Epidemiology of communicable diseases: dynamics of disease transmission and epidemic control from the perspective of epidemic modelling

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17/10/2024 Budapest, University of Technology and Economics, Institute of Mathematics, Farkas Miklós Seminar on Applied Analysis

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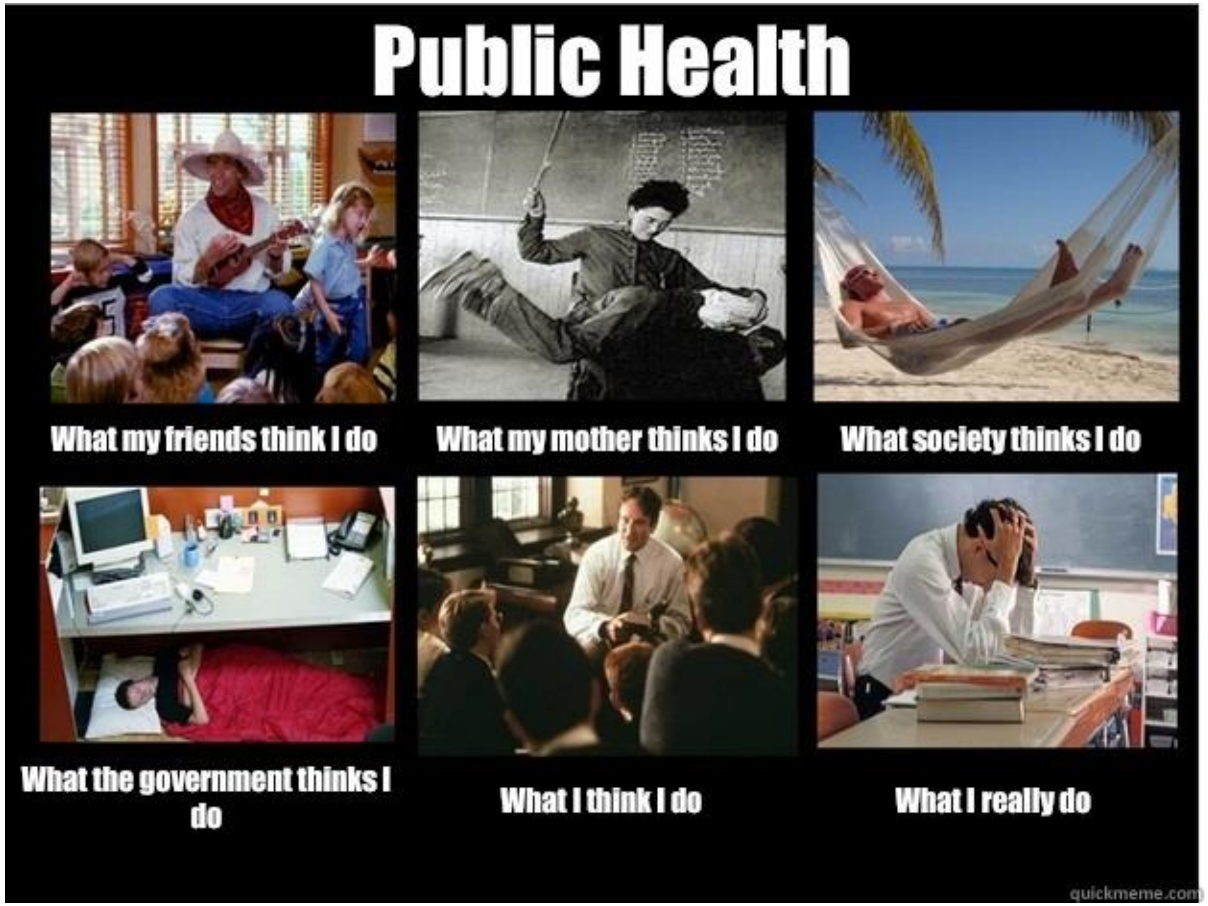
Why me?

“Medical science”

”Public health”

“Epidemiology”

What do we do?



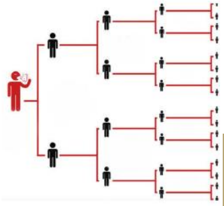
The epidemiologist sometimes thinks in a strange, one might say " weird" way…

- Stick to data and statistics,
- Does not understand why, when there is an epidemic somewhere, epidemiologists are not immediately sent out into the field to investigate it and collect data,
- Does not understand why we do not make enough efforts to identify all cases and investigating the causes of epidemics,
- Want to protect everyone from communicable and noncommunicable diseases (prevention in focus).
- Mission: saving lives and protecting people 24/7.
- **Mathematicians working in modelling of infectious diseases and epidemiologist are natural allies.**

There is an increased risk and impact of emerging epidemics. The reasons are complex

Probability of spillover

- Food demand for growing population
- Large scale of deforestation
- Animal farming with low biosecurity
- Changing ecologies due to climate change



Probability of spread

- Global travel and trade
- Megacities with poor infrastructures
- Industrial farming
- Climate induced migration

Probability of increased impact

- Demographics
- Unhealthy ageing
- Increase in population with chronic diseases
- Socioeconomic inequalities

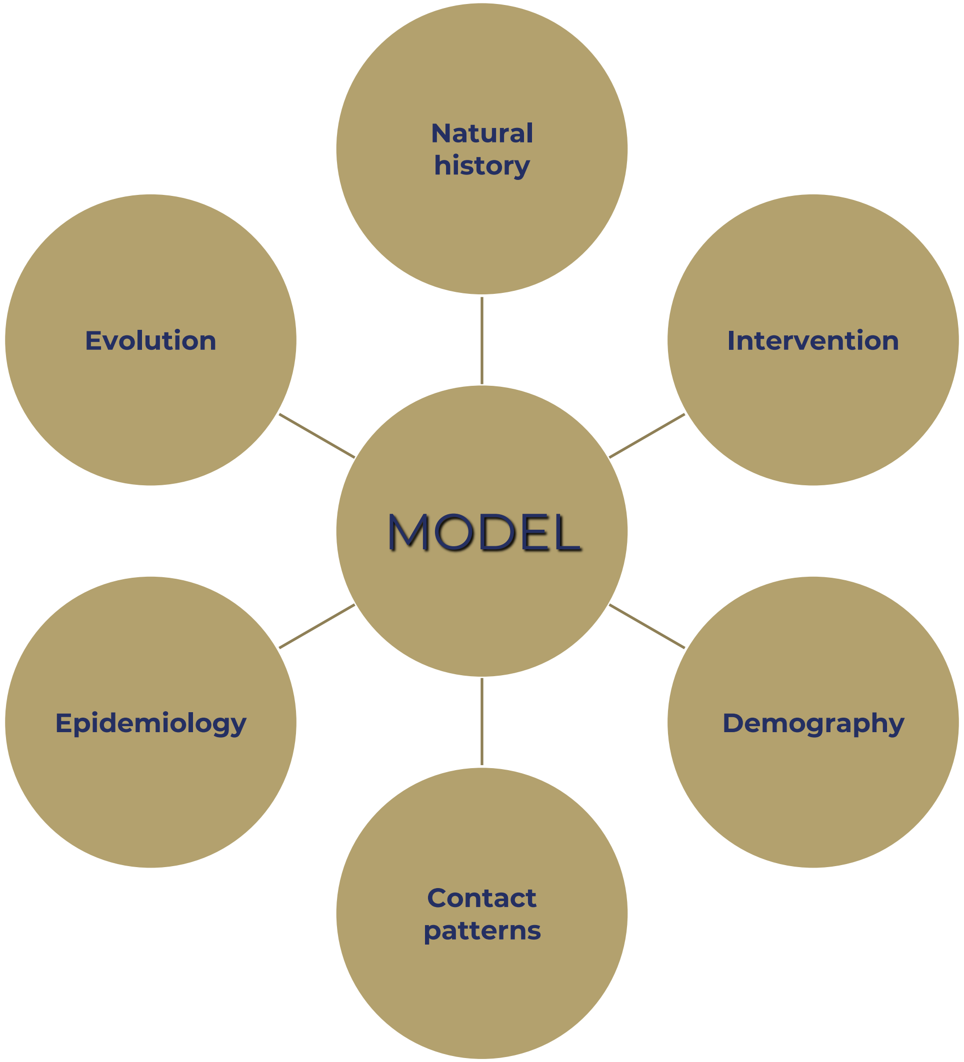
Epidemiological models

- Simplified mathematical description of infectious disease outbreaks/epidemics/pandemics.
- Aim is to understand the course of disease evolution in a population.
- The approach is to combine various inputs of how a disease spreads with characteristics of a population.

What are epidemiological models used for?

- Understand dynamics of disease spread,
- Inform public health measures to manage outbreaks, epidemics, pandemics and elimination of certain infectious diseases,
- Support data driven decision making - determine which interventions are most likely to reduce case numbers effectively.

Knowledge synthesis – multidisciplinary approach



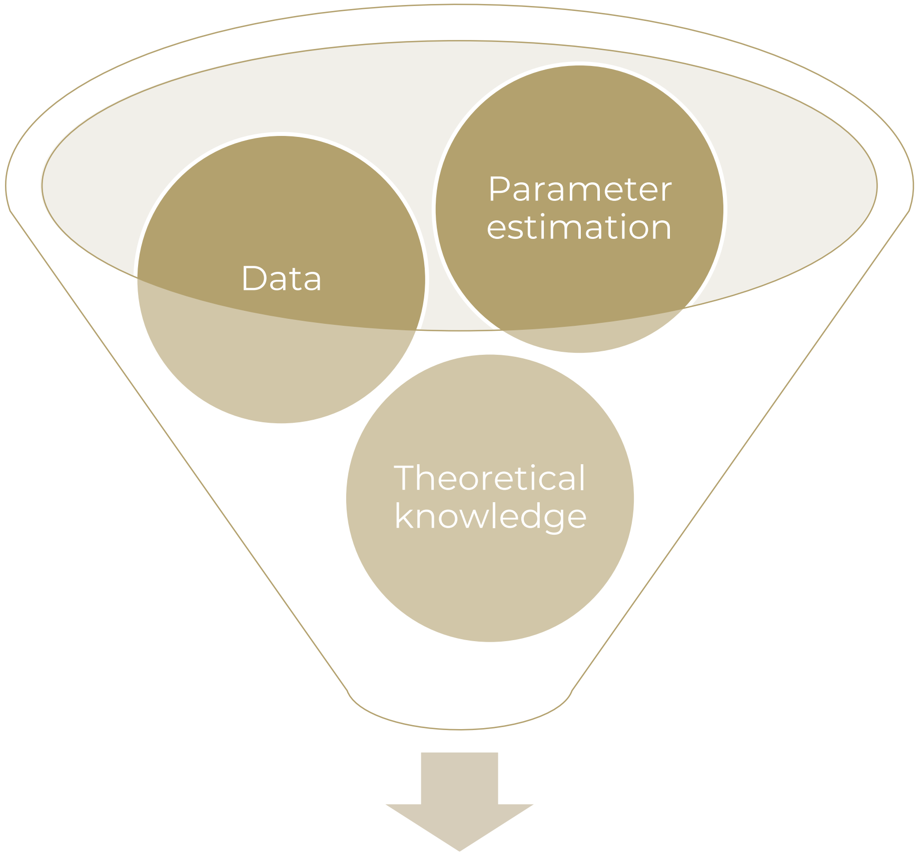
Key questions at the start of the epidemic

- What are the key drivers of the epidemic,
- The expected size of the outbreak (how many people will be infected),
- Duratio … he current …
- Expecte … d peak of epidem …
- Numbe …
- What are the most effective intervention strategies, their timing, target populations,
- What are the possible health, social, economic consequences,
- What are the possible scenarios,

We do not know in advance

Questions should ideally be answered with data to support the answers

- BUT: usually there is not enough data available to answer all these questions when we need them.
- How can a model help?
- A **tool for structured consideration of possible consequences** alongside known and unknown factors and assumptions.
- **It provides quantitative answers.**



Quantitative results

Let's look at an example!

