AARHUS UNIVERSITY

SARS-CoV-2 Pandemic 2019-now

Introduction to the little known

Elena Dudukina, Raquel Raquel Avelar, Deirdre Cronin Fenton

2020-04-07

Epidemics are not new to human history

- **1348-1351 Bubonic plague** (Second plague pandemic, or "Black death")
  - Bacterium *Yersinia pestis*
  - Estimated 25-75 million deaths in Europe and Asia
  - Reduced 30% to 60% of Europe's population (Austin Alchon, 2003)
  - No treatment

*"The trend of recent research is pointing to **45–50% of the European population dying during a four-year period***. *There is a fair amount of geographic variation. In Mediterranean Europe, areas such as **Italy, the south of France and Spain**, where plague ran for about four years consecutively, it was probably closer to **75–80% of the population**. In **Germany and England** it was probably closer to **20%**"* (Philip Daileader, The Late Middle Ages, 2007)

- **1918-1919** 1st pandemic caused by **H1N1 influenza virus** ("Spanish flu")
  - Basic reproductive number (R0): 1.5 (1.2–3.0)(Vynnycky, 2007)
  - ~ 500 million estimated infected (33% of the world's population) (Taubenberger, 2006)
  - 17 to 20 million deaths globally
  - Severe disease with case-fatality rate >2.5%
  - No treatment
  - No prevention (no vaccine)
- **2002-2004 SARS** (SARS-CoV virus)
  - Basic reproductive number (R0): 2.0-4.0 (WHO, 2003)
  - 8096 cases
  - ~774 deaths in 32 countries → case fatality rate 9.6% (WHO, 2004)
  - Vaccine inducing neutrolizing antibodies (Chien-Te Tseng, 2012)
- **2009** 2nd pandemic caused by **H1N1 influenza virus** (H1N1/09, or "Swine flue")
  - Basic reproductive number (R0): 1.5 (1.3–1.7)
  - ~ 0.7–1.4 billion estimated infected worldwide
  - ~ 151,700–575,400 estimated deaths worldwide
  - Vaccine available

- **2012-present MERS** (MERS-CoV)
  - Basic reproductive number (R0) <1 (WHO, 2019)
    - Heterogenous R0: 1.0-5.7 at the start of the outbreak → < 1.0 Bernard-Stoecklin, 2019
  - 2012-2016: 1841 laboratory confirmed cases → 80% in the Kingdom of Saudi Arabia
  - ~ 35% (n=652) died
- **2014-2016 Ebola**
  - Basic reproductive number (R0): 1.7-2.0 (WHO Ebola Response Team, 2016)
  - ~ 28,542 cases
  - ~ 11,299 deaths
  - CFR ~ 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

Rothman KJ, Modern Epidemiology, 3rd Edition

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

  Simulating individuals not the population groups

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

Dr. Samuel Jenness, 2020; Imperial College London

Key definitions

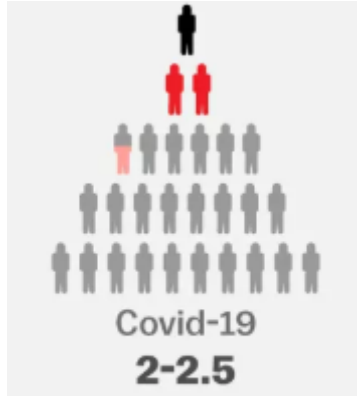
- Attack rate
  - The proportion of the population which contracts the disease fro the population at risk
- Case-fatality risk (CFR)
  - The probability that a person dies from an infection given that they are a case
- Infection-fatality risk (IFR)
  - Defines a case as a person who has shown evidence of infection, either by clinical detection of the pathogen or by seroconversion or other immune response
- Basic reproductive number **R0** (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

