RECOVERY

Randomised Evaluation of COVID-19 Therapy

Martin Landray

Professor of Medicine & Epidemiology
Clinical Trials Research Director
Health Data Research UK
University of Oxford

Re-inventing randomized trials

Smart design & delivery

PLUS

Integrated with routine healthcare & data systems

SUPPORTED BY

Proportionate trial regulations & guidance

FOR THE BENEFIT OF

Better patient care and public health

Rationale for randomisation

Major public health crisis

- For hospitalised patients, 25-30% mortality
- For ventilated patients, 30-40% mortality

Huge uncertainty about treatment

- Many candidate drugs
- Many opinions (from many sources)
- No reliable data (uncontrolled case series, inconclusive randomized trials)
- Unlikely to be a single “big win” but moderate benefits would be important

- **Large-scale randomisation required to identify effective treatments**

Randomised controlled trials don't have to be complicated... they must be practical

- **Simple eligibility:** Hospitalised patients with SARs-CoV-2
- **Important outcome:** mortality (use of ventilation, duration of hospitalisation)
- **Randomization:** assigns patient between suitable and available treatments
- **Follow-up:** 1 page case report form + extensive linkage to NHS datasets via NHS DigiTrials

RANDOMISED EVALUATION OF COVID-19 THERAPY (RECOVERY)

Hospital: Patient Name:

1. **Information about the study has been provided to me:** I confirm that I have read and understood the Participant Information Leaflet (V1.0 13-Mar-2020) I have had the opportunity to consider the information and ask questions. These have been answered satisfactorily.

2. **Voluntary participation:** I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected.

3. **Access to study data about me:** I give permission for relevant sections of my medical notes and information collected during the study to be looked at, in confidence, by authorised individuals from this hospital, the University of Oxford, and regulatory authorities to check that the study is being carried out correctly.

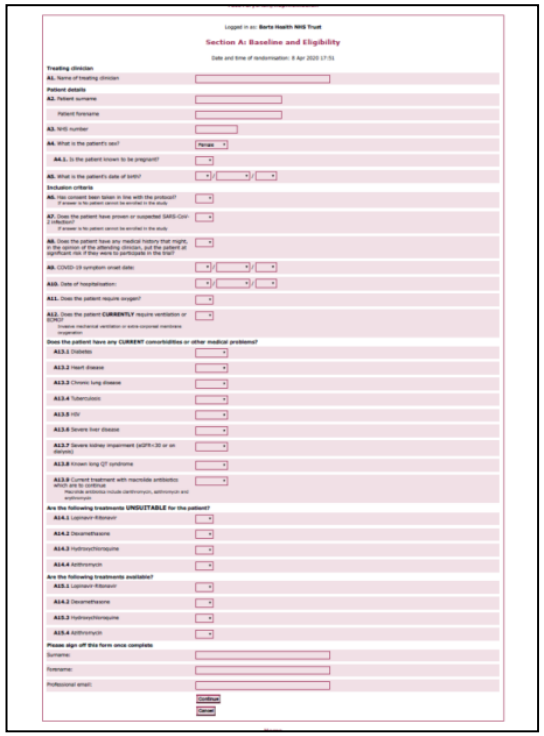
4. **Access to my medical information:** I agree that medical information collected by the doctors and hospitals which provide me with care and which may be located in local or national health and research organizations (including hospital admission, civil registration, audit and research data) may be provided to the study coordinating centre both during and for up to 10 years after the scheduled follow-up period. I understand that information that identifies me will be passed securely to such bodies to make this possible and that I can opt out of this at any time by writing to the coordinating centre team.

5. **Data stored on computer:** I understand that information about my progress in the study will be recorded on a computer database, and that this data will be stored on computers supervised by the University of Oxford. I understand that this information will be kept securely and confidentially.

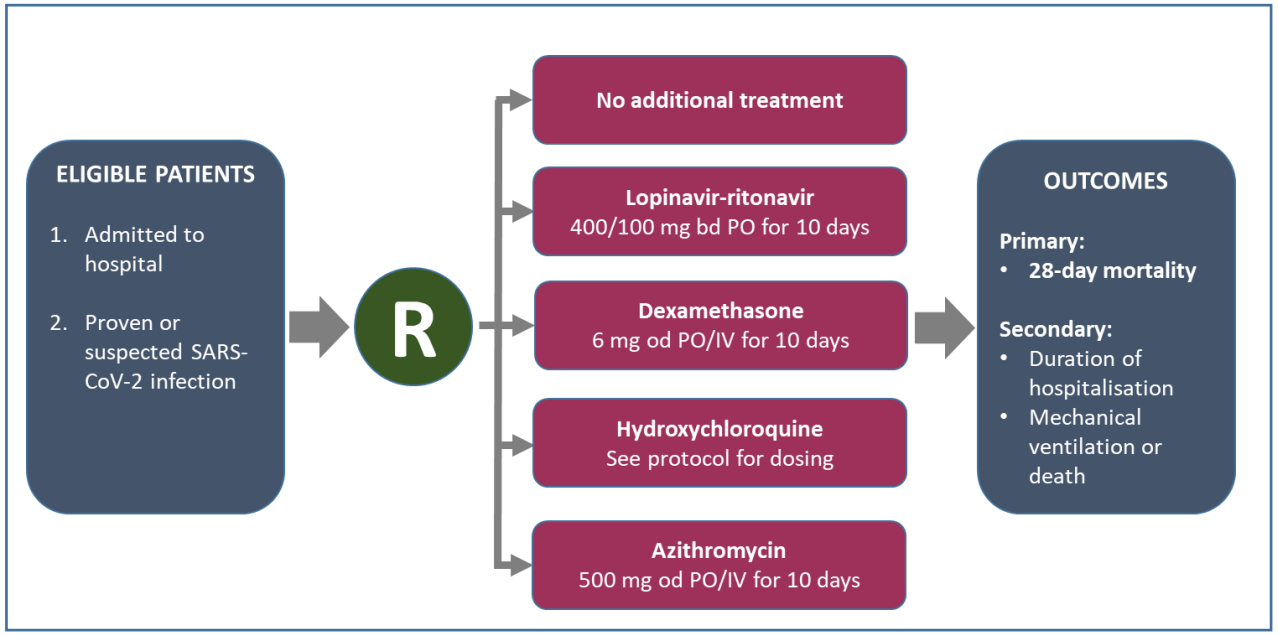
6. **Agreement to take part:** I have read the information (or had it read to me), had an opportunity to ask questions and agree to take part in the above study.

.....	.....	...../...../.....
PRINTED name of participant	Signature	Today's date
.....	.....	...../...../.....
PRINTED name of person taking consent	Signature	Today's date

*1 copy for participant; 1 copy for researcher site file; 1 (original) to be kept in medical notes



Section A: Baseline and Eligibility



Centrally collected routine data

Hospitalisation datasets

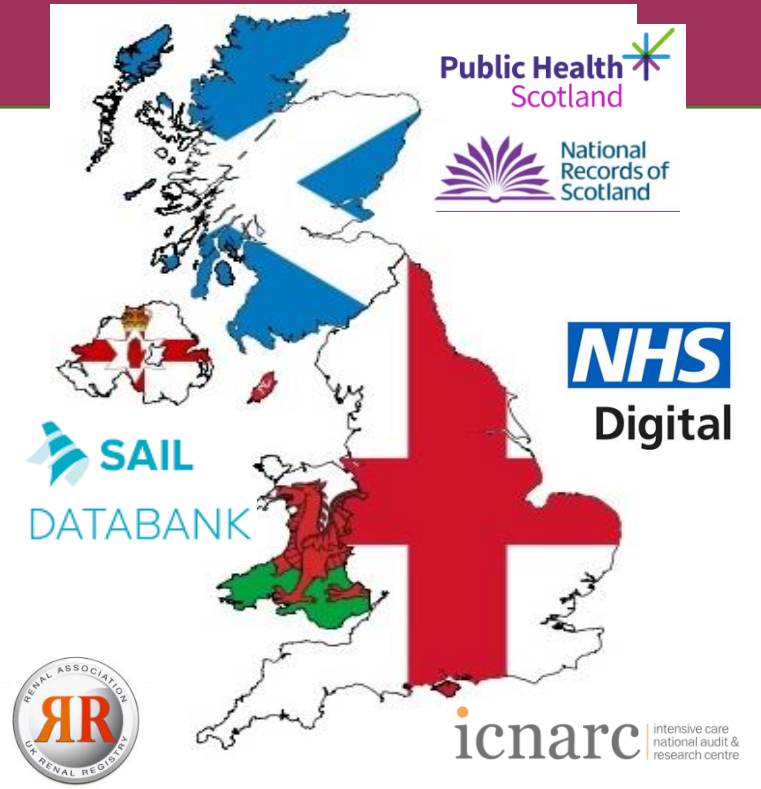
- ✓ Scottish Morbidity Records (SMR)
- ✓ Hospital Episode Statistics Admitted Patient Care (HESAPC)
- ✓ Secondary Uses Service Admitted Patient Care (SUSAPC)
- ✓ Patient Episode database for Wales (PEDW)

Mortality datasets

- ✓ Personal Demographics Service
- ✓ Civil Registrations
- ✓ NHS Scotland Central Register PDS
- ✓ Welsh Demographics Extract

Disease specific datasets

- ✓ UK Renal Registry
- ✓ Cancer Registry



Primary care datasets

- ✓ Business Services Authority (BSA) prescribing and dispensing data
- ✓ General Practice Extraction Service (GPES) Data for pandemic planning and research (GDPPR)

