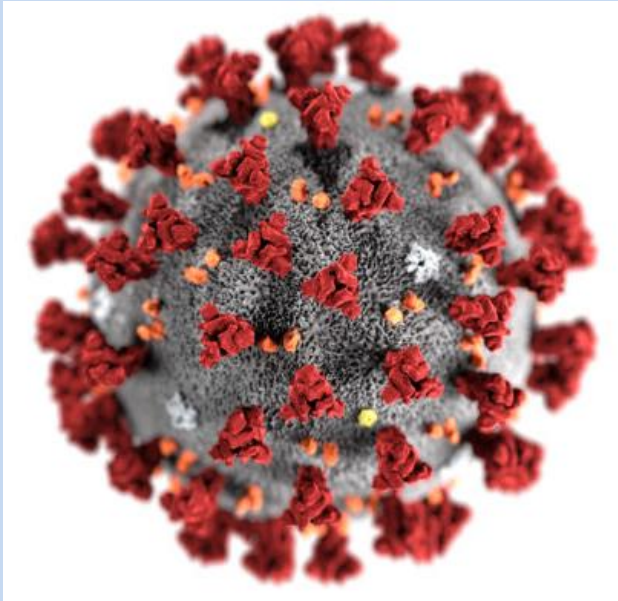
Introduction to science (via COVID-19)



EATG GA – 19 Sept 2020

Simon Collins
i-Base.info

Expectations

What you expect / want from this training ?

- Gain more knowledge
- Use of scientific data for advocacy purposes
- Learning more about HIV and advocacy
- Rapid med and vaccine development and access

Specific questions for this training ?

- How to do advocacy online (without F2F meetings)?
- Models of care and new meds. Covid impact HIV+?
- When do we know that meds are not effective? etc
- Vaccine: cost, efficacy, access, activist roles etc ?

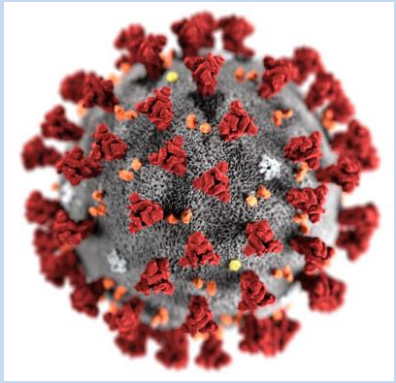
Why us? - current COVID work?

EATG, ACT-UP, EAC, TAC..

Basic answers

- Science can find out whether an idea is true, or provable: facts vs opinion, fake vs real.
- If results are true the study should be repeatable.
- Community involvement produces better science – better questions, engagement and enrolment – faster answers.
- Different types of study are better for answering different types of questions.

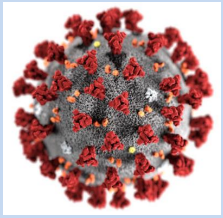
17 September 2020 *



WHO COVID-19 dashboard report:

- 29.36 million cases
- 930,260 deaths

* as of 5:45am EDT.



HIV and COVID-19

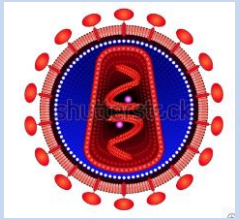
COVID-19: global

• 29.36 million cases & 930,260 deaths: 9 months.

Initially no treatment, high mortality.

Vaccine needed as part of a cure

HIV: global



• 70 million cases, ~35 m deaths: 40 years

~35 m cases now, 24 m on effective treatment

Initially no treatment, high mortality, now 10x single pills.

Vaccine needed as part of a cure

Many comparisons

https://i-base.info/htb/37705

i-base

HTB

Comparing HIV/AIDS and COVID-19 pandemics

17 April 2020. Related: COVID-19: on the web, COVID-19.

Articles that draw parallels between the COVID-19 health crisis and the response to HIV/AIDS.

Later articles will be added to this page as appropriate.

Twenty-seven questions for writers and journalists to consider when writing about COVID-19 and HIV/AIDS
HIV DOULA collective (April 2020).
http://hivdoula.work/27-questions

10 lessons from HIV for the COVID-19 response
Daniel Wolfe. (12 June 2020)
https://www.opensocietyfoundations.org/voices/10-lessons-from-hiv-for-the-covid-19-response

How to survive yet another plague: I lived through the AIDS epidemic – here's how to live through coronavirus.
Mark Shoofs. (20 March 2020).
https://www.buzzfeednews.com/article/markschoofs/how-to-survive-yet-another-plague

Lessons the AIDS epidemic has for coronavirus
Interview with Sarah Schulman. (5 April 2020).
https://www.cnn.com/2020/04/05/politics/coronavirus-aids-hiv-sarah-schulman/index.html

i-base

COVID-19: The HIV research advocacy movement offers lessons
Stacey Hannah. (6 April 2020).
https://www.avac.org/blog/covid-19-hiv-research-advocacy-movement-offers-lessons

For HIV survivors, a feeling of weary déjà vu
Jacob Bernstein. (8 April 2020)
https://www.nytimes.com/2020/04/08/style/coronavirus-hiv.html

Lessons of Aids for COVID-19: Don't sacrifice science to expediency
Robin Gorna. (9 April 2020).
https://www.dailymaverick.co.za/article/2020-04-09-lessons-of-aids-for-covid-19-dont-sacrifice-science-to-expediency

COVID-19 and HIV are not the same. But they're similar in many ways that matter
Mathew Rodriguez (9 April 2020)
https://www.thebody.com/article/covid-19-aids-not-same-but-similar-in-many-ways

Covid-19 and HIV

1. Nine months of COVID-19 compresses 40 years of HIV experience: New infection, high mortality, risk groups, social/behaviour impact, search for treatment, vaccines.

1. Lack of data on risks from COVID-19 in people living with HIV: potential for better or worse outcomes, very limited data. *Larger studies perhaps show higher HIV risk.*

Basic scientific principles

- Evidence-based medicine is an essential activist tool to get the best healthcare.
- But we often don't have a science background = training - *take notes*.
- This talk will look use examples from COVID research to cover main issues.
- Two hours to explore this way of 'searching for the truth' – ask questions...

Outline

- Principles of research, language.
- Types of evidence: COVID-19.
- - epidemiology – sources and example.
- - pathogenesis – example.
- - treatments – HCQ, remdesivir and dexamethasone examples.
- Peer review papers.
- Politics vs science – HCQ, FDA etc.
- Vaccines

“Evidence-based medicine (EBM)”

- Recent development: 1992.
- Aims to use best evidence (rather than experience) to deliver best care – and to stop use of out-of-date practice.
- Involves “scientific method” – designing experiments to answer a question. (Longer history – James Lind, first TB drugs).
- “Hierarchy of evidence” – where results from some study designs are more likely to be true.
- EDM doesn’t cover everything – still in development.

Hierarchy of research

- RCT – randomised **controlled** trial.
- Non-randomised studies – single arm, open label, historical controls etc
- Observational cohorts: retrospective and prospective.
- Meta-analyses, systematic literature reviews.
- Case reports.
- Expert opinion.

Three key concepts

Experimental vs observational.

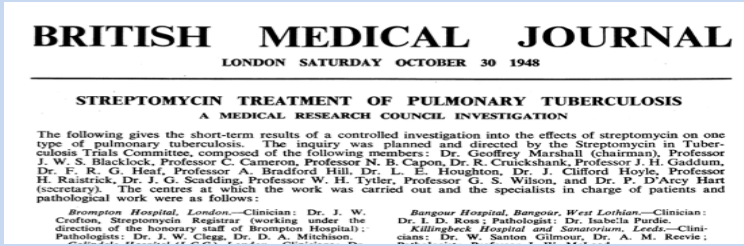
Prospective vs retrospective.

Longitudinal vs cross-sectional.

James Lind - Scurvy

1747: Sailors health at sea N=12 scorbutic sailors (with scurvy) into six groups of two.
Sea water, cider, sulphuric acid, citrus fruit: stopped after six days when they ran out of fruit.
1794: eventually used in practice.
Prospective, experimental, longitudinal.

Streptomycin – BMJ 1948



BRITISH MEDICAL JOURNAL

LONDON SATURDAY OCTOBER 30 1948

STREPTOMYCIN TREATMENT OF PULMONARY TUBERCULOSIS

A MEDICAL RESEARCH COUNCIL INVESTIGATION

The following gives the short-term results of a controlled investigation into the effects of streptomycin on one type of pulmonary tuberculosis. The inquiry was planned and directed by the Streptomycin in Tuberculosis Trials Committee, composed of the following members: Dr. Geoffrey Marshall (chairman), Professor J. W. S. Blacklock, Professor C. Cameron, Professor N. B. Capon, Dr. R. Cruickshank, Professor J. H. Gaddum, Dr. F. R. G. Heaf, Professor A. Bradford Hill, Dr. L. E. Houghton, Dr. J. Clifford Hoyle, Professor H. Raistrick, Dr. J. G. Scadding, Professor W. H. Tytler, Professor G. S. Wilson, and Dr. P. D'Arcy Hart (secretary). The centres at which the work was carried out and the specialists in charge of patients and pathological work were as follows:

Brompton Hospital, London.—Clinician: Dr. J. W. Crofton, Streptomycin Registrar (working under the direction of the honorary staff of Brompton Hospital): Pathologists: Dr. J. W. Clegg, Dr. D. A. Mitchison.

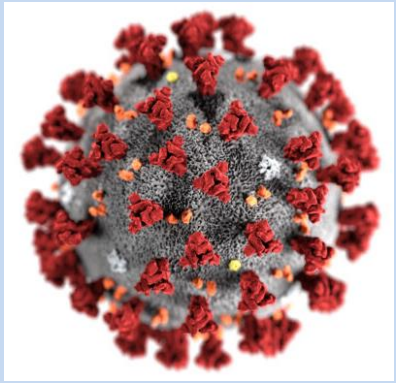
Bangour Hospital, Bangour, West Lothian.—Clinician: Dr. I. D. Ross; Pathologist: Dr. Isabella Purdie.

Killingbeck Hospital and Sanatorium, Leeds.—Clinicians: Dr. W. Santon Gilmour, Dr. A. M. Reevie;

Streptomycin Registrar (working under the direction of the honorary staff of Killingbeck Hospital): Pathologist: Dr. Isabella Purdie.

