

SARS-CoV-2 Pandemic 2019-now

Introduction to the little known

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2020-04-08

Key definitions

- Attack rate
 - The proportion of the population which contracts the disease from the population at risk
- Case-fatality risk (CFR)
 - The probability that a person dies from an infection given that they are a case
- Infection-fatality risk (IFR)
 - Defines a case as a person who has shown evidence of infection, either by clinical detection of the pathogen or by seroconversion or other immune response
- Basic reproductive number **R_0** (often pronounced "*R naught*")
 - The **average number of secondary cases** of an infection that occur **in a completely susceptible population following a single infectious case**

[Lipsitch, 2015](#); case-fatality risk and infection-fatality risk are sometimes referred to as "rates".

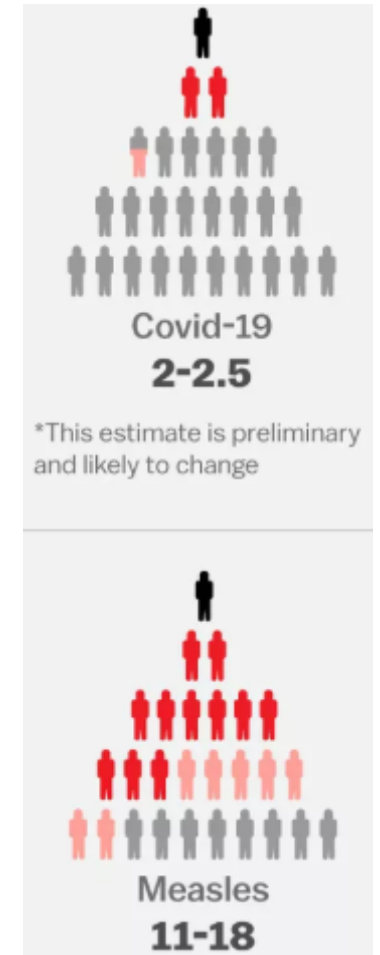
Basic Reproductive Number

How many other people one contagious individual will infect in non-immune population?

- Mathematical modeling of transmission within populations

Vox, 2020

NEJM, 2020



Contemporary epidemics history

- **2002-2004 SARS** (SARS-CoV virus)
 - R_0 : 2.0 to 4.0 ([WHO, 2003](#))
 - 8096 cases
 - 774 deaths in 32 countries → case fatality rate 9.6% ([WHO, 2004](#))
 - Vaccine inducing neutralizing antibodies now available ([Chien-Te Tseng, 2012](#))
- **2009** 2nd pandemic caused by **H1N1 influenza virus** (H1N1/09, or "Swine flue")
 - R_0 : 1.5 (1.3 to 1.7)
 - 0.7–1.4 **billion** estimated infected worldwide
 - 151,700–575,400 estimated deaths worldwide
 - Vaccine now available

- **2012-present MERS** (MERS-CoV)
 - $R_0 < 1$ ([WHO, 2019](#))
 - Heterogenous R_0 : 1.0-5.7 at the start of the outbreak $\rightarrow < 1.0$ ([Bernard-Stoecklin, 2019](#))
 - 2012-2016: 1841 laboratory confirmed cases \rightarrow 80% in the Kingdom of Saudi Arabia
 - 35% (n=652) died
- **2014-2016 Ebola**
 - 28,542 cases
 - 11,299 deaths
 - CFR was 40%

Emerging Infectious Diseases

Identification of infectious agents and diseases that were not recognized before

Infection states

- Progression-Related

State of Infection	Definition
Colonization	Transient colonization tissue invasion
Subclinical infection	Agent is present in host tissues without signs, symptoms, or laboratory evidence of tissue damage
Latency	Infection in which the agent has invaded the host and is in a nonreplicating, noninfectious, but viable state
Disease	Agent is replicating in host tissues with signs, symptoms, or laboratory evidence of tissue damage
Cure	Agent has been eliminated from host tissue (may persist on surface)

Infection states

- Transmission-Related

State of Infection	Definition
Preinfectious	Host is infected but has not become infectious
Infectious	Host is capable of transmitting agent to others
Postinfectious	Host is no longer capable of transmission

Modeling infectious diseases spread

- **Aims**
 - Prediction
 - Consequences of intervention ("causal" flavour and counterfactual reasoning)
- **Models**
 - **Deterministic compartmental models (DCMs)**
 - SIR (Susceptible → Infectious → Recovered)
 - SIRS (Susceptible → Infectious → Recovered → Susceptible)
 - SEIR (Susceptible → Exposed → Infectious → Recovered)
 - Modifications accomodating other compartments to model post-infection immunity, vaccination, etc.
 - Straightforward, transparent, does not always reflect real-life complexities

Simulating individuals not the population groups

- **Agent-based models (ABMs)**
 - **Network models**
- Calibration, Validation, Sensitivity analyses

