Where do people acquire SARs-CoV-2 infection, and the creation of herd immunity by mass vaccination

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PREPARE Workshop, 16th December 2020

In January/February 2020 governments were told there are - "no good options"

"Governments will not be able to minimise both deaths from coronavirus disease 2019 (COVID-19) and the economic impact of viral spread. Keeping mortality as low as possible will be the highest priority for individuals; hence governments must put in place measures to ameliorate the inevitable economic downturn."

Lancet, March 21st 2020

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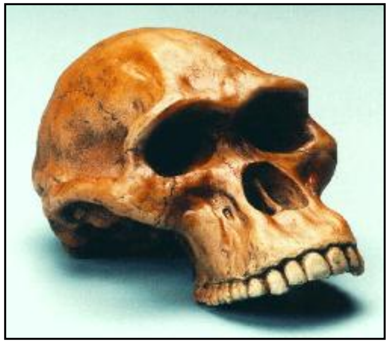
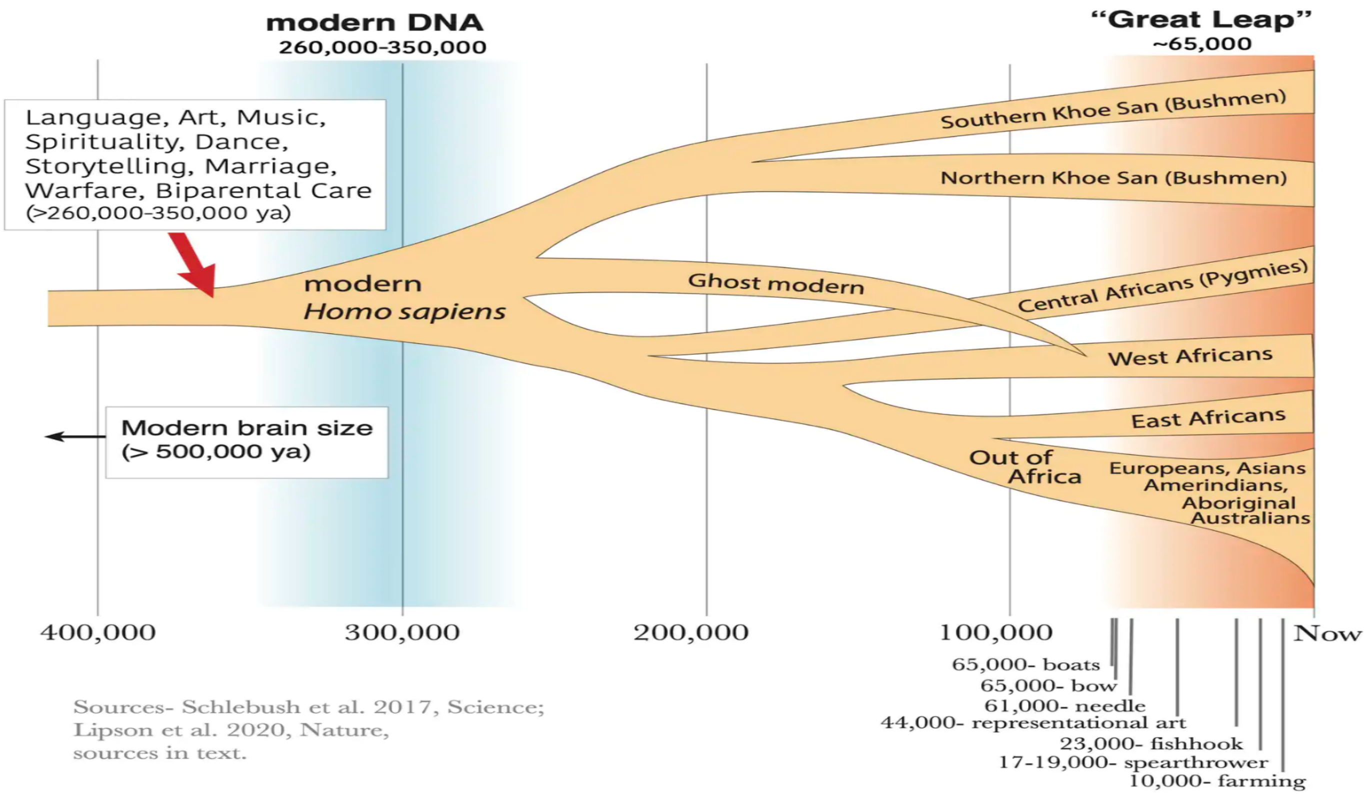
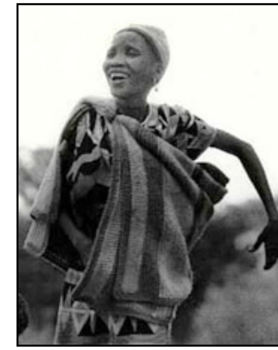
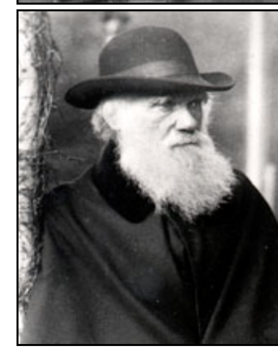
Human evolution

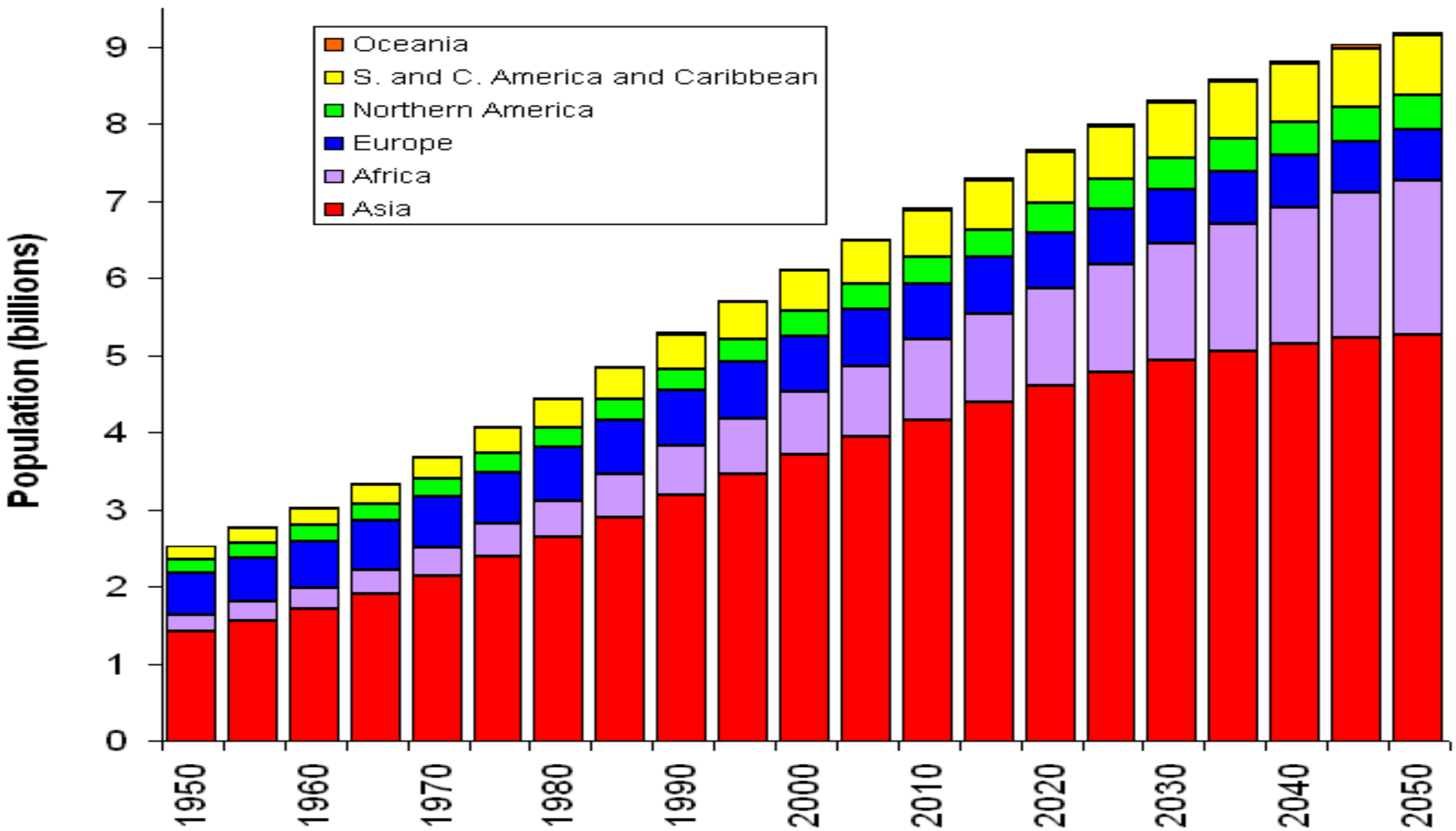








World population growth by continent: past and predicted



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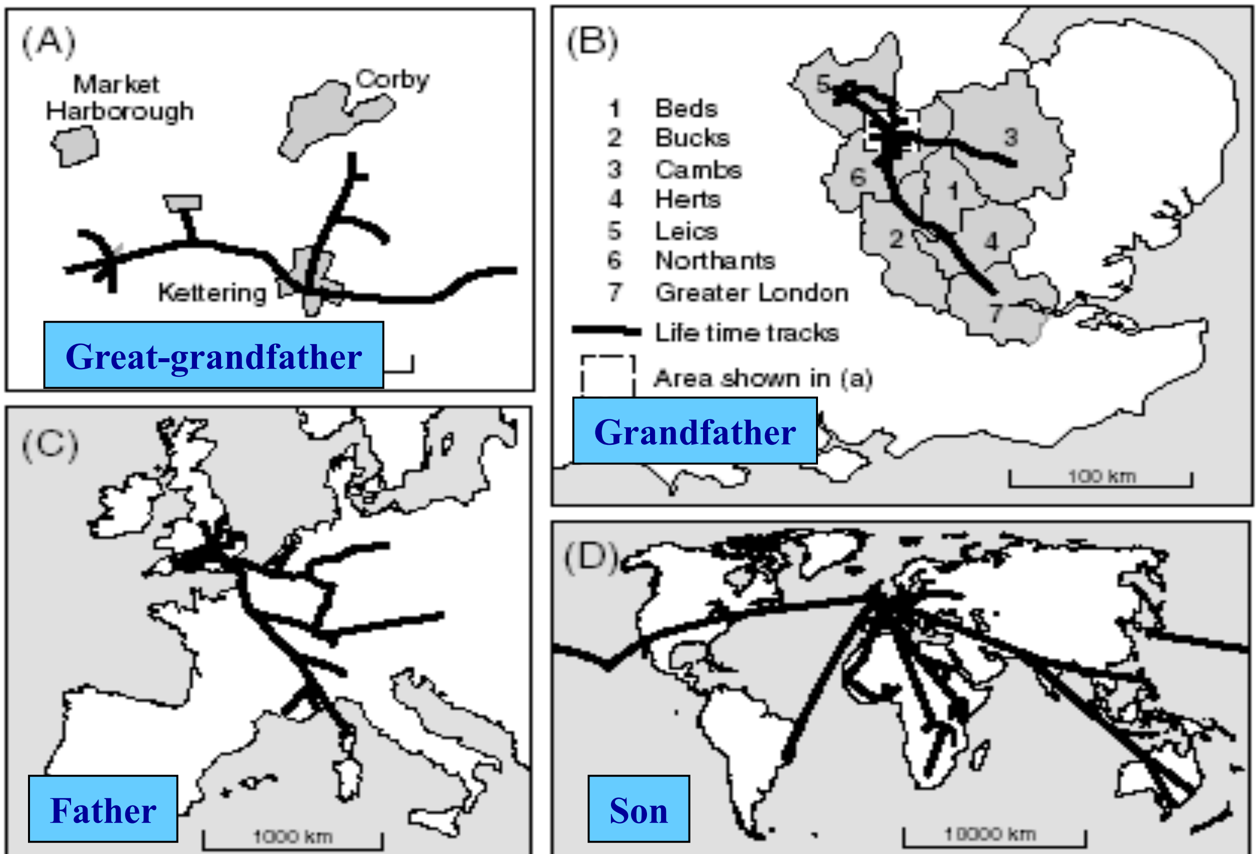
Record of increasing travel over four male generations of the same family.

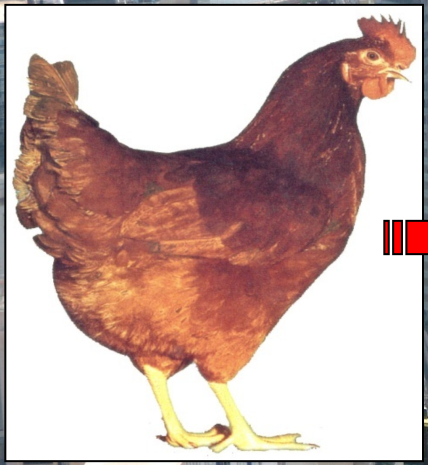
(A) Great-grandfather. (B) Grandfather. (C) Father. (D) Son. Each map shows in a simplified manner the individual's 'life-time tracks' in a widening spatial context, with the linear scale increasing by a factor of 10 between each generation (Bradley, 1994 Geog. Ann. 76:91-104).

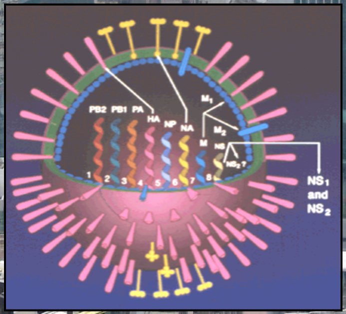


Air traffic flow – world picture - 2014

Hong Kong

Re-assortment of bird and human influenza viruses





Evolution of SARS-CoV 2 in mink

Less Developed Regions

	1970	1994	2000	2015
Africa	0	2	2	3
Asia	2	10	12	19
Latin America	3	3	4	5

More Developed Regions

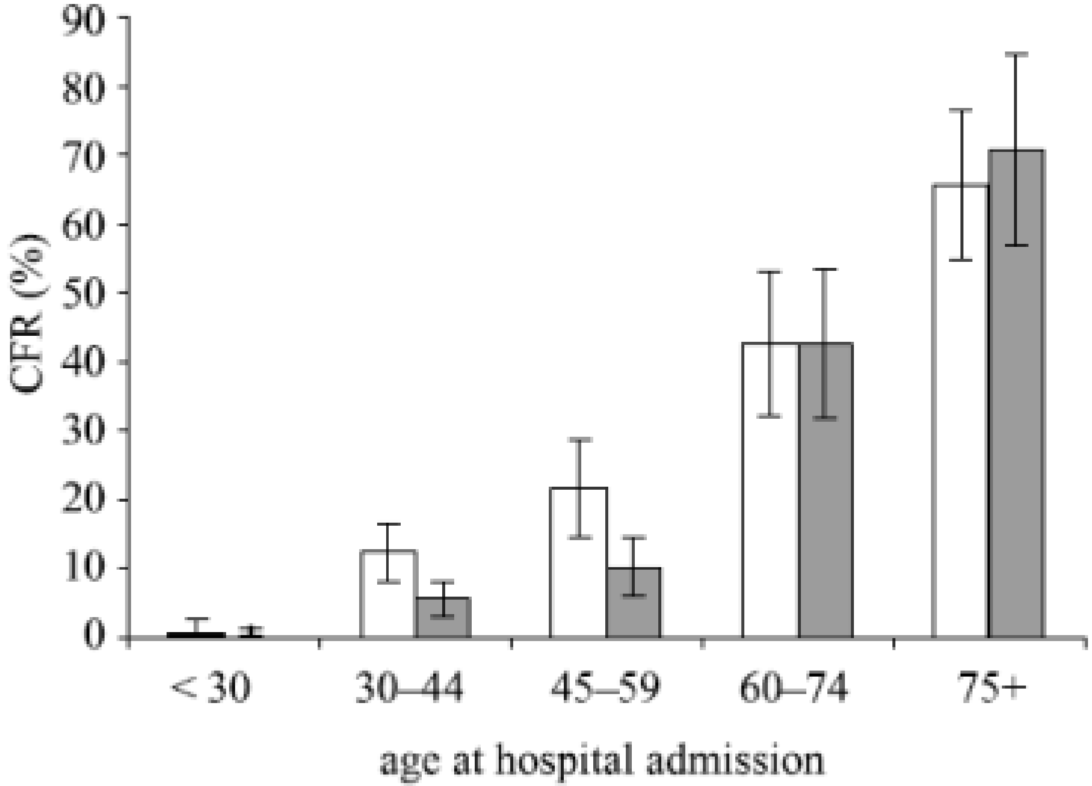
Europe	2	2	2	2
Japan	2	2	2	2
North America	2	2	2	2