1948: first modern RCT – for TB
Good paper, includes gender.
Limited drug, no consent,
Prospective, experimental, longitudinal.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2091872

17 September 2020*



WHO COVID-19 dashboard reports:

- 29.73 m cases (350,000)
- 937,391 deaths (+7,100)

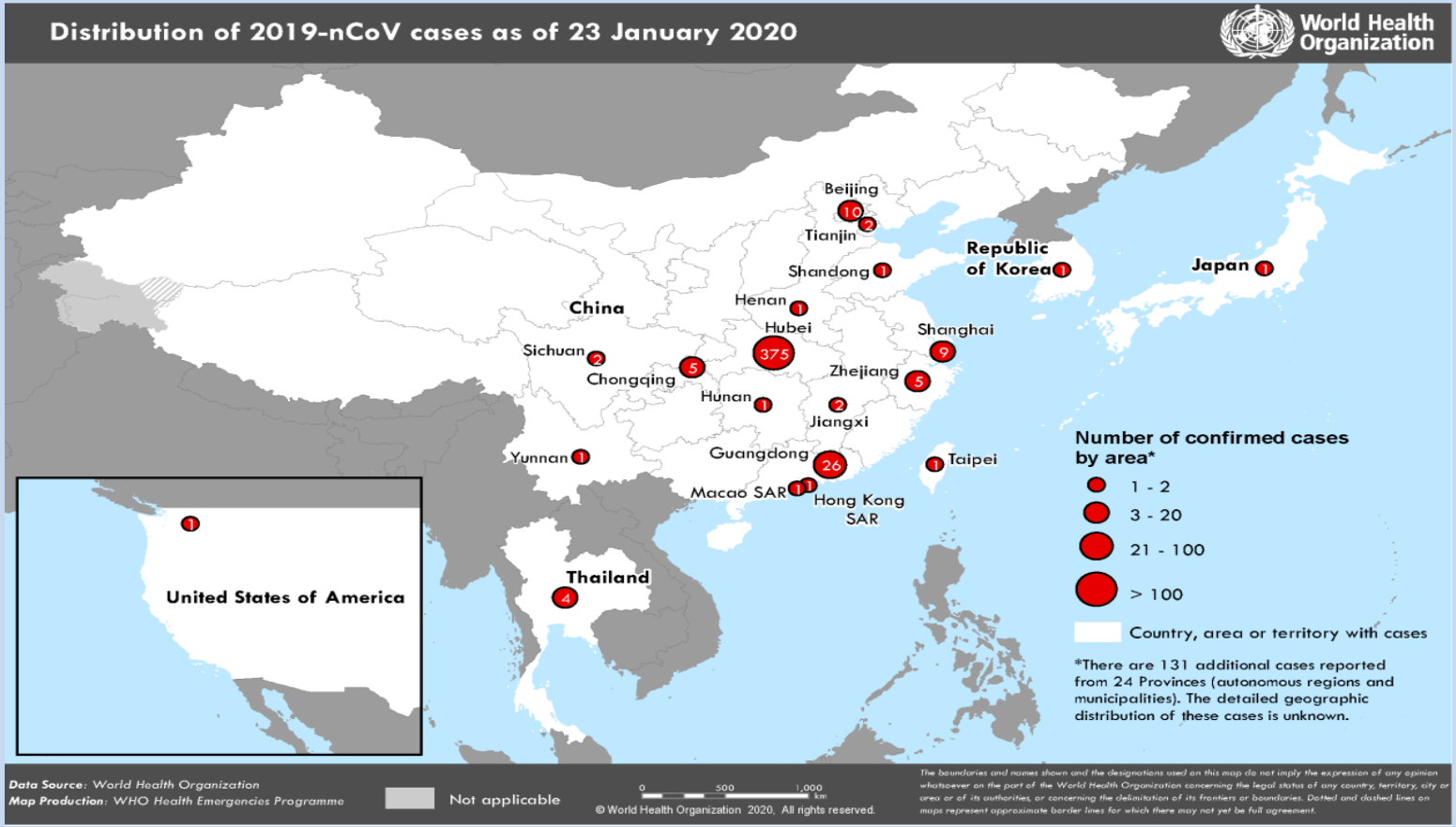
* as of 3:35pm CEST.

COVID-19: Case reports

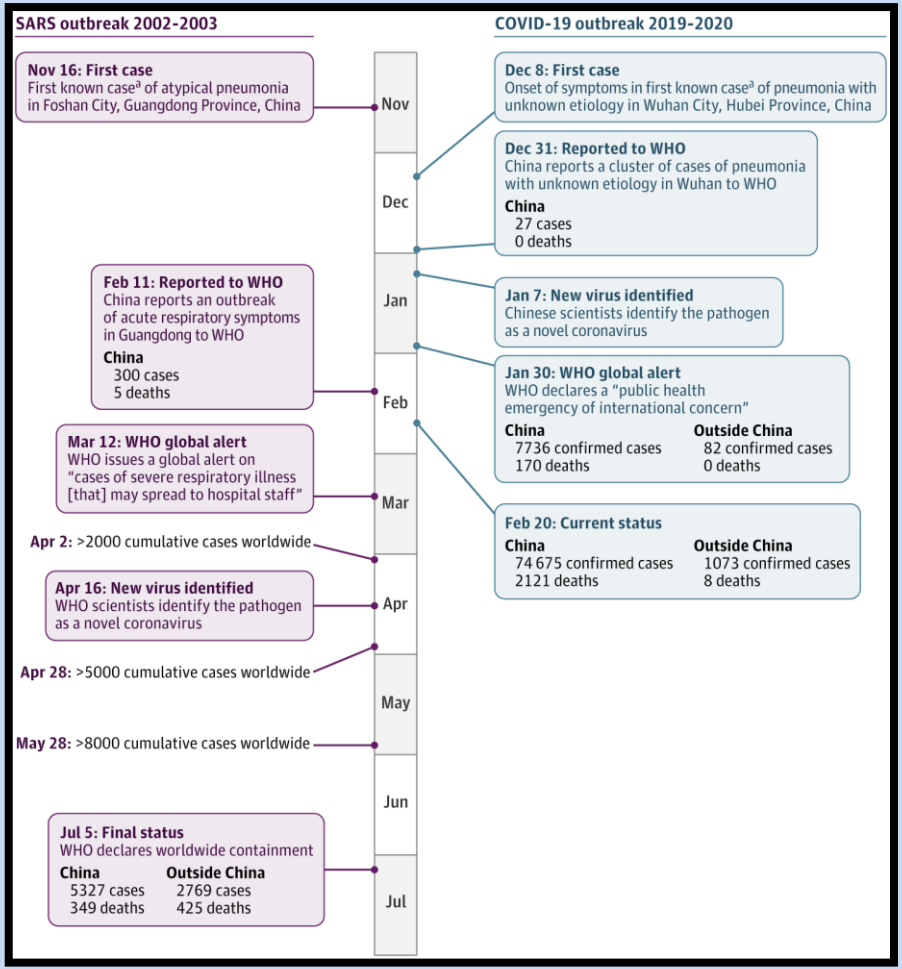
- 17 Nov 2019 – first backdated case, then 1 to 5 cases daily.
- 15 Dec – 22 total cases.
- 20 Dec – 60 cases.
- 27 Dec – 180 cases.
- 27 Dec - Dr Zhang Jixian (SARS) – 3/7 cases of pneumonia in Wuhan, in 1 family (infectious).
- 30 Dec – Dr Li Wenliang cautions other doctors on social media (he died on 7 Feb).

