

**ISARIC and COVID-19**  
**The International Severe Acute Respiratory**  
**and emerging Infection Consortium's work**  
**to accelerate outbreak research and response**

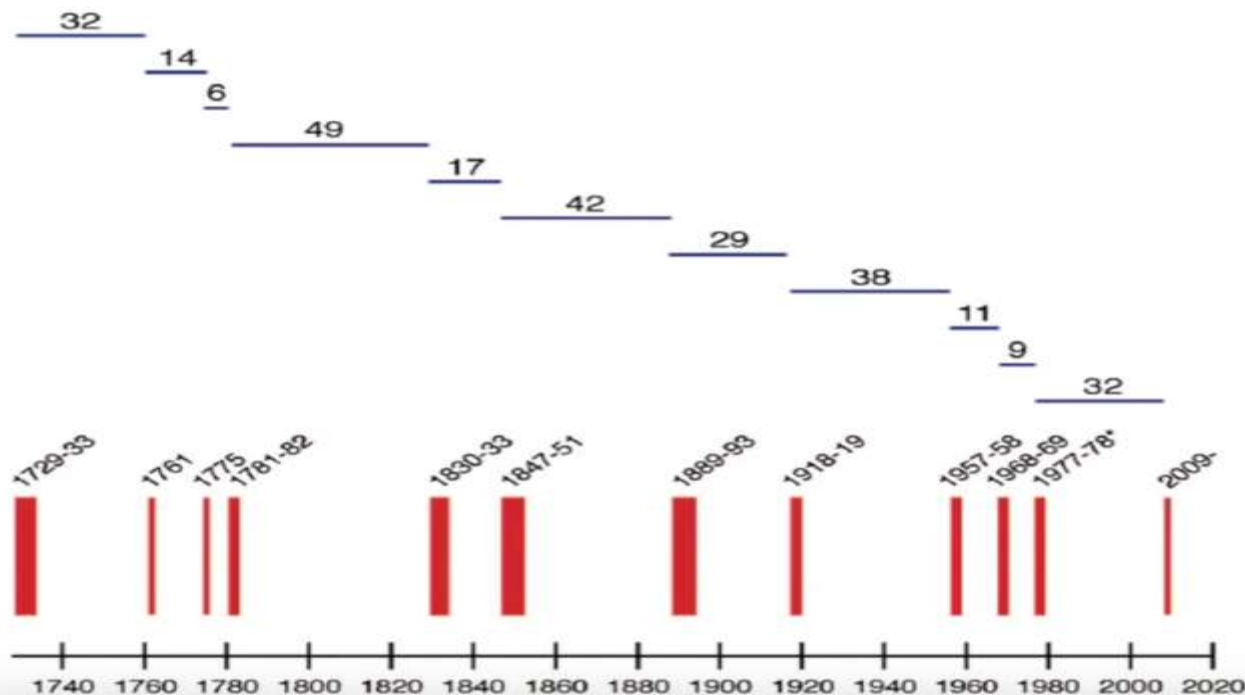
Calum Semple, Annemarie Docherty, Ewen Harrison,  
Peter Openshaw, Kenneth Baillie  
for the ISARIC 4C Investigators



@CCPUKstudy

ISARIC4C.net

## Pandemics occur roughly every 23 years



# Pandemics are certain

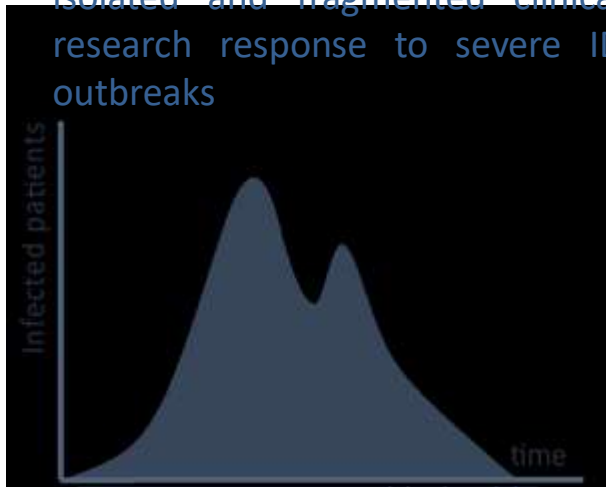
But we do not really know

- What the pathogen will be
- What the disease will be
- How the disease will impact on
  - groups / society / health care / case fatality
- How diagnostics will perform
- If infection control will work
- If current therapeutics or vaccines will work