Comparisons with influenza A and SARS-CoV-1

Virus	Incubation period	Asymptomatic and infectious	Infectious period	Basic Reproductive number R_0	Case fatality rate (CRF) (age dependent)
Influenza A (H1N1)	1-2 days	Yes - ½ -1 day	3-4 days	1.1-1.5	0.001- 0.1%
SARS-CoV-1	4-5 days	No	7-8 days	2-3	6-8% for those less than 60 years of age and 55% for those over 60
SARS-CoV-2	3-5 days	Yes - many days	10-14 days	2-4	0.5% to 1% across all age groups

Case fatality rate SARS-CoV-1 in Hong Kong

(Anderson et al, 2004)

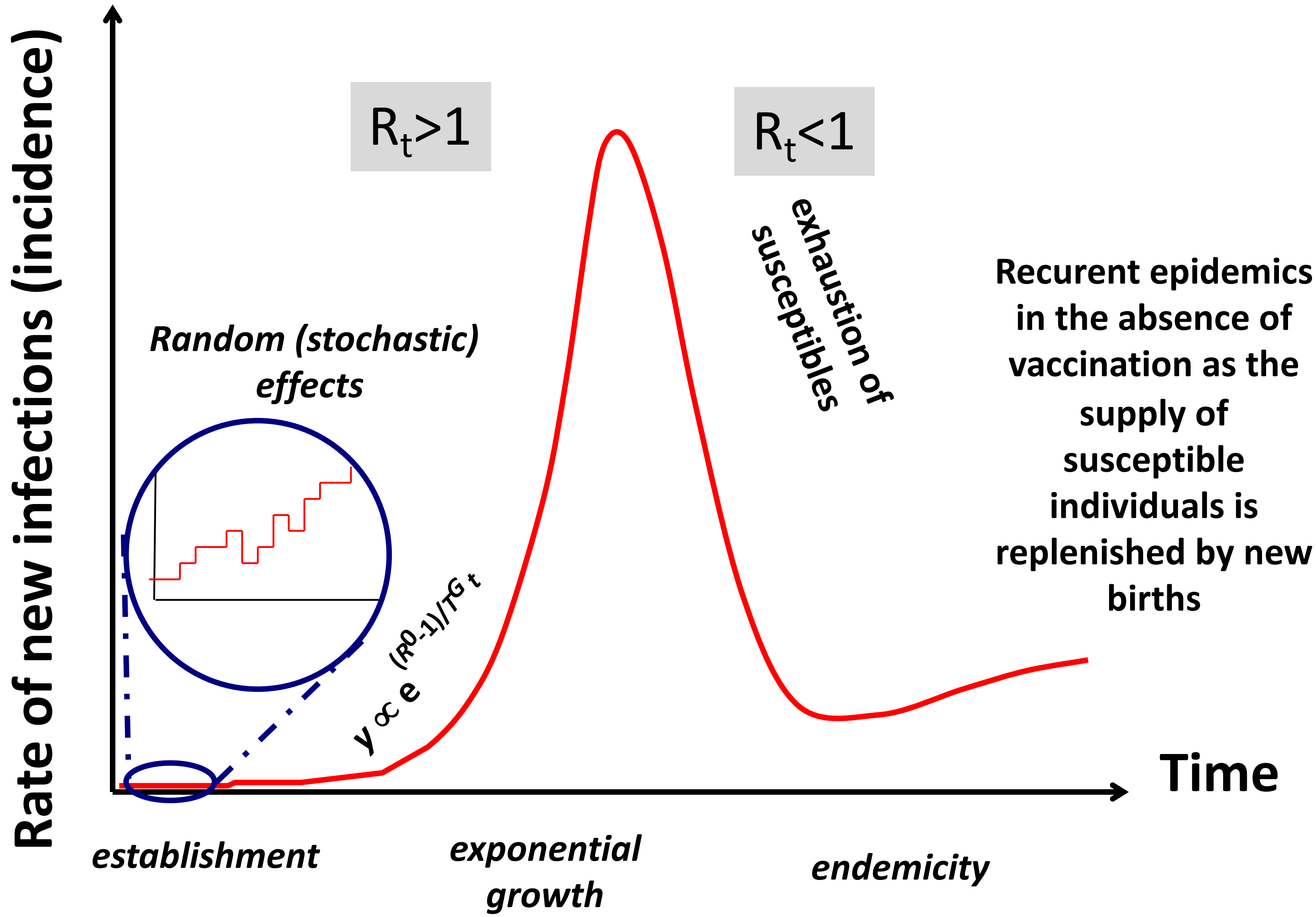


The epidemic curve

T^G = Generation time of infection – can be influenced by social distancing measures

R^0 = Basic Reproductive number

y (growth rate of epidemic) $\asymp \exp\{[(R_0\text{-}1)/(T_G)]t\}$



Simulations of impact of mitigation measures (social distancing) calculations done in January to February 2020

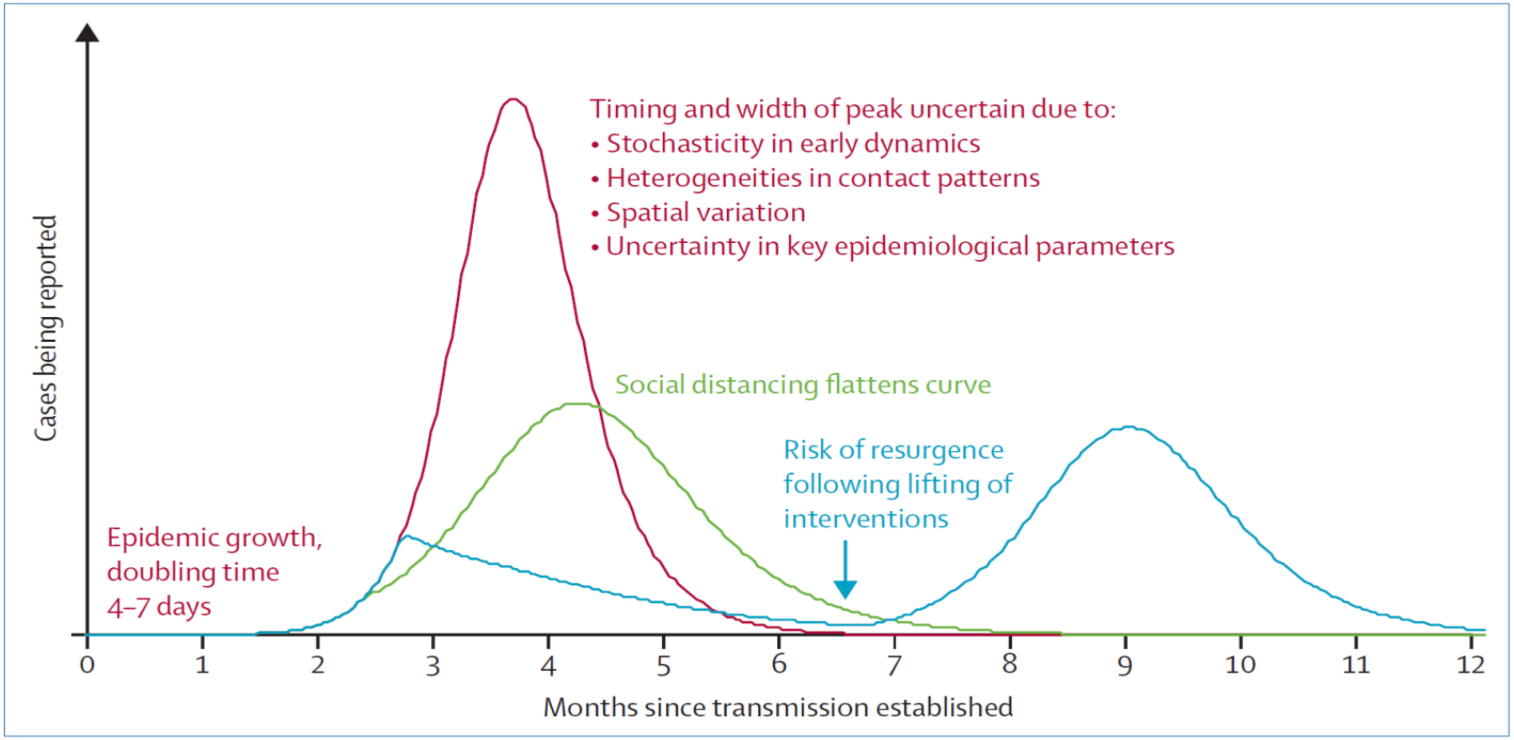
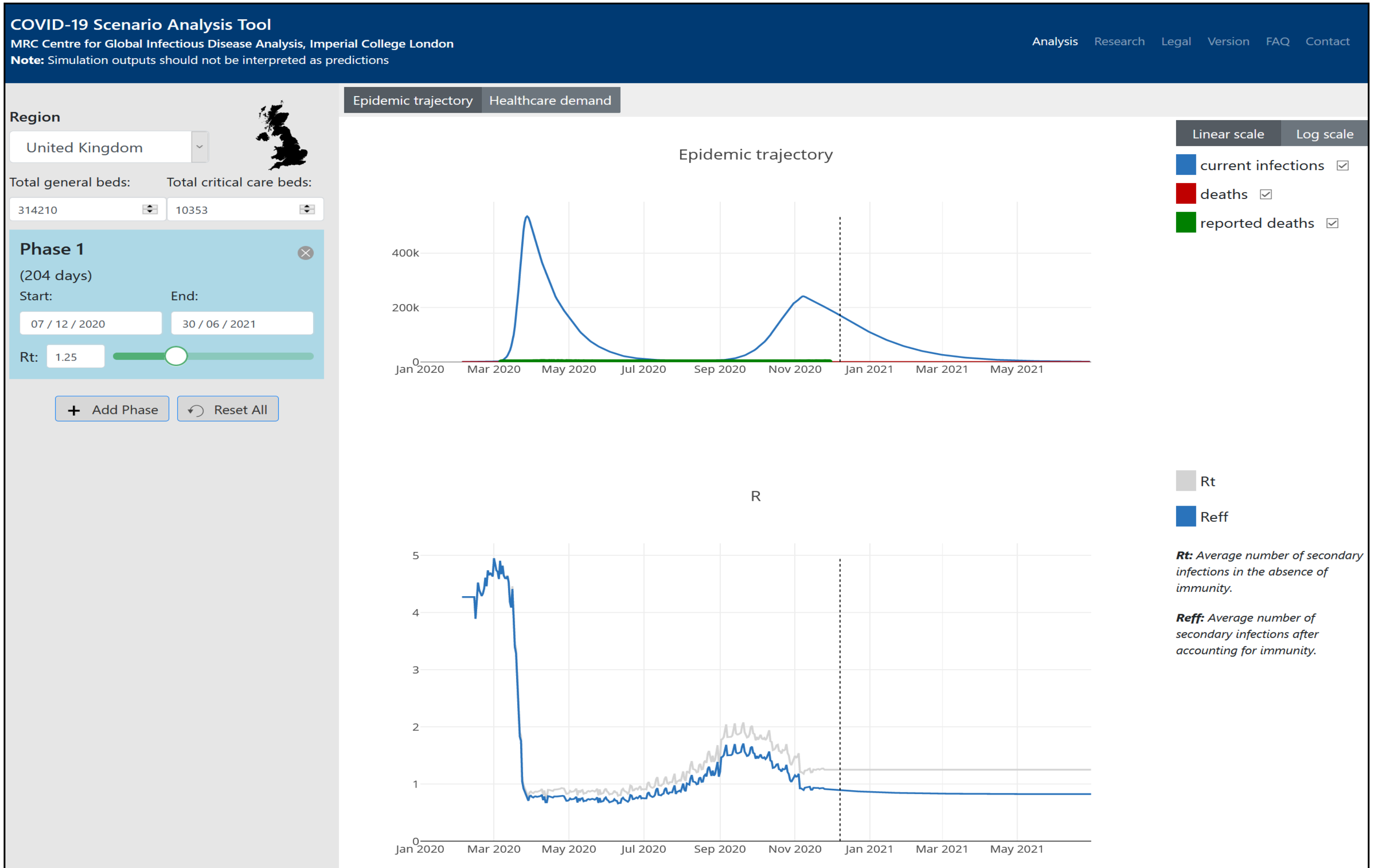


***Figure:* Illustrative simulations of a transmission model of COVID-19**

A baseline simulation with case isolation only (red); a simulation with social distancing in place throughout the epidemic, flattening the curve (green), and a simulation with more effective social distancing in place for a limited period only, typically followed by a resurgent epidemic when social distancing is halted (blue). These are not quantitative predictions but robust qualitative illustrations for a range of model choices.

Transmission dynamic models of Covid-19 and impact of interventions (Imperial College London & BioNano)



Estimates of the Basic Reproductive Number, R_o

Infection	Location	Time	R_0
Measles	England	1947-50	13-15
Varicella	USA	1943	7-8
Mumps	Netherlands	1970-80	11-14
Rubella	West Germany	1970-79	6-7
Polio	USA	1955	5-6
HIV-1	1981-85	1981-85	11-12
Smallpox	1940	1940	4-6
Influenza A	England	2010	1.1-1.5
SARS-CoV-1	Hong Kong	2002-3	4-5
SARS CoV-2	China	2020	2.5-4.8