South China Morning Post (13 March 2020) https://www.scmp.com

COVID-19: WHO reports

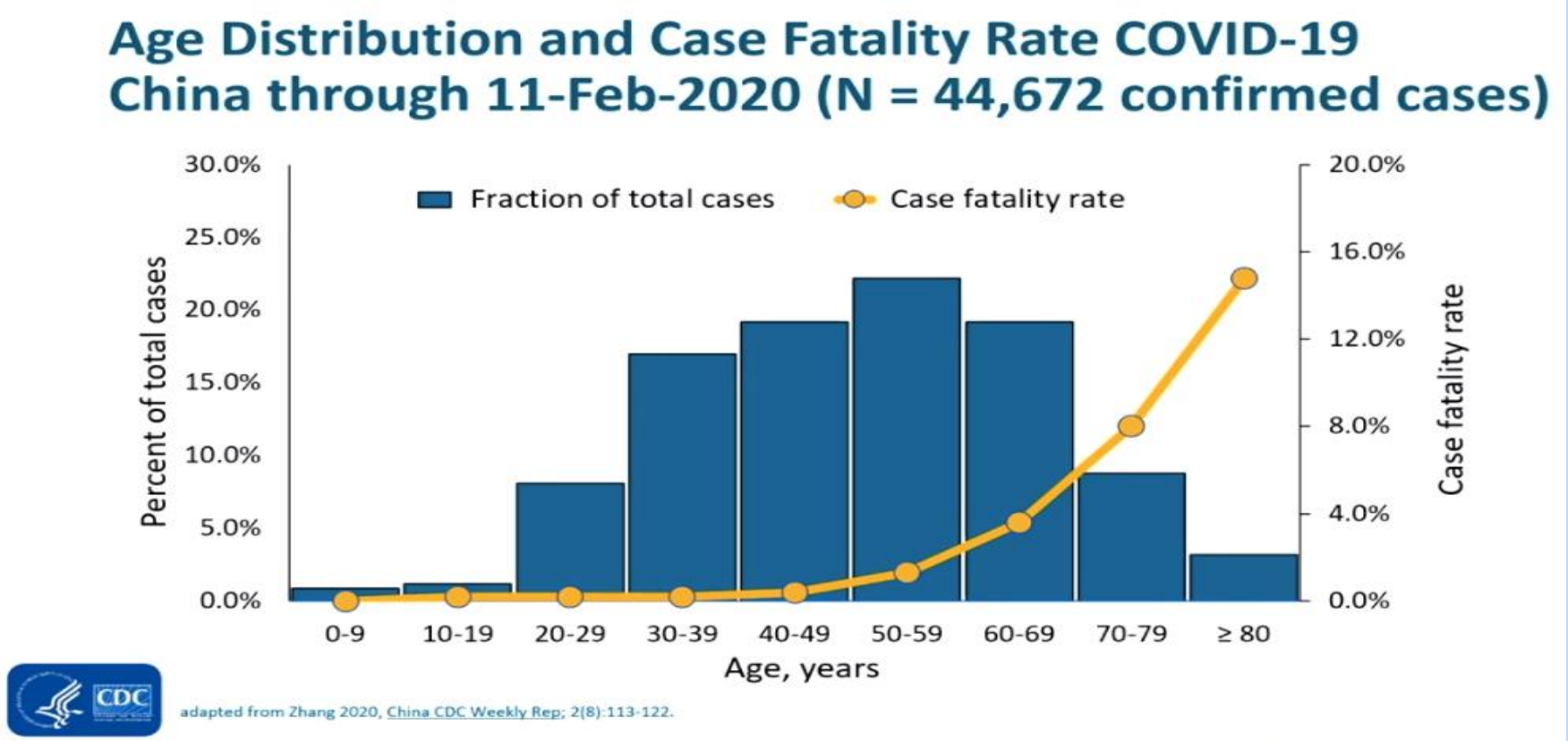


WHO situation report 3 – 23 January 2020 ~ 450 cases



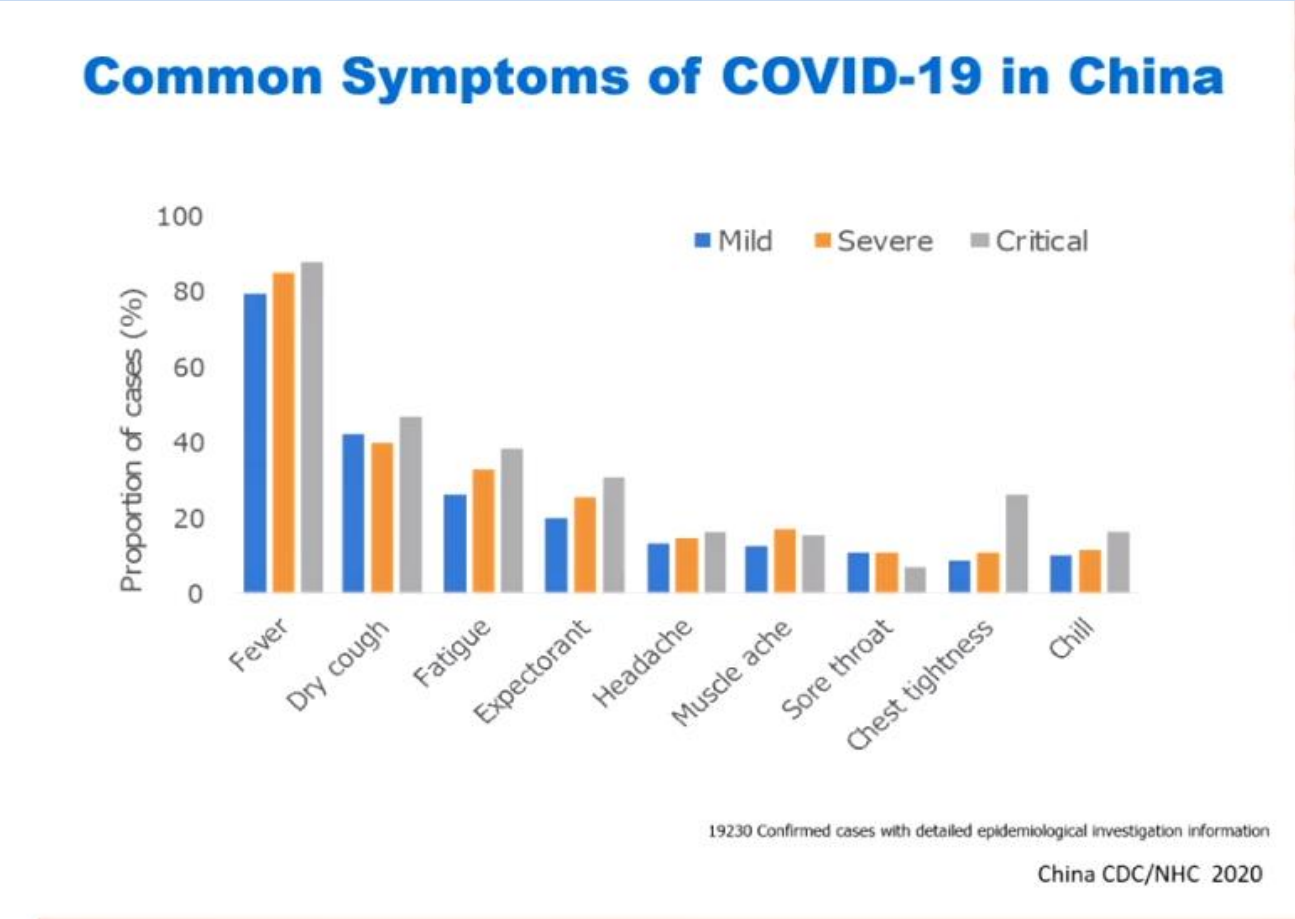
Timelines: SARS-1 vs -2

COVID-19: US MMWR



https://www.cdc.gov/mmwr/Novel_Coronavirus_Reports.html

COVID-19: China CDC



Early studies: all tell a story

• Characteristics of and important lessons from the COVID-1) outbreak in China: summary of of 72,314 cases. JAMA. (20 February 2020). Age, severity, symptoms. https://jamanetwork.com/journals/jama/fullarticle/2762130

• Li Q et al. Early transmission dynamics in Wuhan, China, of novel coronavirus–infected pneumonia. N Engl J Med 2000. (26 March 2020). First 425 cases. https://www.nejm.org/doi/full/10.1056/nejmoa2001316

Eary studies: both tell a story

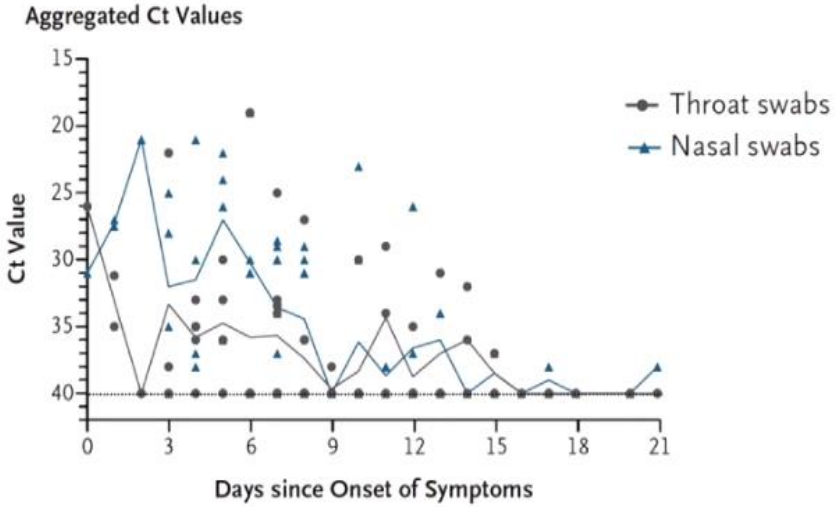
These and similar retrospective observational studies were used to design public heath strategies to reduced further transmission and to protect people at highest risk.

Identified highest risk factors: age, gender, comorbidities etc and person-to-person transmission.

Transmission linked to viral load

Viral Shedding Greatest At Time Symptoms Start

- SARS-CoV-2 viral loads in 17 symptomatic patients
- No data regarding duration of replication-competent virus shedding (e.g., culture)



Zou 2020, N Engl J Med; DOI: 10.1056/NEJMc2001737

Transmission

- Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1
https://i-base.info/htb/37421

- Median estimated incubation period of COVID-19 is five days – but can be two weeks
https://i-base.info/htb/37423

- Four papers on CoV-2 transmission: sometimes easy, sometimes rare
https://i-base.info/htb/37652

- Studies stoke concern about coronavirus contagion through air via speech
https://i-base.info/htb/37659

Epidemiology: questions

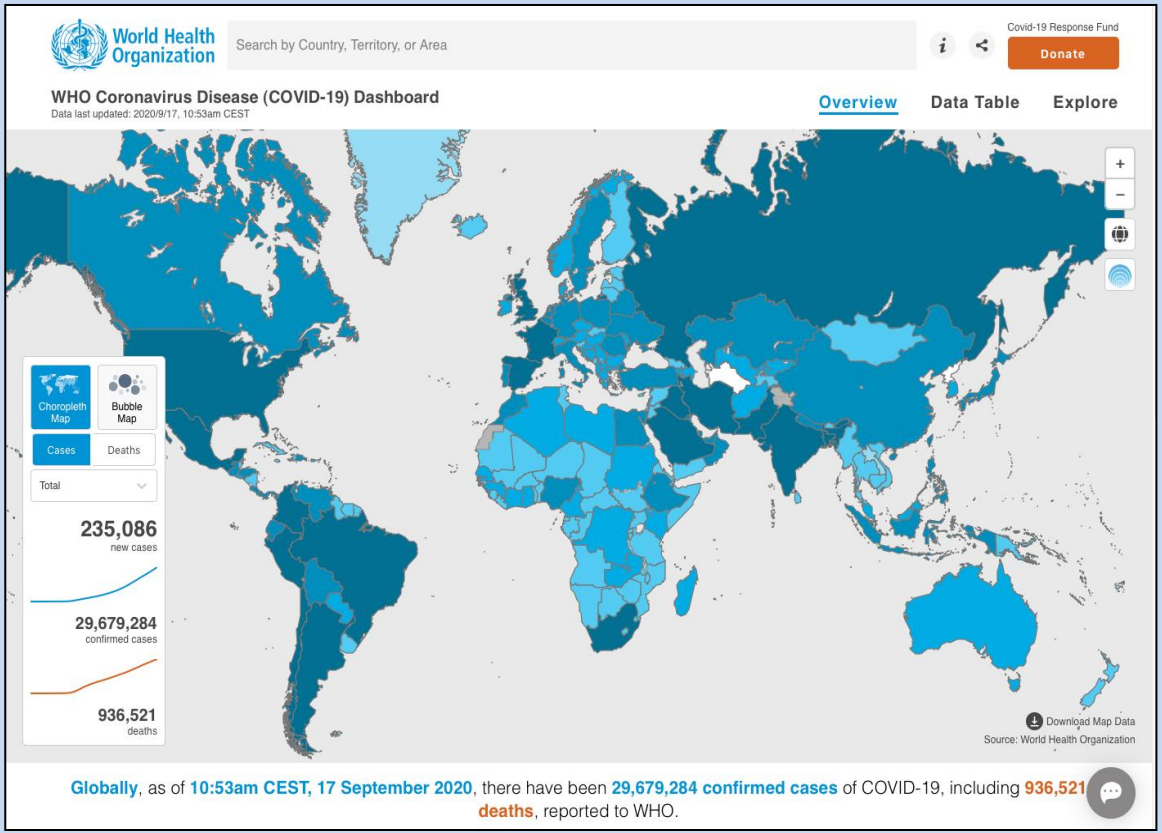
- How many people have COVID-19?
- Where do they live?
- How many people die? % of cases?

- Absolute vs relative numbers, accounting for population size etc
- Rate of change over time etc
- Relation to healthcare setting (data, testing etc)

Early data: epidemiology

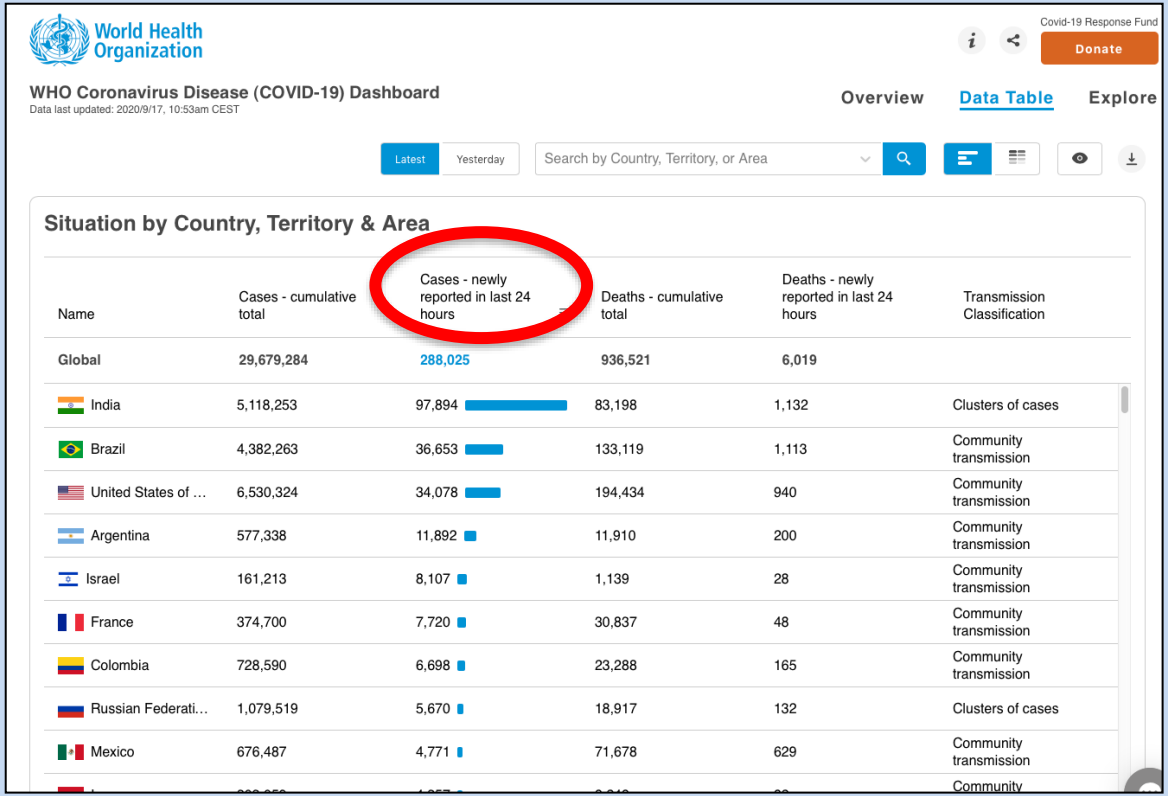
UK data – every EU country with have similar
https://coronavirus.data.gov.uk/cases
WHO daily situation reports from
Januaryhttps://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports
Johns Hopkins University:
https://coronavirus.jhu.edu
Worldometers
https://www.worldometers.info/coronavirus/#repro