Example of an imaginary event –
Is Vitaland country adequately prepared for an influenza pandemic?

- It is May 2025 and you are the Chief Modeller of the Modelling Expert Group at the Infectious Disease Centre in Vitaland country. There is news of **human-to-human transmission of the H5N1 influenza strain** in Faraway Country. Although this information has involved only a few people, and the flu season usually starts around week 40 each year, your government and the press have become extremely alarmed about the **possibility of a major flu pandemic**, even more so because the COVID-19 pandemic is still fresh in everyone's minds.

- The government's pandemic plan is based on the assumption that the first wave will be mild with very few cases, which can be achieved through non-pharmacological measures. To date, the country has not stockpiled antivirals for use during a pandemic. However, it has negotiated a contract with a vaccine manufacturer who has promised **to provide it with enough doses of vaccine to cover 20% of the population** (Vitaland's total population is 10 million) for use 4-5 months after the start of the first wave. The effectiveness of the future flu vaccine in preventing flu is unknown, but is likely to be less than 60% in the first 6 months after vaccination. **The government is also considering closing schools and nurseries once the daily number of new cases reaches a threshold.**

Example of an imaginary event - questions to be answered

- What level of effective vaccination coverage in the entire population does it need to control transmission in the event of a pandemic?
- If vaccination were to be provided only for individuals in a single age group (0-4, 5-14, 15-44, 45-year-olds and above), what level of effective coverage in that age group would be needed to control transmission?
- Given the facts that both the supply of vaccine and hospital facilities are limited, and assuming vaccine effectiveness of 30-60%, how would you target vaccination to prevent most of the number of influenza cases, and the number of patients seen at the peak of the epidemic?
- What is the threshold value of the reported daily number of new flu cases you would suggest for the government to trigger the shutting down/reopening of schools and nurseries?
- What effect would a 6-week shutdown of schools and nurseries have :

    - On the size of the pandemic?

    - On the duration of the pandemic?

    - On the numbers of cases seen at the peak?

- After the second wave and the vaccination of 2 million people, can a third wave be expected? If yes, when?

Example of an imaginary event – the following should be clear to the readers of your report

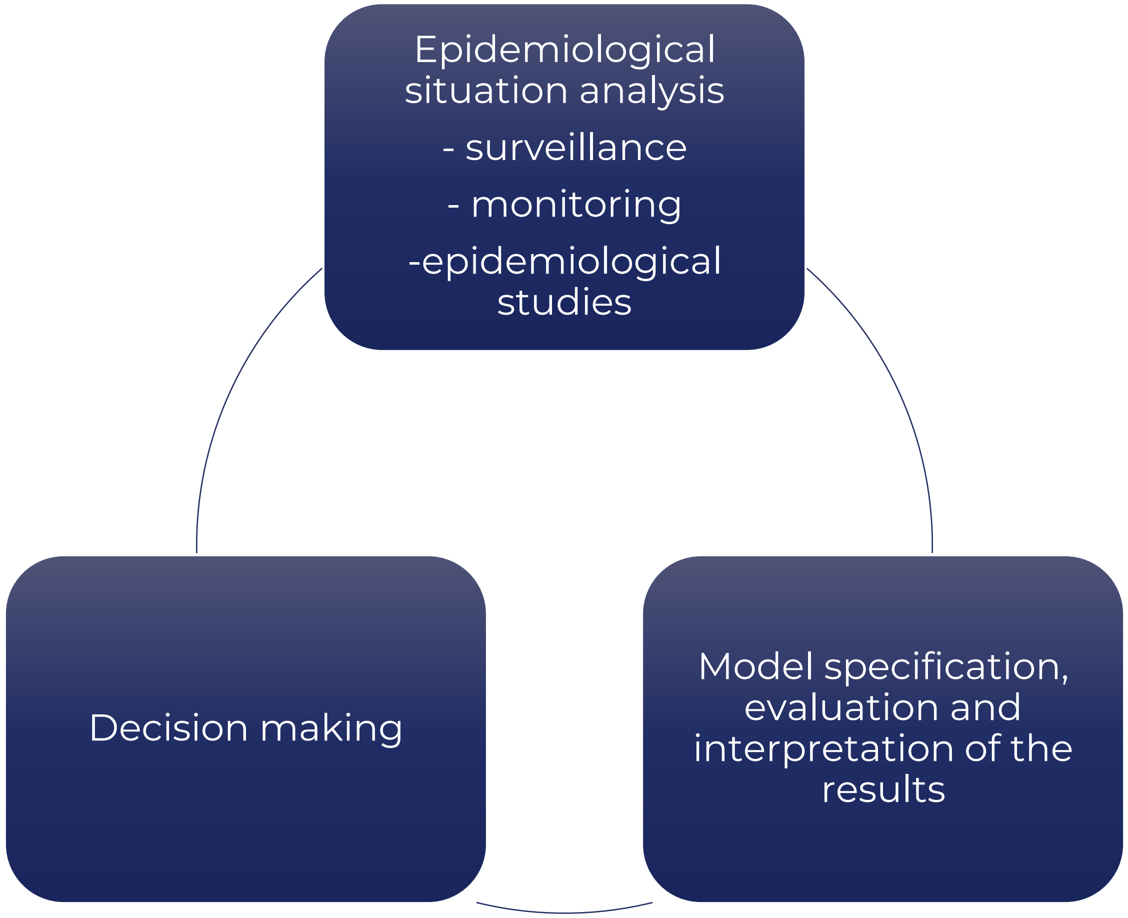
- The general structure and equations of the model,
- Input data used,
- Methods of calculations of the key parameters,
- Assumptions that you have made,
- What are the key findings,
- Limitations of the model,
- Recommendations.

Example of an imaginary event – the task

Between now and the forthcoming emergency meeting on next Saturday, you need to:

- produce a model which describes influenza transmission between different age groups in Vitaland county,
- use the model to answer the questions asked,
- write a short report documenting your methods, results and conclusions and make a presentation about it.

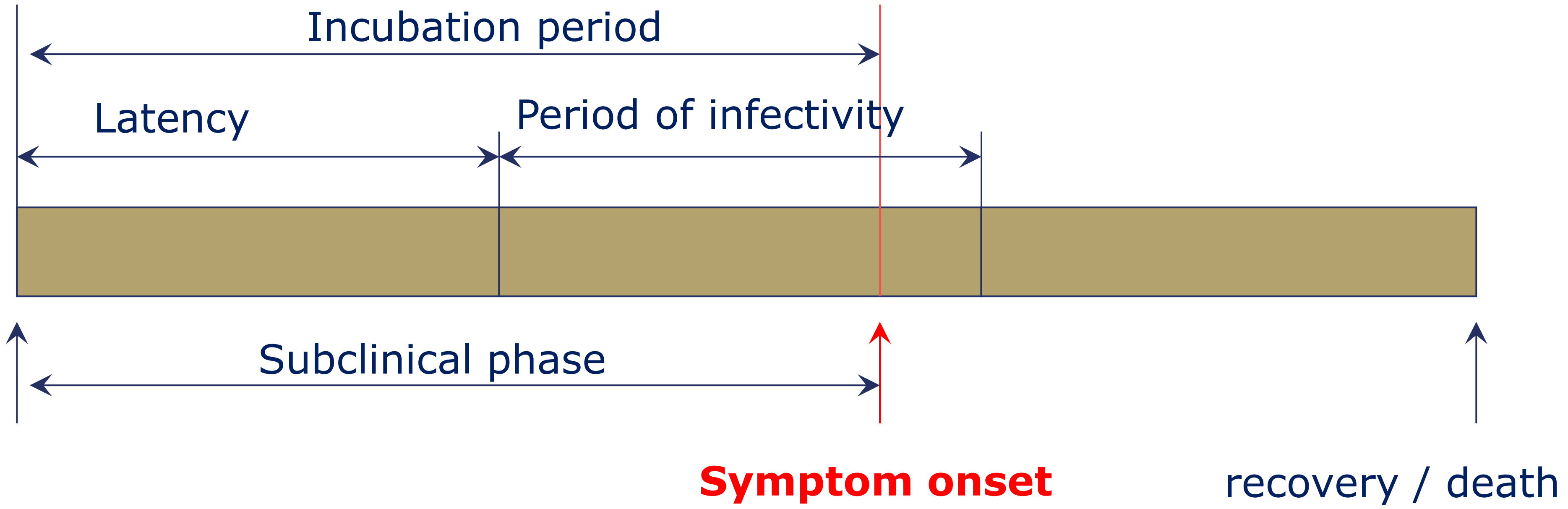
Framework


Epidemiological situation analysis
- surveillance
- monitoring
-epidemiological studies
Model specification, evaluation and interpretation of the results
Decision making

How would you start your work? What do you need?

- Team
- Data (input parameters)
  - Population,
  - Epidemiological characteristics of the new strain (incubation period,latency period, proportion of asymptomatic patients, infectiousness, case fatality rate/infection fatality rate, immunity in the population etc.)
  - Contact patterns in the population
  - Data on weekly number of new carses, total and by age
  - GP consultation habits
  - Etc.
- Assumptions
- Model specification (differential equations)

Basic epidemiological concepts related to the time course of infectious diseases



Incubation period (subclinical period): from infection to symptom onset

Latency: from infection to start of infectiousness

Period of infectivity: Time period, while the infected person can infect others

Examples for key input parameters

Infectious disease	Incubation time (days)	Start and period of infectiousness
Morbilli	Fever: 7-18 (median 10), rash: 14	It starts just before the fever and lasts for 4 days after the rash
Chickenpox	13-17	Starts 1-2 days before the rash and lasts for 5 days after the blisters appear
Rubella	16-18	It starts 7 days before the rash appears and lasts for 4 days after the rash
SARS CoV-2	4-6 (Omicron) (previously: 2-14, median 5-6)	24-48 hours before onset of symptoms, duration 10 days (may be longer in severe cases)
Influenza	1- 4, median 2	Starts up to 24 hours before symptoms onset and lasts 4-5 days

The main problem at the early stage of a pandemic is often the lack of reliable data and the lack of precision.