Basic Reproductive Number

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

- Mathematical modeling of transmission within populations



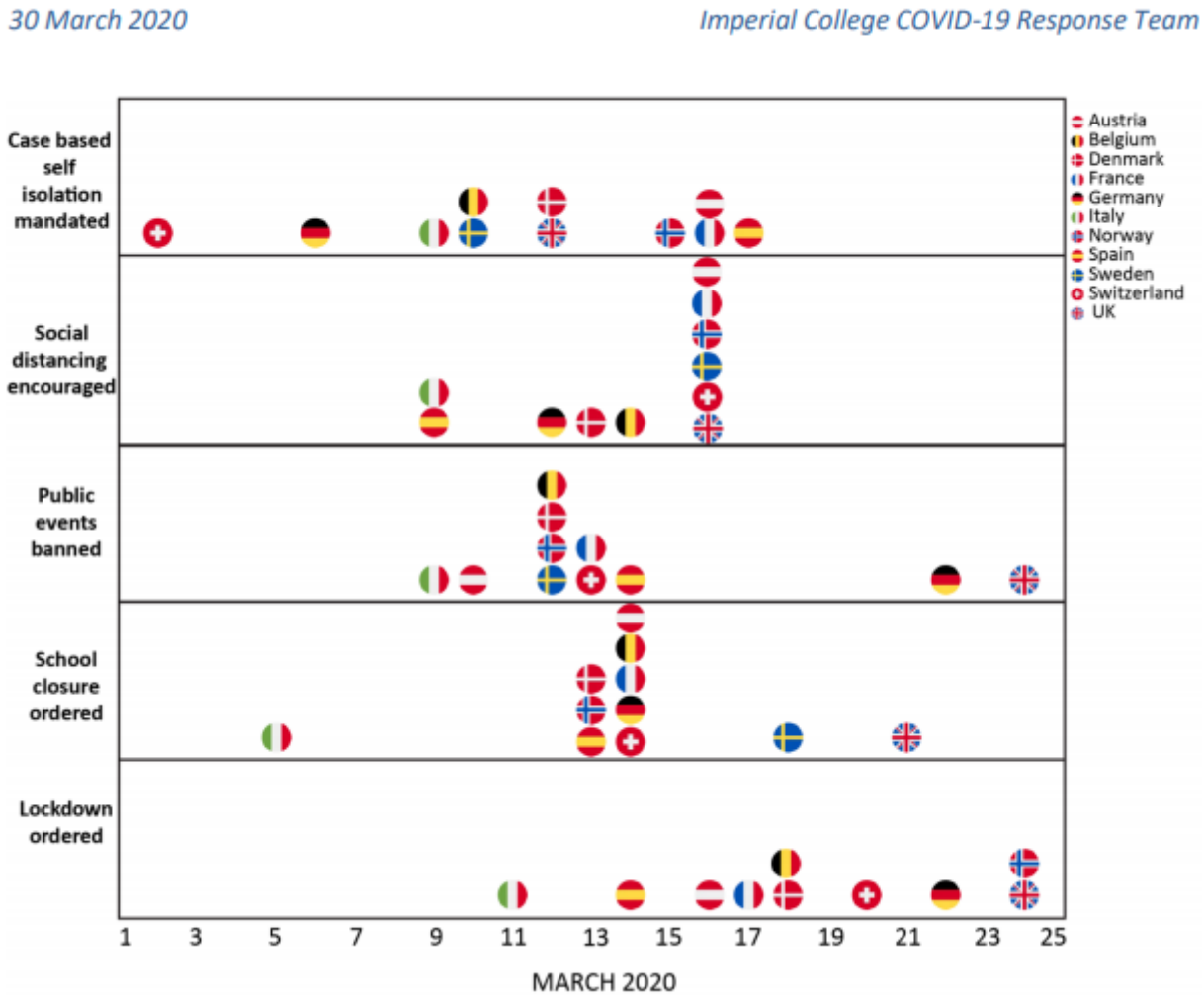
Vox, 2020

NEJM, 2020

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 (95% CI, 4.5 to 5.8 days), and 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 for neutralizing antibodies (Kai-Wang To, 2020; Ju, 2020)

