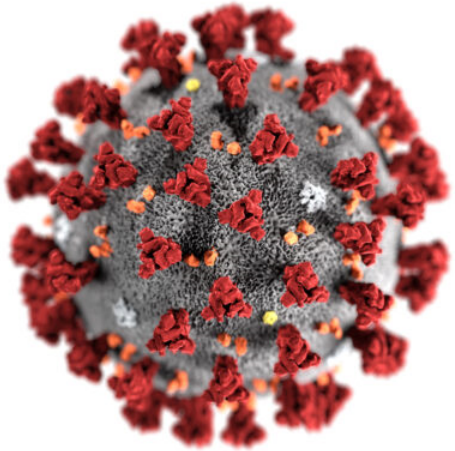
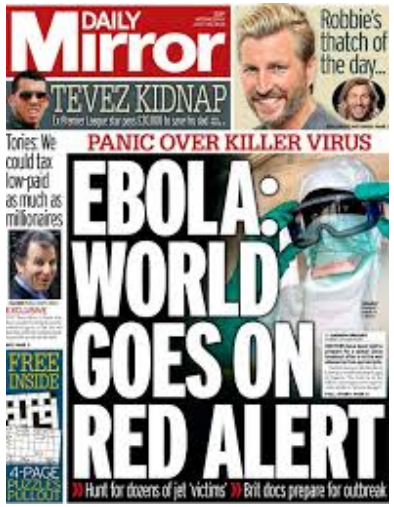
COVID-19. An initial view.



Christopher Whitty
Gresham College 2020

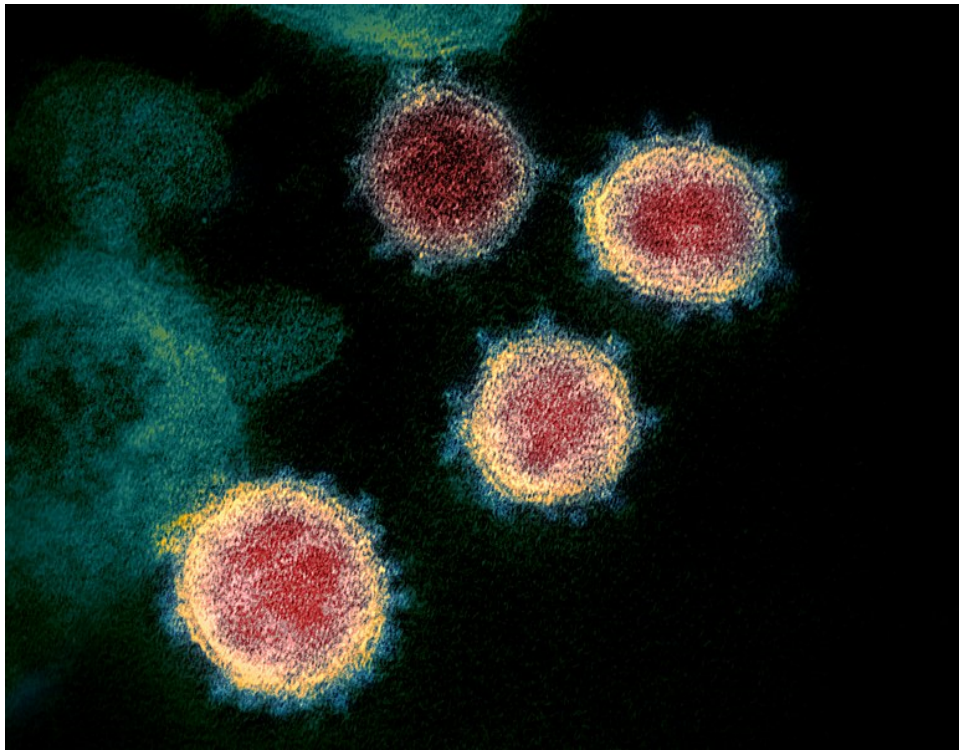
Epidemics can have profound medical and social impact. COVID-19 (SARS-CoV-2) definitely will.

- They are more common than popularly imagined, but most are localised.
- The COVID-19 pandemic is the most serious medically and socially since HIV, and more indiscriminate.
- In the last century only ‘flu pandemics have had this wide an impact.
- We are still in the very early stages. We will know a lot more in 6 months.
- Many things in this talk will undoubtedly be superseded.



This talk will cover:

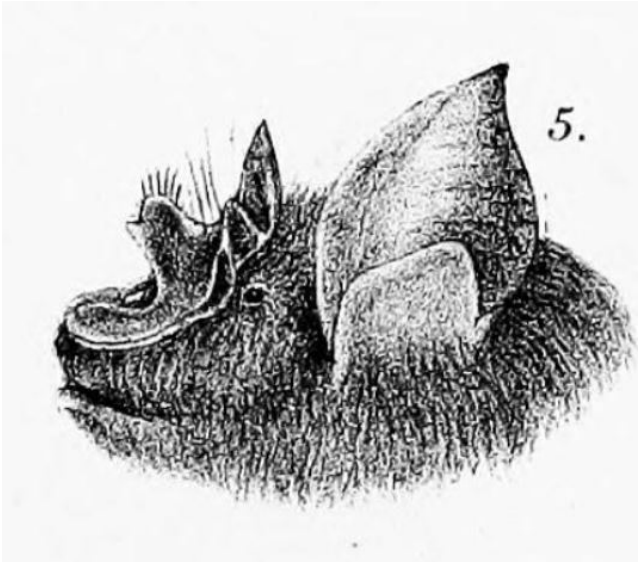
- Epidemiology, including mortality, routes of transmission, force of transmission (R_0).
- Epidemiological countermeasures.
- Clinical picture.
- Medical countermeasures including vaccines, drugs, diagnostics.
- Global picture.



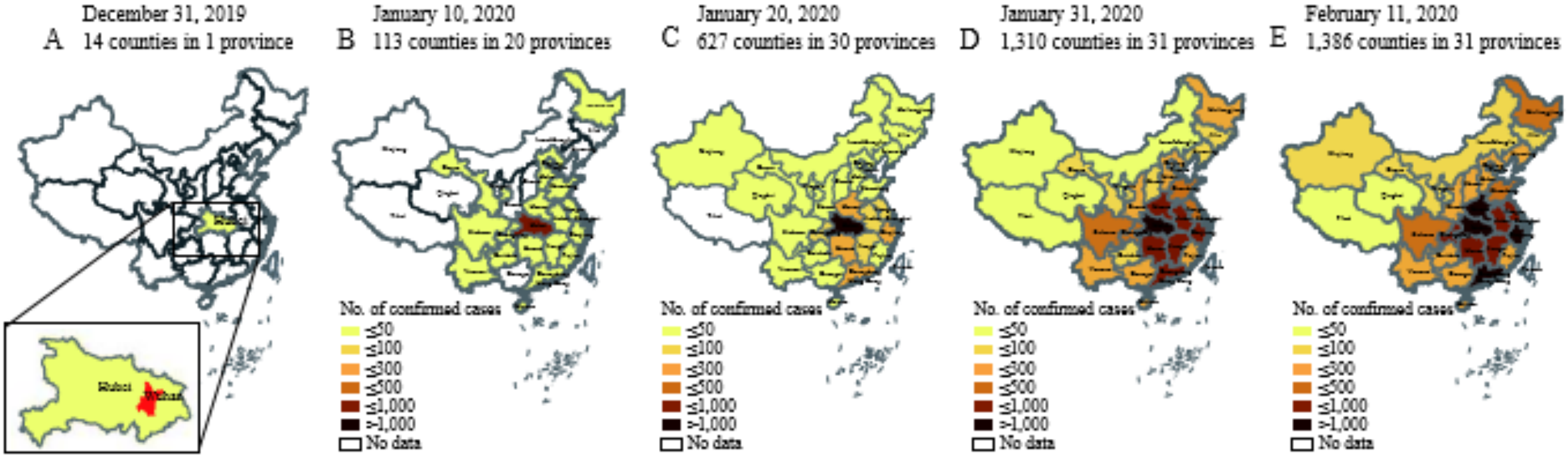
NAIAD

At some point in late 2019 a new coronavirus jumped species into humans.

- Hubei province, China.
- Probably horseshoe bats are the initial reservoir.
- Initial reports suggested pangolins but evidence still weak.
- It had one major advantage for spreading in humans: it can use a common receptor in human upper respiratory tract ACE-2 to infect.



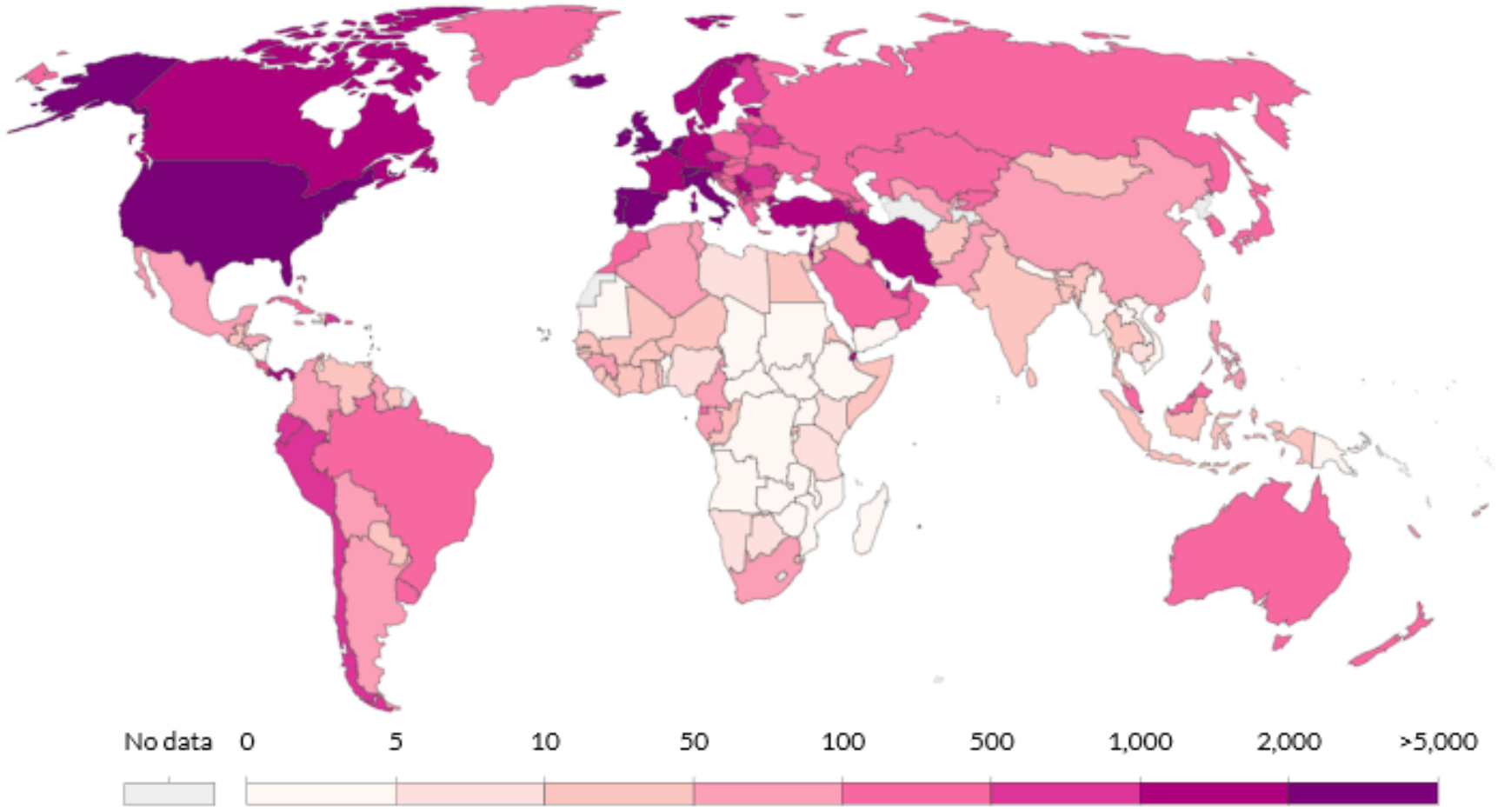
Initial spread in China was rapid. China CDC Dec 31st-Feb 11th.



After a short delay, rapid spread around the world.

WHO declared it a pandemic on March 11th. Current Situation.

3,041,777 cases, 211,169 deaths reported. Johns Hopkins.



Our World in Data.

Epidemics have to be addressed systematically.

How we respond depends on:

Mortality, severity (virulence).

Route and duration of transmission.

Treatment available?

Vaccine available?

Force of transmission.

COVID-19.

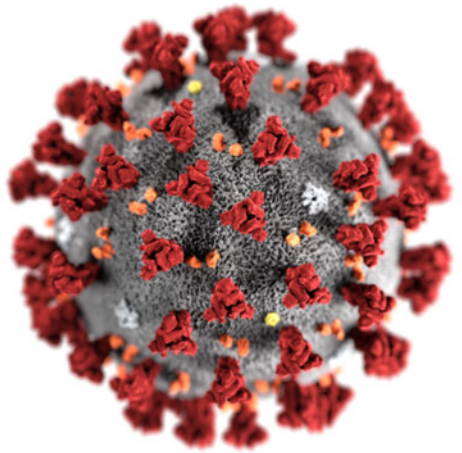
Mortality, severity (virulence).

Route and duration of transmission.

Specific treatment available? **X**

Vaccine available? **X**

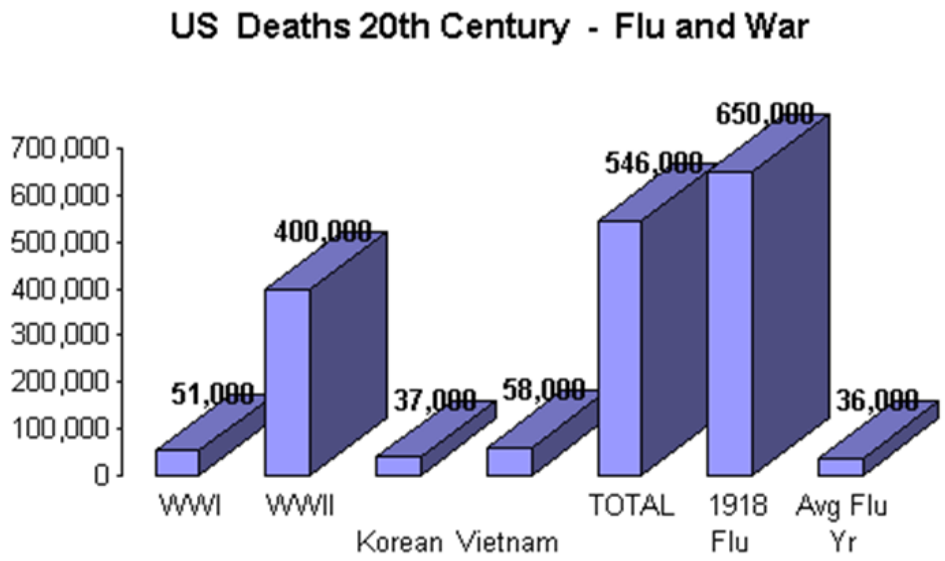
Force of transmission.



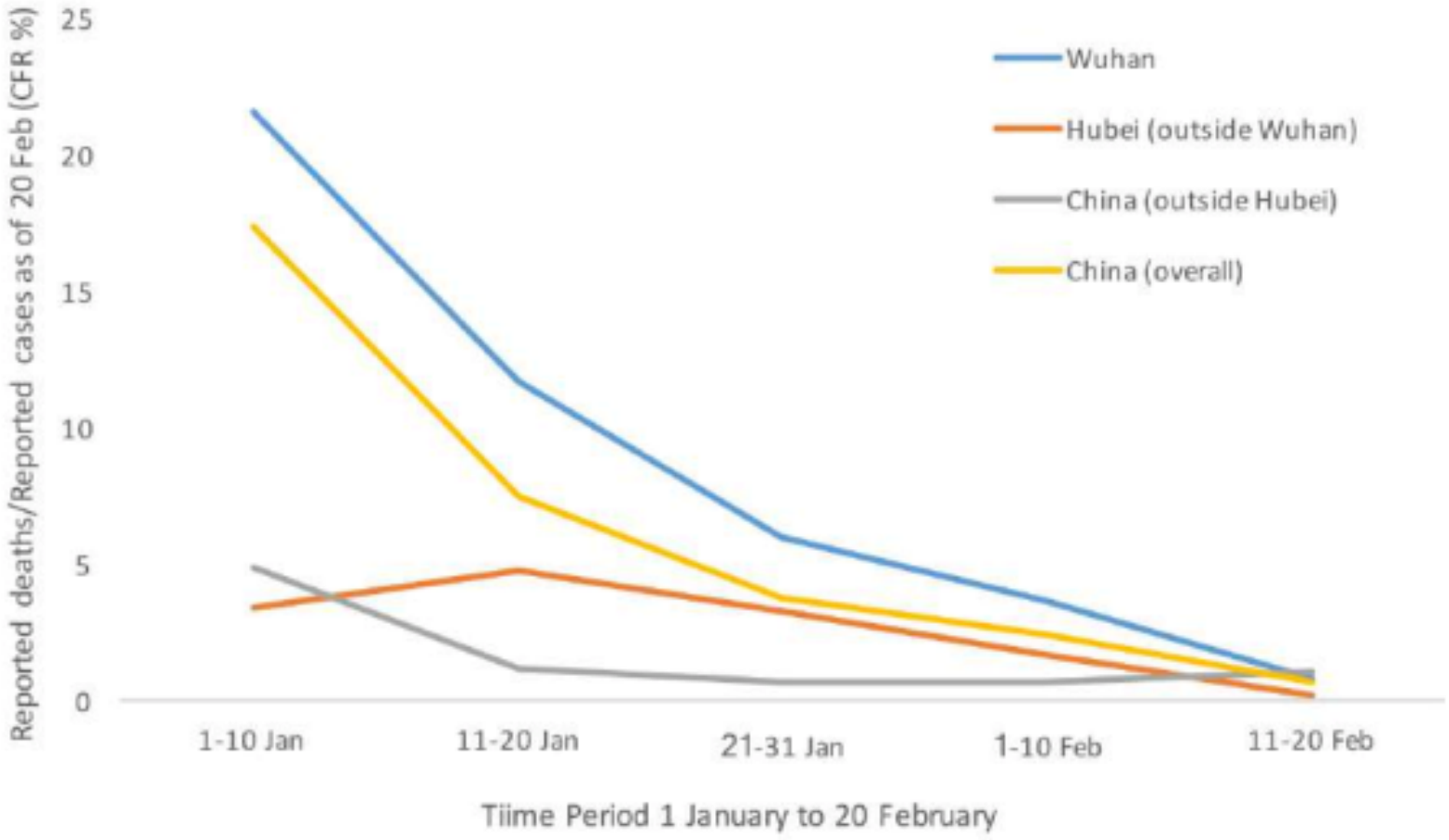
CDC

Mortality determined by fatality rate and how many infected.