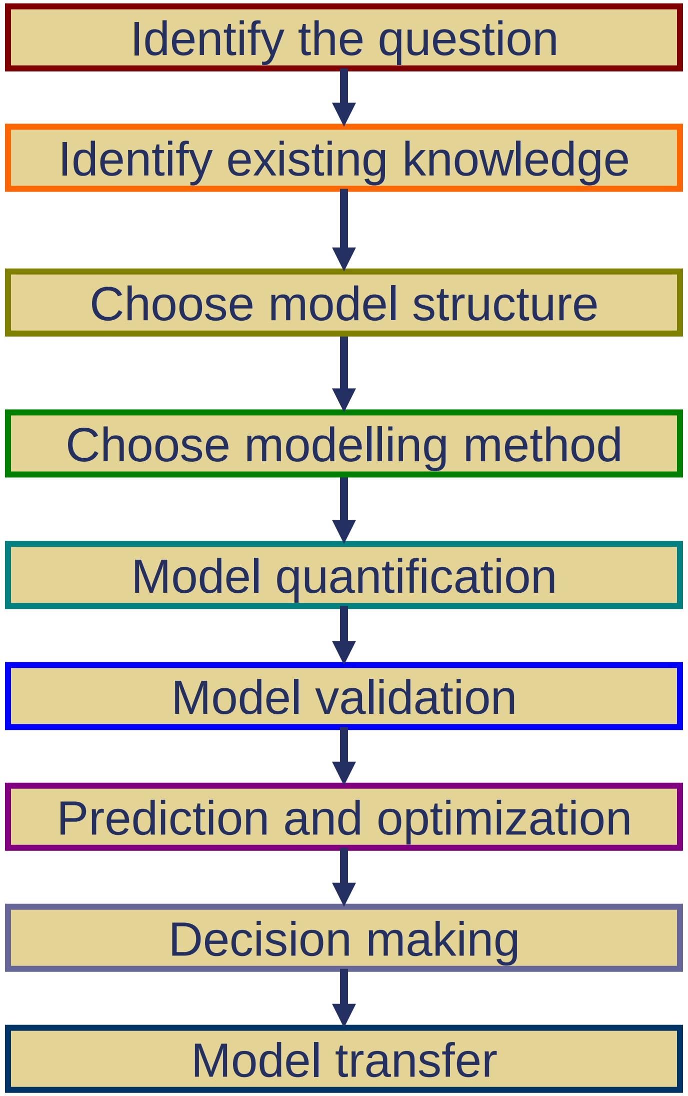
Model development steps

Questions before you start

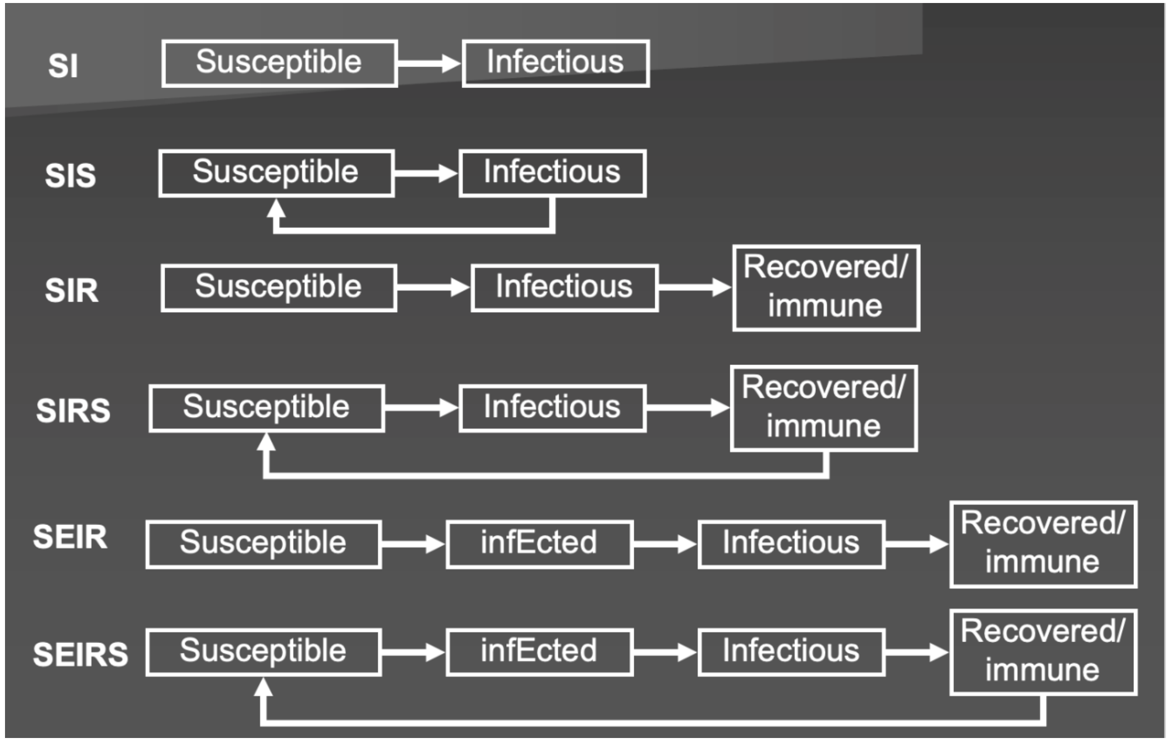
Would you like to:

- Understand observed patterns and trends?
- Explore what happens if...?
- Derive epidemiological parameters?

Make the model relevant!



Choose model structure – adequate to the time course of the infectious disease



Other considerations:

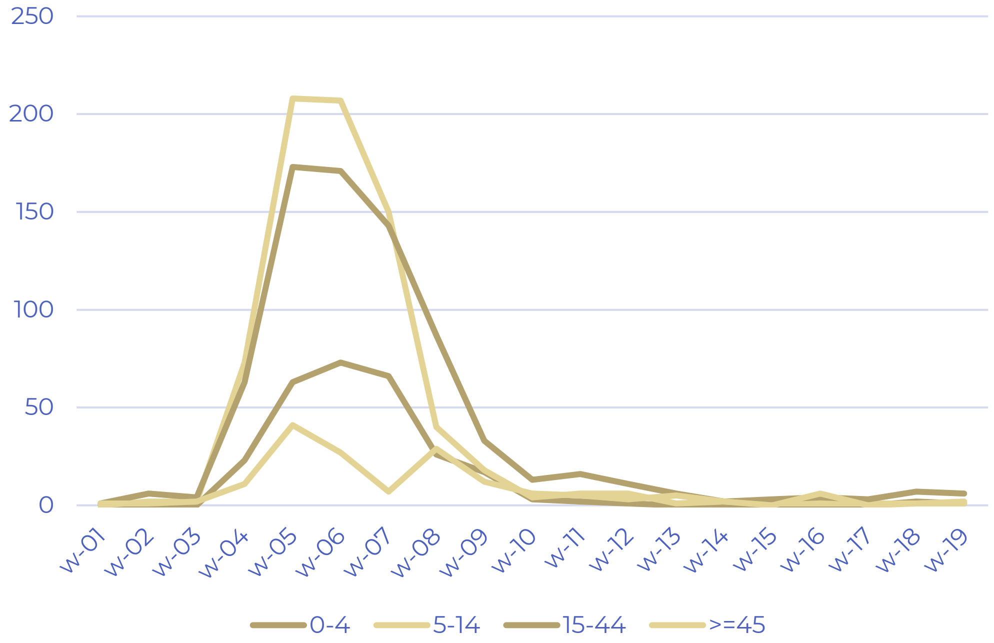
- Age structure
- Birth, death
- Vaccination
- Severity
- Reinfections
- Etc.

Models should be as simple as possible and no simpler.

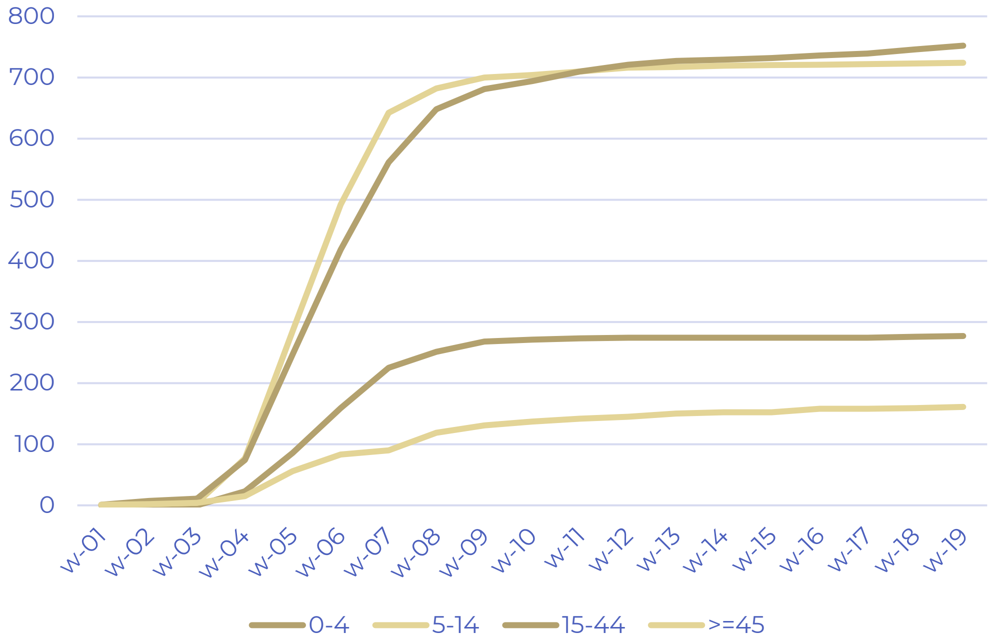
You receive data from a previous pandemic flu season from a GP practice

The contact parameters can be obtained by fitting model predictions of the (cumulative) number of cases to the observed (cumulative) numbers of cases reported to the GP practice shown in the figure

Number of cases reported to the GP per week



Cumulative number of cases reported to the GP



Age structured deterministic SEIR model

Input parameters used in the model:

Symbol	Definition	Assumed value
f	Rate at which infected individuals developed infectious disease (1/latent period)	0.5/day
r	Recovery rate from infectious disease (1/infectious period)	0.5/day
β_{ij}	Probability of an effective contact between individuals in age group i with age group j in the absence of school closures. Following school closures, Beta values equal one third of their value in the absence of school closures	Estimated using data from the GP practice
p_r	Proportion of infectious individuals who experienced disease and were reported to the GP practice.	45%
p_c	Proportion of infectious individuals who experience clinical symptoms	65%
N_j	Number of individuals in age group j in the GP practice from where surveillance data come from	0-4: 949 5-14: 1690 15-44: 3467 >=45: 1894

Summary of the variables in the model

Symbol	Definition
$S_j(t)$	Number of susceptible individuals in age group j at time t
$E_j(t)$	Number of infected (but not yet infectious) individuals in age group j at time t
$I_j(t)$	Number of infectious individuals in age group j at time t
$R_j(t)$	Number of immune individuals in age group j at time t
$C_j(t)$	Cumulative number of cases in age group j reported to the GP at time t
$\Lambda_j(t)$	The force of infection among individuals in age group j.

Description of the model

- The number of new cases in age group j at time t is: $p_c f E_j(t)$
- The expression for the force of infection among the 0-4 year old, 5-14 year old, 15-44 year old, and >=45 year olds is:

$$\lambda_y(t) = \beta_{yy} I_y(t) + \beta_{yc} I_c(t) + \beta_{ya} I_a(t) + \beta_{ym} I_m(t)$$

$$\lambda_c(t) = \beta_{cy} I_y(t) + \beta_{cc} I_c(t) + \beta_{ca} I_a(t) + \beta_{cm} I_m(t)$$

$$\lambda_a(t) = \beta_{ay} I_y(t) + \beta_{ac} I_c(t) + \beta_{aa} I_a(t) + \beta_{am} I_m(t)$$

$$\lambda_m(t) = \beta_{my} I_y(t) + \beta_{mc} I_c(t) + \beta_{ma} I_a(t) + \beta_{mm} I_m(t)$$

Where y, c, a and m reflects those aged 0-5, 5-14, 15-44, >=45 years old.