March 2020: recap

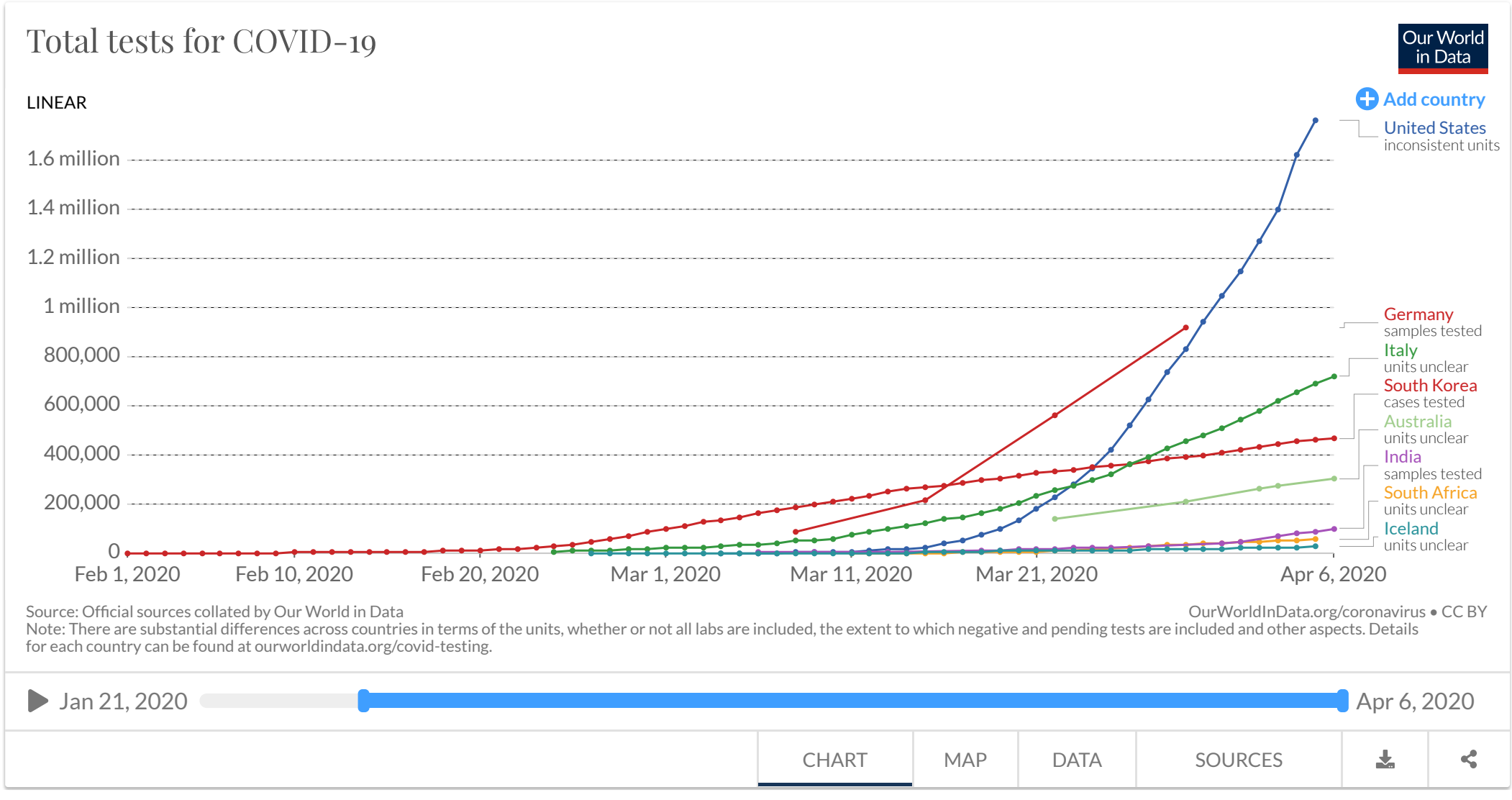


Imperial College London

Testing for COVID-19

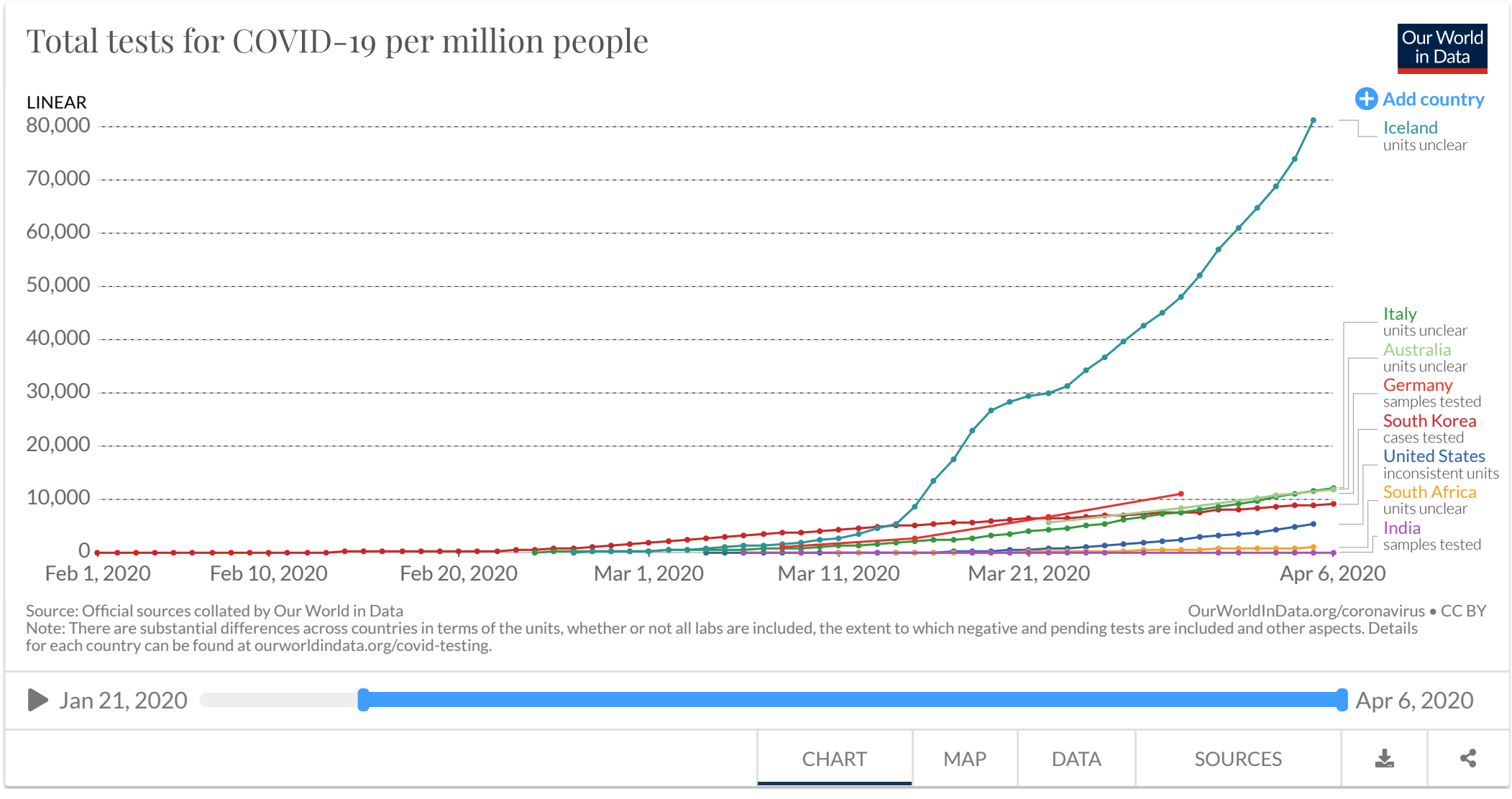
- Different testing capacity/kits
- Different ways of recording/sharing data
- Probability of being tested is not independent of disease severity and of the outcome
- RT-PCR:
    - Tests are not perfect
        - Analytical Sensitivity 95%
        - Positive (COVID-19_N_P) – positive for all targets detected (Ct < 40)
        - Analytical Specificity: no cross-reactivity
- No reliable data on comparative accuracy of oropharyngeal vs nasopharyngeal swabs for diagnosis of COVID-19