- Infection fatality rate of COVID-19 probably around or just below 1% (depending on age structure of country- and how many asymptomatic).
- Comparison with other diseases:
- Ebola around 70% when first emerged.
- HIV 100% when first emerged.
- Smallpox 30%.
- H1N1 2009 flu 0.1%.
- H1N1 1918-20 ‘Spanish’ flu around 3%.



Initial reports of the case fatality rate were high. As milder cases were identified it went down. (WHO Joint Mission to China).



COVID-19 (SARS-CoV-2) compared to other 6 coronaviruses that affect humans.

- 4 human coronaviruses have low mortality.
- Mainly common cold (up to 15%), some pneumonia esp. young children and the elderly.

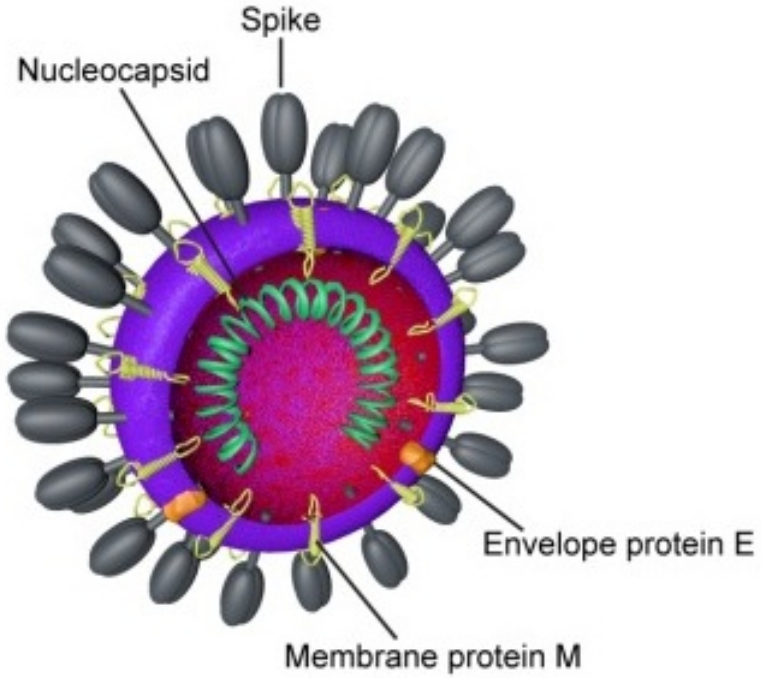
229E (alpha coronavirus)

NL63 (alpha coronavirus)

OC43 (beta coronavirus)

HKU1 (beta coronavirus)

- MERS case fatality around 35%.
- SARS case fatality around 11-15%.



Transmissibility and virulence (mortality) of coronaviruses.

Data approximate.

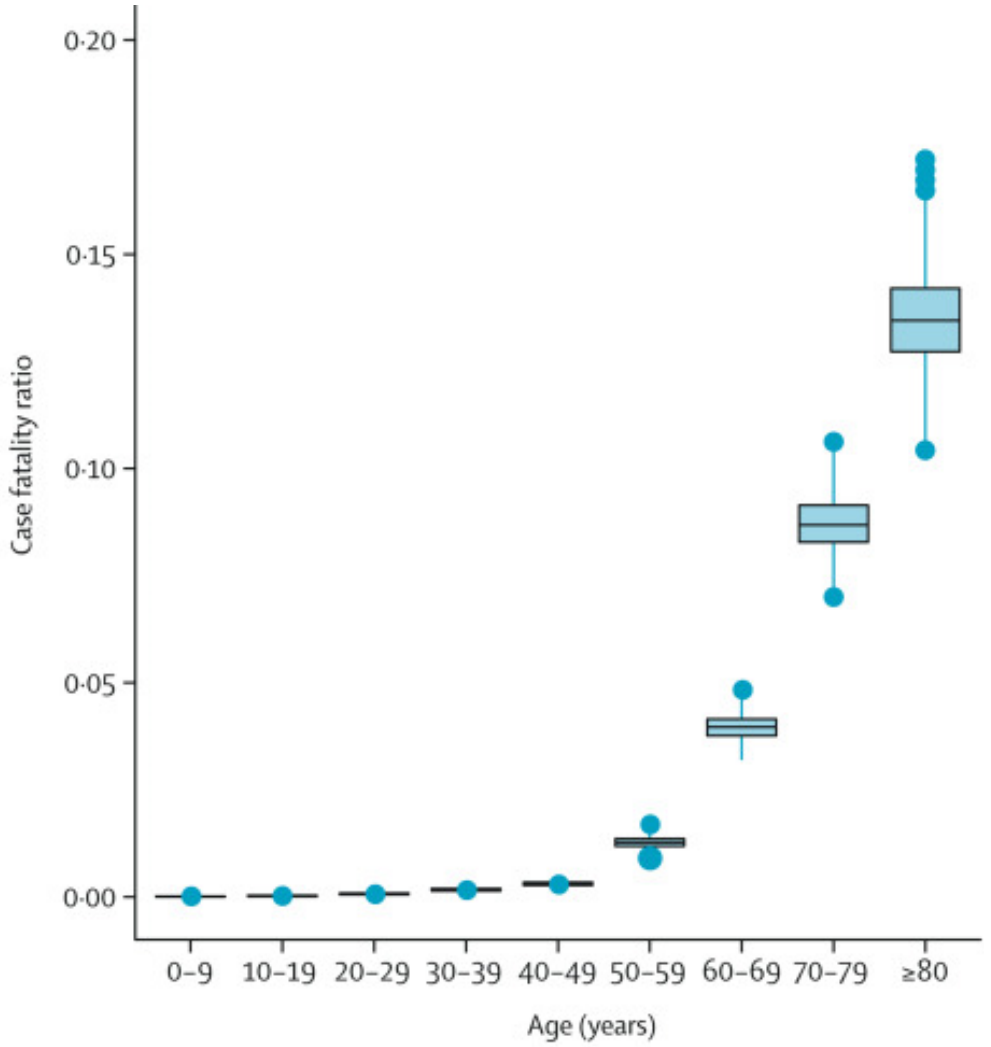
	Low mortality	**Higher mortality**
High transmission	**Current human coronaviruses 229E, NL63, OC43, HKU1.**	**COVID-19. Around 1% mortality, CFR around 1.5%. Very high transmissibility.**
Low Transmission	**Not worth worrying about.**	**MERS. 2494 cases, 858 deaths. 35% CFR. SARS. 8422 cases 774 deaths. 11-15% CFR.**

At an individual level the chances of dying of coronavirus are low.

- Over the whole epidemic, even if there is no vaccine, a high proportion will not get it.
- Of those who do, a significant proportion (exact number not yet clear) have no symptoms.
- Of the symptomatic cases, the **great majority** (around 80%) a mild-moderate disease.
- A minority have to go to hospital, most need only oxygen. The great majority of these survive.
- A minority of those need ventilation.
- A minority of every agegroup sadly die with current treatment, but even of the oldest group most do not.

Initial data from China suggested a strong trend of case fatality to increase by age. Infection fatality lower. *Verity R et al Lancet ID 2020*

- 0-9 years CFR 0.003%
- 10-19 years 0.01%
- 20-29 years 0.06%
- 30-39 years 0.15%
- 40-49 years 0.3%
- 50-59 years 1.25%
- 60-69 years 4%
- 70-79 years 8.6%
- 80+ year 13.4% (IFR 7%?)
- We do not currently know asymptomatic infection rate.



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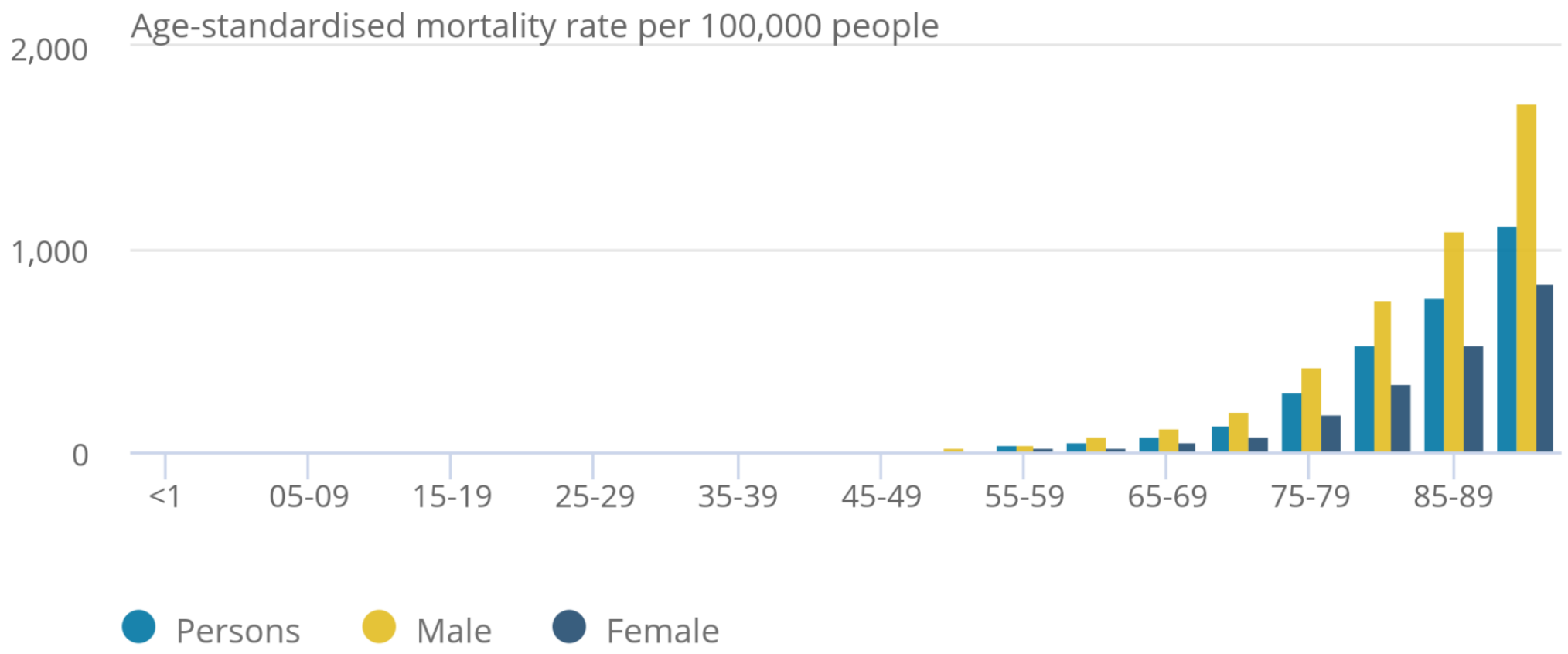
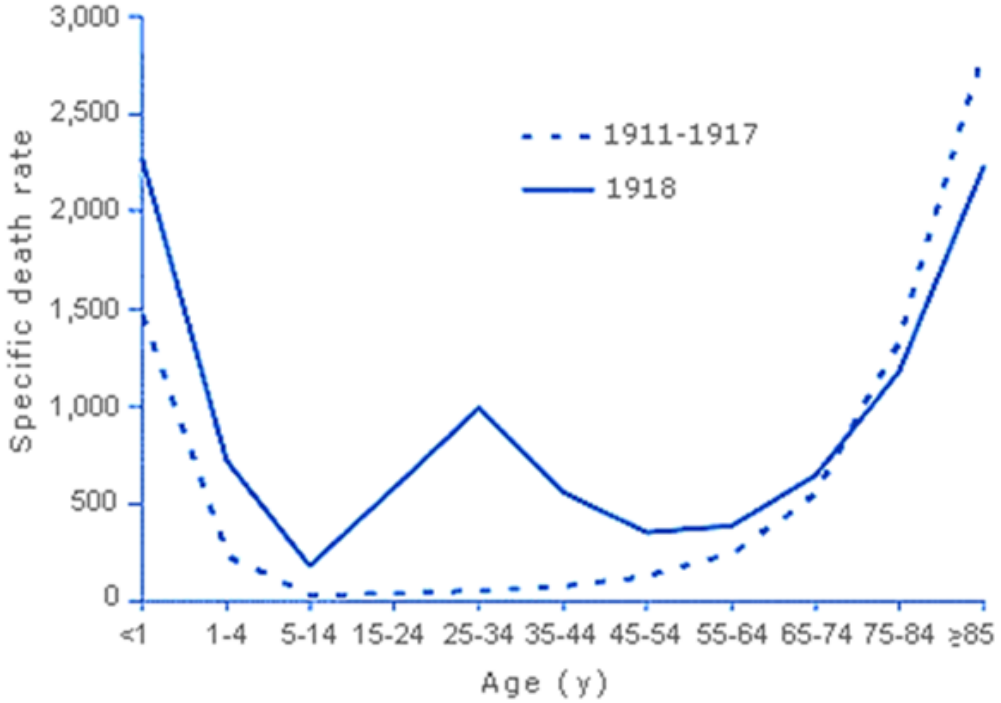
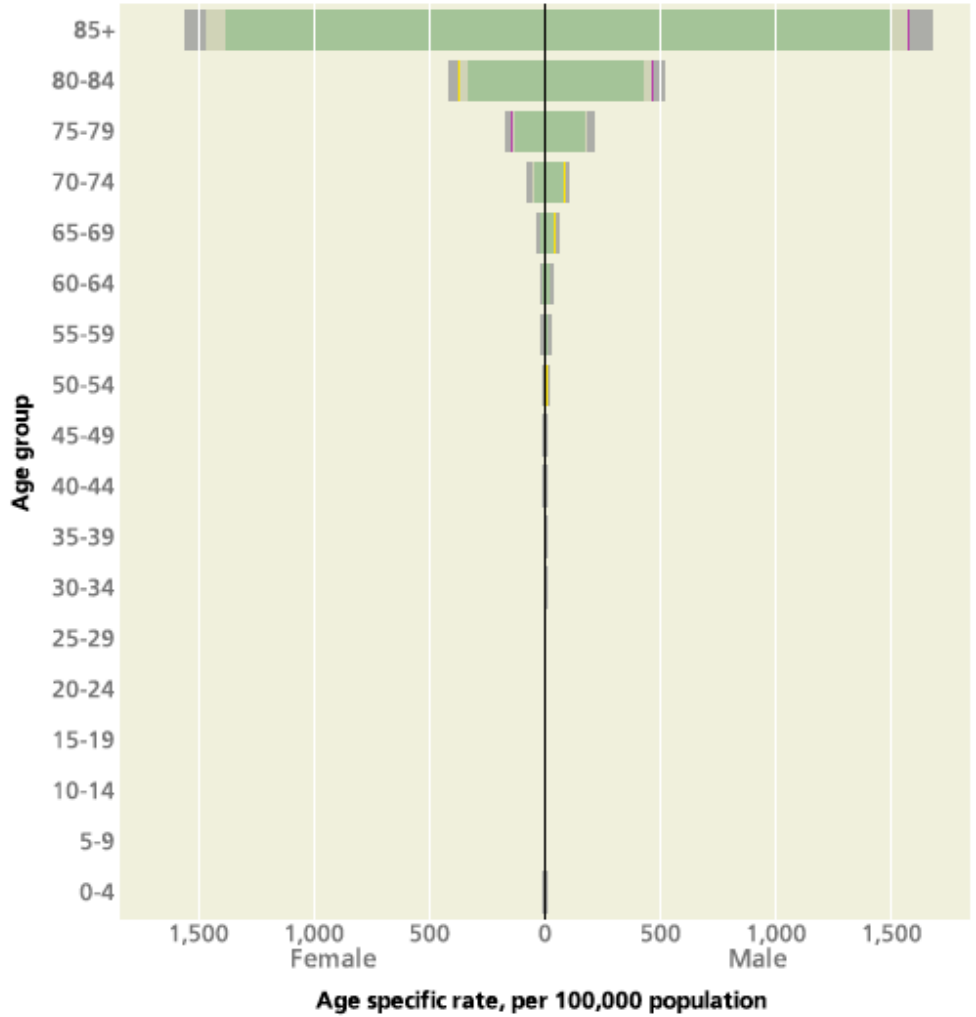
Age and gender. ONS data for England and Wales, March 2020.



Age and infections often have complex interactions. Influenza mortality 1918 USA (L) and UK infectious mortality (R).