- The number of infected and immune individuals in each age group at the start of the epidemic was assumed to be zero.
- The number of infectious individuals in each age group at the start was assumed to equal the number adjusted for the proportion which had been reported (number reported /p_r)
- The number of susceptible individuals in each age group at the start was assumed to equal the population size in that age group after subtracting the number of infectious individuals.

- At a later phase you can scale up your model or the model results to reflect the population of Vitaland.

Limitations

- Assumptions
- Uncertainties
- Errors in the surveillance dataset on which the model is fitted
- Errors in the parameter estimation

Identify the question
↓
Identify existing knowledge
↓
Choose model structure
↓
Choose modelling method
↓
Model quantification
↓
Model validation
↓
Prediction and optimization
↓
Decision making
↓
Model transfer

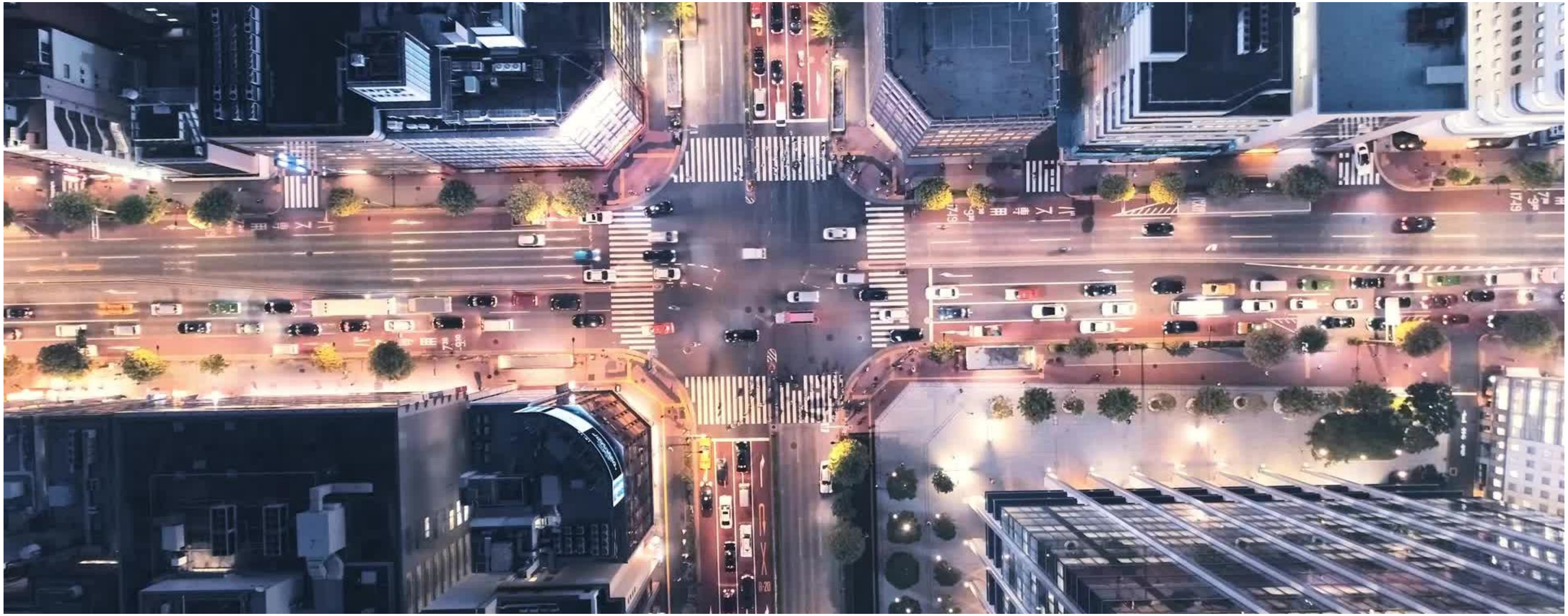
Examples for assumptions

Do not forget to specify exactly the assumptions that you made!

- Latent period, infectious period (estimations),
- Birth and death in the general population (taken into account or not),
- Contact between individuals (e.g. age dependent, random mixing with others of the same age, but not random with the others)
- Population size and age composition and GP practice size and age composition (if number of new cases are collected from GP practices),
- Death attributable to infection,
- Immunity of individuals at the start of the pandemic,
- Number of sources of infection in each age group at the start (e.g. proportional to what was reported to the GP practice),
- Individuals with symptoms were as infectious as those who were asymptomatic, or else different,
- Onset of infectiousness occurred at the same time as onset of clinical symptoms,
- Contact between individuals remained unchanged over time, or it changes,
- ?% of infected individuals experienced clinical symptoms and visited their GP. Are there delays in reporting?
- Reporting was the same for all age groups and did not change during the pandemic, or different,
- All case reported in the GP experienced clinical flu attributable to the pandemic strain,
- Since the onset of the symptoms is unknown, is it assumed that all individuals who were reported in a given week had onset (and were reported) in the same day?
- Vaccination is introduced into the population by the start of the simulated pandemic wave, or else…
- Vaccination provides a given % (and same) protection against infection and subsequent disease,
- The age distribution of Vitaland country is similar to that in the GP practice,
- Etc.

Do not forget to discuss limitations of your modelling results!

Let's make this a bit more complex!



What happened at the very beginning of the COVID-19 pandemic?

1

Models predicted an increase in morbidity and overburdened hospitals

and governments had to act on the results (there was no other information)

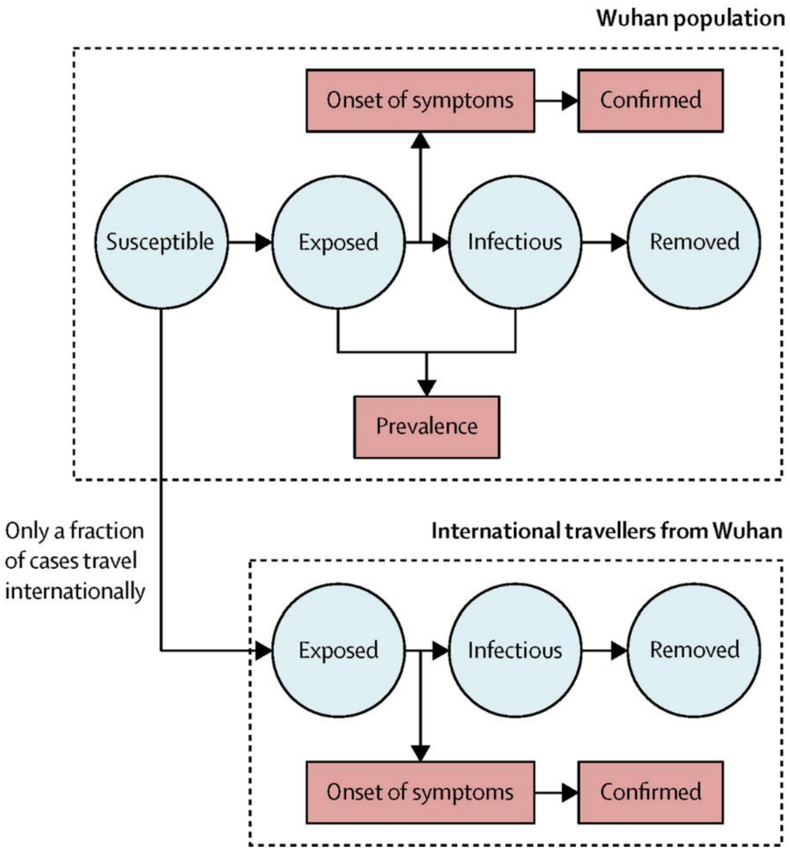
2

Epidemic modellers' predictions contributed (in part, but significantly) to the strict pandemic measures right at the beginning of COVID-19 pandemic.

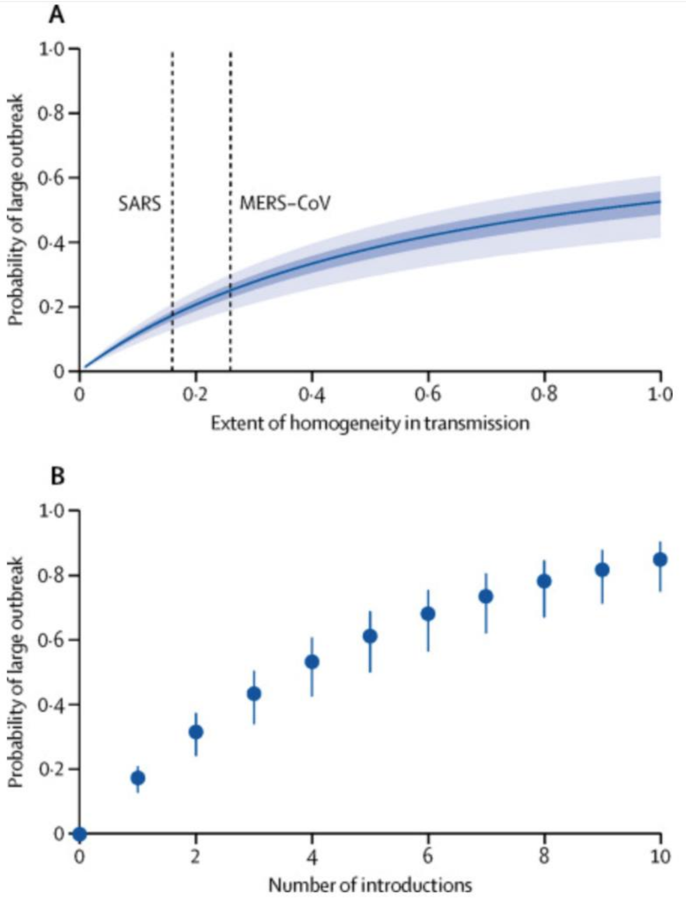
Early dynamics of COVID-19 transmission and control: a mathematical modelling study
(publ. May 2020, preprint Feb. 18, 2020)

- Coronavirus disease **showed a sustained spread in China in early 2020**, posing a significant risk of spreading the infection to other countries and causing epidemics.
- If SARS-CoV-2 **has transmission variability** at the individual level similar to Middle East Respiratory Syndrome Coronavirus or SARS, multiple introductions may be required before epidemic spread starts.
- -If **there are at least four independently introduced cases, there is more than a 50% probability that the introduction will initiate a chain of infection within the population (epidemic wave)**

Source: Kucharski et al, Lancet, 2020



A modell felépítése



A behurcolt fertőzések új populációban való megtelepedésének kockázata

The first modelling reports has given rise to much debate…

Person in the News Neil Ferguson + Add to myFT

Neil Ferguson, a virus modeller sounds the alarm

The epidemiologist and his team revealed the UK's coronavirus 'mitigation' plan could cost thousands of lives

© Joe Cummings

Pilita Clark MARCH 20 2020 312

16 March 2020 *Imperial College COVID-19 Response Team*

Report 9: Impact of non-pharmaceutical interventions (NPIs) to reduce COVID-19 mortality and healthcare demand

Neil M Ferguson, Daniel Laydon, Gemma Nedjati-Gilani, Natsuko Imai, Kylie Ainslie, Marc Baguelin, Sangeeta Bhatia, Adhiratha Boonyasiri, Zulma Cucunubá, Gina Cuomo-Dannenburg, Amy Dighe, Ilaria Dorigatti, Han Fu, Katy Gaythorpe, Will Green, Arran Hamlet, Wes Hinsley, Lucy C Okell, Sabine van Elsland, Hayley Thompson, Robert Verity, Erik Volz, Haowei Wang, Yuanrong Wang, Patrick GT Walker, Caroline Walters, Peter Winskill, Charles Whittaker, Christl A Donnelly, Steven Riley, Azra C Ghani.

