Randomised Evaluation of COVID-19 Therapy: the RECOVERY trial

Collaborators' Meeting

1st November 2021

Agenda

RECOVERY
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1. Introductions
2. Update on progress
3. REGEN-COV
4. Dimethyl fumarate
5. Baricitinib
6. Empagliflozin
7. Trial procedures including changes to consent process
8. Future plans
9. Pregnancy update
10. Q&A

Introductions

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- One of the central study team will talk to the agenda
- If you have questions please enter them into the “Q&A” on the right side of your screen.
- Questions may be answered directly or to the whole group

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PROGRESS UPDATE

Planned design (adults)

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ELIGIBLE PATIENTS

early immunomodulation - 1

A — Dimethyl fumarate *or* Usual care alone

SGLT-2i comparison

F — Empagliflozin *or* Usual care alone

Participants enter ≥1 randomisation A, D, E or F

R

Outcomes collected at earliest of death, discharge or 28 days

OUTCOMES

For hypoxic patients only:

corticosteroids

E — High-dose corticosteroids *or* Usual care alone

early immunomodulation - 2

D — Baricitinib *or* Usual care alone

Recruitment by site and by time

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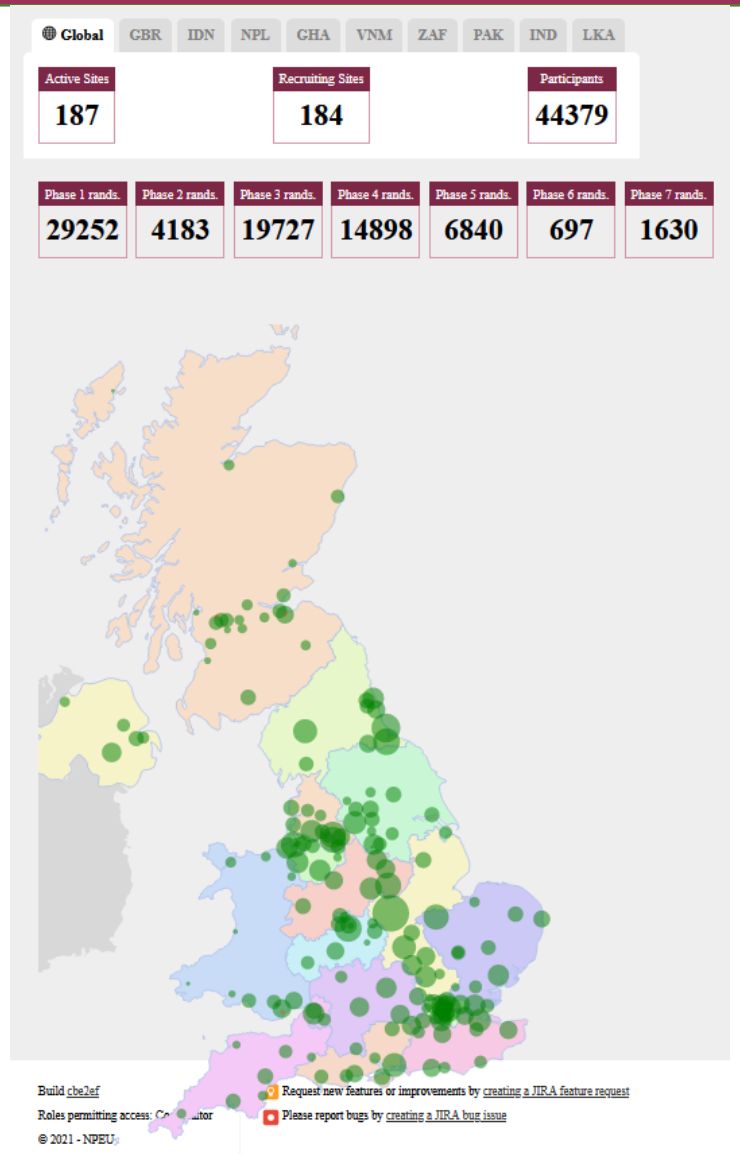

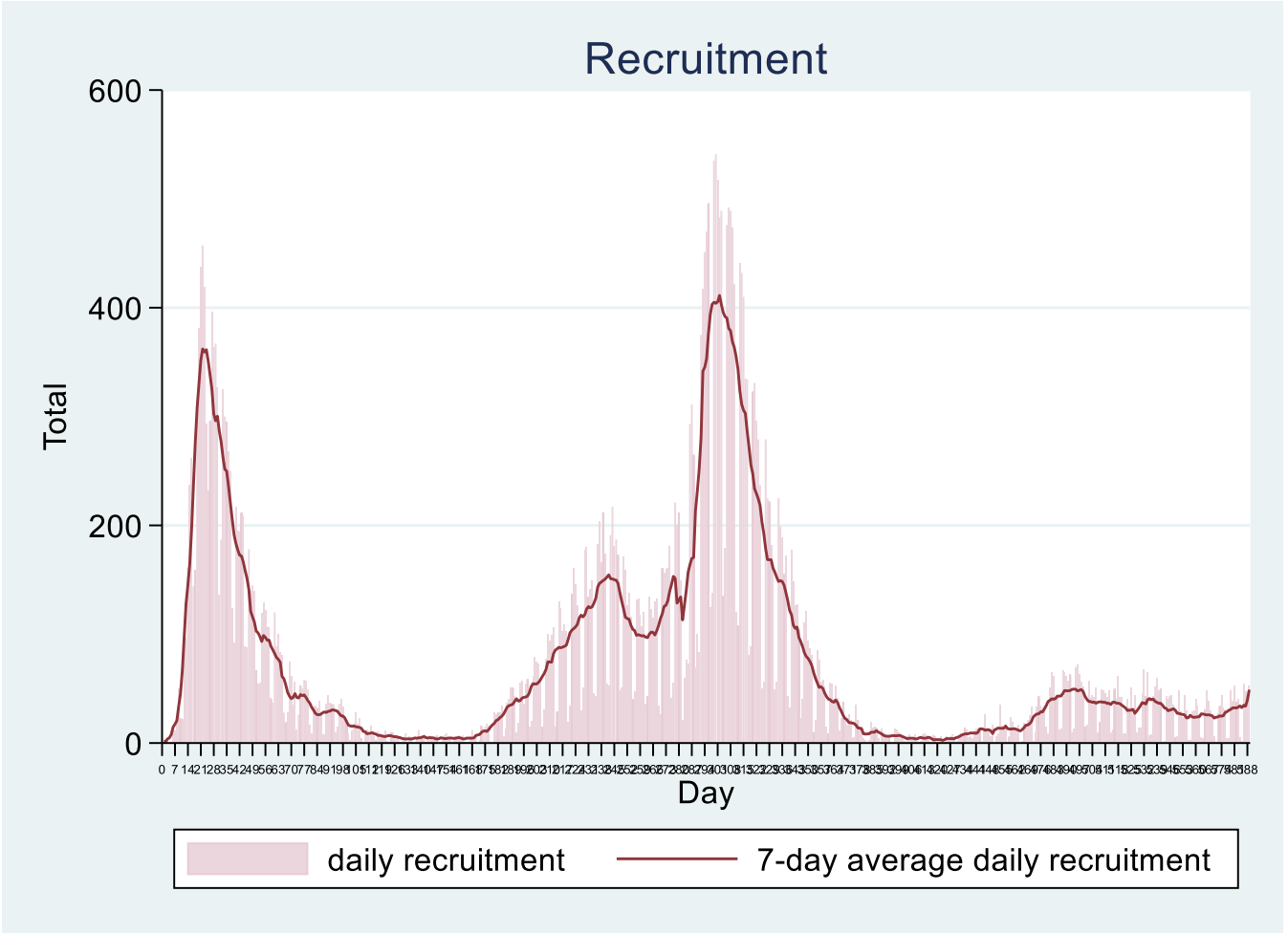

Current numbers in comparisons

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- Baricitinib *vs* usual care: ~6800
- Dimethyl fumarate *vs* usual care: 640
- Empagliflozin: ~1600
- High-dose corticosteroids: ~700

Recruitment

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- Many staff will be returning to previous research studies, but please do ensure that your site continues to have a strategy to identify, invite and recruit patients presenting with COVID-19

- Numbers being admitted is fairly static, but remains important to offer trial to as many as possible

- Proportion of admitted patients has fallen from average of 10% to about 3%

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REGEN-COV (CASIRIVIMAB AND IMDEVIMAB)

REGEN-COV

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- Results published online earlier this year; currently under peer-review
- REGEN-COV = REGN-COV2 = Ronapreve = Casirivimab and imdevimab
- Analysis plan slightly different to previous analyses: focus on seronegative participants because of earlier trials with REGEN-COV showing effects different among seronegative and seropositive individuals