WHO dashboard



https://covid19.who.int/

WHO dashboard



World Health Organization

Covid-19 Response Fund

Donate

WHO Coronavirus Disease (COVID-19) Dashboard

Data last updated: 2020/9/17, 10:53am CEST

Overview | Data Table | Explore

Latest | Yesterday | Search by Country, Territory, or Area

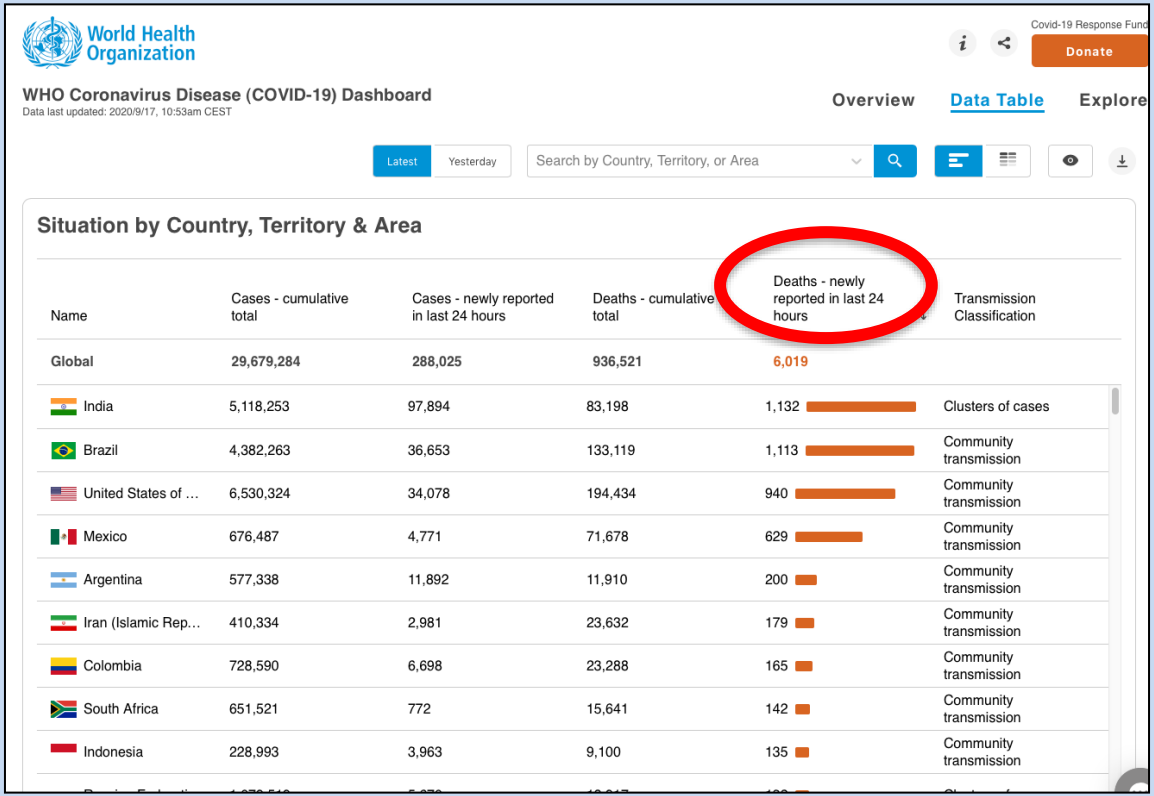
Situation by Country, Territory & Area

Name	Cases - cumulative total	Cases - newly reported in last 24 hours	Deaths - cumulative total	Deaths - newly reported in last 24 hours	Transmission Classification
Global	29,679,284	288,025	936,521	6,019	
India	5,118,253	97,894	83,198	1,132	Clusters of cases
Brazil	4,382,263	36,653	133,119	1,113	Community transmission
United States of …	6,530,324	34,078	194,434	940	Community transmission
Argentina	577,338	11,892	11,910	200	Community transmission
Israel	161,213	8,107	1,139	28	Community transmission
France	374,700	7,720	30,837	48	Community transmission
Colombia	728,590	6,698	23,288	165	Community transmission
Russian Federati…	1,079,519	5,670	18,917	132	Clusters of cases
Mexico	676,487	4,771	71,678	629	Community transmission
					Community

https://covid19.who.int/

Sorted by number of cases in the last 24 hours.

WHO dashboard



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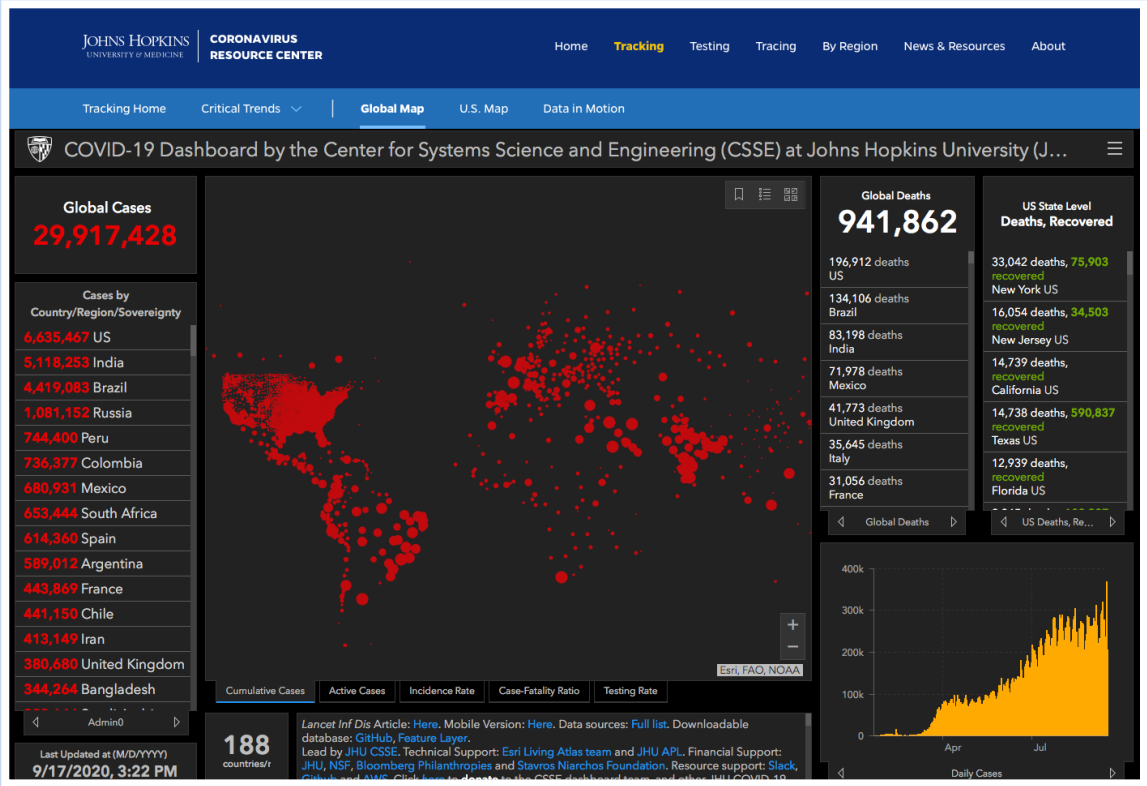
Mexico	676,487	4,771	71,678	629	Community transmission
Argentina	577,338	11,892	11,910	200	Community transmission
Iran (Islamic Rep…	410,334	2,981	23,632	179	Community transmission
Colombia	728,590	6,698	23,288	165	Community transmission
South Africa	651,521	772	15,641	142	Community transmission
Indonesia	228,993	3,963	9,100	135	Community transmission

https://covid19.who.int/

Sorted by deaths reported in the last 24 hours.

Johns Hopkins Univ. dashboard



https://coronavirus.jhu.edu/map.html

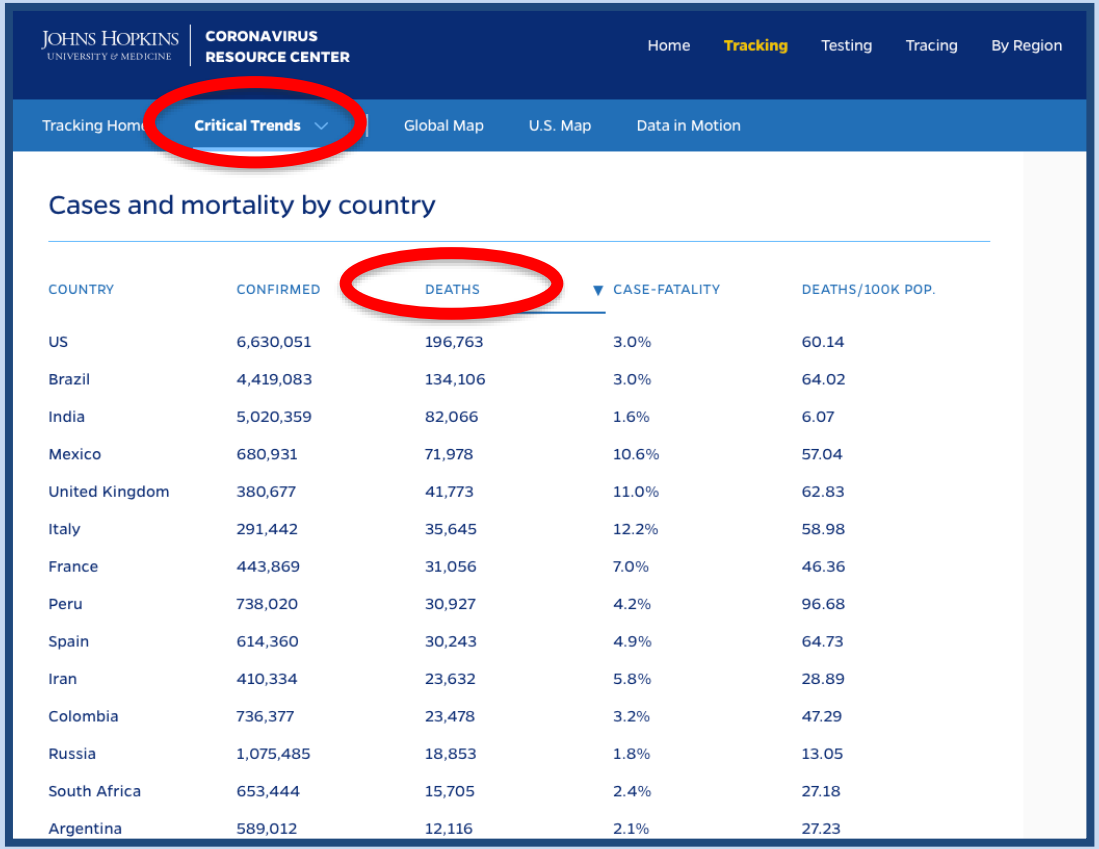
Johns Hopkins Univ. dashboard

COUNTRY	CONFIRMED	▼ DEATHS	CASE-FATALITY	DEATHS/100K POP.
US	6,630,051	196,763	3.0%	60.14
India	5,020,359	82,066	1.6%	6.07
Brazil	4,419,083	134,106	3.0%	64.02
Russia	1,075,485	18,853	1.8%	13.05
Peru	738,020	30,927	4.2%	96.68
Colombia	736,377	23,478	3.2%	47.29
Mexico	680,931	71,978	10.6%	57.04
South Africa	653,444	15,705	2.4%	27.18
Spain	614,360	30,243	4.9%	64.73
Argentina	589,012	12,116	2.1%	27.23
France	443,869	31,056	7.0%	46.36
Chile	439,287	12,058	2.7%	64.38
Iran	410,334	23,632	5.8%	28.89
United Kingdom	380,677	41,773	11.0%	62.83
Bangladesh	342,671	4,823	1.4%	2.99