On behalf of the Imperial College COVID-19 Response Team

WHO Collaborating Centre for Infectious Disease Modelling
MRC Centre for Global Infectious Disease Analysis
Abdul Latif Jameel Institute for Disease and Emergency Analytics
Imperial College London

Correspondence: neil.ferguson@imperial.ac.uk

Summary

The global impact of COVID-19 has been profound, and the public health threat it represents is the most serious seen in a respiratory virus since the 1918 H1N1 influenza pandemic. Here we present the results of epidemiological modelling which has informed policymaking in the UK and other countries in recent weeks. In the absence of a COVID-19 vaccine, we assess the potential role of a number of public health measures – so-called non-pharmaceutical interventions (NPIs) – aimed at reducing contact rates in the population and thereby reducing transmission of the virus. In the results presented here, we apply a previously published microsimulation model to two countries: the UK (Great Britain specifically) and the US. We conclude that the effectiveness of any one intervention in isolation is likely to be limited, requiring multiple interventions to be combined to have a substantial impact on transmission.

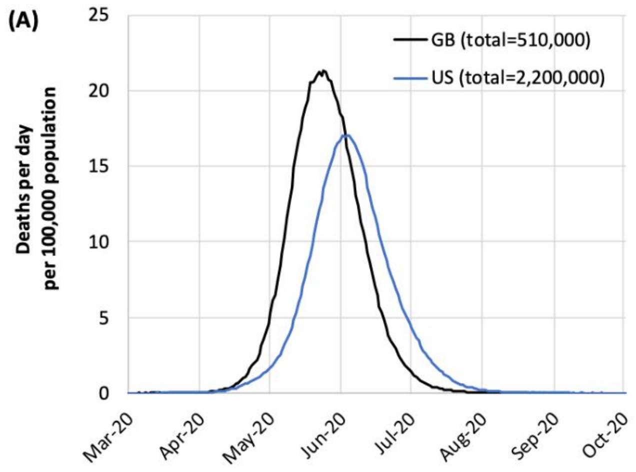
Available: https://www.imperial.ac.uk/media/imperial-college/medicine/sph/ide/gida-fellowships/Imperial-College-COVID19-NPI-modelling-16-03-2020.pdf

Mitigation or suppression - a strategic choice at the start of a pandemic

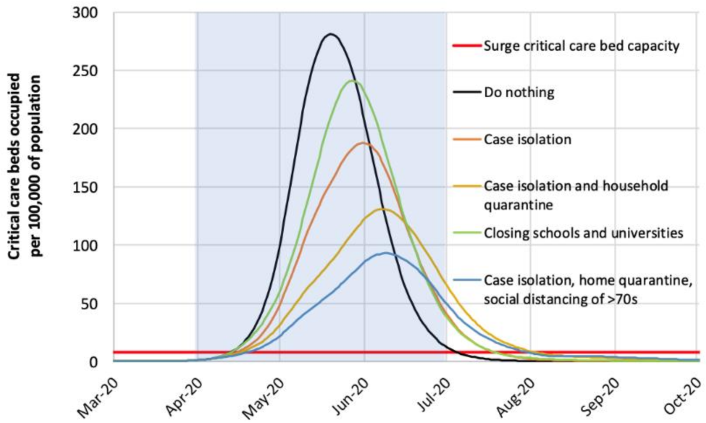
Basic scenarios:

- **Do nothing:** it is not a real option it is just for comparison
- **Suppression:** aims to reduce the reproductive number, R, below 1, and thus reduce the number of diseases drastically,
- **Mitigation:** aims only to slow down the spread by reducing R, but not below 1

Without intervention



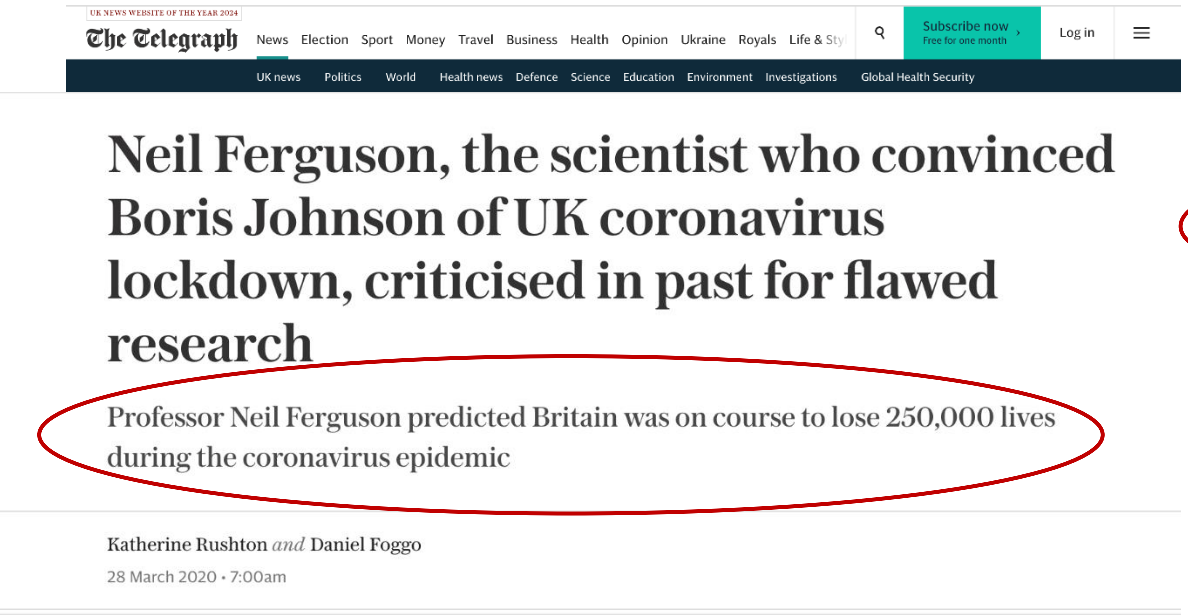
With mitigation



Forrás: Imperial College Response team, Report 9. 2020. március

March 2020

2024



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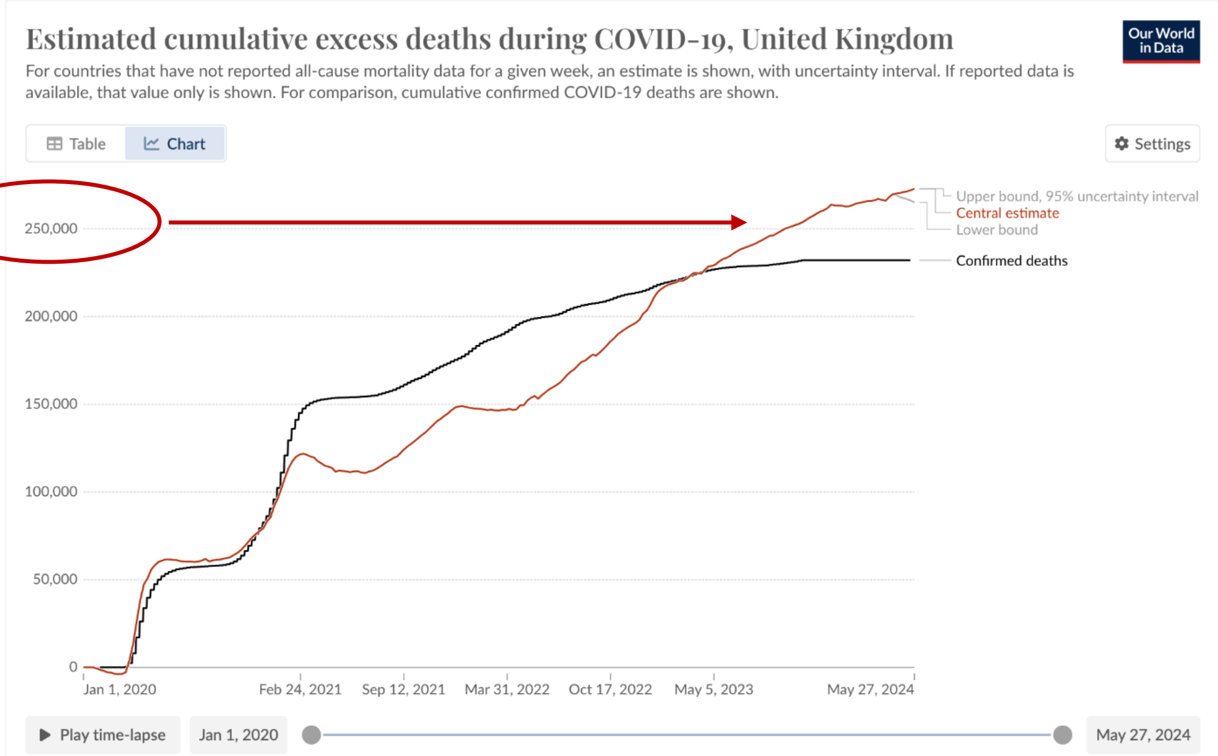
Neil Ferguson, the scientist who convinced Boris Johnson of UK coronavirus lockdown, criticised in past for flawed research

Professor Neil Ferguson predicted Britain was on course to lose 250,000 lives during the coronavirus epidemic

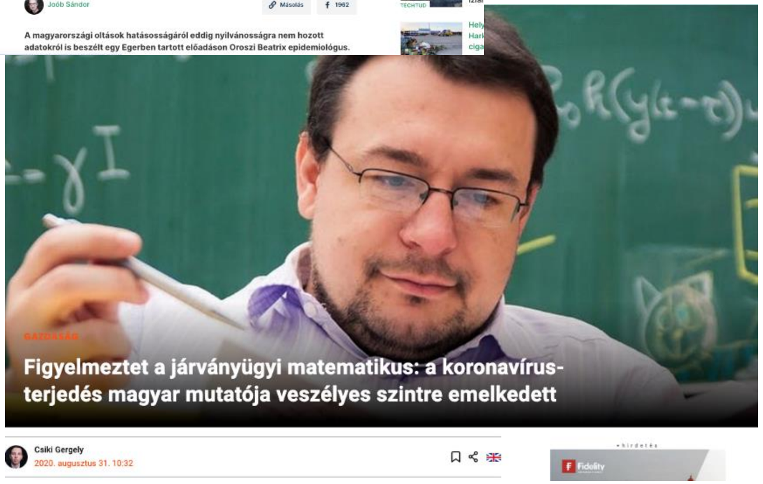
Katherine Rushton *and* Daniel Foggo

28 March 2020 • 7:00am



„Mr. Lockdown"

In Hungary, there has never been a time before when epidemic modelling was as much in the media and debates as it was during COVID-19

