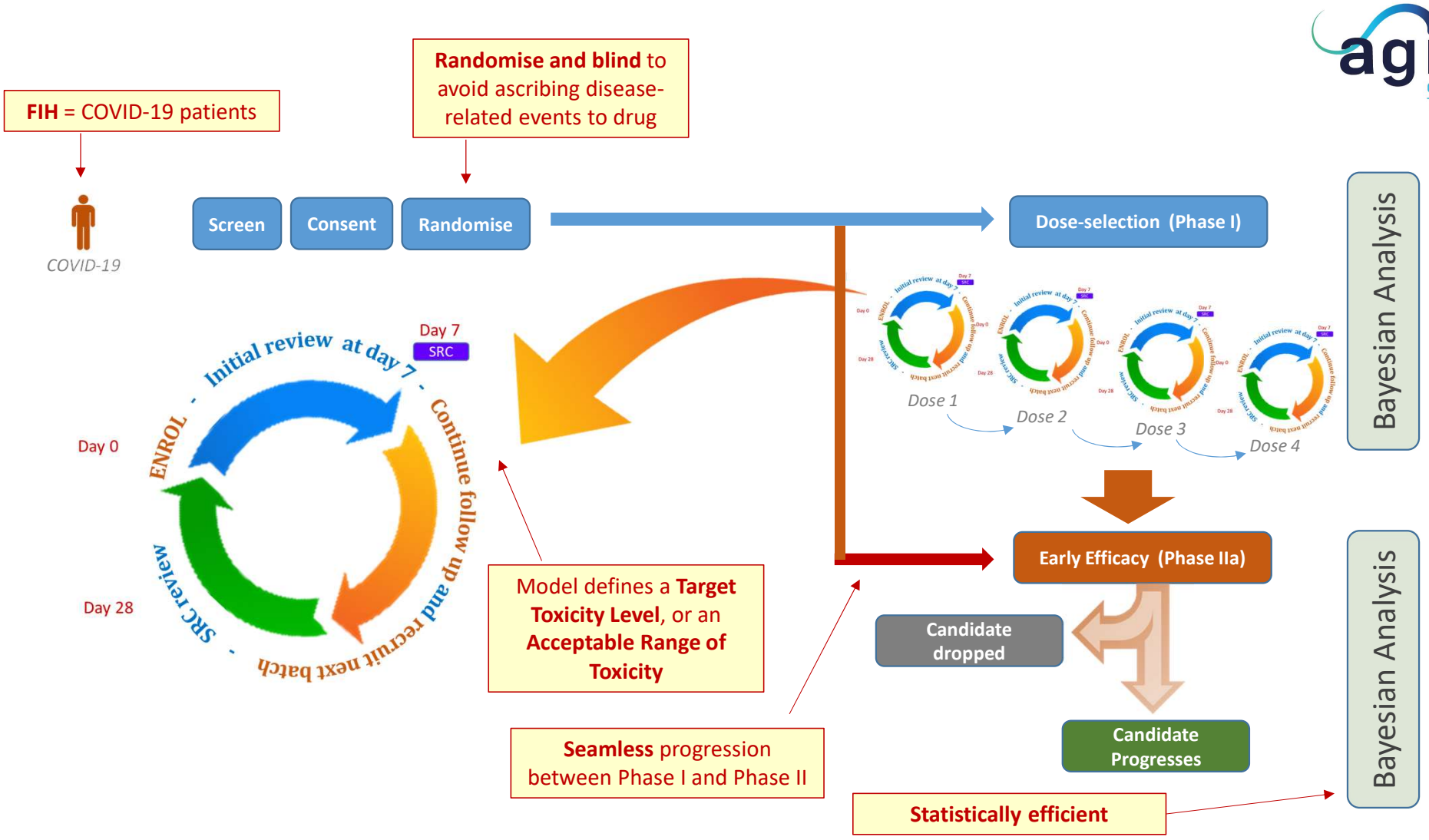
RECOVERY Randomised Evaluation of COVID-19 Therapy

PANORAMIC



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

- **Pragmatic** — FIH in COVID patients
- **Flexible** — endpoints tailored to drug action
  population tailored to expected deployment
- **Seamless** — phase I → II
- **Efficient** — Bayesian approach to decision-making