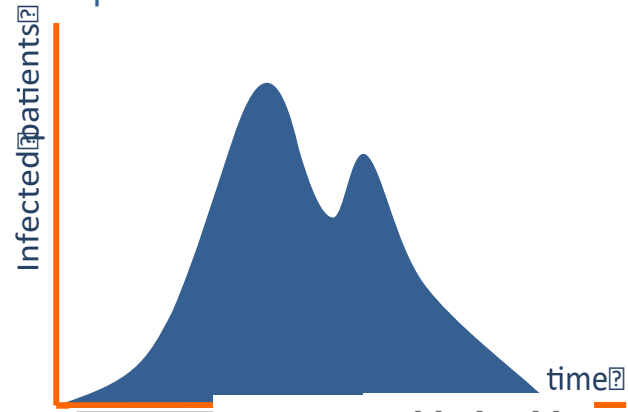


We need rapid research capacity

**Situation in 2009:** delayed, isolated and fragmented clinical research response to severe ID outbreaks



**Future ideal:** rapid, integrated and harmonised clinical research response to severe ID outbreaks



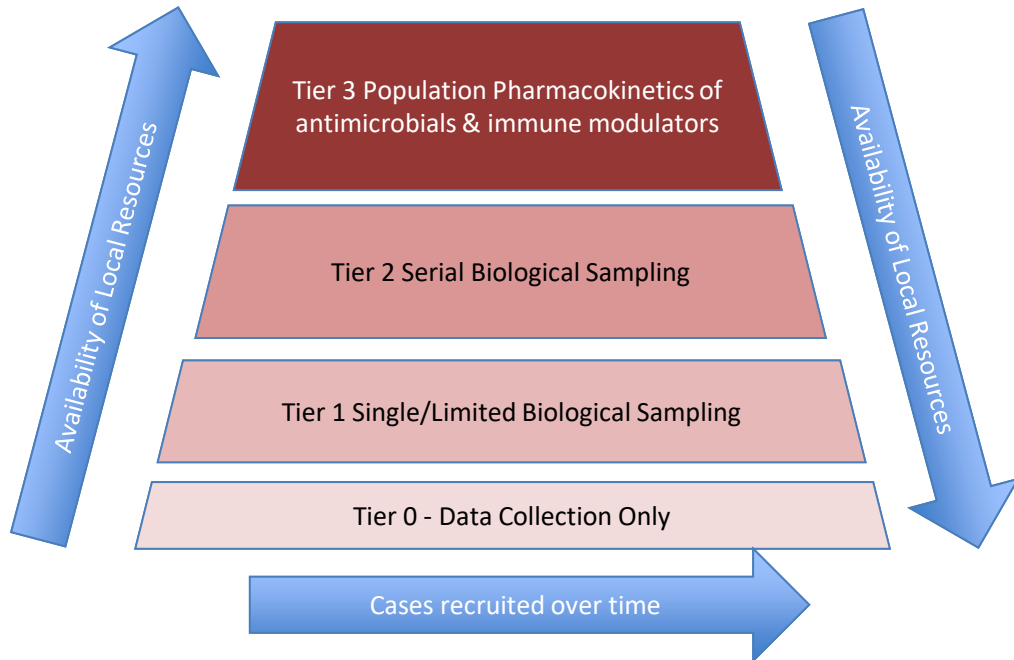
## ISARIC Tools – Oven ready protocols



- What kinds of studies are needed?
  - Clinical Characterisation Protocol - who what why
  - Drug Trial
  - Vaccine Trial
  - Convalescent Plasma Trial
- Develop protocols in readiness
  - Data elements, CFR, Common Outcomes, Ethics and Regulatory approvals
- Pathogens deliberately not named
- Activation exercises e.g. **SPRINT-SARI**

# ISARIC WHO Clinical Characterisation Protocol UK “WHO CCP (UK)”

## A Tiered Protocol - sensitive to setting





## 43 Network members >130 countries

- Launched December 2011
- Led first by Jeremy Farrar
- Chair Peter Horby

**ISARIC Coordinating Centre**  
Nuffield Department of Medicine's  
Centre for Tropical Medicine and  
Global Health  
University of Oxford

Funding CCP-UK



**National Institute for  
Health Research**



Department  
for International  
Development

BILL & MELINDA  
GATES foundation

Partners supporting research preparedness and response



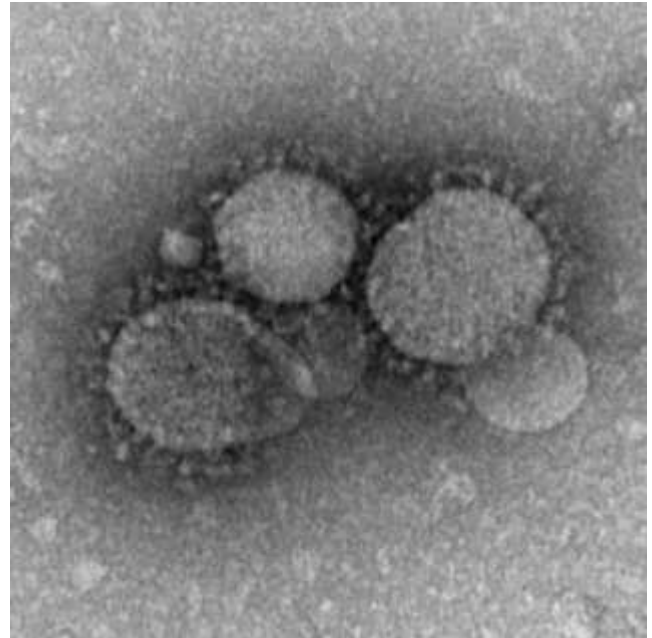
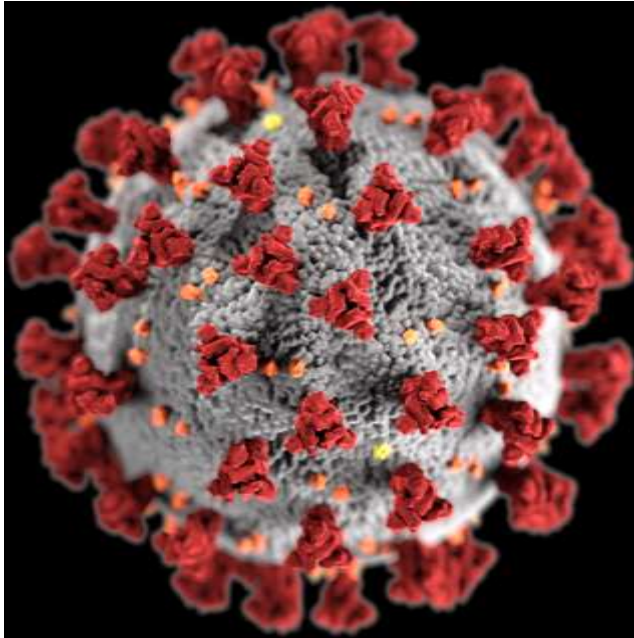
# WHO ISARIC Clinical Characterisation Protocol NIHR Urgent Public Health Research Portfolio

Chief Investigator	Institution	Funder (& reference if applicable)	Project Title	UK CRN ID
Professor Steve Goodacre	University of Sheffield	NIHR- NETSCC (Ref 11/46/07)	The PAINTED study: PAndemic INfluenza Triage in the Emergency Department.	<a href="#">12725</a>
Dr Marian Knight	University of Oxford	NIHR- NETSCC (Ref 11/46/12)	Maternal and perinatal outcomes of pandemic influenza in pregnancy.	<a href="#">14162</a>
Dr MG (Calum) Semple	University of Liverpool	NIHR- NETSCC (Ref 11/46/22)	Real-time evaluation and refinement of tools and criteria used in primary care to aid hospital referral decisions for patients of all ages during an influenza pandemic.	<a href="#">12827</a>
Professor Mervyn Singer	University College London	GSK	An open-label, multi-centre, single arm study to evaluate the safety, tolerability and pharmacokinetics of intravenous zanamivir in the treatment of hospitalised adult, adolescent and paediatric subjects with confirmed influenza infection	<a href="#">7444</a>
Dr MG (Calum) Semple	University of Oxford	Wellcome Trust	ISARIC/WHO Severe Acute Respiratory Infection Biological Sampling Study	<a href="#">14152</a>
Dr Wei Shen Lim	Nottingham University Hospitals	NIHR- NETSCC (Ref 11/46/14)	Double-blinded randomised controlled trial of early low dose steroids in patients admitted to hospital with influenza infection during a pandemic.	<a href="#">15318</a>