Total number of tests for COVID-19



Tests per 1 million population

AARHUS UNIVERSITY



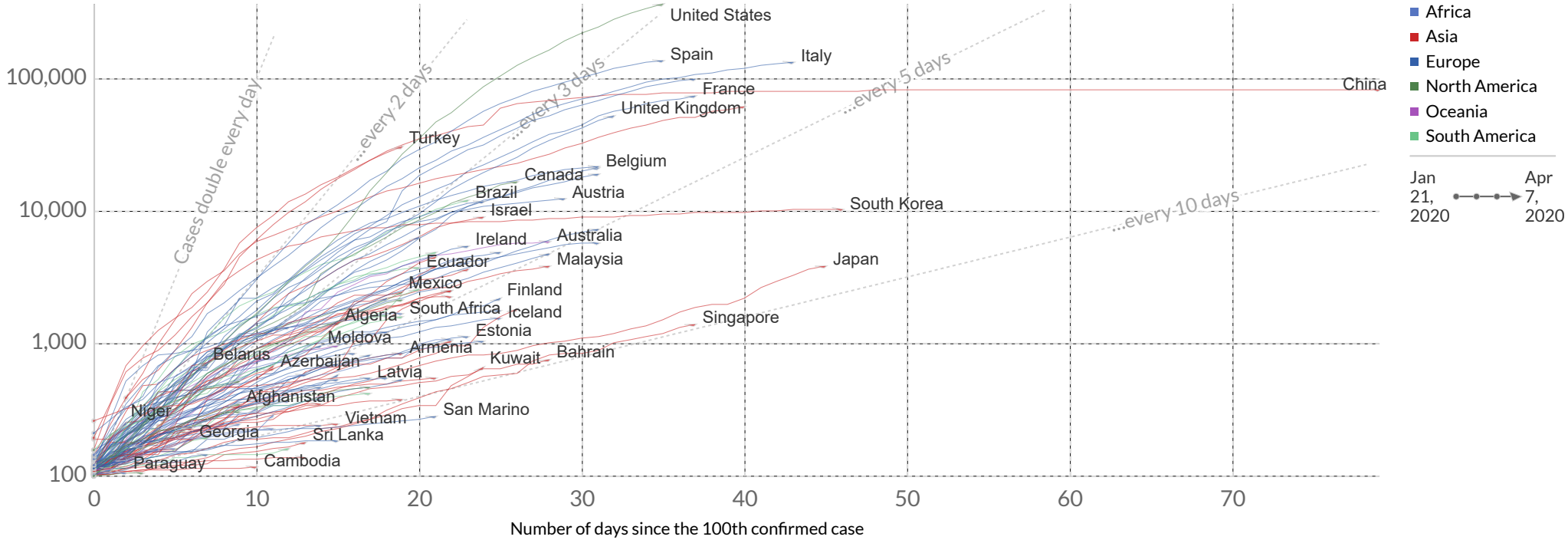
Number of registrered/confirmed COVID-19 cases

AARHUS UNIVERSITY

Total confirmed cases of COVID-19

The number of confirmed cases is lower than the number of total cases. The main reason for this is limited testing.

