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Two years of the COVID-19 pandemic from a infectious disease modeller's perspective: confirmed premonitions, new insights, and unsolved puzzles

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Jan 10, 2022

Overview

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1. Insights from past epidemics/pandemics
   - the basic conceptual framework: SIR model
   - the basic reproduction number R_0
   - fatality risk (CFR, IFR)
   - examples: SARS 2003/4, pandemic influenza 2009
2. SARS-CoV-2/COVID-19 specific insights
   - R_0 of SARS-CoV-2 variants
   - IFR, IHR
   - waning immunity
   - vaccines and their efficacy
3. Aspects I/we still do not understand
   - abrupt seasonality
   - epidemic saturation

Premonitions

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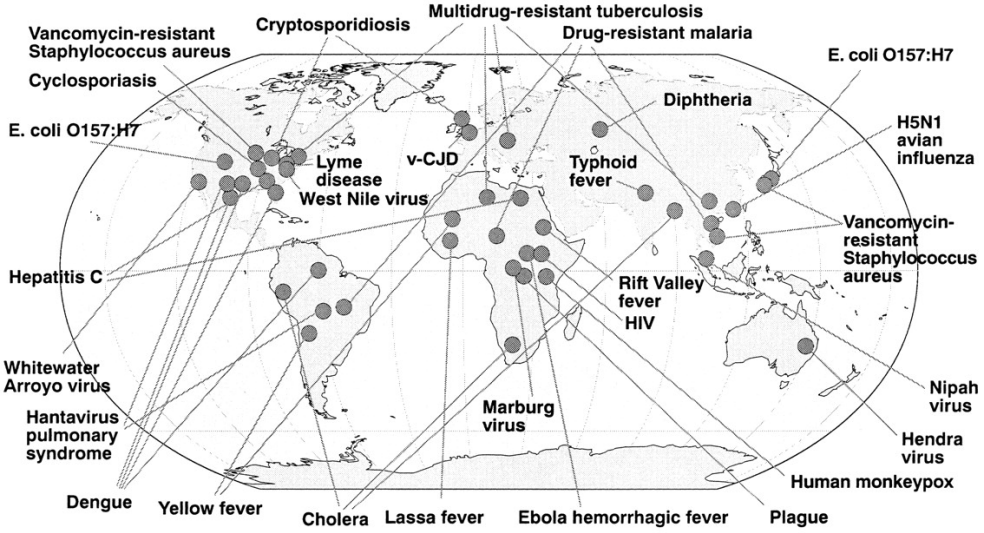
(Re-)emergent diseases



Fauci, *Clin Inf Dis* 2001, Figure 1

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The first mathematical study on infectious diseases preventions

Daniel Bernoulli (1700-1782)

Fig. 1 in Dietz & Heesterbeek, *Math Biosc* 2002

"section from a painting by Nicholaus Grooth 1760"

> *without the mortality caused by smallpox . . . France would gain 25'000 persons every year.*

Bernoulli D, Essai d'une nouvelle analyse de la mortalité causée par la petite vérole, *Mem Math Phy Acad Roy Sci Paris* 1766.

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Ronald Ross (1857 — 1932)

- discovered that bird malaria is transmitted by mosquitoes (Nobel Prize in physiology or medicine 1902)
- laid foundations of dynamical modeling of infectious diseases
  - independent discovery of mass-action infection
  - *mosquito theorem*
  - *a priori* pathometry
  - *theory of happenings*

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Ross' theory of happenings

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- his *theory of happenings* also defines explicitly the dynamical feedback that sets infectious diseases apart from other conditions:

> *Different kinds of happenings may be separated into two classes, namely (a) those in which the frequency of the happening is independent of the number of individuals already affected; and (b) those in which the frequency of the happening depends on this quantity...to class (b) belong infectious diseases, membership of societies and sects with propagandas, trade-unions, political parties, etc., due to propagation from within, that is, individual to individual.*

Ross *Proc Roy Soc* 1916, p211

cited in Halloran, Longini & Struchiner *Design and Analysis of Vaccine Studies* (2010), p4