Primary outcome, by serostatus

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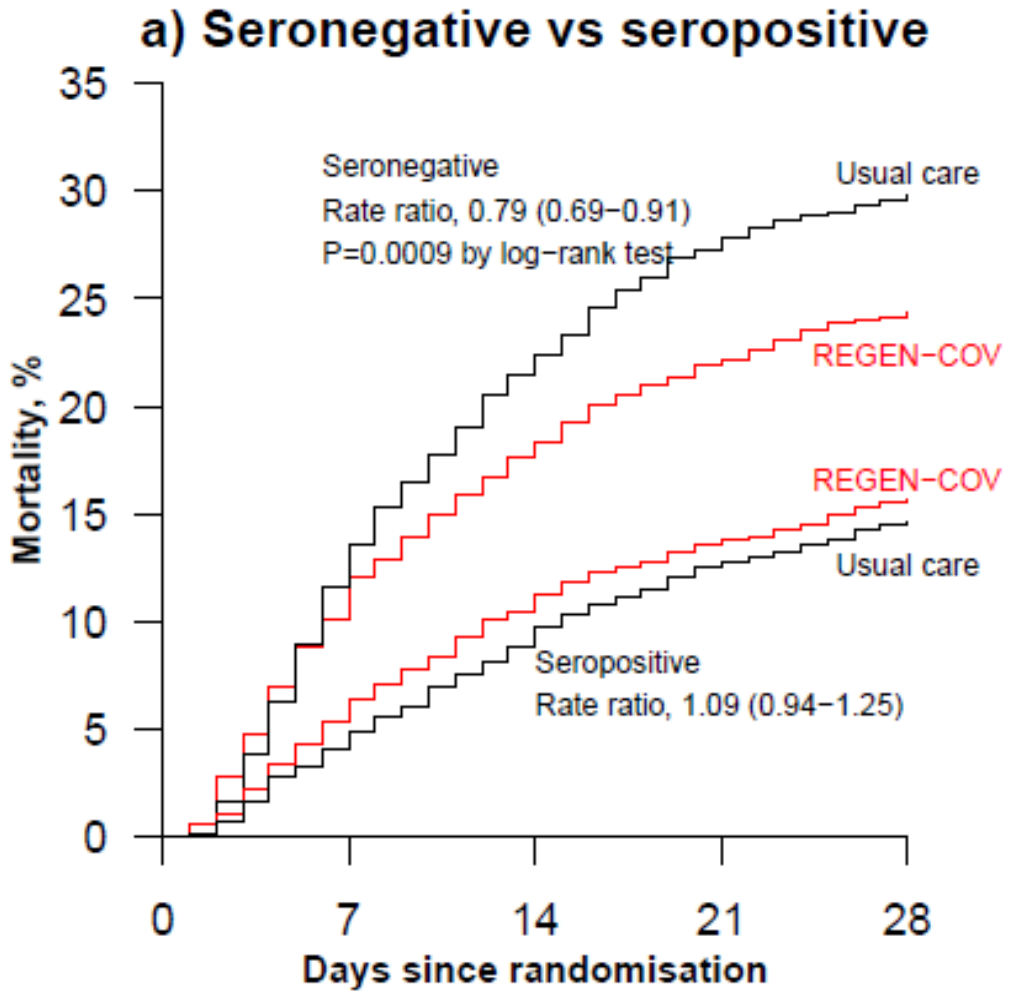

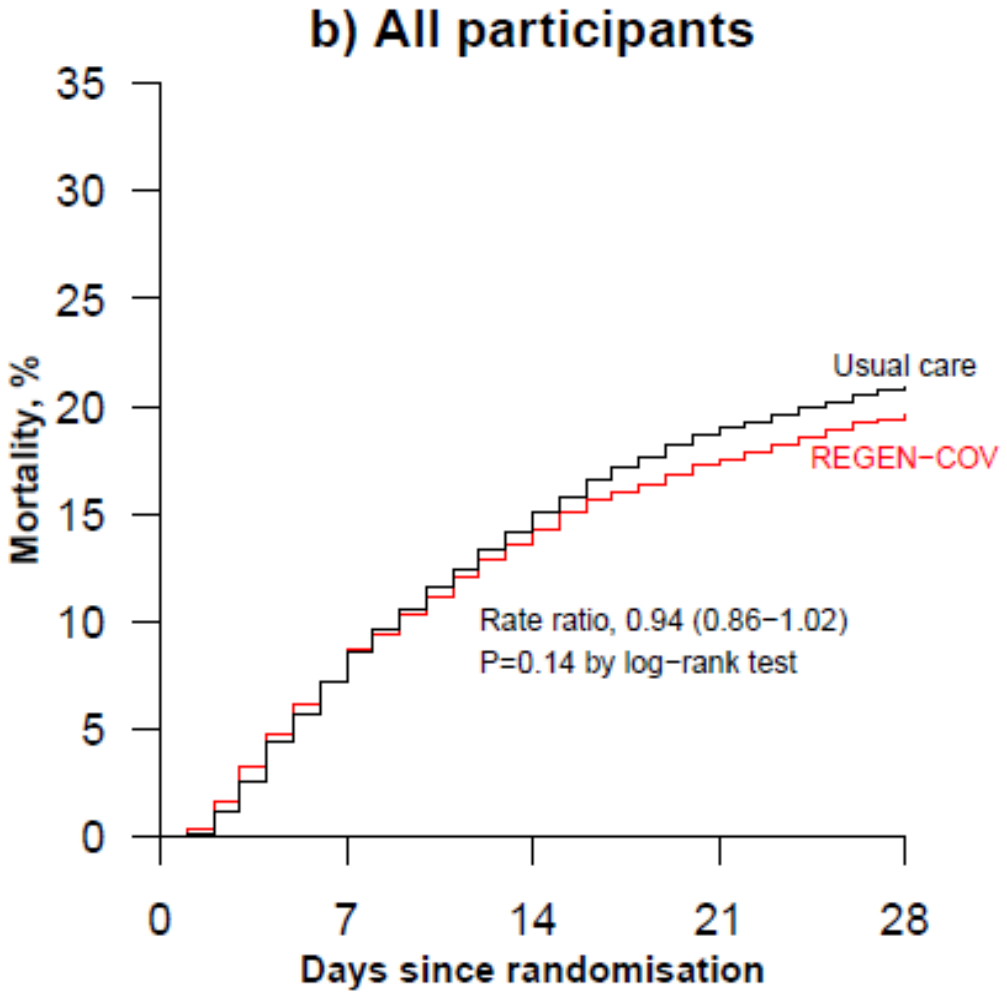

Impact

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- REGEN-COV has been licensed by MHRA for treatment of outpatients
- NHS England are preparing guidance on use (off license initially) in hospitalised patients, based on RECOVERY results
- RECOVERY results will be submitted to international regulators to update the license to include hospitalised patients

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DIMETHYL FUMARATE

Dimethyl fumarate

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- Recently added to protocol and has been piloted at some sites

- Includes extra data collection on:
  - S/F_{94} (measurement of oxygenation function of lungs)
  - WHO scale
  - Lab results
  - Tolerability of DMF

- Sites can still express an interest in participating in this arm

Dimethyl fumarate

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- Analysis of blinded data so far shows that duration of admission has shortened, so many participants do not have day 5 S/F_{94} measurement recorded as they have left hospital
- Some sites have not recorded measurements for participants in control arm. **All participants in DMF comparison (both on DMF and in usual care group) must have S/F_{94} measurements.**
- Protocol amendment has been made to change primary outcome to WHO score (which can account for discharge before day 5) and consequent increase in sample size to 700 participants

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BARICITINIB

Baricitinib in COVID-19

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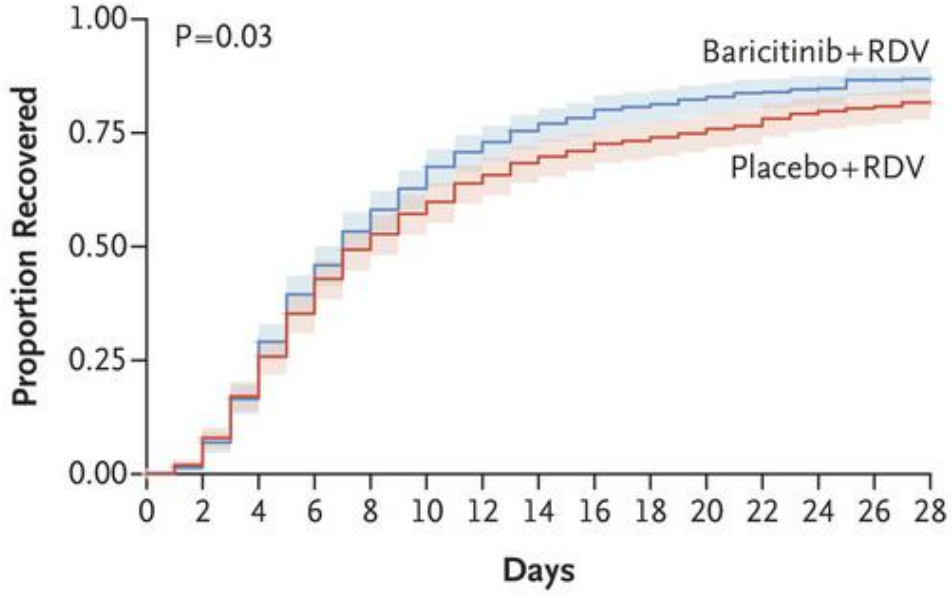
- JAK/STAT system is key to immune activation so modulating it may be beneficial

- Data from ACTT-2 show quicker time to recovery



No. at Risk

Baricitinib+RDV	515	497	418	302	233	186	145	121	107	95	87	80	76	63	30
Placebo+RDV	518	495	417	322	251	211	178	156	143	131	123	115	102	92	44