 UK CCP



# Severe Acute Respiratory Syndrome Coronavirus 2 =SARS-CoV-2

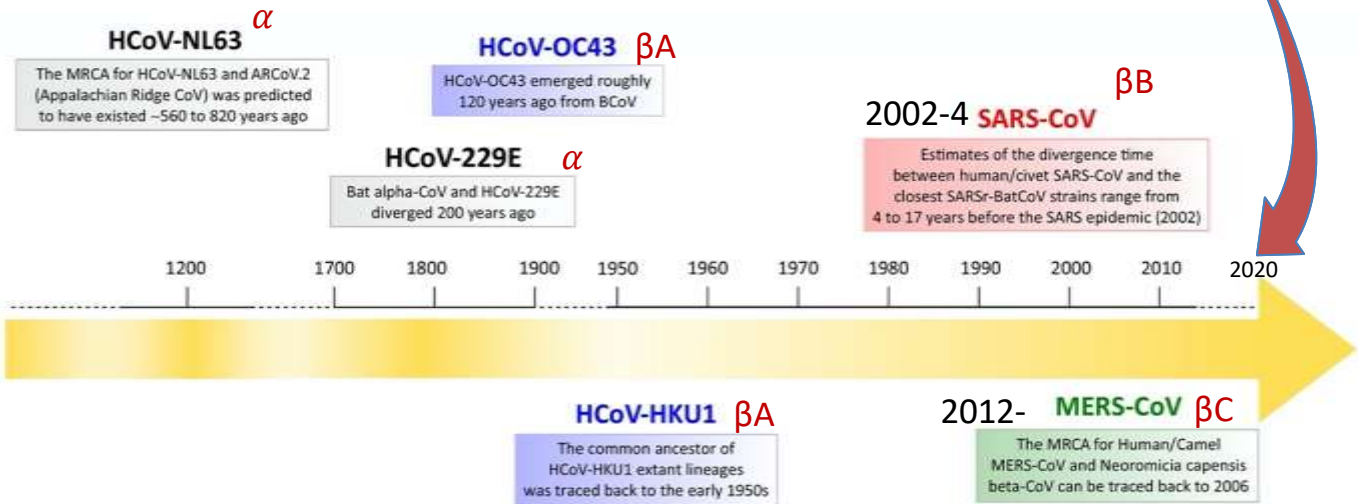
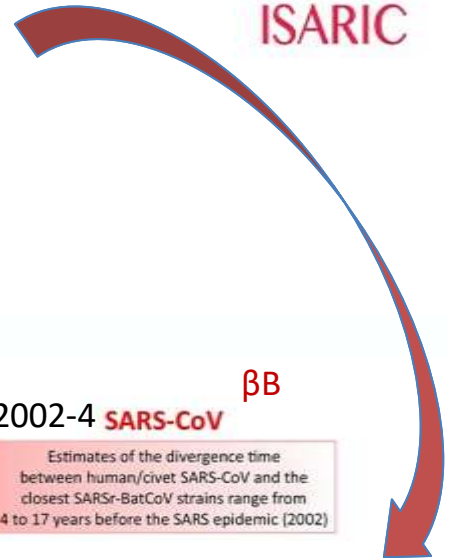


Alissa Eckert, Dan Higgins, Maureen Metcalfe, Cynthia Goldsmith & Azaibi Tamin (CDC USA)



# SARS-CoV-2

$\beta\text{B}$



31/12/2019	27 cases of pneumonia of unknown aetiology reported in Wuhan
09/01/2020	Preliminary determination of novel coronavirus
13/01/2020	First case outside China (Thailand)
17/01/2020	CCP-UK activated in readiness for any Coronavirus case (took one email to DCMO)
21/01/2020	293 cases in mainland China, including 15 healthcare workers and 6 deaths
25/01/2020	First person-to-person transmission identified outside China (Vietnam) First confirmed case in Europe (France)
30/01/2020	WHO declares Public Health Emergency of International Concern (PHEIC)
31/01/2020	UK nationals repatriated from Wuhan. First two UK cases confirmed (CCP-UK cases #1-2)
06/02/2020	Third case in UK confirmed (Case #3)
08-10/02/2020	Contacts of UK case #3 confirmed as cases in UK nationals in England (Cases #4-8), other cases in France (5) and Spain (1)
12/02/2020	One new UK case confirmed – (case #9)
15/02/2020	A US Citizen tested positive on arrival at Malaysia having left the M/V Westerdam on 13/2/2020
18-19/02/2020	Eight UK nationals tested positive from the Diamond Princess, docked in Japan
23/02/2020	Further four UK nationals from Diamond Princess repatriated to Arrowe Park tested positive in Japan (cases #10-13)
24/02/2020	First case in Wales
25/02/2020	Iran, certain regions of Italy and South Korea are now category 1 countries
28/02/2020	First case in Northern Ireland
01/03/2020	Family cluster of 4 cases (3 family members of non-travel UK case). 35 of 39 cases recruited
01/03/2020	First case in Scotland
01/04/2020	4063 cases recruited to CCP-UK tier zero (data only) 471 cases sampled



## Tier Zero of CCP-UK (Data only) = CO-CIN COVID-19 Clinical Information Network

- “PHE take the case epi to the hospital door, CCP-UK follows the admission journey”

N=53,903



- Deep data dig

- Who

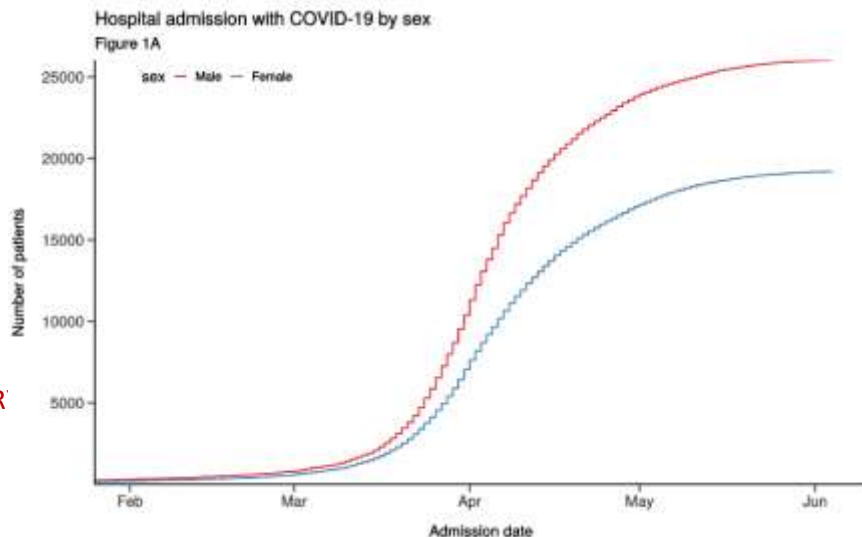
- Demographics
- Co-morbidities
- Presenting symptoms

- What

- Treatment
- Outcomes

- Why

- Underpins sampling
- Underpins trial **RECOVER**



# CO-CIN Dynamic Report

## Dynamic CO-CIN report to SAGE and NERVTAG

### [OFFICIAL-SENSITIVE PROTECT]

Dynamic content updated: 2020-04-01 10:05:04.

### Executive summary

The COVID-19 Clinical Information Network (CO-CIN) collated clinical information from the usual health care records of people of all ages admitted to hospital in the UK.

Up to 10th March people with positive swabs were admitted to hospital as part of the containment strategy. Since 10th March, admission is mostly based upon need for treatment of COVID-19 disease. The great majority of cases in the community do not require hospital admission.

In total up until 01 April 2020, CO-CIN has recruited **4063 patients** with confirmed Coronavirus (Figure 1).

While The CO-CIN dataset represents NA% (4063/NA) of cases of confirmed Coronavirus cases in the UK per the PHE daily reports (last updated 9am on 31 March 2020).