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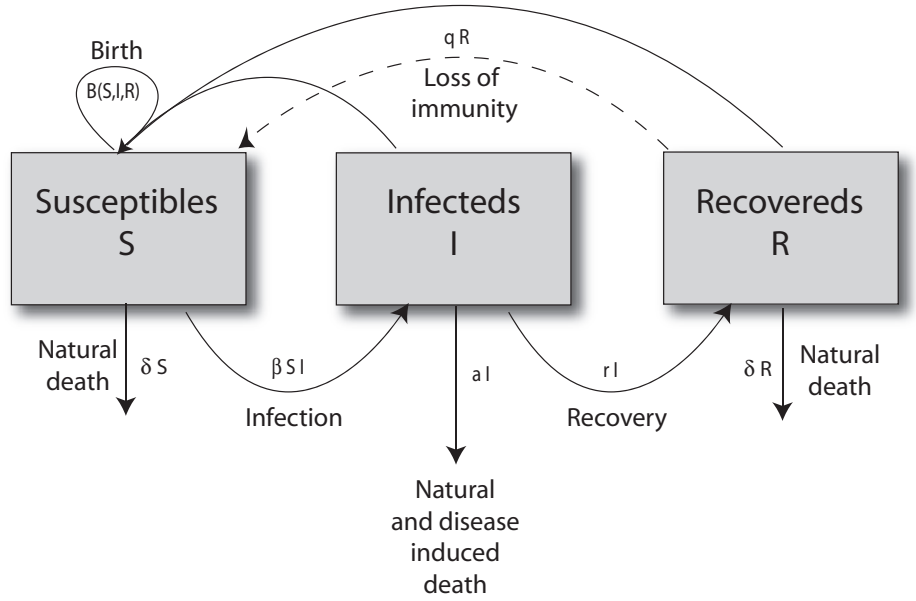
The SIR model

SIR model (Kermack and McKendrick 1927)



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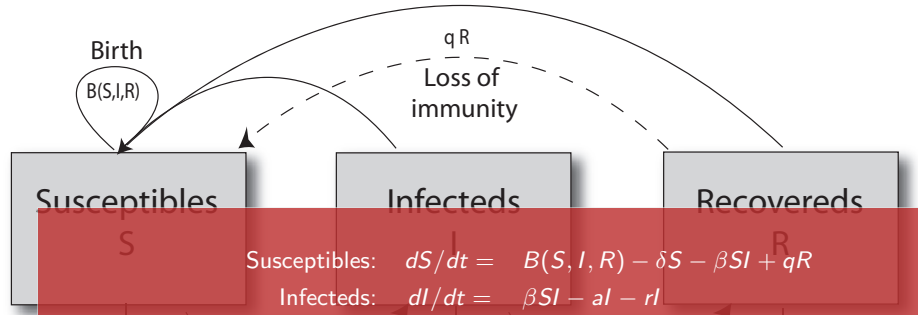
SIR model (Kermack and McKendrick 1927)



$$
\begin{aligned}
\text{Susceptibles:} \quad dS/dt &= B(S,I,R) - \delta S - \beta SI + qR \\
\text{Infecteds:} \quad dI/dt &= \beta SI - aI - rI \\
\text{Recovereds:} \quad dR/dt &= rI - \delta R - qR
\end{aligned}
$$

Parameters:

$B(S,I,R)$	:	birth rate of susceptibles
δ	:	natural death rate
β	:	infectivity (per contact between S and I)
a	:	natural + disease induced death rate
r	:	recovery rate
q	:	rate of loss of immunity

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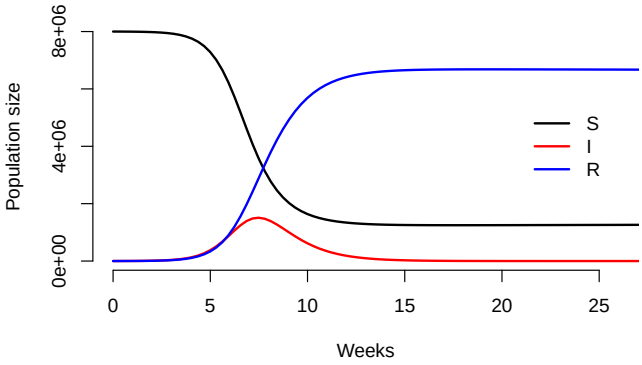
Time courses of the SIR model