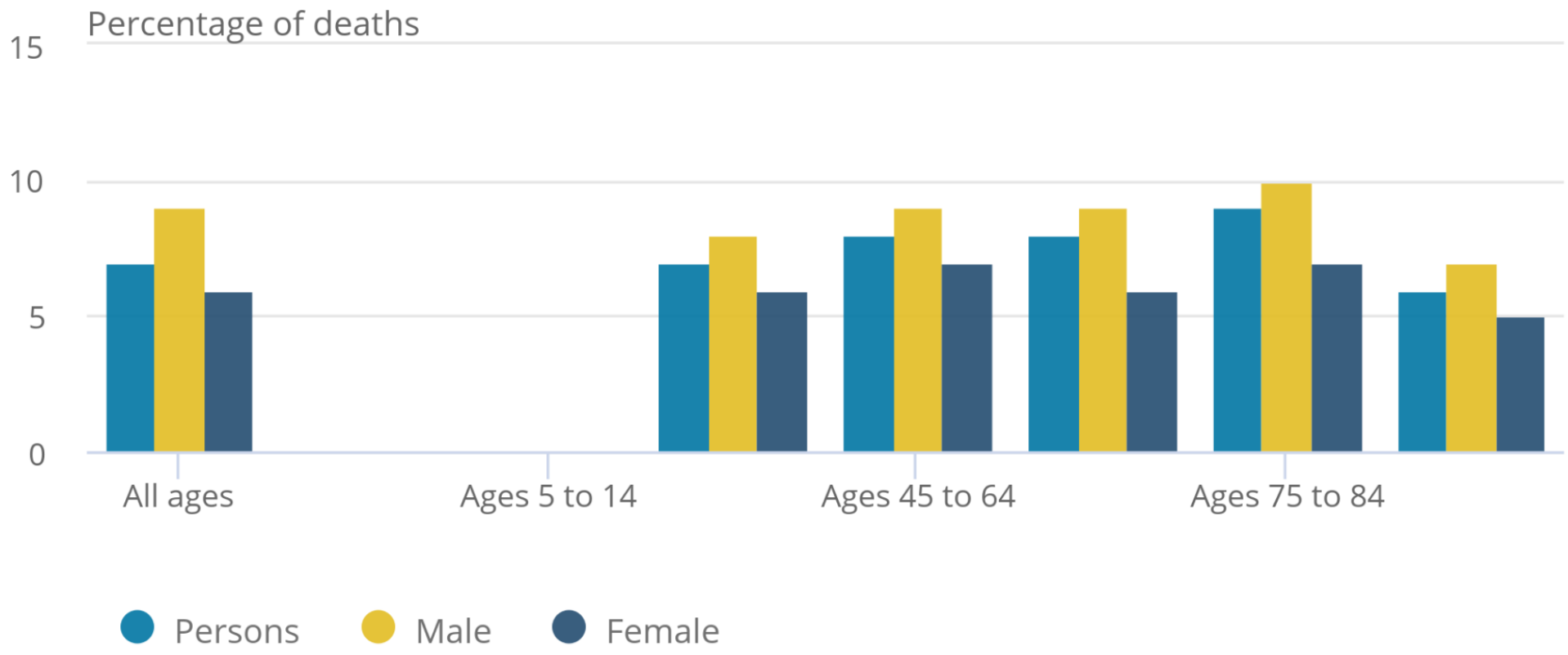


Source: CDC Emerging Infectious Diseases · Vol. 12, No. 1, January 2006
Link: http://www.cdc.gov/ncidod/EID/vol12no01/05-0979.htm

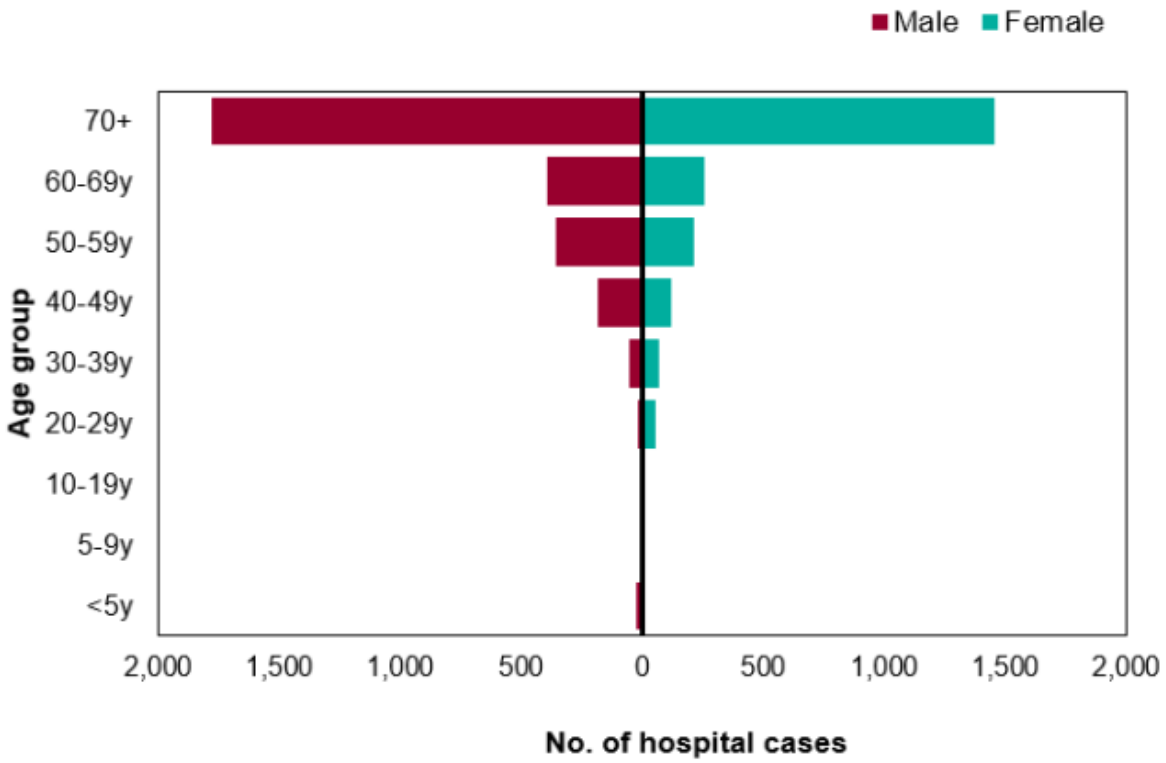


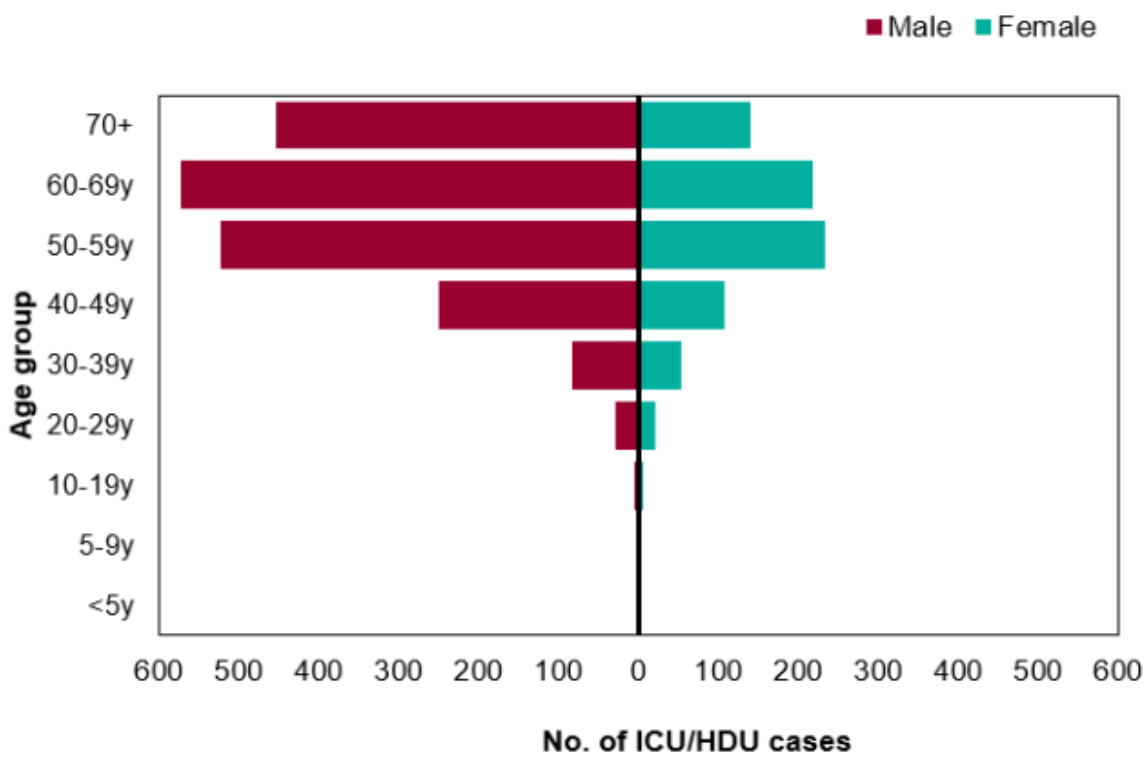
Looked at another way, in March 2020 proportion of deaths in E&W in each agegroup ascribed to COVID-19 (ONS).

7% of all deaths, rate in men higher at every age.

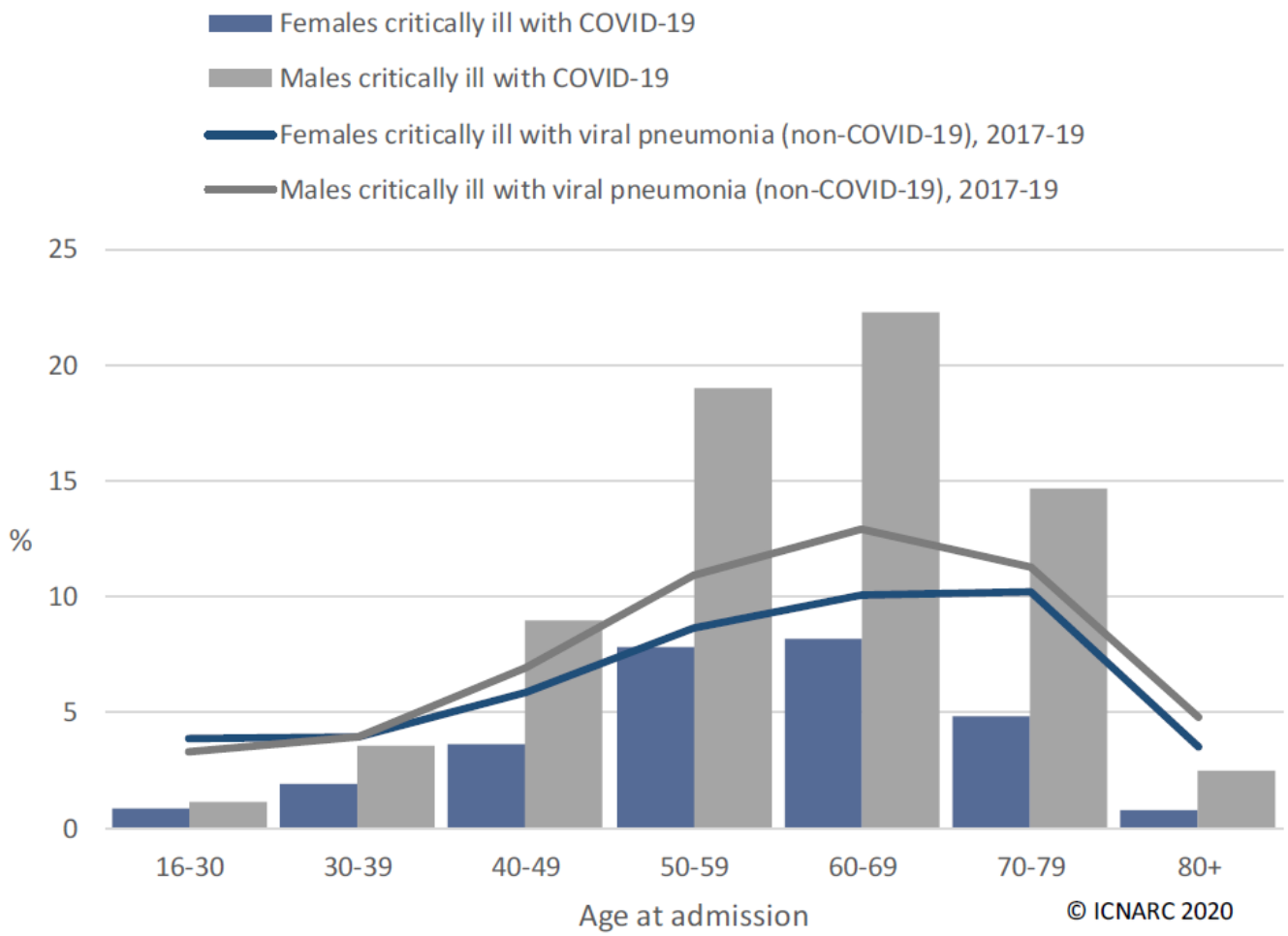


Hospitalised cases (L) and ICU/HDU cases (R). PHE, data from England.





This sex differential is very atypical. ICNARIC ICU data.



Other risk factors for mortality.
In ONS data 91% had at least one comorbidity.

Comorbidities including:

- Cardiovascular disease.
- Diabetes.
- Chronic lung disease.
- Immunosuppressed.
- Chronic kidney and liver disease.
- Obesity.

- Probably some ethnic groups at greater risk.

Routes of transmission of COVID-19.

Primary route of transmission:

- Respiratory. COVID-19, SARS, MERS, flu.
- Sexual/blood. HIV.
- Touch. Ebola.
- Water/food. Cholera.
- Vector (insect). Zika, malaria.

- Secondary route COVID-19 touch, then to face.

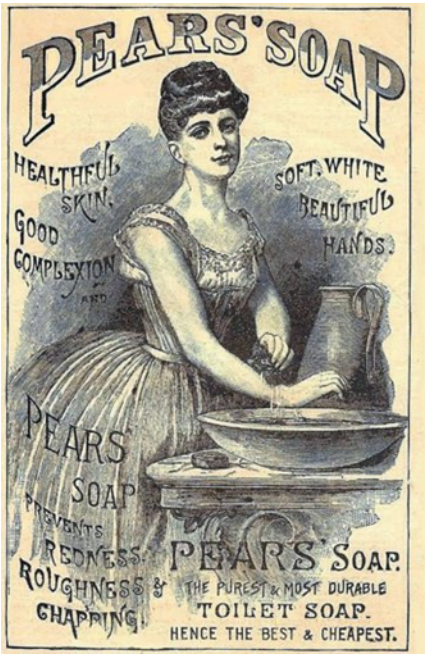
CDC

Outside healthcare settings the main transmission mechanisms.

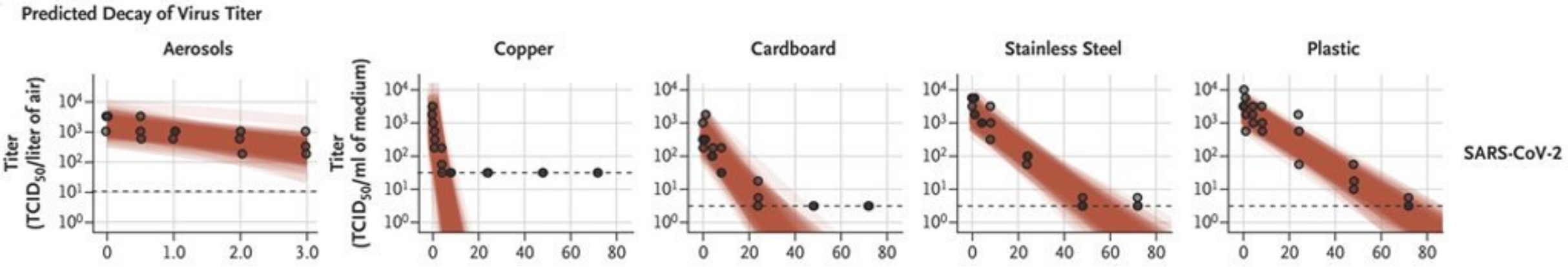
- All get in via mouth, nose, possibly eyes.
- Droplets (eg >5-10 µm) from coughing, sneezing, talking, (singing), direct to mucus membrane.
- These are usually carried no more than 1m (WHO), but can be further.
- Touching surfaces which have been contaminated, then touching face.

Preventing transmission via objects and hands.

- Washing hands- soap and water, or alcohol gel.
- Soap damages the lipid around the virus.
- Most normal detergents and soaps will kill the virus.
- Rapid drop off of viability of the virus. May be a few hours depending on temperature, humidity, surface.
- Very unlikely to be viable beyond 72 hours.