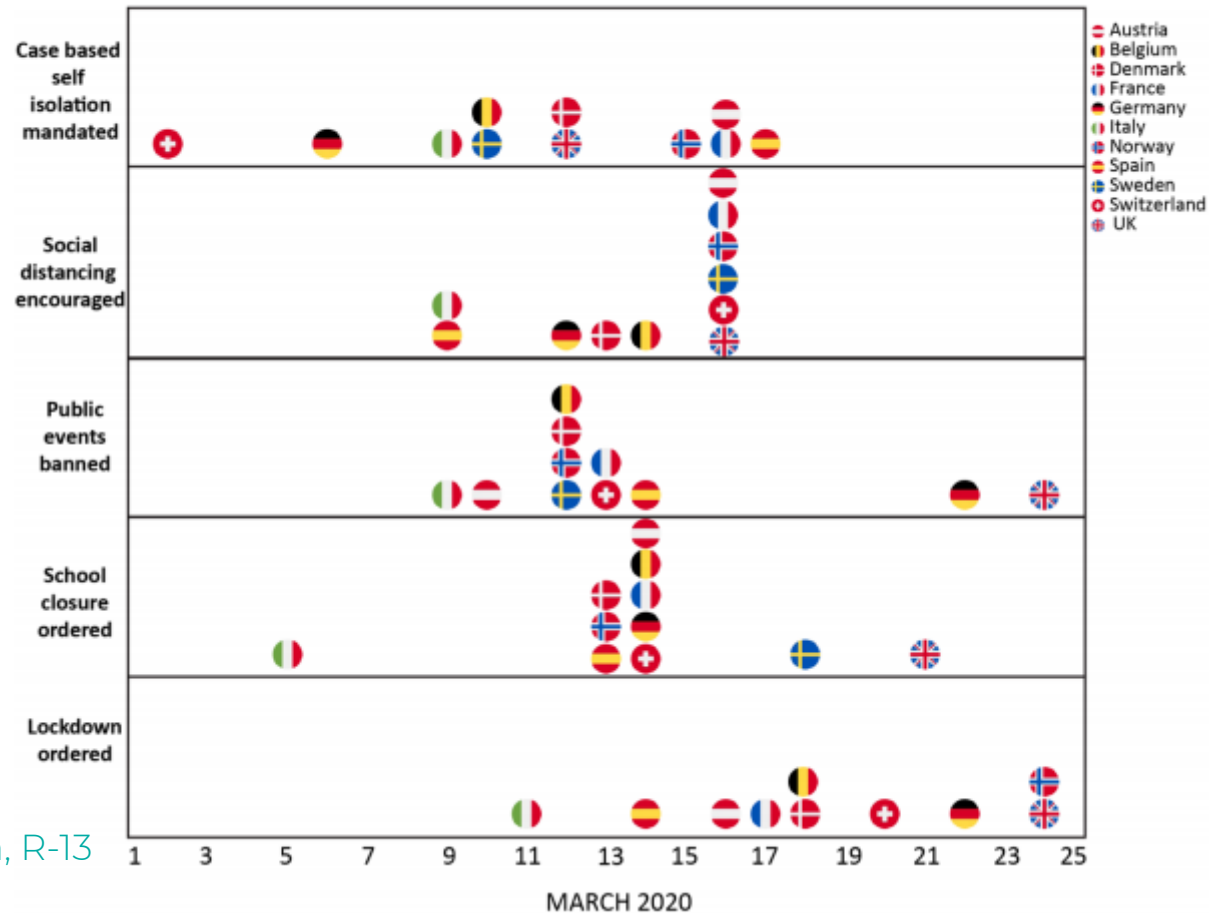
Coronavirus disease (COVID-19) outbreak

- **SARS-CoV-2**
- β -coronavirus (other two known β -CoVs are SARS-CoV and MERS-CoV)
- Origin: bats via unknown intermediate hosts to infect humans
- Uses angiotensin-converting enzyme 2 (ACE2), the same receptor as SARS-CoV, to infect humans
- Incubation period
 - Median 5.1 days (4.5 to 5.8 days)
 - 97.5% of those who develop symptoms will do so within 11.5 days ([mainland China data](#))
 - China CDC: 10-14 days
 - USA CDC: [2-14 days](#)
- Period of infectivity: 90% negative viral RNA tests on nasopharyngeal swabs by 10 days after the onset of symptoms ([Liu, 2020](#))
- Immunity: preliminary data showing that neutralizing antibodies ([Kai-Wang To, 2020](#); [Ju, 2020](#))