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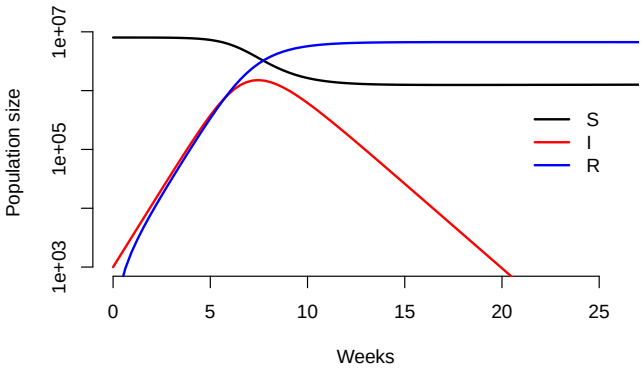
Time courses of the SIR model



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Not using this framework can lead to wrong conclusions

Abstract

The COVID-19 has been successfully contained in China but is spreading all over the world. We calibrate the logistic growth model, the generalized logistic growth model, the generalized Richards model and the generalized growth model to the reported number of infected cases from for the whole of China, 29 provinces in China, and 19 countries and regions that are undergoing major outbreaks. We dissect the development of the epidemics in China and the impact of the drastic control measures both at the aggregate level and within each province. We quantitatively document four phases of the outbreak in China with a detailed analysis on the heterogeneous situations across provinces. The extreme containment measures implemented by China were very effective with some instructive variations across provinces. Borrowing from the experience of China, we made scenario projections on the development of the outbreak in other countries. We identified that Europe and US have passed the inflection point and entered into an after-peak trajectory, which is estimated longer than what a classical Logistic model predicts, in contrast to most provinces in China where the after-peak trajectory is much faster. We expect Europe to have 1.83 million final total confirmed cases (2452 per million population) and US to have 1.26 million final total confirmed cases (3851 per million population). We identified three groups of countries in different level of outbreak progress, and provide informative implications for the current global pandemic.

Keywords

Novel coronavirus (COVID-19), logistic growing, epidemic modeling, prediction

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The basic reproduction number R_0

Formal definition of R_0

Question: Under which (mathematical) condition can the epidemic spread?

Growth rate of infecteds is larger 0, if

$$dI/dt = \beta SI - aI - rI > 0 \quad \Longrightarrow \frac{\beta S}{a+r} > 1$$

Hence, infecteds can spread in an uninfected population if

$$\text{Basic reproduction number: } R_0 = \frac{\beta S(0)}{a+r} > 1$$

Intuitive explanation:

$1/(a+r)$ is average duration of infection

$\beta S(0)$ new infections caused per day by one infected initially

At later stages, t, in the epidemic, one defines

$$\text{Effective reproduction number: } R_e = \frac{\beta S(t)}{a+r}$$

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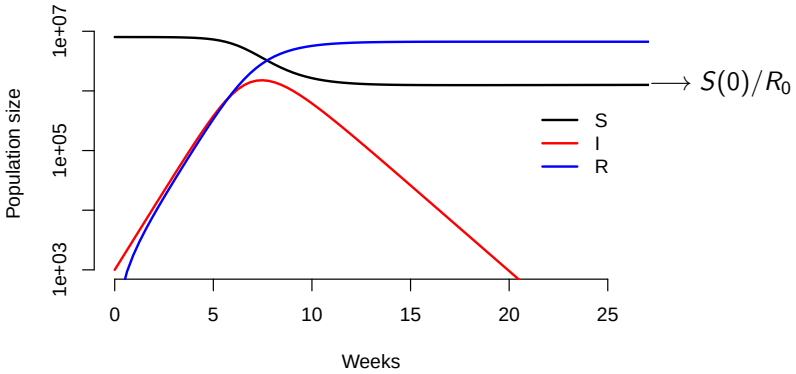
R_0 and time courses



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R_0 estimates across diseases

Virus	R_0	Reference
Measles	∼15	Anderson & May, *Infectious Diseases of Humans* '91, Table 4.1
Polio	∼6	ibid
Chicken pox	∼10	ibid
Mumps	∼10	ibid
Rubella	∼10	ibid
HIV	2–5	ibid
SARS	2–5	Lipsitch et al, *Science* '03
1918 flu	2–3	Mills et al, *Nature* '04
2009 pandemic flu	1.2–1.7	Yang et al, *Science* '09
		Fraser et al, *Science* '09
2014 Ebola	1.2–3.6	Althaus et al, *PLoS Curr* '14
		Stadler et al, *PLoS Curr* '14
		WHO Ebola Response Team, *N Engl J Med* '14