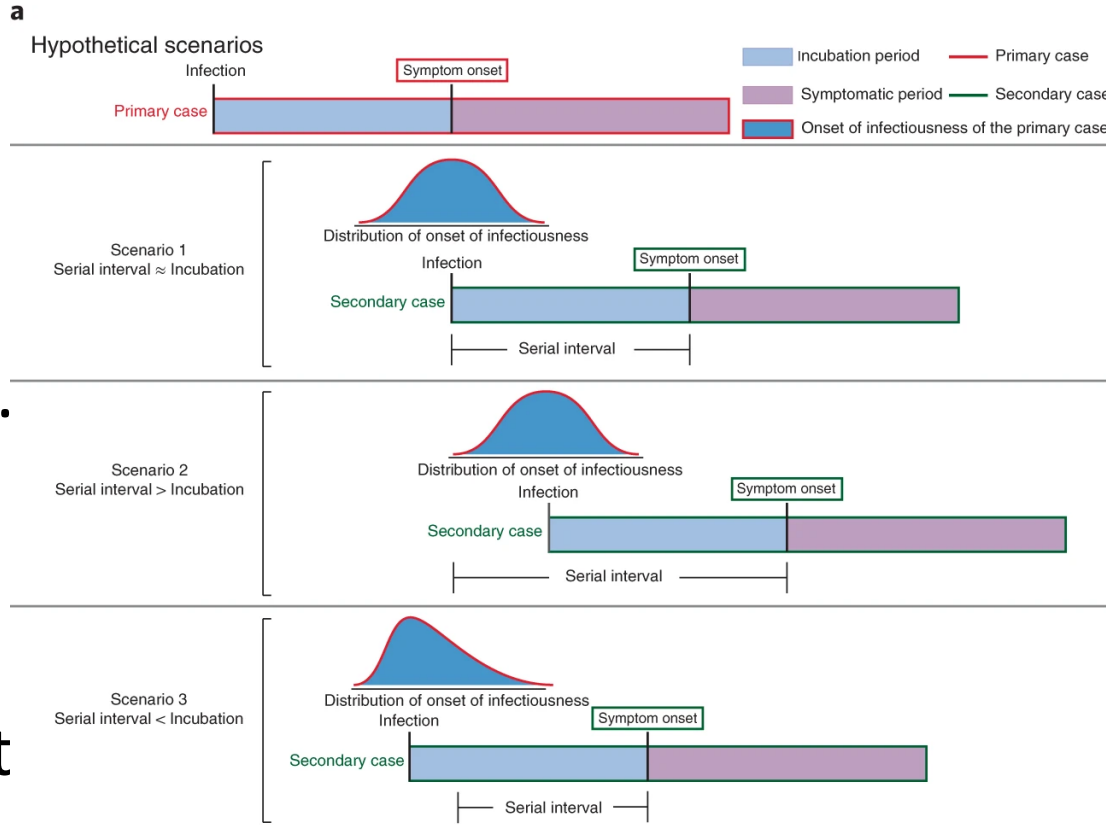


van Doremalen et al, NEJM, 2020



Asymptomatic and pre-symptomatic transmission.

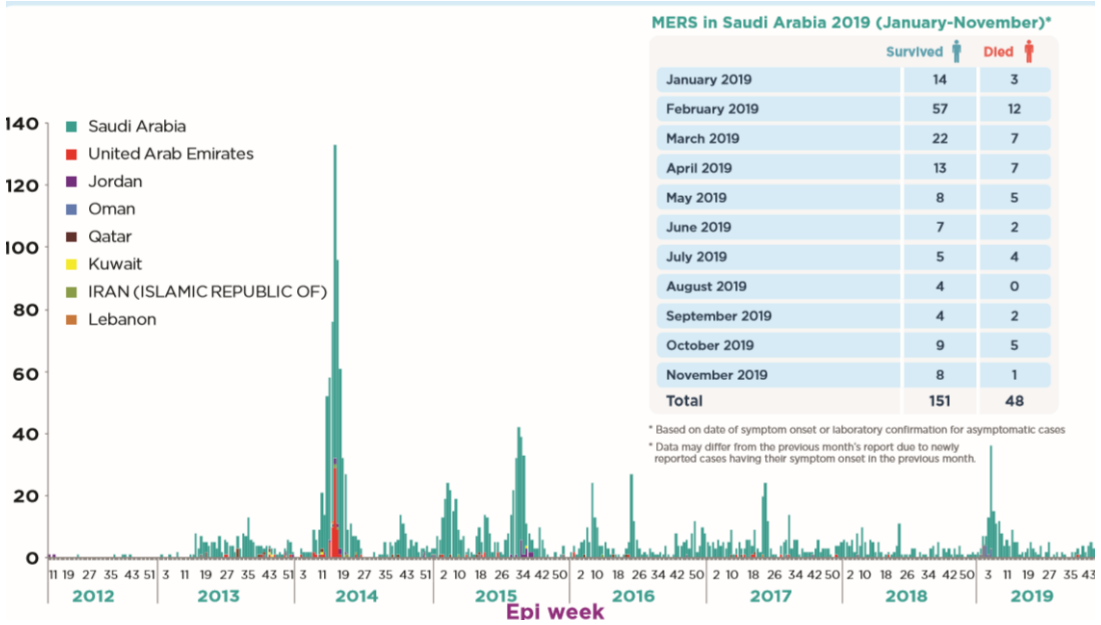
- People with symptoms are most infectious around the start of symptoms.
- They can be infectious before symptoms (or with minimal symptoms).
- Infectiousness declines rapidly to 7 days post symptoms.
- A significant proportion of people have the virus without symptoms. We do not know what proportion of infections are from these people.



Xi He et al Nature 2020

MERS-CoV

- From dromedaries to humans, and some human-to-human.
- 35% of people with MERS die.
- Cases in Arabian peninsular every year since 2012 but small numbers.
- One significant outbreak in South Korea in 2015 (185 confirmed cases) brought under control.



MERS in Saudi Arabia 2019 (January-November)*

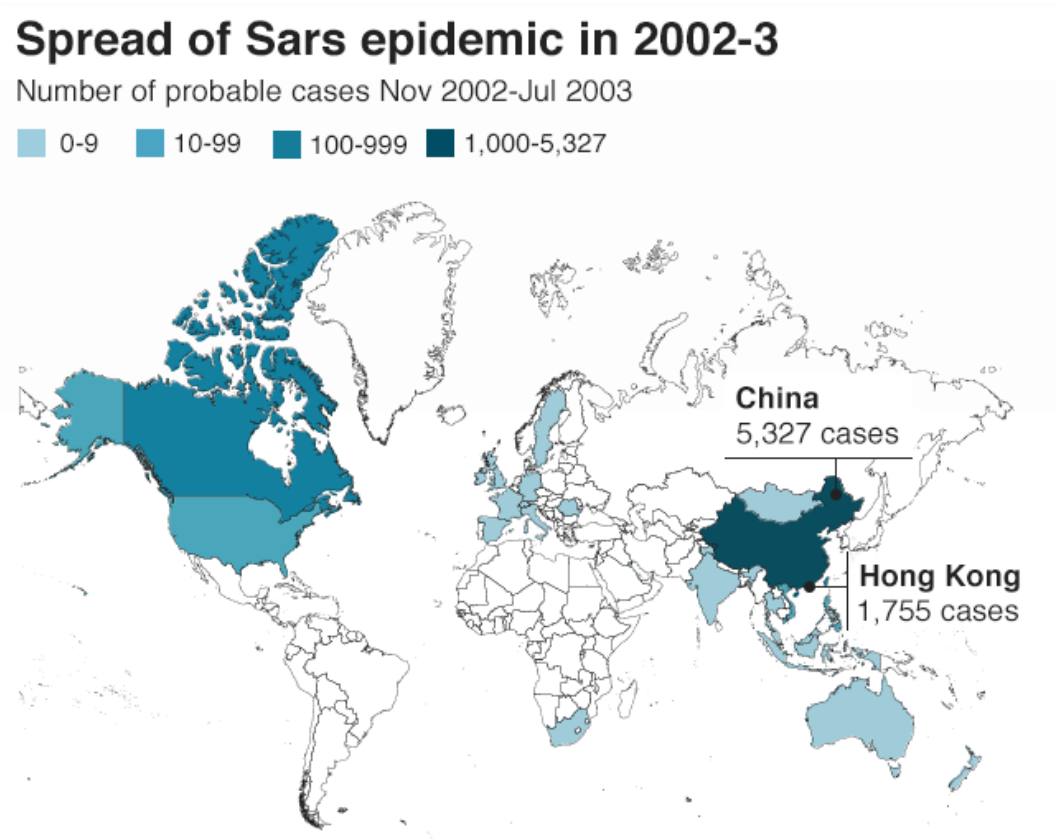
	Survived	Died
January 2019	14	3
February 2019	57	12
March 2019	22	7
April 2019	13	7
May 2019	8	5
June 2019	7	2
July 2019	5	4
August 2019	4	0
September 2019	4	2
October 2019	9	5
November 2019	8	1
Total	151	48

* Based on date of symptom onset or laboratory confirmation for asymptomatic cases
* Data may differ from the previous month's report due to newly reported cases having their symptom onset in the previous month.

WHO/Wiki

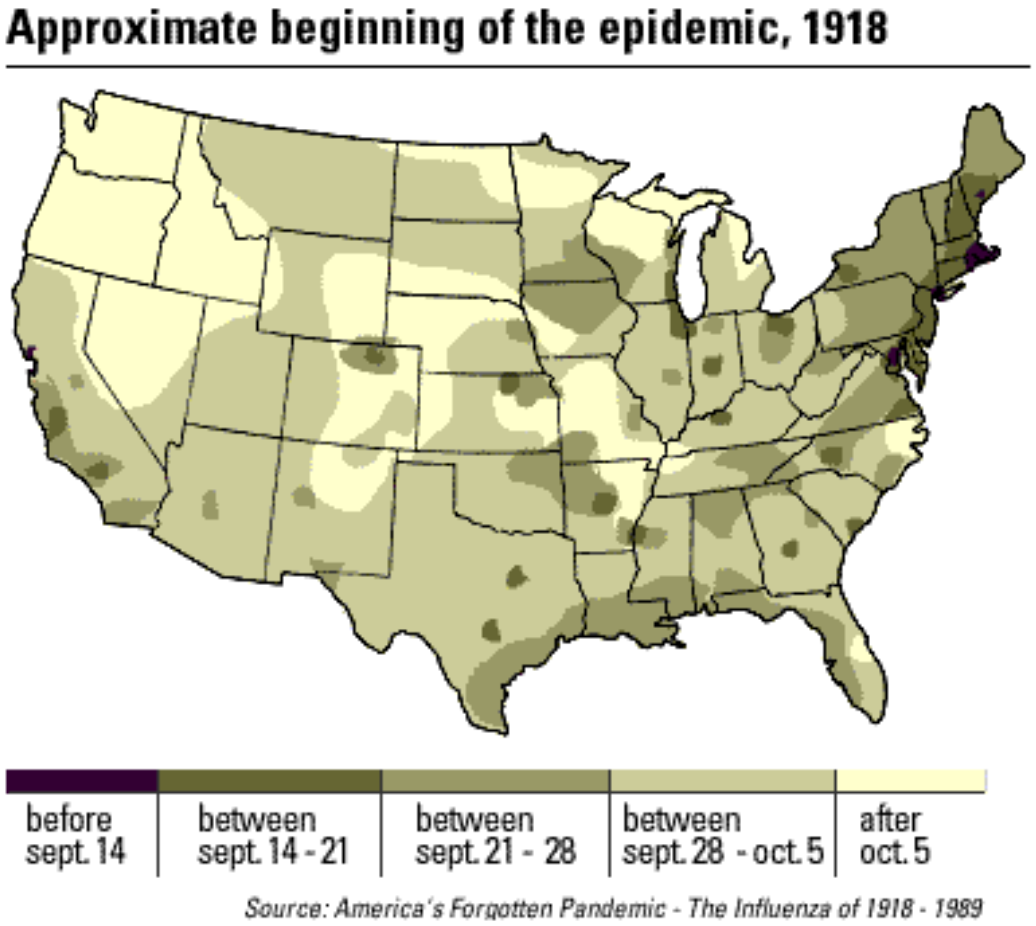
SARS

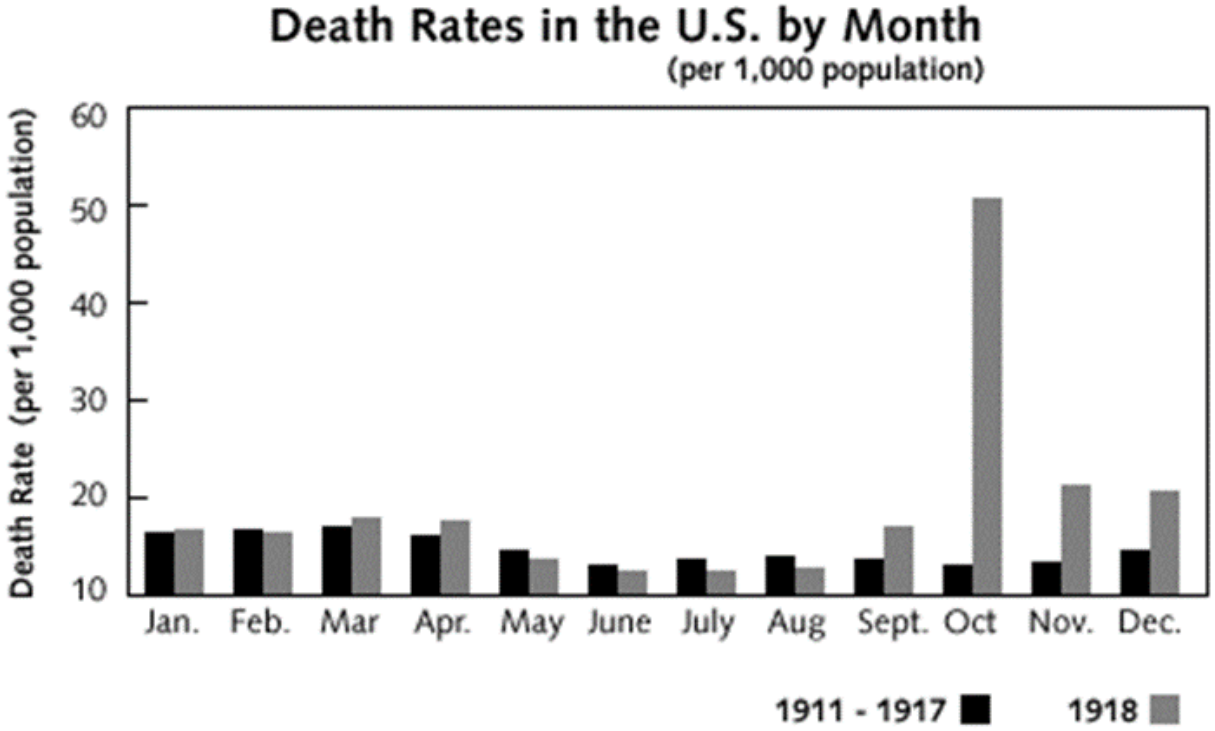
- 2002-3. Coronavirus from bats.
- Around 8422 cases, 774 deaths. Significant mortality (11-15% CFR).
- Especially in healthcare workers.
- Infectiousness probably all post symptoms.
- Great majority of cases in China and Hong Kong, with significant numbers (low hundreds) Taiwan, Canada and Singapore.
- Some spillover cases but small numbers in Europe (4 UK) or rest of world.
- Never returned.



WHO/BBC

The 1918-19 influenza pandemic. Worst on record: 17-100m deaths. 3 waves over 2 years- the second was worst.

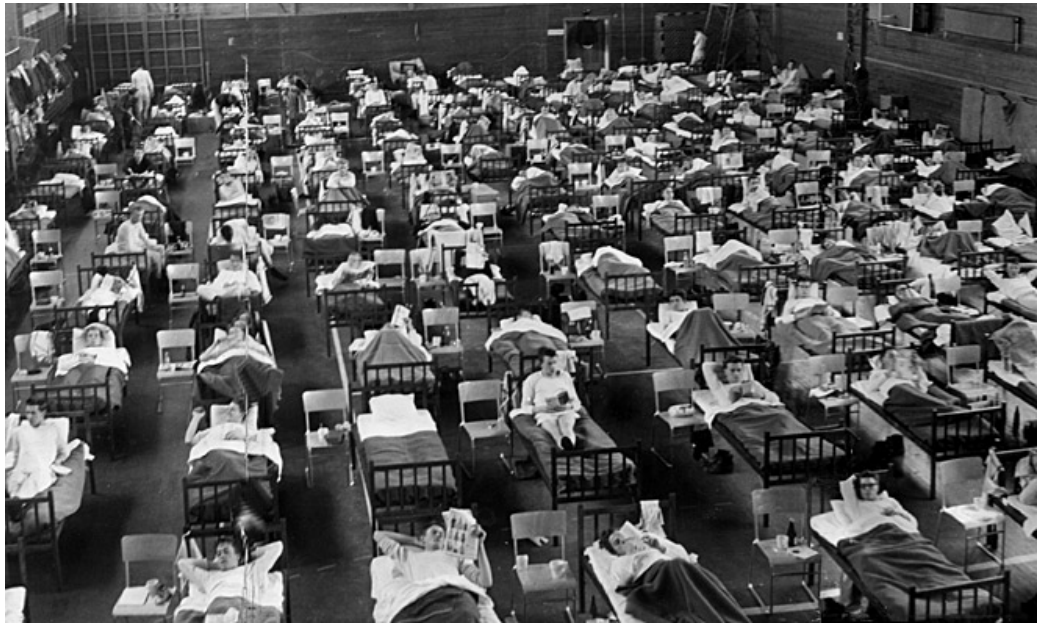




GRESHAM COLLEGE

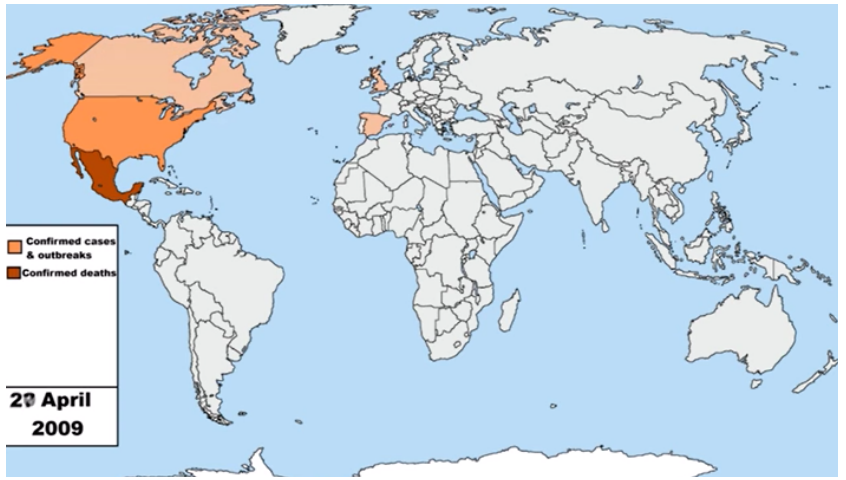
1957 (H2N2 ‘Asian’) and 1968 (H3N2 ‘Hong Kong’) flu pandemics.