https://coronavirus.jhu.edu/data/mortality

Viewed by confirmed number of cases per country

Johns Hopkins Univ. dashboard



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Mexico	680,931	71,978	10.6%	57.04
United Kingdom	380,677	41,773	11.0%	62.83
Italy	291,442	35,645	12.2%	58.98
France	443,869	31,056	7.0%	46.36
Peru	738,020	30,927	4.2%	96.68
Spain	614,360	30,243	4.9%	64.73
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South Africa	653,444	15,705	2.4%	27.18
Argentina	589,012	12,116	2.1%	27.23

https://coronavirus.jhu.edu/data/mortality

Viewed by confirmed number of deaths per country

Johns Hopkins Univ. dashboard

COUNTRY	CONFIRMED	DEATHS	CASE-FATALITY	DEATHS/100K POP.
Yemen	2,019	583	28.9%	2.05
Italy	291,442	35,645	12.2%	58.98
United Kingdom	380,677	41,773	11.0%	62.83
Mexico	680,931	71,978	10.6%	57.04
Belgium	95,948	9,935	10.4%	86.98
Ecuador	121,525	10,996	9.0%	64.36
Chad	1,090	81	7.4%	0.52
France	443,869	31,056	7.0%	46.36
Netherlands	90,425	6,303	7.0%	36.58
Sweden	87,575	5,860	6.7%	57.55
Canada	141,852	9,244	6.5%	24.94
Sudan	13,535	836	6.2%	2.00
Liberia	1,332	82	6.2%	1.70

https://coronavirus.jhu.edu/data/mortality

Viewed by case:fatality ratio per country

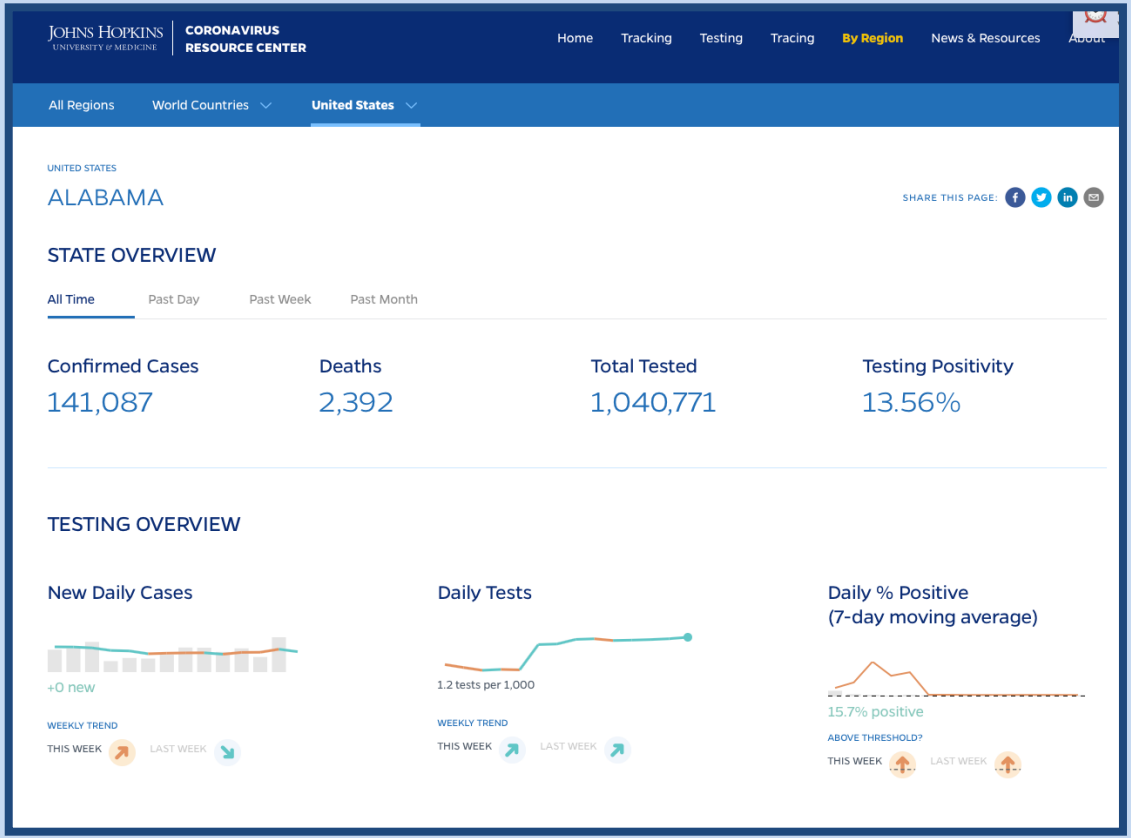
Johns Hopkins Univ. dashboard

COUNTRY	CONFIRMED	DEATHS	CASE-FATALITY	DEATHS/100K POP.
San Marino	723	42	5.8%	
Peru	738,020	30,927	4.2%	96.68
Belgium	95,948	9,935	10.4%	86.98
Andorra	1,483	53	3.6%	68.83
Bolivia	128,872	7,478	5.8%	65.87
Spain	614,360	30,243	4.9%	64.73
Chile	439,287	12,058	2.7%	64.38
Ecuador	121,525	10,996	9.0%	64.36
Brazil	4,419,083	134,106	3.0%	64.02
United Kingdom	380,677	41,773	11.0%	62.83
US	6,630,051	196,763	3.0%	60.14
Italy	291,442	35,645	12.2%	58.98
Sweden	87,575	5,860	6.7%	57.55