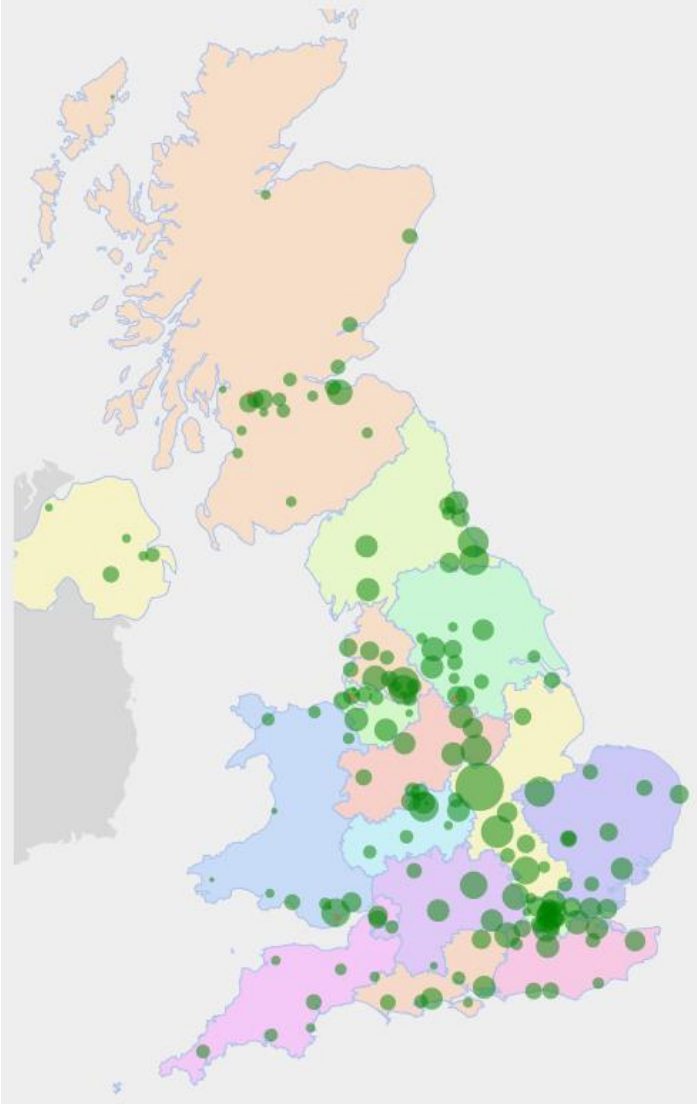
Critical care datasets

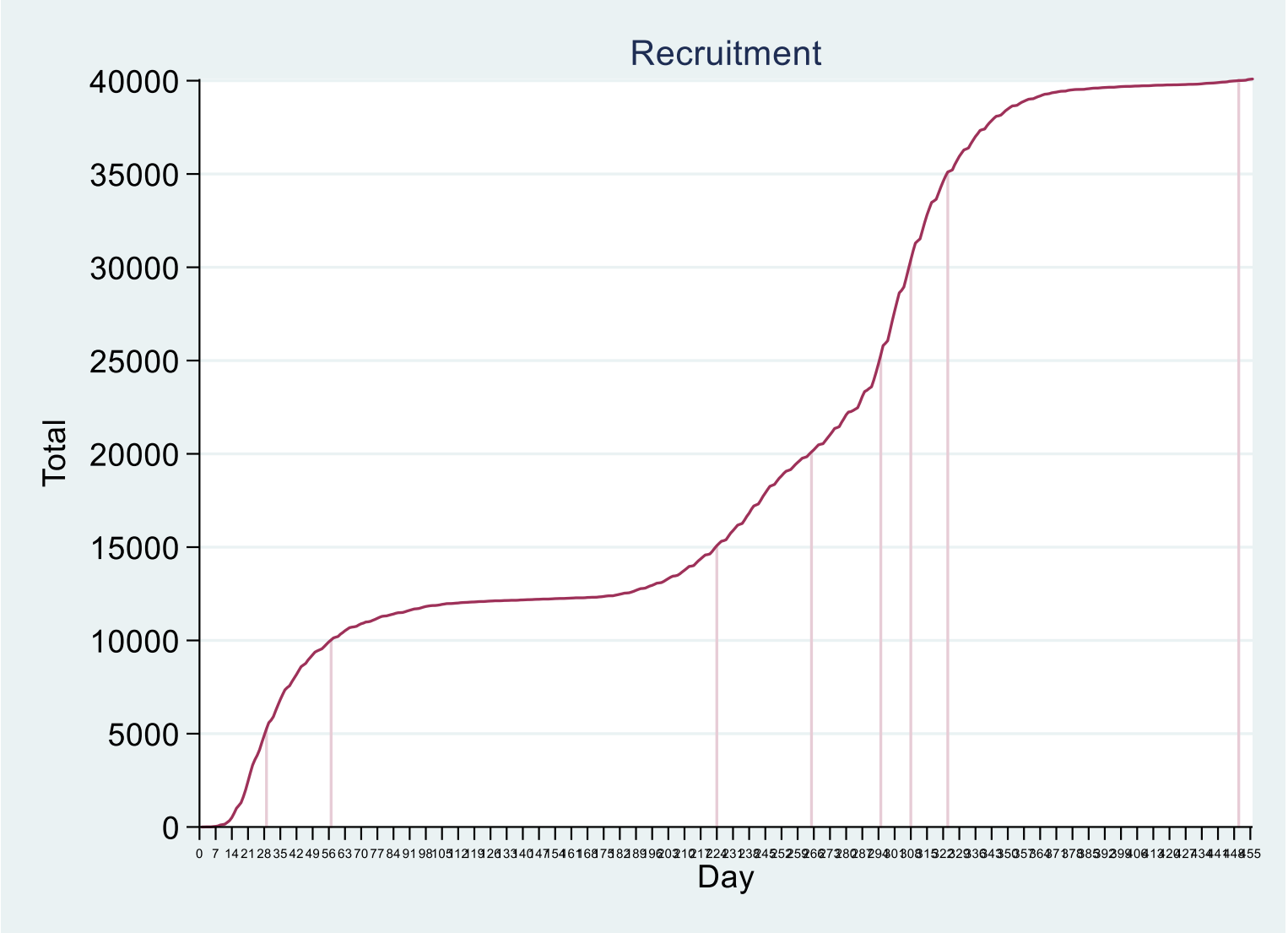
- ✓ Scottish Intensive Care Society Audit Group (SICSAG)
- ✓ Intensive Care National Audit and Research Centre (ICNARC)
- ✓ HES Critical Care Dataset (CCDS)
- ✓ PEDW Critical Care Dataset (CCDS)

COVID datasets

- ✓ COVID-19 Hospitalisation in. England Surveillance System
- ✓ Second Generation Surveillance System (SGSS)
- ✓ Electronic Communication of Surveillance in Scotland (ECOSS)
- ✓ Welsh Results Reporting Service (WRRS)

COVID can affect anyone... RECOVERY is open to everyone

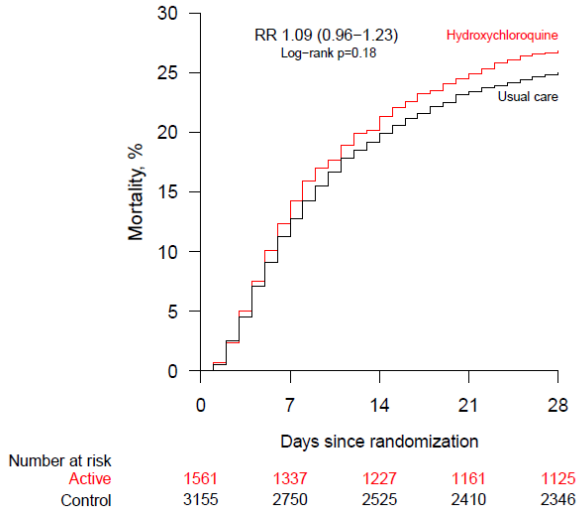




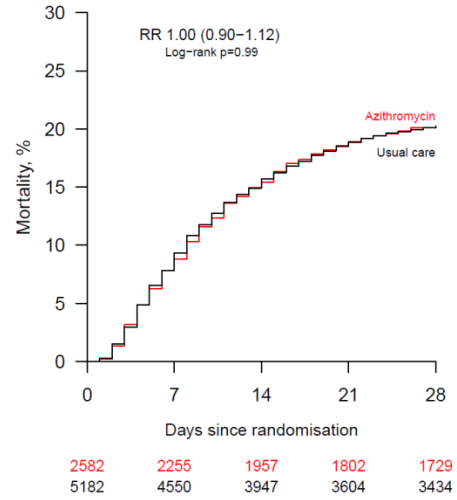
Widely recommended, loudly promoted, widely used...

Hydroxychloroquine, lopinavir, azithromycin, convalescent plasma...