March 2020: recap

30 March 2020

Imperial College COVID-19 Response Team

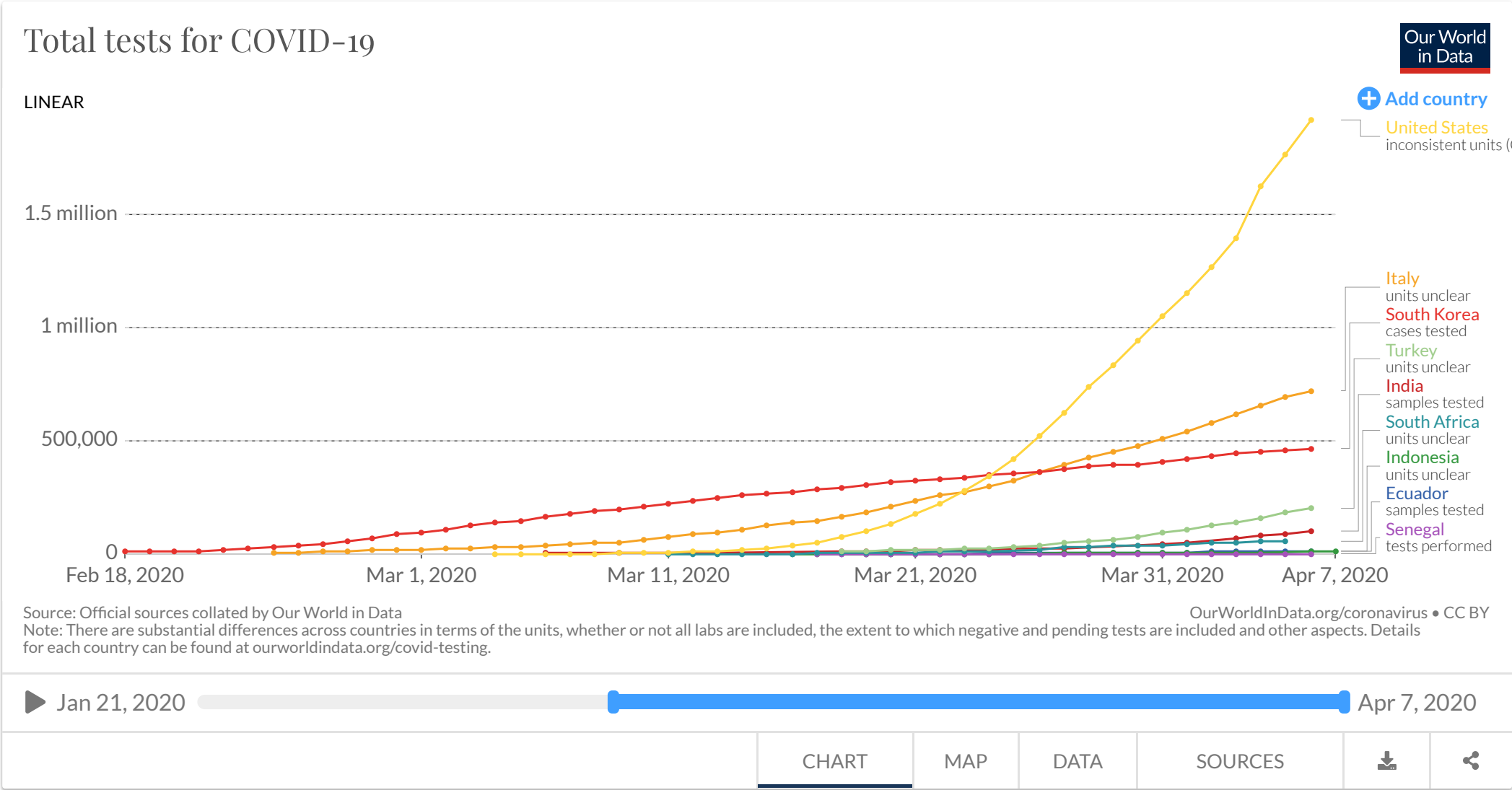


Imperial College London, R-13

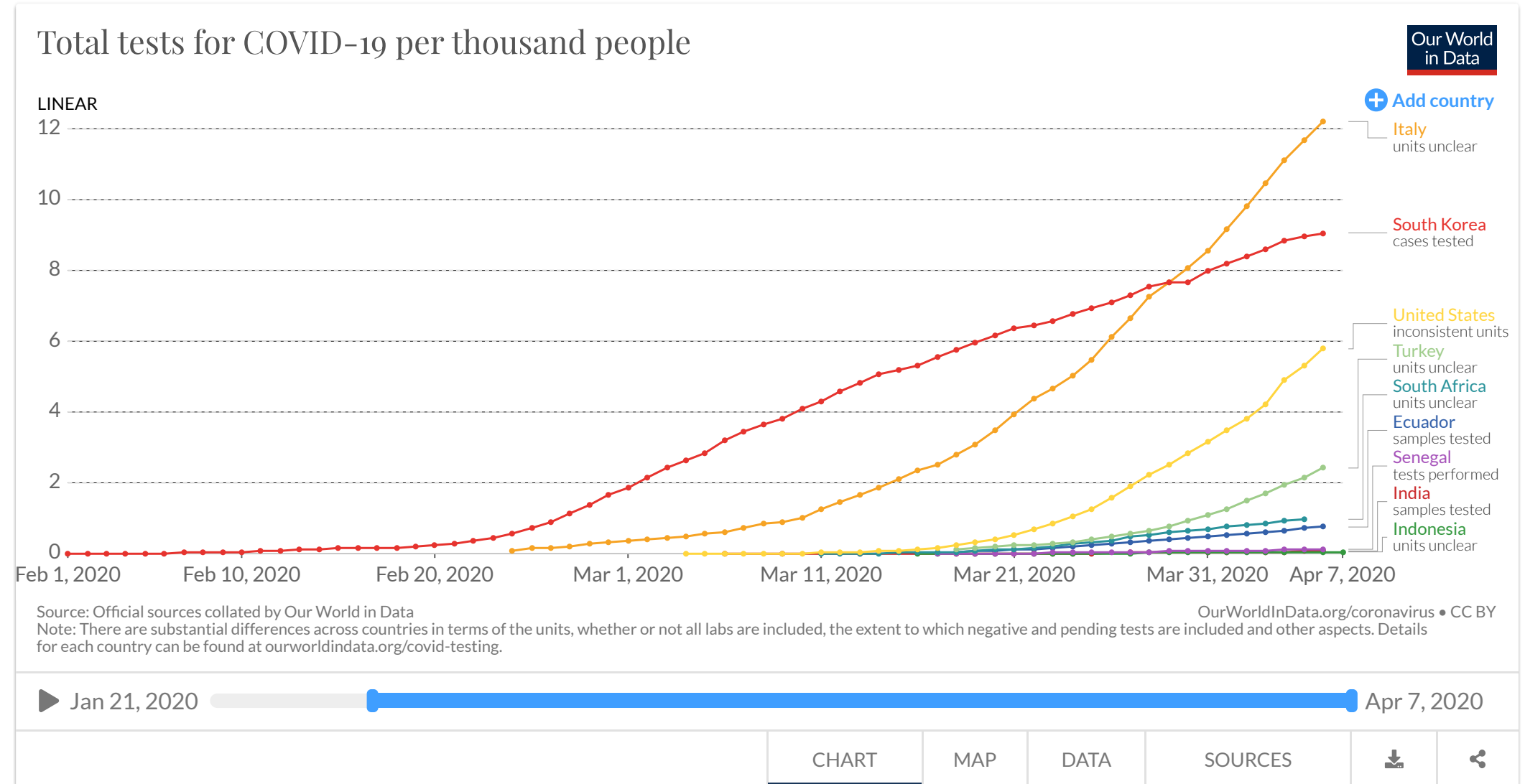
Testing for COVID-19

- Different testing capacity/kits
- Different ways of recording/releasing/sharing data
- Probability of being tested is not independent of disease severity and of the outcome
- RT-PCR:
 - Tests are not perfect
 - Analytical sensitivity 95%
 - Positive (COVID-19_N_P) – positive for all targets detected ($Ct < 40$)
 - Analytical Specificity: no cross-reactivity ([FDA, 2020](#))
- No reliable data on comparative accuracy of oropharyngeal vs nasopharyngeal swabs for diagnosis of COVID-19 ([The Centre for Evidence-Based Medicine, Oxford University](#))