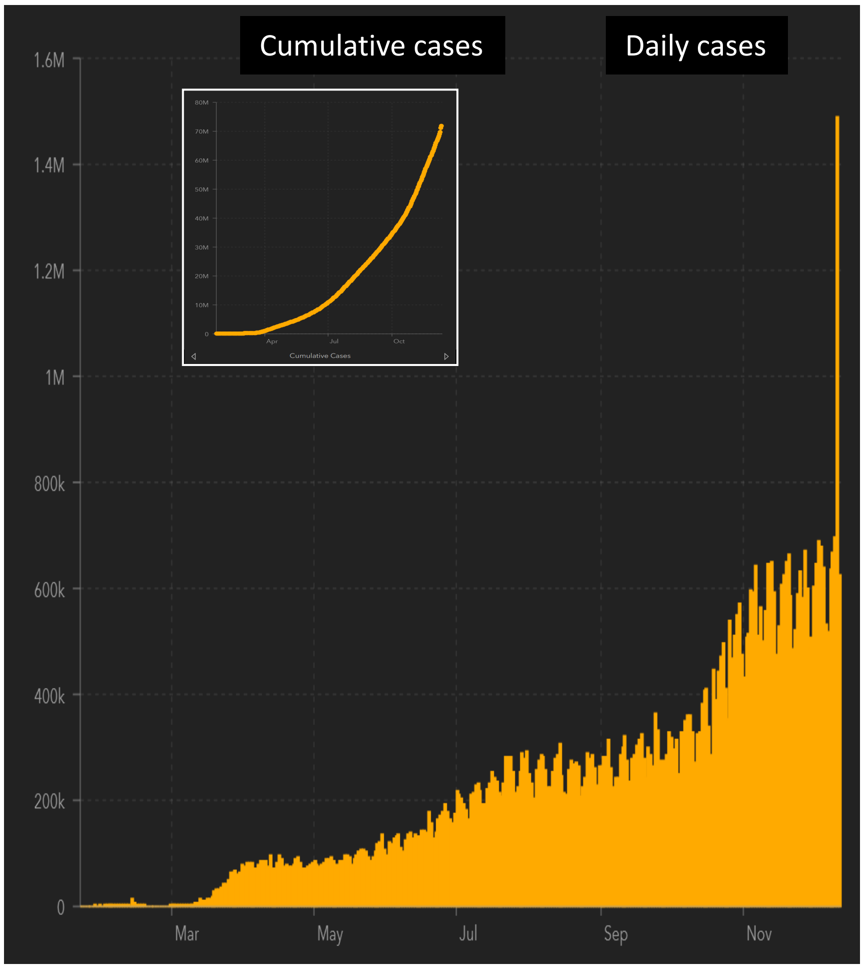
Estimates of R_0 for SARS-CoV-2

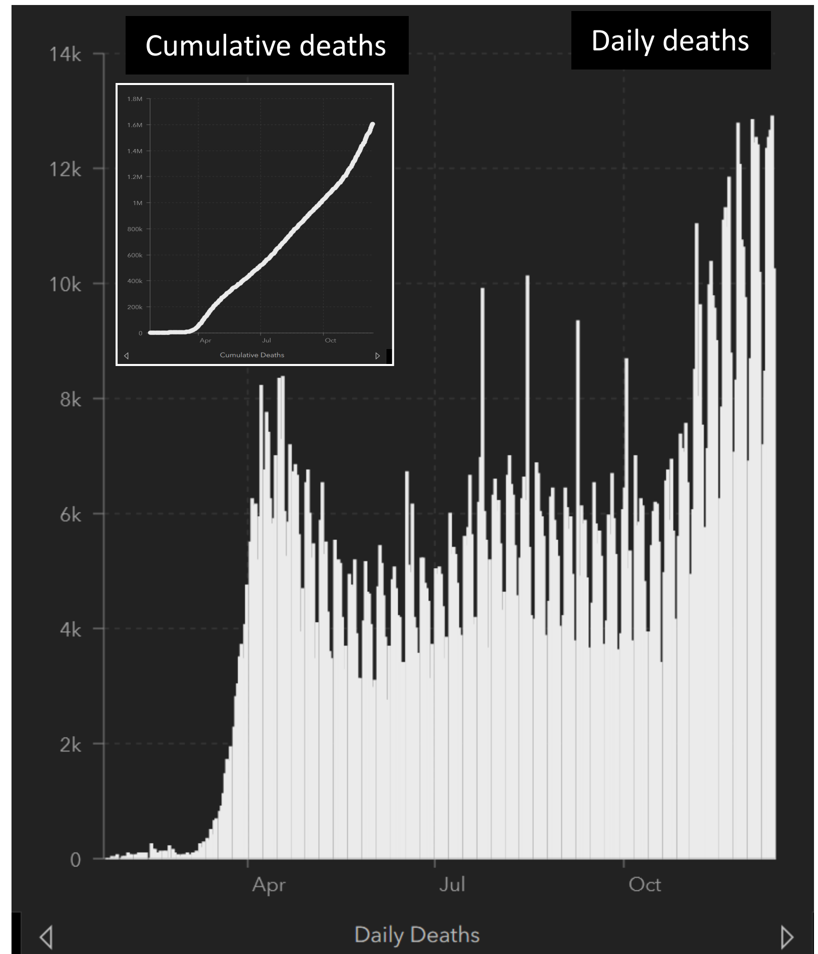
Authors	Date	R_0 estimate
Ferguson N, Laydon D, Nedjati-Gilani G, *et al*[287]	16/03/2020	2.4 (2.0 – 2.6)
Lourenço J, Paton R, Ghafari M[288]	Pre-print	2.25 or 2.75
Chen X, Dong Y, Xiaoyue Y[289]	05/04/2020	4.8 (4.7 – 4.9)
Jarvis C, Zandvoort I, Gimma K[290]	07/05/2020	2.6 (SD 0.54) pre-lockdown 0.62 (0.37 – 0.89) post-lockdown
Lonergan M, Chalmers J[291]	01/06/2020	2.1 (1.8 – 2.3) pre-lockdown, 0.99 (0.96 – 1.02) post-lockdown (based on confirmed cases) 2.6 (2.4 – 2.9) pre-lockdown, 0.85 (0.80 – 0.90) post-lockdown (based on confirmed deaths)
Tang J, Young S, May S[292]	19/05/2020	1.13 hospitalised patients 1.38 community patients 1.21 hospital staff
Brett T, Rohani P[293]	Pre-print	2.3
Jit M *et al*[294]	07/05/2020	2.0 (1.9 –2.1)
Goscé L, Phillips A, Gupta P[295]	24/05/2020	2.56 (post-lockdown, no interventions) 2.07, 1.94, 1.87 (less stringent social distancing with weekly universal testing x1, x2, x3 a week) 3.07 (shielding 60< year olds) 1.92 (weekly universal testing, and face covering use) 0.5, 0.44, 0.27 (during lockdown with weekly universal testing, face coverings, face covering and contact tracing) 2.23, 1.59, 1.53, 0.64 (post-lockdown with 30% facemask and face coverings, 50% facemasks and coverings, 80% facemasks and 50% face coverings, 80% facemasks and face coverings)
Althouse B, Wenger E, Miller J[296]	Pre-print	2.6
European Centre for Disease Prevention and Control[297]	23/04/2020	3.28

NB All available estimates of R_t and R_0 Figures in the UK. Estimates provided at both a high level across the UK, or for specific demographics such as hospital staff members.

Global- daily reported cases of Covid-19 and deaths

(source – John Hopkins University)





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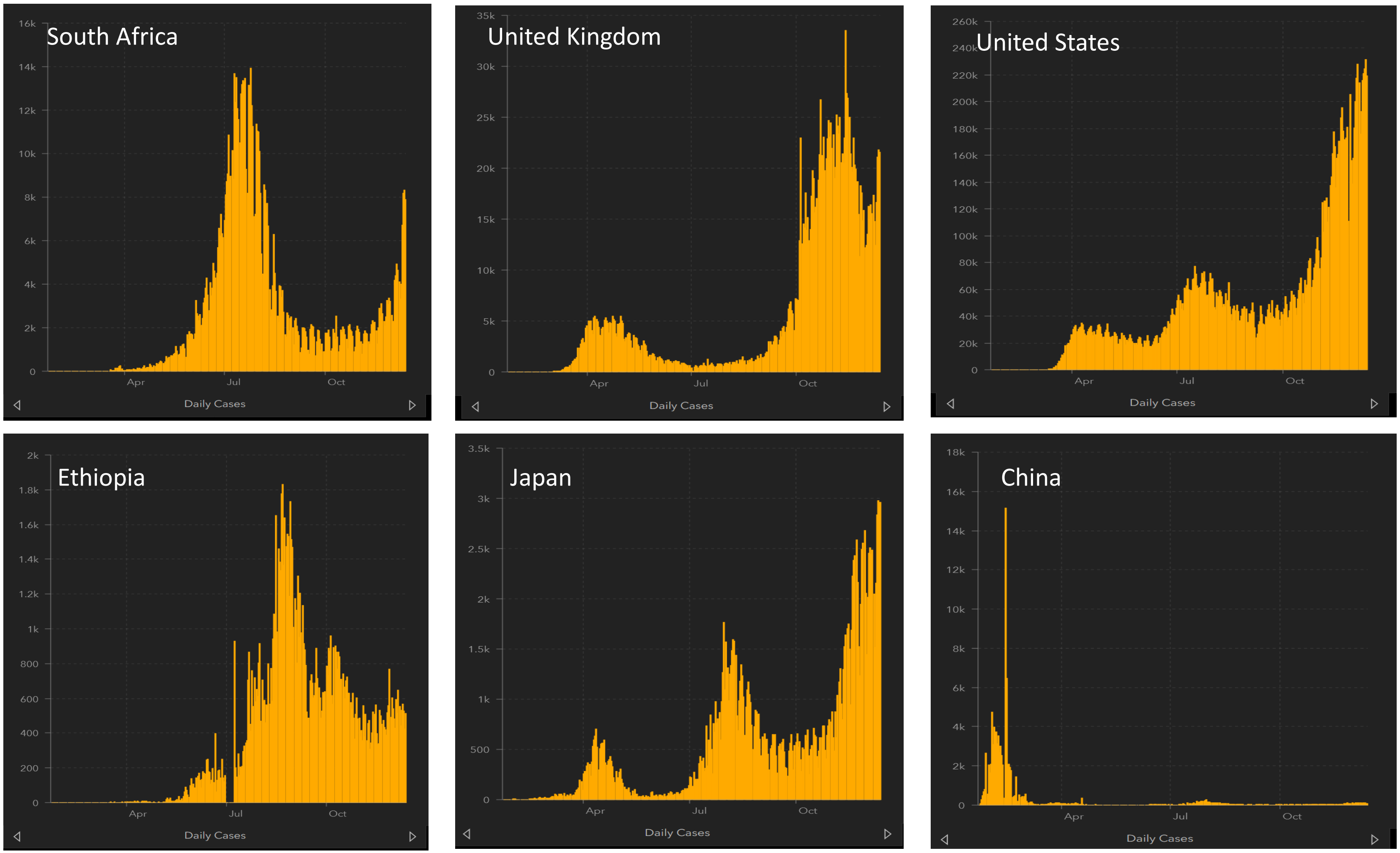
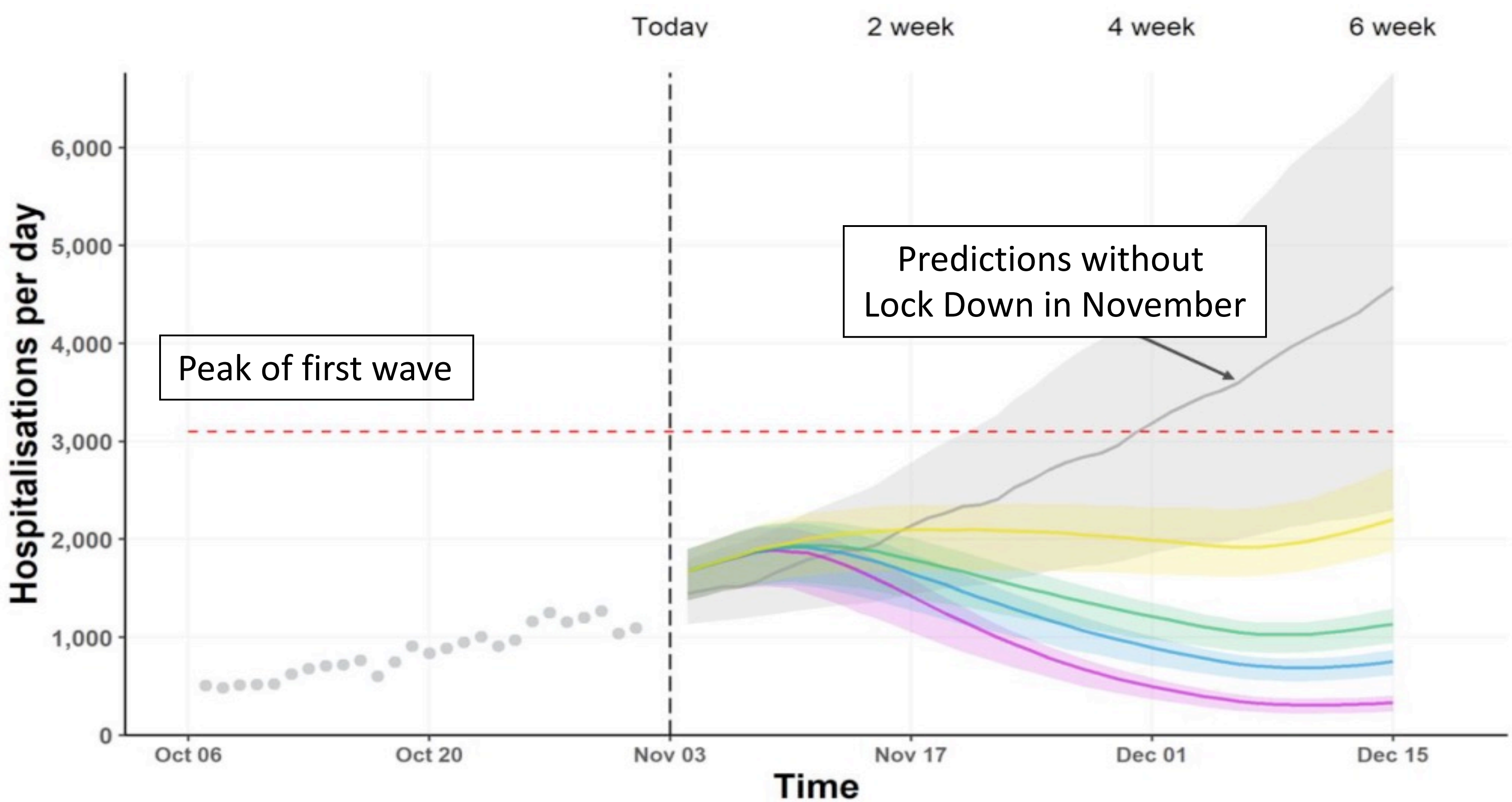
Much heterogeneity in epidemic patterns between countries

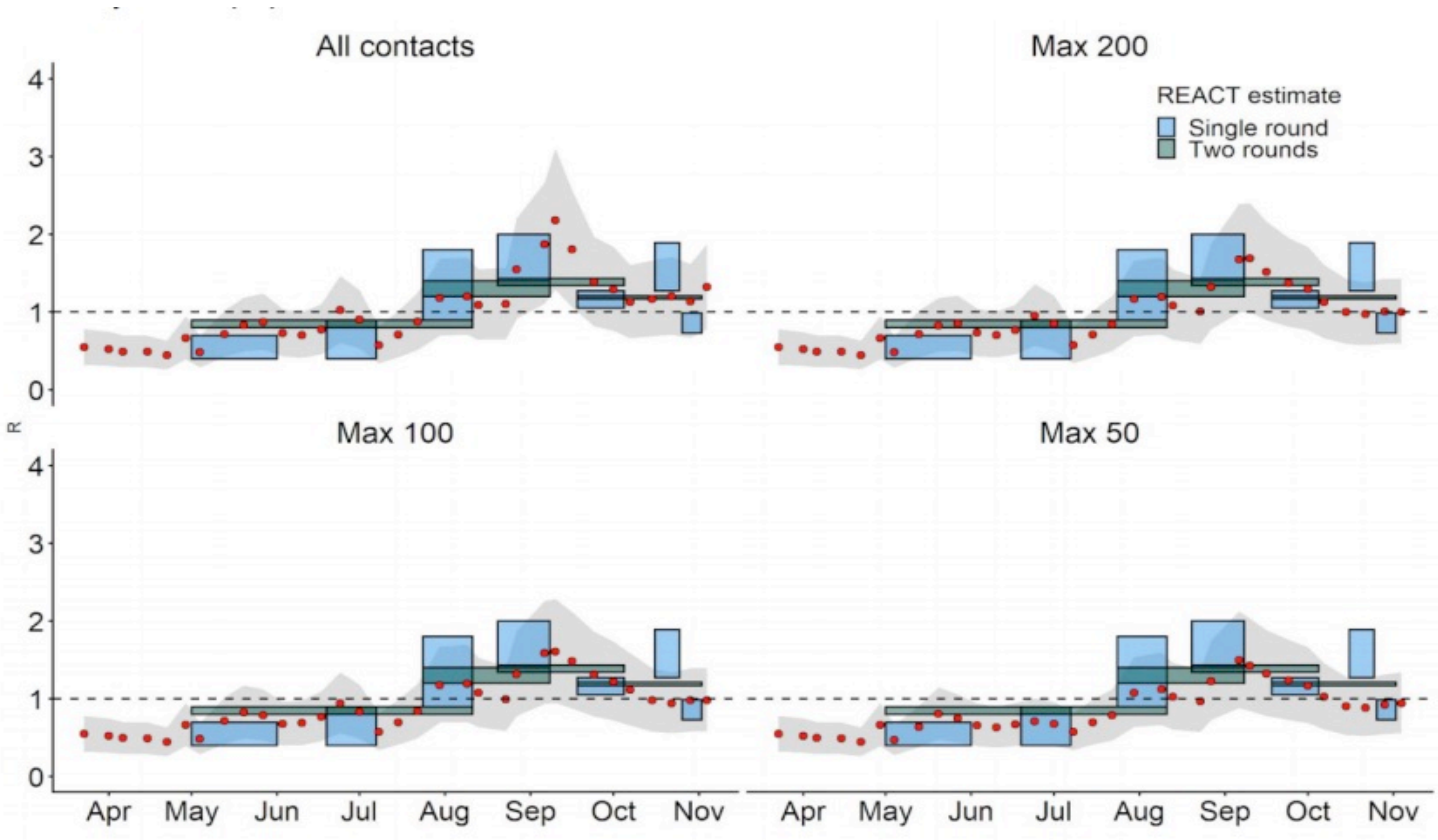


Social distancing measures (Non Pharmaceutical Interventions NPIs)

The second wave in the UK – hospitalisation and deaths a better measure of the course of the epidemic?