LOG



Source: European CDC – Situation Update Worldwide – Last updated 7th April, 12:15 (London time)

OurWorldInData.org/coronavirus • CC BY

Jan 21, 2020 — Apr 7, 2020

Select countries | CHART | DATA | SOURCES

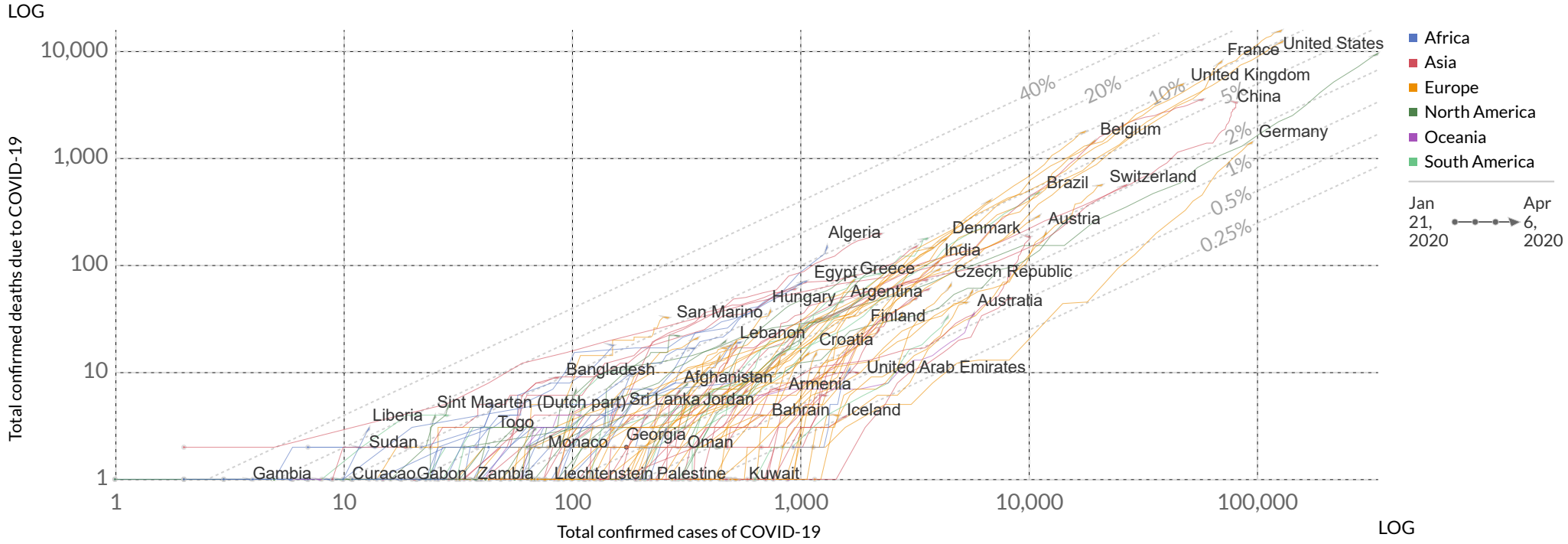
Number of registered/confirmed COVID-19 cases and case-fatality rates

AARHUS UNIVERSITY

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

Our World in Data

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 7th April, 12:15 (London time)

