SARS-CoV-2 Pandemic 2019-2020

Introduction to the little known

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

Infection states

- Transmission-Related

State of Infection	Definition	Alternative Terms
Preinfectious	Host is infected but has not become infectious	Latency, preinfective period
Infectious	Host is capable of transmitting agent to others	Contagiousness, infective period
Postinfectious	Host is no longer capable of transmission	Cure, postinfective period

Rothman KJ, Modern Epidemiology, 3rd Edition

Modeling infectious diseases

- Agent-based models
- Multi-level models
- Network models
- Compartmental models
  - SIR (Susceptible → Infectious → Recovered)
  - SEIR (Susceptible → Exposed → Infectious → Recovered)
  - SEIS (Susceptible → Exposed → Infectious → Susceptible)
  - Other modifications to accomodate duration of post-infection immunity, vaccination, etc.

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

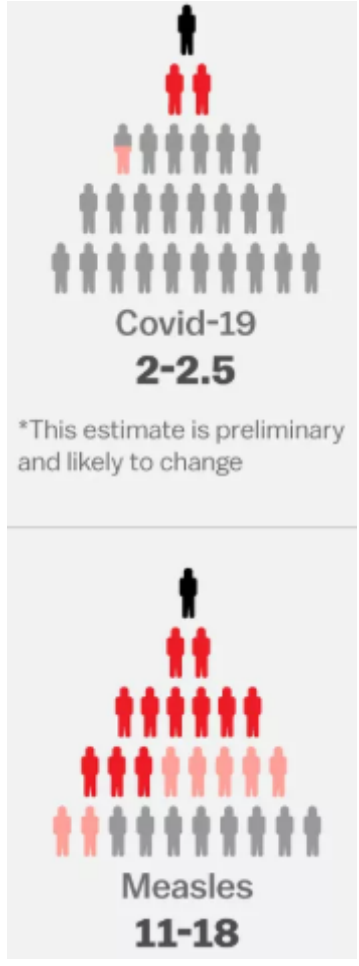
Lipsitch, 2015

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**

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

  - Mathematical modeling of transmission within populations



Vox, 2020

NEJM, 2020

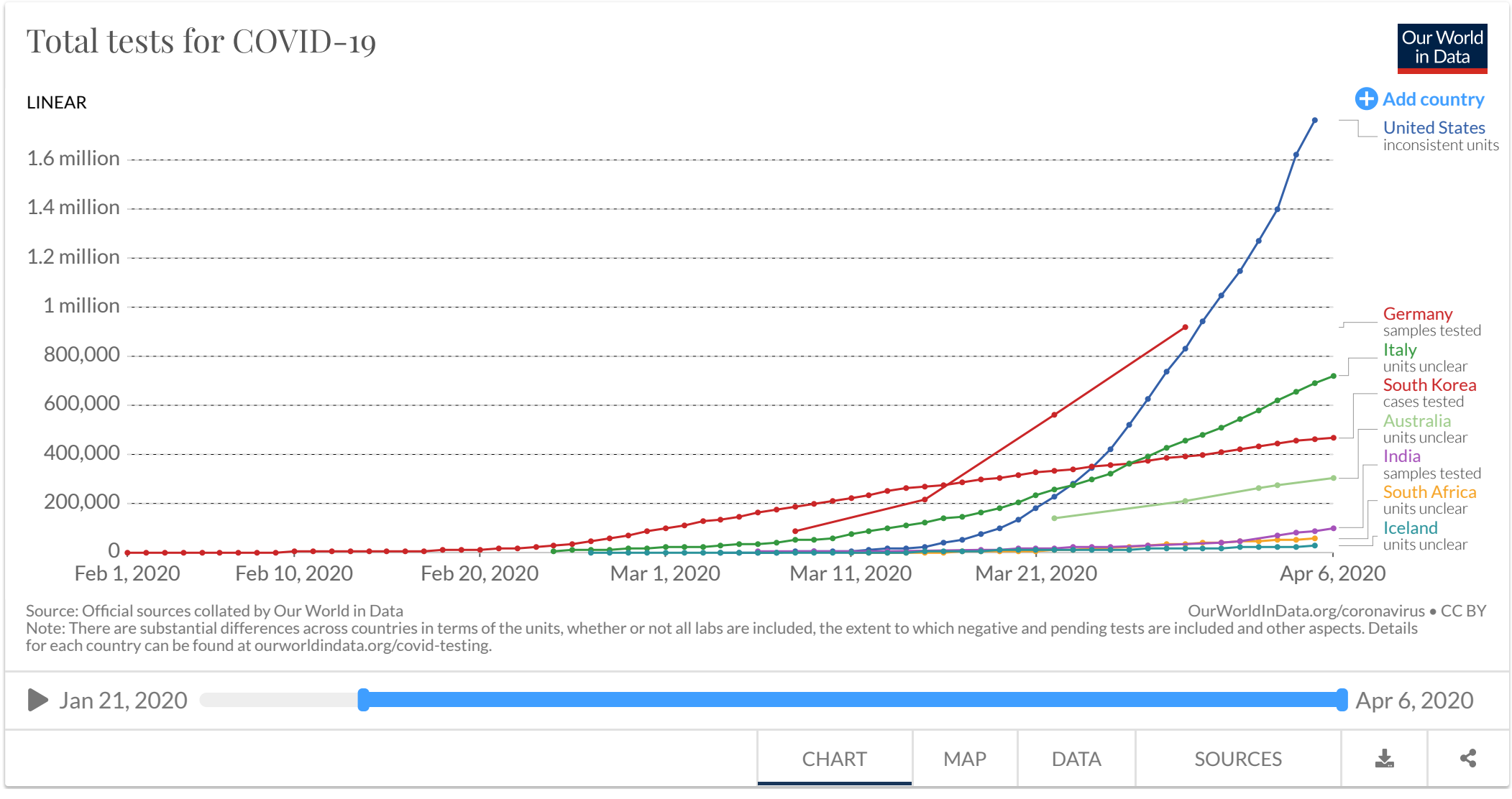
Coronavirus disease (COVID-19) outbreak

- 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)

Testing for COVID-19

- Different testing patterns/kits in different countries
- 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

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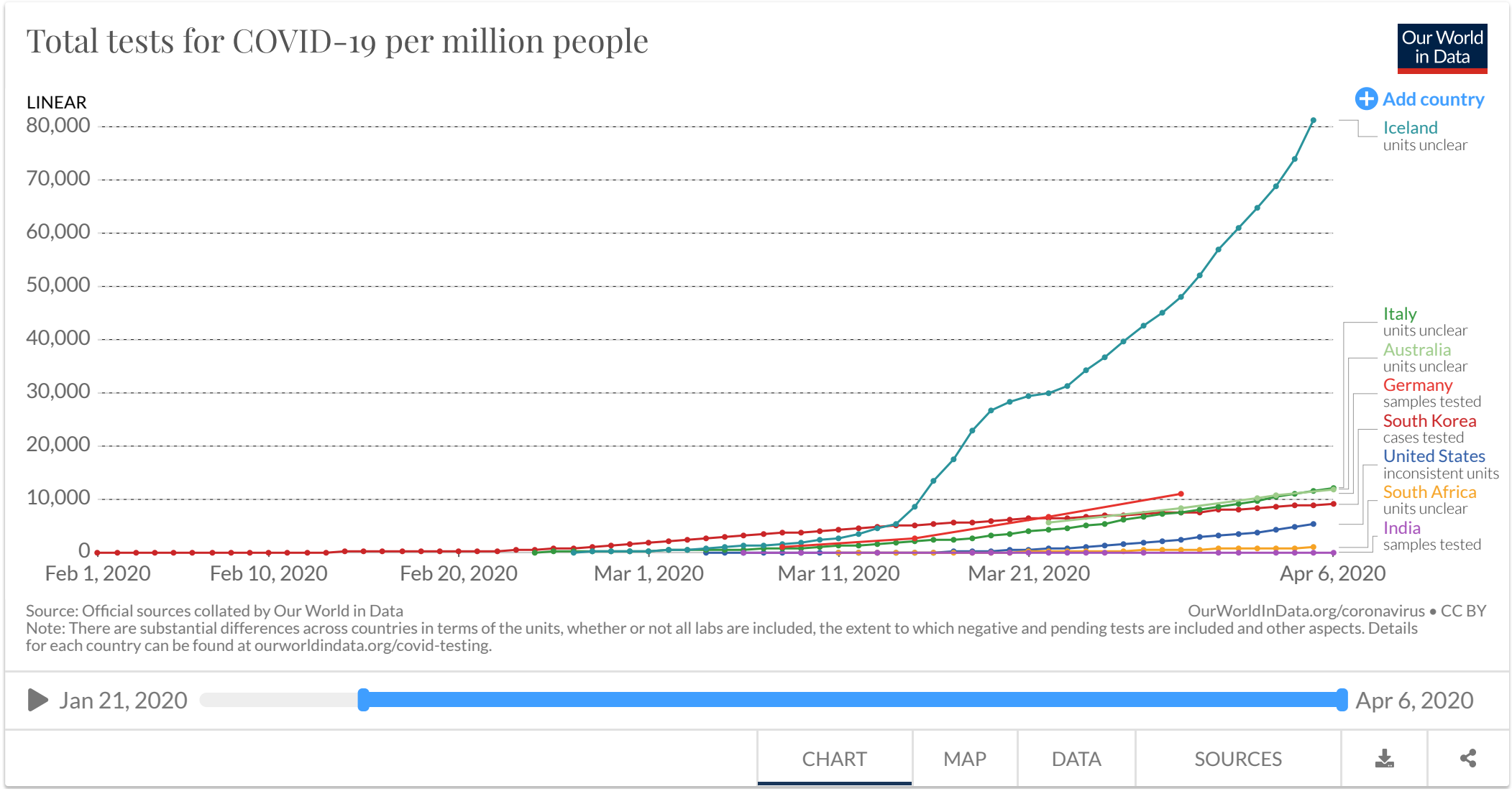