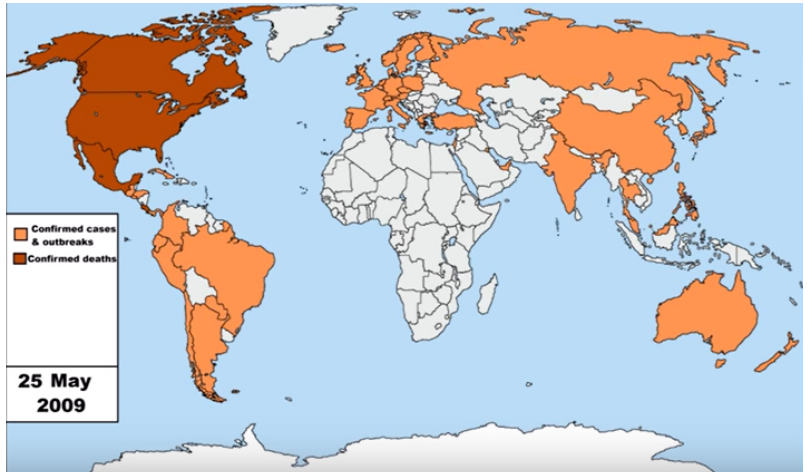
- 1957 0.3% mortality. 1.1 million people worldwide, 116,000 USA (CDC).
- 1968 1 million worldwide, 100,000 deaths USA (CDC) but lower mortality in UK. Occurred in 2 waves, second killed more than the first.

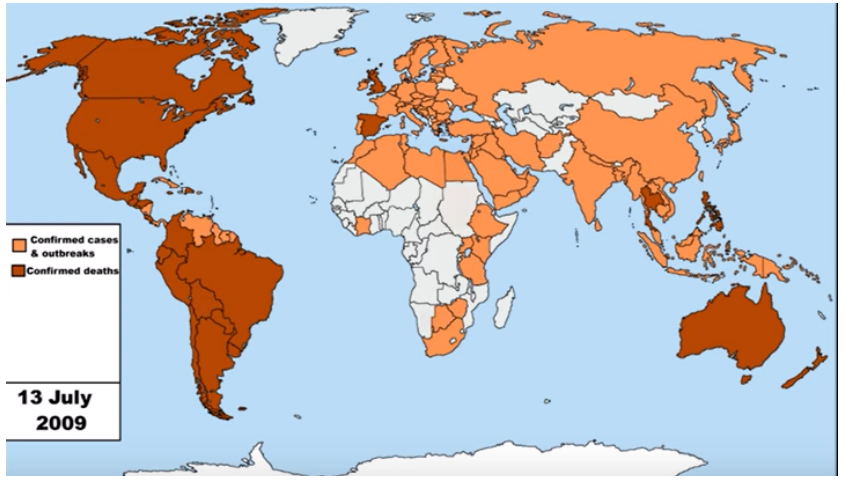


Asian flu, Sweden

H1N1 2009. Officially 457 deaths in UK. 2 waves.







43-89 million cases 2009-10 (CDC)

8-18 thousand deaths (CDC)

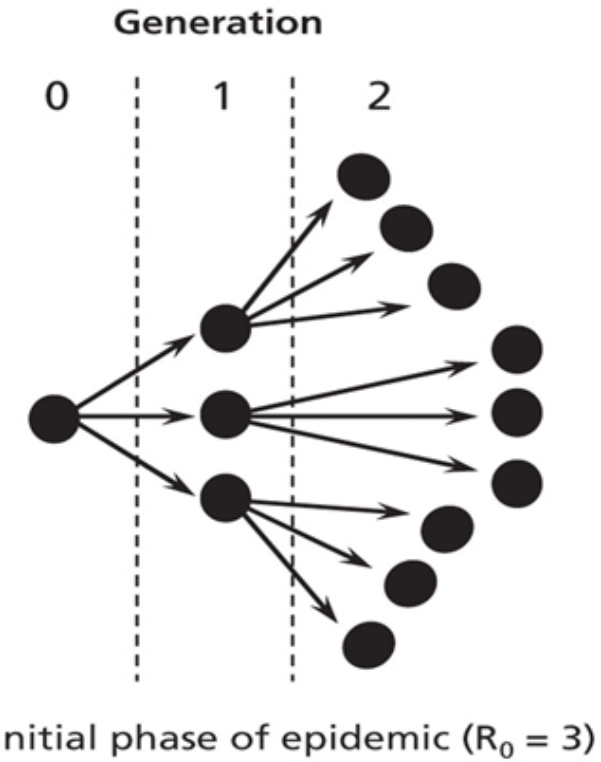
Wide estimates on numbers.

Mark Honigsbaum

Force of transmission- R_0

By definition an epidemic must have R_0 over 1.

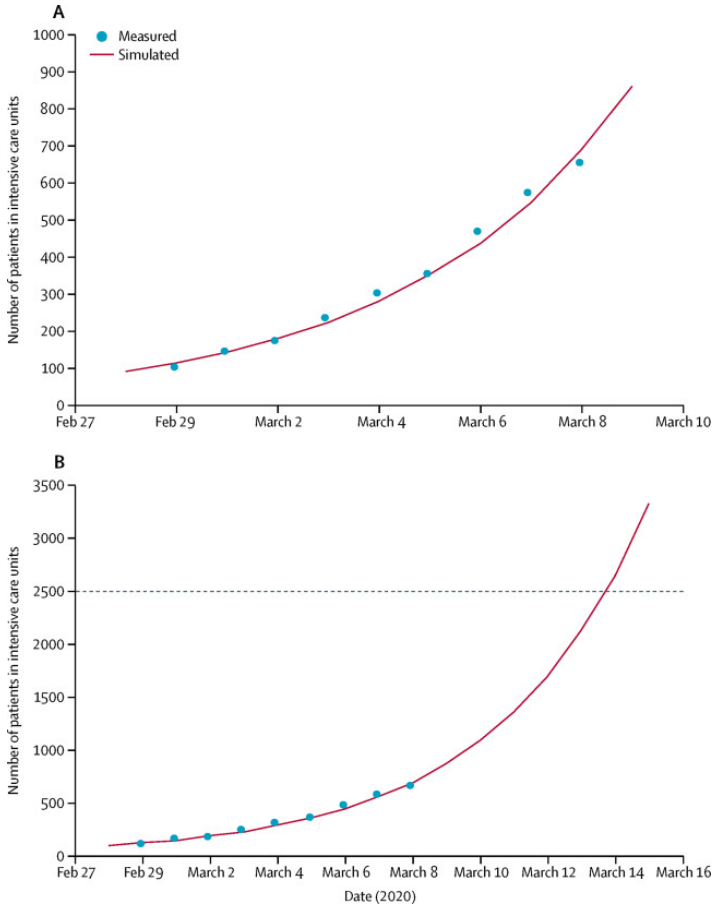
- ***If*** you can get R below 1 the epidemic dies back.
- COVID-19. R_0 around 3 in UK.
- Ebola epidemic- R 1.2-2.5
- 1918 'flu pandemic R 2-3
- HIV expansion phase R 2-5
- Measles R >10
- Malaria in parts of Africa R >100



Initial phase of epidemic (R_0 = 3)

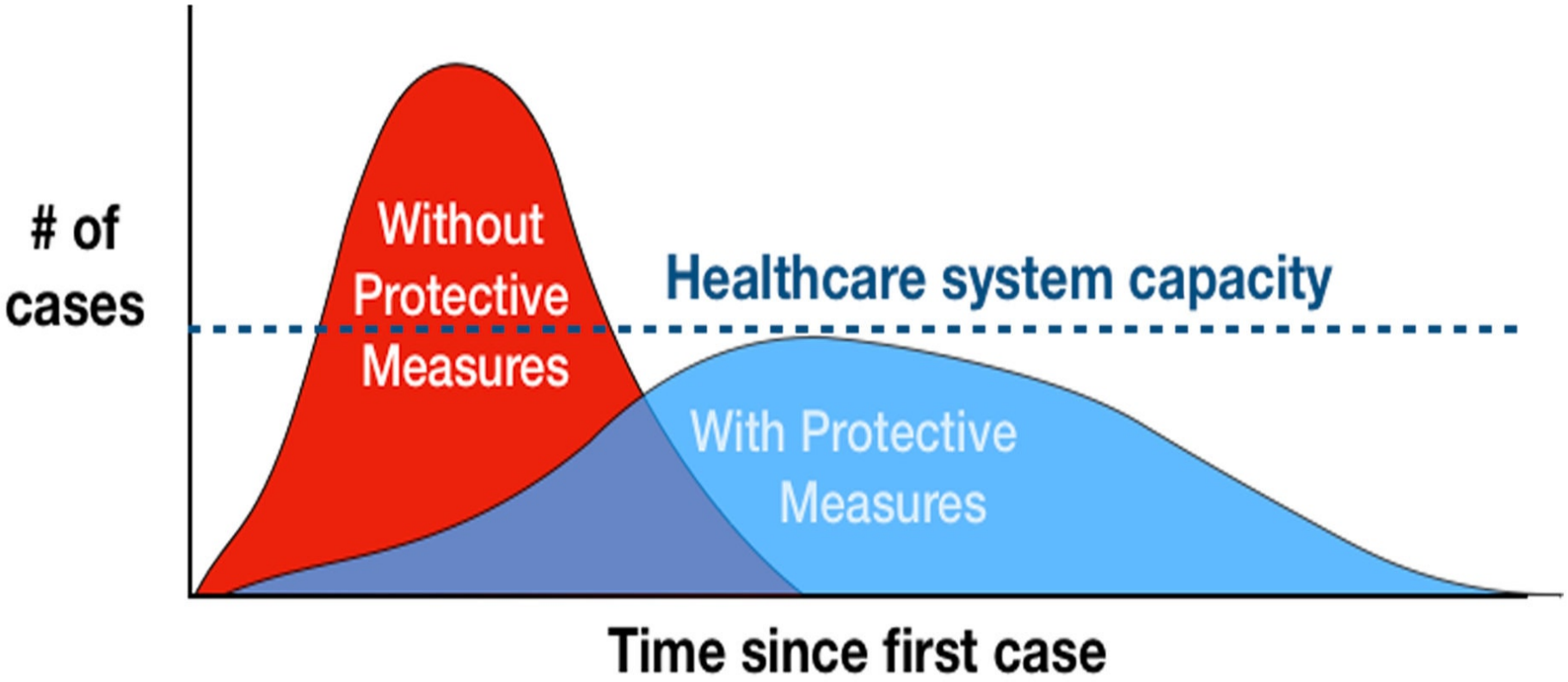
If R0 is above 1….

- Even by a small amount you will get exponential growth.
- This may be slower if R is low.
- In the case of COVID-19 it is fast. Initial unmitigated doubling times were around 3-5 days.
- This means without intervention you get from low numbers to very high numbers very fast.
- Health service becomes overwhelmed.



Remuzze & Remuzzi, data from Italy, 2020

In the absence of a vaccine or effective drug we have to rely on social and public health measures. ‘Flattening the curve’.
And raising the bar (expand capacity).
Keeps within healthcare capacity. Prevents overshoot of COVID-19 cases.

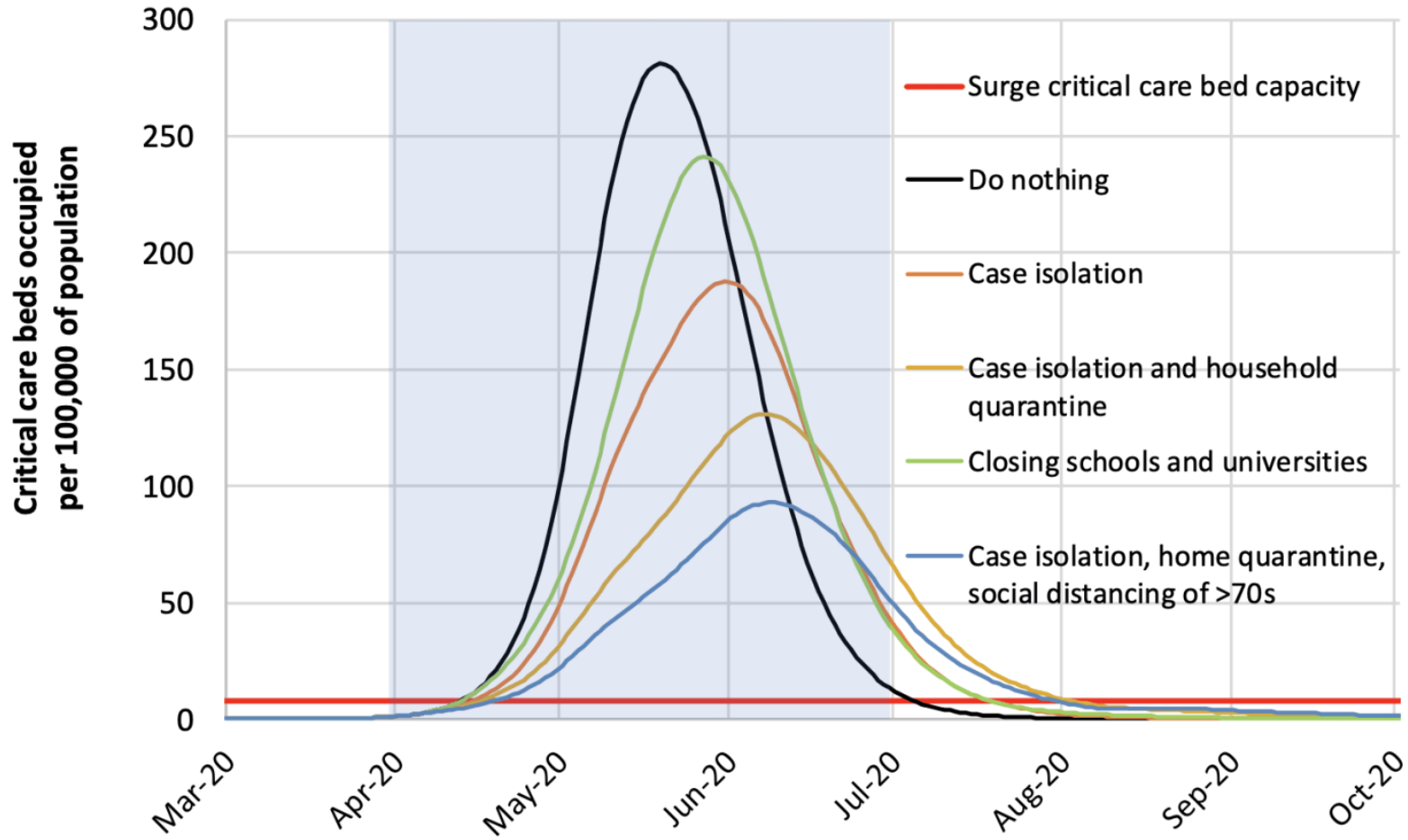


CDC/ECON/NYT

Broadly four approaches, if you have no vaccines or drugs.

- Reduce chance of infection- handwashing, respiratory hygiene.
- Isolate cases, their households, ideally their contacts.
- Reduce links between households.
- Make it less likely that the most vulnerable are exposed.

No one measure is sufficiently effective for COVID-19.