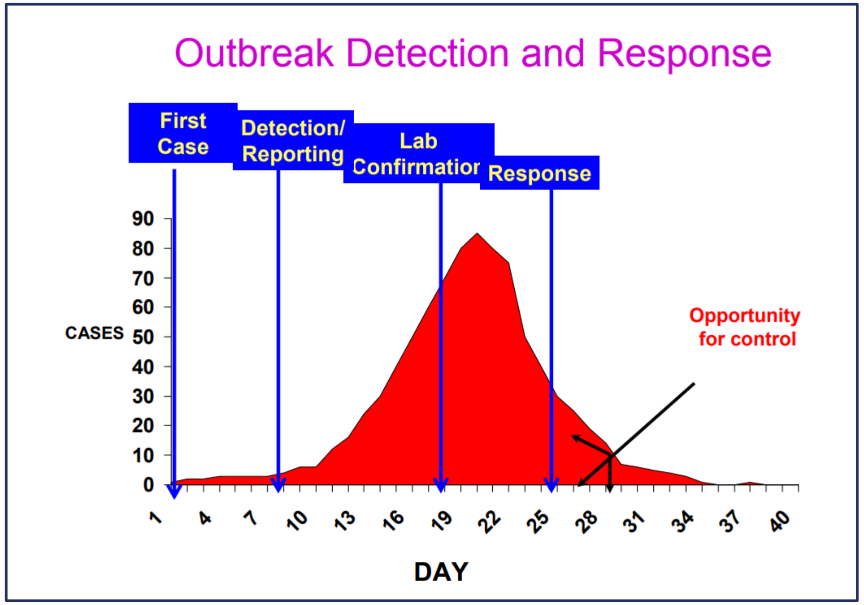


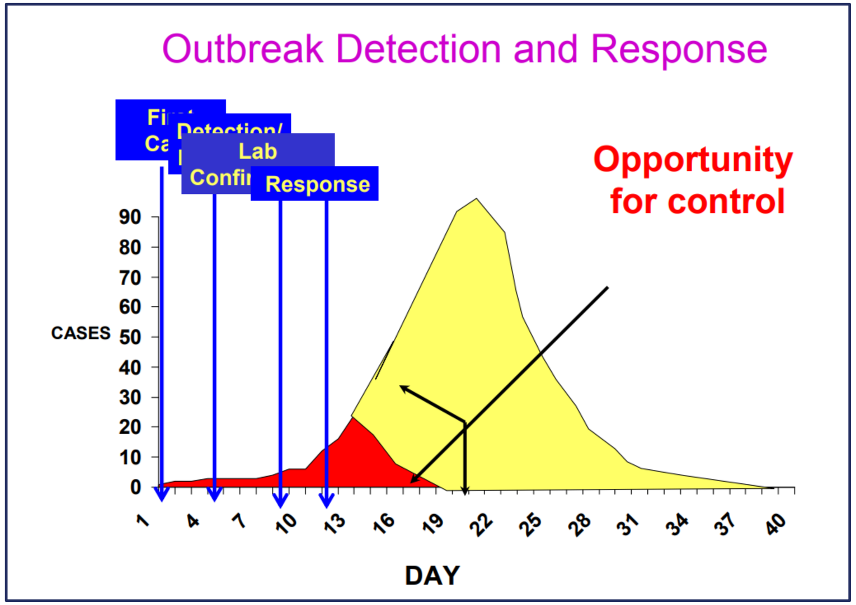
The first COVID-19 pandemic wave

No vaccines, no specific therapy was available.

4 keys to success for non-pharmacological interventions (NPIs)

- Fast response
- Adequately designed package of measures
- Facilities and resources for implementation (institutional system, professionals)
- Whenever possible, targeted use to minimise undesirable socio-economic damage (requires a very good epidemiological background)

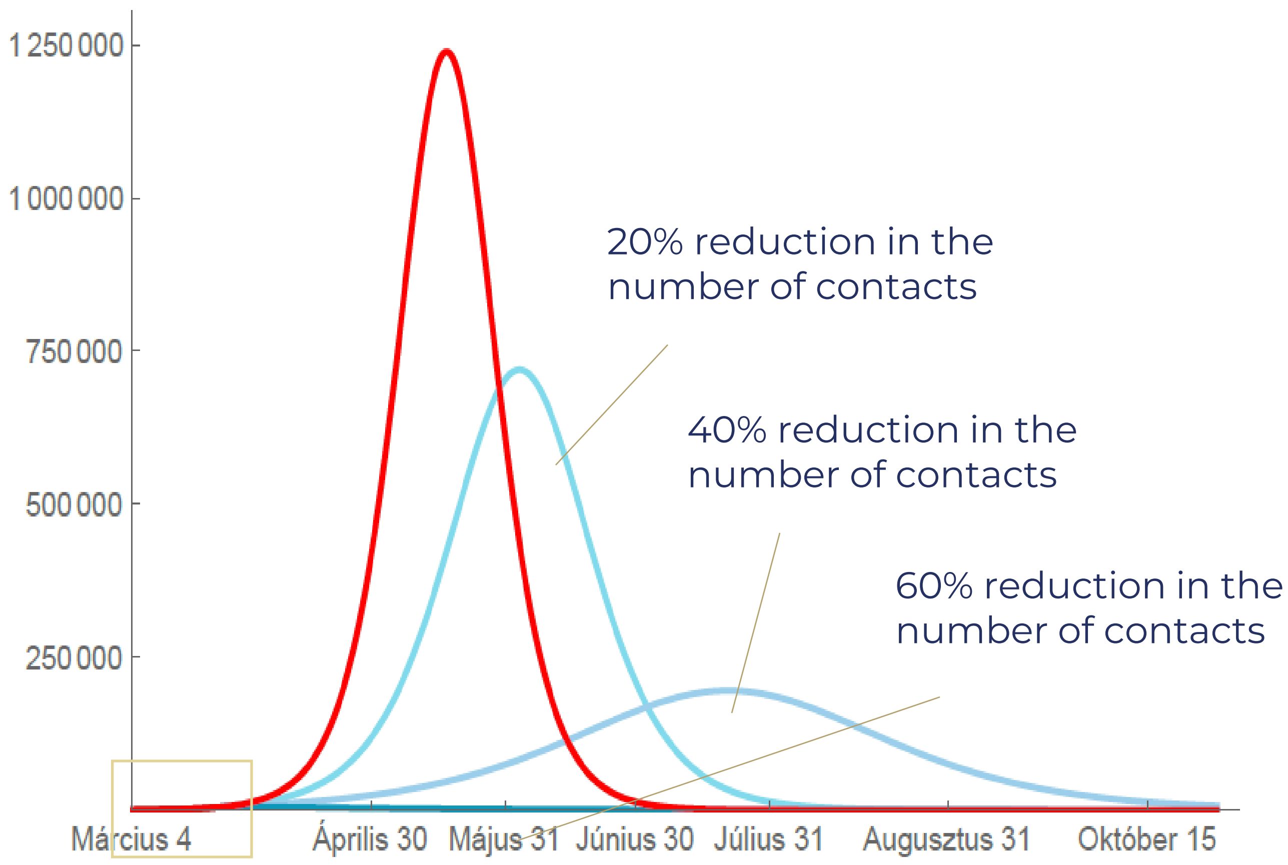


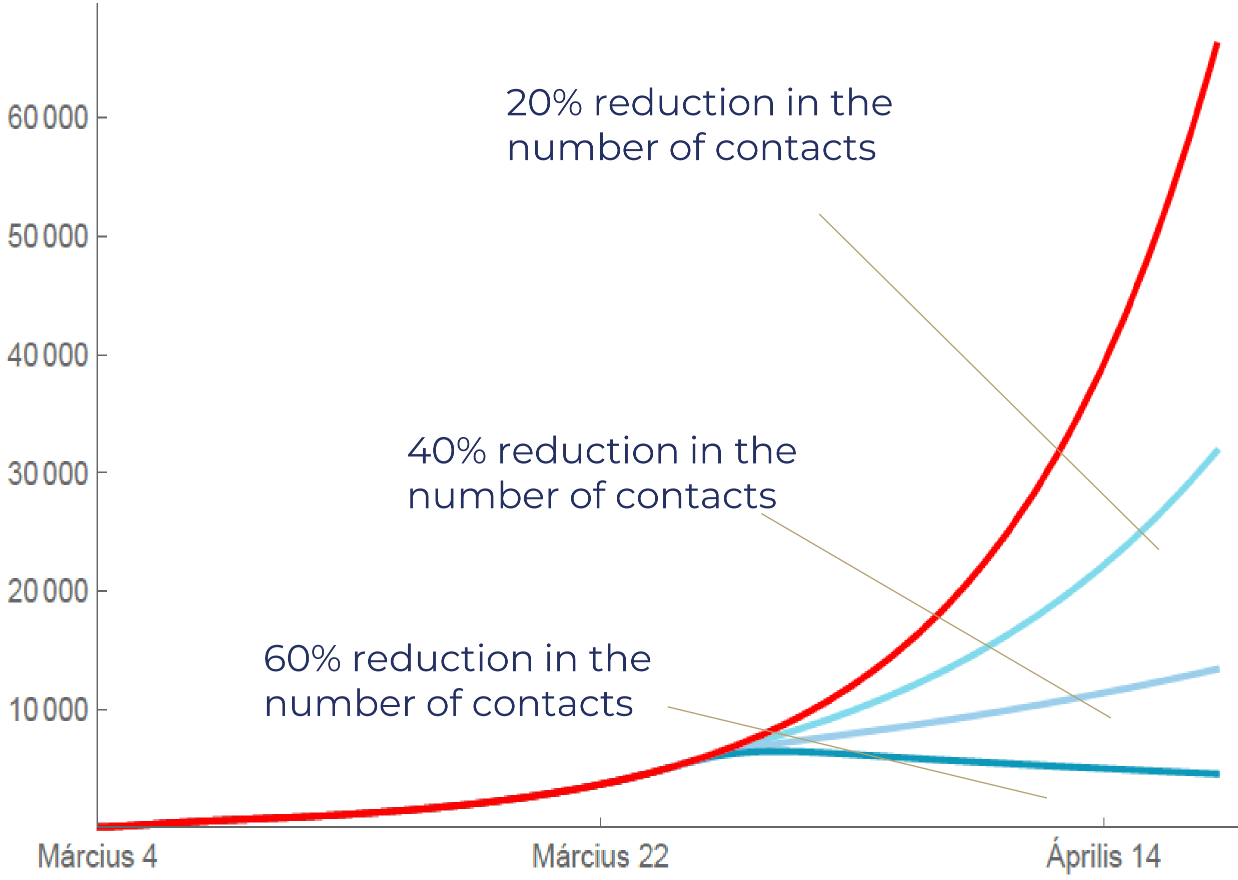


A significant reduction in the number of contacts (40-60%) can ensure a low spread of the epidemic, but it will also delay its course. A contact reduction of more than 60% will suppress the epidemic

(Source: Mathematical Modelling and Epidemiology Task Force report, 23 March 2020)

Predicted effect of action: red: no action. blue: 20% contact reduction, 40% contact reduction, 60% contact reduction



