Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia

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MEDICAL RESEARCH INSTITUTE OF NEW ZEALAND

anzic research centre

Disclosure Statement

REMAP-CAP

Employment

SJOG Healthcare, Monash University, Royal Perth Hospital

Research support from industry

Hospira/Pfizer, Vifor, Orion

Research support from non-industry sources

NHMRC, WA Department of Health, NZ Health Research Council, European Union FP7, Wellcome Trust, Intensive Care Foundation, Medical Research Future Fund, Canadian Institute of Health Research

Institutional

ANZICS CTG, ANZIC RC, George Institute, ISARIC, InFACT, MRINZ, ACTA, PREPARE, APPRISE

REMAP

- Randomised
- Embedded
- Multifactorial
- Adaptive
- Platform

Conventional (frequentist) trial designs require making multiple assumptions at time of trial design

Those assumptions are held as being constant throughout the trial, even if the assumptions are known to be false

Invalid assumptions can be a source of regret

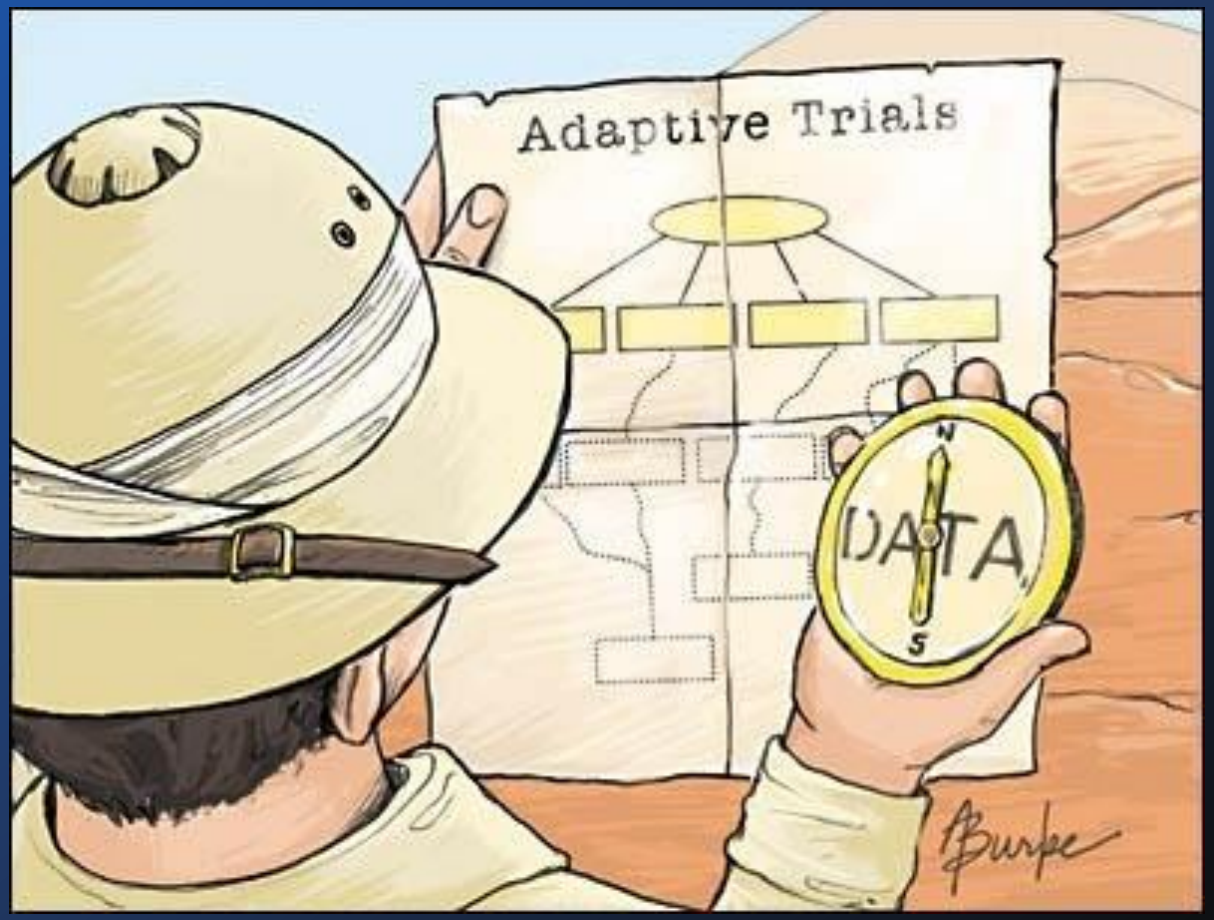
Assumptions in a conventional trial

- Control of type I error
- Size of treatment effect and control of type II error
- Right population is specified
- Not going to be any external information that will result in loss of equipoise
- Control of type III error (evaluating the right intervention)