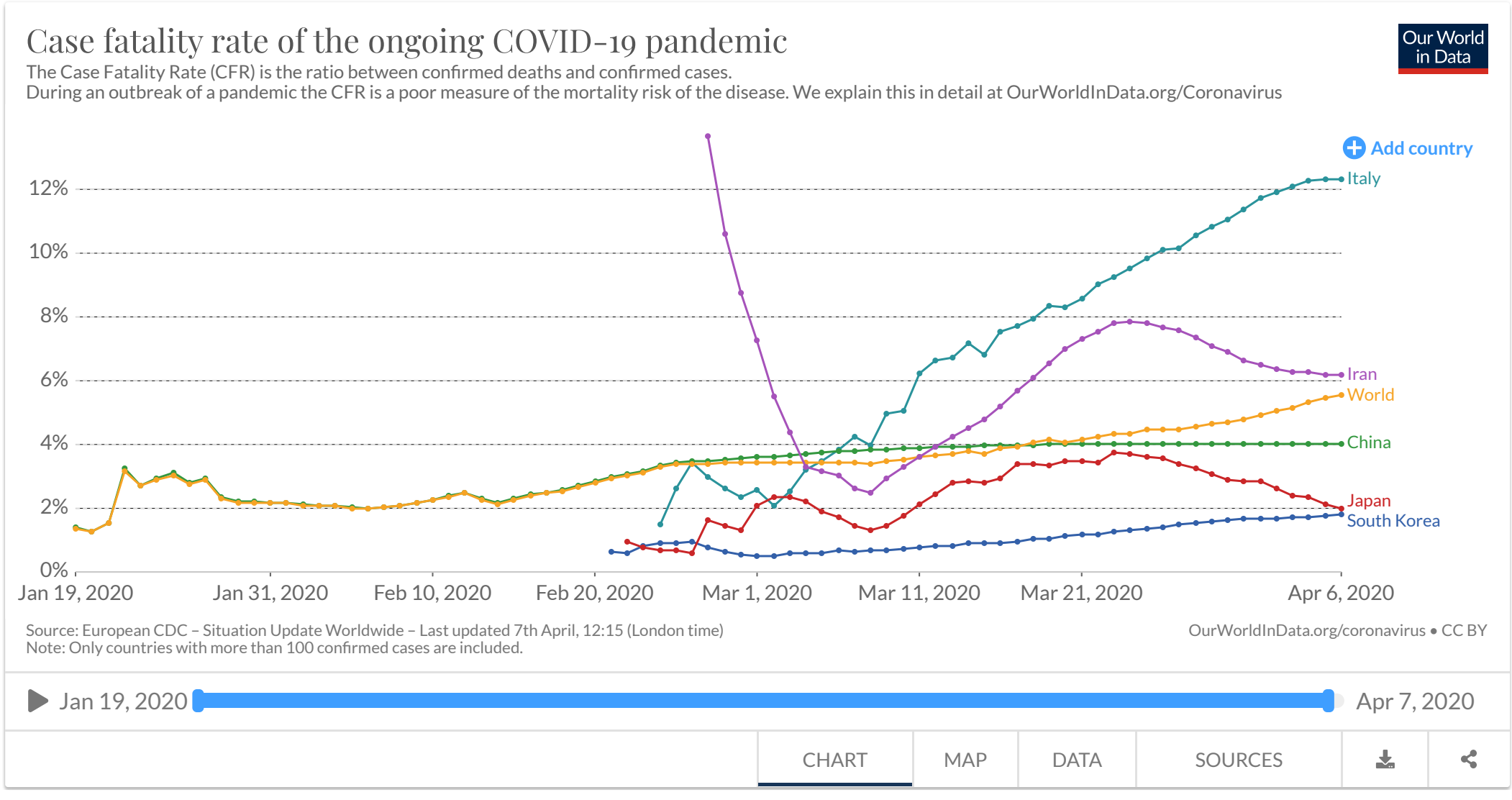
OurWorldInData.org/coronavirus • CC BY

Jan 21, 2020 — Apr 7, 2020

Select countries | CHART | DATA | SOURCES

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

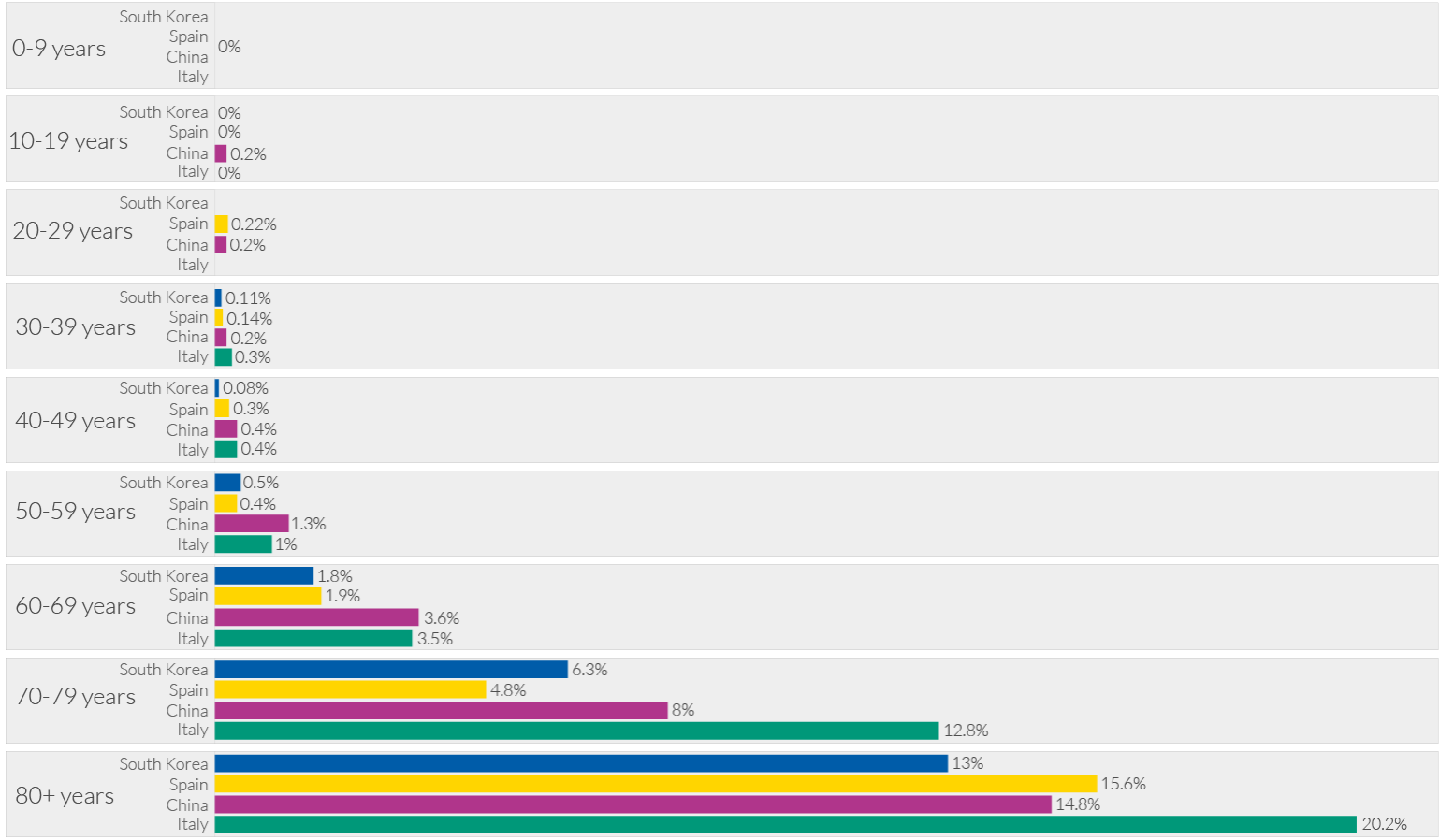
AARHUS UNIVERSITY



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*.

Beware of bias when interpreting case-fatality rate

AARHUS UNIVERSITY

- 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
        - Suvivorship
        - Selection
        - Confounding

- Inference is never based on available data alone
    - Data collection + what we did not collect + what we collected + assumptions

Lipsitch, 2015