Baricitinib in COVID-19

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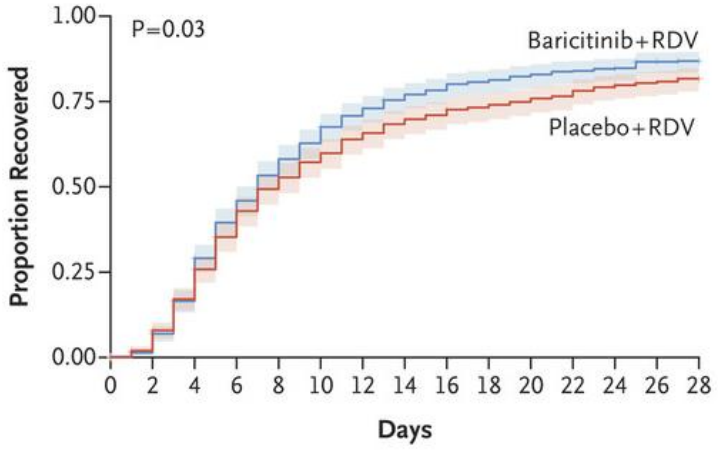
- JAK/STAT system is key to immune activation so modulating it may be beneficial
- Data from ACTT-2 show quicker time to recovery
- Data from COV-BARRIER show possible mortality benefit (and reassuring safety data)



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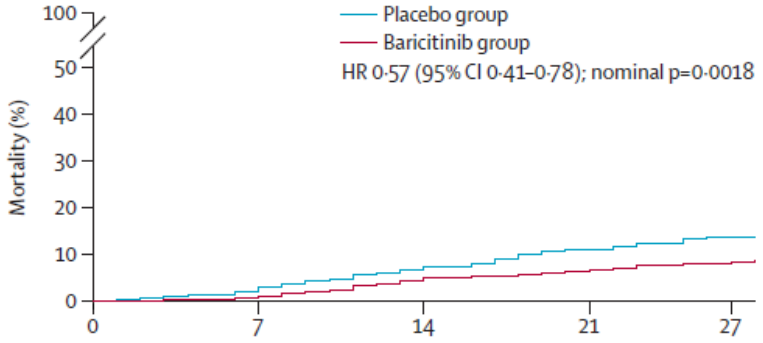

Number at risk (number censored)					
Placebo group	761 (0)	717 (20)	679 (28)	639 (40)	617 (44)
Baricitinib group	764 (0)	725 (30)	684 (44)	664 (50)	648 (55)

Baricitinib in RECOVERY

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- >6800 participants recruited to date
- Overall 28 day mortality rate is ~13% (compared to 20-25% earlier in pandemic)
- This means about 7500 participants are needed to identify a 20% reduction (e.g. 13% to 10.5%) reliably

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EMPAGLIFLOZIN

SGLT-2 inhibitors and Empagliflozin (empa)

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- Empagliflozin is an SGLT-2 inhibitor (SGLT-2i)
- SGLT-2 = sodium-glucose co-transporter 2 and is the main process by which glucose filtered into the urine is reabsorbed by the kidney
- SGLT-2i were developed as treatments for diabetes because they can lower blood sugar
- In addition to lowering blood sugar they have also been found to reduce the risk of:
  - Atherosclerotic cardiovascular events (eg, myocardial infarction) in people with type 2 diabetes
  - Cardiovascular death in people with heart failure
  - Progression of chronic kidney disease in people with diabetes and CKD

SGLT-2i in COVID-19

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- SGLT-2i may have beneficial effects in COVID-19
  - Shift in energy metabolism from glucose (which SARS-CoV-2 may rely on) to lipids
  - Improve endothelial function
  - Anti-inflammatory effects

- DARE-19 trial compared dapagliflozin with placebo among 1250 patients hospitalised for COVID-19 with another ‘risk factor’ (eg, diabetes, cardiovascular disease)

SGLT-2i in COVID-19: DARE-19 results

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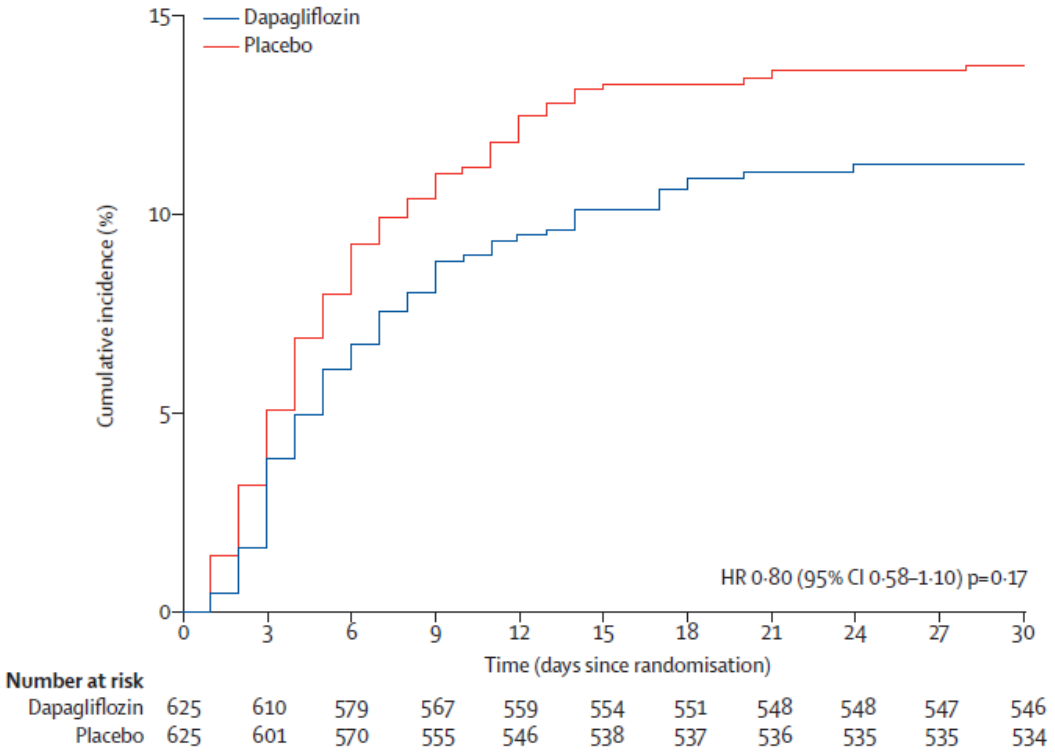
Primary outcome: organ failure or death

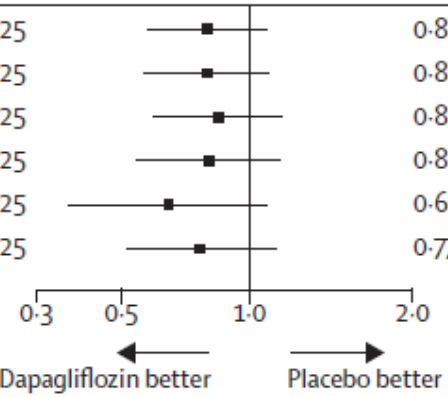


Number at risk

Dapagliflozin	625	610	579	567	559	554	551	548	548	547	546
Placebo	625	601	570	555	546	538	537	536	535	535	534

Primary outcome: components

	Dapagliflozin n/N	Placebo n/N	HR (95% CI)
Primary composite outcome	70/625	86/625	0·80 (0·58–1·10)
New or worsening organ dysfunction	64/625	80/625	0·80 (0·57–1·11)
Respiratory decompensation	58/625	70/625	0·85 (0·60–1·20)
Cardiac decompensation	47/625	58/625	0·81 (0·55–1·19)
Kidney decompensation	24/625	35/625	0·65 (0·38–1·10)
Death from any cause	41/625	54/625	0·77 (0·52–1·16)



Empagliflozin in RECOVERY

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- Available in all countries
- Separate factorial randomisation to others (so can be given in addition to other study treatment allocations)
- **Dose: 10 mg once daily for up to 28 days** (stopped at discharge if sooner)
- **Exclusions:**
  - Type 1 diabetes mellitus* or post-pancreatectomy diabetes mellitus
  - History of ketoacidosis
  - Current blood ketones ≥1.5 mmol/L (or urine ketones ≥2+)
  - Pregnancy or breast-feeding
  - (No exclusions around kidney or liver function)

  * If patient is only on insulin, consider carefully whether diabetes is type 1 and seek advice if necessary

Adverse effects of SGLT-2i

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- Mycotic genital infection (eg, vulvovaginal candidiasis or candidal balanitis)
  - Commonest adverse effect
  - Easily treated with topical antifungal eg, clotrimazole cream
- Hypoglycaemia
  - SGLT-2i do not cause hypoglycaemia unless given with insulin or insulin secretagogue (eg, sulphonylurea such as gliclazide)
- Volume depletion
  - SGLT-2i cause natriuresis and osmotic diuresis so care required with fluid balance

Adverse effects of SGLT-2i

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- Ketoacidosis
  - Defined as combination of both **ketosis** (blood ketones ≥1.5 mmol/L or urine ketones ≥2+) and **metabolic acidosis** (bicarbonate <15 mmol/L)
  - Only occurs in people with diabetes
  - NB can occur with relatively normal blood sugar if on SGLT-2i

- Participants with diabetes should have regular checks of ketones
  - Twice daily blood ketones (or once daily urine ketones if blood ketone testing not available) or if clinical concern*
  - If ketosis (blood ketones ≥1.5 mmol/L or urine ketones ≥2+) develops:
    - Ensure adequate fluid and calorific intake
    - Refer to local diabetes team (if available) and follow local protocols for ketosis
    - Consider increasing insulin (if participant on it) and withholding empagliflozin while ketotic