Impact of "Lock down" in the UK after first (March) and second (September) waves as reflected in longitudinal changes in R_t



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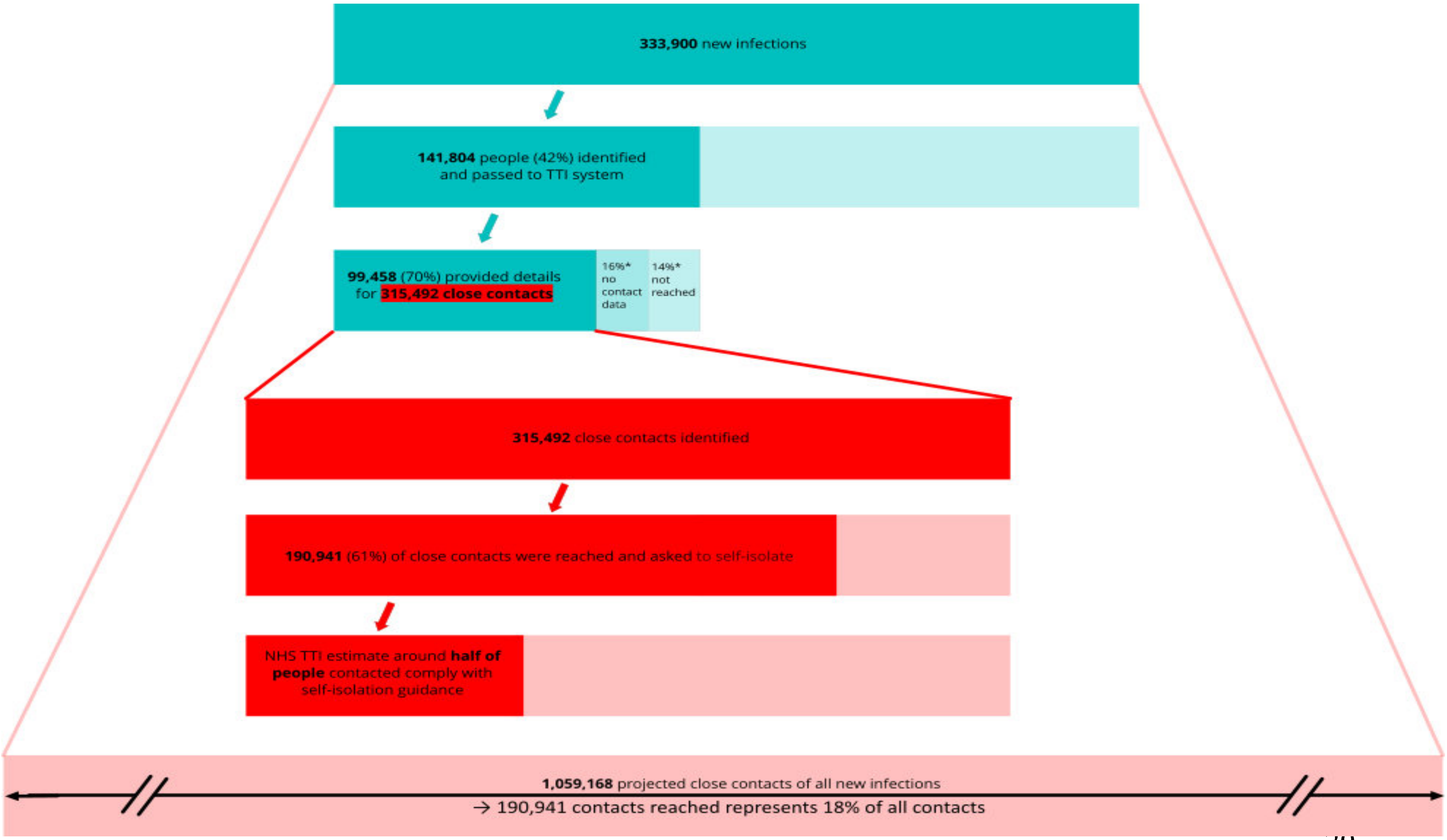
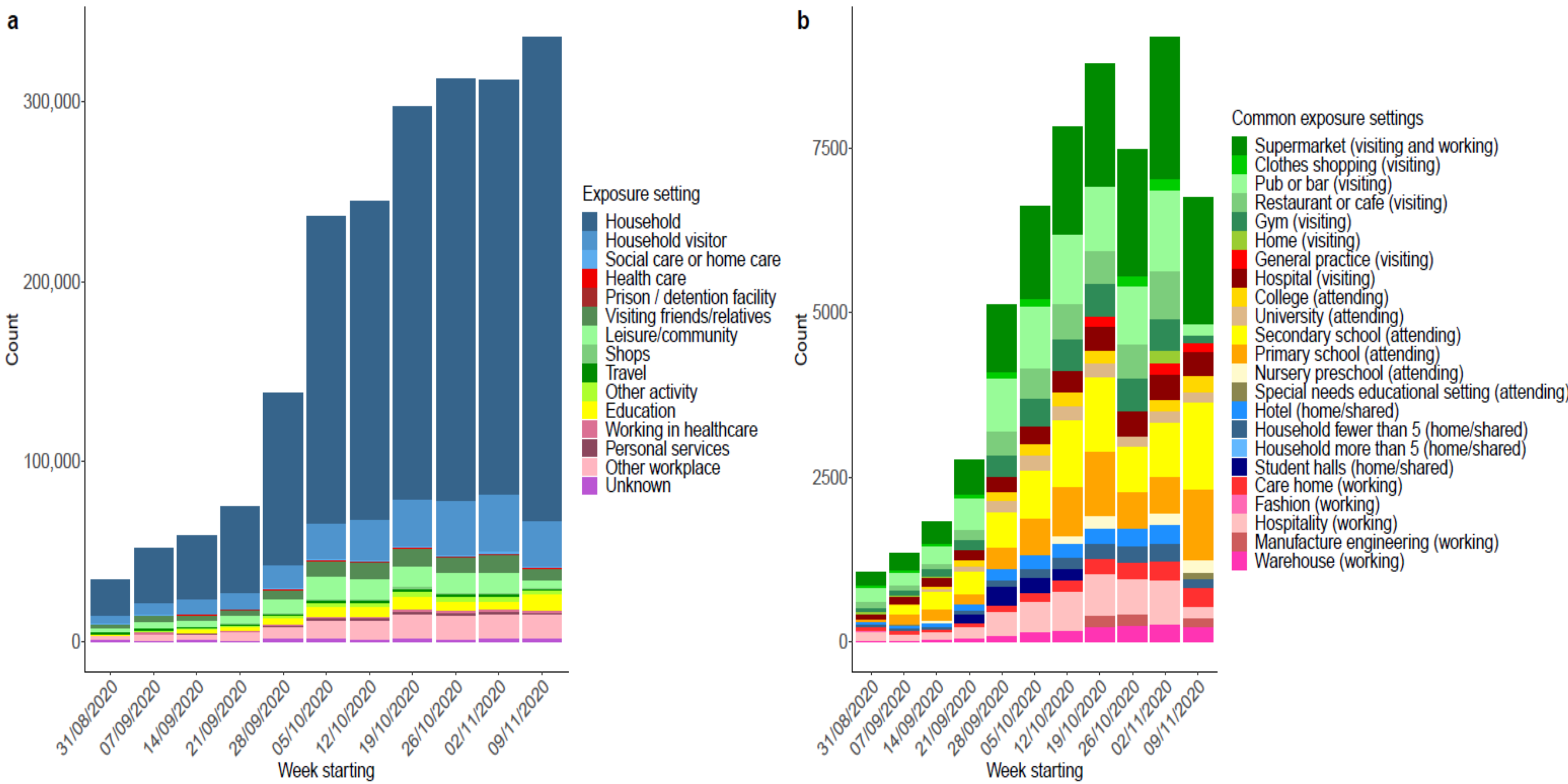
Contact tracing only works in early stages

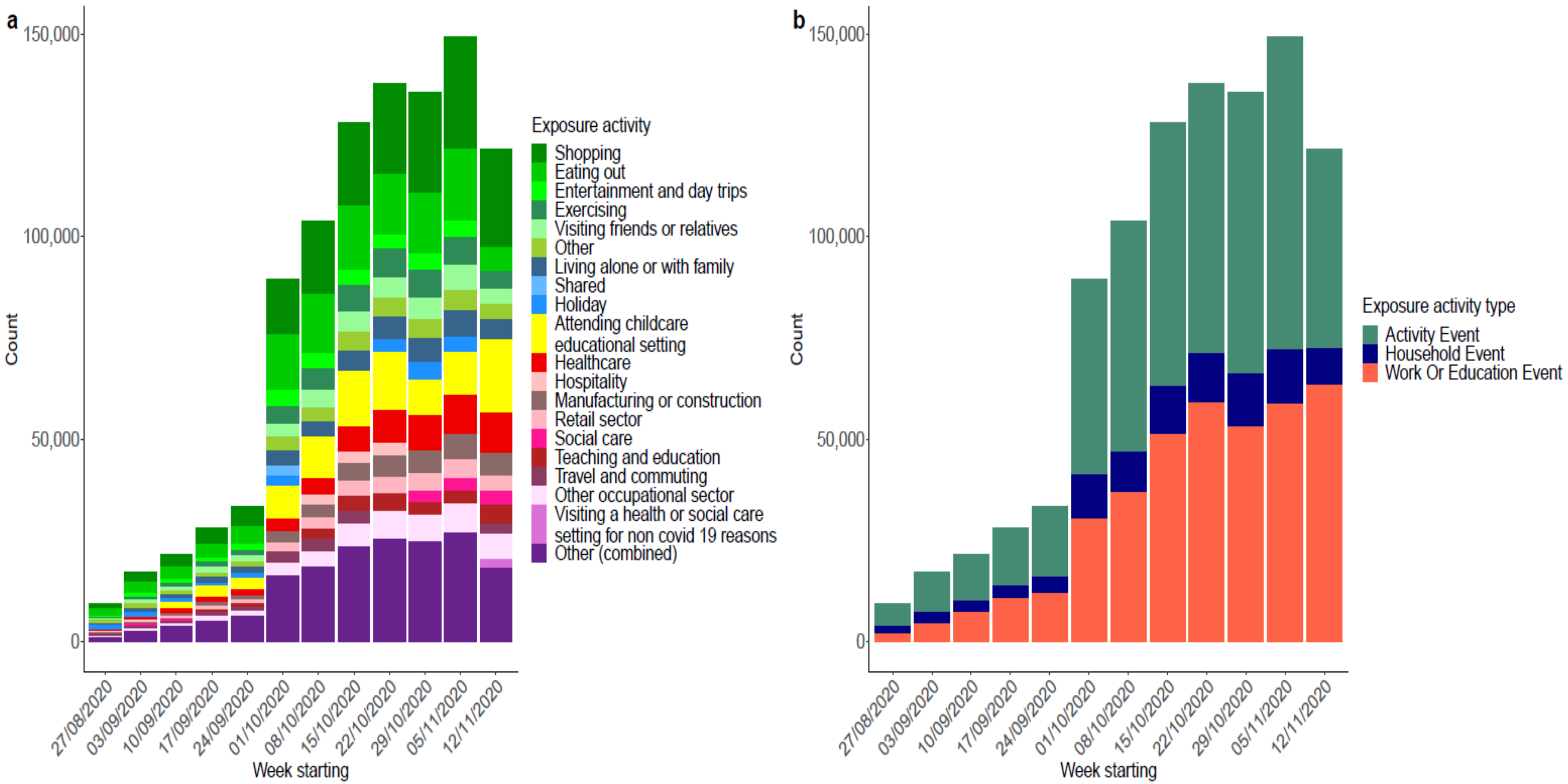
due to exponentially growing work-load as virus spreads - a week in November in the UK



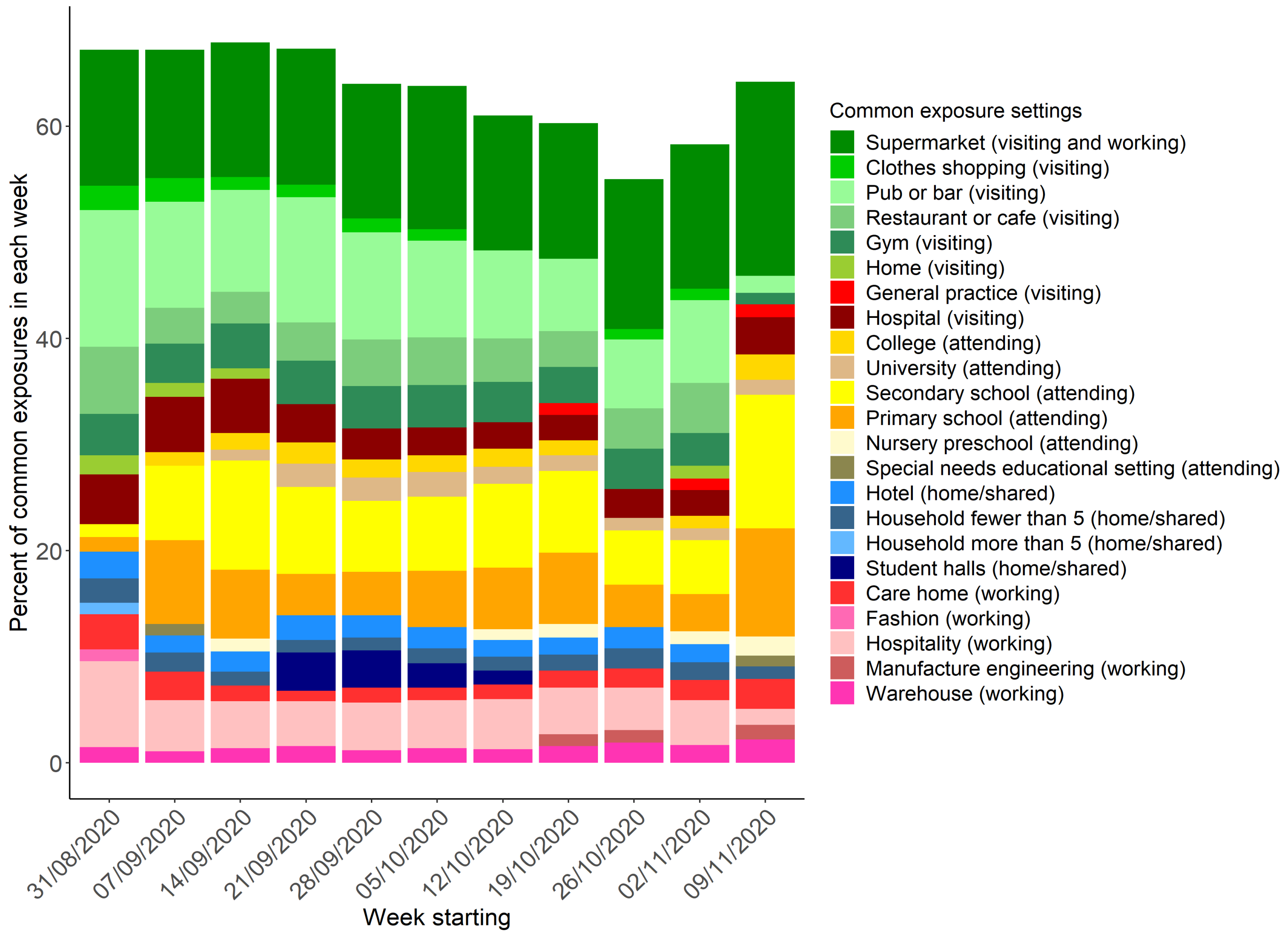
Where do people get infected - exposure settings in England derived from TTI system



Where do those who seed households typically acquire infection – England TTI system