FIH = COVID-19 patients
Randomise and blind to avoid ascribing disease-related events to drug
COVID-19
Screen
Consent
Randomise
Dose-selection (Phase I)
Bayesian Analysis
Day 0
Day 7
SRC
Day 28
ENROL
Initial review at day 7
Continue follow up and recruit next batch
SRC review
Dose 1
Dose 2
Dose 3
Dose 4
Model defines a Target Toxicity Level, or an Acceptable Range of Toxicity
Early Efficacy (Phase IIa)
Candidate dropped
Candidate Progresses
Seamless progression between Phase I and Phase II
Statistically efficient
Bayesian Analysis

How the Bayesian Model Works

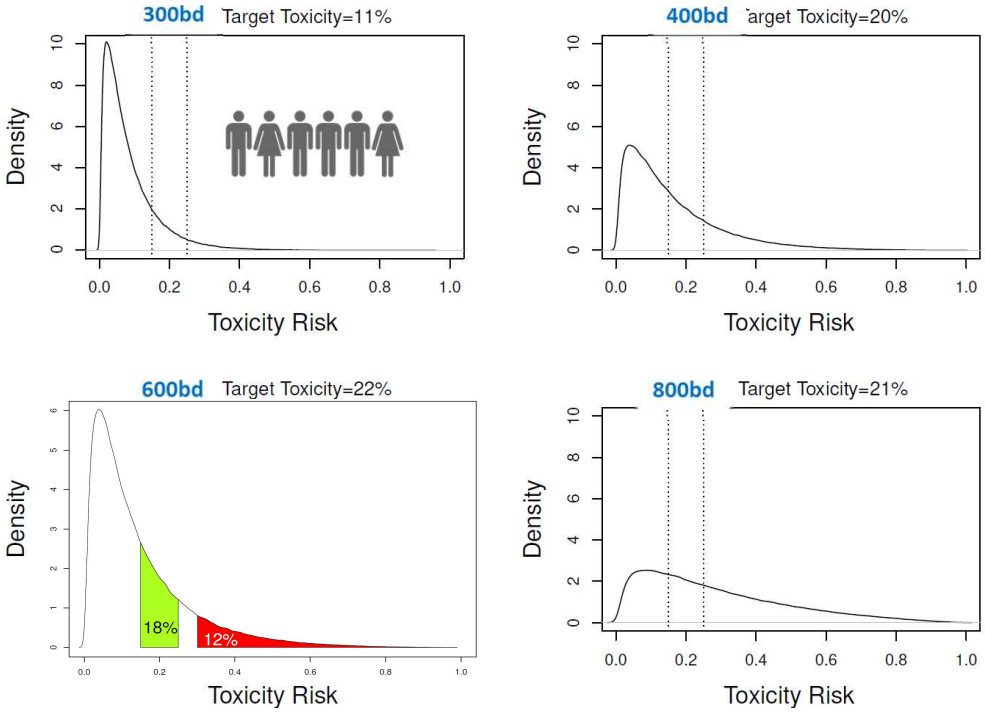
- Efficient use of Information
- **Accelerates Decision-Making**

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 ≥25% chance that treatment gives ≥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

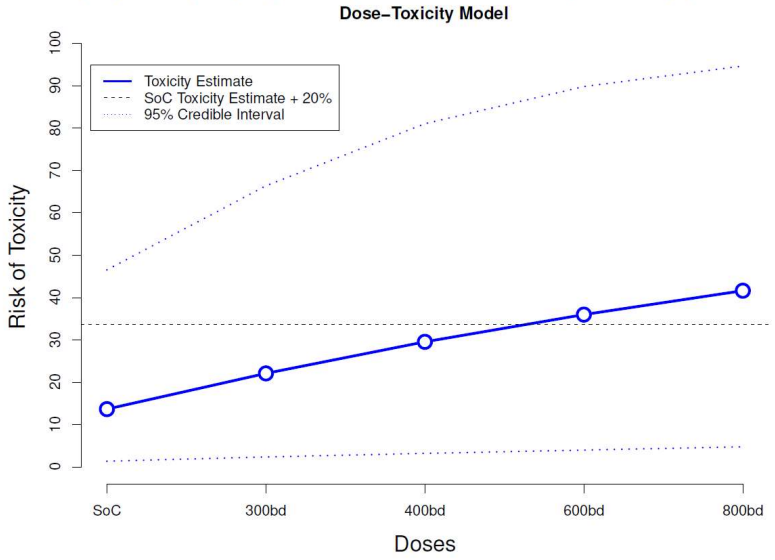
Prior Distribution on Each Dose



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;