* Blood ketones are quantitative whereas urine ketones only semi-quantitative

Additional outcomes to be collected

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- Ketoacidosis: defined as combination of both **ketosis** (blood ketones ≥1.5 mmol/L or urine ketones ≥2+) and **metabolic acidosis** (bicarbonate <15 mmol/L
- Severe hypoglycaemia i.e. hypoglycaemia causing a reduced conscious level requiring another person to recover
- Hyperglycaemia requiring new insulin or with hyperosmolar state
- Peak creatinine during admission

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TRIAL PROCEDURES

Consent

- RECOVERY allows consent to be given:
  - By patient (either in person or witnessed)
  - By legal representative (either relative or – if not available in person – independent doctor) if patient does not have capacity

- Some issues have been identified with consent by legal representative:
  - Original protocol required consent to be sought from such patients if they regain capacity
  - Doctors acting as legal representative not always independent (as defined by regulations)

Consent

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- We strongly recommend that sites identify a small group of doctors to act as legal representatives
  - Such individuals can complete trial training (so they understand trial) but should not be involved in trial in any other way
  - Number of such individuals can be determined depending on the site size and organisation

Consent

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- Participants whose consent was given by legal representative should be informed of their participation prior to discharge
  - From 8 November (when protocol V18.1 goes 'live') such participants do **not** need to give written consent
  - They **do** need to be given written information (e.g. PIS) about the trial which informs them of their rights and how to exercise them
  - **Please** document in medical notes that such information has been provided

- Please also include participation in RECOVERY in discharge summaries

Consent monitoring

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- It has always been intention to monitor consent process, but delayed until now

- All sites will be asked to review a random sample of 20-40 consent forms
  - Precise number depends on number recruited at site
  - Sites who recruited ≤20 patients will review all

- CCO in Oxford will do random selection and provide tool for completion

Consent training

- Consent training materials will be updated

- **All staff** who will continue to obtain consent for RECOVERY will be required to complete new training (and online confirmation form)

Newsletters

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- Earlier this year we wrote to ~8000 participants to inform them of trial results etc

- We will soon mail all participants to:
  - Inform them of trial results and their impact
  - Remind them of their participation and how to withdraw if they wish

- CCO may receive contact from participants. REC were keen that they could speak to site team if they wish, so some contacts may be passed to site PIs if requested by participants

Completeness of follow-up

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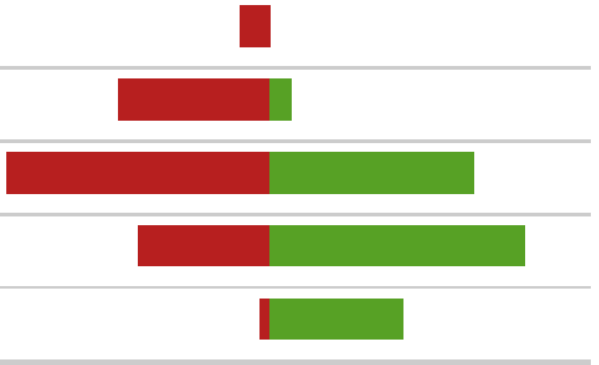
- Weekly reminders highlighting participants randomised >28 days ago without complete form

Follow-up form completion summary

Days Since Rand.	FU Not Completed	FU Completed	Total Rands.
7 ≤ 14	3 (100.0%)	0 (0.0%)	3
14 ≤ 21	15 (88.2%)	2 (11.8%)	17
21 ≤ 28	26 (56.5%)	20 (43.5%)	46
28 ≤ 35	13 (34.2%)	25 (65.8%)	38
> 35	1 (7.1%)	13 (92.9%)	14
Total	**58 (49.2%)**	**60 (50.8%)**	**118**



- Please keep filling them in!

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FUTURE PLANS

RECOVERY international

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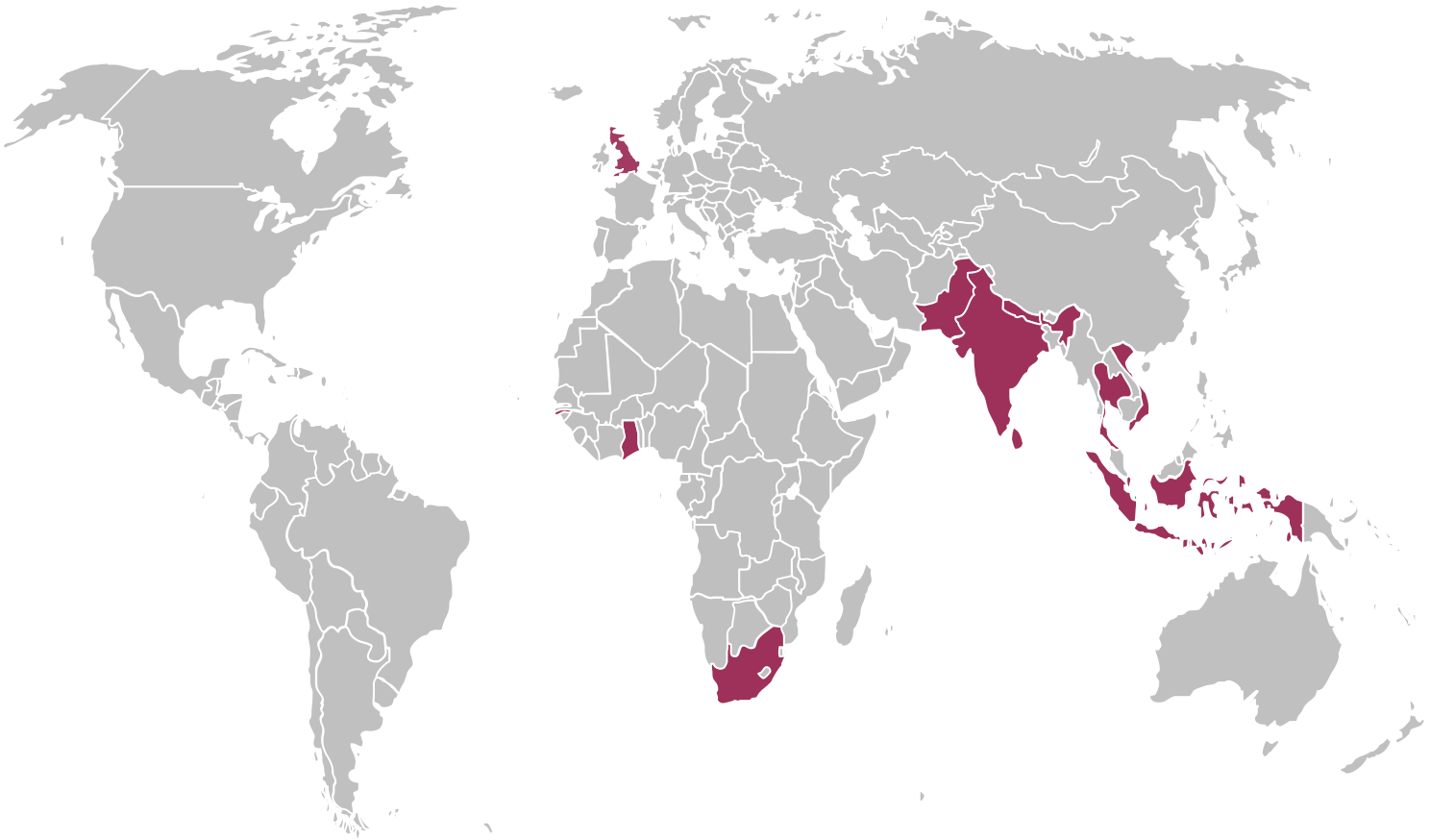

Influenza

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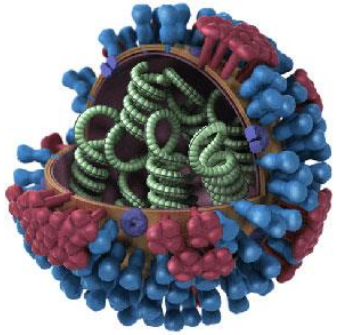
- Seasonal influenza often kills several thousand patients a year in the UK
- Social distancing meant that 2020/21 season was much attenuated, so community resistance levels are low
- 2021/22 season could therefore be more significant
- RECOVERY is ideally positioned to assess treatments for hospitalised patients
  - Antiviral therapies
  - Corticosteroids



Carry on recruiting!

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- RECOVERY remains the largest global trial in COVID-19 and is an exemplar of what trials can do (both in and after pandemic)
- Current therapies are exciting, but need reliable data before they should be used routinely
- THANK YOU for all your support to date and please don't forget RECOVERY!