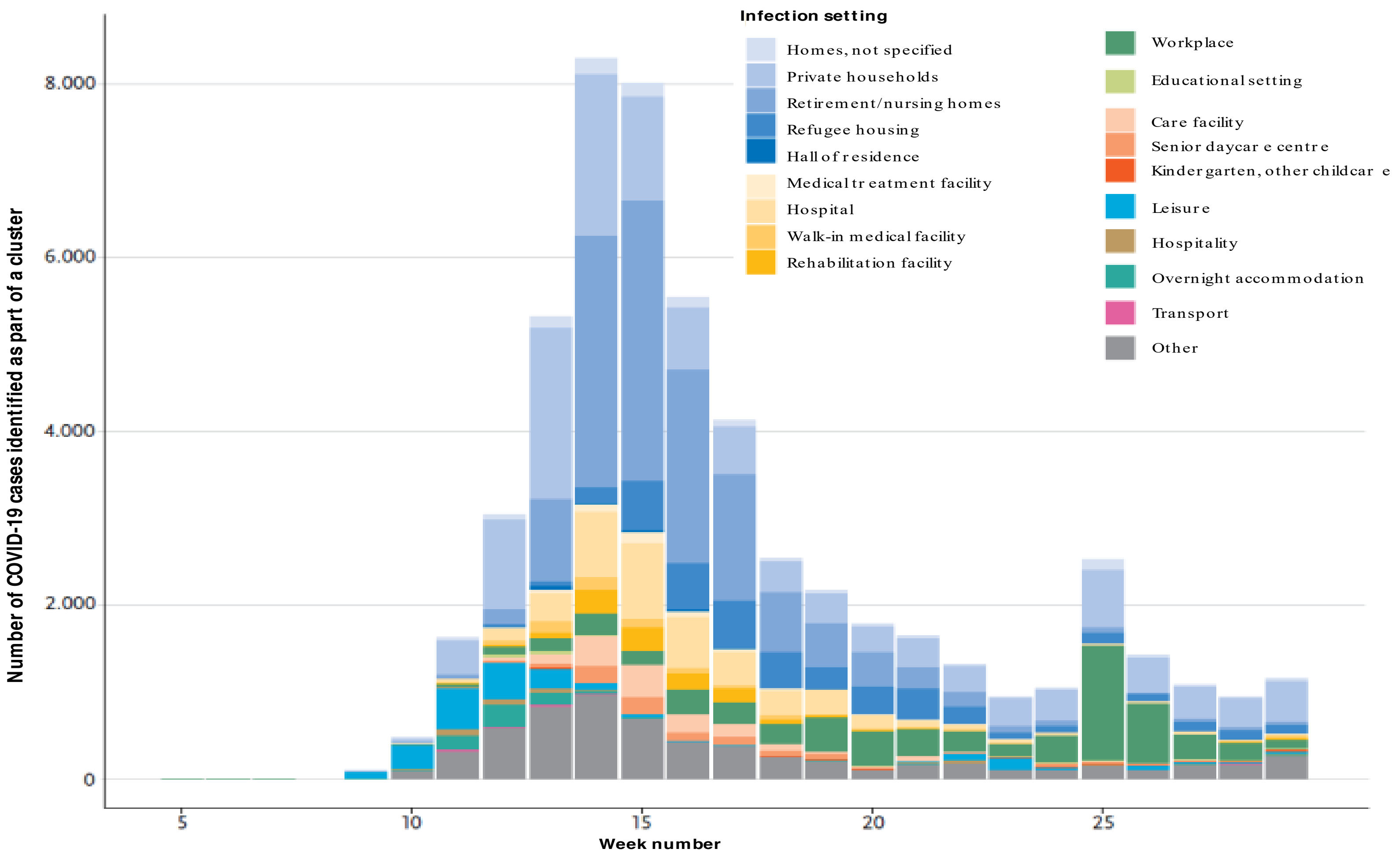


Common exposure settings England TTI system



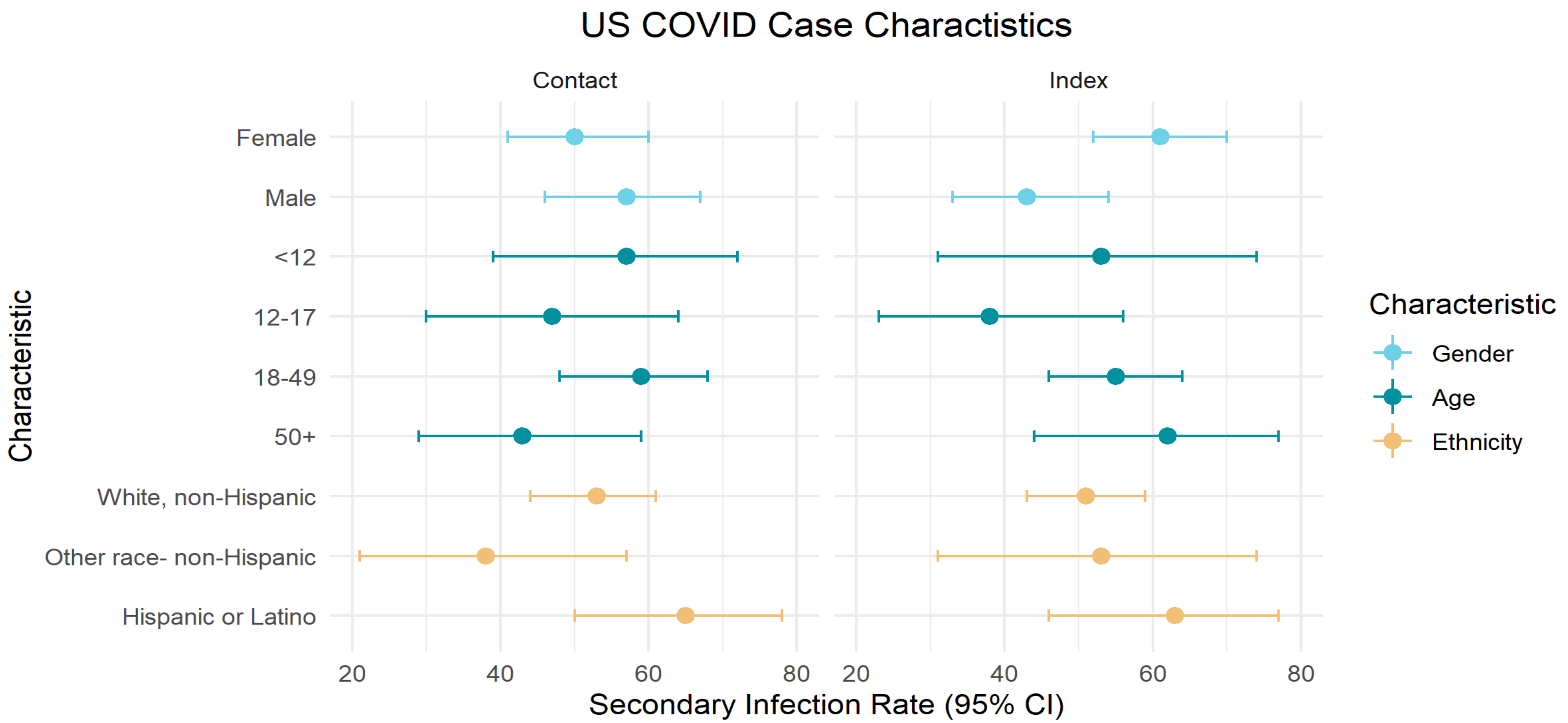
Germany – contact tracing first wave

Laboratory-confirmed COVID-19 cases assigned to an outbreak, by infection setting and reporting week (up to 11th August 2020). Graph adapted from Robert Koch Institute report, 17th September 2020.

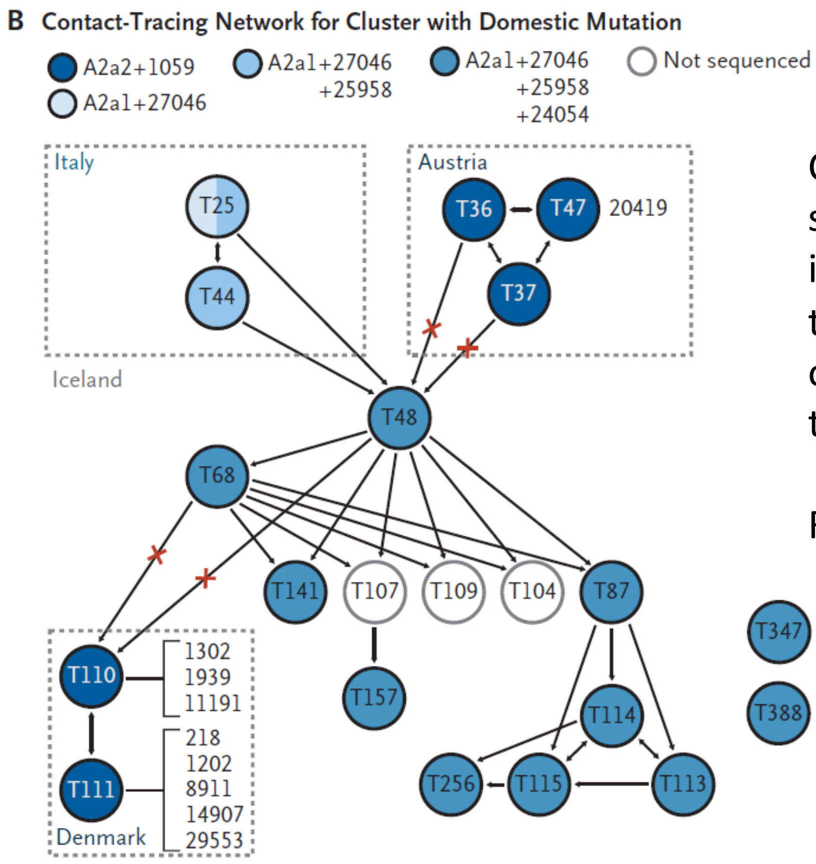


Household studies (secondary attack rates R_0 distribution)

US data (CDC) measuring index and contact case characteristics; namely age, gender and ethnicity (US only). Overall, the data show mirrored rates between index and contacts. US data measures secondary infection rate.



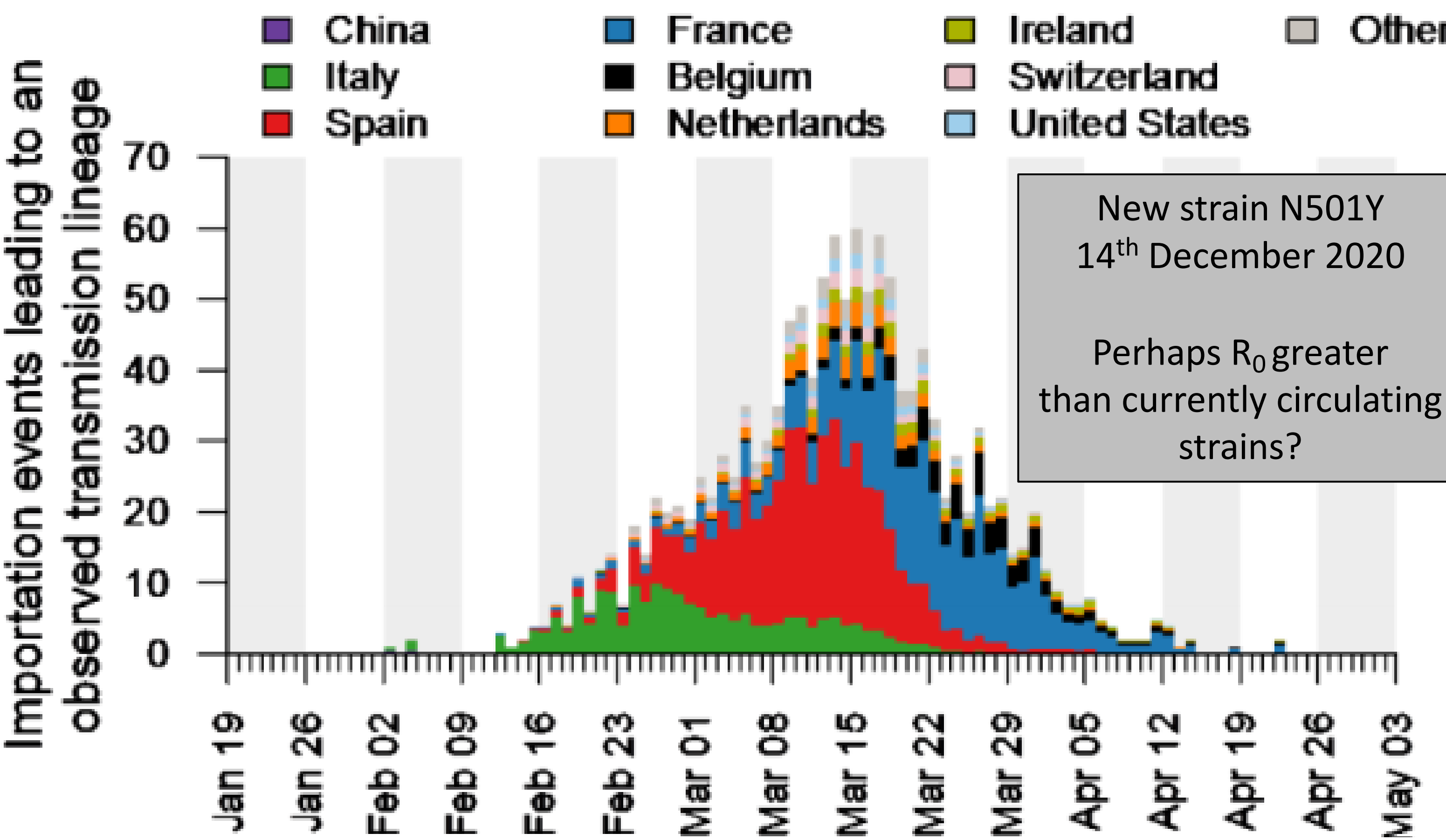
Molecular Epidemiology – whole genome sequencing



Contact tracing network overlaid by whole-gGenome sSequencing (WGS) information that enabled the identification of the source of origin of the transmission cluster and led to the identification of two previously unlinked cases to the same transmission cluster.

Figure taken from Gudbjartsson et al, 2020[14].

Estimated number of COVID-19 importation events attributed to inbound travellers to the UK from different countries of embarkation. Figure taken from du Plessis et al (2020).



New strain N501Y
14th December 2020

Perhaps R_0 greater than currently circulating strains?

Reinfection – documented cases

Reported re-infections in published and pre-print reports, available as of 9/28/2020

Table 1:	Location	Age (yrs) / Sex	Interval between episodes	Stageb (1st episode)	Stage (2nd episode)	CT values (1st/2nd episodes)		Epidemiology for 1st case	Epidemiology for 2nd case
To et al. [2]	Hong Kong	33 / M	17.5 wks	Mild	No symptoms	NR	26.69	NR	Travel to Europe
Tillett et al. [unpublished data]	Nevada, USA	25 / M	4.5 wks	Mild	Severe (Hospitalized, required oxygen)	35.24	35.31	NR	Confirmed household exposure
Larson et al. [3]	Virginia, USA	42 / M	7 wks	Mild	Severe (O2 sat 92-94% on RA)	NR	NR	Occupational exposure	Confirmed household exposure
Gupta et al. [4]c	North India	25 / M	14 wks	No symptoms	No symptoms	36	16.6	NR	NR
	North India	28 / F	14 wks	No symptoms	No symptoms	28.16	16.92	NR	NR
Van Elslande et al. [5]	Belgium	51 / F	13 wks	Mild	Mild, lesser magnitude of symptoms	25.6 (N1) & 27.2 (N2)	32.6 (N1)& 33.2 (N2)	NR	NR
Shastri et al. [unpublished data]c	India	24 / F	8 wks	Mild	Mild	32 (N)	25 (N)	NR	NR
	India	27 / M	8 wks	No symptoms	Mild	33 (N)	36 (N)	NR	NR
	India	31 / M	3 wks	No symptoms	Mild	36 (N)	21 (N)	NR	NR
	India	27 / M	7 wks	Mild	Mild	32 (N)	17 (N)	NR	NR
Goldman et al. [unpublished data]	Washington, USA	60s	12 wks	Severe	Severe (O2 requirement lower when compared to 1st hospitalization)	22.8 (E)& 26.5 (RdRP)	43.3 (E) & 39.6 (N2)	Exposure in skilled nursing facility	Exposure in another skilled nursing facility

Vaccination and herd immunity

“The shot that rang across the world - Pfizer’s and BioNTech’s vaccine is the start of the end of the pandemic”

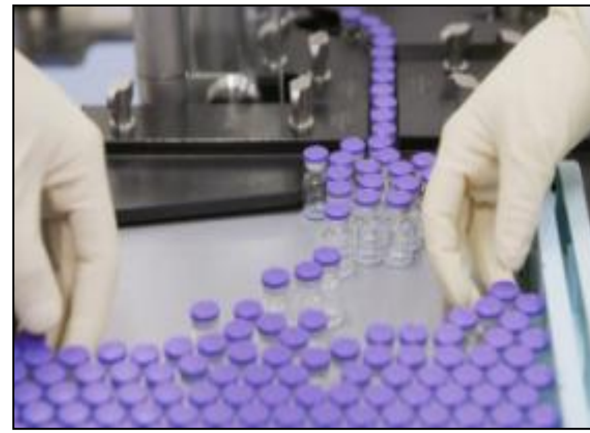
The Economist 9th November 2020

“Its 90% effectiveness is as good as it gets, and bodes well for other vaccines. But getting them quickly to the right people will be hard.”

In October 2020 the IMF estimated that the Covid-19 disaster has wiped off **$28 trillion** dollars of global economic activity.