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Relevance of R_0 and fraction infected people

- a fraction of $\approx 1 - 1/R_0$ will be infected (**according to this rough consideration!**)
- herd immunity threshold (leading to eventual eradication) achieved if the fraction of completely immune hosts is $p_c = 1 - 1/R_0$

- heterogeneities in susceptibilities and contacts lead to a lower herd immunity threshold

$\longrightarrow$ Britton et al, *Science* 2020: $p_c = 43\%$

APPENDIX TABLE 2. Normalized age-specific contact rates c_{ij} as estimated from self-reported data for a typical week, after correction for reciprocity, Utrecht, the Netherlands, 1986*

Age class (years) of contacts	Age class (years) of participant					
	1–5	6–12	13–19	20–39	40–59	≥60
0–5	169.14	31.47	17.76	34.50	15.83	11.47
6–12	31.47	274.51	32.31	34.86	20.61	11.50
13–19	17.76	32.31	224.25	50.75	37.52	14.96
20–39	34.50	34.86	50.75	75.66	49.45	25.08
40–59	15.83	20.61	37.52	49.45	61.26	32.99
≥60	11.47	11.50	14.96	25.08	32.99	54.23

* To obtain a matrix with transmission rates for a specific infection in a specific population, these entries should be multiplied by the disease-specific value of the infectivity parameter q and divided by the total population size.

Wallinga et al *Am J Epi* 2006

- **complete herd immunity is difficult to achieve if**
  - vaccines are not perfect
  - immunity is waning

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Fatality risk

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Problems calculating fatality risks

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Fatality risk are often biased because

- not all cases reported (under-ascertainment)

$\Longrightarrow$ over-estimated fatality risk

- of time delays from infections to death ("right-censoring")
  when incidences are increasing $\Longrightarrow$ under-estimated fatality risk

case fatality risk (CFR) — based on reported cases, adjusted for delay effects

infection fatality risk (IFR) — based on cumulative incidence as measured by sero-surveys

Kobayashi et al *J Clin Med* 2020

The IFR is required to parameterize the SIR model: IFR$= \frac{a-d}{a+r}$

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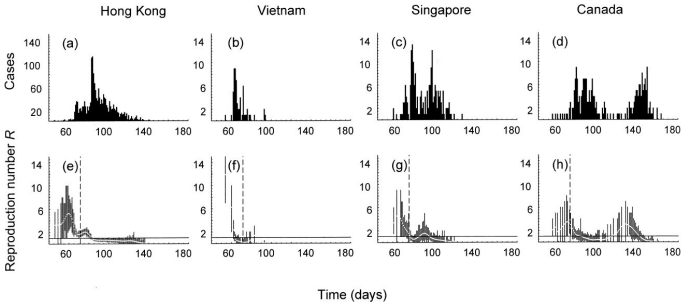
Past epidemics/pandemics

SARS 2002-2004

- $\approx$ 8000 confirmed cases
- $\approx$ 800 deaths
- $CFR = 10\%$



Wallinga and Teunis 2006 Amer J Epi, Fig 1

- $R_0 \approx 3$
- R_e declined after intervention
- resurgence in Canada

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Second wave of SARS 2003 in Canada

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Phase II of the Toronto SARS Outbreak

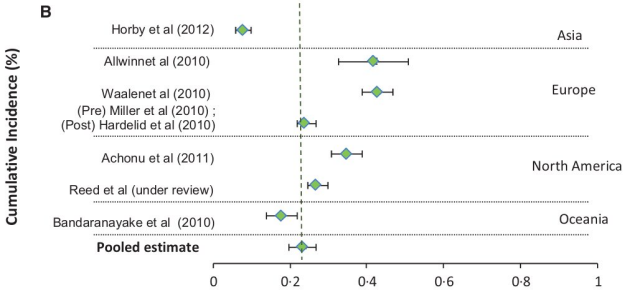
During early and mid-May, as recommended by provincial SARS-control directives, all hospitals discontinued SARS expanded precautions (i.e., routine contact precautions with use of an N95 or equivalent respirator) for non-SARS patients without respiratory symptoms in all hospital areas other than the emergency department and the ICUs. In addition, staff no longer were required to wear masks or respirators routinely throughout the hospital or to maintain distance from one another while eating.