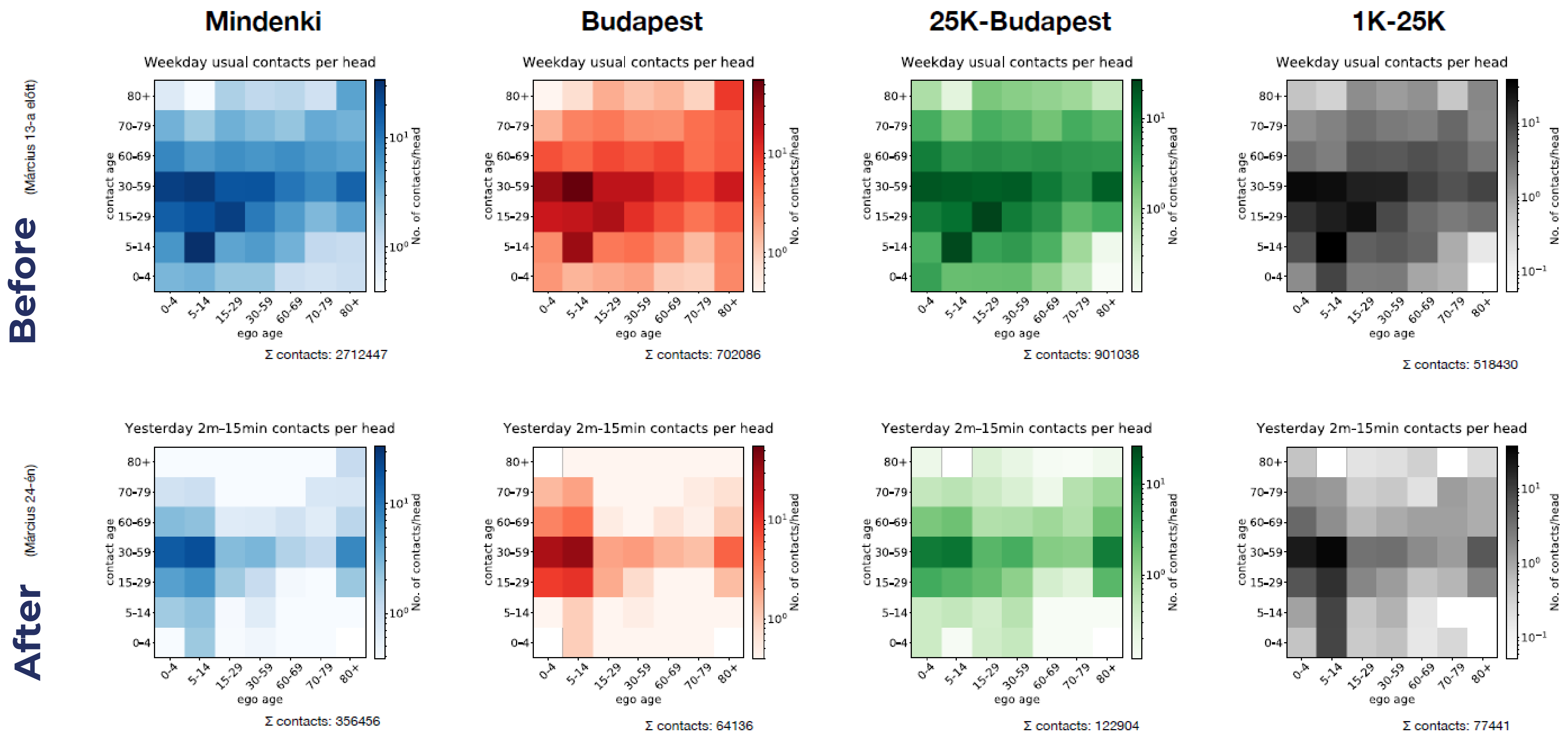


Measures

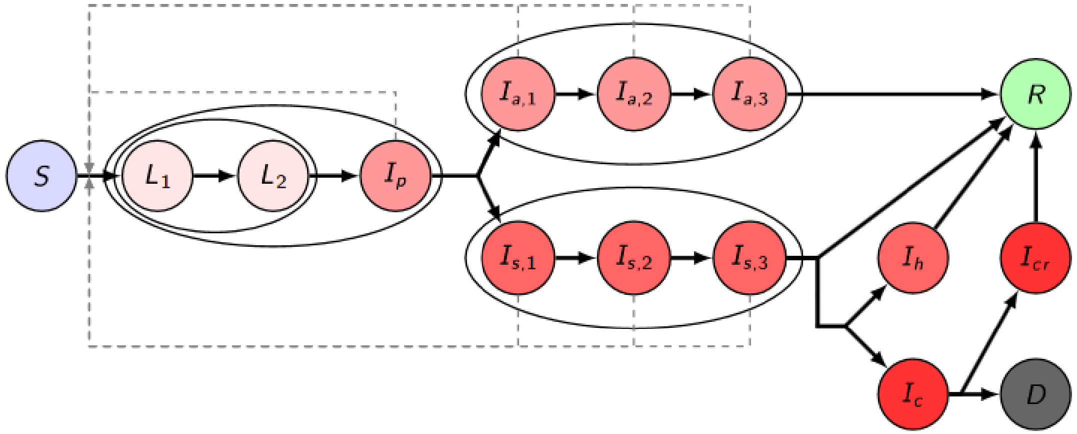
- On 11 March, Gergely Gulyás, Minister of the Prime Minister's Office, announced that the Government has decided to introduce a national state of emergency.

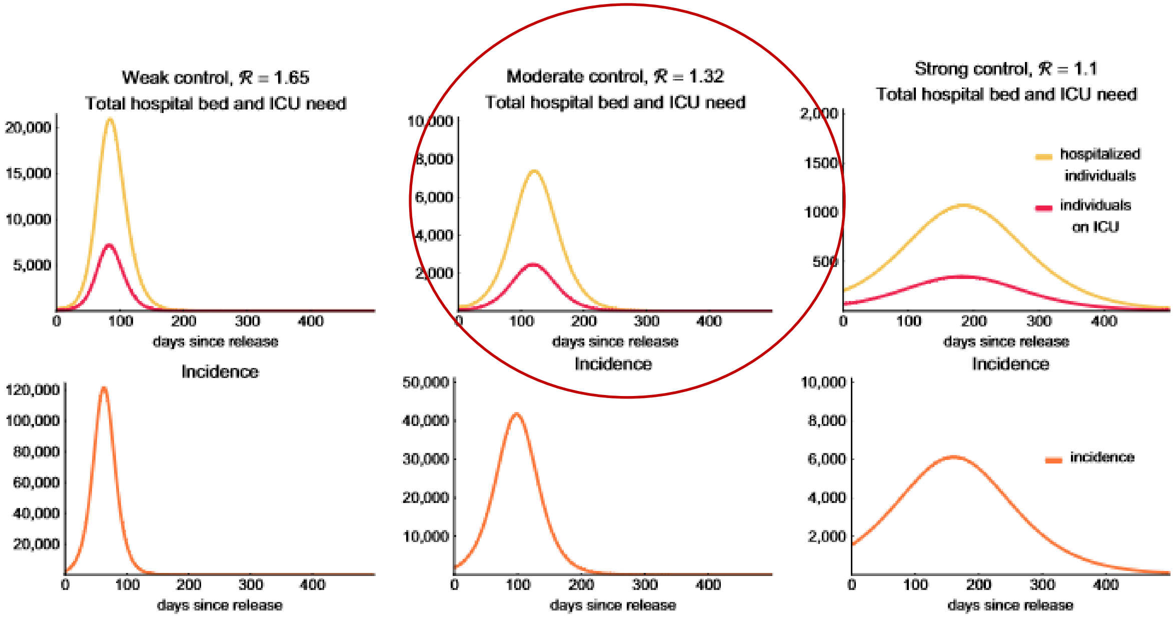
- On **27 March** 2020**, it was announced that curfews would be imposed throughout the country** from the following day.

Results of the MASZK online questionnaire: contact numbers down by 80-90 percent after 13 March



First pandemic wave: R monitoring, suppression by contact reduction, post-lockdown scenarios





Compartment model

- Age-structured
- ~200 differential equation
- Built-in: presymptomatic phase
- Gamma-distributed time domain
- Different severity

Multiple possible future scenarios

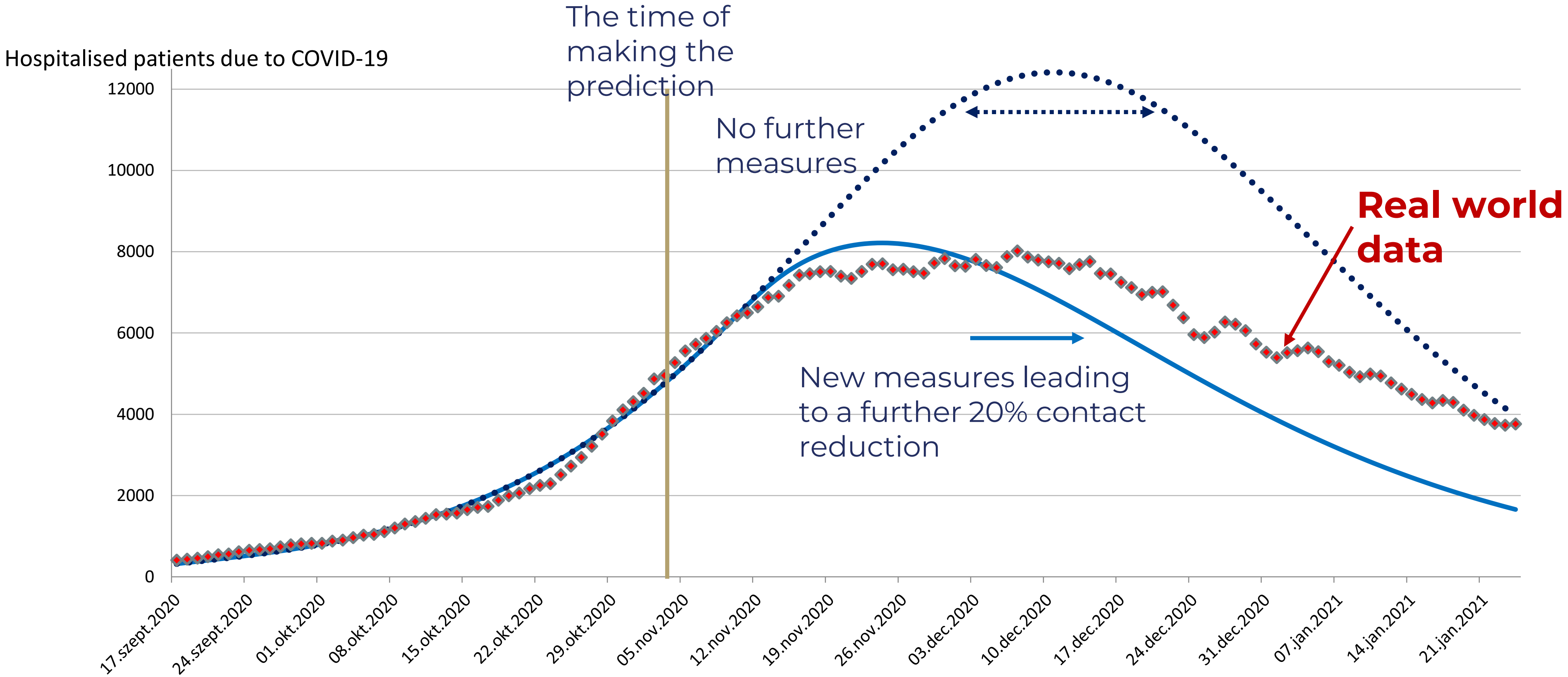
Age specific measures

Extended later

New variant
Immunity
Seasonality

Röst et al, Viruses, 2020

Early November projection of the peak of the second wave in the absence of further measures AND in the case of new measures leading to a further 20% contact reduction, Hungary, from September 2020 to January 2021



Source: Oroszi et al., Scientai et Securitas, 2021. Figure presented at the top-level consultation on 7 November 2020, supplemented with subsequent factual data

The forecast and the figure were prepared by Ferenc Bartha, Norbert Bogya, Gergely Röst, Zsolt Vizi

"All models are wrong, but some of them are useful"

Why models can go wrong?