Randomised Evaluation of COVID-19 Therapy: the RECOVERY trial

Collaborators' Meeting for Pregnancy

1 November 2021

RECOVERY for pregnant women

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1. Update on covid-19 and pregnancy
2. Update on adaptions
3. Update on UKOSS
4. Future plans
5. Q&A

Covid-19 and pregnancy

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RESEARCH

OPEN ACCESS

Check for updates

Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-CoV-2 infection in UK: national population based cohort study

Marian Knight,[1] Kathryn Bunch,[1] Nicola Vousden,[2] Edward Morris,[3] Nigel Simpson,[4] Chris Gale,[5] Patrick O'Brien,[6] Maria Quigley,[1] Peter Brocklehurst,[7] Jennifer J Kurinczuk,[1] On behalf of the UK

BMJ: first publ

PLOS ONE

PUBLISH ABOUT BROWSE

OPEN ACCESS PEER-REVIEWED

RESEARCH ARTICLE

The incidence, characteristics and outcomes of pregnant women hospitalized with symptomatic and asymptomatic SARS-CoV-2 infection in the UK from March to September 2020: A national cohort study using the UK Obstetric Surveillance System (UKOSS)

Nicola Vousden, Kathryn Bunch, Edward Morris, Nigel Simpson, Christopher Gale, Patrick O'Brien, Maria Quigley, Peter Brocklehurst, Jennifer J Kurinczuk, Marian Knight, on behalf of the UKOSS

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Comments (3)

Impact of SARS-CoV-2 variant on the severity of maternal infection and perinatal outcomes: Data from the UK Obstetric Surveillance System national cohort

Nicola Vousden, Rema Ramakrishnan, Kathryn Bunch, Edward Morris, Nigel Simpson, Christopher Gale, Patrick O'Brien, Maria Quigley, Peter Brocklehurst, Jennifer J Kurir, Marian Knight

doi: https://doi.org/10.1101/2021.07.22.21261000

Morbidity and Mortality Weekly Report

Update: Characteristics of Symptomatic Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status — United States, January 22–October 3, 2020

Laura D. Zambrano, PhD[1,*]; Sascha Ellington, PhD[1,*]; Penelope Strid, MPH[1]; Romeo R. Galang, MD[1]; Titilope Oduyebo, MD[1]; Van T. Tong, MPH[1]; Kate R. Woodworth, MD[1]; John F. Nahabedian III, MS[1]; Eduardo Azziz-Baumgartner, MD[1]; Suzanne M. Gilboa, PhD[1]; Dana Meaney-Delman, MD[1]; CDC COVID-19 Response Pregnancy and Infant Linked Outcomes Team

Maternal, Newborn and Infant Clinical Outcome Review Programme

MBRRACE-UK

Saving Lives, Improving Mothers' Ca

Rapid report: Learning from SARS-CoV-2-related and associated maternal deaths in the UK

Maternal, Newborn and Infant Clinical Outcome Review Programme

MBRRACE-UK
Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK

Saving Lives, Improving Mothers' Care

Rapid report 2021: Learning from SARS-CoV-2-related and associated maternal deaths in the UK

June 2020-March 2021

EDITORIALS

Check for updates

Include pregnant women in research—particularly covid-19 research

Adapting interventions and changing attitudes will drive scientific progress

Marian Knight,[1] R Katie Morris,[2] Jenny Furniss,[3] Lucy C Chappell[4]

The UK Confidential Enquiries into Maternal Deaths have repeatedly highlighted inequities in the medical treatment of pregnant and postpartum women, noting

or breastfeeding allows safety concerns to be allayed for women, their families, and healthcare professionals.

1 National Perinatal Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK

2 Institute of Applied Health Research, University of Birmingham, Birmingham, UK

3 UK Obstetric Surveillance System

BMJ: first published a

RESEARCH

OPEN ACCESS

Check for updates

FAST TRACK

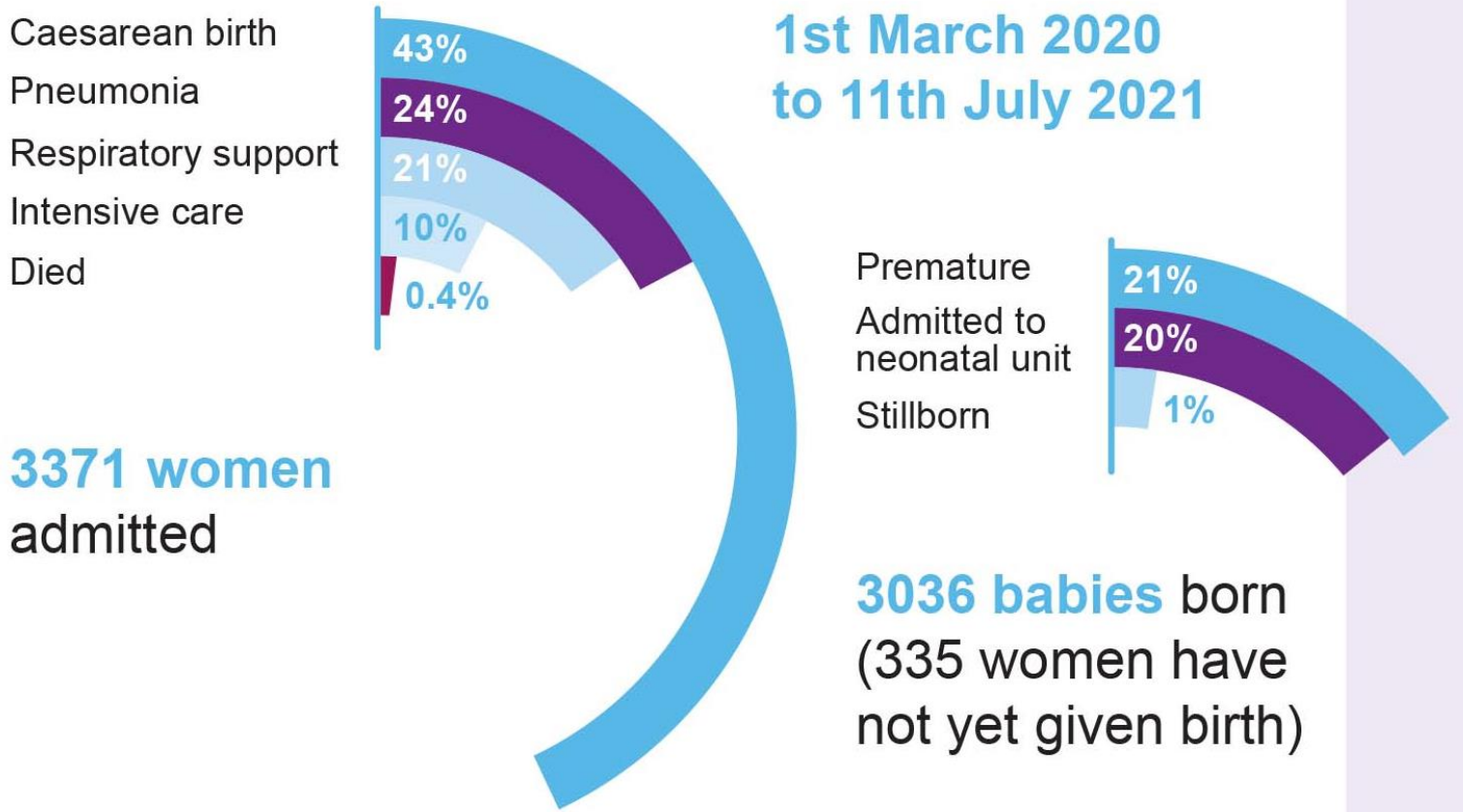
Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis

John Allotey,[1,2] Elena Stallings,[3,4] Mercedes Bonet,[5] Magnus Yap,[6] Shaunak Chatterjee,[6] Tania Kew,[6] Luke Debenham,[6] Anna Clavé Llavall,[6] Anushka Dixit,[6] Dengyi Zhou,[6] Rishab Balaji,[6] Siang Ing Lee,[1] Xiu Qiu,[7,8,9] Mingyang Yuan,[1,7] Dyuti Coomar,[1] Madelon van Wely,[10] Elizabeth van Leeuwen,[11] Elena Kostova,[10] Heinke Kunst,[12,13] Asma Khalil,[14] Simon Tiberi,[12,13] Vanessa Brizuela,[5] Nathalie Broutet,[5] Edna Kara,[3] Caron Rahn Kim,[5] Anna Thorson,[5] Olufemi T Oladapo,[5] Lynne Mofenson,[15] Javier Zamora,[3,4,16] Shakila Thangaratinam,[2,17] for PregCOV-19 Living Systematic Review Consortium

BMJ: first published as 10.1136/bmj.m33

UKOSS
UK Obstetric Surveillance System

Outcomes of COVID-19 for pregnant women and their babies after admission to hospital with symptoms



3371 women admitted

3036 babies born (335 women have not yet given birth)

https://www.medrxiv.org/content/10.1101/2021.07.22.21261000v1

Who is at greatest risk?