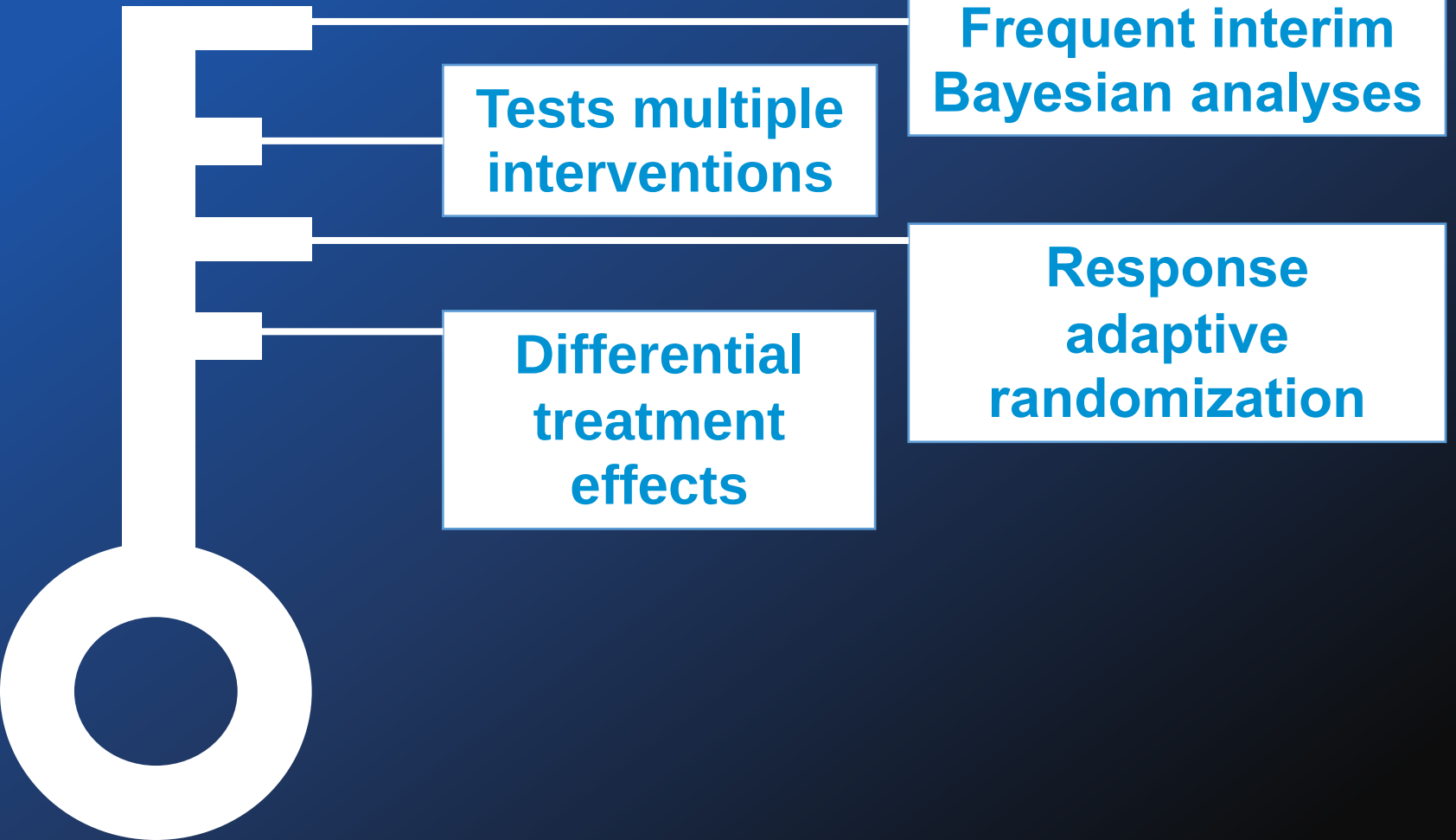
Assumptions in a conventional trial

- Right dose and right duration of treatment
- Made right choice between superiority, non-inferiority, or equivalence
- No heterogeneity of treatment effect
- No interaction between trial treatment and concomitant treatment

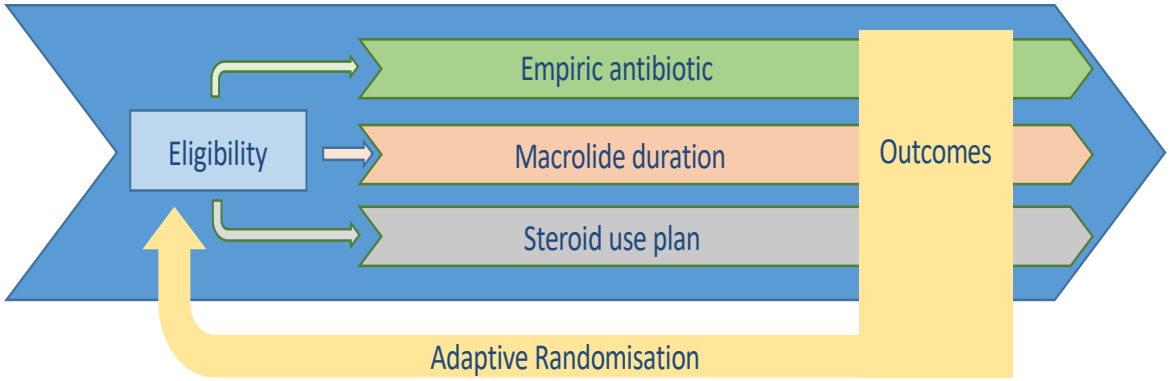
Adaptive Trials



Key Design Features of Platform Trials




Int A1
Int A2
Int A3…5