On May 20, five patients in a rehabilitation hospital in Toronto were reported with febrile illness. One of these five patients was determined to have been hospitalized in the orthopedic ward of North York General (NYG) Hospital during April 22 to 28, and a second was found on May 22 to have SARS-associated SCoV by nucleic acid amplification test. On investigation, a second patient was determined to have been hospitalized in the orthopedic ward of NYG hospital during April 22 to 28. After the identification of these cases, an investigation of pneumonia cases at NYG hospital identified eight cases of previously unrecognized SARS among patients.

Low 2004

2009 influenza pandemic

- $< 1'000'000$ reported cases, $> 18'000$ reported deaths
- $R_0 \approx 1.4 \Longrightarrow 1 - 1/R_0 \approx 1 - 1/1.4 = 29\%$



Van Kerkhove et al 2012, Fig 3B

- estimated cumulative incidence 24%

$\Longrightarrow \approx 2 \times 10^9$ infected people

- estimated $IFR = 0.02\%$ (they call it CFR)

$\Longrightarrow \approx 400'000$ deaths

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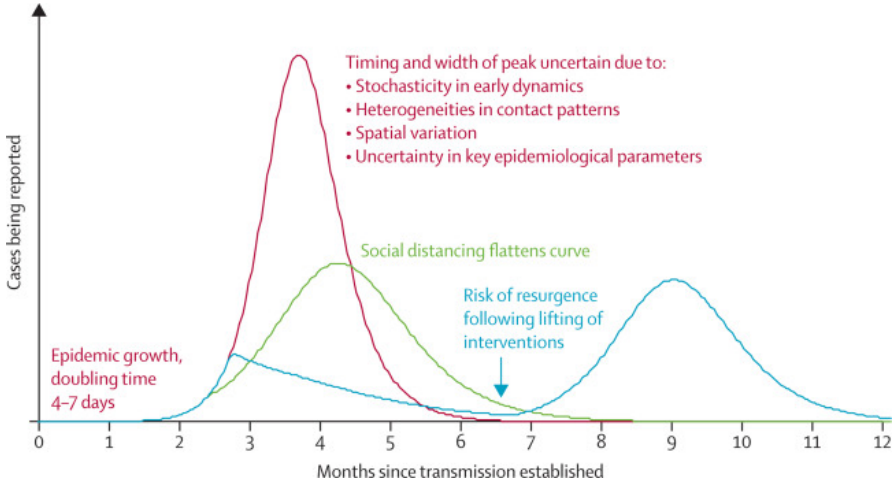
Epidemic SARS-CoV-2 dynamics with interventions



Anderson et al *Lancet* 2020

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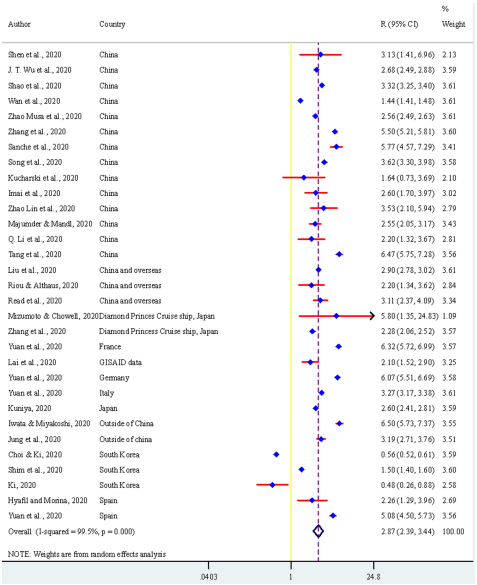
SARS-CoV-2/COVID-19 specific insights