Patient data is collected and uploaded from start of admission, however a complete patient data set is not available until the episode of care is complete. This causes a predictable lag in available data influenced by the duration of admission which is greatest for the sickest patients.

The geographical location of our patients can be seen in Figure 2; of these 262 had travelled abroad recently, and 569 reported visiting or working in a hospital where COVID-19 cases are being managed.

The median age is 72 (range: 0-107), Male/Female 1743/1118.

The most common symptoms were cough (72%), fever (69%) and shortness of breath (60%) (Figure 3A). 125/2571 (5%) of patients have reported no symptoms. Comorbidity can be seen in Figure 3B). The most common comorbidities were chronic cardiac disease (39%), diabetes (without complications) (25%) and chronic pulmonary disease (19%). 609/2989 (21%) of patients have reported no co-morbidity. 13/161 (8%) of women were recorded as being pregnant.

For patients not already in hospital, the median time from onset of symptoms to presentation at hospital was 4 days (range: 0 - 128 days).

The median length of hospital stay was 5 days (range: 1-163, n = 630). 167/1394 (12%) patients required high-flow oxygen after day 1 of treatment.

Currently 361 patient(s) have died and 484 required ICU. 563 have been discharged home.

Interpretation: The dataset is increasingly more representative of the burden of disease requiring hospitalisation and captures the early exponential rise of disease incidence that is now increasingly driven by domestic transmission events in the community.

Furthermore, we can now see 'hot spots' of disease incidence that largely reflect areas of high population density (most notably London) with a few exceptions to this. There are more men than women, consistent with reports from other countries. The proportion of pregnant women affected is broadly in line with the proportion of pregnant women in the general population.

The commonest comorbidity is chronic cardiac disease, reflecting patterns seen in other countries, although nearly a quarter of patients admitted do not have underlying somatoid disease.

Patients documented as being admitted to ICU are mainly 60-75 years old. When interpreting admission to ICU it is important to remember that we are currently unable to capture treatment limiting decisions regarding level of care.

Prof Celen Sengul, Professor in Child Health and Outbreak Medicine, University of Liverpool.

Dr Anvaramee Docherty, Academic Consultant Intensive Care University of Edinburgh.

Dr Chris Green, Academic Consultant Infectious Disease University of Birmingham.

Prof Ewan Hearnson, Director Centre for Medical Informatics, Usher Institute, University of Edinburgh (analysed).

Professor Tom Solomon, Director HPRU Emerging and Zoonotic Infection.

ISARIC Investigators (Prof. Peter Horby, Prof. Peter Openshaw, Dr Dale Carson, and Dr Kenneth Baillie).

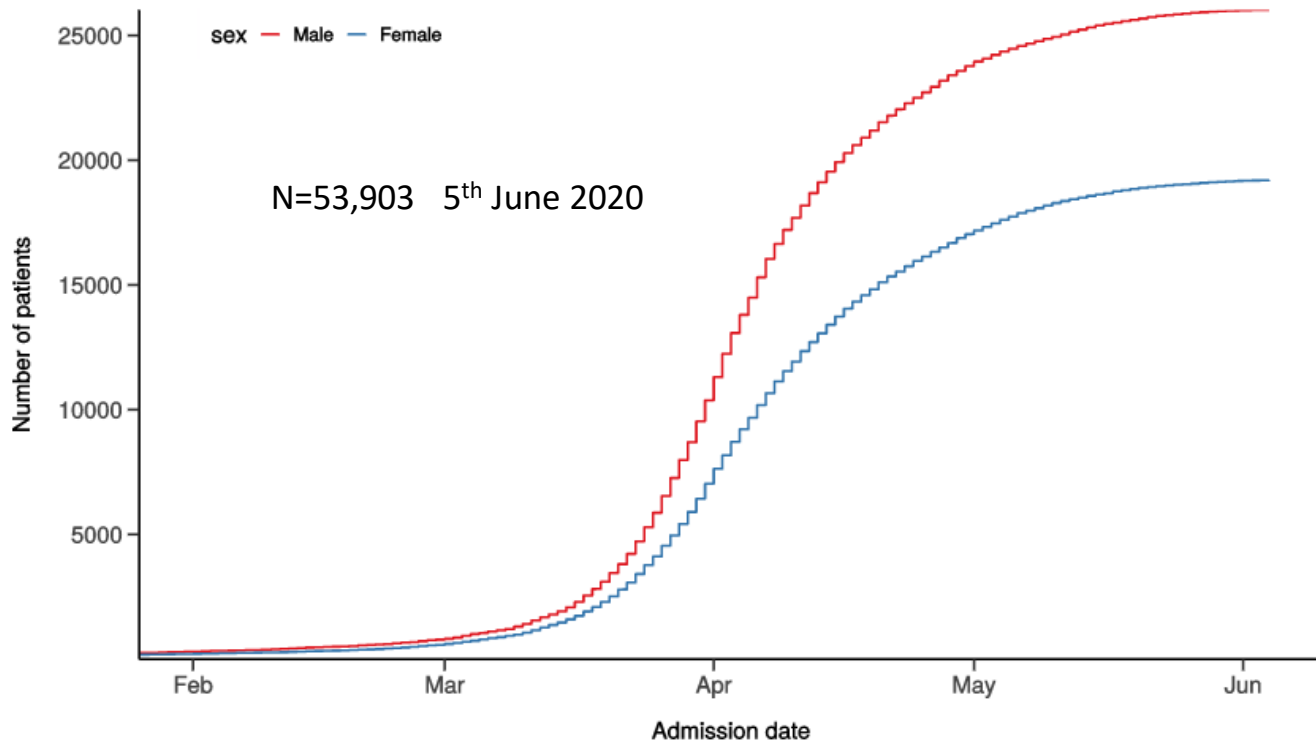
Analysts: Lisa Norman, Niran Plus, Thomas Datta, Cameron Fairhead, Stephen Knight, Kenneth McLean, Katie Shaw.

- Real-time analysis of raw data
- Minimal cleaning
- Initially signals rather than messages
- Updated every ~~30 minutes~~ 4 hours 2x daily
- Accessed by
  - CMOs / DCMOs
  - Scientific Advisory Group for Emergencies (SAGE)
  - Scientific Pandemic Influenza Modellers (SPI-M)
  - New and Emerging Respiratory Viral Threat Advisory Group (NERVTAG)
  - PHE & PHS
- Line list available to Scientific Pandemic Influenza Modelling (SPI-M) group