Mind the populations

> This is a misreading of the data from China, interepreting 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.

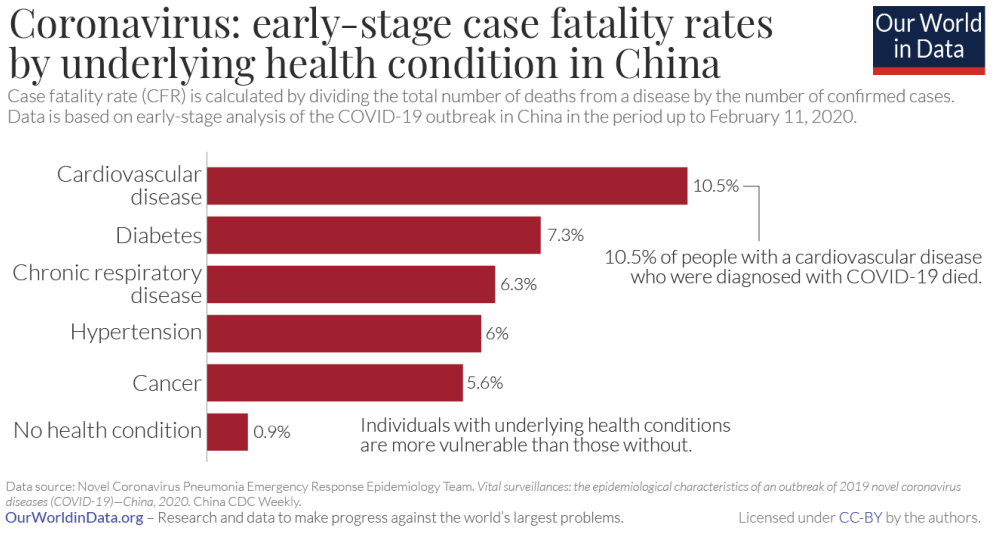
We note that the asymptomatic number from B and C is much larger than that from A (849:226 as of April 1), but the 16 conversions are all from A. This suggests that many of the current reported asymptomatic cases from international arrival are pre-symptomatic. The high ratio between asymptomatic cases 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/be27dc3c4a9544b081e2233537e762c3.shtml
http://www.nhc.gov.cn/xcs/yqtb/202004/4786774c1fd84e16b29d872f95241561.shtml