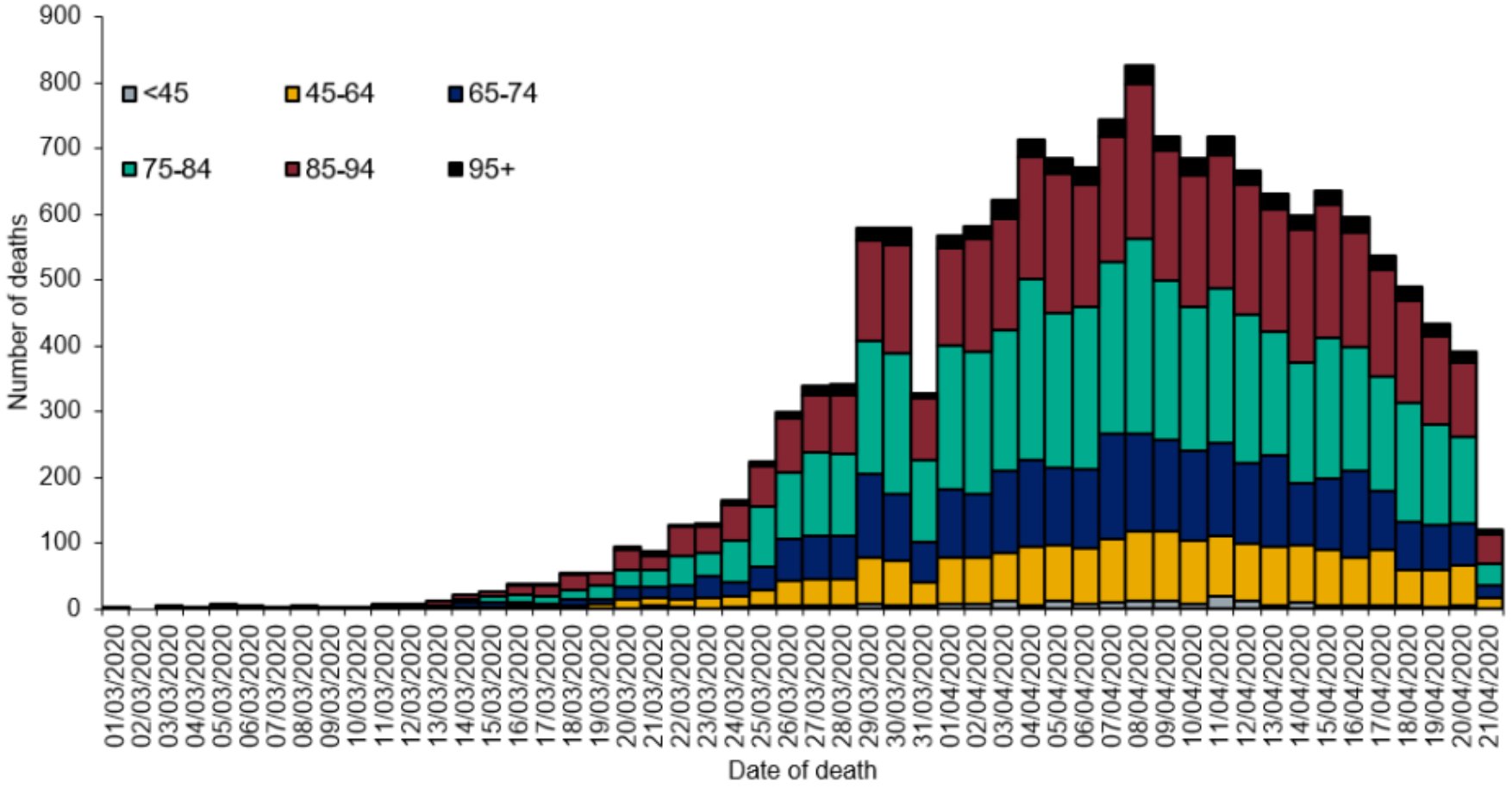
Gresham College

Imperial College COVID Response team. 2020

Hospital deaths by date of death and agegroup. 1/3 to 21/4.

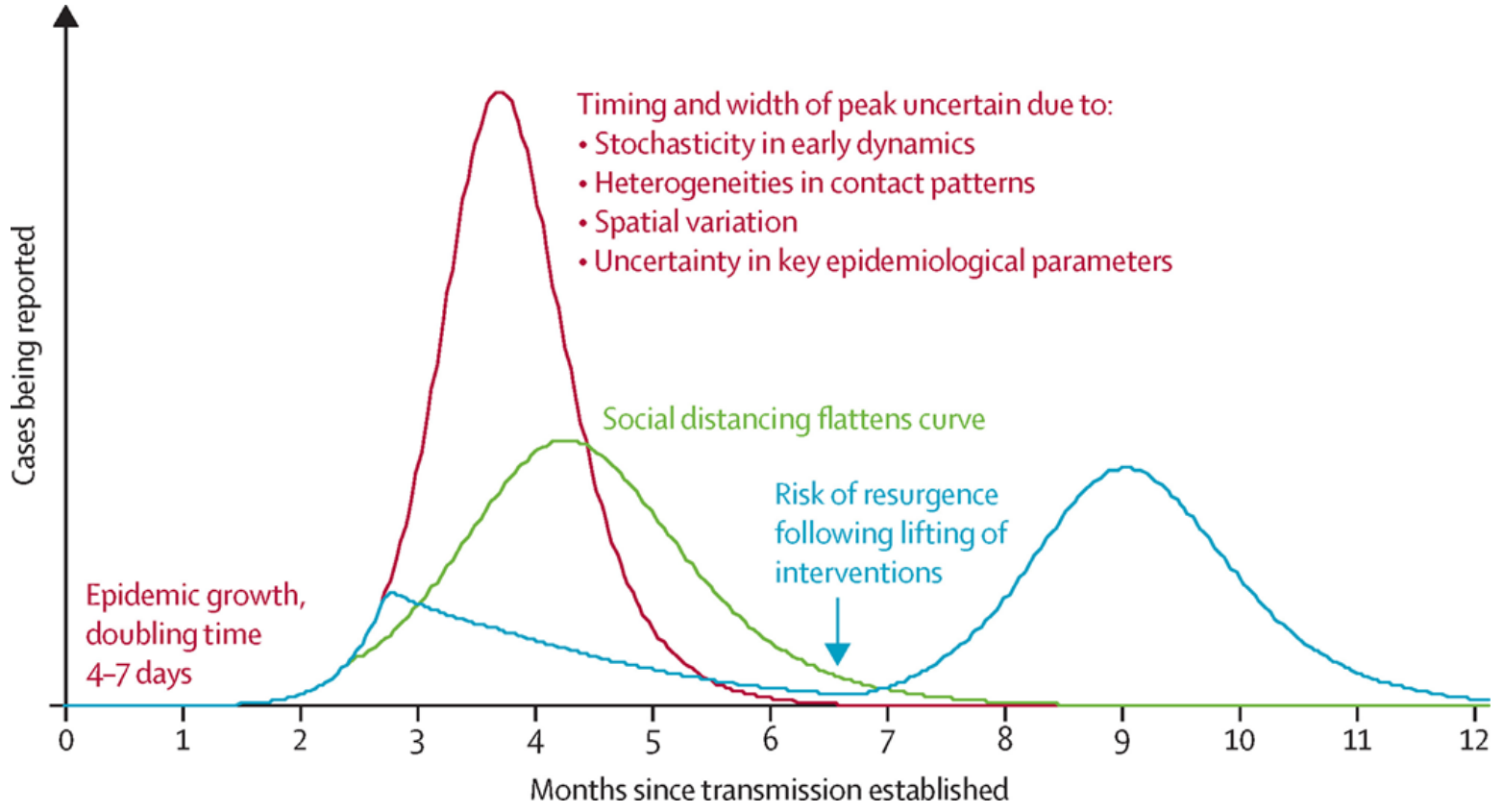
Public Health England.

But note that total all-cause age-adjusted mortality is the key metric.



If R goes back above 1 there will be a second wave.

Since we think the great majority of the population have not had COVID-19, without mitigation this could even be larger than the one we have just had.



Anderson R et al Lancet 2020

There are 4 ways this epidemic will cause excess mortality and morbidity.

A) Direct deaths from coronavirus, assuming a functioning health service so optimal care.

B) Indirect deaths because the health service is overwhelmed.

C) Indirect deaths because non-urgent serious treatment or prevention is put off, or people do not come for treatment.

D) If interventions lead to increased deprivation. This is a complex area but deprivation and ill health are strongly linked.

In unwinding lockdowns every country has a difficult balancing act. There are no easy solutions.

- Allowing R_0 to go above 1 for any sustained period will lead to exponential growth again.
- COVID-19 is a long way from finished, and eradication is technically impossible.
- From a health perspective the optimal answer from a COVID-specific mortality point of view may be different than for indirect mortality.
- Very important social and economic considerations.

Maurice/wiki

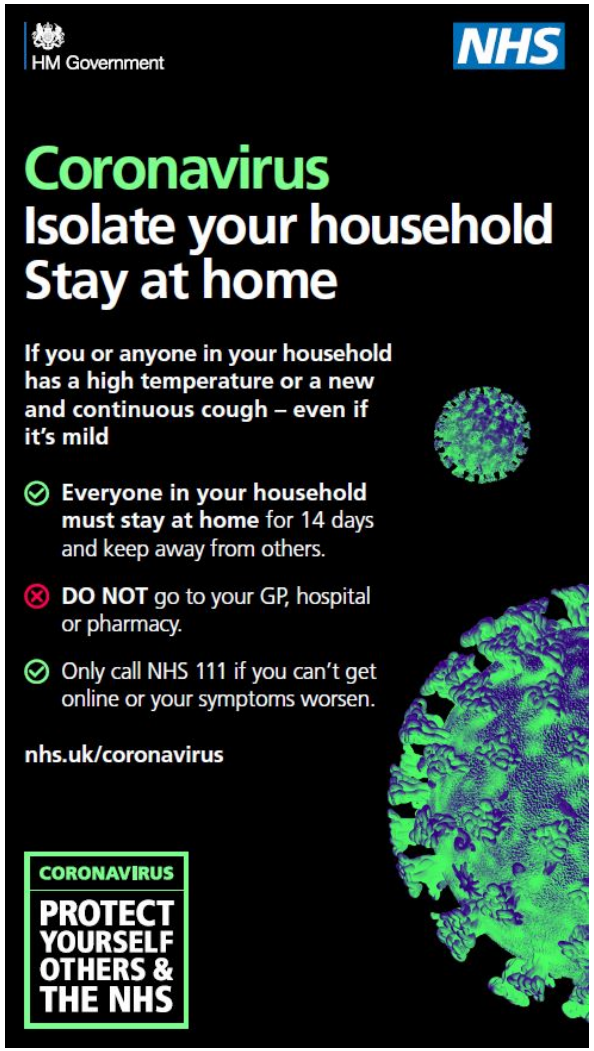
Winter is coming….

- Seasonality?
- Makes syndromic diagnosis and isolation more difficult.
- NHS and all other health systems under greater pressure.
- (Social distancing may reduce flu and other URTI).

Peter Breugel the elder 1565

Symptoms of mild/early COVID-19.

- The great majority of people who are symptomatic have a fever or cough.
- Myalgia (muscle aches), headaches, shortness of breath, chills, sore throat also common.
- These can also occur in other infections.
- Losing sense of smell or taste.
- Most people do not need to seek medical help provided they do not deteriorate.
- They must self-isolate immediately.



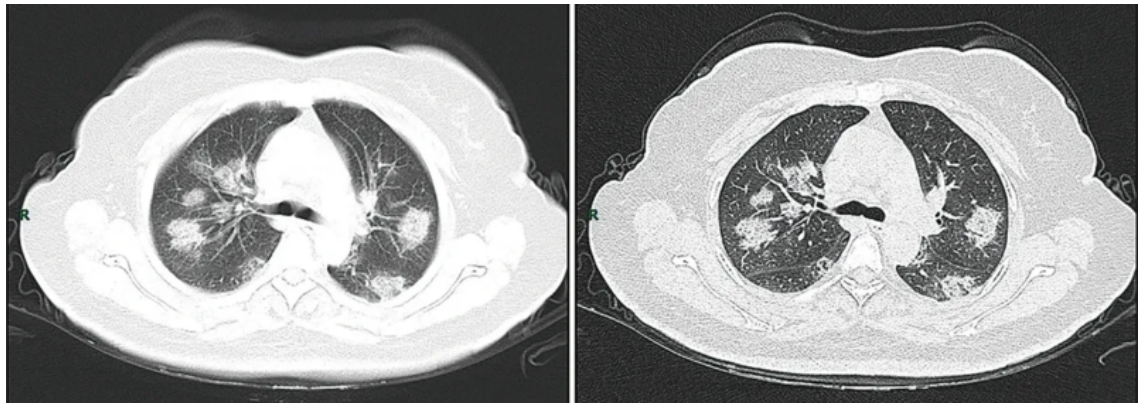
Course of more severe COVID-19.

- Most people recover within 7 days. May have a persistent cough for some weeks.
- A minority fail to settle, and then deteriorate often at about a week.
- Respiratory failure requiring oxygen in most, can have other organ failure.
- Probably an immunological reaction in part or whole.

James Heilman Wiki

Severe/critical disease requiring ICU/HDU level care.

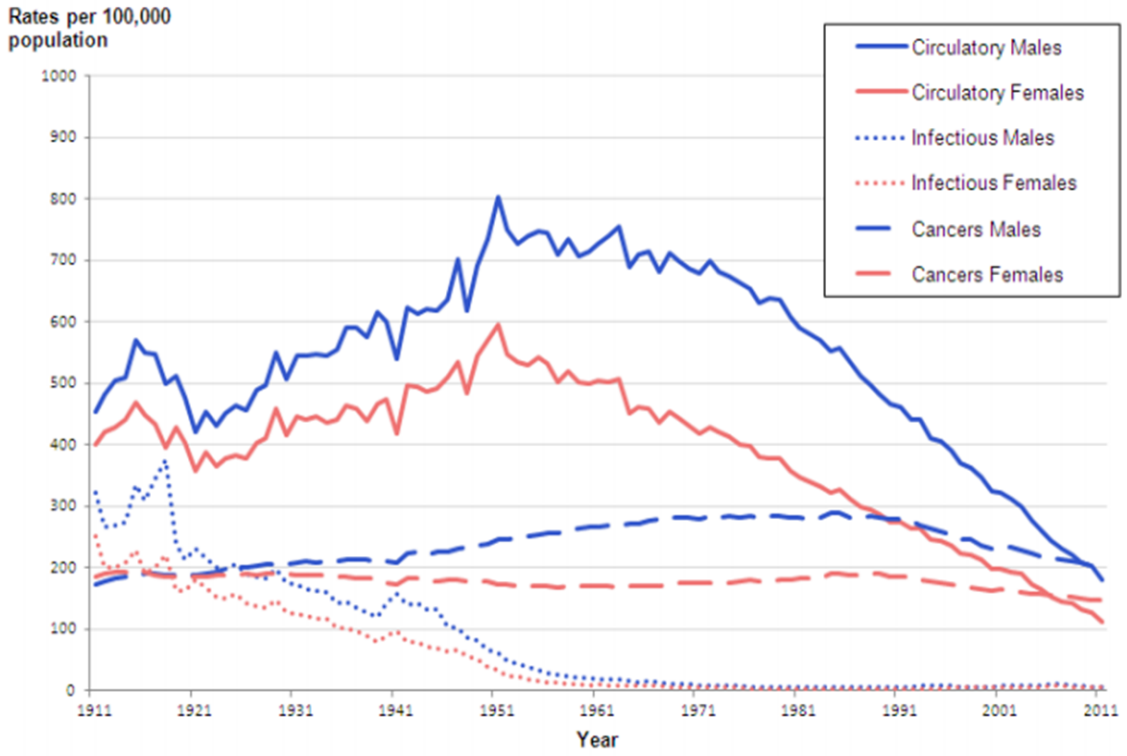
- Can have rapid deterioration.
- Views about how best to manage severe disease evolving.
- Debate about the place of mechanical ventilation.
- Strong risk of clots- pulmonary embolism, stroke included.
- Can have kidney or multi-organ disease. 25% of people requiring ventilation require renal support.



Wiki

Will new technology dig us out of this hole?

- Undoubtedly, eventually.
- We have proved highly effective at tackling multiple infections.
- The question is how, and how quickly. Includes:
- Diagnostics
- Vaccines
- Drugs.



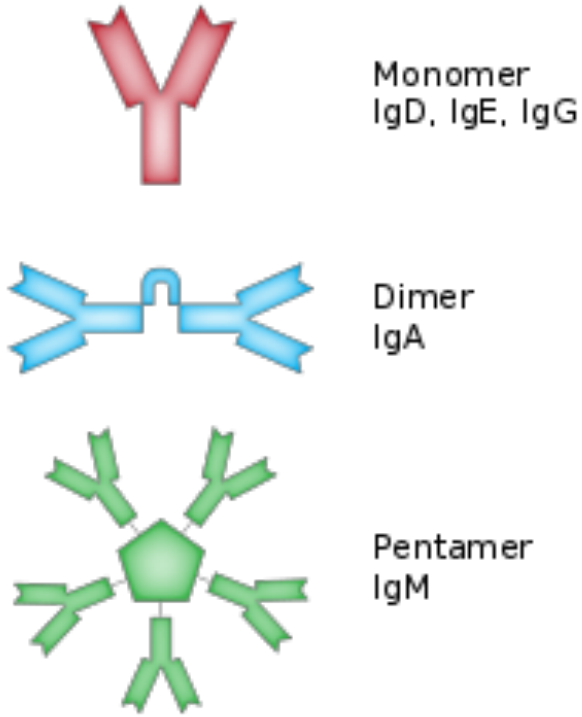
ONS

Direct virus testing.

- The early release of the genome allowed PCR tests for the virus to be developed rapidly.
- Done to test current viral infection.
- Started good, and steadily improving, in the sense of being even more accurate.
- Sampling strategy and how to use varies, especially for asymptomatic people?
- Need faster tests to detect virus early especially in those coming into hospitals.

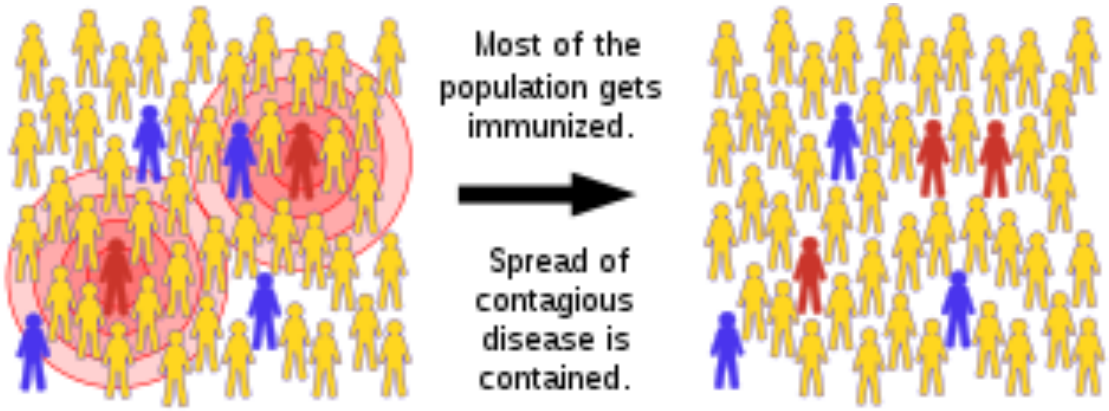
Serology (antibody testing).