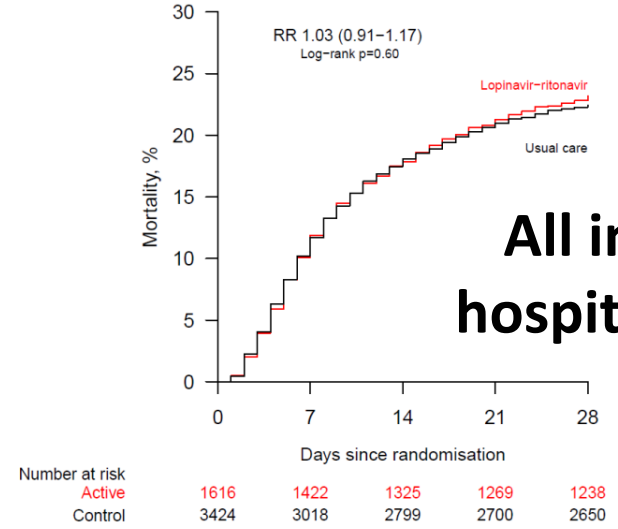
Hydroxychloroquine



Azithromycin

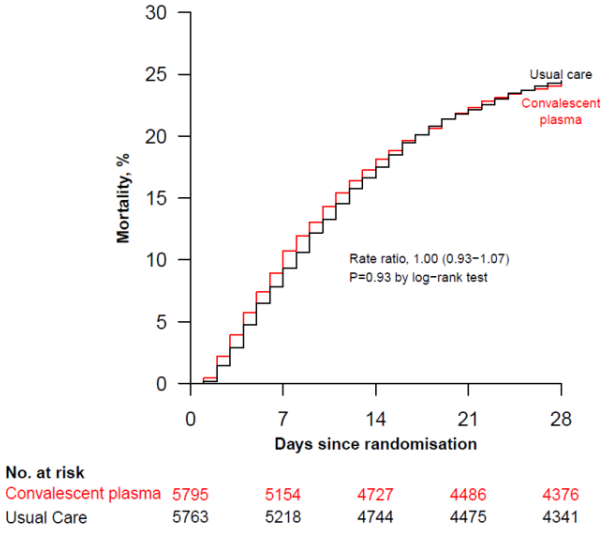


Lopinavir



All ineffective for hospitalised patients

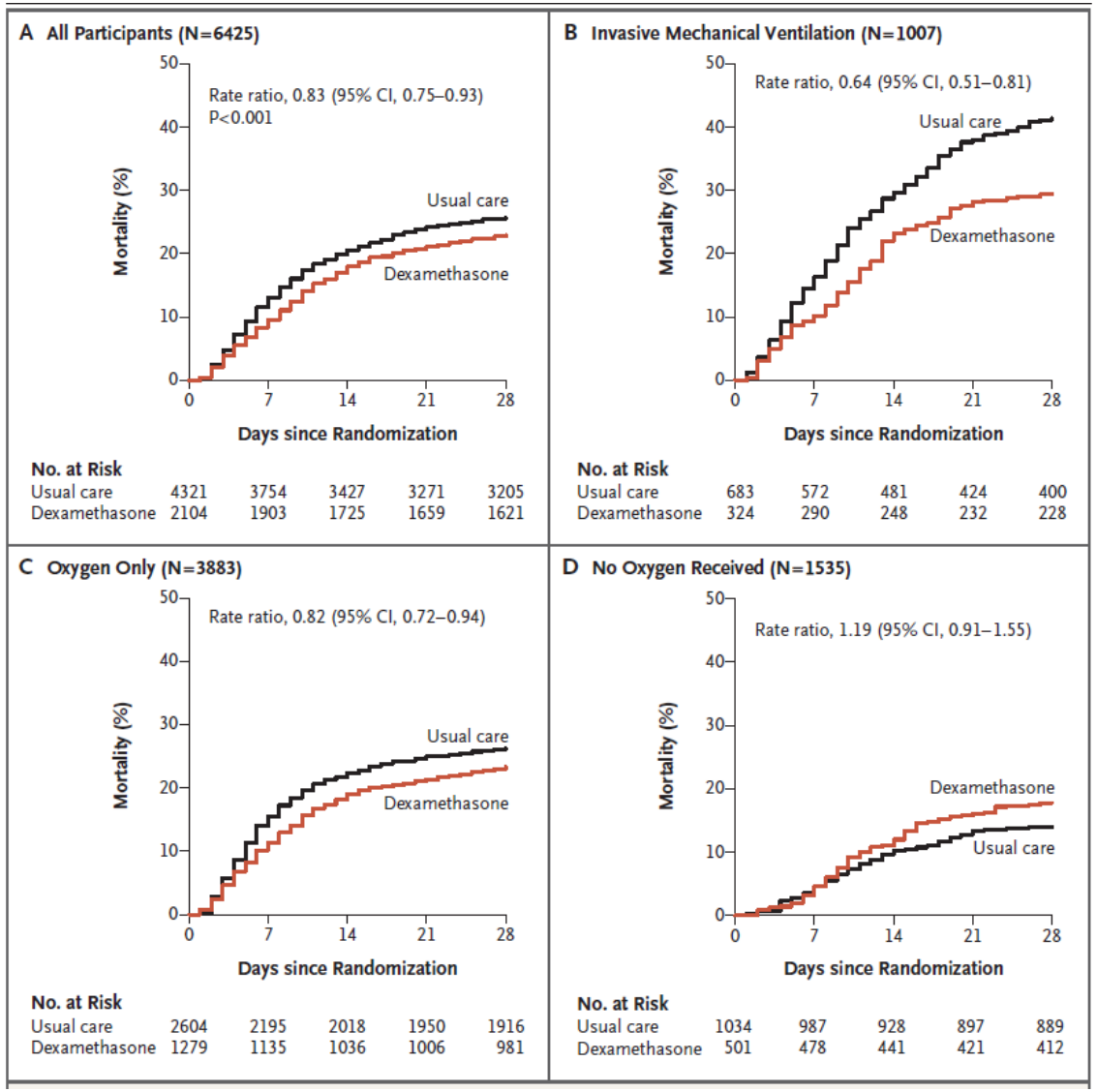
Convalescent plasma

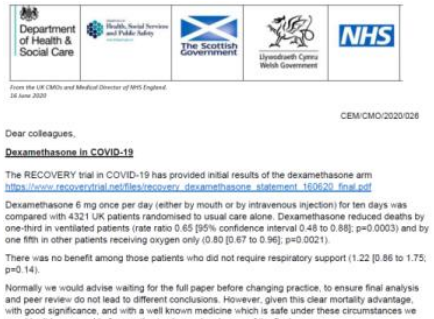


Dexamethasone:

Reduces mortality in patients requiring oxygen or ventilation

DOI: 10.1056/NEJMoa2021436




Department of Health & Social Care
The Scottish Government
NHS

CEM/CMO/2020/026

Dear colleagues,

Dexamethasone in COVID-19

The RECOVERY trial in COVID-19 has provided initial results of the dexamethasone arm

Dexamethasone 6 mg once per day (either by mouth or by intravenous injection) for ten days was compared with 4321 UK patients randomised to usual care alone. Dexamethasone reduced deaths by one-third in ventilated patients (rate ratio 0.65 [95% confidence interval 0.48 to 0.88]; p=0.0003) and by one fifth in other patients receiving oxygen only (0.80 [0.67 to 0.96]; p=0.0021).

There was no benefit among those patients who did not require respiratory support (1.22 [0.86 to 1.75]; p=0.14).

Normally we would advise waiting for the full paper before changing practice, to ensure final analysis and peer review do not lead to different conclusions. However, given this clear mortality advantage, with good significance, and with a well known medicine which is safe under these circumstances we consider it is reasonable for practice to change in advance of the final paper.

Please find more informati

Best wishes,

Dr Frank Atherton
Chief Medical Officer for Wales

Professor Stephen Powis
National Medical Director
NHS England and NHS Improvement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EMA endorses use of dexamethasone in COVID-19 patients on oxygen or mechanical ventilation

News 18/09/2020

ORIGINAL ARTICLE

Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group*


NATIONAL / SCIENCE & HEALTH

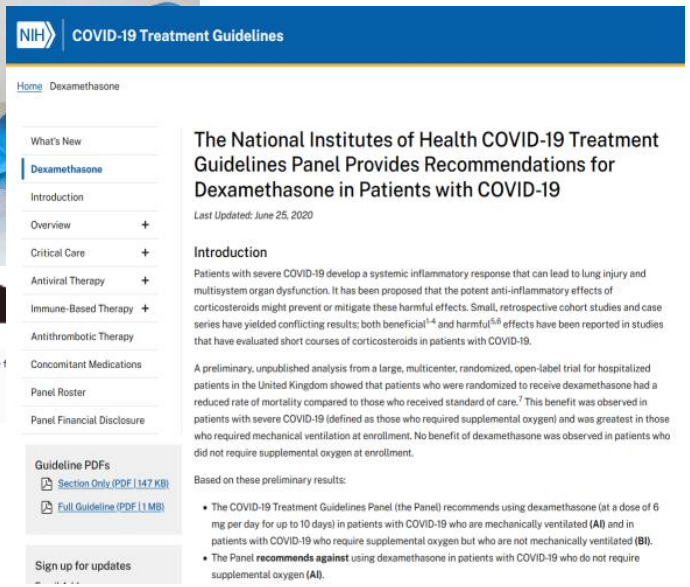
Japan approves dexamethasone as second drug for coronavirus treatment

Dexamethasone Tablets 2 mg 100 Tablets

thejapan

The health ministry has approved the use of the steroid drug dexamethasone f patients. | GETTY IMAGES / VIA KYODO

KYODO


NIH COVID-19 Treatment Guidelines

Home Dexamethasone

What's New
Dexamethasone
Introduction
Overview
Critical Care
Antiviral Therapy
Immune-Based Therapy
Antithrombotic Therapy
Concomitant Medications
Panel Roster
Panel Financial Disclosure

Guideline PDFs
Section Only (PDF | 147 KB)
Full Guideline (PDF | 1 MB)

Sign up for updates

The National Institutes of Health COVID-19 Treatment Guidelines Panel Provides Recommendations for Dexamethasone in Patients with COVID-19

Last Updated: June 25, 2020

Introduction

Patients with severe COVID-19 develop a systemic inflammatory response that can lead to lung injury and multisystem organ dysfunction. It has been proposed that the potent anti-inflammatory effects of corticosteroids might prevent or mitigate these harmful effects. Small, retrospective cohort studies and case series have yielded conflicting results; both beneficial[1-4] and harmful[5,6] effects have been reported in studies that have evaluated short courses of corticosteroids in patients with COVID-19.

A preliminary, unpublished analysis from a large, multicenter, randomized, open-label trial for hospitalized patients in the United Kingdom showed that patients who were randomized to receive dexamethasone had a reduced rate of mortality compared to those who received standard of care.[7] This benefit was observed in patients with severe COVID-19 (defined as those who required supplemental oxygen) and was greatest in those who required mechanical ventilation at enrollment. No benefit of dexamethasone was observed in patients who did not require supplemental oxygen at enrollment.

Based on these preliminary results:

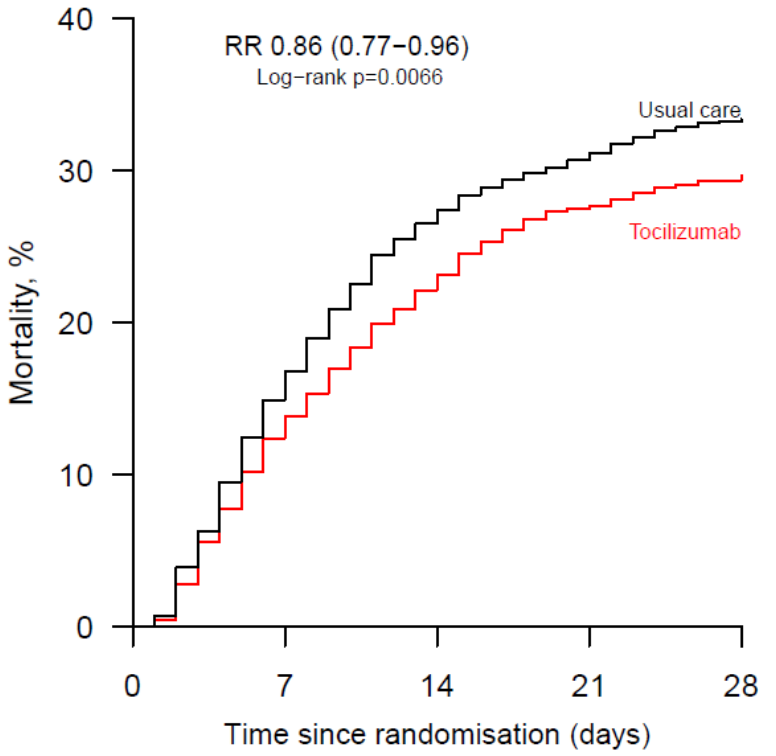
- The COVID-19 Treatment Guidelines Panel (the Panel) recommends using dexamethasone (at a dose of 6 mg per day for up to 10 days) in patients with COVID-19 who are mechanically ventilated **(AI)** and in patients with COVID-19 who require supplemental oxygen but who are not mechanically ventilated **(BI)**.
- The Panel **recommends against** using dexamethasone in patients with COVID-19 who do not require supplemental oxygen **(AI)**.

Saved hundreds of thousands of lives

Tocilizumab:
Reduces mortality in patients with hypoxia and inflammation

DOI: 10.1016/S0140-6736(21)00676-0

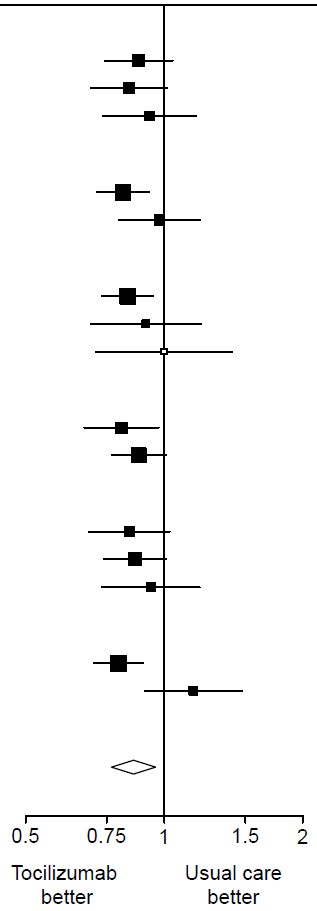
(a)