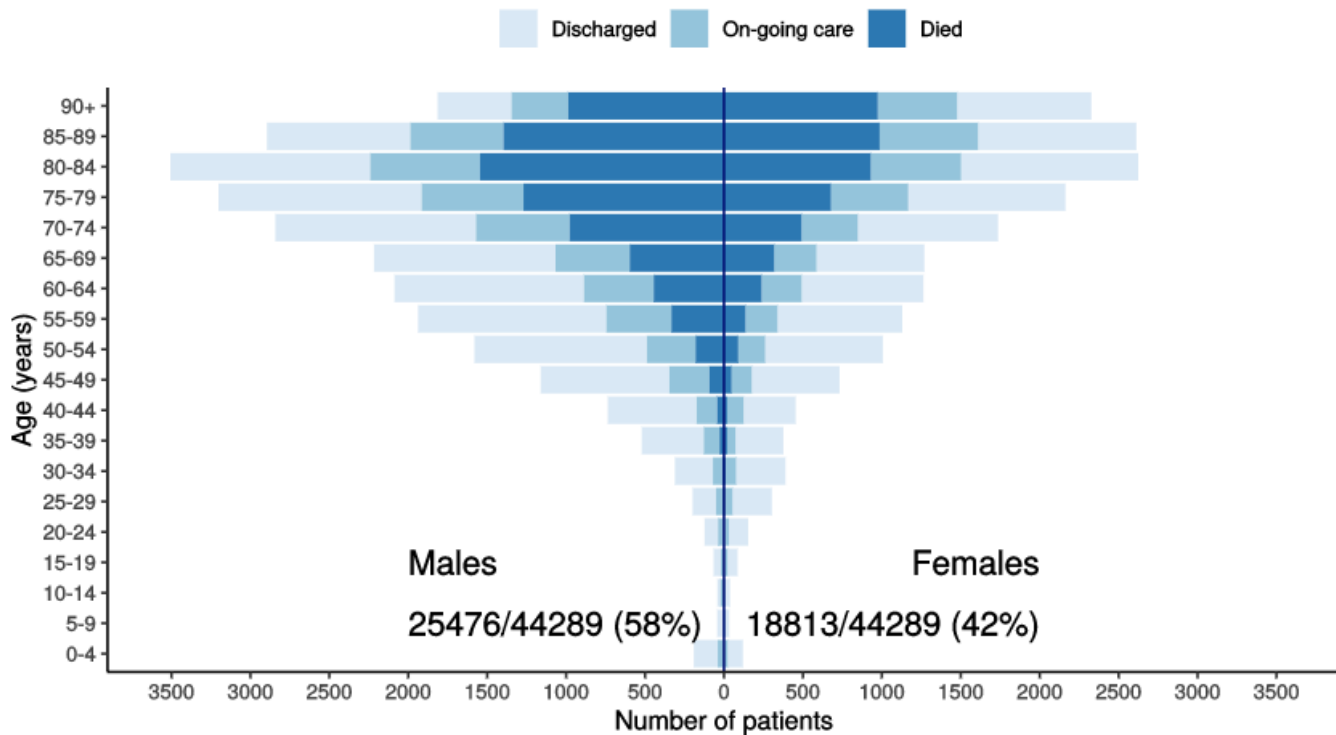
## Admission by Sex

Hospital admission with COVID-19 by sex

Figure 1A



## Age, Sex and Outcome

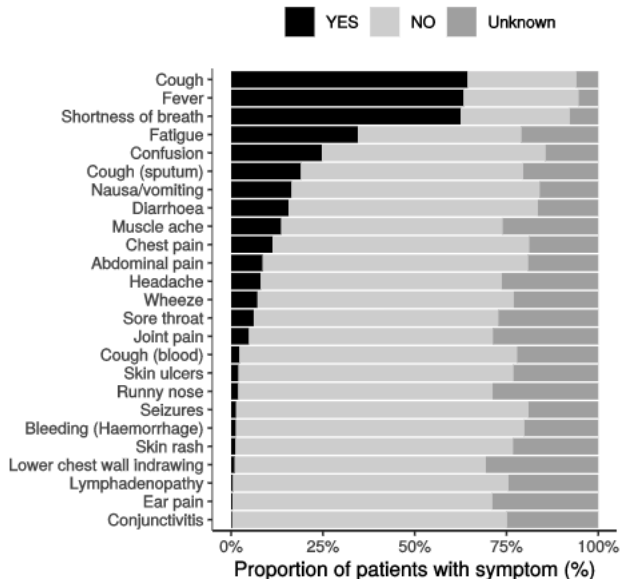




# Admission Features

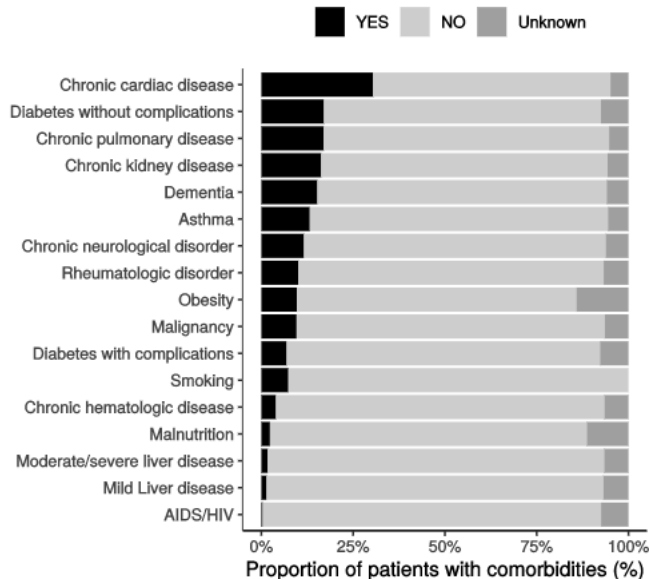
Symptoms on presentation to hospital (% patients, n = 42796)

Figure 3A



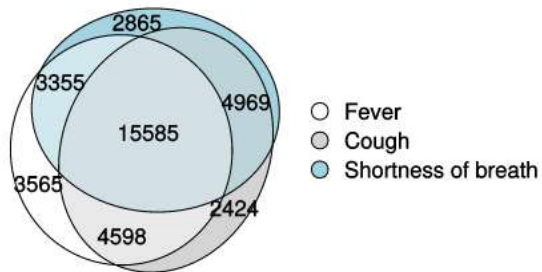
Comorbidity (% patients, n = 42887)