https://coronavirus.jhu.edu/map.html

Viewed by confirmed number of deaths per 100,000 population

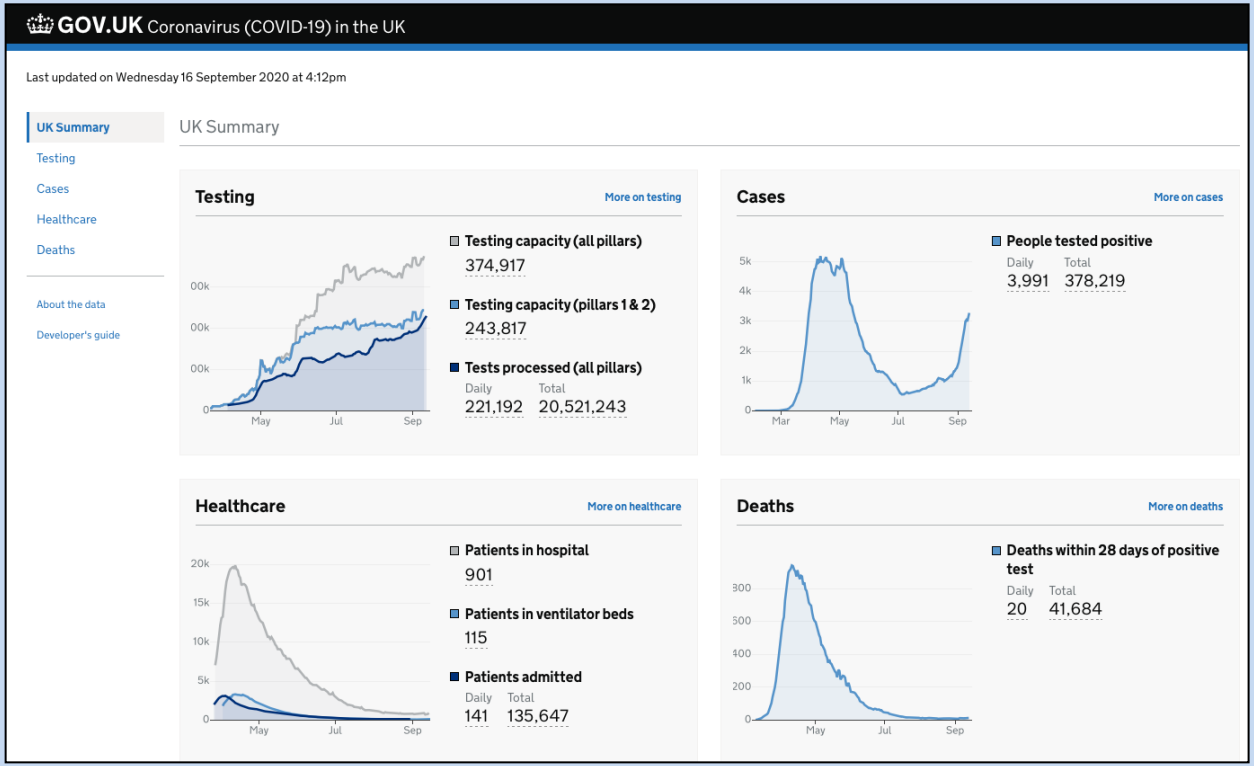
Johns Hopkins Univ. dashboard



https://coronavirus.jhu.edu/region/us/alabama

Results by State: Total, past day/week/month

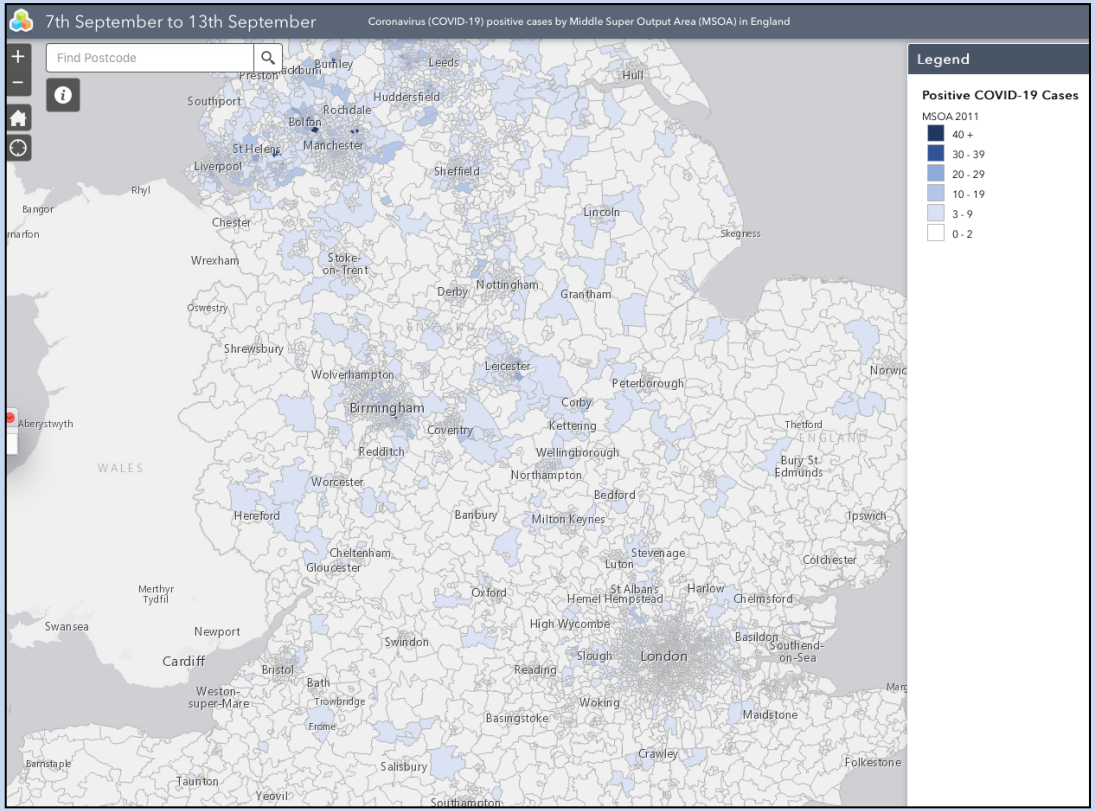
UK data: - map



https://coronavirus.data.gov.uk

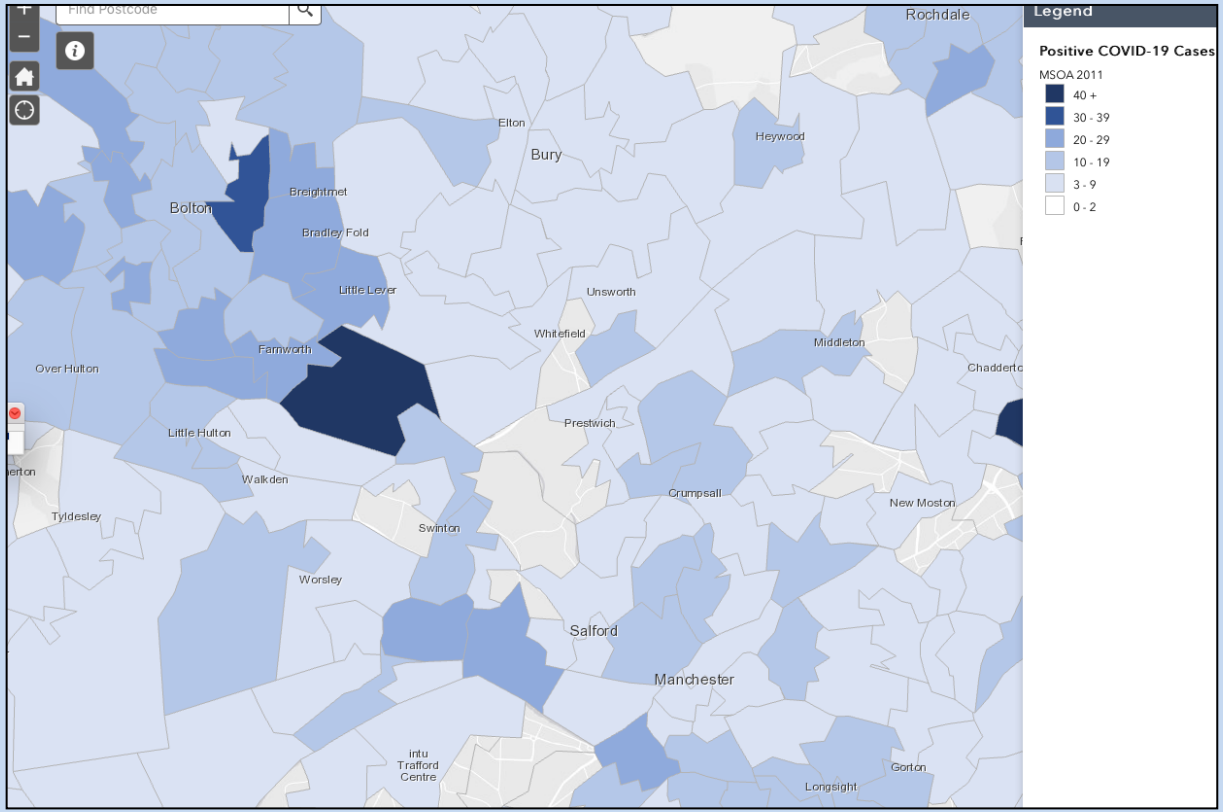
Daily updates:
Testing overall
Positive reults
Healthcare use
Mortality

UK data: - map



https://www.arcgis.com/apps/webappviewer/index.html

UK data: - map

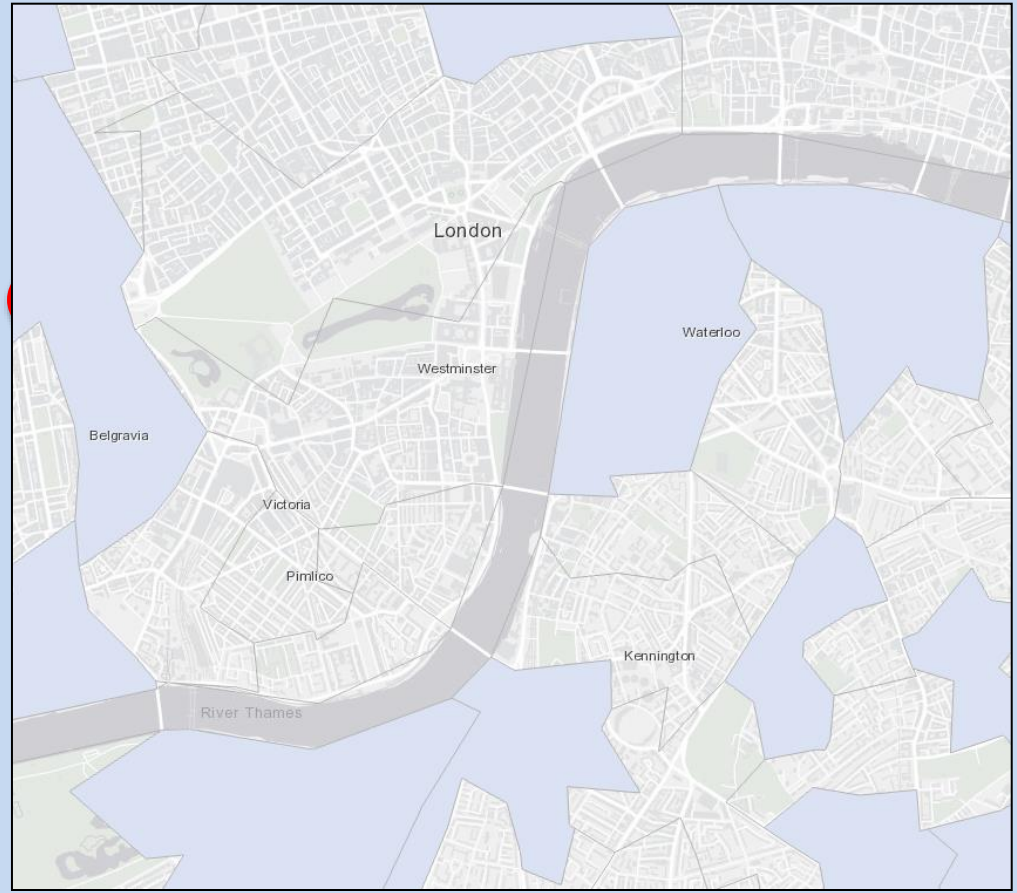


https://www.arcgis.com/apps/webappviewer/index.html

Zoom to district: Manchester and Bolton

Daily – based on rolling 7-day average

UK data: - map



https://www.arcgis.com/apps/webappviewer/index.html

Zoom to district: London

Daily – based on rolling 7-day average.

HIV and COVID-19 coinfection

- Is HIV linked to higher risk of COVID-19 – and getting worse symptoms?
- Is HIV linked to lower risk of COVID-19 – and getting milder symptoms?
- Are ***some*** HIV positive people at higher/lower risk?
- What is impact of ART? Or not being undetectable?
- Is impact of comorbidities the same? etc

All these Q's need real data/evidence to inform the answers. Need to adjust for baseline factors, stage of COVID-19 etc. Earlier isolation???

HIV/COVID coinfection papers

- 1st reports: single cases, small groups
  + expert opinion – BHIVA/|EACS
- 2nd reports: Larger cohorts n=20-100
  Retrospective observational cohorts.
  Lack on clinical data on CD4, VL, ART, comorbidities.
  + expert opinion – BHIVA/|EACS
- 3rd reports: Larger cohorts n=100-400
  Sometimes prospective, still limited data in important areas. Sometimes reporting HIV as an independent risk factor.

HIV/COVID statements

- BHIVA/EACS made approximately 10 statements over the first 4-6 weeks – revising and modifying advice on risk relating to HIV, CD4 counts etc.
- Recognised limited evidence to comment.
- Optimistic – based on "lack of evidence to show higher level of risk compared to general population".
Controversial: lack of evidence doesn't imply lack of risk.
- Included reviews of accumulating evidence – though all studies were small, observational, underpowered etc.

HIV and COVID-19 coinfection - 1

- COVID-19 symptoms in 8/1168 HIV positive people - similar to general population in Wuhan, March 2020. [1] http://i-base.info/htb/37542
- 5 HIV+ people/600 in Barcelona [2] http://i-base.info/htb/37661
- HIV is not linked to higher risks in 43/5700 in New York cohort. [3] http://i-base.info/htb/37739
- Case studies showing no impact of DRV/r. [4] https://i-base.info/htb/37830

1. Guo et al , 2. Blanco et al., 3. Richardson et al. 4. Riva et al.

HIV and COVID-19 coinfection - 2

By June >20 studies - from China, Germany, Italy, Spain, the UK and the US with >10 in last month, getting larger: http://i-base.info/htb/38000

- South London: n=18 (12M, 6W). Most (17/18) were black, on long-term ART and <50 c/mL. Comorbidities common. 5 died and 1is still in hospital. [1]
- Madrid: n= 51 (43M, 8W): 1.8% of 2873 cohort. 6 critically ill, 2 have died. [2]
- South Bronx: n=9 (7M, 2W). All had comorbidities and 7/9 died (78%). [3]
- Milan: n=47 (36M, 11W). 45/47 (96%) fully recovered and 2/47 died (4%). [4]
- Germany: n=33 (30M, 3W). Mean age 48 years (range 26–82). Med CD4 670 (range 69 to 1715). 3/33 died. [5]
- UK – ISARIC etc ~ 120 cases, 45 deaths. >20,000 records (30% of total). Approx 83/17,000 (55M, 28W) with HIV data. No full report yet. [6]

1. Childs et al , 2. Vizcarra et al., 3. Suwanwongse et al. 4. Gervasoni et al. 5. Härter et al. 6. ISARIC personal comm.)

HIV and COVID-19 coinfection - 3

Larger data sets – start to report HIV effect.

- Large South African dataset – HIV 2-3x higer risk [1] https://i-base.info/htb/38232
- UK ISARIC data - n=115 – reported HIV impact. [2] https://i-base.info/htb/38726
- Goldacre et al. OpenSAFELY – HIV+ (28,000/17 million) - GP/primary care records. [3] https://i-base.info/htb/38726
- IAS2020 – 3 cohorts including VACS. [4] https://i-base.info/htb/38793
- US cohort – n=287 HIV+, prospective registry reporting CD4 effect <200. [5] https://i-base.info/htb/38980

1. Davies et al , 2. Geretti et al., 3. Goldacre et al. 4. Parks et al, 5. Dandachi et al.

Basic questions

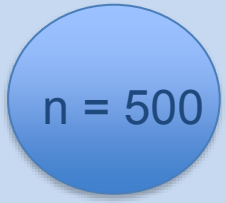
1. Why do we need evidence?