Number at risk

Active	2022	1741	1553	1386	1284
Control	2094	1740	1518	1372	1250

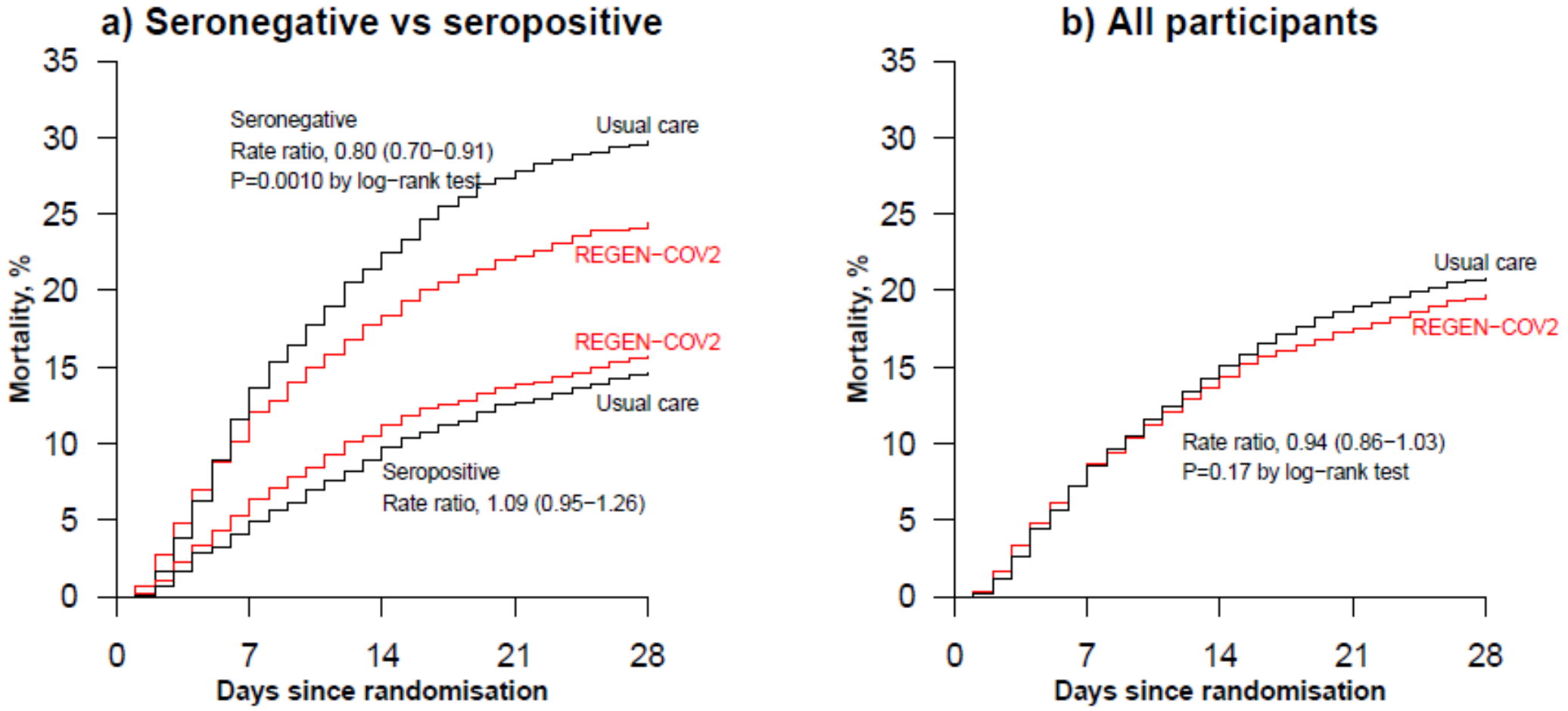
	Tocilizumab	Usual care	RR (95% CI)
Age, years (χ^2_1=0.1; p=0.80)			
<70	256/1332 (19%)	289/1354 (21%)	0.88 (0.74−1.04)
≥70 <80	206/477 (43%)	234/480 (49%)	0.84 (0.69−1.01)
≥80	134/213 (63%)	171/260 (66%)	0.93 (0.74−1.17)
Sex (χ^2_1=2.2; p=0.14)			
Men	400/1335 (30%)	504/1437 (35%)	0.81 (0.71−0.93)
Women	196/687 (29%)	190/657 (29%)	0.98 (0.80−1.20)
Ethnicity (χ^2_1=0.3; p=0.56)			
White	429/1356 (32%)	519/1426 (36%)	0.83 (0.73−0.95)
Black, Asian, or Minority Ethnic	98/341 (29%)	110/357 (31%)	0.91 (0.69−1.20)
Unknown	69/325 (21%)	65/311 (21%)	1.00 (0.71−1.41)
Days since symptom onset (χ^2_1=0.6; p=0.46)			
≤7	210/668 (31%)	245/660 (37%)	0.81 (0.67−0.97)
>7	386/1354 (29%)	449/1433 (31%)	0.88 (0.77−1.01)
Respiratory support at randomization (χ^2_1=0.4; p=0.52)			
No ventilator support*	175/935 (19%)	202/933 (22%)	0.84 (0.69−1.03)
Non−invasive ventilation†	296/819 (36%)	350/867 (40%)	0.86 (0.74−1.01)
Invasive mechanical ventilation‡	125/268 (47%)	142/294 (48%)	0.94 (0.73−1.19)
Use of corticosteroids$ (χ^2_1=7.1; p=0.01)			
Yes	457/1664 (27%)	565/1721 (33%)	0.80 (0.70−0.90)
No	139/357 (39%)	127/367 (35%)	1.16 (0.91−1.48)
Unknown	0/1 (0%)	2/6 (33%)	
All participants	**596/2022 (29%)**	**694/2094 (33%)**	**0.86 (0.77−0.96) p=0.0066**



Benefits additional to dexamethasone

DOI: 10.1101/2021.06.15.21258542

Effect of REGEN-COV on 28-day mortality



Benefits additional to dexamethasone

Randomised trials are an essential component of high quality clinical care

- Arbitrary use of unproven treatments is damaging to patient care & public health
- Compelling results change practice

- But trials must be:
  - Designed in accordance with the principles of Good Randomised Trials
  - Feasible for patients and clinical staff
  - Inclusive of relevant patient groups
  - Focused on outcomes that matter

- **Health data can broaden participation and increase quality & relevance of results**

These lessons are important not only for the current COVID-19 pandemic

but also for the tackling the burden of many other common diseases

Acknowledgements

- UK Research & Innovation
- National Institute for Health Research
- Wellcome Trust
- Bill & Melinda Gates Foundation
- Department for International Development
- Department of Health & Social Care
- National Health Service in England, Wales, Scotland, and Northern Ireland
- Regeneron provided REGEN-COV
- Roche provided tocilizumab
- NIHR Clinical Research Network
- NHS DigiTrials
- NIHR Oxford Biomedical Research Centre
- Medical Research Council Population Health Research Unit

with enormous thanks

to the very many doctors, nurses, & other healthcare & research staff at 179 NHS hospitals

and, most importantly

to the thousands of patients who participate

in this extraordinary project

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Health Data Research Hub

June 2021

Using real world data to improve care pathways for COVID-19

Prof. E. Sapey
Director of PIONEER – HDR UK Health data Hub in Acute Care

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ACUTE **CARE**

Acute Care is any unplanned health episode

110 million urgent same-day patient contacts

Numbers rising year on year.

There are known health inequalities.

The increased demand for emergency services has a significant impact on planned NHS services.

Chronic disease accounts for two-thirds of emergency medical admissions.

10% of acute presentations are the new diagnosis of a chronic illness, at a late stage

Complex health environment with care delivered across

- Primary care
- Out of hours
- Help lines
- Ambulances
- Hospitals
- Community Care

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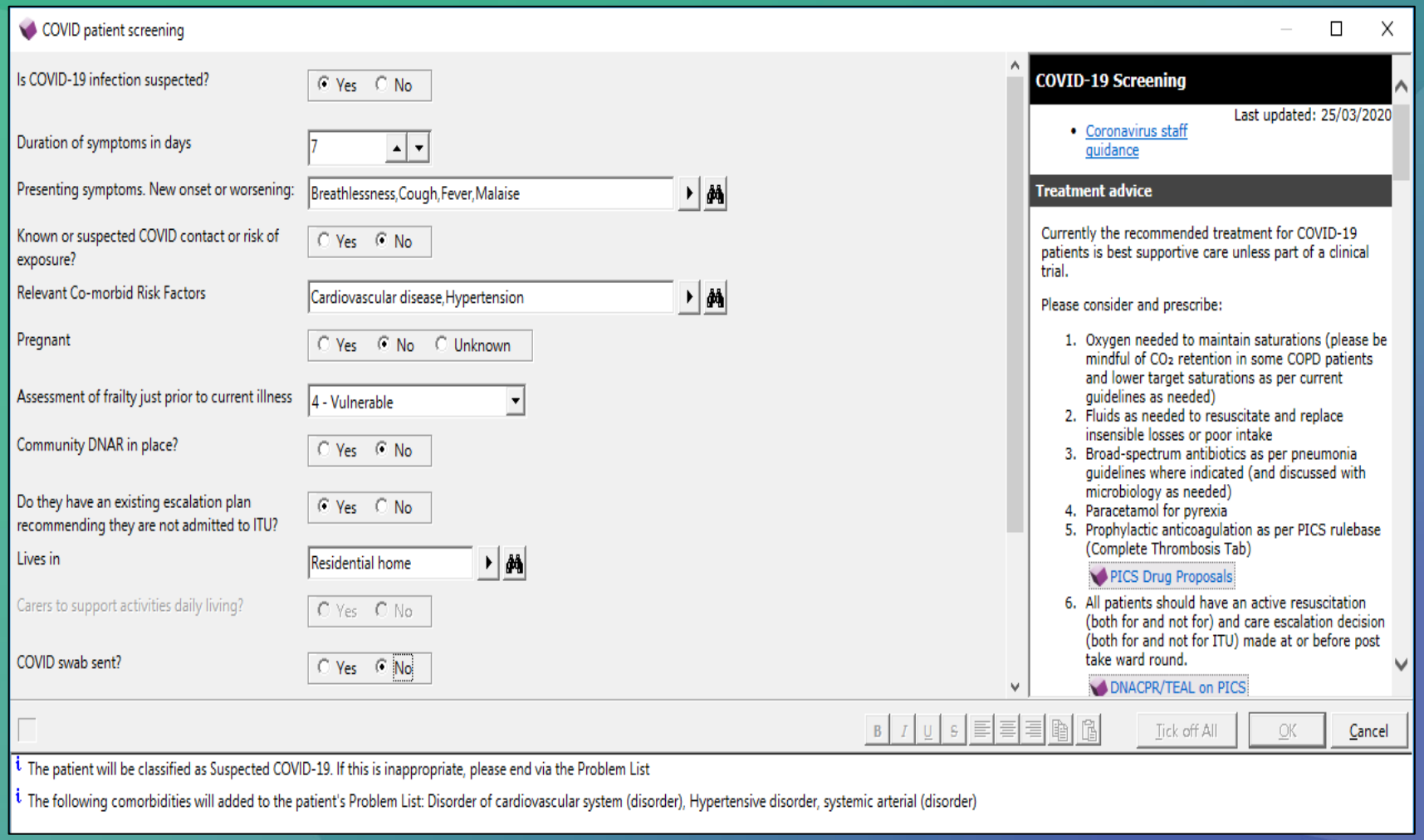
PREPARING **RESPONSES**