Antibiotic trial
Outcomes
Int B1
Int B2
Macrolide trial
Outcomes
Int C1
Int C2
Steroid use trial
Outcomes


Eligibility
Empiric antibiotic
Macrolide duration
Steroid use plan
Outcomes
Adaptive Randomisation

Pre-specified statistical triggers / frequent interim analyses

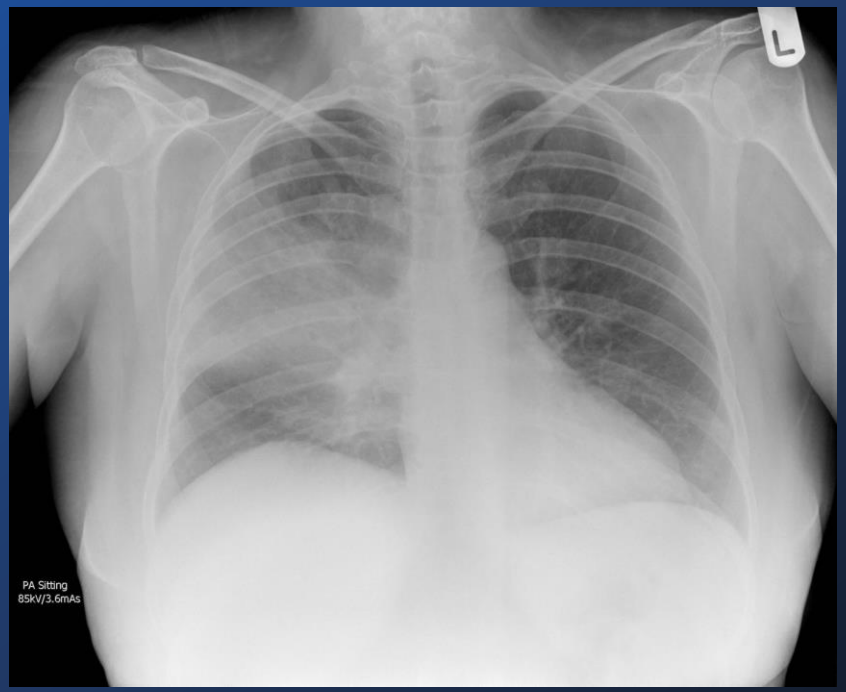
- Ordinal scale that is a composite of
  - in-hospital mortality
  - In survivors, days free of organ failure up to Study Day 21