Another two shots in the arm – the Moderna and AstraZeneca vaccines

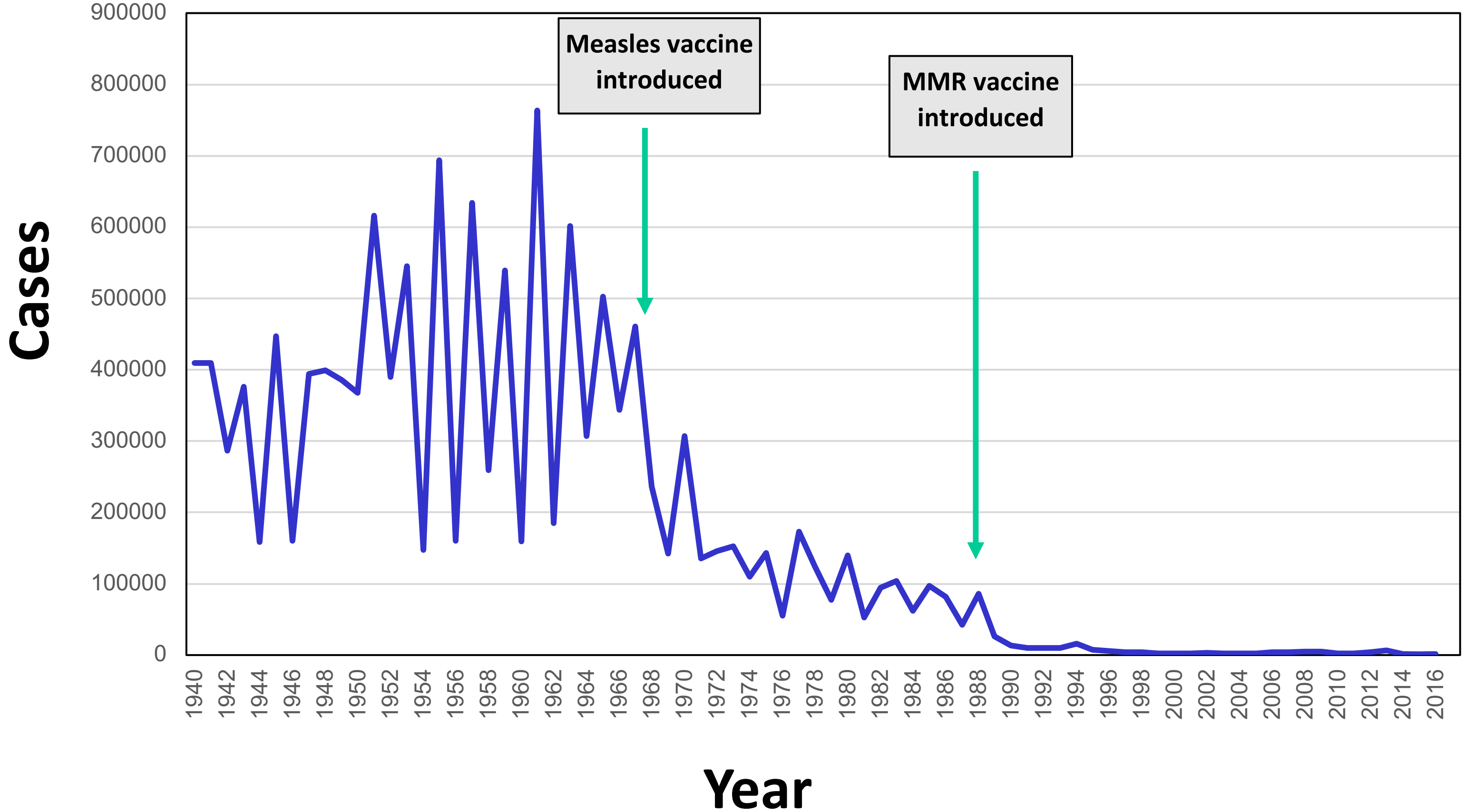
- 16th November 2020 – Moderna vaccine has 94.5% efficacy
- 90 cases in placebo arm of 15,000 people of whom 11 had serious disease.
- Another 15,00 given the vaccine – 5 became infected but none had serious disease.
- Can be kept at -20^{o}C.
- 23rd November 2020 - AstraZeneca/ Oxford vaccine has a 70.4% or 90% efficacy - depending on dosage can be stored at 2-8^{o}C in normal fridges



Edward Jenner (1749-1823)

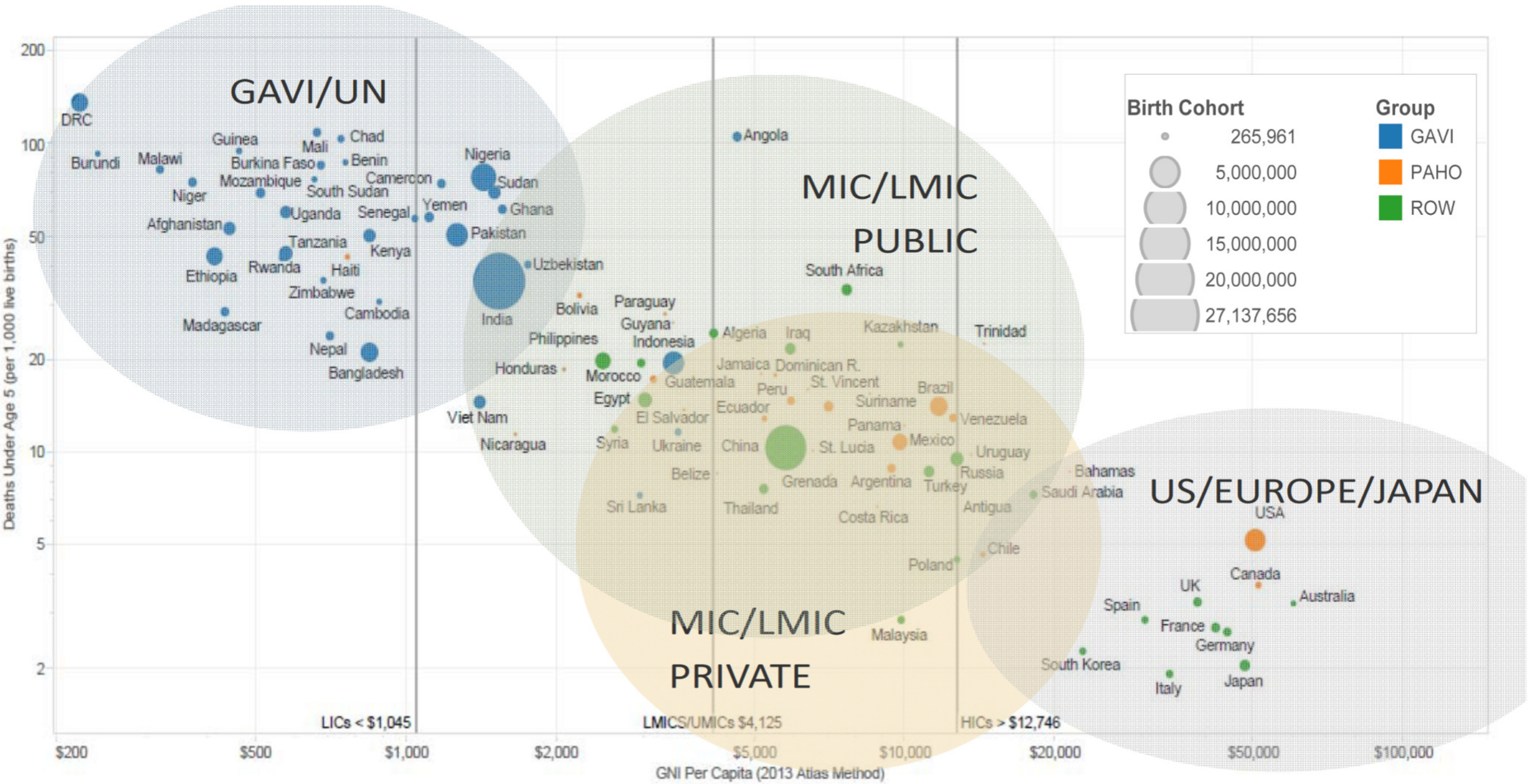
Inoculation, hereafter referred to as variolation (=vaccination), was likely practiced in Africa, India, and China long before the 18th century, when it was introduced to Europe. Jenner in 1796 concluded that cowpox not only protected against smallpox but also could be transmitted from one person to another as a deliberate mechanism of protection.

Great success - Measles decline in England & Wales



Global vaccine market

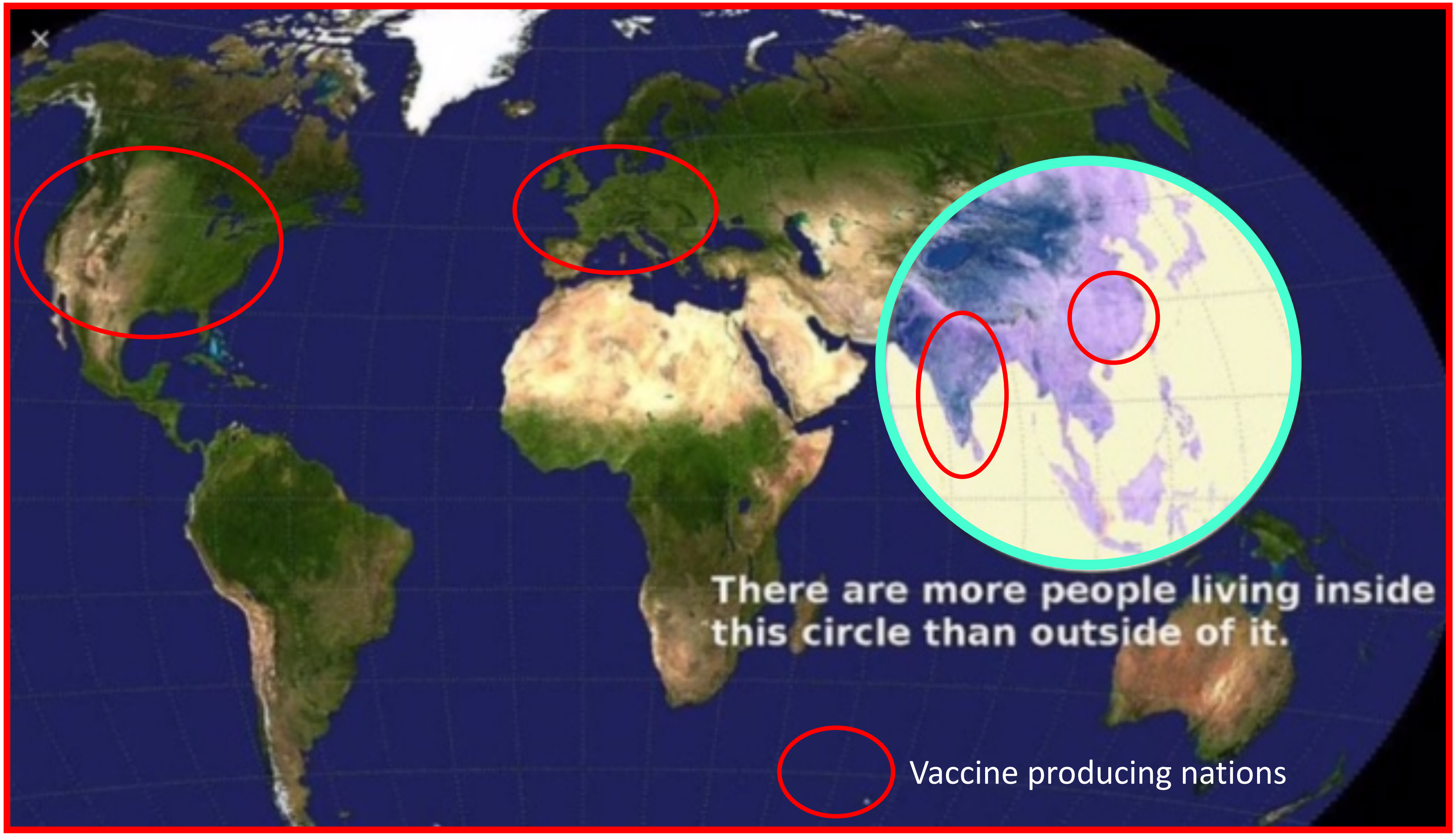
(sources WHO, PATH, World Bank and GAVI)



Note: Only non-PAHO countries with >250,000 annual birth cohort included.
Source: World Bank GNI 2013, UNPD Population Prospects 2012 Edition, GAVI Website, September 2014

PATH

Vaccine producing nations and world population distribution



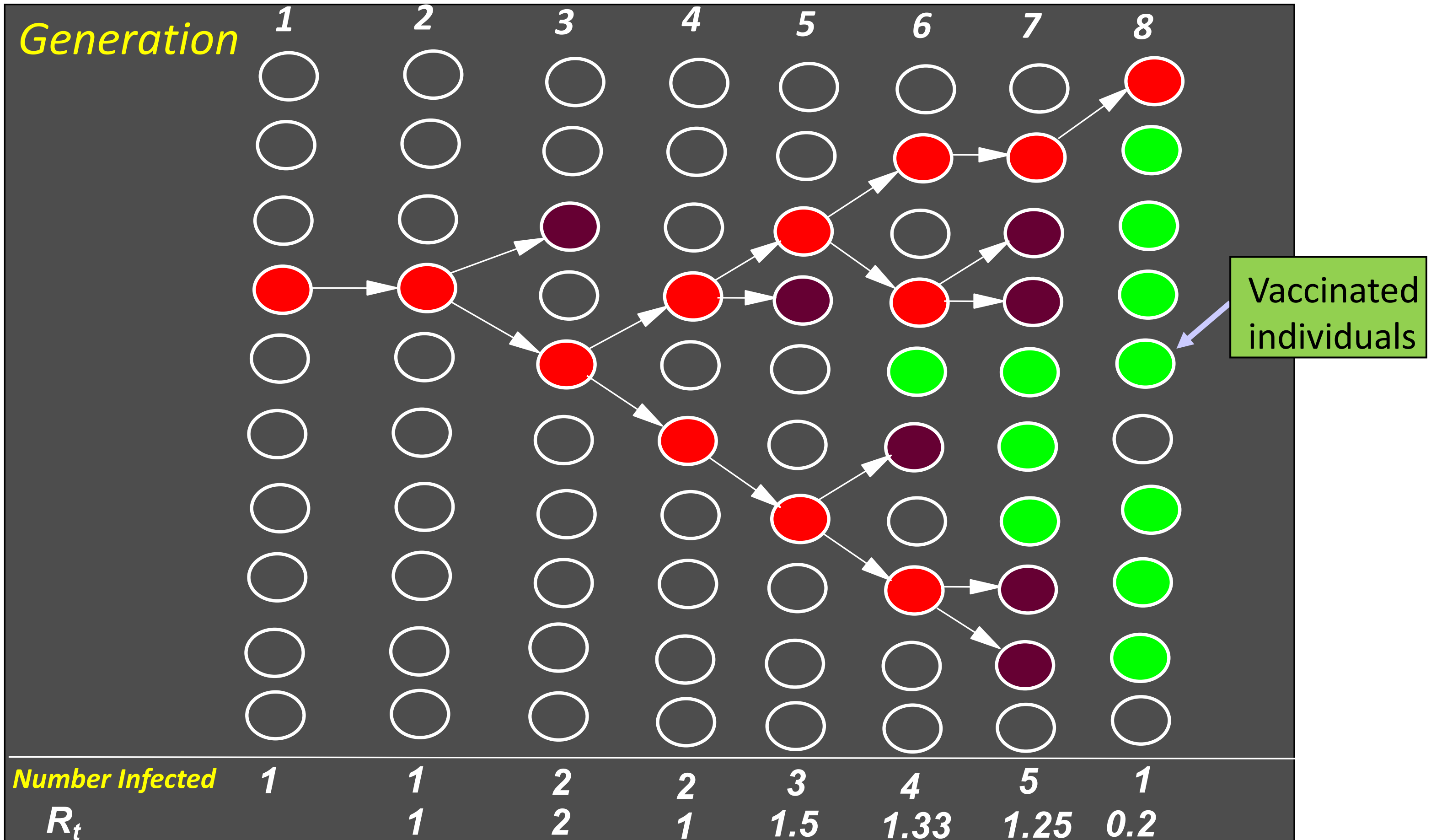
What is Herd Immunity?

- The impact of the fraction immune in the community on the per capita rate of transmission of an infectious agent.

- The level of herd immunity can be measured by reference to the magnitude of reduction in the value of the reproductive number R_t at time t relative to the basic reproductive number R_0.