2. What is wrong with expert opinion?

3. How do we get good evidence?

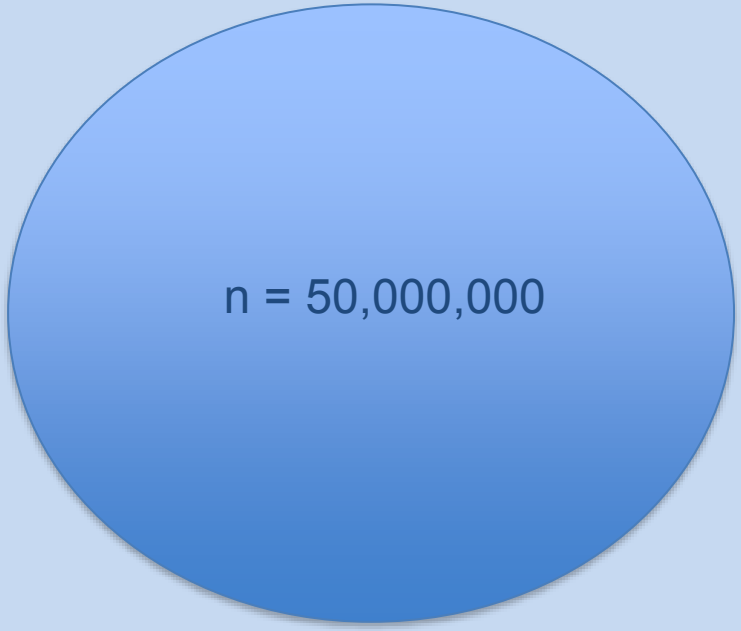
Results are repeatable and generalisable

Research study

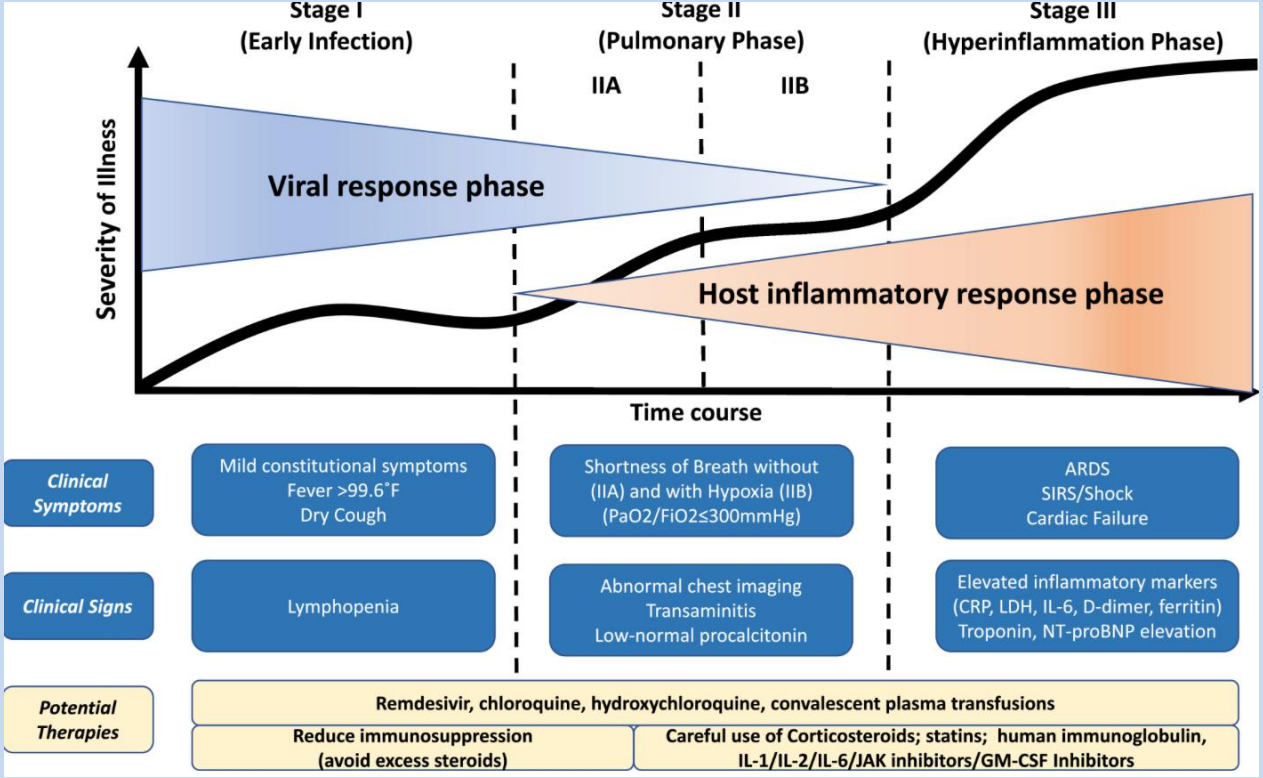


Research needs to be designed so that there is confidence in the results.
Results will be used on a population level.
The study needs to reflect the population.

Population results



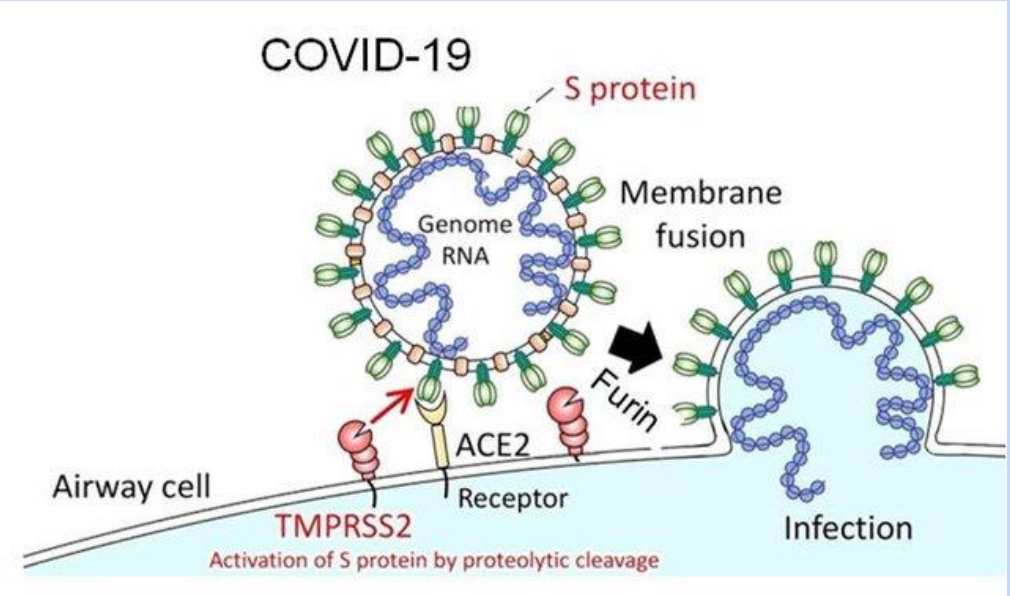
Pathogenesis: how disease progresses



Later expanded:
(i) other organ involvement.
(ii) coagulation and blood clots in lungs and other organs.
(iii) Much longer time to recover and return to normal ('long-COVID').

Ref: COVID-19 illness in native and immunosuppressed states: A clinical–therapeutic staging proposal. Siddiqi HK et al. DOI:10.1016/j.healun.2020.03.012. (20 March 2020).

ACE2 receptor enable infection



ACE2 receptors are primary route for SARS CoV-2 to attach to cells.

They normally cut up angiotensin protein to reduce blood pressure. Concentrated in lungs, heart, gut – but also in the nose.

ACE2 inhibitors slow down this process – might protect against COVID-19.

COVID repurposed drugs

- 1st compounds: antivirals potential based on in vitro activity – including some ARVs and hydroxychloroquine.
- Corticosteroids (China but not WHO) - due to use in lung infections.
- 2nd compounds: ACE inhibitors (targeting early infection).
- 3rd compounds: immune modulators to reduce inflammation - with anakinra, tocilizumab, anticoagulants, convalescent plasma, interferon, BCG and HCV DAAs.

All small, open-label studies – “need for RCTs”

Define outcomes? Critical for any RCT.

When to use? On confirmed diagnosis? When hopsitalised? Before or after intubation? Dose and duration? Etc

- Virologic endpoints – reduce viral load?

- Clinical endpoints - % recovered? Or time to recovery? Or time to discharge?

- Impact on mortality? Counting deaths? Survival at 28 days?

Each endpoint could produce different results.

COVID repurposed drugs

- Remdesivir - approved in US and EU – for hospitalised people not on intubation. Access problems.
- Dexamethasone approved - for people on oxygen and intubation – most seriously ill.
- Inhaled INF-beta – reported significant benefit in reducing time to recovery – in earlier infection – further studies. 20 July.
- Hydroxychloroquine “greatest medical breakthrough this century” –proven no benefit. RECOVERY 6 June. (1100 d.)
- Lopinavir/r proven to have no benefit – RECOVERY 29 June.
- Tocilizumab – no benefit in COVACTA – 29 July, pub 1 Sept.

All though RCTs.

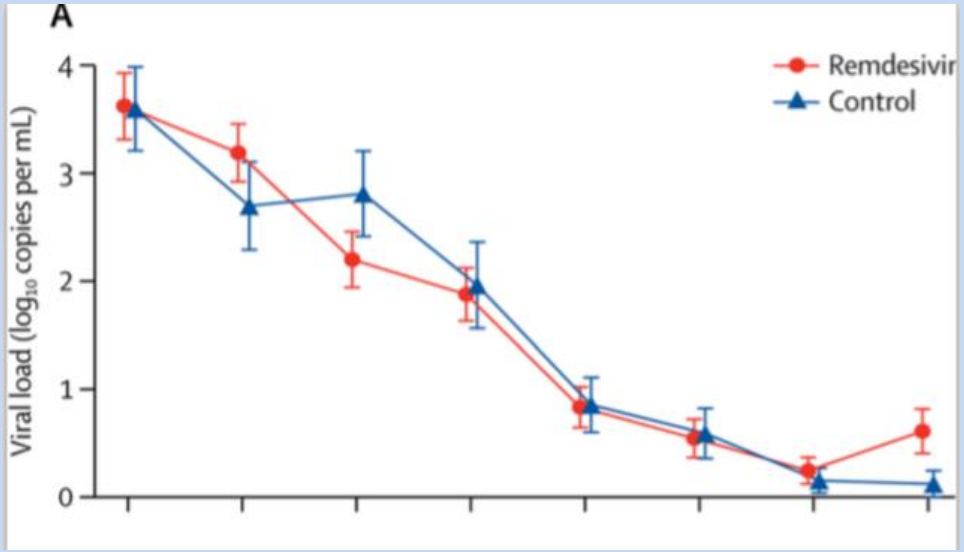
COVID drugs: Remdesivir

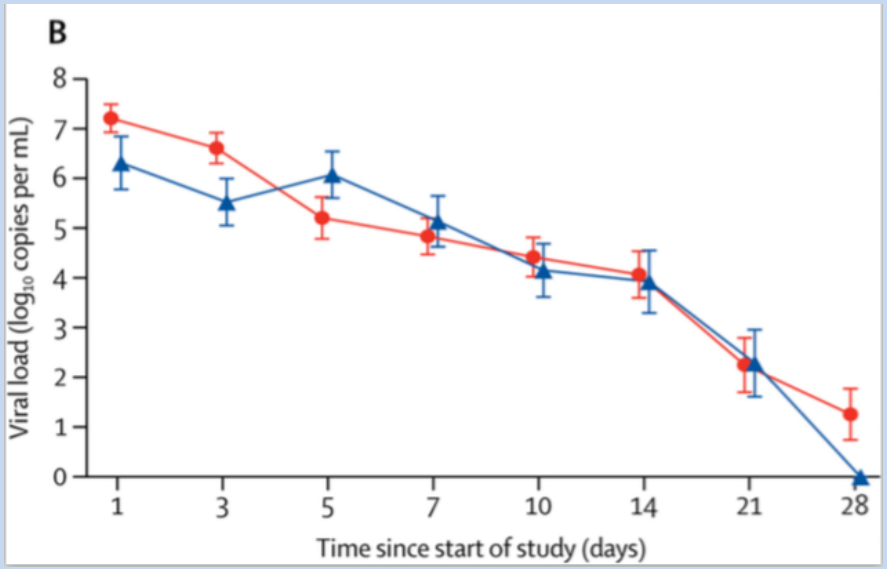
Controversial history – developed for Ebola – rapid scale=up and commitment to donated drugs - contradictory results reported, unfinished RCT from China showed no benefit, leaks reporting benefit, anecdotal reports from White House.