- Odds Ratio greater than one = benefit

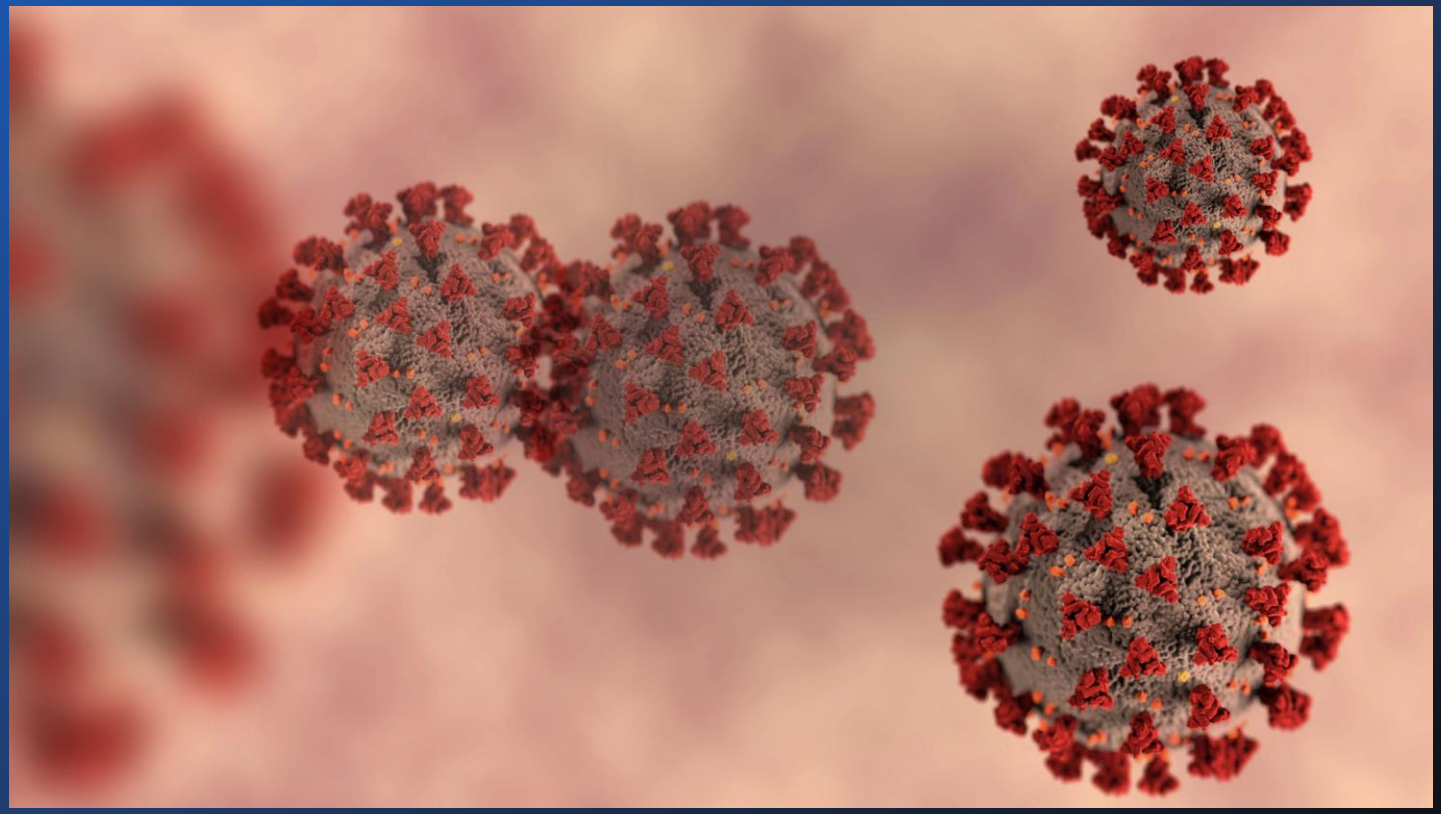
Pre-specified statistical triggers for interventions in a domain