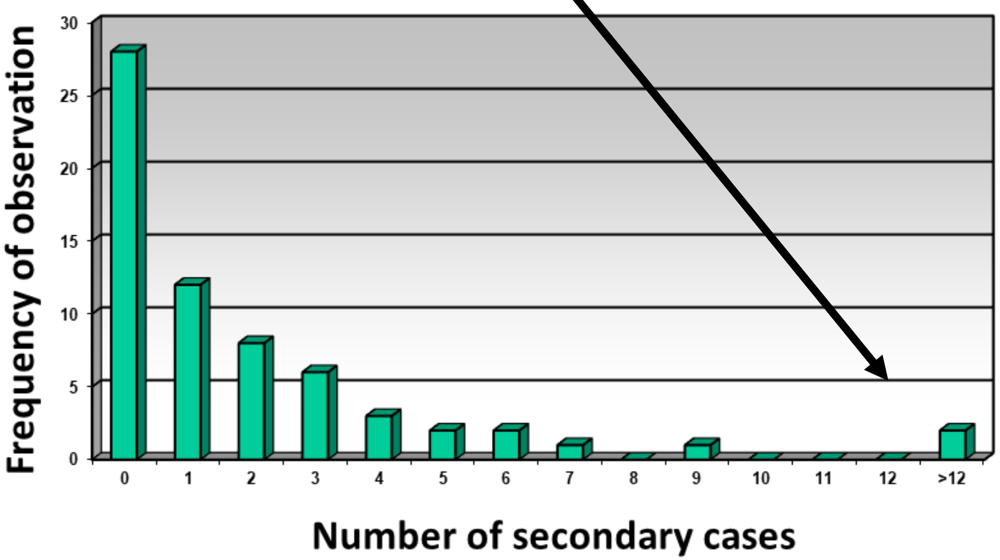
The generation of secondary case - with vaccination

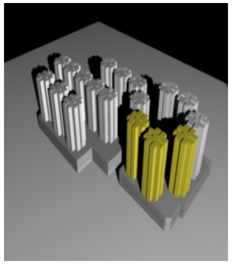
To create effect herd immunity by mass vaccination the effective reproductive number, R, must be reduced to less than unity in value (R<1)



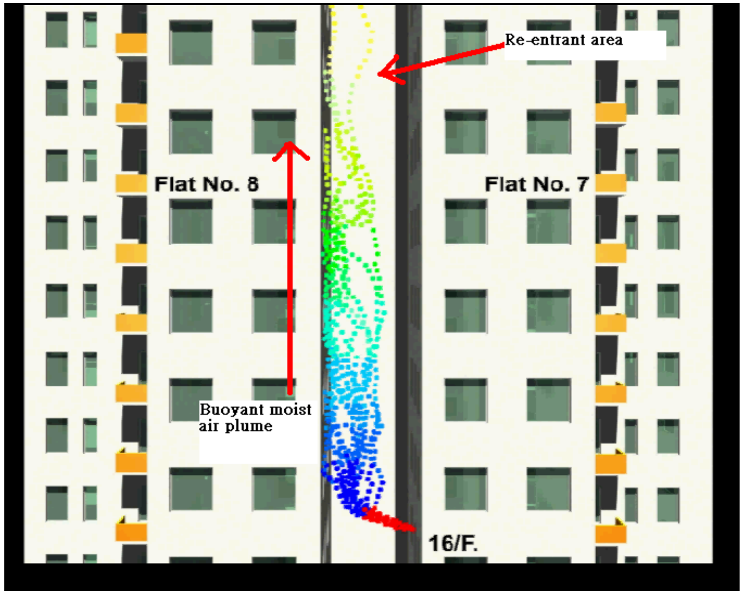
SARS-CoV-1 - distribution of R

Super spreading events (person, place & setting)





Rapid SARS Virus Spread in Flats 7 and 8, Block E Amoy Garden, Hong Kong. 1st March 2003 –
292 people infected by one index case



Creation of Herd Immunity

Fraction who must be immune via vaccination to stop viral transmission p given by:

$$p = [1 - 1/R_0]$$

for a vaccine with perfect efficacy.

If efficacy as a fraction protected who received the vaccine is ε – then:

$$p = [1 - 1/R_0]/\varepsilon$$

If R_0= 2.5, and vaccine has 90% efficacy (ε=0.9):

p = 0.67 – 67% of the population must be vaccinated to stop transmission

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Vaccine efficacy

(Christensen & Bottiger,1991; Clarkson & Fine,1987; Ramsey et. al.,1994)

MEASLES	90%-95%
MUMPS	72%-88%
RUBELLA	95%-98%
SARS-Cov-2	90% + ?

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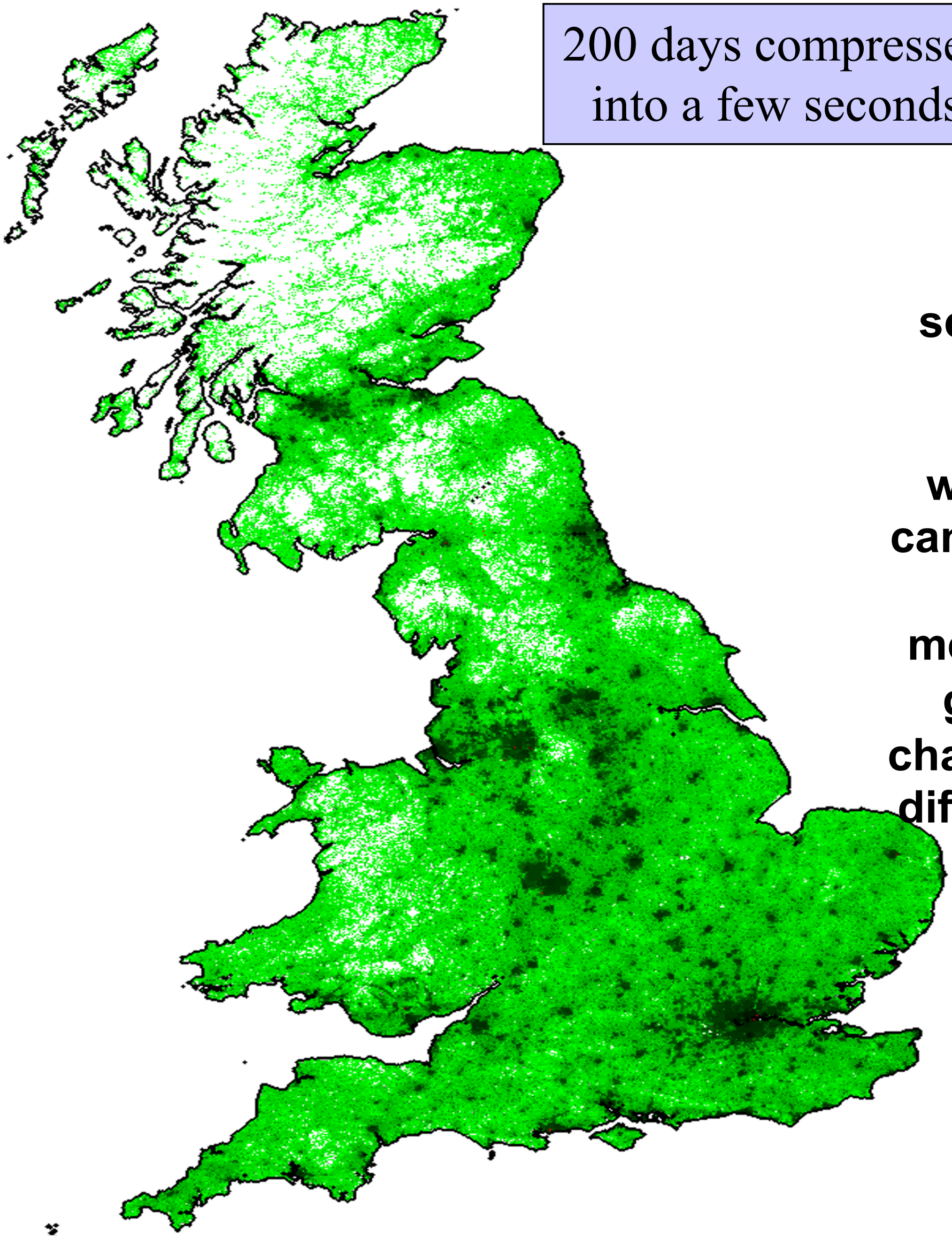
Level of herd immunity that needs to be created by vaccination with a long duration of protection vaccine (for life)

R_0	ε	p (%)
2	1	50
3	1	67
4	1	75
5	1	80
2	0.95	52.6
3	0.95	70.2
4	0.95	78.9
5	0.95	84.2
2	0.9	55.6
3	0.9	74.4
4	0.9	83.3
5	0.9	89
2	0.8	62
3	0.8	83.75
4	0.8	93.75
5	0.8	>100



200 days compressed into a few seconds

Individual based stochastic simulation model with three scales of mixing and movement – plus extensive sensitivity analysis for outcome with different parameter values – can chart the temporal course in the absence of 'social distancing measures. Simulating with the fine granularity/details of behaviour change in heterogeneous settings is difficult – wide confidence limits on outcomes

Ferguson et al, 2006 – Nature - on line April 27th 2006

Vaccines for Covid-19 (SAR-CoV-2) (1)

- At last count 45 candidates in trials, 10 in phase III, one set of phase III results announced.

- Aim to minimize mortality or create herd-immunity so life returns to normal?

- Three key factors – **efficacy**, **duration of protection** and **uptake**, if aim is to create herd immunity and minimize mortality plus serious morbidity.

What if the vaccine has good efficacy but a short duration of protection

The expression for the degree of herd immunity required and the percentage of the population who must be vaccinated (2 doses) per year becomes much more complex.

Where $p_c(T)$ is the number of vaccinations (2 doses) required as a proportion of the population to stop transmission(turn R_t,1) is given by:

$$p_c(T) = \frac{R_0 - 1}{\varepsilon R_0^{\,2}}\left[\gamma_2 T R_0 + (R_0 - 1)\left(1 - e^{-R_0\gamma_2 T}\right)\right]$$

Here T is the duration of time after vaccination started, ε is efficacy (0-1), and $1/\gamma_2$ is the average duration of protection and R_0 is the basic reproductive number.

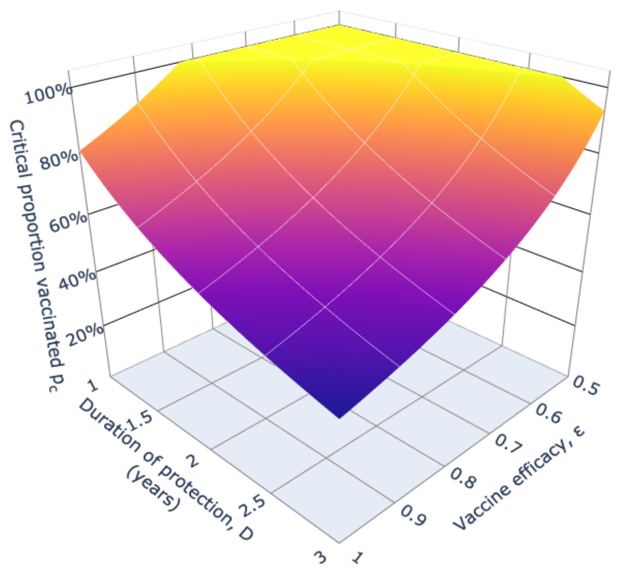
After a few years as the system equilibrates and most of the population are vaccinated the proportion requiring vaccination per year is given by:

$$p_c = (\gamma_2/\varepsilon)[1-1/R_0]$$

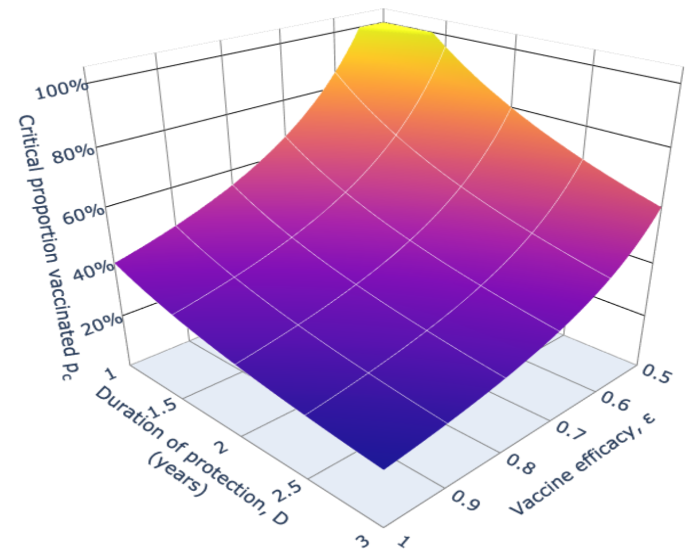
Creating herd immunity for SARS-CoV-2 (2)

(Anderson et al (2020) Lancet, Nov 4th 2020)

Year 1



At Equilibrium

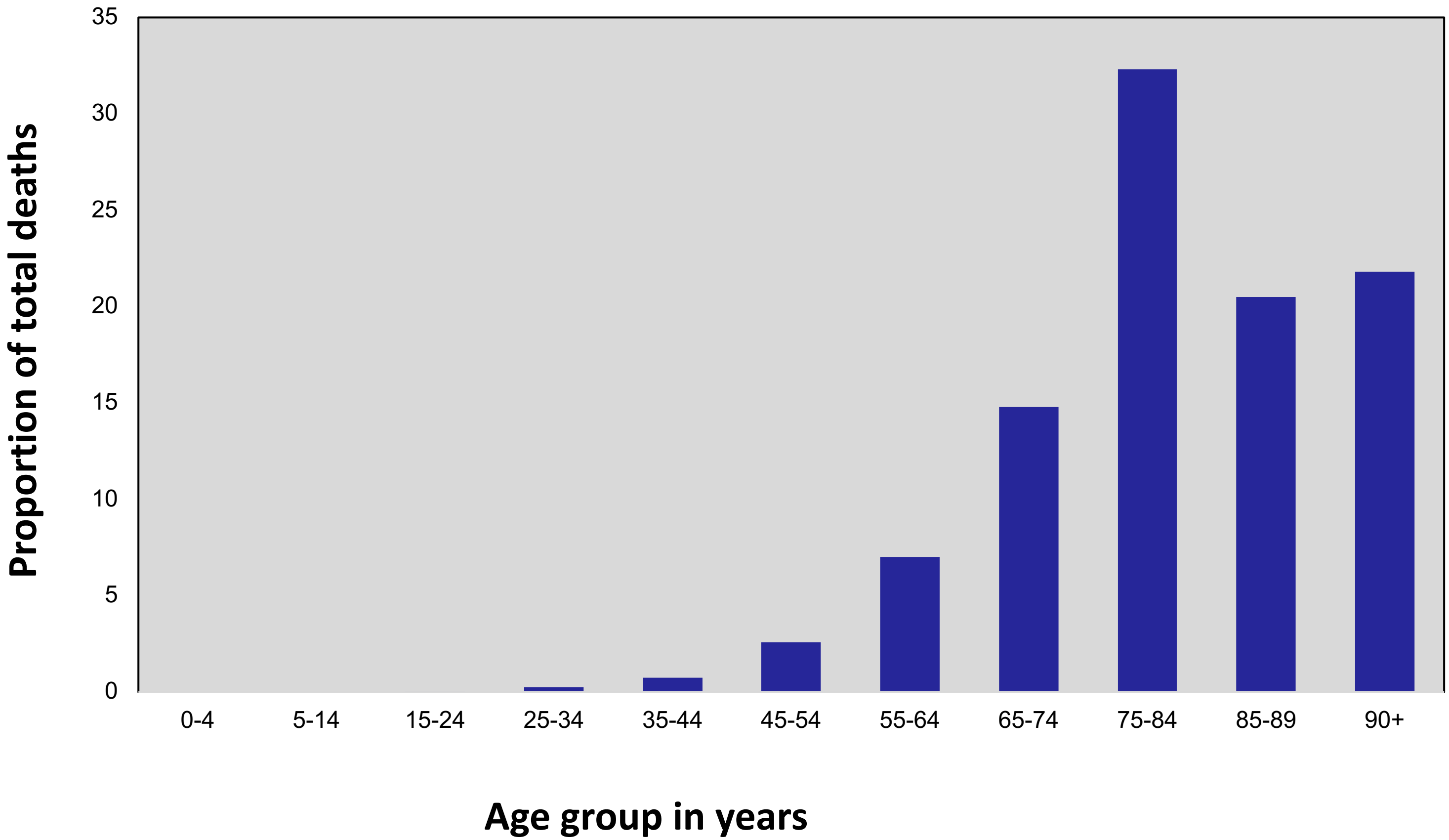


The impact of vaccine efficacy and duration of protection on what percentage of the population must be vaccinated in the fist year and when the system equilibrates (R_0=2.5)

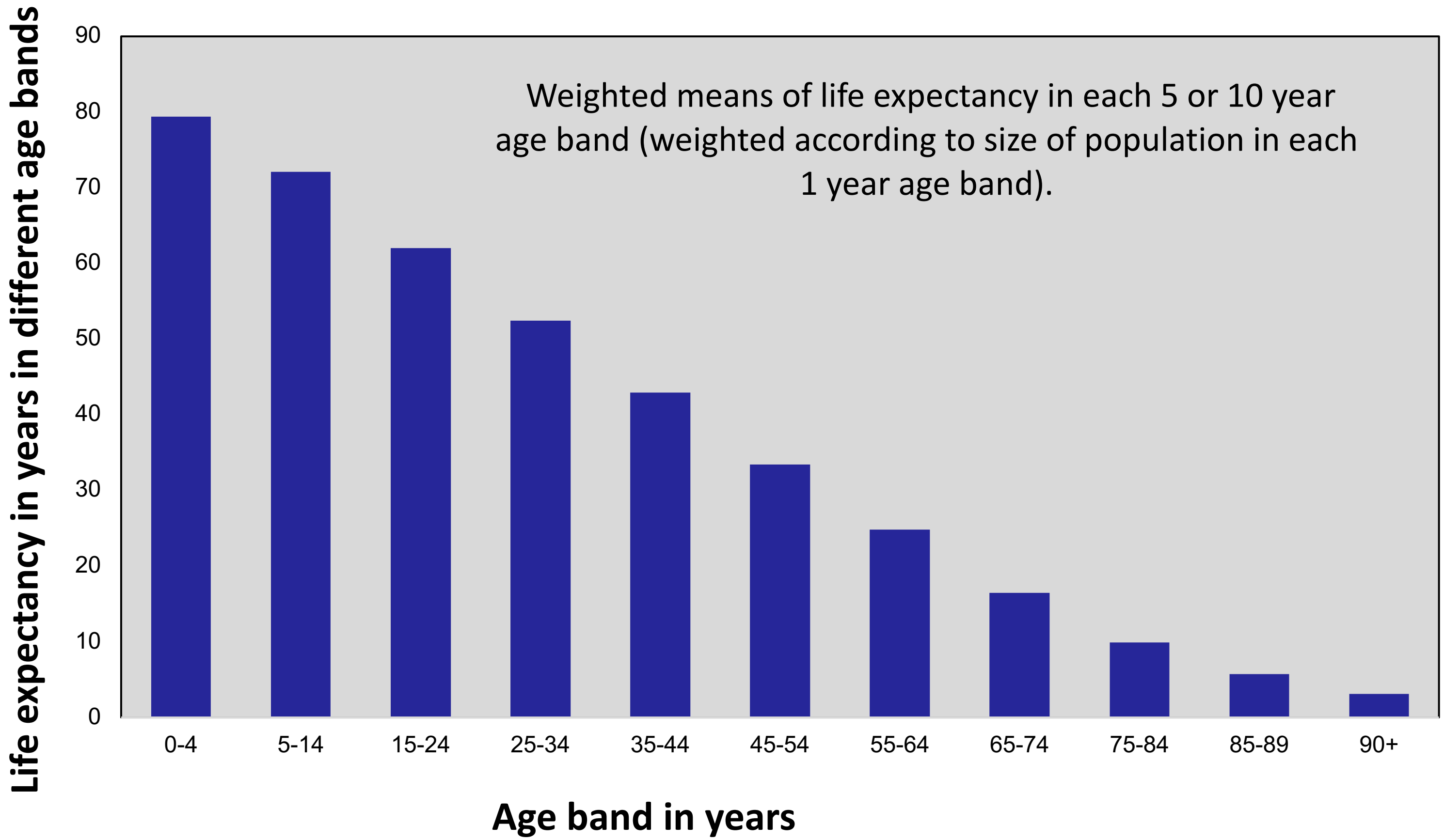
Who to vaccinate first – SARS-CoV-2?