Reproduction number estimates for SARS-CoV-2



Billah et al *PLoS ONE* 2020, Fig 2

$\Longrightarrow R_0 \approx 3$

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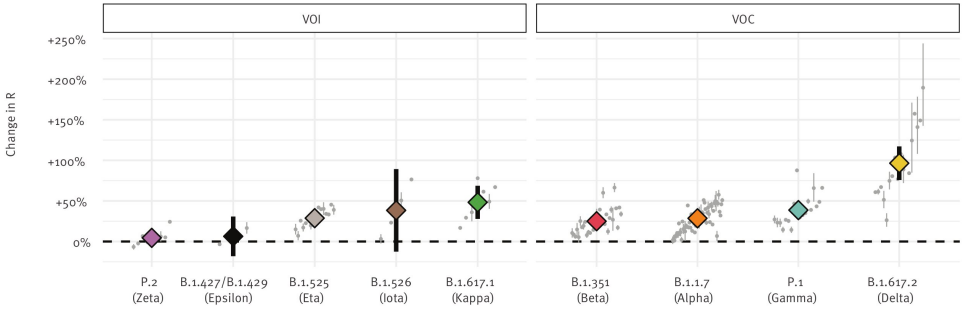
Transmission advantages of new variants



Campbell et al *Eurosurveillance* 2021, Fig 1

- $R_0(\text{Alpha}) \approx 4$
- $R_0(\text{Delta}) \approx 6$

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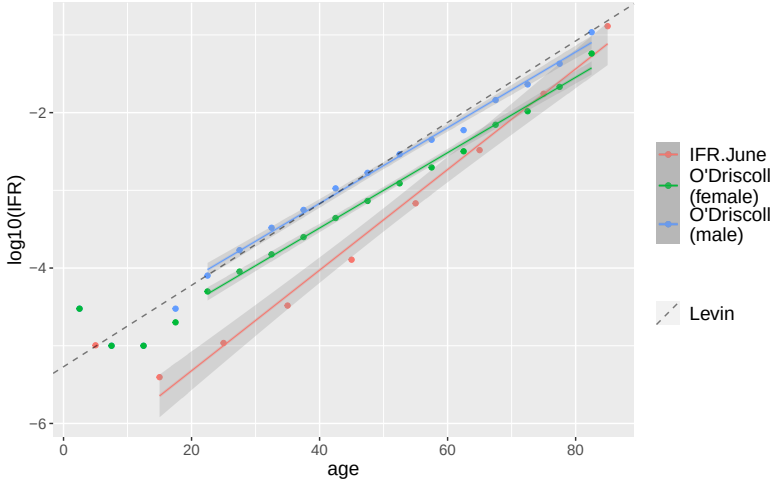
Infection Fatality Risk

- Geneva sero-survey: ascertainment rate (ratio reported cases/infection) by age
- extrapolate to all of Switzerland (adjusting for epidemic burden via deaths)



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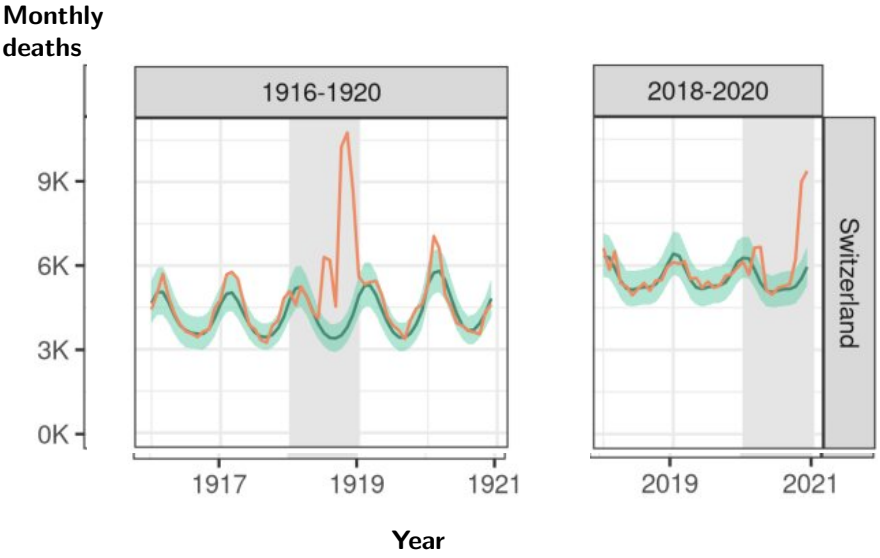
Excess mortality in Switzerland comparable to 1918 influenza



Staub et al medRxiv 2021

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Immunity

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Immunity — induced by infection or vaccination — can prevent