Number of registrered/confirmed COVID-19 cases

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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.

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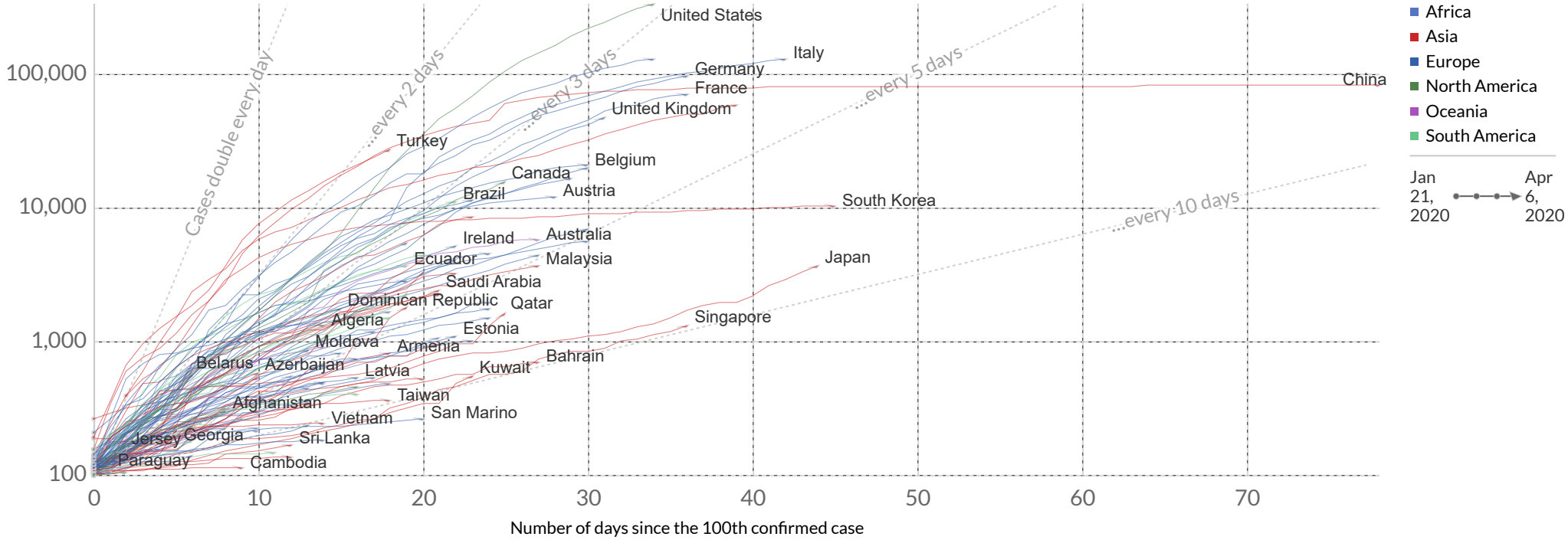