- The design of a country wide vaccination programme depends on the main aim.
- Is it to minimize mortality in the short term?
- Or is it to maximize the number of healthy years of life gained by vaccination?
- Each of these choices may require different designs – it will depend on demography and age dependent case fatality rates

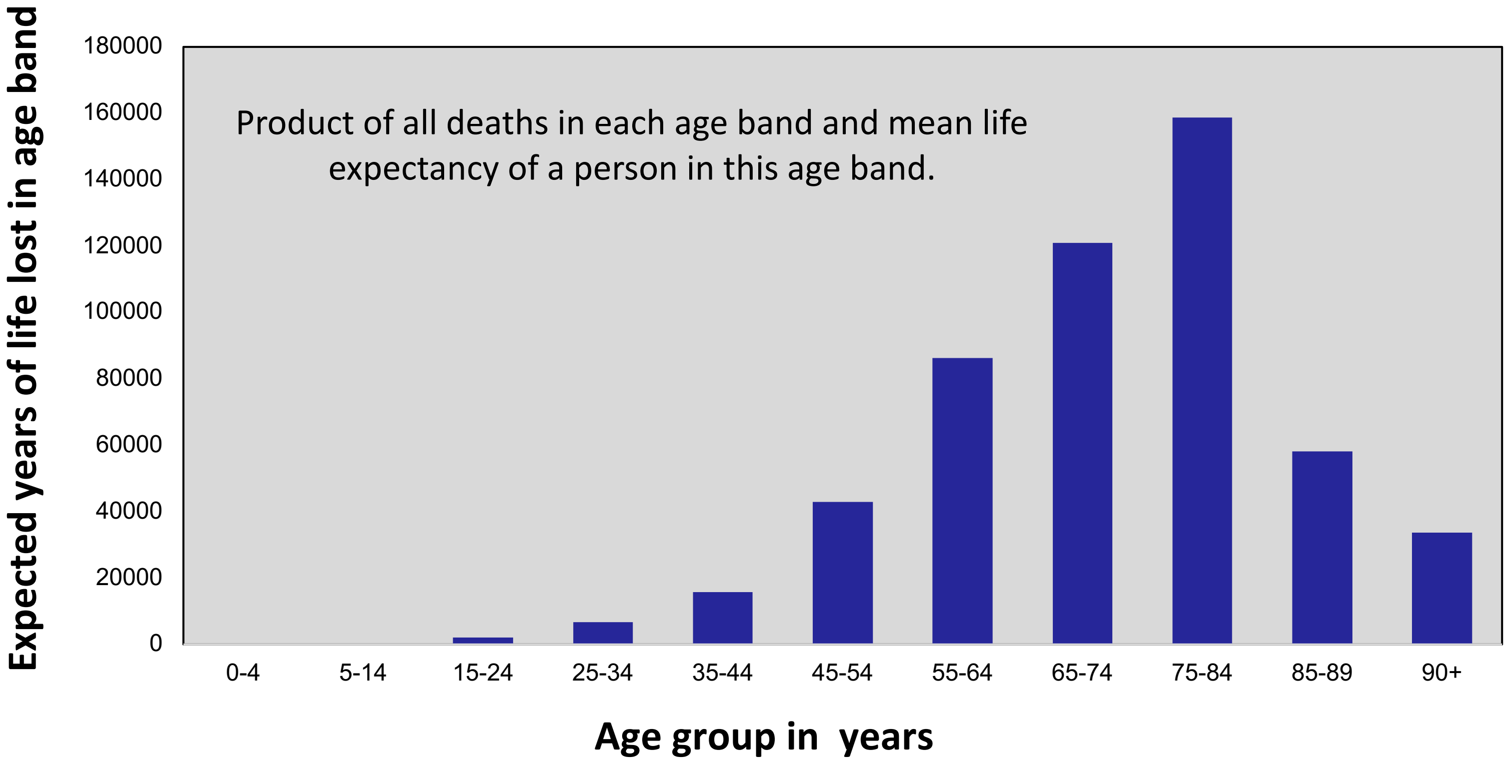
Proportion of total deaths due to Covid-19 in each age band (united Kingdom)



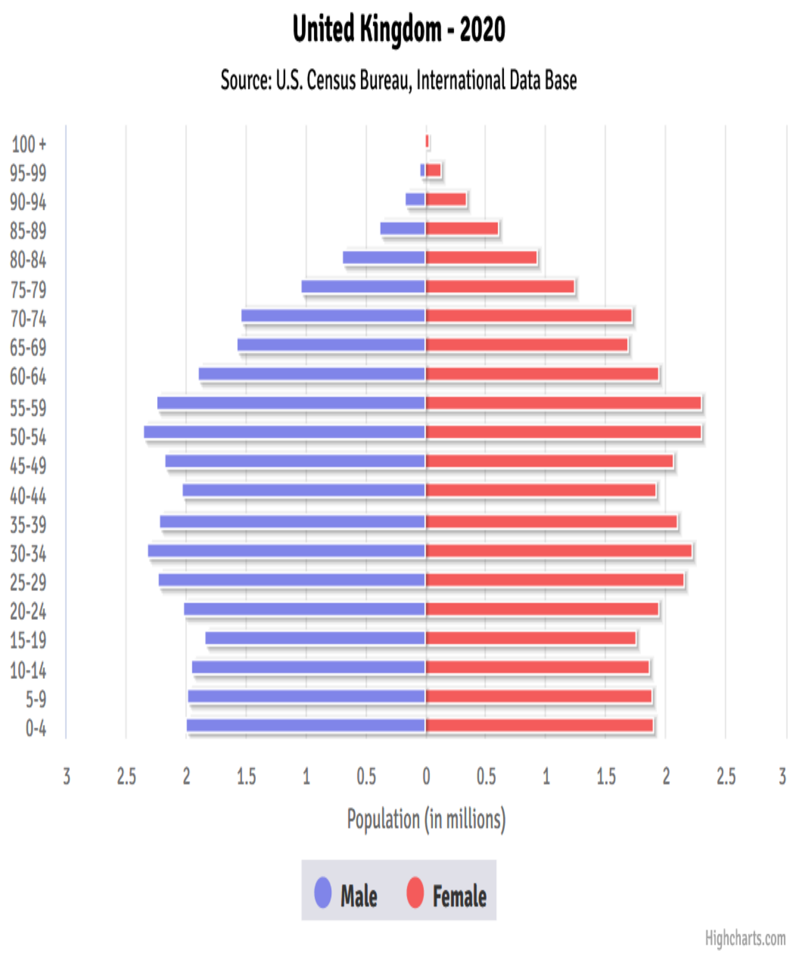
Life expectancy by age band (United Kingdom)

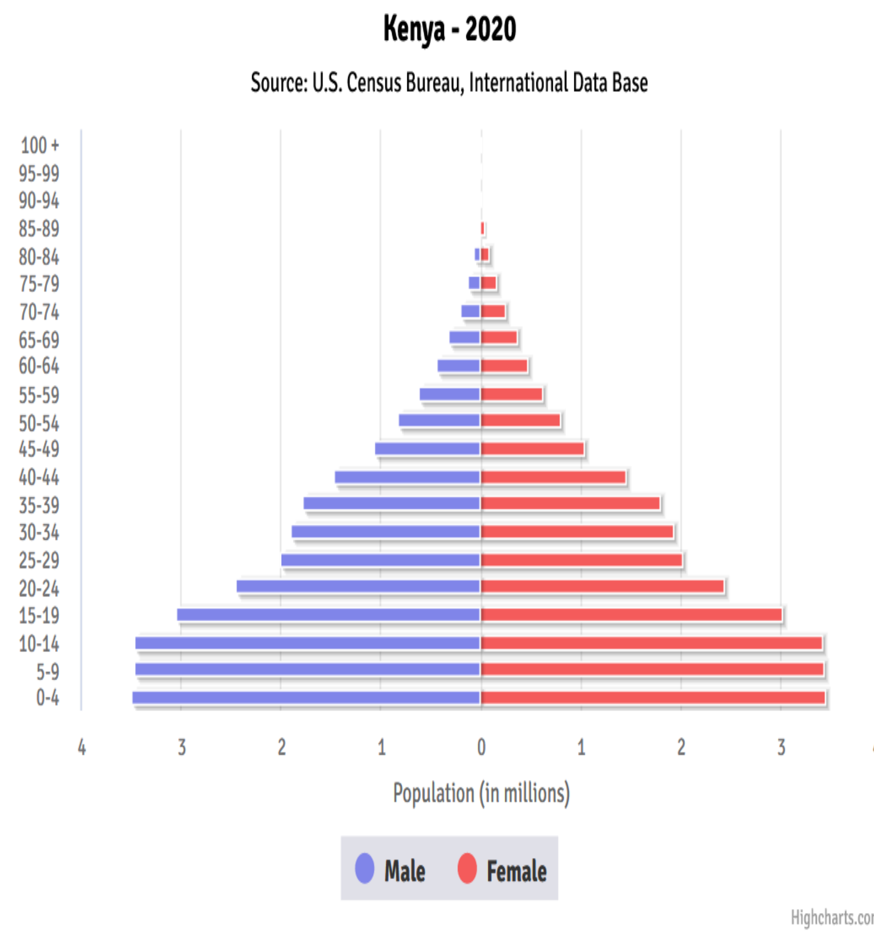


Expected years of life lost due to Covid-19 infection by age class (United Kingdom)



Demography matters for net mortality and the design of vaccination programmes

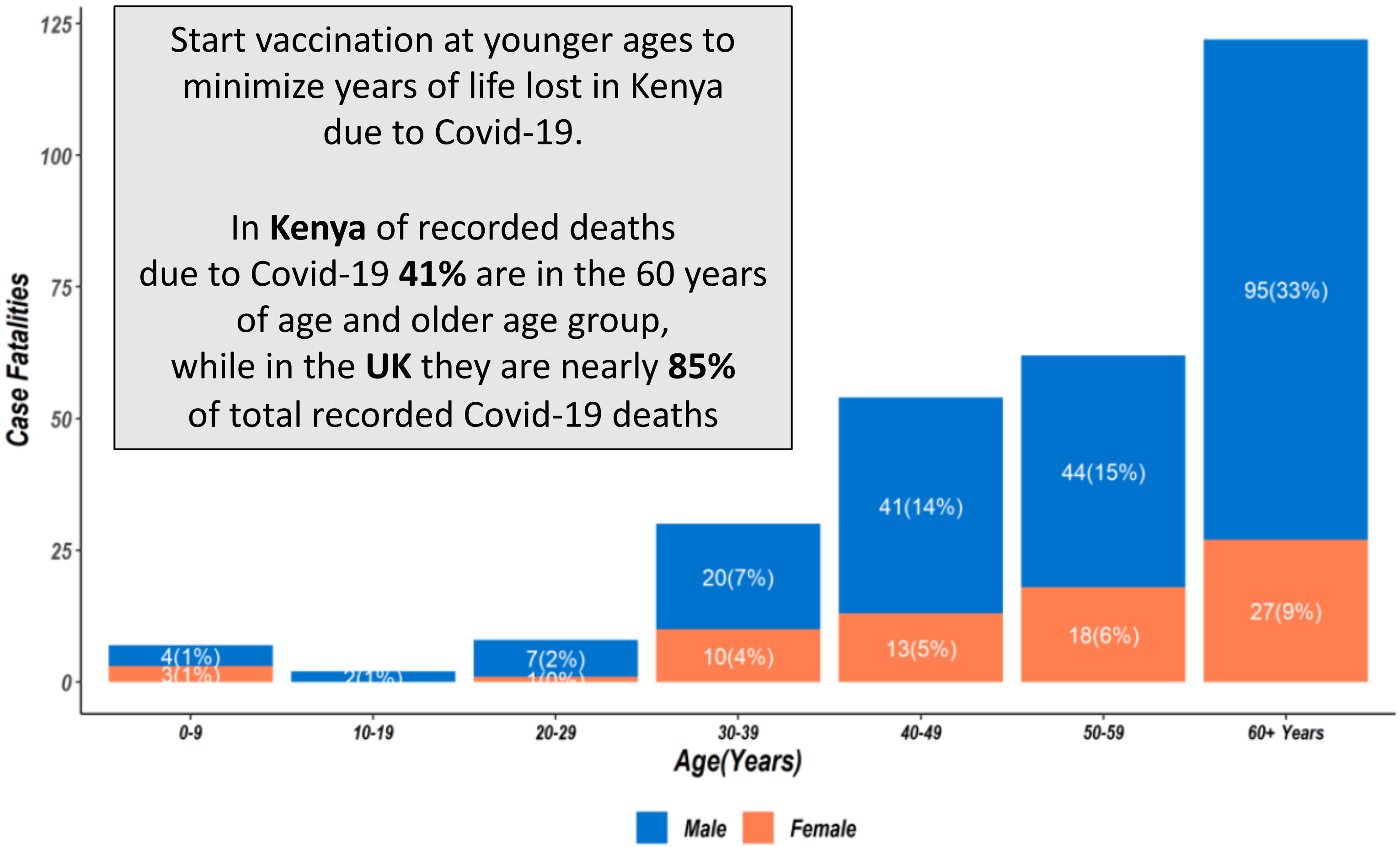




Case fatality numbers by age and gender reported in Kenya, October 2020

Start vaccination at younger ages to minimize years of life lost in Kenya due to Covid-19.

In **Kenya** of recorded deaths due to Covid-19 **41%** are in the 60 years of age and older age group, while in the **UK** they are nearly **85%** of total recorded Covid-19 deaths



Conclusions – the 2021 year

1. The virus will remain endemic in most countries.
2. Creating herd immunity by vaccination difficult when R_o large and population density plus net birth rate high.
3. Heterogeneity in population density and vaccine coverage important.
4. Starting mass vaccination in cities (high density locations) a sensible strategy
5. In a national programme most years of life are gained by vaccination the over 70s first in developed countries
6. Vaccines with a short duration of protection either to infection (ideal) and or disease will require very high coverage levels to create herd immunity
7. Vaccine coverage must be maintained at high and uniform levels to avoid the immigration of infectives stimulating epidemics in susceptible pockets.
8. Vaccine 'hesitancy' may be a problem in Western societies – education of the public essential - projecting themselves also protects others in their families, communities and workplace (the core principle of herd immunity)

The End

Many thanks to my colleaques Drs Carolin Vegvari, Becky Baggaley, Rosie Maddren, Ben Collyer and James Truscott