Case Study - Molnupiravir

Cohort 1 – 300mg bd

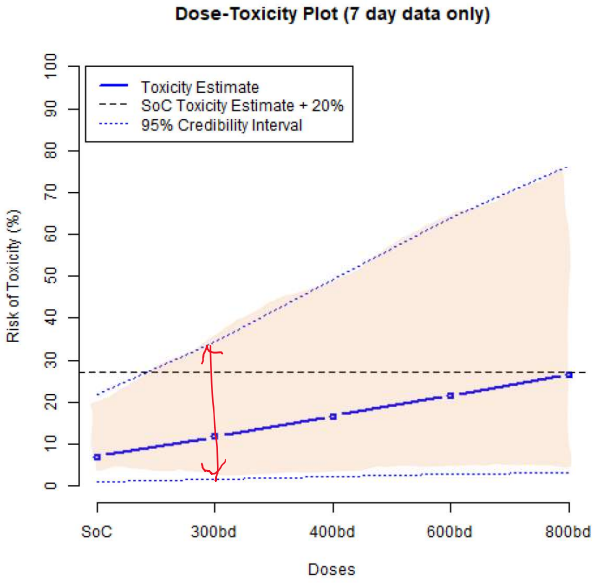


Figure 1: Dose-toxicity plot based on seven-day data only

Cohort 2 – 600 mg bd

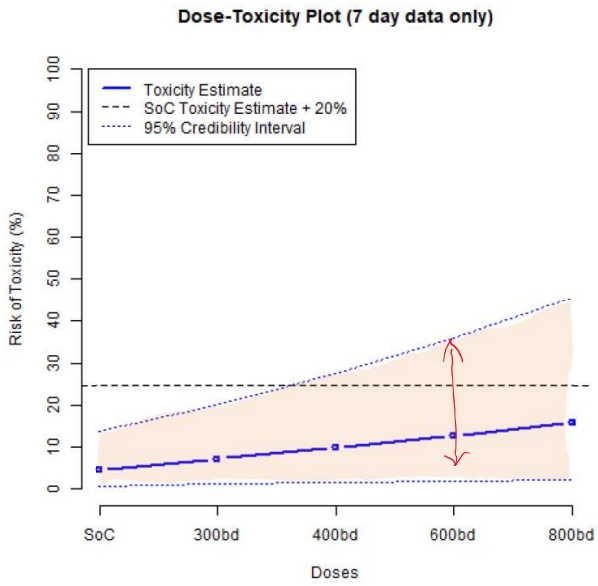


Figure 5.1: Dose-toxicity plot based on seven-day data only

Cohort 3 800mg bd

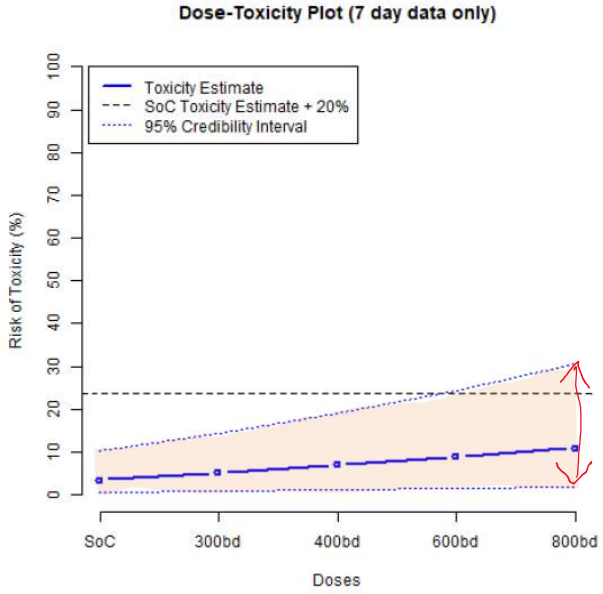


Figure 5.1: Dose-toxicity plot based on seven-day data only

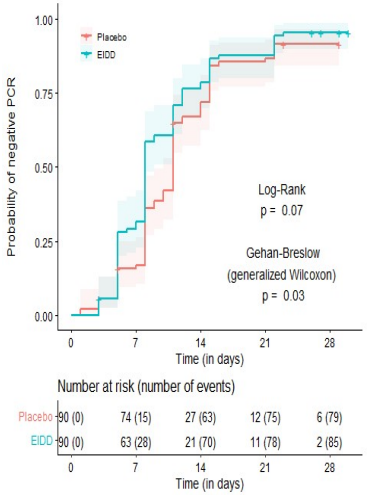
Khoo et al. J Antimicrob Chemother 2021 Aug 27

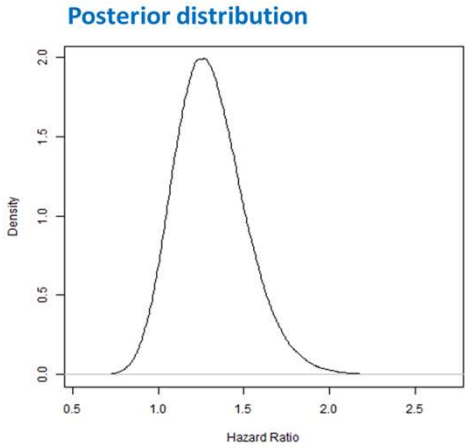
How the Bayesian Model Works

- Efficient use of Information
- Accelerates Decision-Making

Establishing Early Efficacy (Phase IIa)

- **Virological endpoints as markers of killing activity**
- Cannot extrapolate to clinical efficacy
- 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