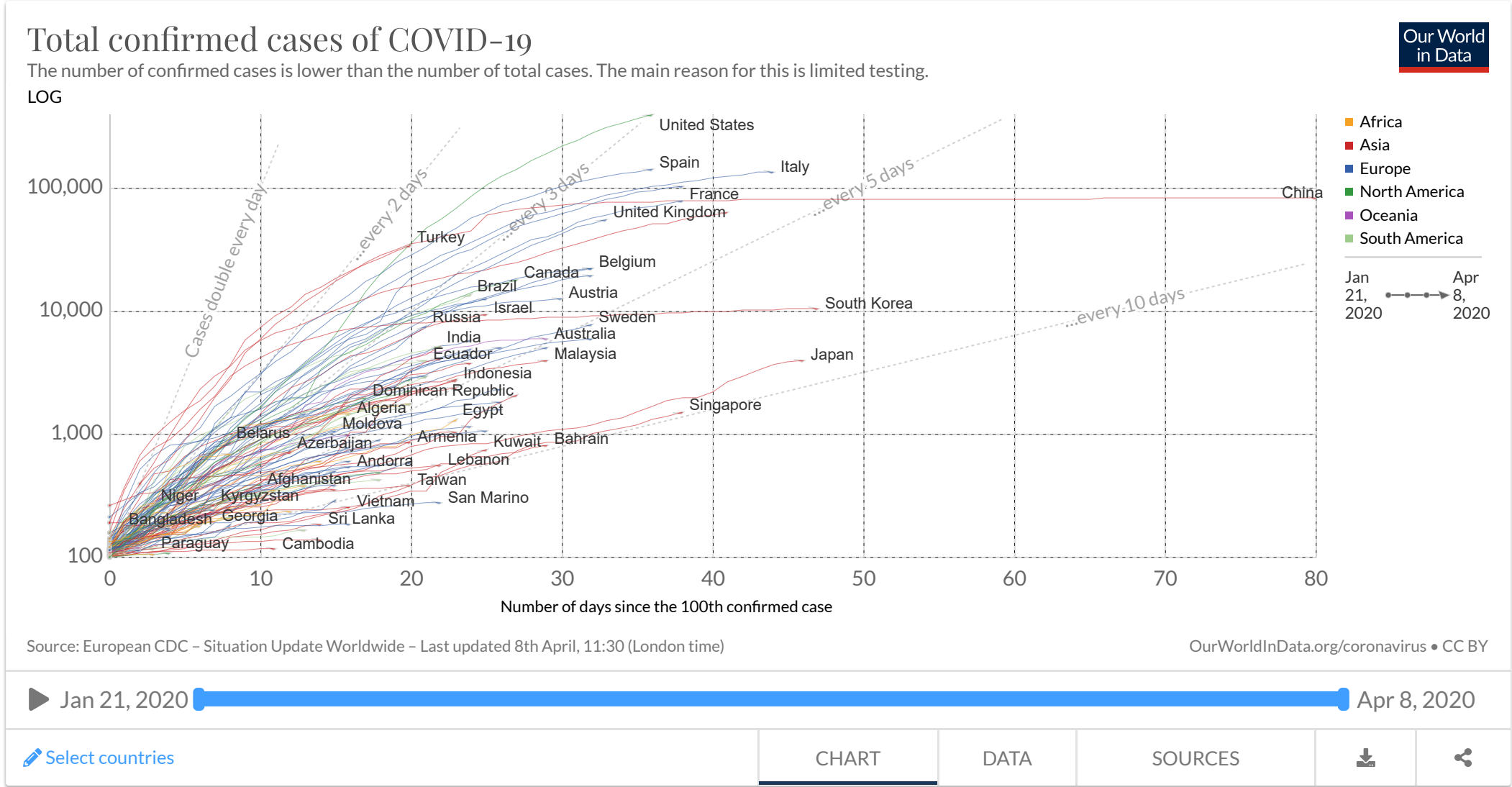
Total number of tests for COVID-19



Tests per 1 million population



Number of registrered/confirmed COVID-19 cases

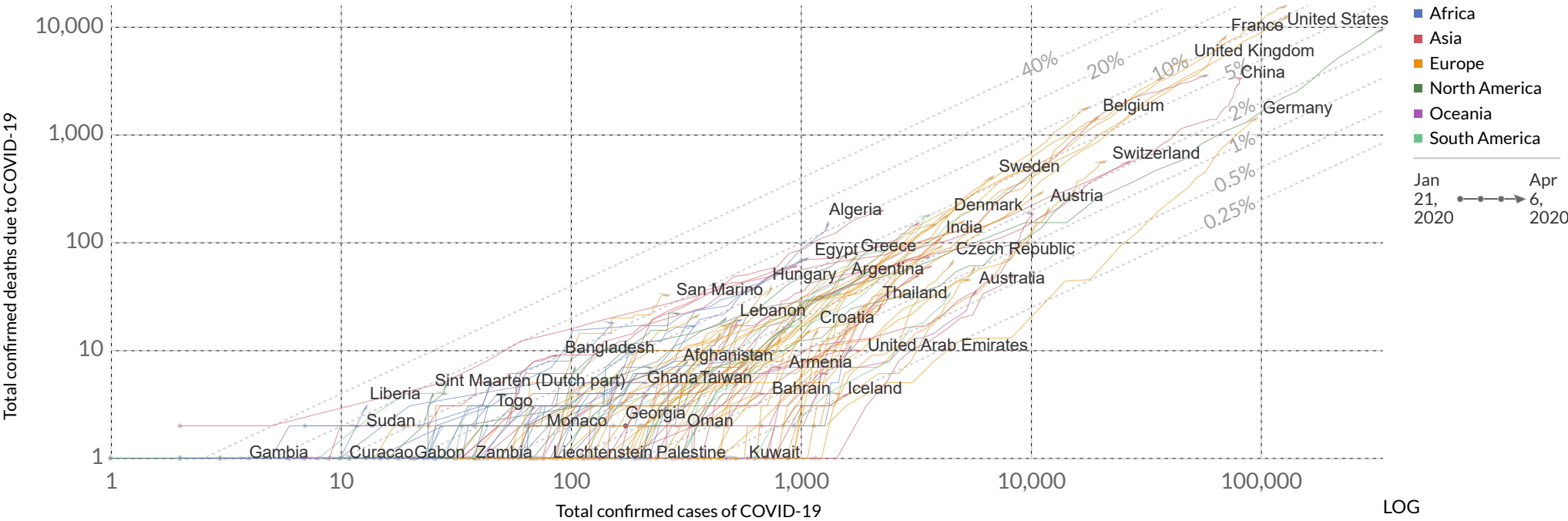


Number of registered/confirmed COVID-19 cases and case-fatality rates

Our World
in Data

COVID-19: Total confirmed cases vs. Total confirmed deaths, Jan 21, 2020 to Apr 6, 2020

The number of confirmed cases is lower than the number of total cases. The main reason for this is limited testing.
The grey lines show the corresponding case fatality rates, CFR (the ratio between confirmed deaths and confirmed cases).