Figure 3B

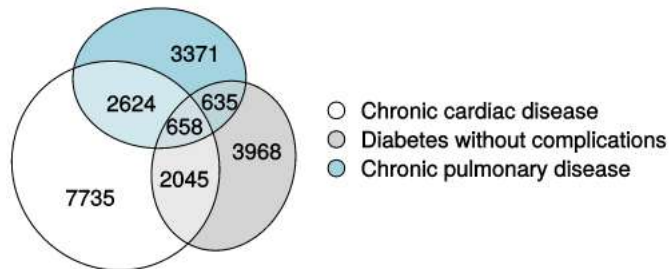


## Symptoms and comorbidity

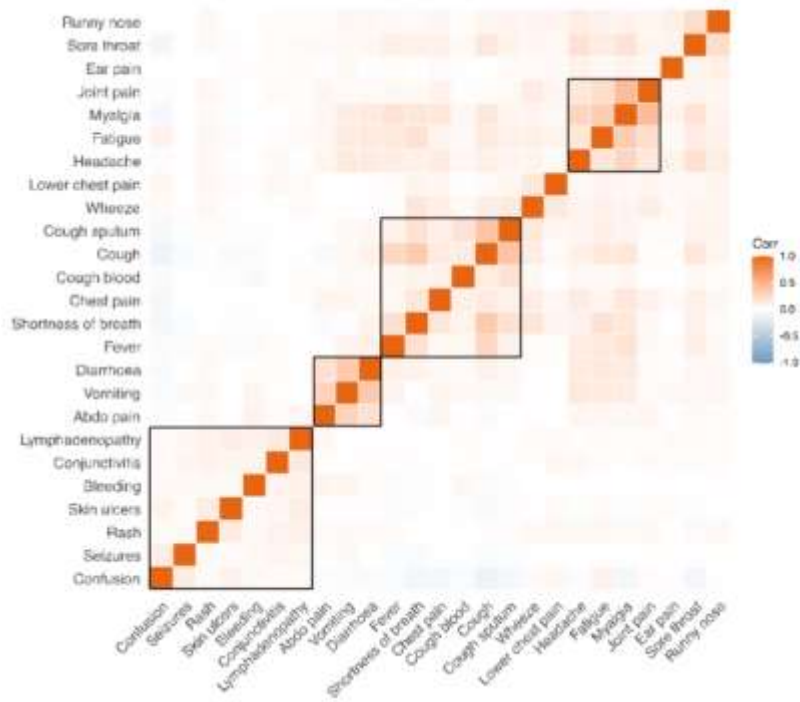
### Three most common symptoms



### Three most common co-morbidities



# Correlation matrix of symptoms

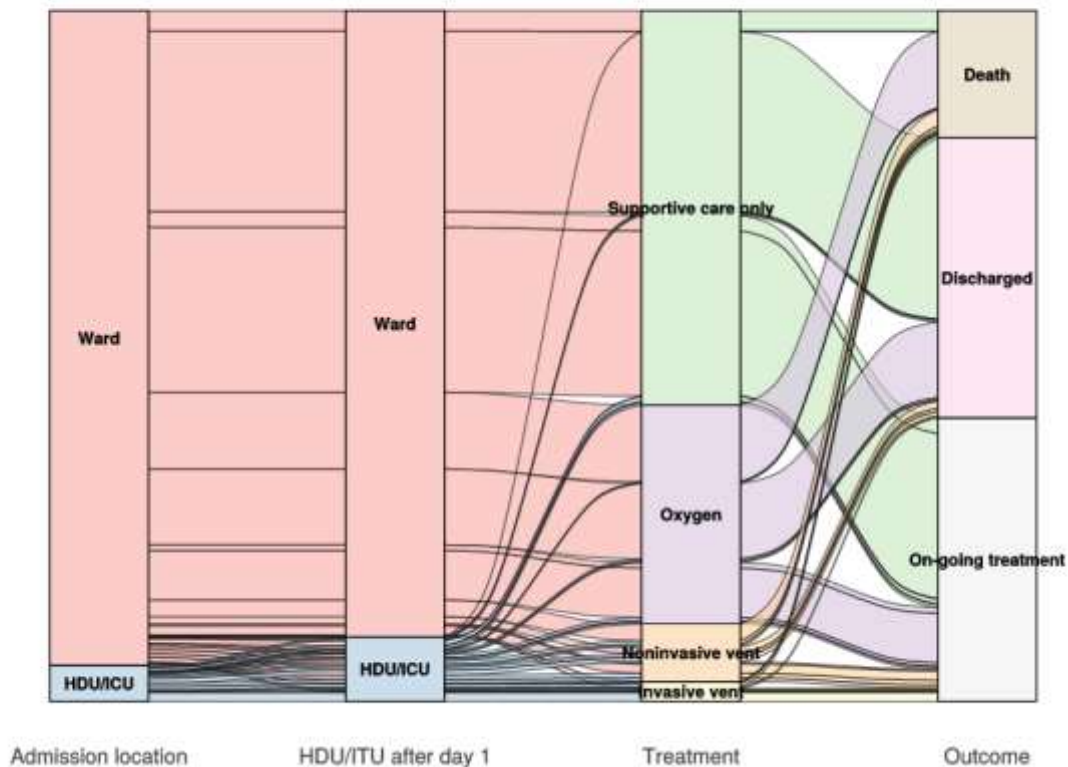


BEST APPRECIATED BY BLURRING YOUR EYES

# Patient Flow

Figure 7B - Patients admitted  $\geq 14$  days and  $\leq 28$  days ago

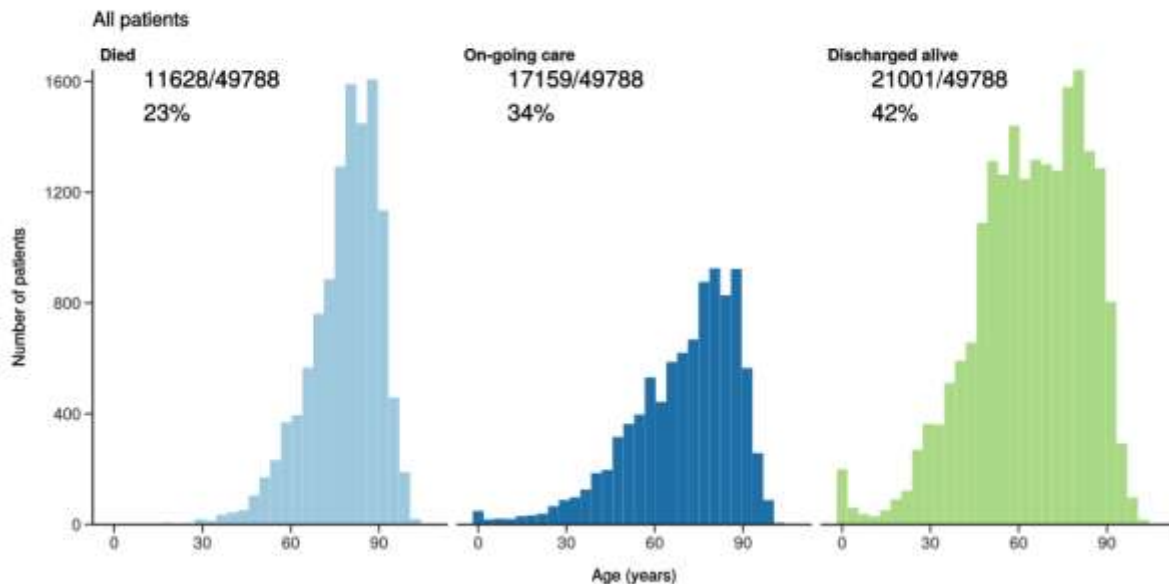
N = 1850



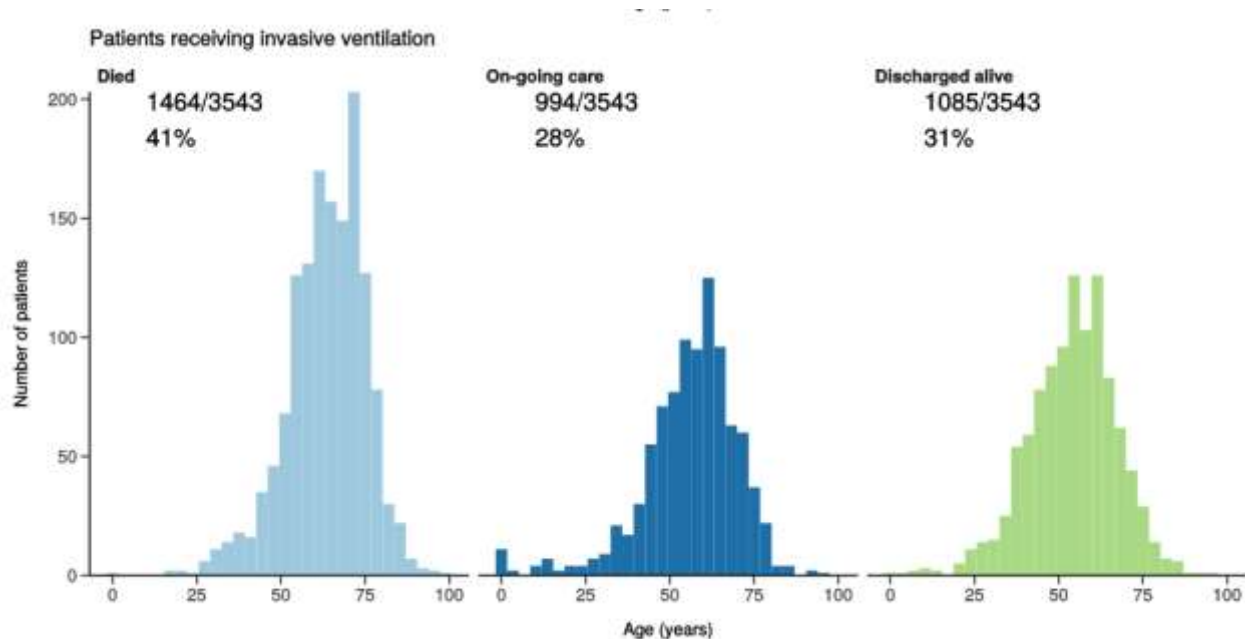
## Outcome: all admission

### Status in patients admitted $\geq 14$ days from today

Figure 10

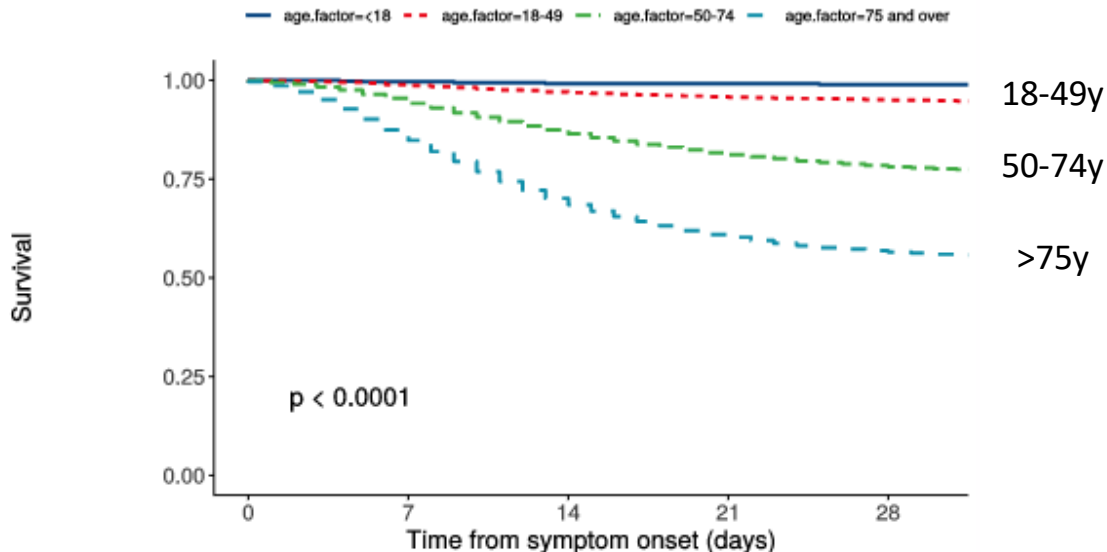


# Outcome: Invasive Mechanical Ventilation





## Survival



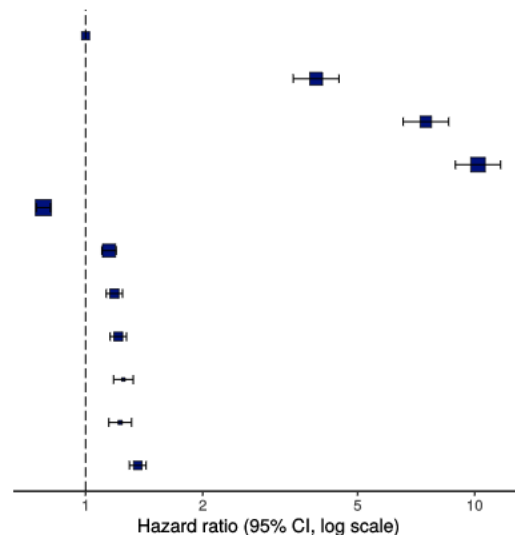
Number at risk

	0	7	14	21	28
age.factor=<18	545	478	447	445	441
age.factor=18-49	5548	5173	4822	4646	4578
age.factor=50-74	17109	15362	13309	12010	11381
age.factor=75 and over	21193	17090	12885	10936	10069

# COVID-19 hazard of death by age, sex and co-morbidities: Multivariable Cox proportional hazard model

Survival: HR (95% CI, p-value)

Age on admission (years)	<50	-
	50-69	3.91 (3.42-4.48, p<0.001)
	70-79	7.49 (6.54-8.57, p<0.001)
	80+	10.19 (8.92-11.65, p<0.001)
Sex at Birth	Female	0.78 (0.75-0.81, p<0.001)
Chronic cardiac disease	YES	1.15 (1.10-1.20, p<0.001)
Chronic pulmonary disease	YES	1.19 (1.13-1.24, p<0.001)
Chronic kidney disease	YES	1.21 (1.16-1.27, p<0.001)
Malignancy	YES	1.25 (1.18-1.33, p<0.001)
Obesity	YES	1.23 (1.15-1.31, p<0.001)
Dementia	YES	1.36 (1.30-1.43, p<0.001)