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UKOSS
UK Obstetric Surveillance System

- Risk of admission and risk of severe infection is greatest in:

➢aged over 35	x 2.1	
➢BMI > 30	x 2.7	risk of
➢pre-existing comorbidity	70%	ICU admission[1]
➢non-White ethnicity	66%	
➢Third trimester	83% of those admitted	

https://www.medrxiv.org/content/10.1101/2021.07.22.21261000v1

Respiratory support needs during Wildtype, Alpha and Delta variant periods

UKOSS UK Obstetric Surveillance System

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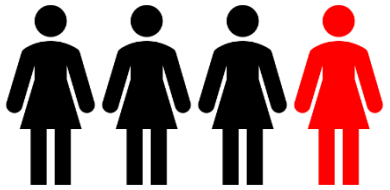
	Wildtype N=1435 (%)	Alpha N=1765 (%)	Delta N=171 (%)	OR Alpha vs. Wildtype (95% CI)	aOR Alpha vs. Wildtype (95% CI)	OR Delta vs. Alpha (95% CI)	aOR Delta vs. Alpha (95% CI)
Composite indicator of moderate to severe infection	350 (24.4)	631 (35.8)	77 (45.0)	1.72 (1.48-2.01)	1.75 (1.48-2.06)	1.47 (1.07-2.02)	1.53 (1.07-2.17)
Evidence of pneumonia on imaging	274 (19.1)	486 (27.5)	63 (36.8)	1.61 (1.36-1.90)	1.65 (1.38-1.98)	1.54 (1.12-2.13)	1.64 (1.14-2.35)
Respiratory support required	183 (20.3)	466 (27.2)	52 (33.3)	1.47 (1.21-1.78)	1.39 (1.13-1.71)	1.34 (0.95-1.90)	1.43 (0.97-2.11)
Critical Care received	111 (7.7)	199 (11.3)	26 (15.2)	1.52 (1.19-1.94)	1.61 (1.24-2.10)	1.41 (0.91 -2.20)	1.60 (0.99-2.59)

https://www.medrxiv.org/content/10.1101/2021.07.22.21261000v1

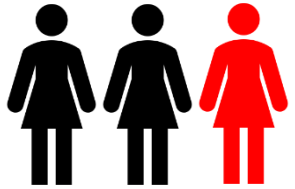
Disease severity

The proportion of hospitalized symptomatic women with moderate to severe COVID-19 has increased

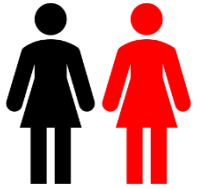
- First wave:



- Alpha variant:



- Delta variant:

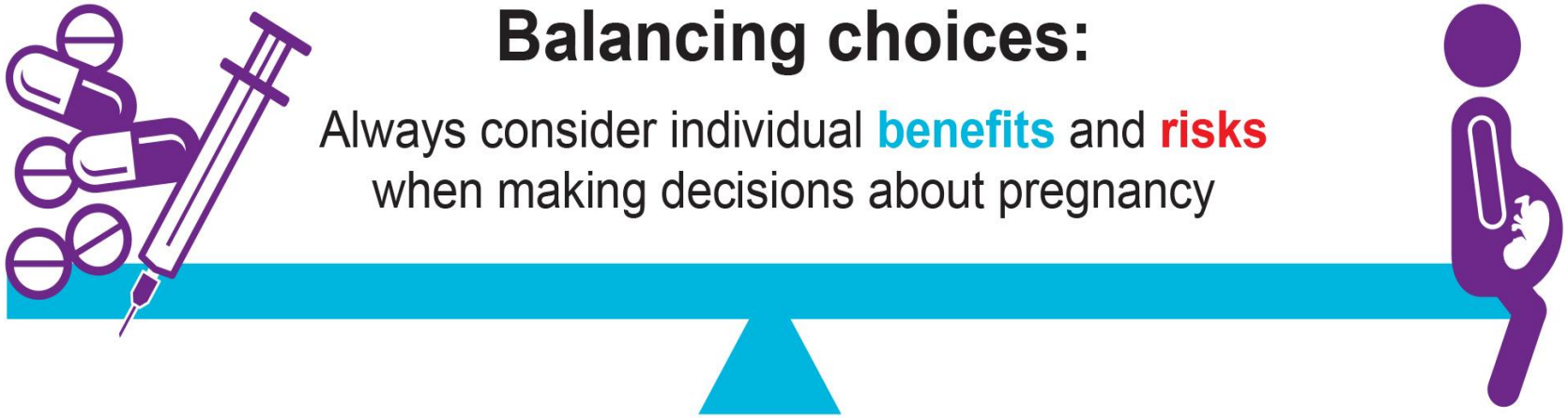


Pregnant and postpartum women appear disproportionately severely affected compared to non-pregnant people of reproductive age

https://www.medrxiv.org/content/10.1101/2021.07.22.21261000v1

Covid-specific medical therapies in pregnant women

- Covid-specific medical therapies are still used infrequently, even for women who are critically ill
- Steroids for maternal indication administered to only around a quarter of pregnant women admitted to intensive care



Delta variant and perinatal outcomes

UKOSS
UK Obstetric Surveillance System

Overall:

- 1 in 100 have a stillbirth
- 1 in 3 have a preterm birth
- 1 in 5 babies admitted to neonatal unit

Delta variant:

- 1 in 100 have a stillbirth

- In Alpha variant: 23% increase in NNU admission

UKOSS
UK Obstetric Surveillance System

1st February 2021 to 30th September 2021

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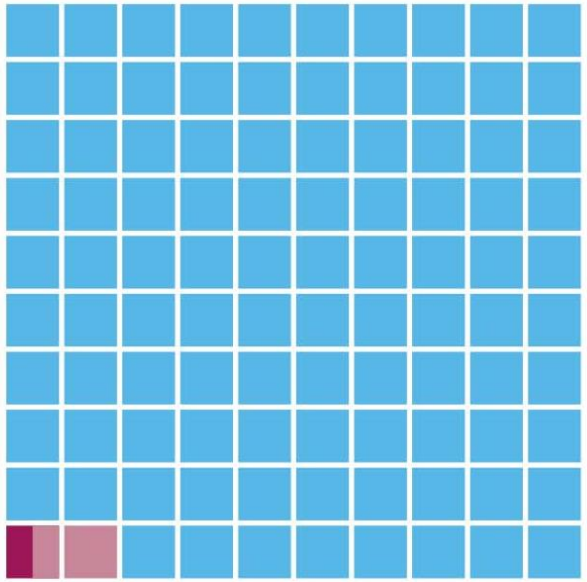
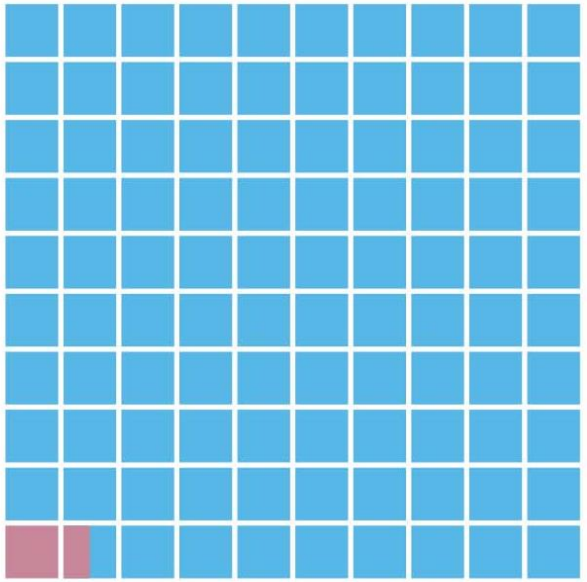
1714 pregnant women admitted to hospital with symptomatic COVID



98.1% unvaccinated
1.5% one dose
0.4% two doses

235 of whom (14%) were admitted to intensive care



98.7% unvaccinated
1.3% one dose

UKOSS
UK Obstetric Surveillance System

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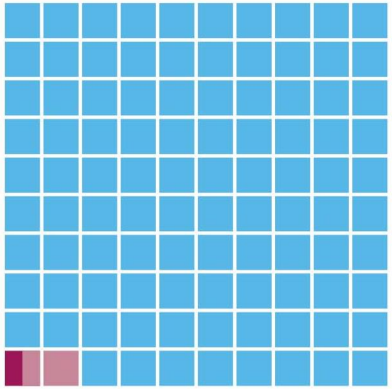
Randomised Evaluation of COVID-19 Therapy

Hospital admissions with

1st February 2021 to 30th September 2021

1714 pregnant women admitted to hospital with symptomatic COVID



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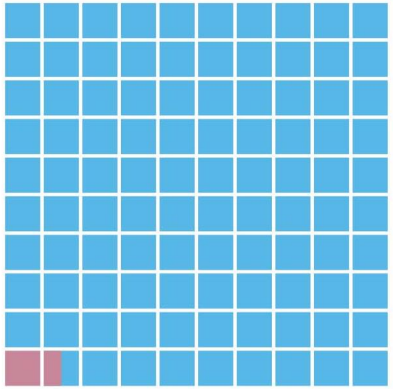
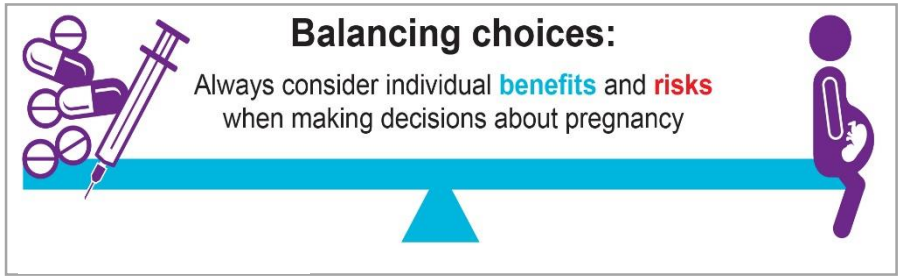
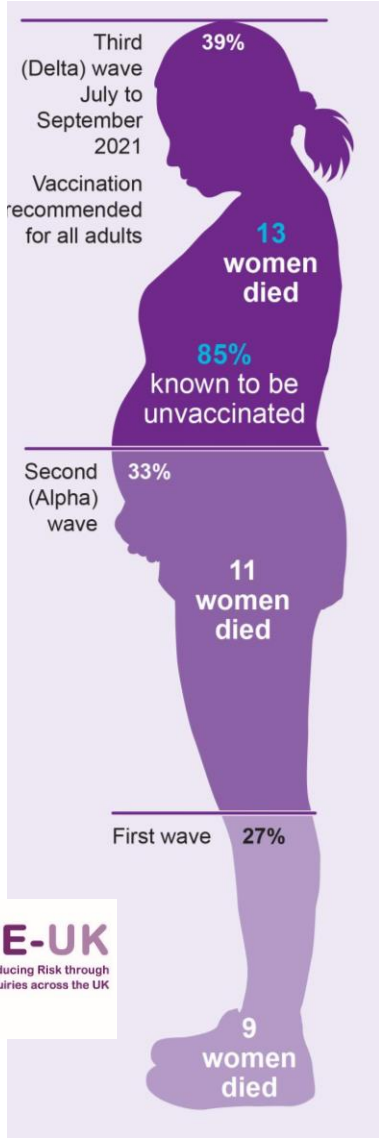