Source: European CDC – Situation Update Worldwide – Last updated 8th April, 11:30 (London time) OurWorldInData.org/coronavirus • CC BY

▶ Jan 21, 2020 Apr 8, 2020

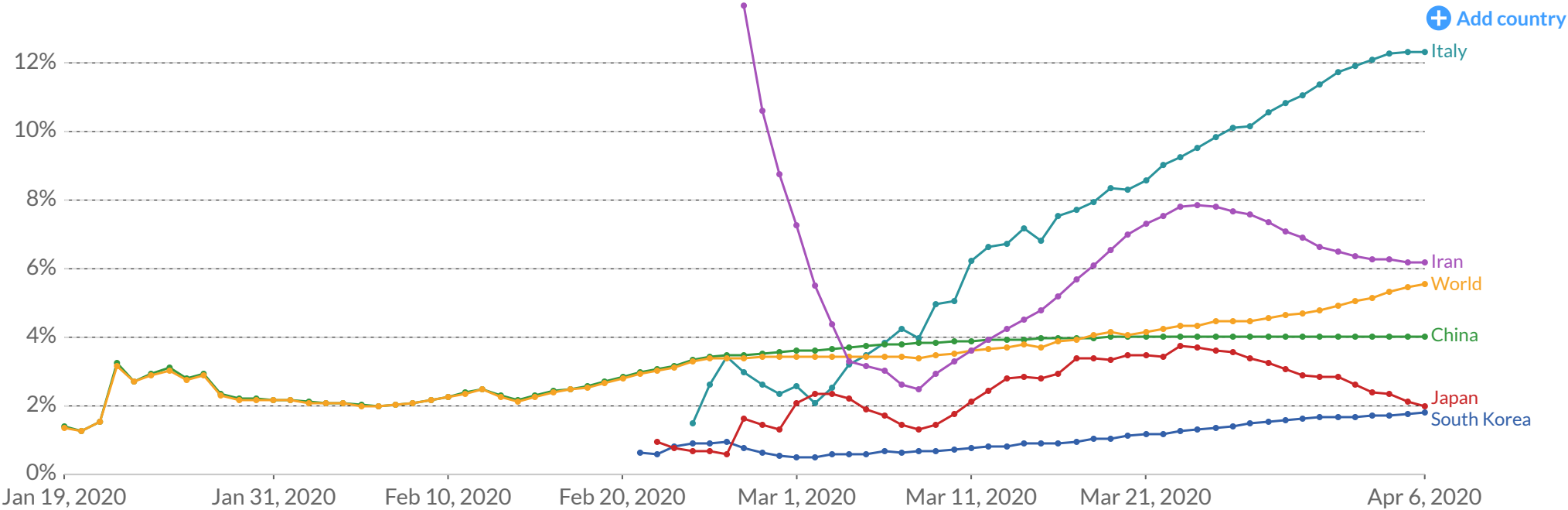
Select countries CHART DATA SOURCES  

Case-fatality rates among registrered/confirmed COVID-19 cases



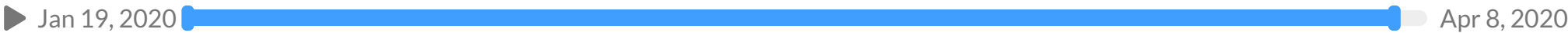
Case fatality rate of the ongoing COVID-19 pandemic

The Case Fatality Rate (CFR) is the ratio between confirmed deaths and confirmed cases. During an outbreak of a pandemic the CFR is a poor measure of the mortality risk of the disease. We explain this in detail at OurWorldInData.org/Coronavirus



Source: European CDC – Situation Update Worldwide – Last updated 8th April, 11:30 (London time)
Note: Only countries with more than 100 confirmed cases are included.

OurWorldInData.org/coronavirus • CC BY



CHART

MAP

DATA

SOURCES

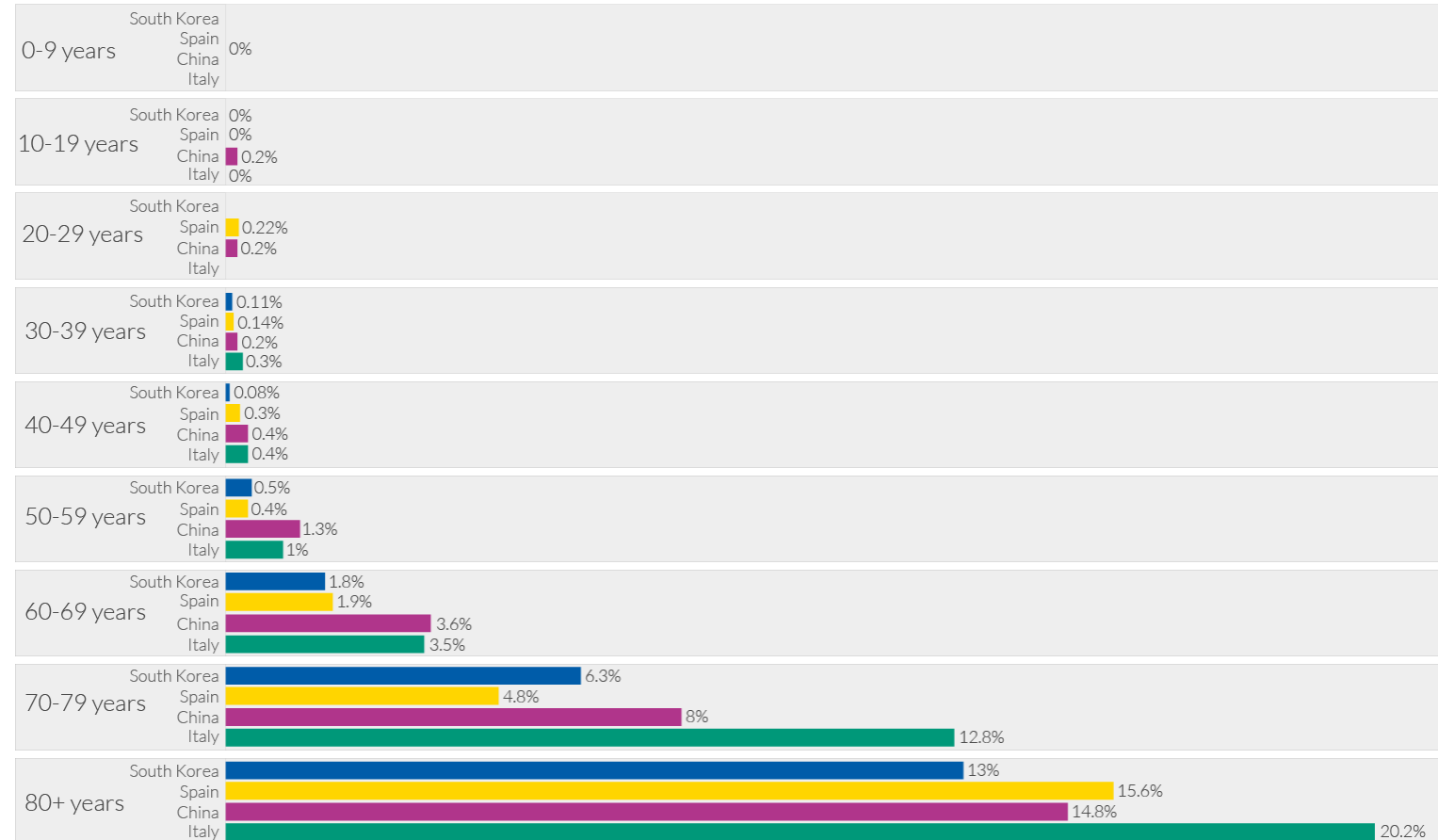


Coronavirus: case fatality rates by age

Case fatality rate (CFR) is calculated by dividing the total number of confirmed deaths due to COVID-19 by the number of *confirmed* cases.