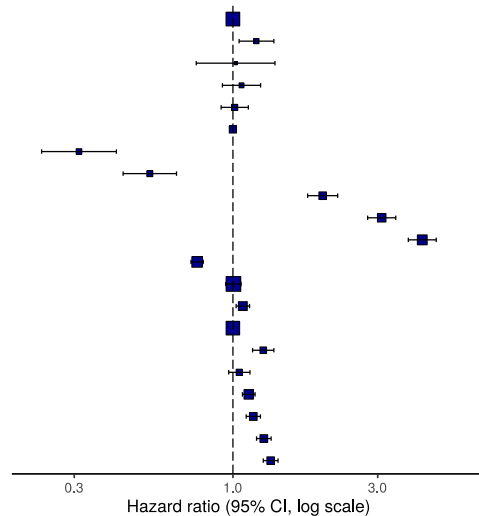




# COVID-19 and Ethnicity

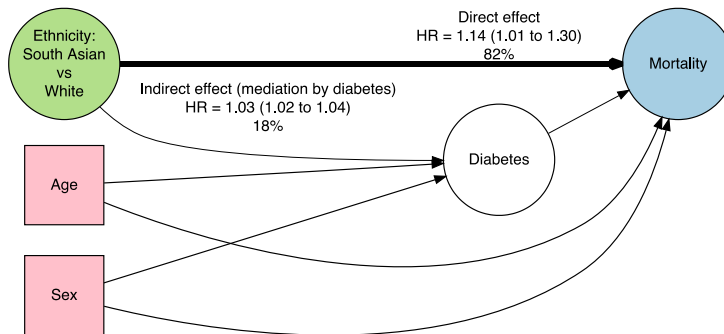
## C In-patient survival: hierarchical with potential mediators

Ethnicity	White	-
	South Asian	1.20 (1.05-1.36, p=0.008)
	East Asian	1.02 (0.76-1.38, p=0.890)
	Black	1.07 (0.92-1.23, p=0.380)
	Other Ethnic Minority	1.01 (0.91-1.12, p=0.790)
Age on admission (years)	50-59	-
	18-39	0.31 (0.23-0.41, p<0.001)
	40-49	0.53 (0.43-0.65, p<0.001)
	60-69	1.98 (1.76-2.22, p<0.001)
	70-79	3.09 (2.78-3.44, p<0.001)
	80+	4.21 (3.79-4.68, p<0.001)
Sex at Birth	Female	0.76 (0.73-0.80, p<0.001)
Deprivation (IMD)	-	1.00 (0.95-1.06, p=0.890)
Diabetes	Yes	1.08 (1.03-1.13, p=0.003)
Obesity	No	-
	Yes	1.26 (1.16-1.37, p<0.001)
	(Missing)	1.05 (0.97-1.14, p=0.240)
Chronic cardiac disease	Yes	1.13 (1.08-1.18, p<0.001)
Chronic pulmonary disease	Yes	1.17 (1.11-1.23, p<0.001)
Chronic kidney disease	Yes	1.26 (1.20-1.34, p<0.001)
Dementia	Yes	1.33 (1.26-1.41, p<0.001)

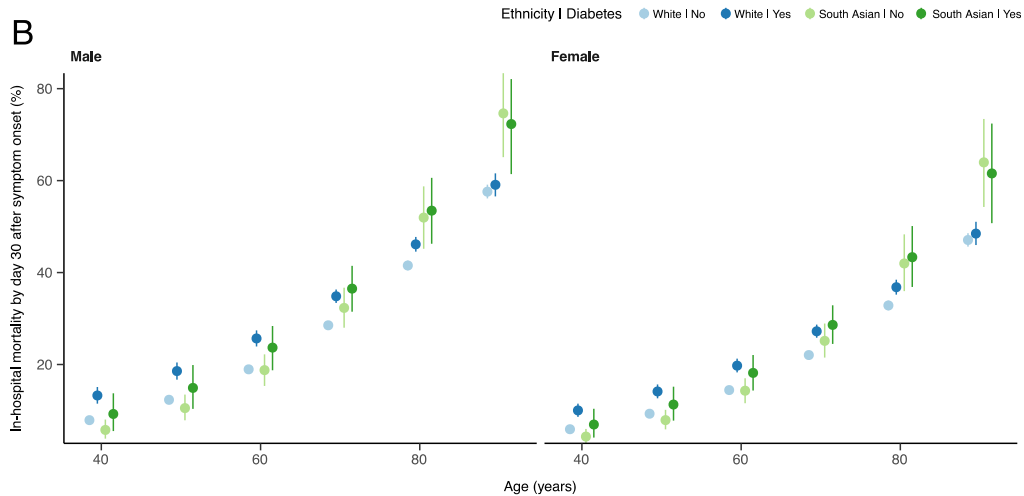


# COVID-19 and Ethnicity

A



B

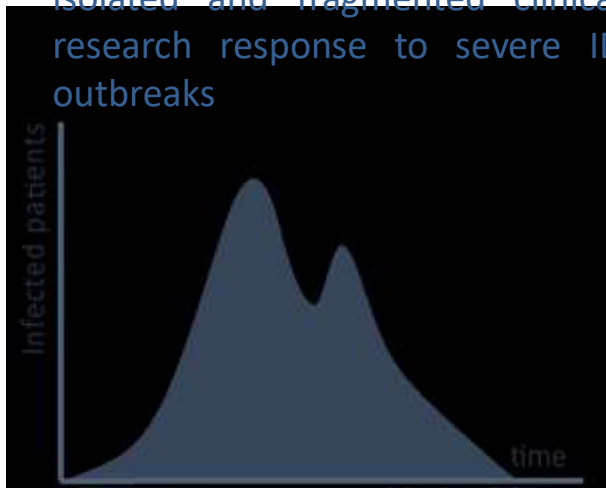


## Conclusion

- Recruitment to Urgent Public Health Research is feasible in response to novel pathogens, and during a pandemic
- Activation events are essential rehearsals
- Success was dependent upon good will and common-sense approach by HSE, Police and site staff
- New administrative regulatory hurdles delayed research activity, but can be resolved

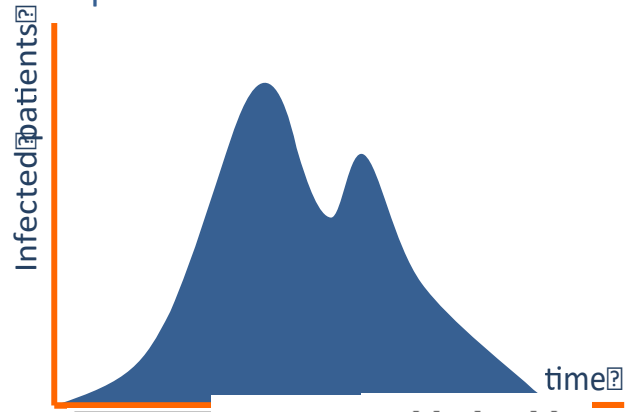
# The PROBLEM

**Situation in 2009:** delayed, isolated and fragmented clinical research response to severe ID outbreaks



# The Solution

**Future situation:** rapid, integrated and harmonised clinical research response to severe ID outbreaks



## ISARIC COVID-19 Clinical Characterisation Consortium

- 2500 Research Nurses & Medical Students
- >200 Site Local Investigators
- >166 R&D Administrators
- Sponsor Office - Oxford
- Legal – Liverpool & Edinburgh
- Finance Team – Liverpool & Edinburgh
- Liverpool University
- Edinburgh University
- Oxford University
- Glasgow University
- Imperial College London
- Office of CMO England



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