- Serology testing for antibodies for past infection.
- Current tests are only moderately sensitive (maybe 70%), but improving rapidly.
- This will tell us how many people have been infected without symptoms.
- We do not currently know whether it will mean people cannot get it again, or will not be infectious.
- Duration of immunity another unknown.



Vaccine strategies in epidemics- epidemic modifying.

- The whole population- epidemic modifying.
- Population immunity- people protect themselves and one another.



- High transmitters.
- Ring vaccination.

Probably not relevant for COVID-19.

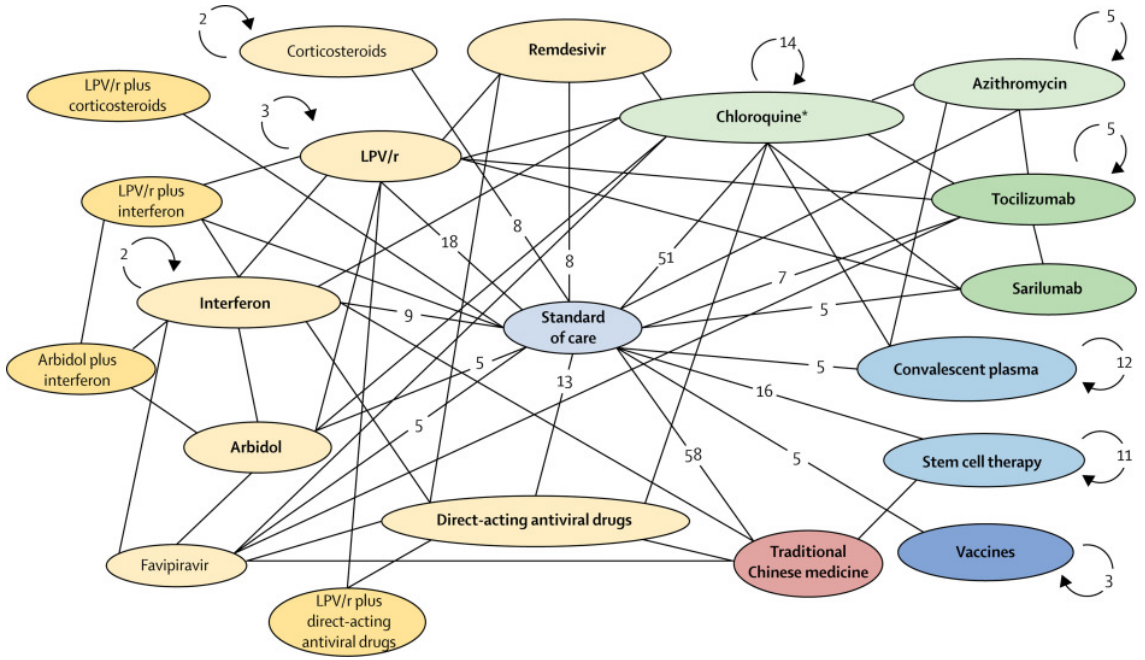
Disease modifying vaccines.

- First generation vaccines may be only partially effective.
- May still have an important role, especially if they reduce disease as well as (or instead of) infection.
- High risk groups.
- Someone can still catch COVID-19, and possibly transmit it, but much less likely to have severe disease.

Drug treatments.

- Treatments can be:
- to prevent mild cases becoming severe, shorten duration
- or to treat severe.

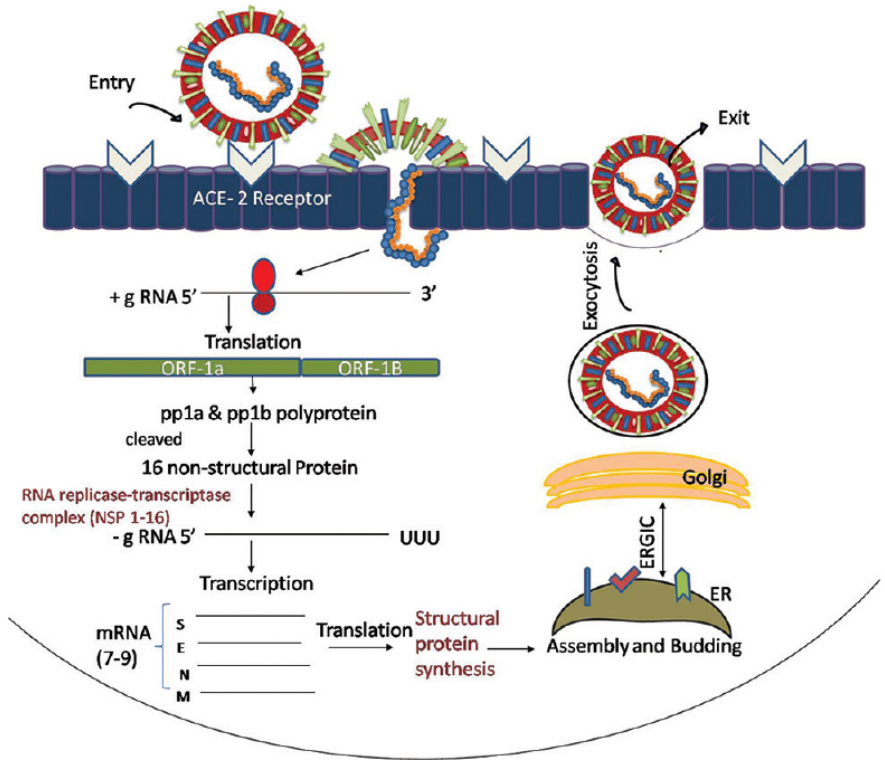
- Antivirals.
- Anti-inflammatory.
- Antibodies against virus.



Thorland et al 2020

Antivirals.

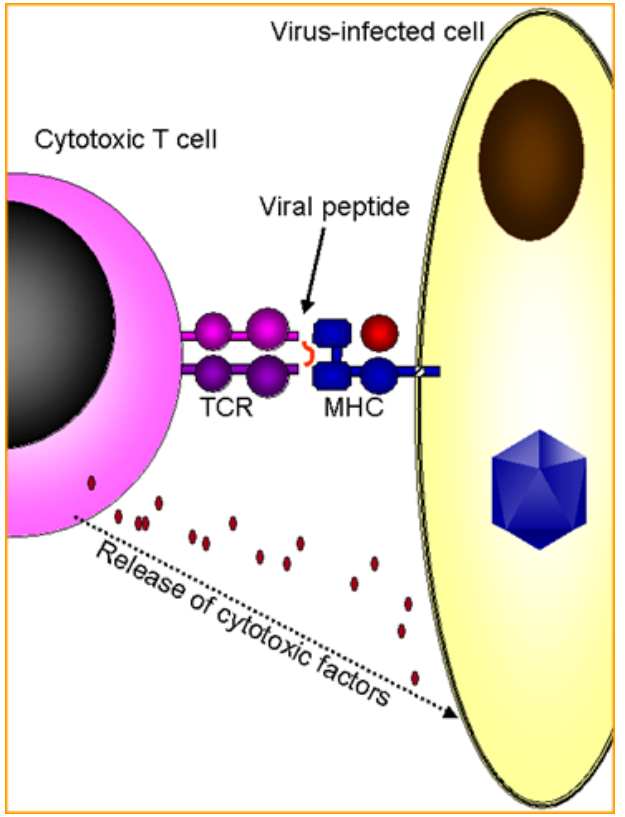
- Especially early disease (or prophylaxis).
- Can act along the virus pathway.
- We now have good antivirals for eg HIV (suppress), Hepatitis C (cure). Both chronic diseases.
- Moderately good for influenza, HSV, (Ebola, Lassa).
- Several existing antiviral being trialled. May have some effect.
- Probably need one to be designed for COVID-19 to have a major effect.



Manisha Prajapat et al 2020

Immune modulating drugs.

- The immune system is complex. Many feedback loops.
- We have powerful drugs which can suppress specific bits of the immune system.
- Include steroids, drugs from rheumatology and inflammatory disease (eg IL6 antagonists), and from transplant.
- Experience of using in infections is mixed.



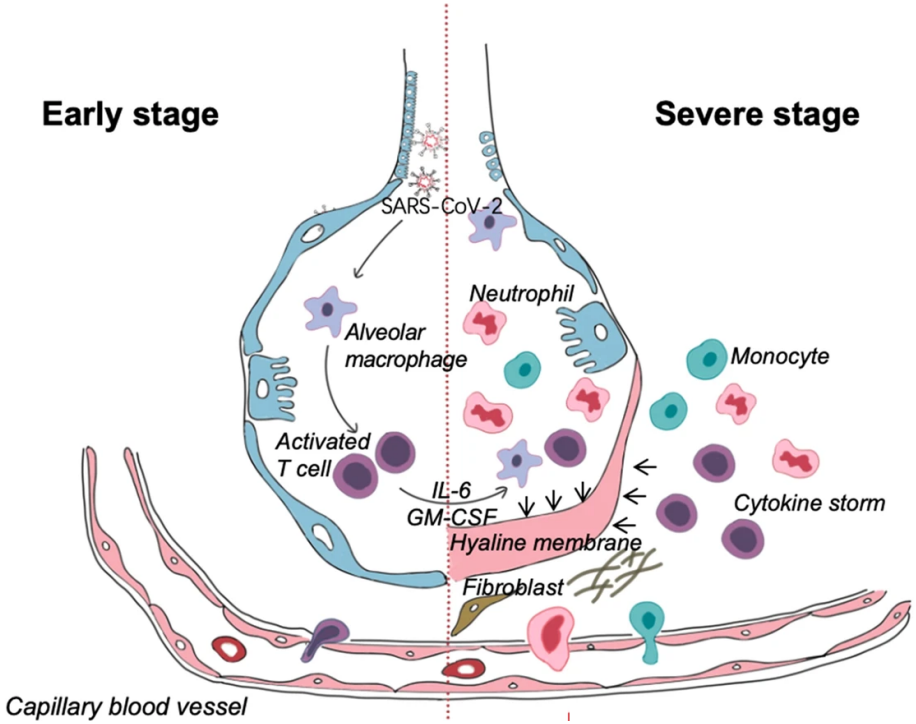
Is severe COVID-19 due to cytokine storm?

- Many white cells activated, release cytokines which activate more white cells. Major inflammation.
- Cytokines that contribute include IL-1, IL-6 and IFN-γ32.
- Antagonist antibodies to:

IL-1 (anakinra, rilonacept and canakinumab)

IL-6 (tocilizumab, sarilumab)

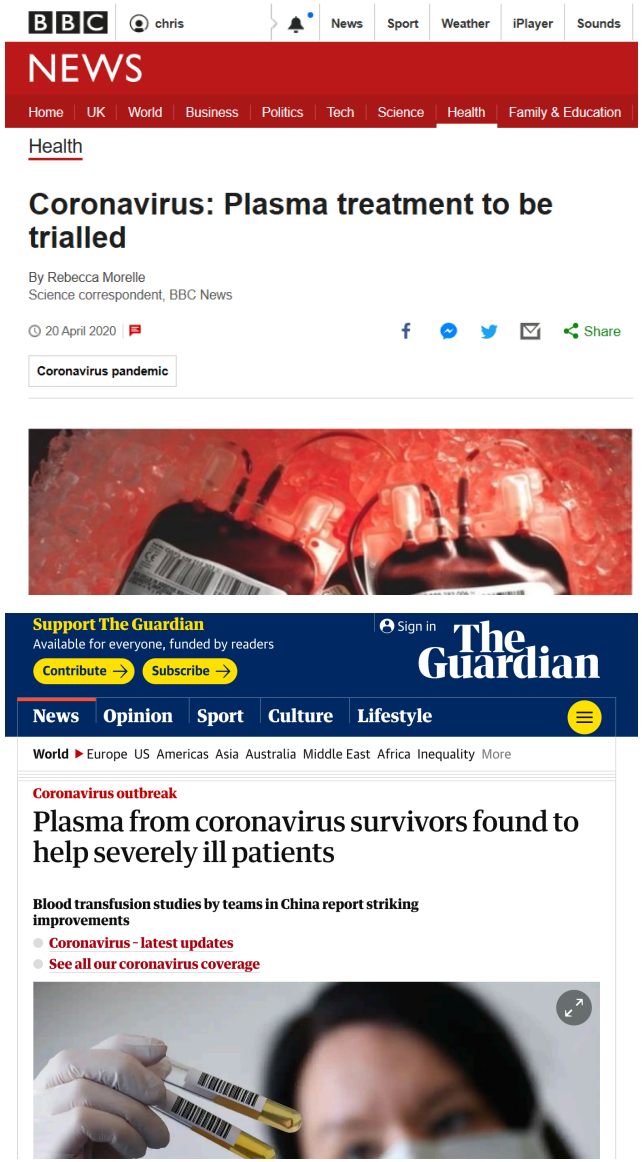
IFN-γ (emapalumab).



Yufang Shi et al 2020

Using immune antibodies to fight disease.

- Conceptually simple.
- Take the blood of people who have recovered, extract their plasma which contains antibodies, and inject them into people with disease.
- If it works can try and manufacture antibodies.

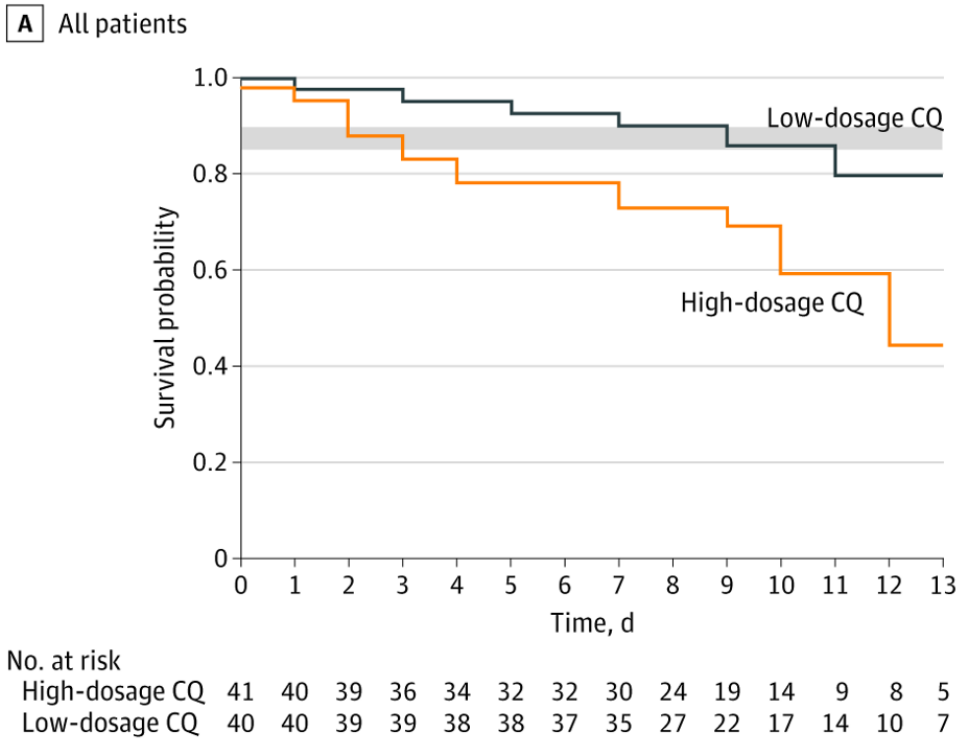


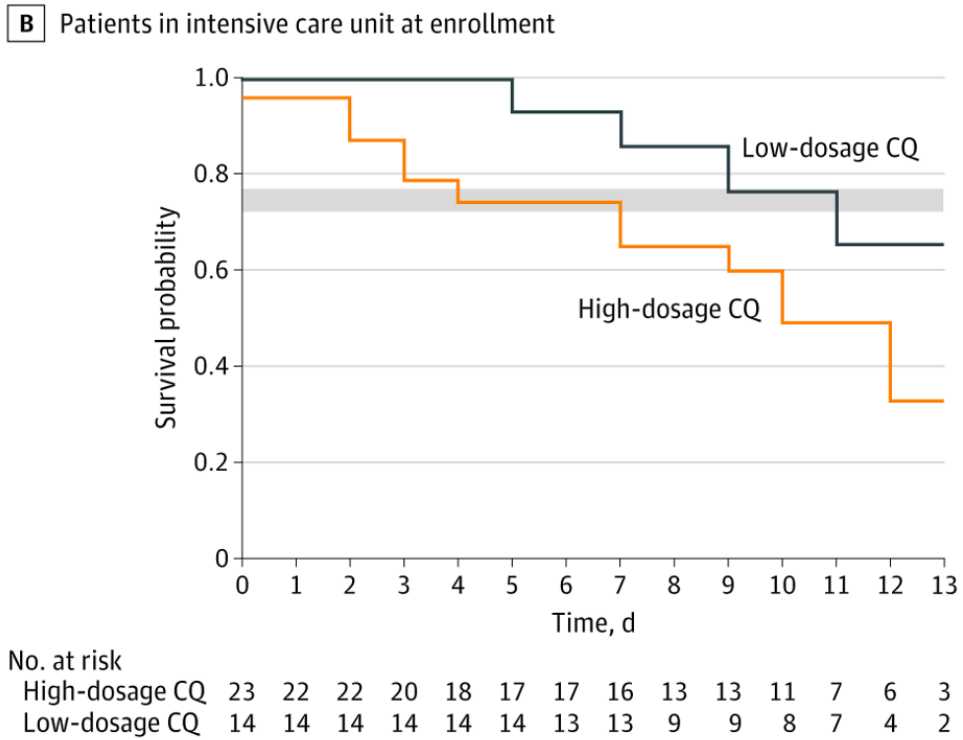
Drugs for prophylaxis.