Two of the main limitations to keep in mind when interpreting the CFR:

- (1) many cases within the population are unconfirmed due to a lack of testing.
- (2) some individuals who are infected will eventually die from the disease, but are still alive at time of recording.



Note: Case fatality rates are based on confirmed cases and deaths from COVID-19 as of: 17th February (China); 24th March (Spain); 24th March (South Korea); 17th March (Italy).

Data sources: Chinese Center for Disease Control and Prevention (CDC); Spanish Ministry of Health; Korea Centers for Disease Control and Prevention (KCDC).

Onder G, Rezza G, Brusaferro S. Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy. *JAMA*.

[OurWorldinData.org](https://www.ourworldindata.org) - Research and data to make progress against the world's largest problems.

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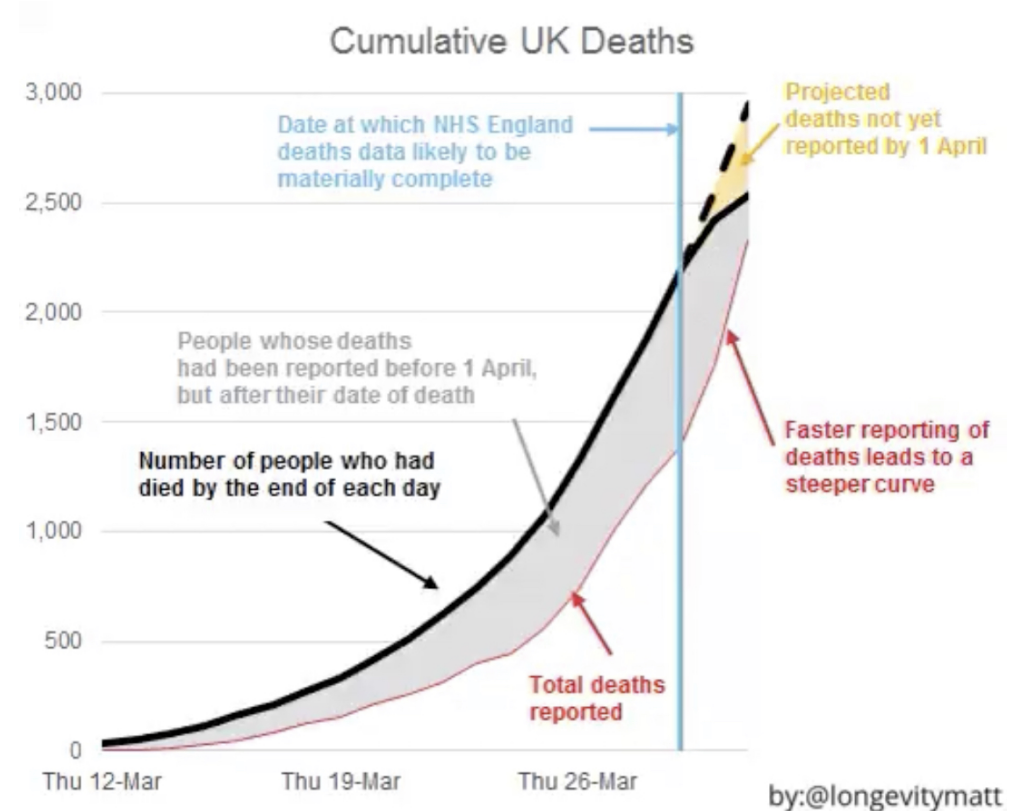
Beware of bias when interpreting case-fatality rate

- The data we use to estimate the CFR are often gathered for other purposes
- Challenging & constantly changing circumstances
- Preferential testing and counting of severe cases → overestimation
- At any point during ongoing epidemic we haven't yet observed disease outcomes for everyone → underestimation
- Delayed reporting: outcomes observed now are reported later
- Forward contact tracing → pre-symptomatic individuals → less prone to bias CFR estimates
- Comparison of CFR across groups
 - E.g., hospitalized vs non-hospitalized → multiple competing biases
 - Survivorship
 - Selection
 - Confounding
- Inference is never based on available data alone
 - Data collection + what we did not collect + what we collected + assumptions

Delayed reporting

To summarise, I think it's better to use the NHS England deaths data to illustrate progression of UK deaths and as a starting point for projections - taking the difference between the total daily death figures from the DHSC gives a misleading shape. 14/ pic.twitter.com/5cQwoXYyUI

— Matt Fletcher (@longevity matt) April 7, 2020



Asymptomatic or pre-symptomatic?

This is a misreading of the data from China, interpreting numbers from one population as being from another. Please see attached and withdraw the manuscript immediately

pic.twitter.com/JTYqMmuCdF

— Yaneer Bar-Yam (@yaneerbaryam)

April 3, 2020

Where do pre-symptomatic and asymptomatic cases come from in China?

Chen Shen and Yaneer Bar-Yam
New England Complex Systems Institute
April 3, 2020

Comment on “Covid-19: four fifths of cases are asymptomatic, China figures indicate”

Michael Day [1] claims there are 78% asymptomatic cases in China based on the daily report of China National Health Commission on COVID-19 cases. The report is based on an incorrect reading of Chinese reports [2], and both its scientific and other inferences are incorrect. Given the importance of these inferences, the article should be retracted immediately.

In particular, the article incorrectly assumes the report from China about 36 symptomatic and 130 asymptomatic are both from the same population. It also assumes that the asymptomatic cases are not pre-symptomatic, i.e. they may develop symptoms later, typically within a few days. Both these assumptions are incorrect and lead to an incorrect understanding and conclusions.