Risk factors for severe illness

- Age 60+
- Comorbidities
  - Cardiovascular disease
  - Diabetes mellitus
  - Hypertension
  - Chronic lung disease
  - Cancer
  - Chronic kidney disease
- Possibly sex
  - Larger proportion of men was in deceased group than that in recovered group (73% vs 55%)



Jian-Min Jin, 2020; Chen, 2020

Treatment of COVID-19

- No specific treatment available
  - Oxygenation support for severely ill
- Clinical trials for variety of agents (antiviral, immune modulators, etc.)
  - Chloqoquine, hydroxychloroquine and azithromycin, tocilizumab, camostat mesilate, sargramostim, colchicine, imatinib, IFNβ-1a, inhaled steroids, remdesivir, oseltamivir, etc. (EU Clinical Trial Register; laegemiddelstyrelsen.dk)
- 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

ELSEVIER

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 [e, 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
- Number of participants
- Potentially no peer review (pre-print vs printed version)
- "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

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 2002)

- Phase 1 Clinical Trial Of COVID-19 vaccine candidates (WHO, March 2020)

- Countries cannot afford "herd immunity" approach

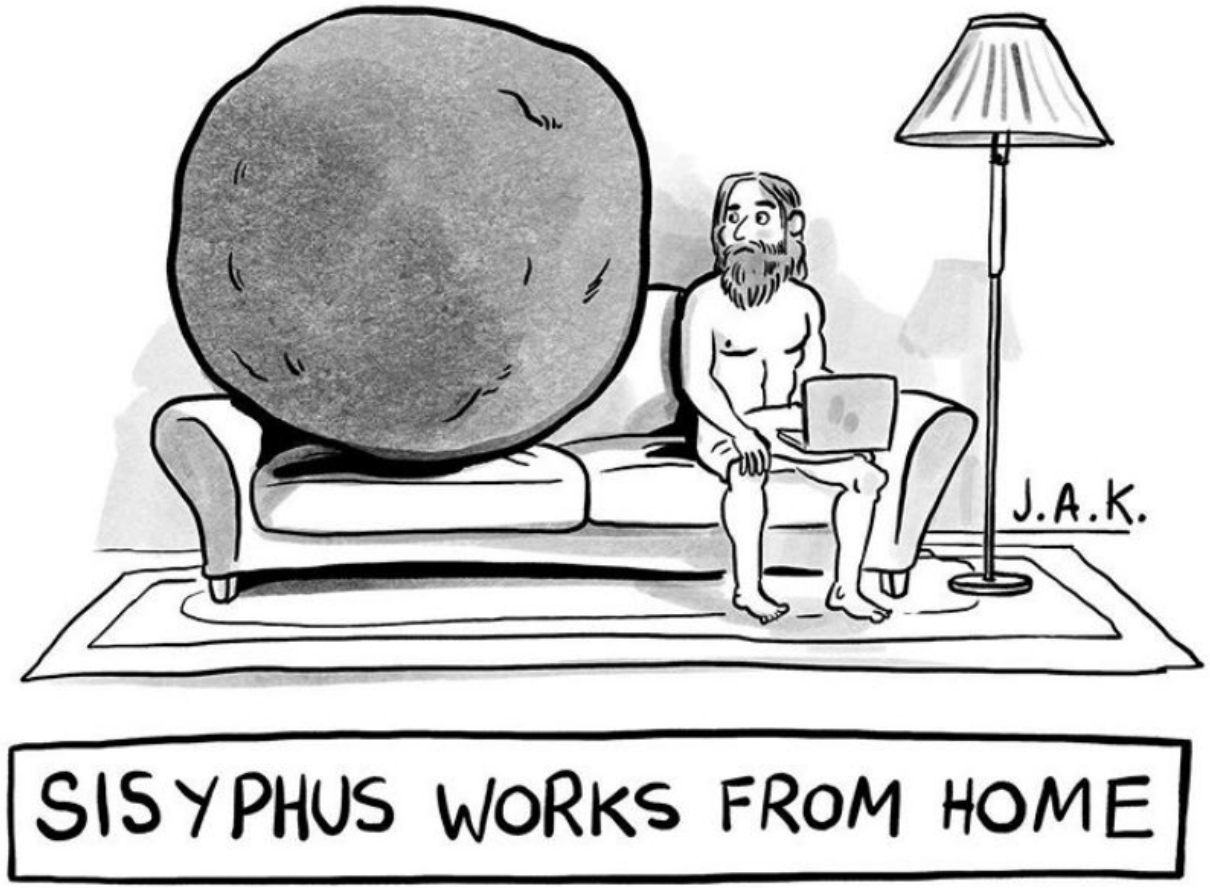
  - 0.41%-15% infected in Europe by the end of March 2020 Imperial College London

> 9/ Substituting in for R, we get:
>
> R<1 => R0*(% susceptible)<1 => %susceptible<1/R0
>
> Solving for R0 = 3, we get %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



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