- It might be possible to have ‘chemical shielding’ of high risk people.
- Could take every day/week like a statin or malaria prophylaxis.
- Or like PREP for high-risk encounters.
- Would need to have low side effect profile. Ideally long lasting.
- Antiviral.

Gaetano Bellei

Whatever we try, we need to do trials.

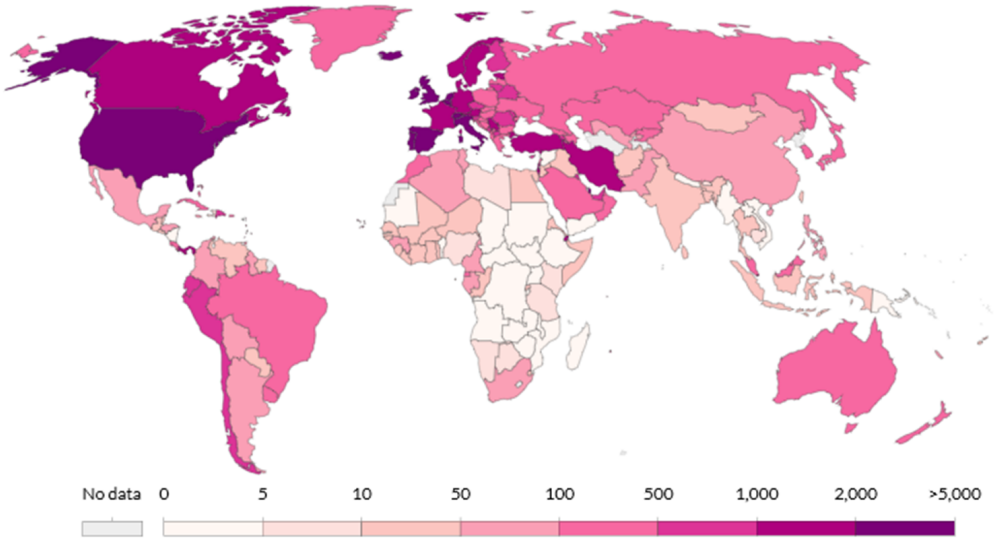




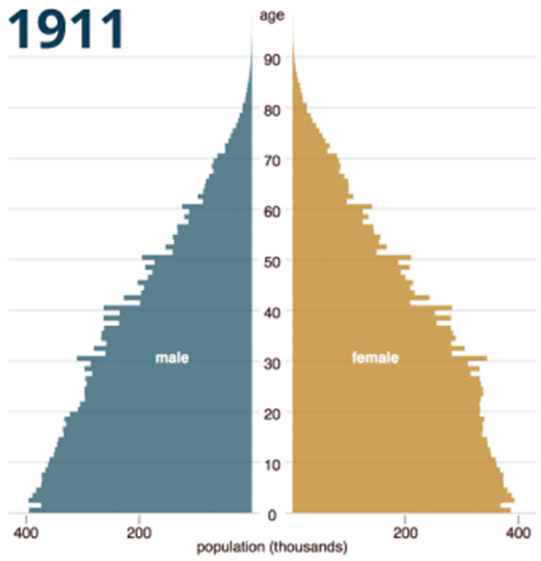
Mayla Gabriela Silva Borba et al JAMA 2020

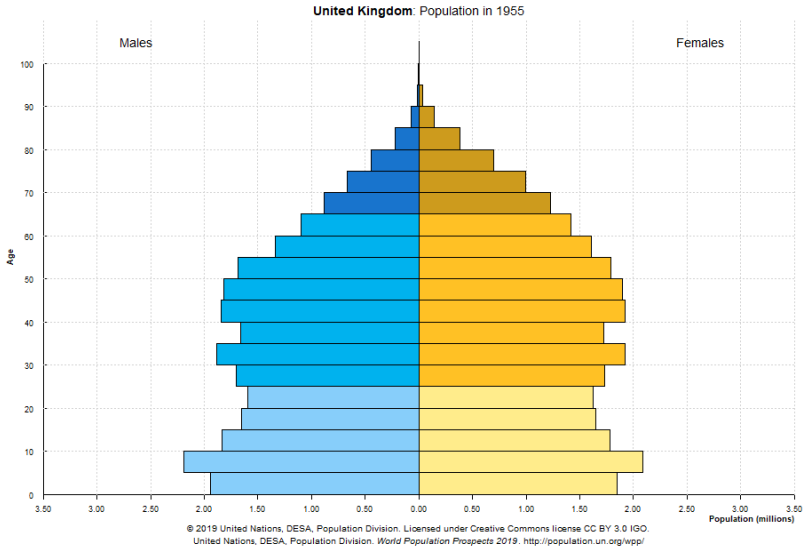
How different is the threat in lower and middle income countries?

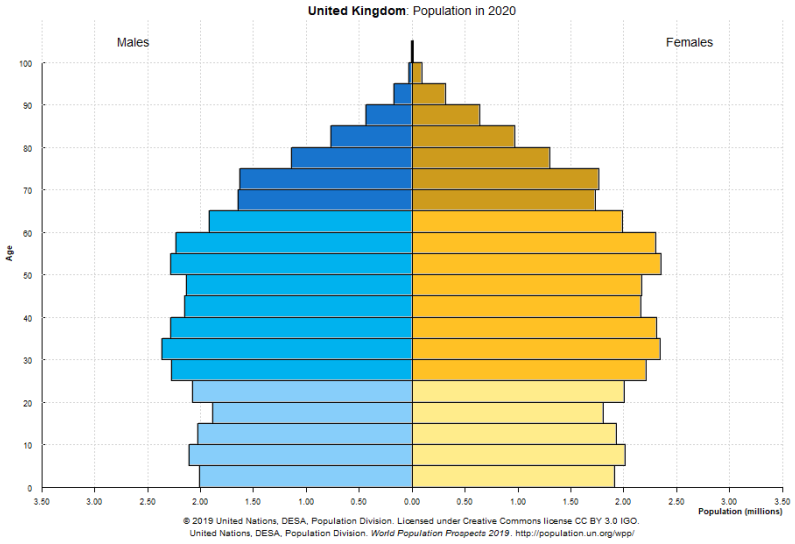
- Poverty, malnutrition.
- Weaker health systems.
- Sometimes better public health infrastructure.
- Climate and seasonality?
- Genetic factors in ethnic risk?
- Demographic structure very different.



UK before 1918 pandemic (L), 1957 pandemic, now. *ONS, UNPD.*

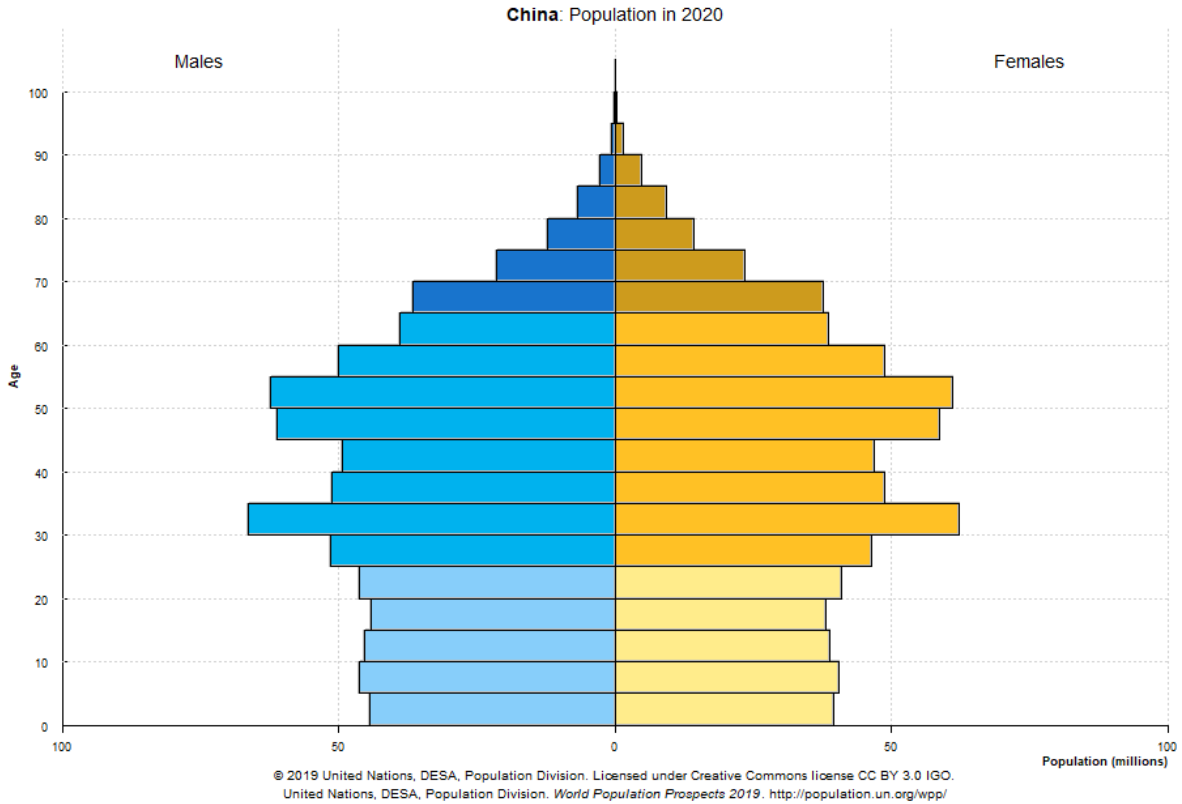






GRESHAM COLLEGE

China, Japan.


China: Population in 2020
Males
Females
Age
100
90
80
70
60
50
40
30
20
10
0
100
50
0
50
100
Population (millions)
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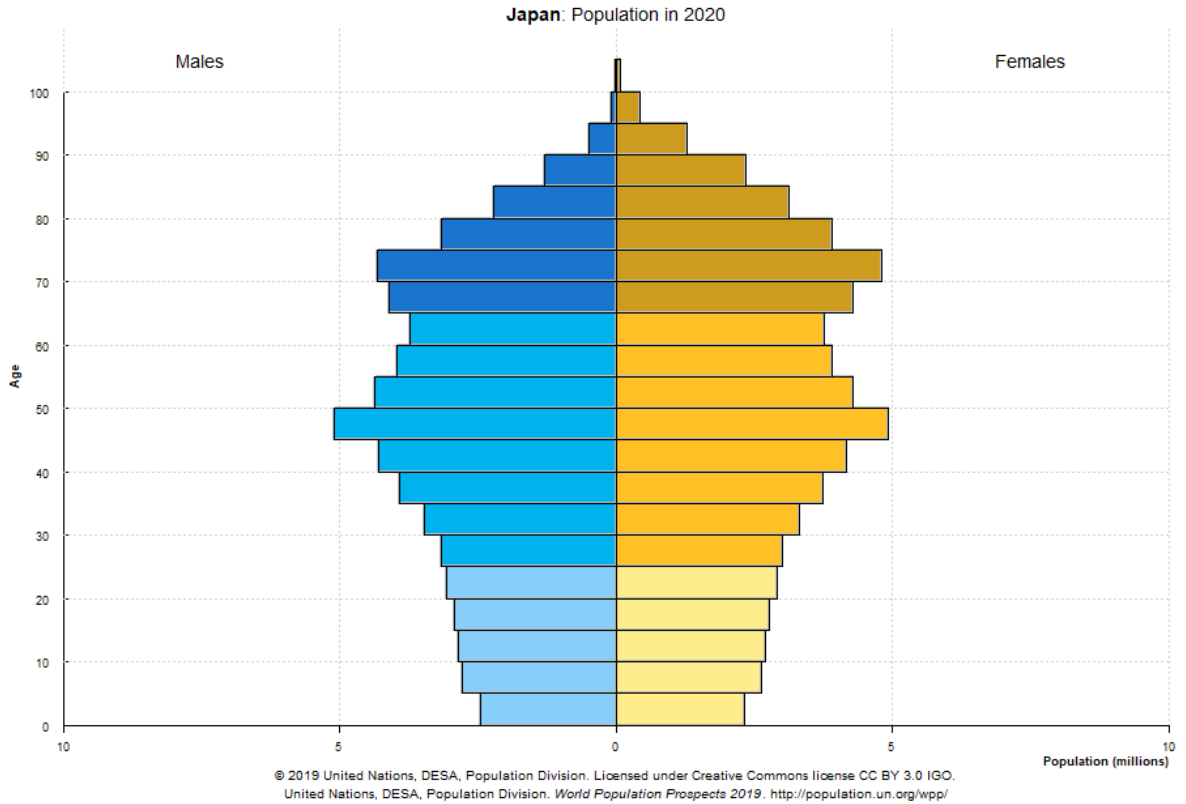
United Nations, DESA, Population Division. World Population Prospects 2019. http://population.un.org/wpp/


Japan: Population in 2020
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Population (millions)
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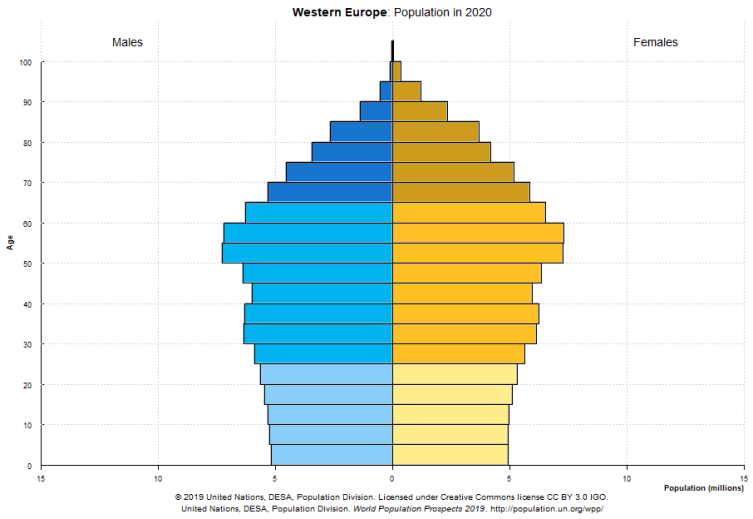
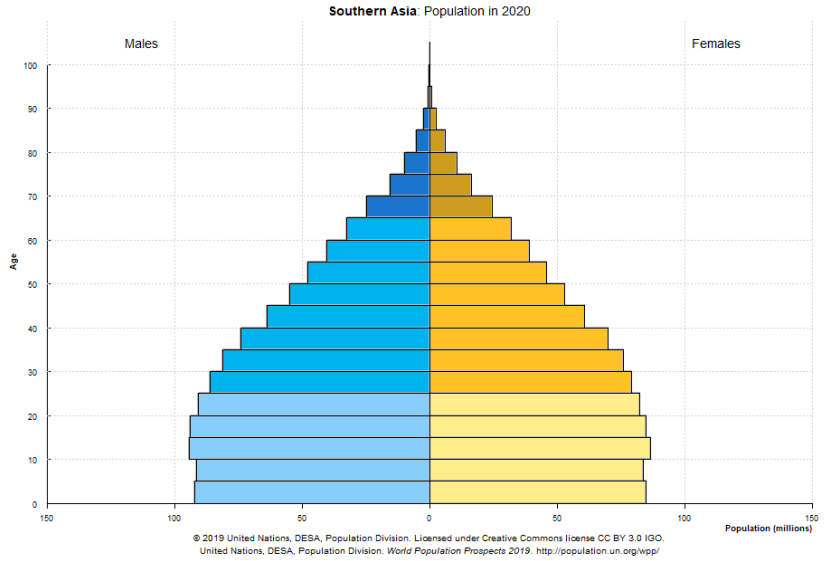
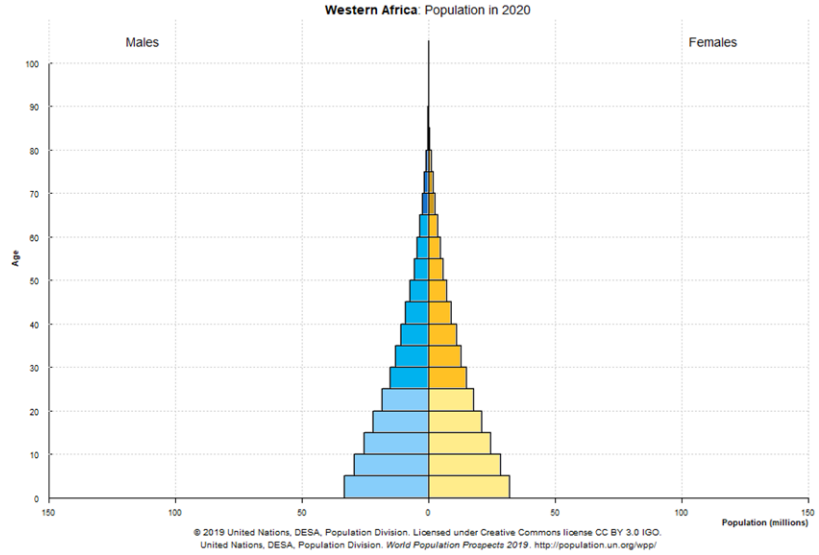
United Nations, DESA, Population Division. World Population Prospects 2019. http://population.un.org/wpp/

Western Europe, Southern Asia, West Africa.







GRESHAM COLLEGE

Many things we do not know, and need to, include:

- Proportion of population infected asymptomatically.
- How long does immunity last?
- Do blood tests correlate with immunity?
- Can children transmit virus?
- Seasonality?
- What is the pathological reason for people deteriorating after a week?
- As well as developing vaccines, drugs, diagnostics.

NIHR | National Institute for Health Research

UKRI Medical Research Council

wellcome

This talk has covered.

- Epidemiology, including mortality, routes of transmission, force of transmission (R_0).
- Epidemiological countermeasures.
- Clinical picture.
- Medical countermeasures including vaccines, drugs, diagnostics.
- Global picture.