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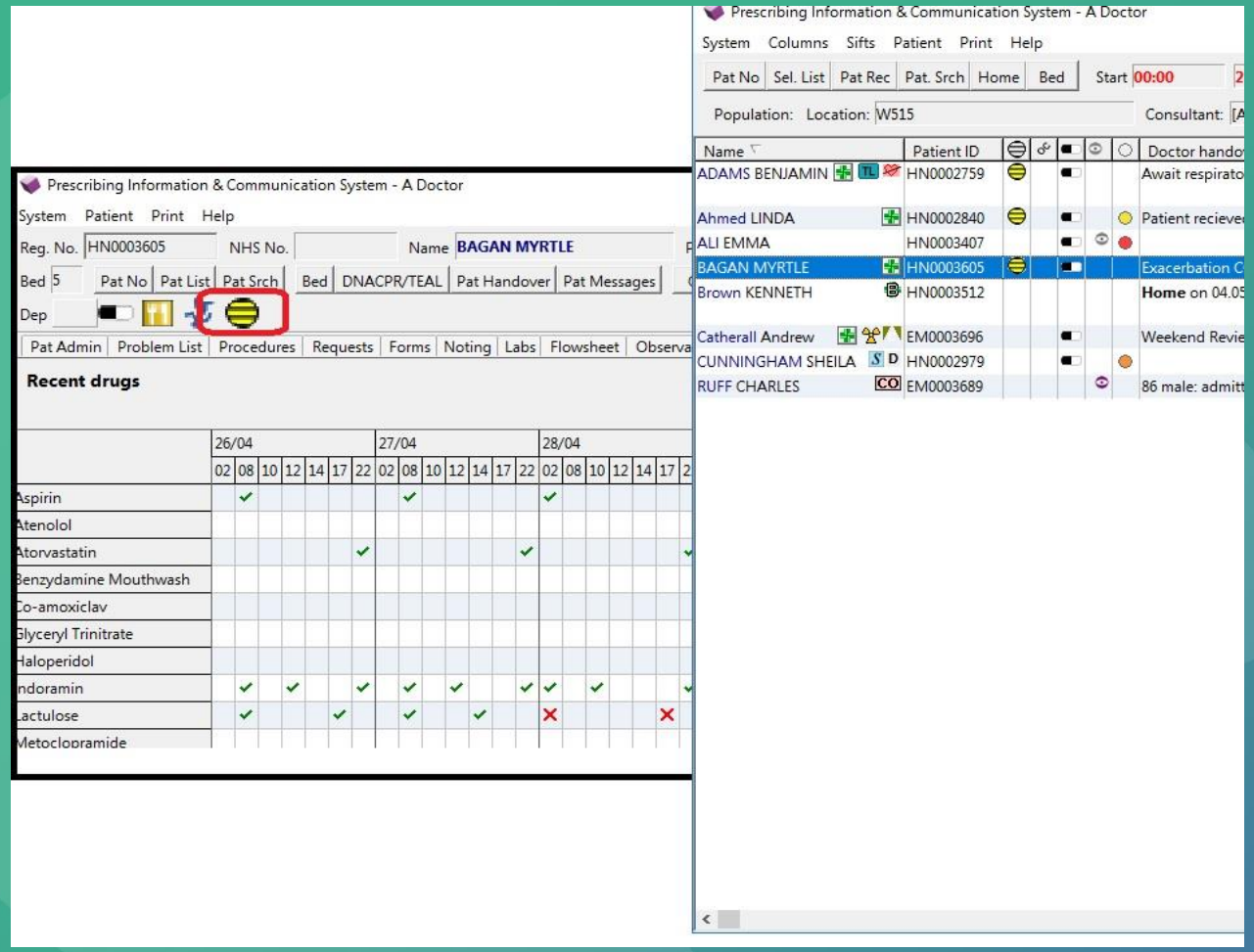

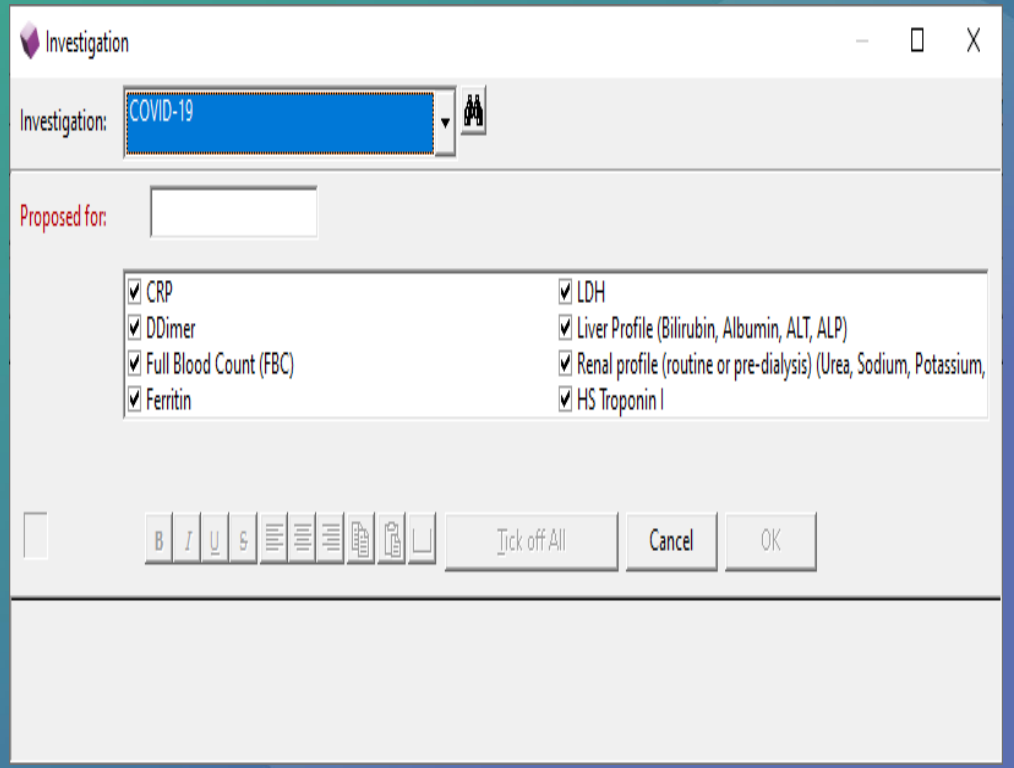

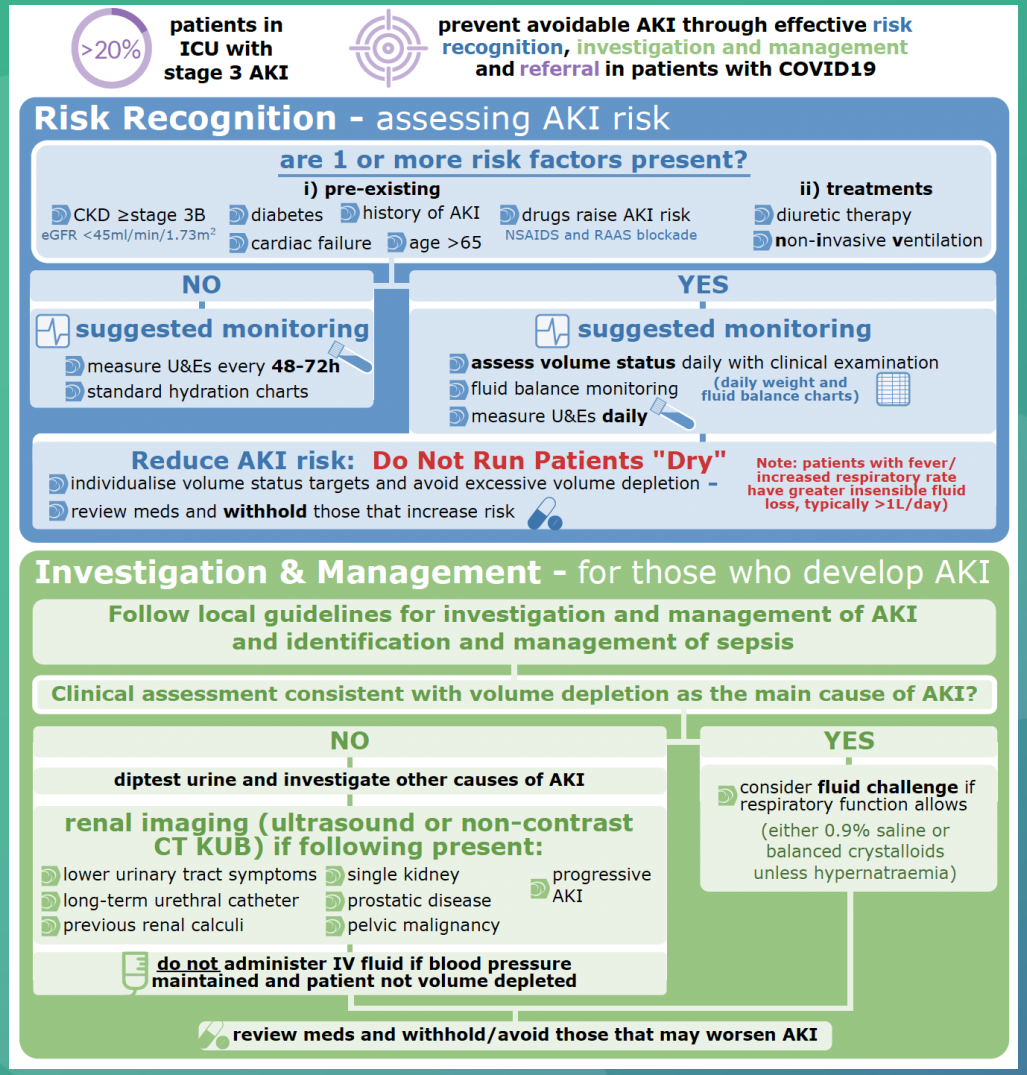

Check

- Check blood glucose (capillary, lab, blood gas) in **all** patients presenting in hospital
- Check capillary ketones in **all** patients with **known diabetes**, even if bloods normal
  - <0.6mmol/L = safe
  - 1.5-2.9 mmol/L = increased risk of DKA
- Check capillary ketones in **any** patient with a **blood glucose >15mmol/L**

Stop

- Stop SGLT-2 inhibitor therapy in **all unwell patients** as can cause euglycaemic DKA
  canagliflozoin, dapagliflozin, empagliflozin, sotagliflozin
- Stop Metformin if patient: dehydrated, has raised lactate or acute kidney injury
- **Never stop** background insulin in patients with T1DM or T2DM
  Lantus, Semglee, Levemir, Tresiba, Humulin I

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Cumulative Summary Report - UHB (04 March 2020 - 14 June 2021)

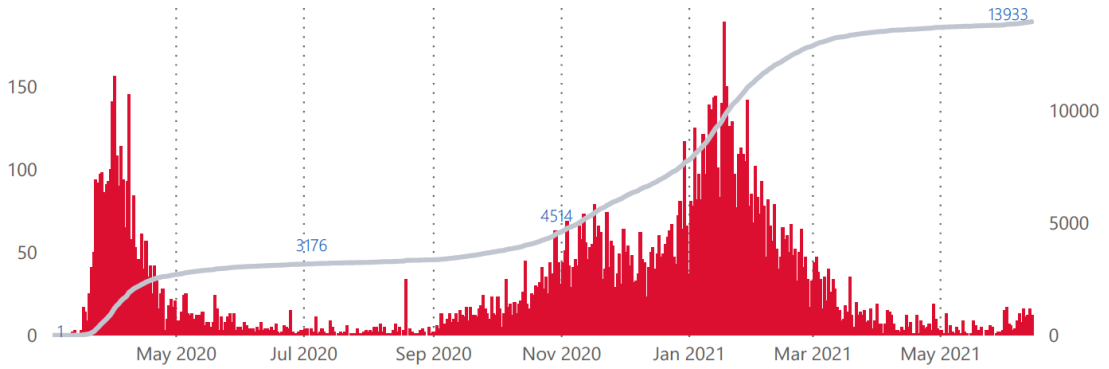
NHS University Hospitals Birmingham NHS Foundation Trust

PIONEER Health Data Research Hub

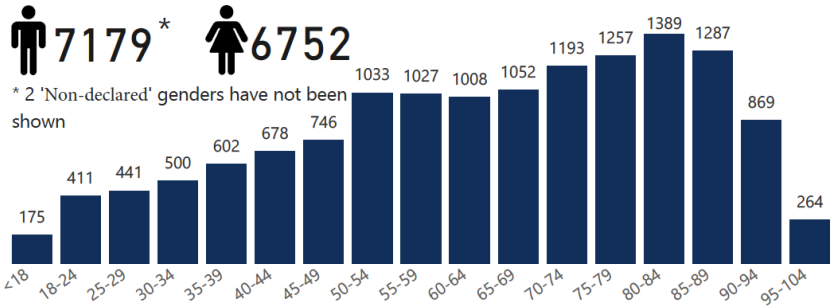
Data Updated - 14:30

Sites	Total Tested	Total Positive	Current Positive Inpatients
Good Hope Hosp.	26554	3006	9
Heartlands Hosp.	54797	5528	19
Queen Elizabeth Hosp.	54457	5075	15
Solihull Hosp.	5565	324	0
Total	**141373**	**13933**	**43**