98.7% unvaccinated
1.3% one dose



Maternal deaths during pregnancy or up to 42 days after pregnancy with COVID-19



MBRRACE-UK
Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK

Update from UKOSS this week

Nuffield Department of POPULATION HEALTH
Medical Sciences Division
UNIVERSITY OF OXFORD

UKOSS
UK Obstetric Surveillance System

Notifications by week

ICNARC data (critical care)

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Randomised Evaluation of COVID-19 Therapy

ICNARC report on COVID-19 in critical care:

England, Wales and Northern Ireland

29 October 2021

Demographics	Patients with confirmed COVID-19	
	Admitted 1 May 2021 to date (N=8720)	Admitted 1 Sep 2020-30 Apr 2021 (N=25,841)
Currently or recently pregnant, n (% of females aged 16-49) [N=1513]		
Currently pregnant	245 (16.2)	169 (7.4)
Recently pregnant (within 6 weeks)	194 (12.8)	150 (6.6)
Not known to be pregnant	1074 (71.0)	1970 (86.1)

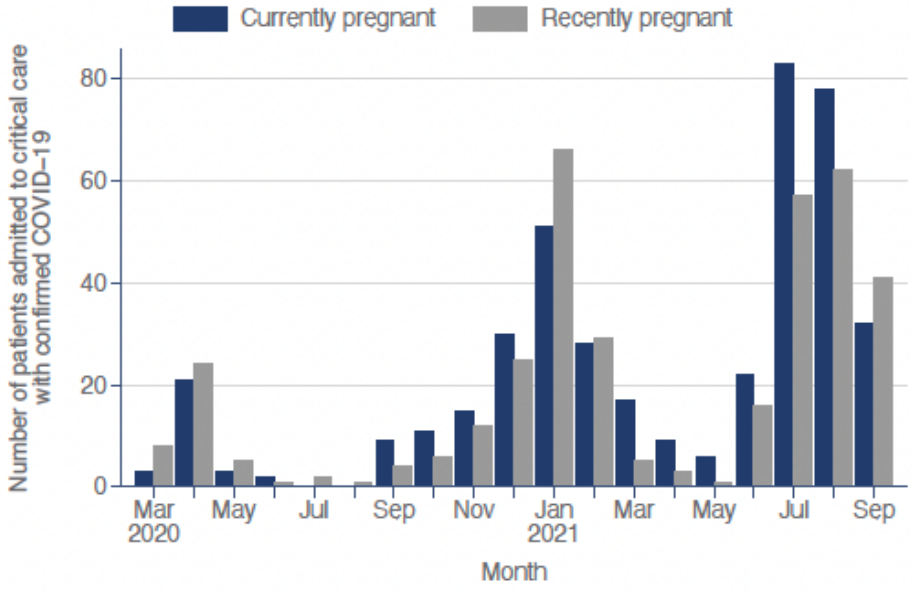

Figure 28. Numbers currently and recently pregnant

Monthly trend in the number of women reported to be currently or recently pregnant on admission to critical care.

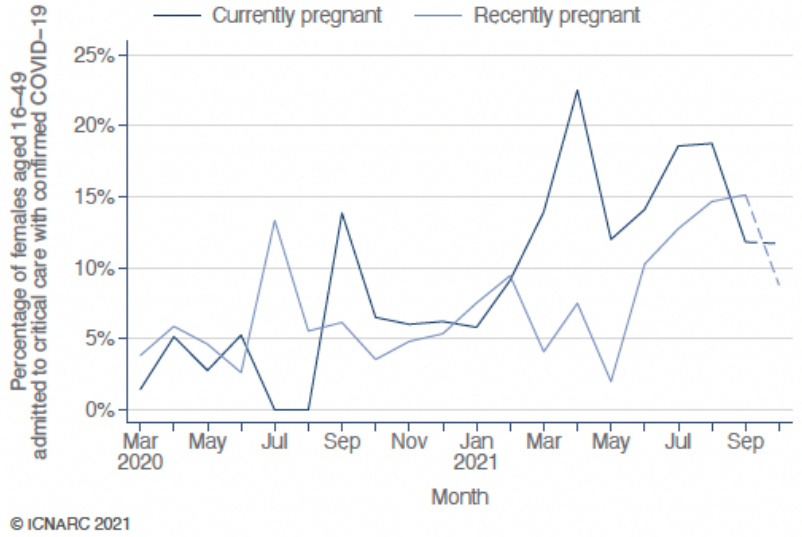

Figure 29. Percentages currently and recently pregnant

Monthly trend in the percentage of women aged 16-49 years reported to be currently or recently pregnant on admission to critical care.

Covid-19 and pregnancy: headlines

RECOVERY
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- Covid-19 affects pregnant women
- Additional risk factors previously identified (ethnic minority groups, increasing gestation, higher maternal age, high BMI, pre-existing comorbidities)
- Impact on preterm birth continues to be major impact
- Ongoing evaluation of increased maternal risk (ICU admission and maternal morbidity) and increased perinatal risk (stillbirth, neonatal infection)

- RECOVERY trial is one of few trials to include pregnant women, and has changed clinical practice, including for pregnant women

Covid-19 and pregnancy: RCOG

RECOVERY
Randomised Evaluation of COVID-19 Therapy

THE ROYAL COLLEGE OF MIDWIVES

Royal College of Obstetricians & Gynaecologists

Coronavirus (COVID-19) Infection in Pregnancy

Information for healthcare professionals

Version 14: Published Wednesday 25 August

Quick reference summary of acute COVID-19 management in pregnancy

Quick reference only, see section 6 for further detail.

- Assess – admit, or discharge with clear advice about symptom deterioration and specific contact details.
- Oxygen to maintain saturations above 94%, escalating with e.g. nasal prongs, masks, CPAP, IPPV, ECMO
- No antibiotics unless additional bacterial infection suspected.
- LMWH for VTE prophylaxis
- Steroids if oxygen is needed (e.g. oral prednisolone 40 mg once daily or IV hydrocortisone 80 mg twice daily, with intramuscular dexamethasone 6 mg twice daily for four doses followed by oral prednisolone as below if fetal lung maturity is also required).
- MDT review – is escalation required? Does birth need expediting?
- Strongly consider tocilizumab (400 mg/600 mg/800 mg single IV infusion depending on weight) if C-reactive protein at or above 75 mg/l or in ICU.
- Strongly consider REGEN-COV monoclonal antibodies (8 g single IV infusion) in those with no SARS-CoV-2 antibodies.

Remdesivir should only be considered for those who are not improving or who are deteriorating.

Azithromycin, hydroxychloroquine and lopinavir/ritonavir have been shown to be ineffective and should not be offered.

Planned design (pregnant adults)

RECOVERY
Randomised Evaluation of COVID-19 Therapy

ELIGIBLE PATIENTS

A — early immunomo[illegible]on — Dimethyl fu[illegible]r — Usual care alone

F —  SGLT-2i comparison — Empagliflozi[illegible] — Usual care alone

Participants enter ≥1 randomisation A, D, E or F

R

Outcomes collected at earliest of death, discharge or 28 days

OUTCOMES

For hypoxic patients only:

E —  corticosteroids — [illegible]-dose corticosteroids *or* Usual care alone

NOT UK

D — early immunomodulati[illegible] — Baricitinib — [illegible]ual care alone

Planned design (postnatal adults) (not breastfeeding)

RECOVERY
Randomised Evaluation of COVID-19 Therapy

ELIGIBLE PATIENTS

early immunomodulation - 1

A — Dimethyl fumarate *or* Usual care alone

SGLT-2i comparison

F — Empagliflozin *or* Usual care alone

Participants enter ≥1 randomisation A, D, E or F

R

Outcomes collected at earliest of death, discharge or 28 days

OUTCOMES

For hypoxic patients only:

corticosteroids

E — [illegible]-dose corticosteroids *or* Usual care alone

NOT UK

early immunomodulation - 2

D — Baricitinib *or* Usual care alone

RECOVERY for pregnant women

RECOVERY
Randomised Evaluation of COVID-19 Therapy

Site teams

This page contains additional information for RECOVERY site team members. Follow these links for guidance on randomisation and how to collect follow-up data.

RECOVERY Privacy Notice for Trial Staff

INTERVENTION INFORMATION

RECOVERY intervention sheet - empagliflozin

RECOVERY intervention sheet - baricitinib

RECOVERY intervention sheet - tocilizumab

RECOVERY intervention sheet - dimethyl fumarate

RECOVERY position statement on baricitinib and tocilizumab

Measurement of additional early phase assessment outcomes SOP v1.3

GUIDES FOR SPECIFIC PATIENT GROUPS

RECOVERY for paediatric patients

RECOVERY for patients with chronic kidney disease

RECOVERY for pregnant and breastfeeding women

RECOVERY and remdesivir

COLLABORATORS' MEETINGS SLIDES

We apologise if you were unable to join the meetings.