23 April – WHO leaked data showing no benefit
29 April – No benefit RCT China – Wang et al, Lancet. (see Fig 3)
29 April – top-line results from NIH ACTT study, n>1000, short recovery.
1 May – FDA emergency authorisation.
1 June – SIMPLE study reports 5 > 10 day dosing.
15 June – contraindication with hydroxychloroquine. ** drug interactions.
3 July - EU conditional approval

Fig 3, remdesivir study.

Wang et al. Lancet.





Remdesivir: mainstream press

Examples of reporting:

Boseley S. First trial for potential Covid-19 drug shows it has no effect. The Guardian. (23 April 2020). https://www.theguardian.com/world/2020/apr/23/high-hopes-drug-for-covid-19-treatment-failed-in-full-trial

Manchini DP. Gilead antiviral drug remdesivir flops in first trial. Financial Times. (23 April 2020). https://www.ft.com/content/0a4872d1-4cac-4040-846f-ce32daa09d99

BBC. Hopes dashed as coronavirus drug remdesivir 'fails first trial'. (24 April 2020). https://www.bbc.co.uk/news/world-52406261

Hydroxychloroquine

Controversial history for COVID-19: Use in China, plus small French study with azithromycin – (Gautret et al). Lead to 100s of studies for treatment and PrEP. Also bulk orders in US and globally – cutting supply for genuine need.

Two issues (can be separated) – ie to support research at a safe dose.

(1) Efficacy – does it work? Questions of dosing for activity, timing after infection/symptoms, stage of infection.

(2) Safety – is it safe? Questions of dose for toxicity, risk (age, CVD etc)

Important because so many large studies included HCQ arms including WHO SOLIDARITY (DISCOVER in EU), RECOVERY (UK >10,600 pts)

Hydroxychloroquine: April-May

Lack of benefit from hydroxychloroquine to treat COVID-19
http://i-base.info/htb/37803

1. No association between HCQ and intubation or death in 1446 consecutive patients at a single centre in New York. [1]
2. Retrospective analysis of 368 patients with COVID-19 in the US Veterans Affairs hospitals (n=97 HCQ; n=113 HCQ+AZ, n=113; n=158 no HCQ). Rates of death were 27.8%, 22.1%, 11.4% and ventilation were 13.3%, 6.9%, 14.1% in the HCQ, HCQ+AZ, and no HC groups, respectively. Compared to the no HCQ group, the risk of death from any cause was higher with HCQ (adj. hazard ratio, 2.61; 95% CI: 1.10 to 6.17; p=0.03). [2]
3. Nature Research paper reported lack of effect from HCQ in vitro and also in macaques. No benefit as PEP. [3]

1. Geleris J et al. 2. MagagnoliJ et al. 3. Maisonnasse P et al. Also Prescrire.

Hydroxychloroquine: 5 June

HTB

UK RECOVERY study stops hydroxychloroquine (HCQ) for COVID-19: more than 1100 deaths question ethics and safety overall | Edit

26 June 2020. Related: COVID-19: investigational drugs, COVID-19.

Simon Collins, HIV i-Base

On 5 June 2020, the large randomised RECOVERY study announced that hydroxychloroquine (HCQ) will no longer be used to treat COVID-19. [1]

The results show that hundreds of people died – both taking HCQ and in the comparison group receiving no investigational drugs – and yet the study was only closed because of a safety request by the UK Medicines and Healthcare products Regulatory Agency (MHRA).

UK RECOVERY study stops HCQ arm on 5 June.

Some other studies stop including WHO DISCOVERY.

https://i-base.info/htb/38188

COVID drugs: dexamethasone

Initial concern to protect immune system: Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Russell CD et al. The Lancet 2020. DOI: 10.1016/S0140-6736(20)30317-2. (7 February 2020). https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30317-2/fulltext

Later RCT RECOVERY study. Low-cost dexamethasone reduces death by up to one third in hospitalised patients with severe respiratory complications of COVID-19. Univ of Oxford, (16 June 2020). http://www.ox.ac.uk/news/2020-06-16-low-cost-dexamethasone-reduces-death-one-third-hospitalised-patients-severe

RECOVERY study - example

Large UK RCT – using adaptive design to rapidly respond to signals of effective or ineffective compounds.

Enrolled >12,000 adults hospitalised with COVID-19.

Randomised to HCG, LPV/r, azithromycin, dexamethasone; later to tocilizumab and convalescent plasma or shared placebo (roughly 1:2).

High mortality ~20-25%. >2250/9000 died.

HCQ results: 25% mortality, ~ 400 HCQ + 700 placebo

Dexa results: n = 2104 – 3% reduced mortality saved 83

LPV/r results: 22.1 vs 21.3% mortality, p=0.58.

tocilizumab

Approved treatment to reduce IL-6 (increased IL-6 is a marker for more severe COVID-19). Broadly safe – many small studies reported hope.

Tocilizumab fails to meet clinical endpoints in randomised COVACTA study: other studies continue. (3 September 2020) https://i-base.info/htb/38965)

Potential for tocilizumab to treat moderate to severe COVID-19. (14 May. https://i-base.info/htb/37877)

Tocilizumab associated with better outcomes from COVID-19 in US study (28 August, https://i-base.info/htb/38827)

Dozens of pre-peer-viewed studies still report benefit. A few no impact. RECOVERY and some other studies continue.

COVID-19 vaccines

Company	Type	Study phase
Moderna and NIAID	mRNA vaccine	phase 3 trial on 27 July 2020 in US.
Pfizer and BioNTech	mRNA vaccine	phase 3 trial on 27 July 2020.
AstraZeneca and Oxford University	ChAdOx replication-defective live-vector	phase 3 trials in the UK, Brazil, and South Africa; US expected in August
Janssen	Ad26 replication-defective live-adenovirus	US phase 1 on 27 July, phase 3 expected mid-September.
Novavax	recombinant-subunit-adjuvanted protein	phase 3 expected in the US by end September
Merck	preclinical	
Imperial College London	Self-amplifying RNA vaccine	Phase 2
Gamaleya (Russia)	Adenovirus	Approved in Russia without phase 3 results.
CanSino (China)	Adeno type-5 vector	China

Vaccines.1

- FDA already agreed that 50% population protection would get approved. – ie with little personal security of benefit.
- Aims: to reduce mortality or transmission?
- All based on animal, in vitro and immune responses - phase 3 needed to show efficacy.
- Some candidate vaccines rolled out before phase 3 data (Russia, China) – ie without efficacy or safety data – might increase risk.
- Political statements separate to science.

Vaccines.2

- Single vs multiple dose
- Duration of effect – need for boosters?
- Results across different ages, genders, ethnicity.
- Reduced susceptibility with age?
- Scale-up, price, access – globally and within countries.
- Enrolment of HIV+ positive people – US activists.
- Safety - Oxford study – paused and then restarted with safety report.

Publications and literature

- Peer review journals are essential process for validating research and defining the evidence for best care.
- COVID-19 papers are now open access in most journals.
- COVID-19 also generates huge volume of online papers before peer review.
- Important to question everything you see, hear and read: does the story make sense, do the fact support it being true?
- Even most rigorous journals got this wrong.

Publications and literature

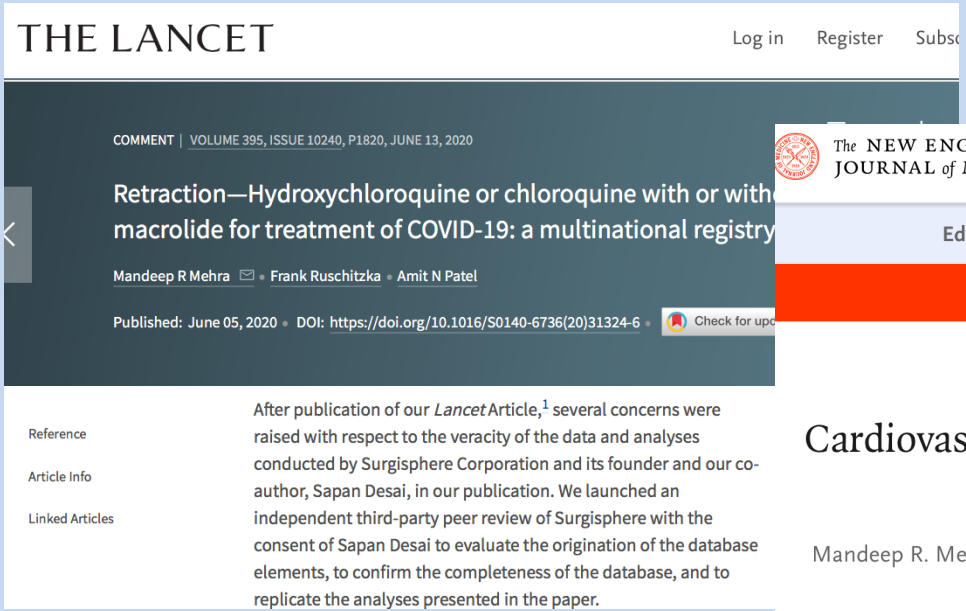
Main subscription journals publish open access:
Lancet, JAMA, NEJM, AIDS, CID etc

Thousands of COVID-19 SARS-CoV-2 preprints from medRxiv and bioRxiv:
https://connect.medrxiv.org/relate/content/181

8775 articles (18 Sept 20): 6884 medRxiv, 1891 bioRxiv

Vs. ~ 90 on HIV and 2200 on other infectious diseases.

Retractions



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COMMENT | VOLUME 395, ISSUE 10240, P1820, JUNE 13, 2020

Retraction—Hydroxychloroquine or chloroquine with or with
macrolide for treatment of COVID-19: a multinational registry

Mandeep R Mehra • Frank Ruschitzka • Amit N Patel

Published: June 05, 2020 • DOI: https://doi.org/10.1016/S0140-6736(20)31324-6 • Check for upc

Reference

Article Info

Linked Articles

After publication of our *Lancet* Article,[1] several concerns were raised with respect to the veracity of the data and analyses conducted by Surgisphere Corporation and its founder and our co-author, Sapan Desai, in our publication. We launched an independent third-party peer review of Surgisphere with the consent of Sapan Desai to evaluate the origination of the database elements, to confirm the completeness of the database, and to replicate the analyses presented in the paper.

The NEW ENGLAND JOURNAL of MEDICINE

Editor's Note: This article was published on May 1, 2020, at NEJM.org.

This article has been retracted.

ORIGINAL ARTICLE

Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19

Mandeep R. Mehra, M.D., Sapan S. Desai, M.D., Ph.D., SreyRam Kuy, M.D., M.H.S., Timothy D. Henry, M.D., et al.

June 18, 2020

N Engl J Med 2020; 382:e102

Conclusions

- Rigorous approach to research is the only way to find and proof effective interventions for COVID-19.

- Study design is a central factors in interpreting results - signals need RCTs to confirm.

- Many examples of politics, hope, intuition proving wrong.

- Question everything – even if published.

Thanks

simon.collins@i-base.org.uk

www.i-base.info