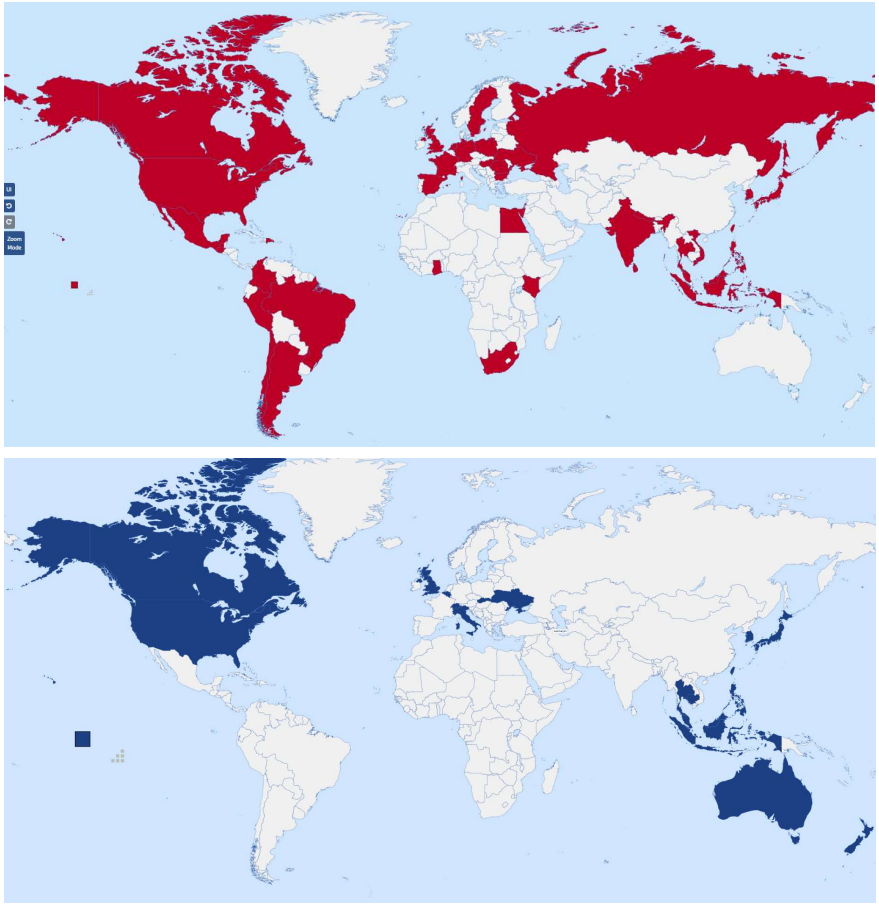


Lessons Learned

- **Tailor efficacy endpoints to Phase of trial**
  - *killing virus ≠ saving lives*
- **Don't conflate 'effective' with 'affordable'**
  - *don't settle for less when repurposing*
- **Importance of publicly-funded trial platforms**
  - *able to develop protocols 'at-risk'*
  - *access candidates from academia and small-medium biotech*
  - *rational design and timely evaluation of combinations*
- **Building 'Peacetime' research, not just research capacity**
  - *build up knowledge 'libraries' for drugs, PK and PK-PD models*
- **Access, access, access**
  - *post-trial access*
  - *role of publicly-funded platforms*

Molnupiravir

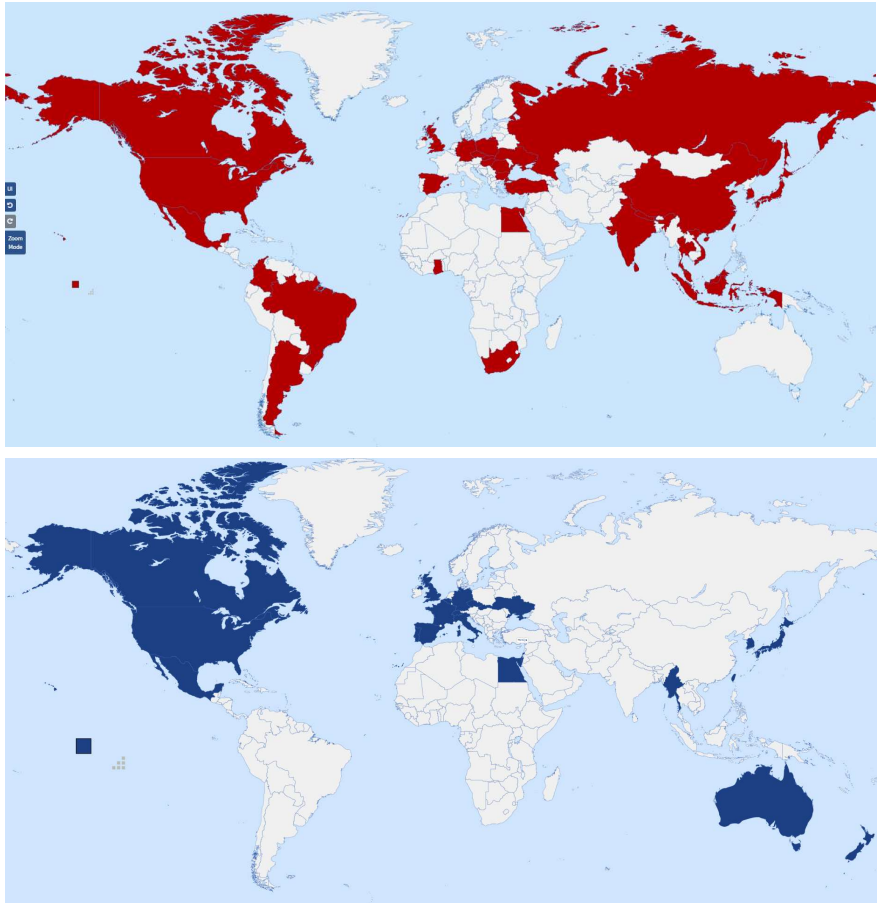
ClinicalTrials.gov 16 studies registered (2nd Oct 2022)



Purchases of molnupiravir (Lagevrio) by country
Excludes generics, and country distribution by Global Fund, ACT-A and UNICEF
Duke Global Health Innovation Center (updated 11th Nov 2022)
https://launchandscalefaster.org/covid-19/therapeutics

Nirmatrelvir/ritonavir

ClinicalTrials.gov 18 studies registered (2nd Oct 2022)



Paxlovid procurement announcements (April 11, 2022)
https://docs.google.com/spreadsheets/d/1fE1sB6VwrrqGTXReJb29IH_b-B6yeOhFRzsg0_D1GrQ/edit#gid=0
Usher. Lancet 2022;399:779-82#
Duke Global Health Innovation Center (updated 11th Nov 2022)
https://launchandscalefaster.org/covid-19/therapeutics

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www.covid19-druginteractions.org

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