26 April 2021	27 April 2021
22 February 2021	23 February 2021
25 January 2021	26 January 2021
4 January 2021	5 January 2021
7 December 2020	8 December 2020
16 November 2020	17 November 2020

Pregnancy information document

RECOVERY
Randomised Evaluation of COVID-19 Therapy

RANDOMISED EVALUATION OF COVID-19 THERAPY (RECOVERY)
for pregnant and breastfeeding women
Pregnancy lead: Prof Marian Knight
With support of UK Teratology Information Service (Dr Ken Hodson, Medical Director)

	RECOVERY trial protocol	**Adaption for pregnancy**
Eligibility	Patients are eligible if all of the following are true: i. Hospitalised ii. SARS-CoV-2 infection (clinically suspected or lab confirmed) iii. No medical history that might, in the opinion of the attending clinician, put the patient at significant risk if they were to participate in the trial	Same eligibility
Interventions	**First randomisation part A** • Dimethyl fumarate (in some sites) **First randomisation part D** • Baricitinib **First randomisation part F** • Empagliflozin	Interventions for pregnant women • No interventions currently available *Not recommended in pregnancy* • *Dimethyl fumarate* • *Baricitinib* • *Empagliflozin*
Follow-up/ outcomes	Ascertained at the time of death or discharge or at 28 days after randomisation (whichever is sooner): ➢ Vital status (alive/ dead, with date and presumed cause of death, if appropriate) ➢ Hospitalisation status (inpatient/ discharged, with date of discharge, if appropriate) ➢ Use of ventilation (none/ previous/ ongoing, with days of use and type, if appropriate) ➢ Use of renal dialysis or haemofiltration (none/ previous/ ongoing)	Same follow-up and outcomes, with **addition of UKOSS COVID-19 case number** (for pregnancy and baby information) to allow later data linkage
		Adaptions for breastfeeding
		The same interventions as in pregnancy should be used. UKOSS COVID-19 case number added if available.

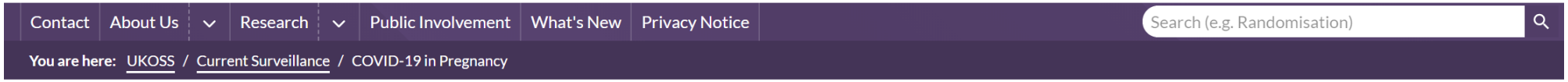
Follow-up = the same, + linkage

RECOVERY
Randomised Evaluation of COVID-19 Therapy

NPEU

Nuffield Department of
POPULATION HEALTH

UNIVERSITY OF OXFORD



COVID-19 in Pregnancy

UKOSS
UK Obstetric Surveillance System

Key points

- Covid-19 is an infectious disease caused by a new strain of coronavirus.
- Covid-19 had not been detected in humans before the outbreak in December 2019.
- As the virus is new, little is known about its effect on certain groups of people, including pregnant women.

Surveillance period

1st March 2020 – 31st March 2021

Background

On this page

Update on progress

RECOVERY
Randomised Evaluation of COVID-19 Therapy

- 160 pregnancy leads identified, supported by research midwives
- Midwife champions on board

- 122 pregnant or postpartum women recruited*
- *10 with pregnancy/postpartum status to be confirmed
- Birmingham Heartlands/Good Hope
- Frimley or Wexham Park
- James Paget
- Hereford
- Epsom & St Helier
- Croydon
- John Radcliffe
- Northumbria
- St Marys/Wythenshawe

Thank you

RECOVERY
Randomised Evaluation of COVID-19 Therapy

Ashford and St Peter's Hospitals NHS Foundation Trust	Leeds Teaching Hospitals NHS Trust	Oxford University Hospitals NHS Foundation Trust
Barts Health NHS Trust	Liverpool University Hospitals NHS Foundation Trust	Pennine Acute Hospitals NHS Trust
Bolton NHS Foundation Trust	Liverpool Women's NHS Foundation Trust	Royal Berkshire NHS Foundation Trust
Bradford Teaching Hospitals NHS Foundation Trust	Luton and Dunstable University Hospital NHS Foundation Trust	Royal Free London NHS Foundation Trust
Cambridge University Hospitals NHS Foundation Trust	Manchester University NHS Foundation Trust	Sheffield Teaching Hospitals NHS Foundation Trust
Chelsea and Westminster Hospital NHS Foundation Trust	Medway NHS Foundation Trust	Sherwood Forest Hospitals NHS Foundation Trust
Chesterfield Royal Hospital NHS Foundation Trust	Milton Keynes University Hospital NHS Foundation Trust	Shrewsbury and Telford Hospital NHS Trust
Croydon Health Services NHS Trust	NHS Greater Glasgow and Clyde: Glasgow Royal Infirmary	St George's University Hospitals NHS Foundation Trust
Epsom and St Helier University Hospitals NHS Trust	NHS Greater Glasgow and Clyde: Queen Elizabeth University Hospital	The Newcastle Upon Tyne Hospitals NHS Foundation Trust
Frimley Health NHS Foundation Trust	NHS Lothian: Royal Infirmary of Edinburgh	United Lincolnshire Hospitals NHS Trust
Guy's and St Thomas' NHS Foundation Trust	North Cumbria Integrated Care NHS Foundation Trust	University College London Hospitals NHS Foundation Trust
Imperial College Healthcare NHS Trust	North Tees and Hartlepool NHS Foundation Trust	University Hospitals Of Leicester NHS Trust
James Paget University Hospitals NHS Foundation Trust	North West Anglia NHS Foundation Trust	Western Sussex Hospitals NHS Foundation Trust
Kettering General Hospital NHS Foundation Trust	Northampton General Hospital NHS Trust	Worcestershire Acute Hospitals NHS Trust
King's College Hospital NHS Foundation Trust	Northumbria Healthcare NHS Foundation Trust	Wye Valley NHS Trust
Kingston Hospital NHS Foundation Trust	Nottingham University Hospitals NHS Trust	

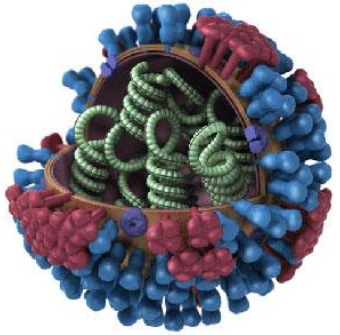
RECOVERY
Randomised Evaluation of COVID-19 Therapy

FUTURE PLANS

Influenza

RECOVERY
Randomised Evaluation of COVID-19 Therapy

- Seasonal influenza often kills several thousand patients a year in the UK
- Social distancing meant that 2020/21 season was much attenuated, so community resistance levels are low
- 2021/22 season could therefore be more significant
- RECOVERY is ideally positioned to assess treatments for hospitalised patients
  - Antiviral therapies
  - Corticosteroids



Influenza in pregnancy

RECOVERY
Randomised Evaluation of COVID-19 Therapy

Vaccine 35 (2017) 5738–5750

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

WHO Report

Influenza epidemiology and immunization during pregnancy: Final report of a World Health Organization working group

Deshayne B. Fell [a,1], Eduardo Azziz-Baumgartner [b,2], Michael G. Baker [c,3], Maneesh Batra [d,4], Julien Beauté [e,5], Philippe Beutels [f,6], Niranjan Bhat [g,7], Zulfiqar A. Bhutta [h,i,8,9], Cheryl Cohen, Bremen De Mucio [l,12], Bradford D. Gessner [m,13], Michael G. Gravett [n,14], Mark A. Katz [o,p,15], Marian Knight [q,17], Vernon J. Lee [r,18], Mark Loeb [s,19], Johannes M. Luteijn [t,20], Helen Marsha, Harish Nair [v,22], Kevin Pottie [w,23], Rehana A. Salam [x,y,24,25], David A. Savitz [z,26], Suzanne J. S, Becky Skidmore [aa,28], Justin R. Ortiz [ab,*], on behalf of the WHO taskforce to evaluate influe, inform vaccine impact and economic modelling

PLOS ONE

RESEARCH ARTICLE

Incidence, risk factors and impact of seasonal influenza in pregnancy: A national cohort study

Nicola Vousden [1,2], Kathryn Bunch [2], Marian Knight [2]*, the UKOSS Influenza Co-Investigators Group [¶]

1 School of Population Health & Environmental Sciences, Faculty of Life Sciences & Medicine, King's College London, London, United Kingdom, **2** Policy Research Unit in Maternal Health and Care, National Perinatal Epidemiology Unit, University of Oxford, Oxford, United Kingdom

¶ Membership of the UKOSS Influenza Co-Investigators Group is provided in the Acknowledgments.
* marian.knight@npeu.ox.ac.uk

Check for updates

Influenza in pregnancy

RECOVERY
Randomised Evaluation of COVID-19 Therapy

- (WHO) Pregnant women with influenza have a higher risk of community-acquired pneumonia than non-pregnant patients with influenza
  (pooled OR 1.8, 95% CI 0.72–4.49)
- (WHO) Pregnant women have a higher risk of hospitalisation with lab confirmed influenza than non-pregnant patients
  (pooled OR 2.44; 95% CI 1.22–4.87)
- (UKOSS) Compared to pregnant women without influenza, pregnant women with influenza are:
  - More likely to be admitted to intensive care (aOR 21.3, 2.78-163.1)
  - More likely to have a caesarean birth (aOR 1·42, 1·02-1.98)
  - Their babies are more likely to be admitted to neonatal intensive care (aOR 1.86, 1·01-3·42)

Q&A

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