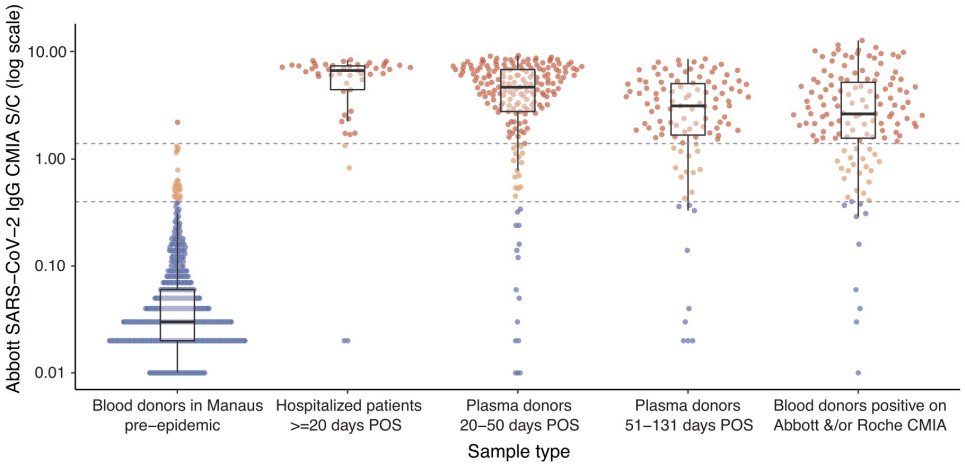
- infection
- severe disease
- death
- transmission

Immune responses, such as antibodies

- can serve as markers for past infection
- can be protective
- which immune responses cause protection has not been definitively determined yet
- neutralizaing antibodies are a "predictive correlate"

(Khoury et al, *Nat Med* 2021; Gilbert et al, Science 2021)

Antibody levels wane



Buss et al, *Science* 2021, Fig 1A

- loss in sero-positivity needs to be adjusted in sero-surveys
- indicated potential loss of protection over time

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Vaccine efficacies against symptomatic infections with original variant

vaccine	VE(sympt inf)	95% CI
mRNA-1273 (Moderna)	94.1%	89.3–96.8%
BNT162b2 (BioNTech)	95%	90.3–97.6%

Baden et al, *N Engl J Med* 2020

Pollack et al, *N Engl J Med* 2020

- epidemiologic studies estimate lower vaccine efficacy against symptomatic infection for Alpha and Delta

variant	VE(sympt inf)	95% CI
Alpha	89%	87-90%
Delta	79%	78-80%

UKHSA, Vaccine Surveillance Report, week 32, 2021

- protection against symptomatic infection also wanes

vaccine	time after vaccination	VE(sympt inf)	95% CI
mRNA-1273 (Moderna)	180 days	59%	18–79%
BNT162b2 (BioNTech)	$>$ 210 days	23%	-2–41%

https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3949410

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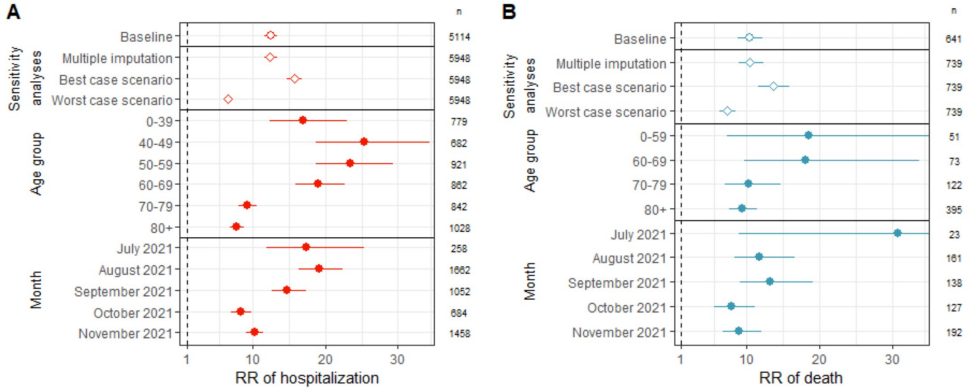
Vaccine efficacies against hospitalization/death in Switzerland



Anderegg et al, preprint 2021, Fig 2

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Waning vaccine efficacies against hospitalization and death in 60-69 year olds