- Superiority = better than all other interventions
- Inferiority = worse than all other interventions
- Effective = better than a SOC control
- Futility = insufficient evidence of substantial benefit
- Equivalent = two or more interventions within an OR delta of 0.2

In 2019, was a CAP trial



In 2020, adapted to be a CAP and a COVID trial



Pandemic infection suspected or proven

DOMAIN	INTERVENTIONS
Antiviral Domain	~~SOC~~ / ~~LPV~~ / ~~HCQ~~ / ~~LPV+HCQ~~
Immune Modulation	~~SOC~~ / interferon / anakinra / tociluzumab / sarilumab
~~Immunoglobulin~~	~~SOC / Convalescent plasma~~
~~Corticosteroid~~	~~SOC / fixed HCT / var HCT~~
Anticoagulation	~~DVT proph / anticoagulation~~
Vitamin C	SOC / vitamin C
Macrolide	3 day v 14 day AZT
Statin	SOC / simvastatin
Antiplatelet	SOC / aspirin / P2Y12 inhib
Ventilation	Protocolised / clinician prefer
Immune Modulation II	Placebo / eritoran / apremalist
ACE2 RAS	SOC / ACEi / ARB +/- DMX-200

Original Investigation | Caring for the Critically Ill Patient FREE

September 2, 2020

Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19

The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial

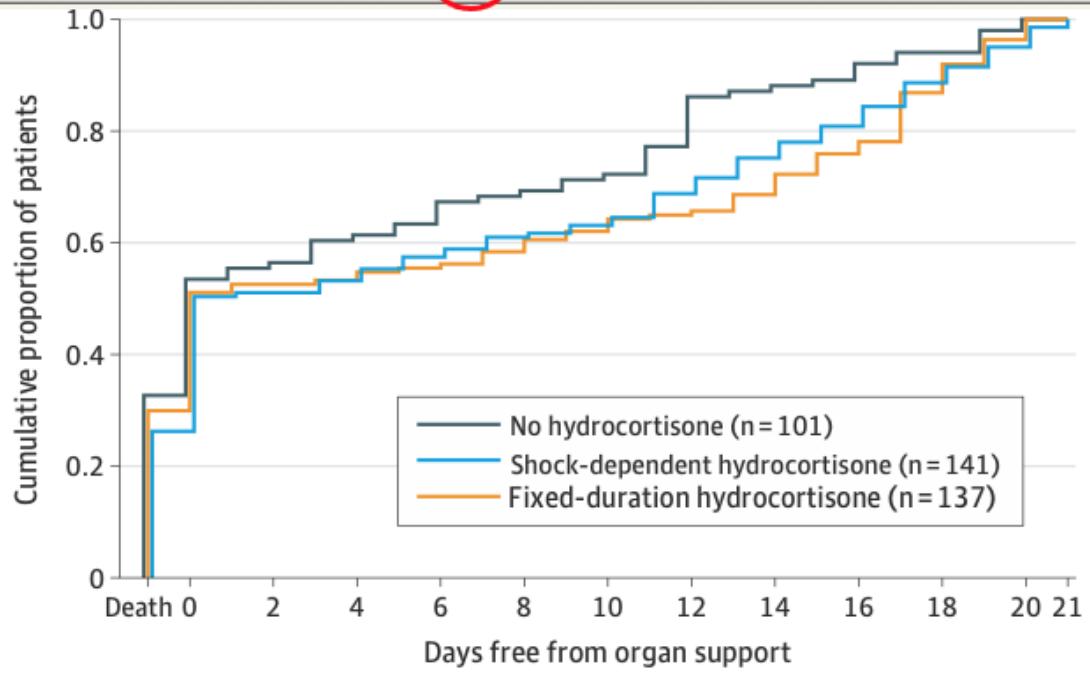
The Writing Committee for the REMAP-CAP Investigators