Source: European CDC – Situation Update Worldwide – Last updated 6th April, 12:00 (London time)

OurWorldInData.org/coronavirus • CC BY

Jan 21, 2020 — Apr 6, 2020

Select countries | CHART | DATA | SOURCES

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

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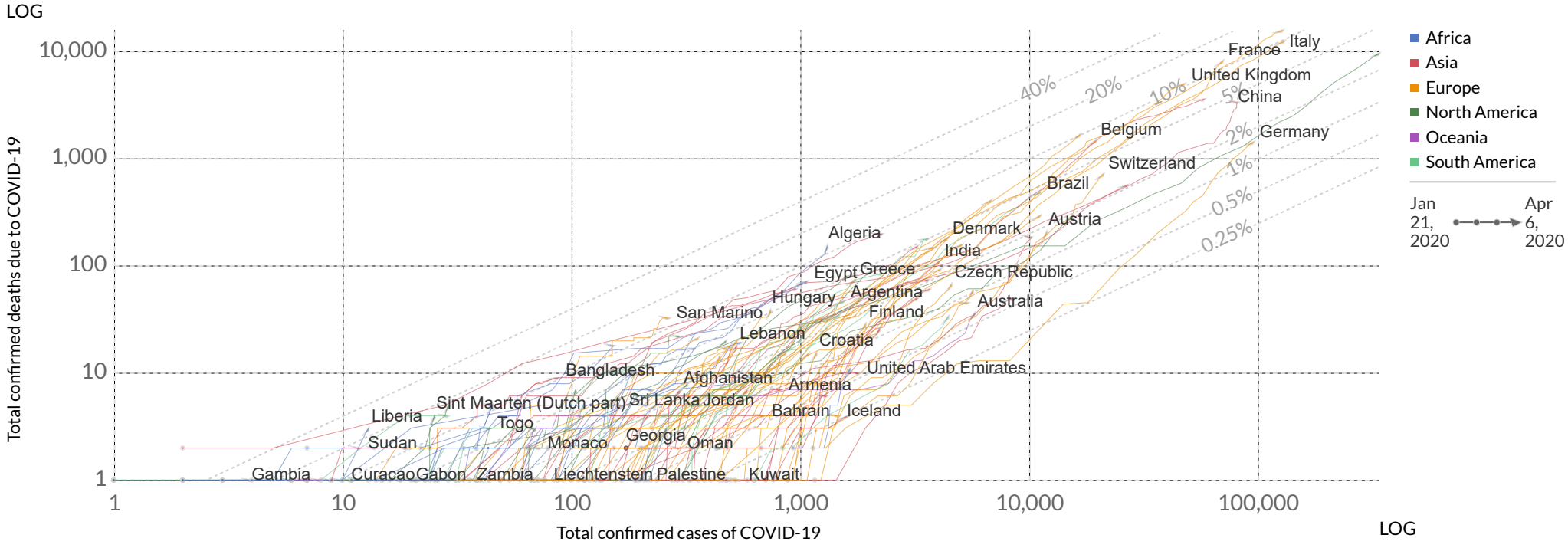
COVID-19: Total confirmed cases vs. Total confirmed deaths, Jan 21, 2020 to Apr 6, 2020

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).