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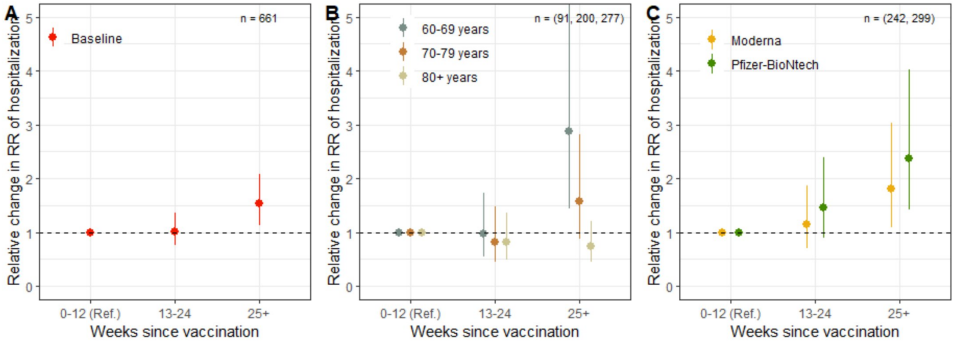

Anderegg et al, preprint 2021, Fig 3

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Remaining puzzles

Why does the transmission drop so abruptly in spring?

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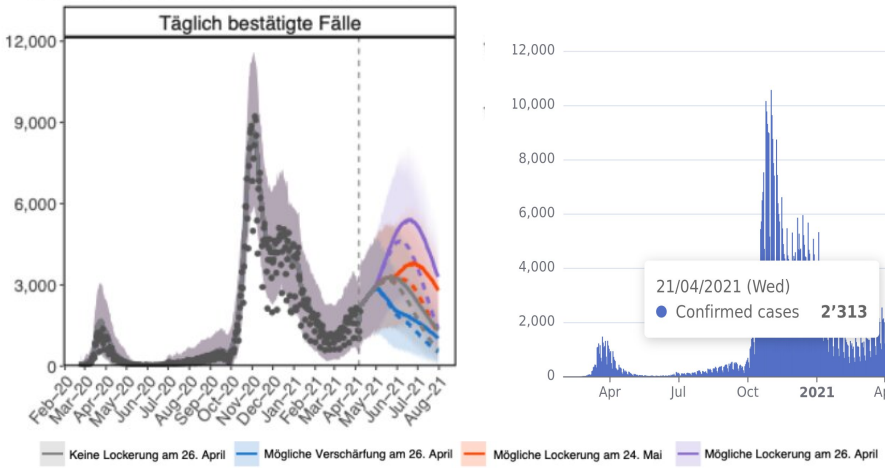
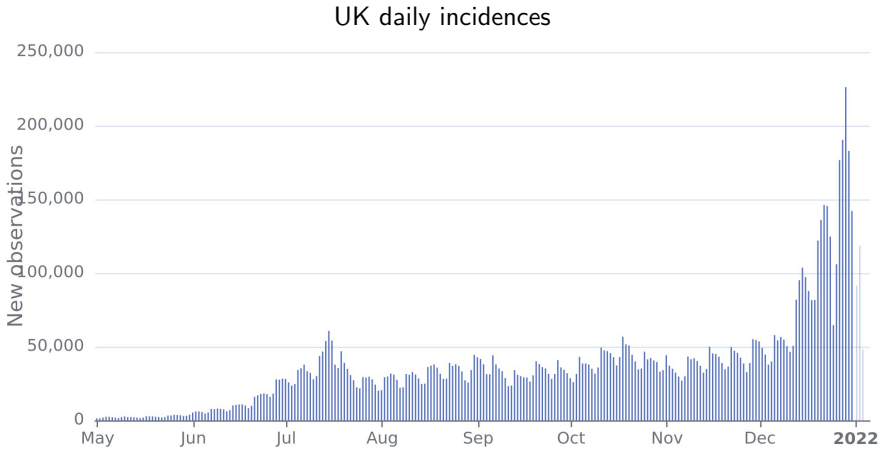
Task force projections



Actual daily incidences

Swiss National COVID-19 Science Task Force. Scientific Update. Apr 20, 2021

Why does the epidemic saturate before all susceptible are depleted?



https://ibz-shiny.ethz.ch/covid-19-re-international/

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