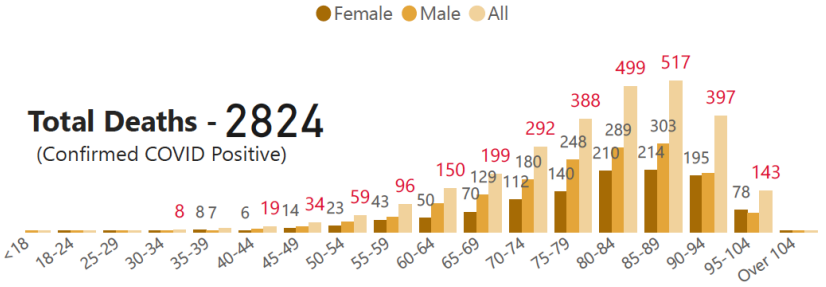
Daily Positives (Bars) & Cumulative (Line)



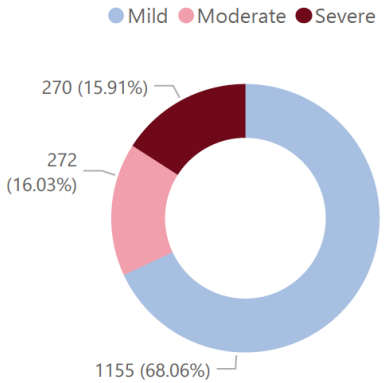
Cumulative Positive Tests - By Age Group & Gender



Deaths - By Age Group & Gender

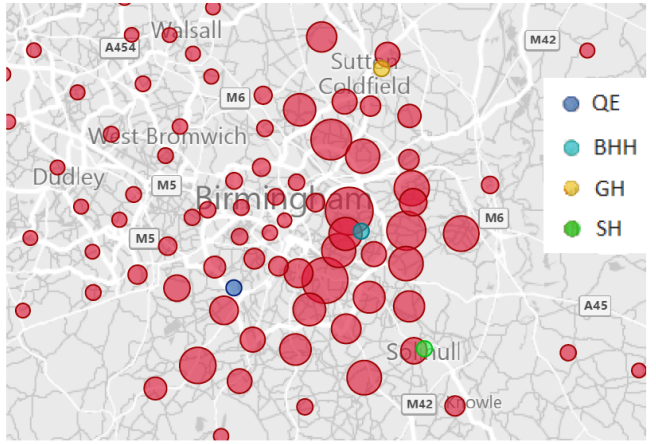


COVID Severity*

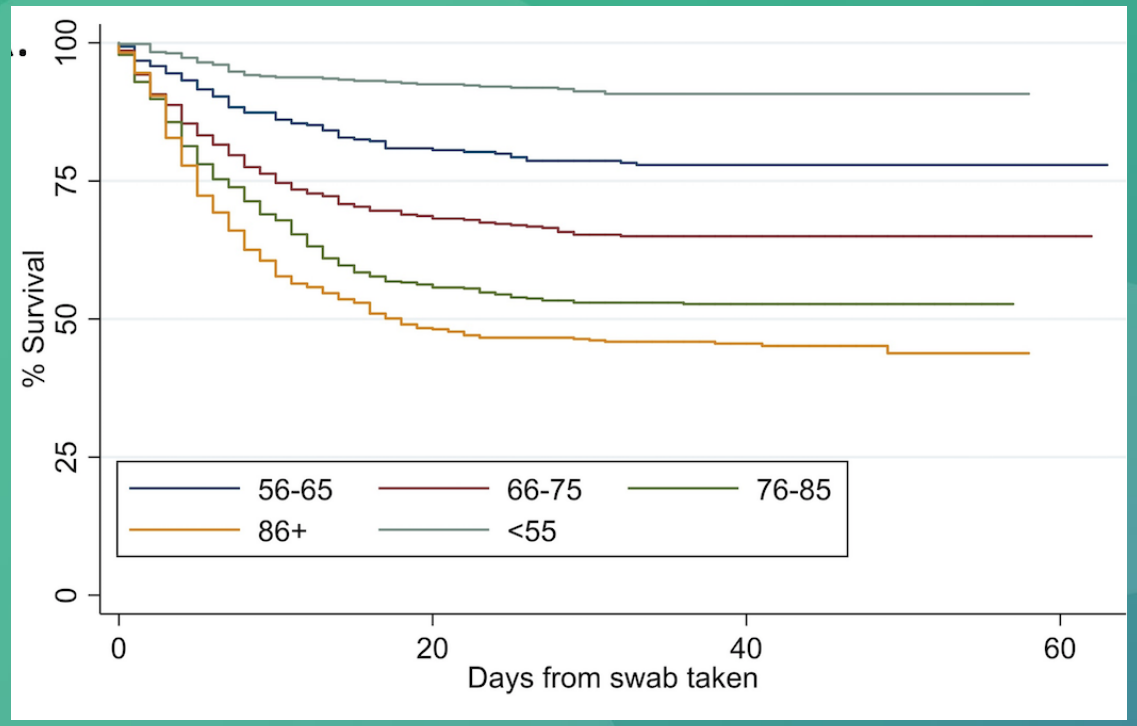


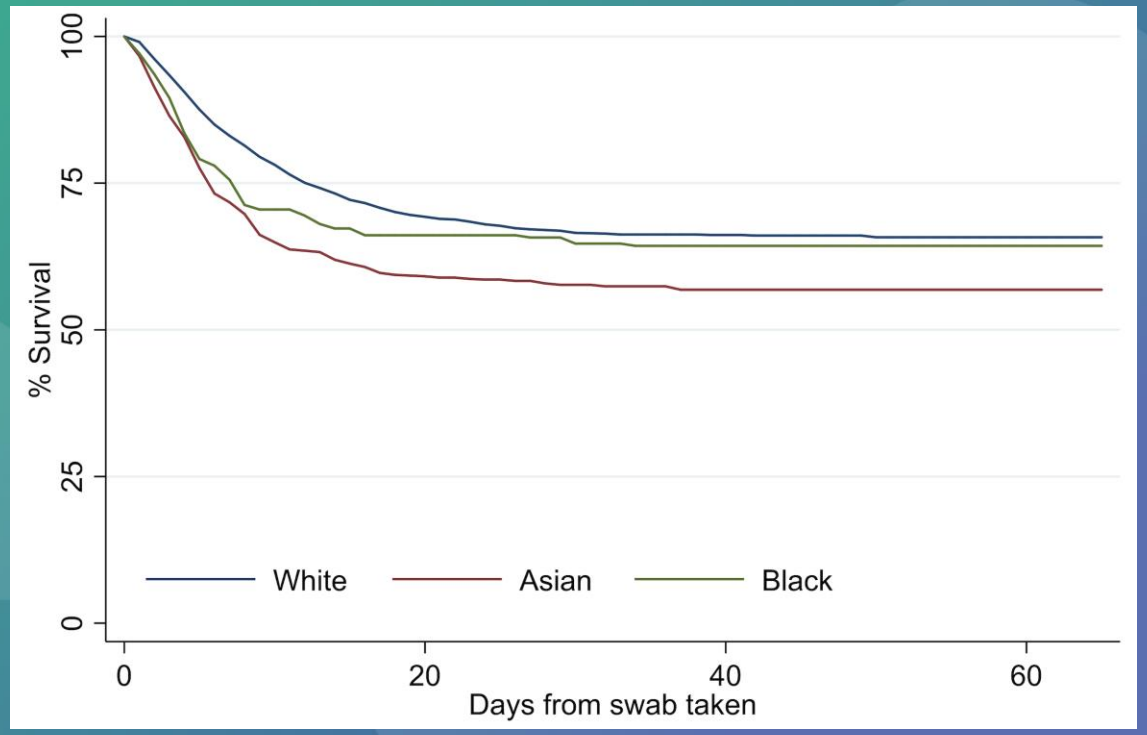
* Severity information at diagnosis for 1697 (33%) COVID positive patients from QEHB

Geographical Distribution of Positive Cases (Size = Total Numbers)