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

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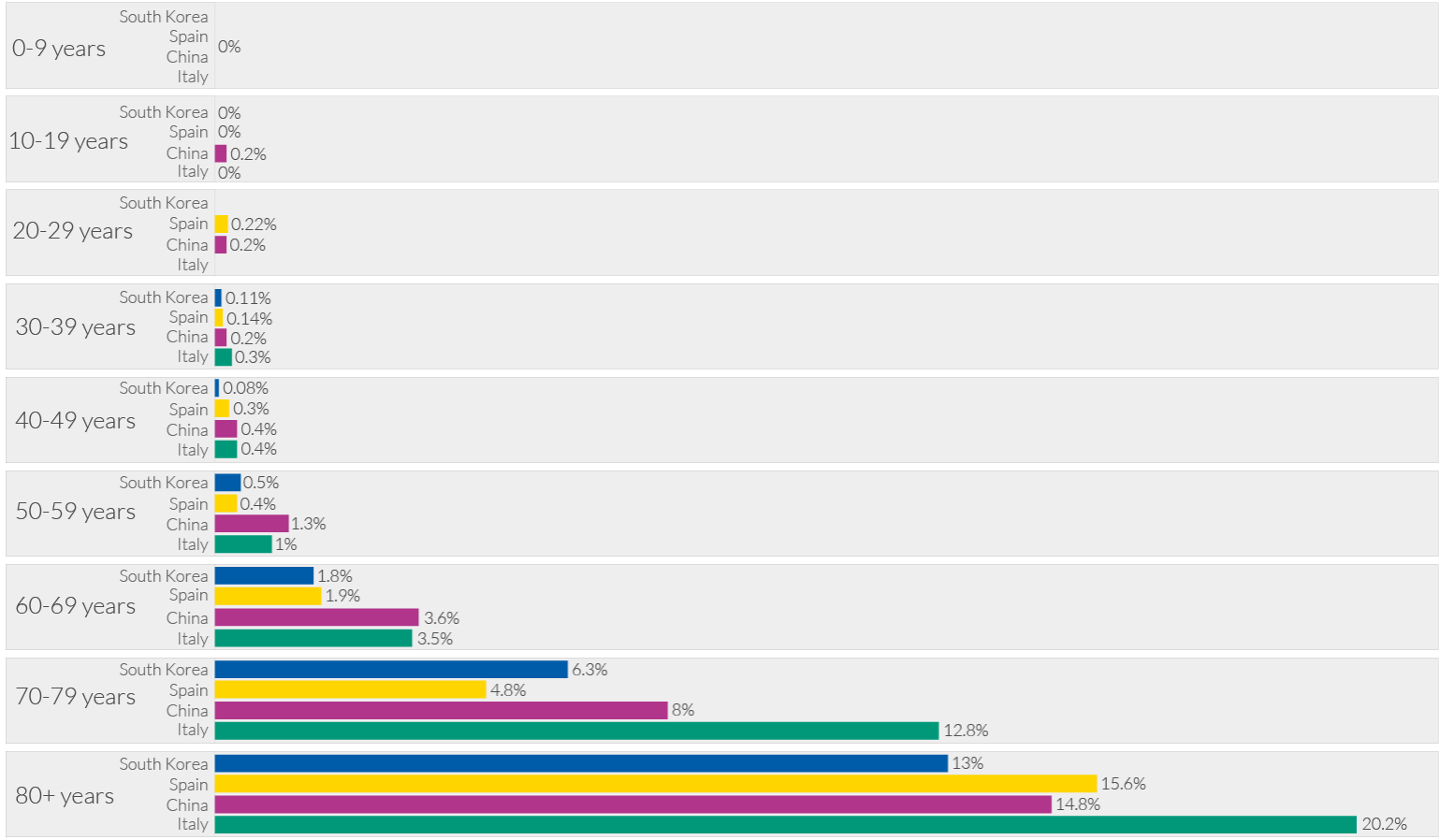
Coronavirus: case fatality rates by age

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 – Research and data to make progress against the world's largest problems.

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Beware of bias when calculating case-fatality rate

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- 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

Lipsitch, 2015

Treatment of COVID19

- Only symptomatic treatment
- Clinical trials for variety of agents (antiviral and other)
- Possibility of low-quality publications

Chloroquine + azytromycin study

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Antibody response and vaccine development

What next?

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Thank you for attention

Resources

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