For clarity, we report below the details of the Chinese report for March 31 through April 2. The newly reported results by China require careful interpretation as we learn what each category represents.

For background, there are 3 distinct populations that the Chinese reports refer to, **A: International arrivals**, **B: Quarantined close contacts**, **C: The general public**. Understanding that there are more than one populations is essential to understanding the Chinese reports.

CHINESE REPORTS

March 31 (reported one day later on April 1, this is the report Day[1] cites):

- 36 new symptomatic, 35 from A
- 130 new asymptomatic from A, B, and C

Comment: If these were from the same population, then the percentage of asymptomatic would be $130/(130+36)=78\%$. However this is not the case, as most of the symptomatic individuals are from population A and most of the asymptomatic are from population B and C (see subsequent days).

April 1:

- 35 new symptomatic, all from A
- 55 new asymptomatic, 17 from A
- 9 asymptomatic cases convert on April 1 to symptomatic, all from A
- 226 cumulative asymptomatic from A

Comment: We see that within population A, there are 35 new symptomatic and 17 new asymptomatic for this day. However, the statement that there are conversions shows they may be pre-symptomatic rather than asymptomatic cases

April 2:

- 31 new symptomatic, 29 from A
- 60 new asymptomatic, 7 from A
- 7 asymptomatic cases convert on April 2 to symptomatic, all from A
- 221 cumulative asymptomatic from A

Comment: As a result, within A, 29 are new symptomatic, 7 are new asymptomatic

To understand the number of cumulative asymptomatic cases from A on April 2 requires additional information from the Chinese report. The report states that 101 asymptomatic cases, 5 of which from A, are released from medical observation on the day of the report, after a 2-week quarantine and consecutive negative test results. On April 2, asymptomatic cases from A start at 226, there are added 7 new imported asymptomatic cases, subtracted 7 converted to symptomatic, and subtracted 5 released, leading to the 221 cumulative asymptomatic from A.

We note that the asymptomatic number from B and C is much larger than that from A (849:226 as of April 1), but the 16 conversions are all from A. This suggests that many of the current reported asymptomatic cases from international arrival are pre-symptomatic. The high ratio between asymptomatic cases from B and C compared to A makes sense due to the presence of long term asymptomatic cases, that continue to test positively, remaining as a residual from the large number of cases in China.

REFERENCES

- [1] BMJ 2020;369:m1375
- [2] <http://www.nhc.gov.cn/xcs/yqtb/202004/28668f987f3a4e58b1a2a75db60d8cf2.shtml>
<http://www.nhc.gov.cn/xcs/yqtb/202004/bc27dc3c4a9544b081e2233537e762c3.shtml>
<http://www.nhc.gov.cn/xcs/yqtb/202004/4786774c1fd84e16b29d872f95241561.shtml>

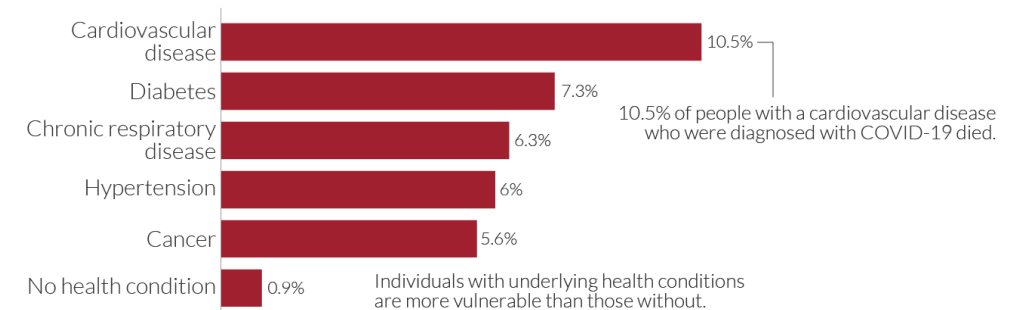
Risk factors for severe COVID-19 illness

- Age 60+
- Comorbidities
 - Cardiovascular disease
 - Diabetes mellitus
 - Chronic lung disease
 - Hypertension
 - Cancer
 - Chronic kidney disease
- Sex
 - China: larger proportion of men was in deceased group than that in recovered group (73% vs 55%) ([Jian-Min Jin, 2020](#); [Chen, 2020](#))
 - Italy: overall CFR of 11.4% in men vs 9.2% in women ([Epidemia COVID-19, Aggiornamento nazionale](#))

Coronavirus: early-stage case fatality rates by underlying health condition in China

Our World
in Data

Case fatality rate (CFR) is calculated by dividing the total number of deaths from a disease by the number of confirmed cases. Data is based on early-stage analysis of the COVID-19 outbreak in China in the period up to February 11, 2020.



Data source: Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. Vital surveillances: the epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19)—China, 2020. China CDC Weekly.
[OurWorldinData.org](#) - Research and data to make progress against the world's largest problems. Licensed under CC-BY by the authors.

Treatment of COVID-19

- No specific treatment available
 - Oxygenation support for severely ill
- Clinical trials for variety of agents (antiviral, immune modulators, antibacterial, monoclonal antibodies, etc.)
 - Chloqoquine, hydroxychloroquine and azithromycin, tocilizumab, camostat mesilate, sargramostim, colchicine, imatinib, IFN β -1a, inhaled steroids, remdesivir, oseltamivir, etc. ([EU Clinical Trial Register; laegemiddelstyrelsen.dk](#))
 - Mind the comparison groups and design features
- Available results
 - Lopinavir-ritonavir vs standard care showed no decrease in mortality of COVID-19 patients ([Cao, 2020](#))
- Possible impact of SARS-CoV-2 epidemic on other ongoing clinical trials ([EMA, 2020](#))
- Need of high-quality evidence and responsible conduct of research

Study of chloroquine + azytromycin




International Journal of Antimicrobial Agents

Available online 20 March 2020, 105949

In Press, Journal Pre-proof ?



Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial

Philippe Gautret ^{a, b, §}, Jean-Christophe Lagier ^{a, c, §}, Philippe Parola ^{a, b}, Van Thuan Hoang ^{a, b, d}, Line Meddeb ^a, Morgane Mailhe ^a, Barbara Doudier ^a, Johan Courjon ^{a, f, g}, Valérie Giordanengo ^h, Vera Esteves Vieira ^a, Hervé Tissot Dupont ^{a, c}, Stéphane Honoré ^{i, j}, Philippe Colson ^{a, c}, Eric Chabrière ^{a, c}, Bernard La Scola ^{a, c}, Jean-Marc Rolain ^{a, c}, Philippe Brouqui ^{a, c}, Didier Raoult ^{a, c} 

Points of concern

- Design
 - In essence - observational study without adjustment for the sources of bias
- "Control group" ascertainment
 - Refused consent to receive active treatment → allocated to "control group"
 - Ethically and methodologically problematic
- Loss-to-follow-up (selection bias)
 - From 26 patients in "treatment group", 6 were excluded (4 out of 6 developed severe disease/died)
 - Could make the treatment look beneficial when it isn't
- Outcome (SARS-CoV-2+/- on day 6)
 - Dichotomization of viral load
 - Day 6
 - No biologic justification
 - Missing outcome data
 - Some patients were positive on day 6 but negative on day 9; one was negative on day 6 but positive on day 8
 - PCR procedure different from the official CDC protocol
 - Clinical relevance of the end-point

Dahly, Gates, Morris, 2020

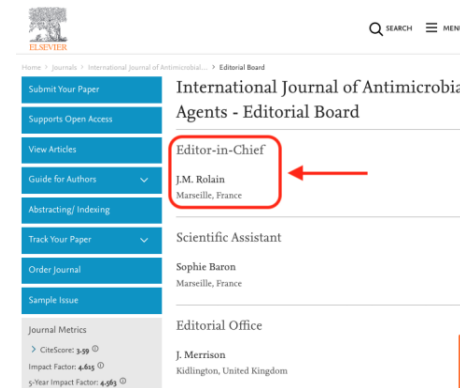
Ethical conduct of research

I asked Newsweek if they could add the link.

Here is that blog post, in case you wondered: <https://t.co/Ez5dnm8hoM>

— Elisabeth StayingAtHome
StayingAlive Bik (@MicrobiomDigest)
April 7, 2020

- Peer-review?
- Conflict of interests



Vaccine development

- **Time** 18 months
- **Funding**
 - Wellcome trust: raising **\$8bn**
 - Coalition for Epidemic Preparedness Innovations (Cepi) + Novavax + University of Oxford
 - Established funding **\$4.4m** and raising **\$2bn** ([Guardian, March 2020](#))
- Phase 1 Clinical Trial Of COVID-19 vaccine candidates ([WHO, March 2020](#))
- Countries cannot afford "herd immunity" approach
 - 0.41% to 15% of population are infected across European countries by the end of March 2020 ([Imperial College London, R-13](#))

9/ Substituting in for R, we get:

$$R < 1 \Rightarrow R_0 * (\% \text{ susceptible}) < 1 \Rightarrow \% \text{ susceptible} < 1/R_0$$

Solving for $R_0 = 3$, we get $\% \text{ susceptible} < 33.3\%$

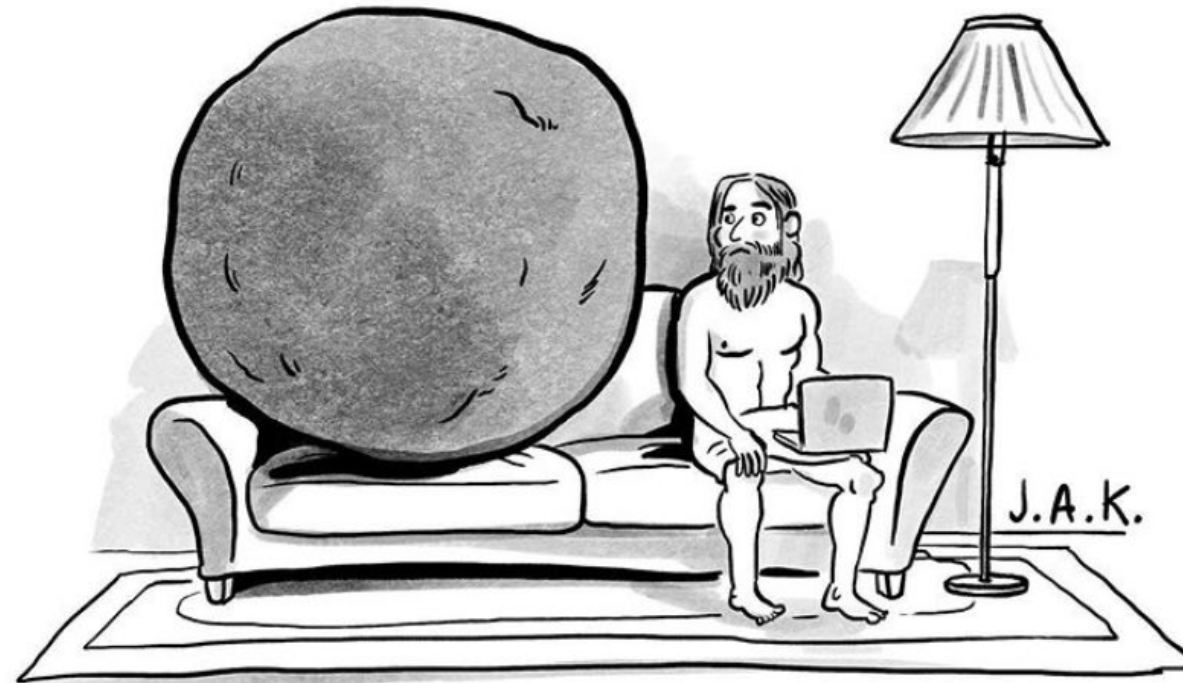
In other words, as long as more than 33% of the population is susceptible, the disease spreads

— Health "Physical Isolation" Nerd (@GidMK) [April 7, 2020](#)

Global consequences

- Economics-related
 - Plummeted stock markets
 - Jobs' losses and unemployment
 - Recession
- Healthcare-related
- People's lives
- Poorest countries and communities are most affected and cannot cope alone
- "A Once-in-a-Century Pandemic?" [Bill Gates](#)
 - "Governments and industry will need to come to an agreement"

Thank you for attention



SISYPHUS WORKS FROM HOME

Useful resources

- <https://ourworldindata.org/coronavirus#>
- <http://www.imperial.ac.uk/mrc-global-infectious-disease-analysis/covid-19/report-13-europe-npi-impact/>
- <https://twitter.com/EpiEllie>
- <https://twitter.com/mlipsitch>
- https://twitter.com/CT_Bergstrom