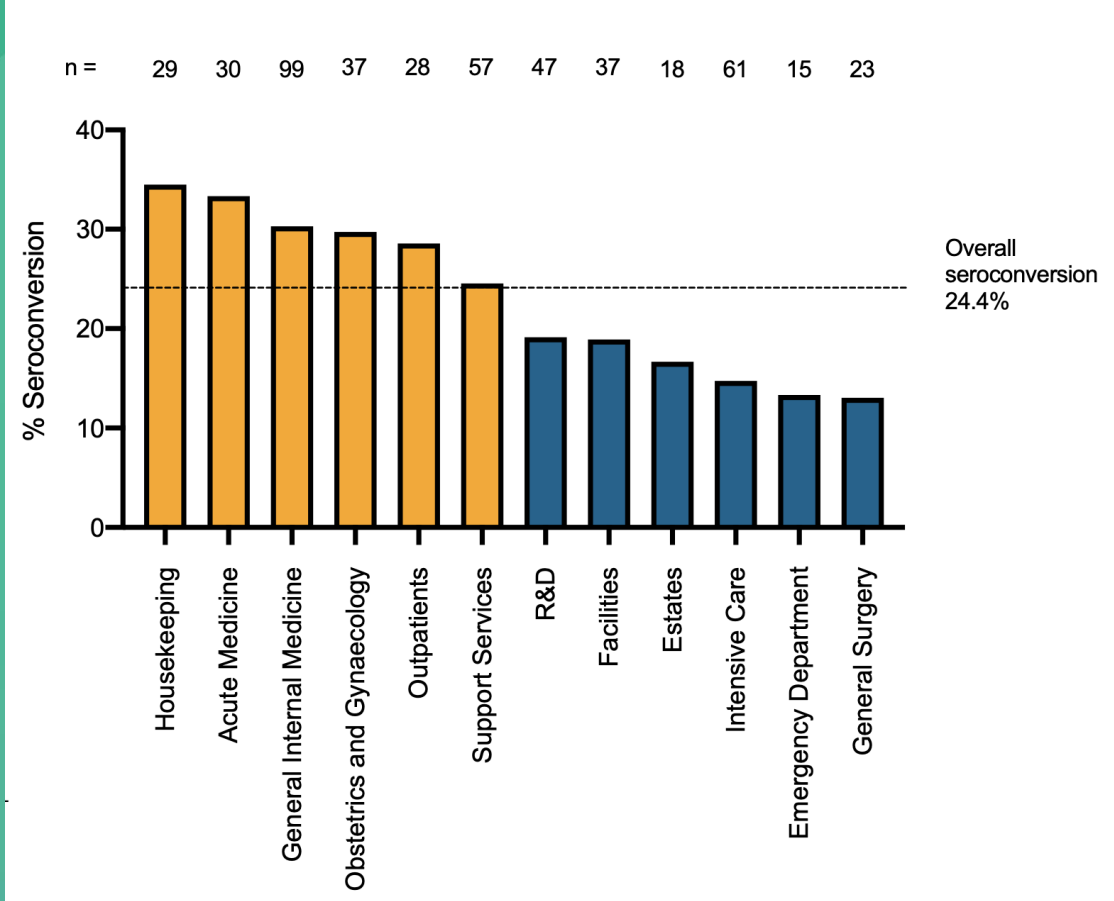


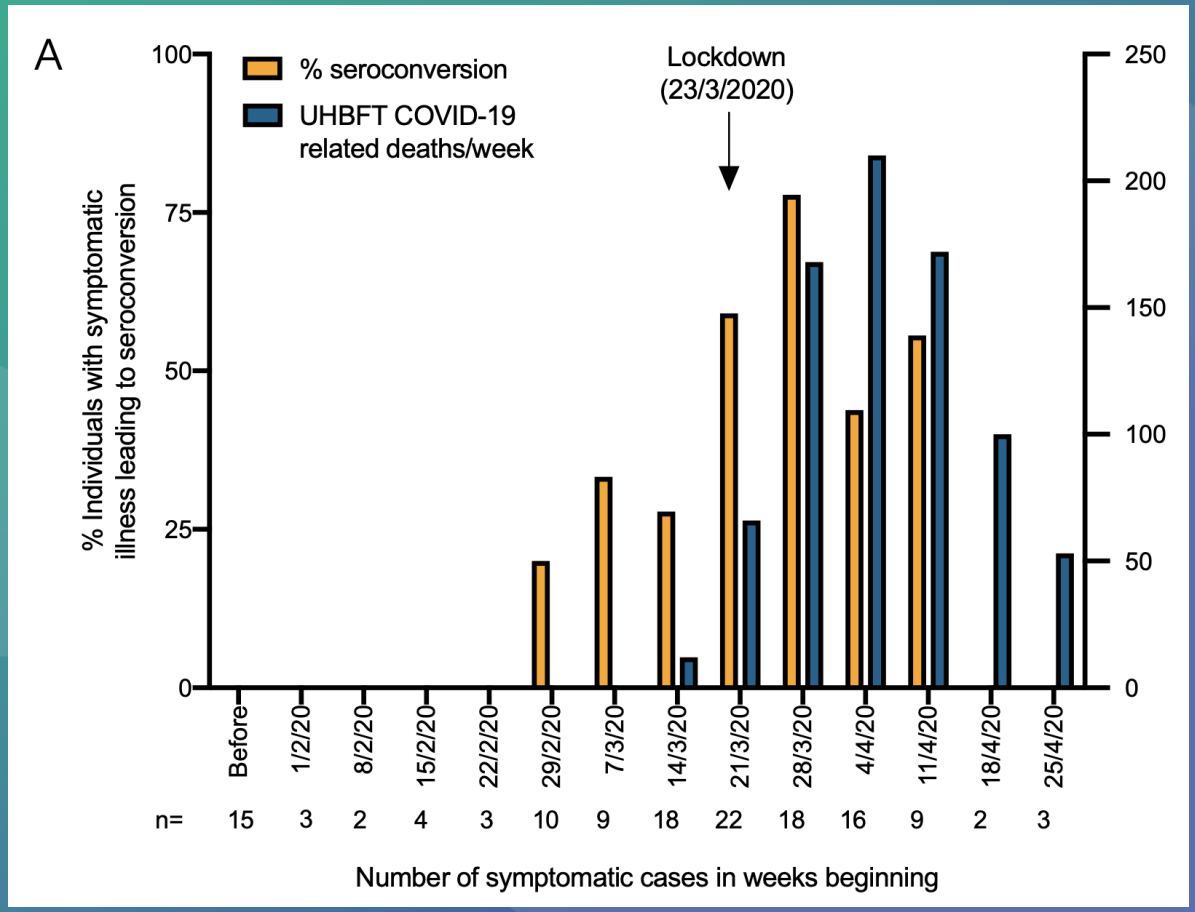
Created by Tabish Ahmed





http://dx.doi.org/10.1136/bmjresp-2020-000644





https://doi.org/10.1101/2020.05.18.20105197

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SUMMARY

1. Being based within the NHS allowed rapid action to curate structured data from first patient
2. Data used in daily analysis to highlight emerging clinical problems associated with COVID
3. Patient mapping in real time enabled patient tracking over 4 NHS sites (suspected/positive/negative)
4. Data fed back to PHE locally to highlight outbreaks prior to community screening
5. Some reassurance to staff about protection from PPE
6. More to come about prescribing support

Our partners

HDRUK
Health Data Research UK

WARWICK
THE UNIVERSITY OF WARWICK

UNIVERSITY OF BIRMINGHAM

NHS
University Hospitals Birmingham
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INSIGNIA
Medical Systems

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Health Data Research Hub

Modelli and

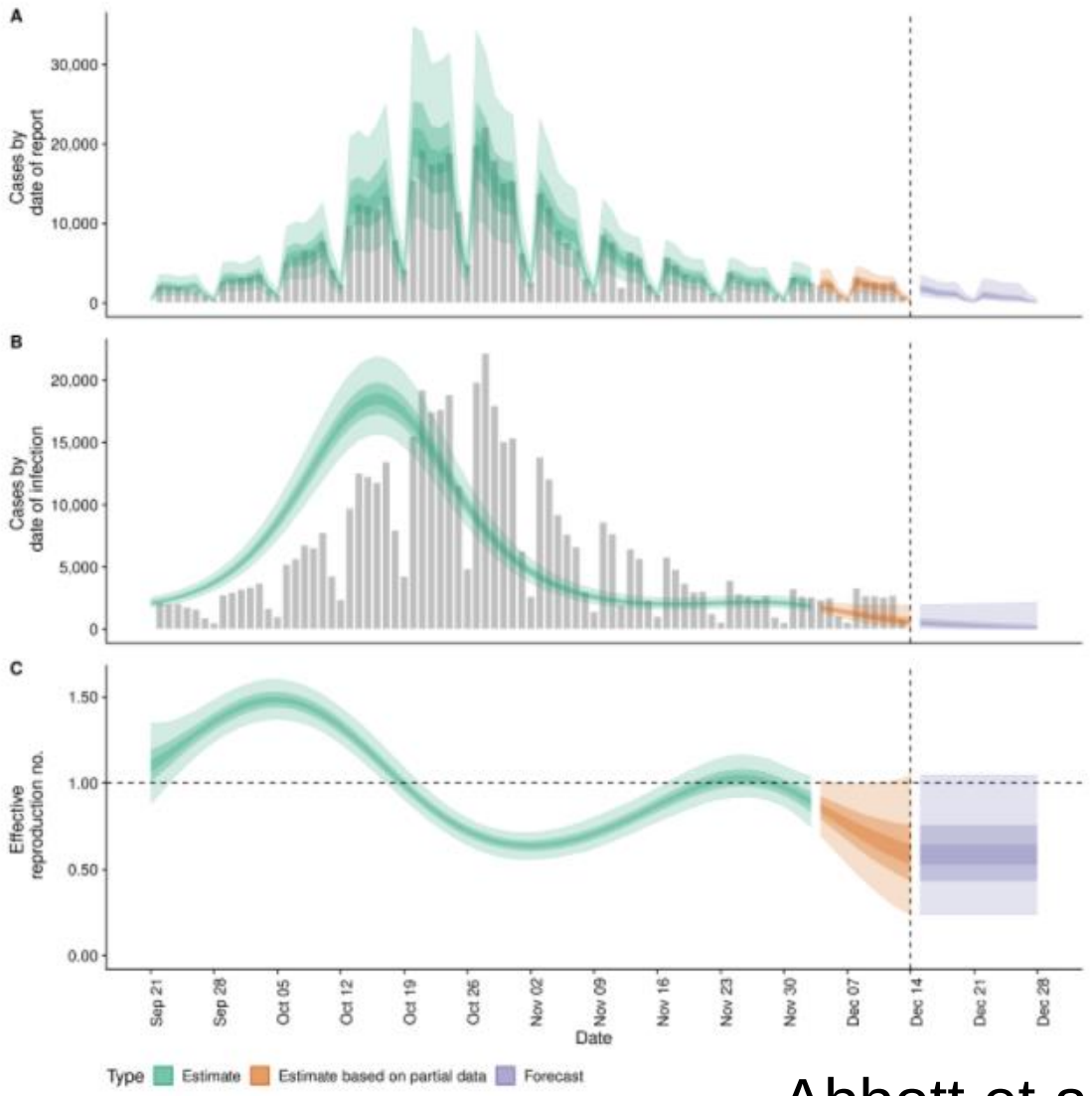
Rosalind Eg
LSHTM
20

Modelling COVID-19

1. Fundamentals of transmission
    - Quantify key epidemiological unknowns
    - How those change
2. Interventions and responses
    - In response to policy questions

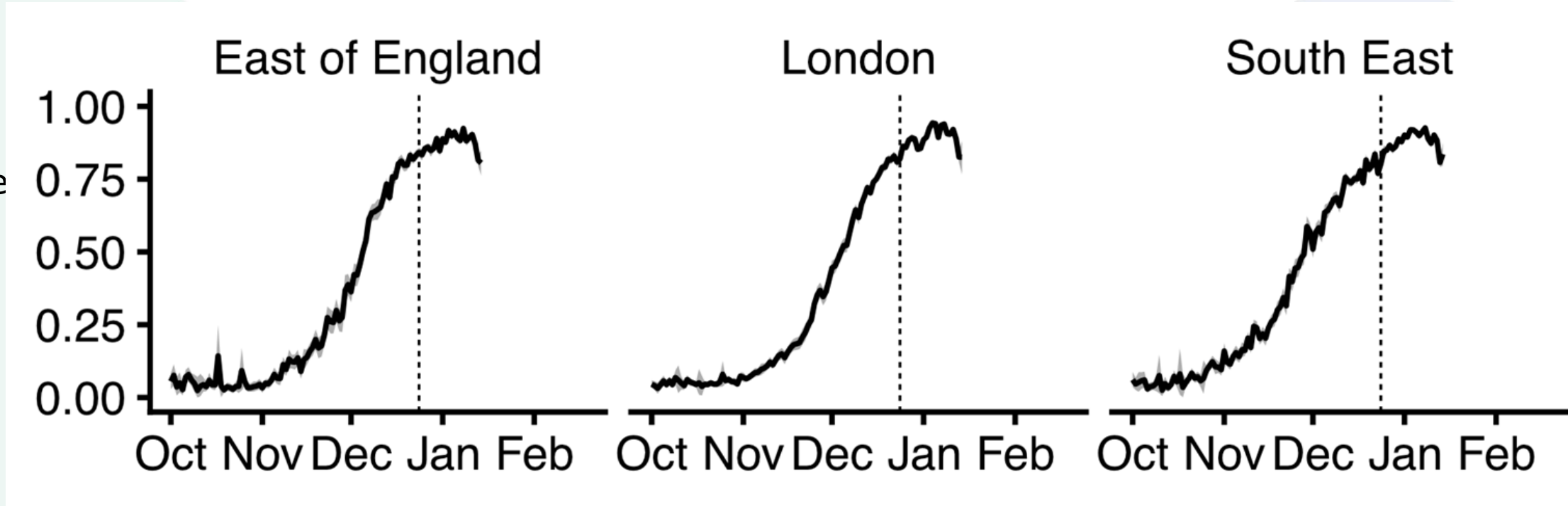
Fundamentals of transmission

- *R*: Real-time reproduction number estimation
- https://epiforecasts.io/
- Provides publicly available R_t estimates in real time for a range of countries
- Used in many downstream analyses



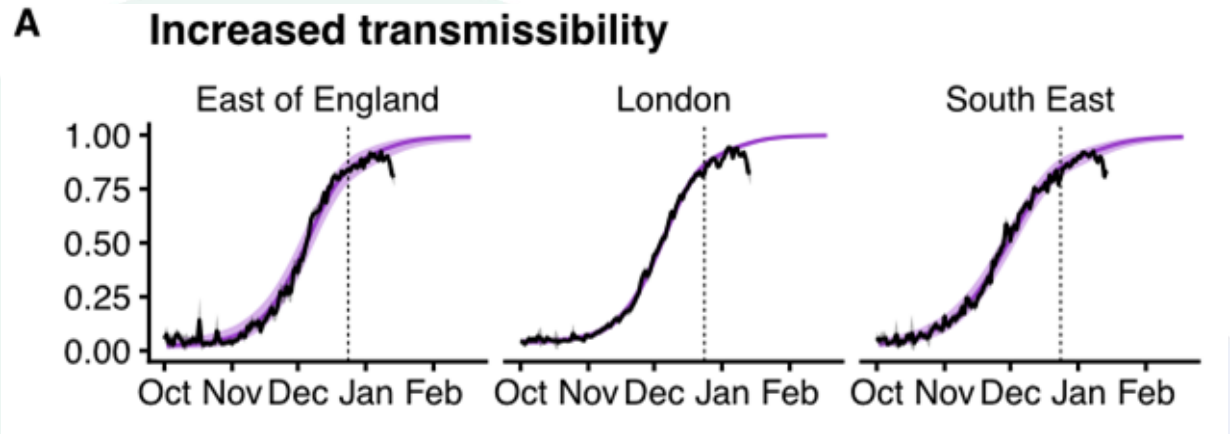
Abbott et al. 2020. W

Fundamentals of transmission: alpha variant



Davies et al. Science. 20

Fundamentals of transmission: alpha variant



Incorporate proposed mechanisms into the transmission model.