Article Information

JAMA. 2020;324(13):1317-1329. doi:10.1001/jama.2020.17022

Cumulative distribution of organ support-free days

Outcome/Analysis[a]	Fixed-dose hydrocortisone (n = 137)	Shock-dependent hydrocortisone (n = 141)	No hydrocortisone (n = 101)
Primary analysis of the primary outcome, using covariate data from all severe-state participants with COVID-19 (n = 576)[b]			
Adjusted odds ratio			
Mean (SD)	1.47 (0.35)	1.26 (0.31)	1 [Reference]
Median (95% CrI)	1.43 (0.91 to 2.27)	1.22 (0.76 to 1.94)	1 [Reference]
Probability of superiority to no hydrocortisone, %	93	80	



Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19 – Preliminary report

The REMAP-CAP Investigators

Table 2. Primary and Secondary Outcomes.

Outcome/Analysis	Tocilizumab (N=353)	Sarilumab (N=48)	Control (N=402)
Primary Outcome, Organ support-free days (OSFDs)			
Median (IQR)	10 (-1 to 16)	11 (0 to 16)	0 (-1 to 15)
Adjusted OR - mean (SD)	1.65 (0.23)	1.83 (0.44)	1
- median (95% CrI)	1.64 (1.25 to 2.14)	1.76 (1.17 to 2.91)	1
Probability of superiority to control, %	>99.9	99.5	-
Subcomponents of OSFDs			
In-hospital deaths, n (%)	98/350 (28.0)	10/45 (22.2)	142/397 (35.8)
OSFDs in survivors, median (IQR)	14 (7 to 17)	15 (6.5 to 17)	13 (4 to 17)
Primary Hospital Survival,			
Adjusted OR - mean (SD)	1.66 (0.31)	2.25 (0.96)	1
- median (95% CrI)	1.64 (1.14 to 2.35)	2.01 (1.18 to 4.71)	1
Probability of superiority to control, %	99.6	99.5	-

Other concluded domains

- Anticoagulation (in combination with ATTACC and ACTIV-4)
  - Recruitment ceased for *futility* in patients with ICU-level care
  - Recruitment ceased for *effectiveness* in ward-level patients
- Convalescent plasma ceased recruitment for *futility*
- Antiviral domain
  - Recruitment of HCQ ceased based on external evidence
  - Lopinavir/ritonavir recruitment ceased for *futility*

Participating Sites

Over 200 sites are participating in the REMAP-CAP trial, across 19 countries.

Expansion to new countries

- Strong local leadership
- Research experience and infrastructure
- Regulatory differences
- Language challenges
- Local relevance and engagement