Fit those models to available data.

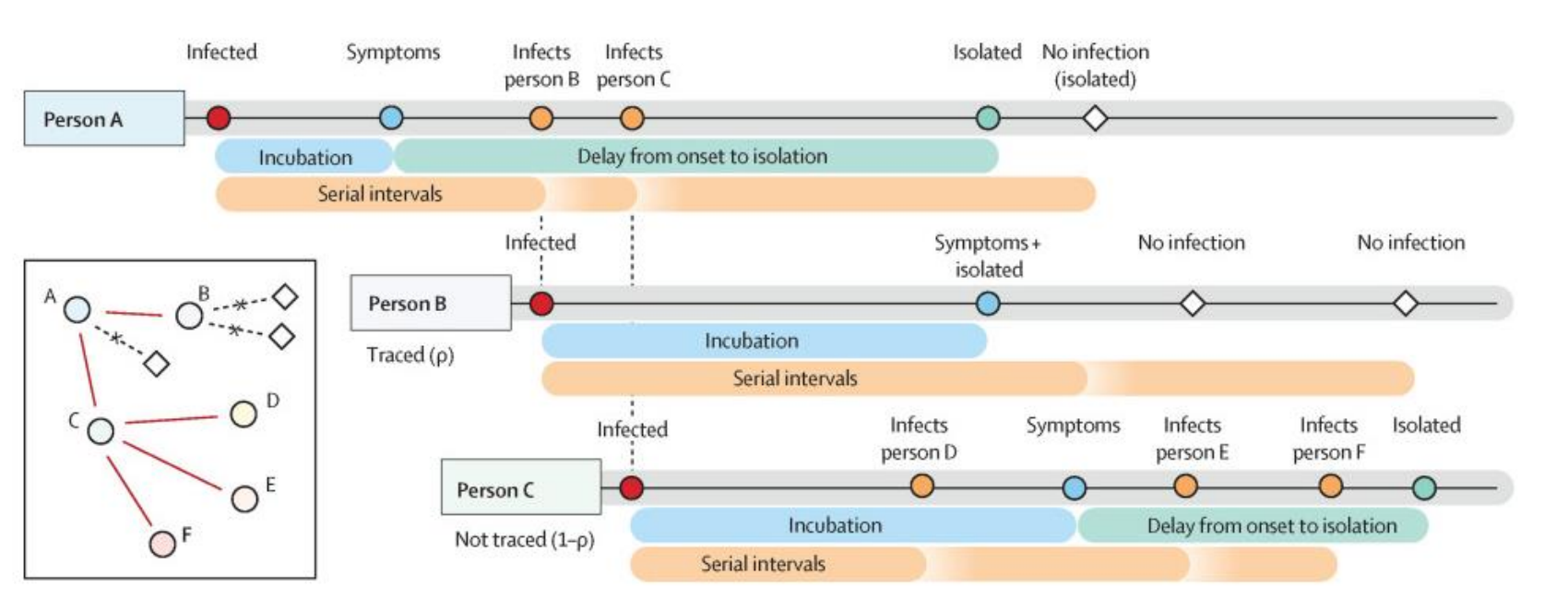
Assess quality of fit for which mechanism is supported by the data.

Increased transmissibility most supported.

Davies et al. Science. 20

Modelling interventions

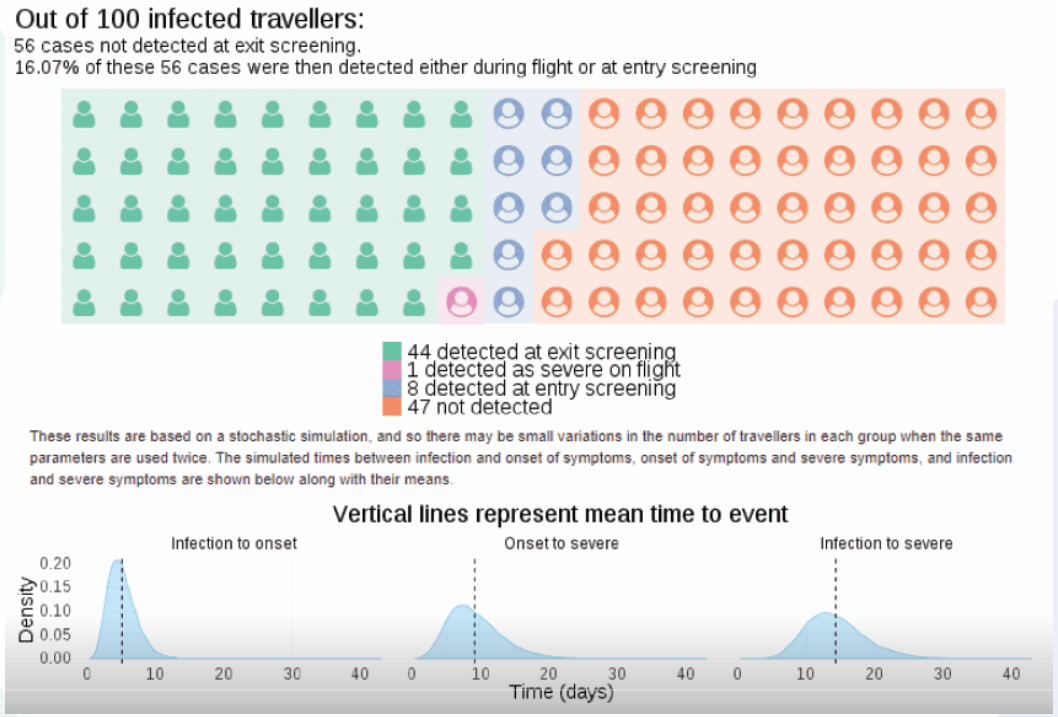
Can contract tracing and isolation of cases control outbreaks of COVID-19?



Hellewell et al. 2020.

Modelling interventions

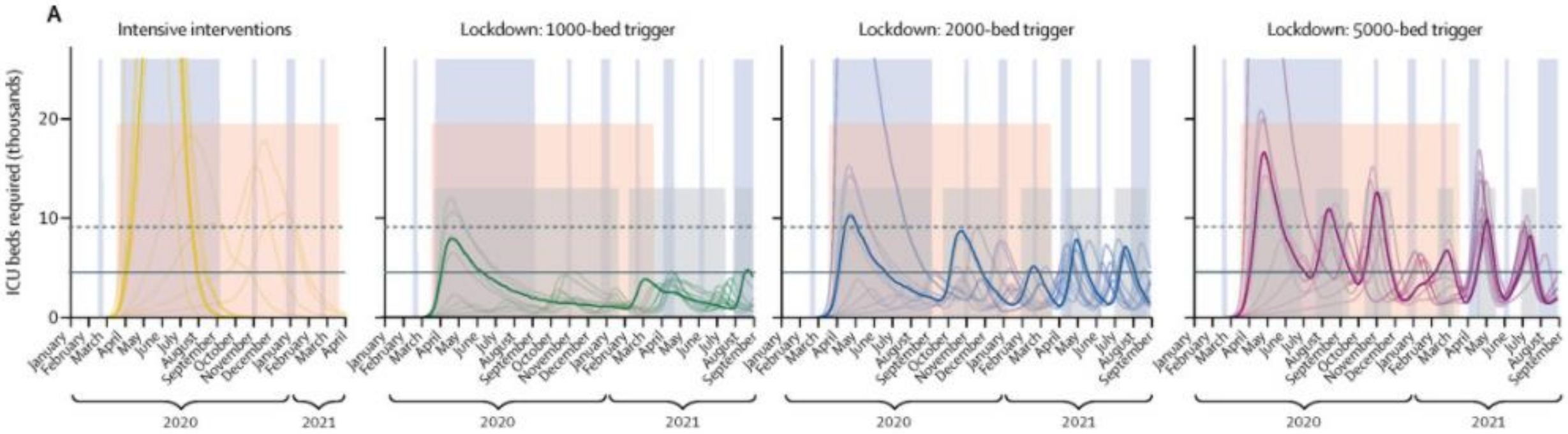
Can interventions aimed at travellers prevent introduction of cases?



Quilty et al. 2020.

Modelling interventions

When should lockdowns be implemented to maintain the epidemic under a healthcare threshold?



Davies et al. 2020. *Lance*

Some examples, but there are many others...

- Models can be used for a range of purposes, and important to assess what the model is trying to do.
- The purpose impacts the methods chosen, and the amount of complexity that is needed.

Key points throughout:

- Understanding of data streams
- Update results as situation changes
- Quantify and convey uncertainty

CMMID at LSHTM

Open code, open access, fair and equitable collaborative working.

CMMID working group repository of papers, apps, and reports:
https://cmmid.github.io/ncov

cmmid

centre *for*
mathematical
modelling *of*
infectious
diseases

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Is There Room for Patient Perspective in a Pandemic?

Kirsty Irvine

Chair, Independent Group Advising (NHS Digital) on the Release of Data (IGARD)

Independent Group Advising (NHS Digital) on Release of Data

- **Independent** from NHS Digital
- **Lay/patient** representatives
- **Advisory**
- Assess against NHS Digital Standards/wider legal and ethical context
- **Consent materials** are considered
- Applications form public data release register –NHS Digital website Register of approved data releases - NHS Digital
- Minutes published weekly - NHS Digital website Independent Group Advising on the Release of Data - NHS Digital

How the landscape changed

Pre pandemic process

- Applications addressed in chronological order according to time of application
- Known data sets
- Known data
- Known review framework and expectations
- Application process => weeks/months

Pandemic environment

- Additional triage processes: NHS X front door
- Additional oversight : PAG
- Additional dissemination routes
- Novel collections (GP data for Pandemic Response)
- Novel data (infections, vaccinations)
- Novel registries (Permission to Contact for Vaccine Research)
- Use of “emergency” legal gateways to collect and flow data => NB the legal requirement for transparency remained the same!
- Requests for data dissemination in days/weeks

IGARD RESPONSE

Reviewed consent materials and provided comments and support for eg RECOVERY trial

Set up and ran an additional weekly meeting for verbal urgent advice “Covid-19 Response”

Provided oversight for expedited applications

REFLECTIONS

CHALLENGES

- Effective triage and prioritisation
- Transparency requirements
- Urgency: both real and perceived
- Maintaining public trust

SOLUTIONS?

- Post dissemination transparency?
- Catch up communications?
- Retrospective review?
- Legislative change?

The benefit of patient perspective and independent oversight may only be realised in retrospect

IGARD@NHS.NET
@KirstyTrapper