REMAP-CAP

A Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia

11,579

Patient randomisations

10,411

Patient randomisations with suspected or proven COVID-19

31

Available interventions in 12 Domains

6,246

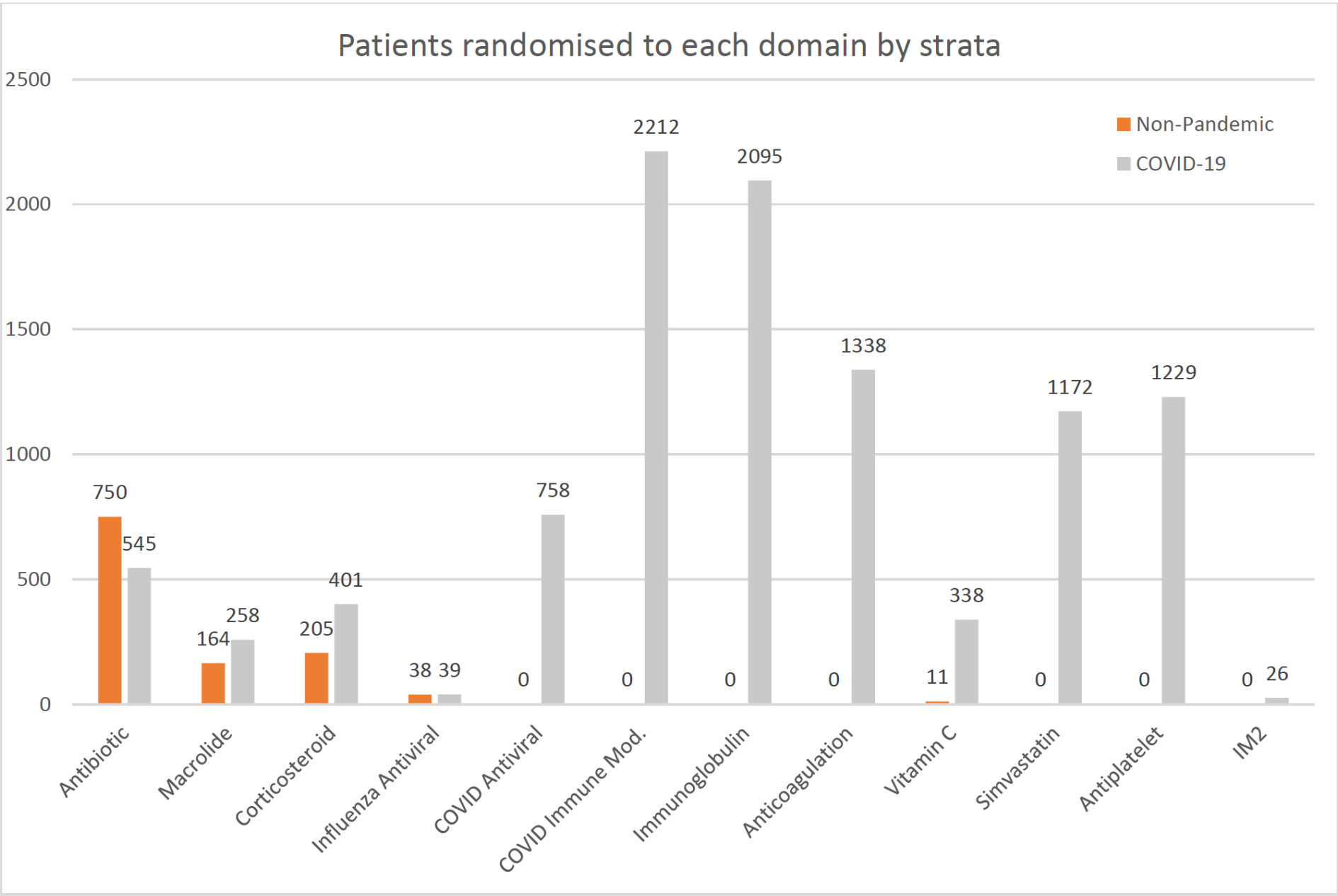
Total patients

5,431

Patients with suspected or proven COVID-19

296

Active Sites


Patients randomised to each domain by strata
2500
2000
1500
1000
500
0
Non-Pandemic
COVID-19
750
545
164
258
205
401
38
39
0
758
0
2212
0
2095
0
1338
11
338
0
1172
0
1229
0
26
Antibiotic
Macrolide
Corticosteroid
Influenza Antiviral
COVID Antiviral
COVID Immune Mod.
Immunoglobulin
Anticoagulation
Vitamin C
Simvastatin
Antiplatelet
IM2

Funders

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Partners

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