Epidemiological data sources

Epidemiological data – various sources

- Census data, demography
- National surveillance system
- Hospital capacity and occupancy data
- National vaccination registry
- Laboratory samples and results records
- Hospital (emergency ward) records
- National Ambulance Service data on ambulance calls, testing
- National surveys (contact numbers)
- Mobility data
- Behavioural risk factor surveys (e.g. vaccine hesitancy)
- Etc.

Mostly routine statistics, some epidemiological studies.

Main challenge: timely access to relevant, reliable, good quality data.

Fitting the model to real world data.

The best choice would be weekly seroepidemiological data, but they are rarely available.

Need for **surveillance** data to fit models to.

As an epidemiological modeler…

- it is crucial to familiarize yourself with the surveillance systems in the country of work
- to comprehend their strengths and limitations.
- This understanding is essential for interpreting time trends, geographical variations, and variations by individual characteristics such as age, sex, and ethnicity.
- It is only with this knowledge that one can make confident decisions about the usability of the surveillance data.

Keep in mind!

- Surveillance is mostly put in place for a specific purpose
- However, surveillance data may be used for other purposes,

BUT

- The methods used will in general be related to this original purposes.

3 requirements of surveillance systems

Reporting network

Case definition

Analysis

Infectious disease surveillance

- Usually collects both disease and laboratory data.
- Case based or aggregated data.
- Use a mixture of methods including sentinel surveillance, notifications by doctors but for most infections they rely on reporting from microbiology laboratories.
- Usefulness depends on completeness, accuracy and consistency.
- Surveillance systems are clearly underestimate the amount of infection in the community but **provided systems remain stable it is a reasonable indicator of trends in disease.**

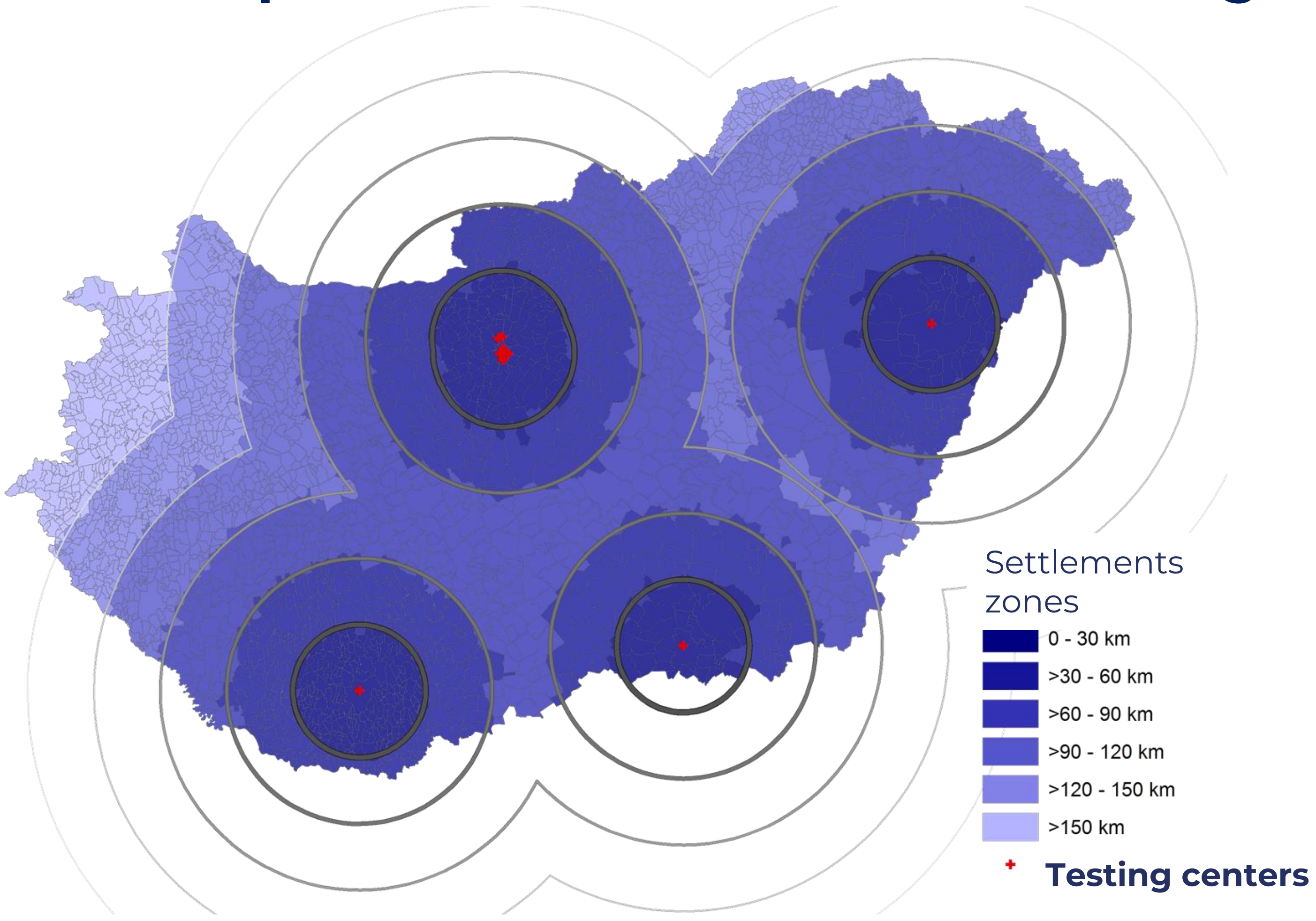
Limitations of surveillance data

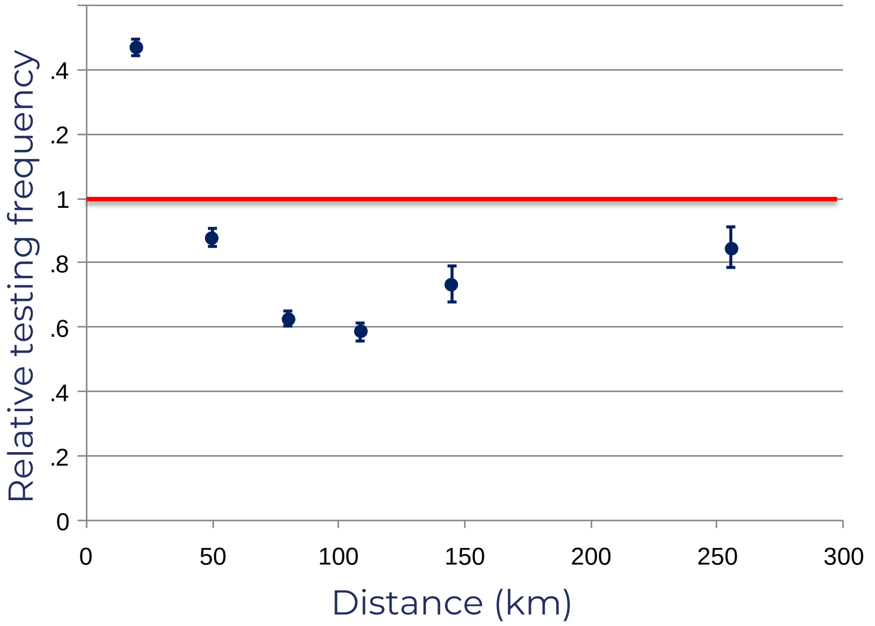
- GP consultation habits,
- Referral patterns,
- Sampling and testing patterns,
- Laboratory testing procedures, capacities,
- Laboratory testing methods,
- Reporting discipline.

All these may change over time,

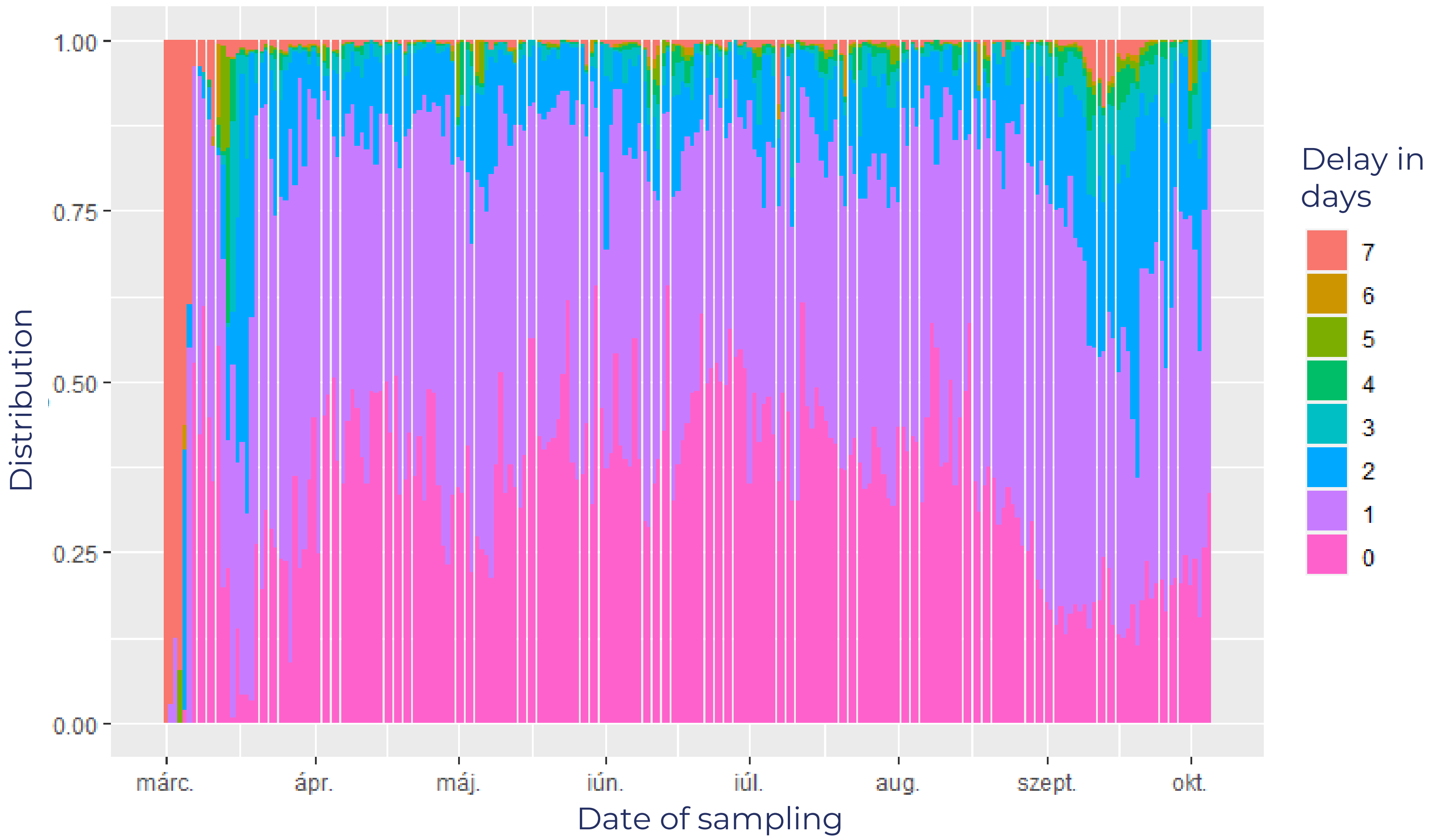
especially in the event of a major epidemic, pandemic.

Example: Relationship between testing frequency and distance from test centres (first pandemic wave)
Highest near the screening centres, decreasing away from centres (indicative of access inequalities and differential underdiagnosis)





Example: laboratory turnaround time

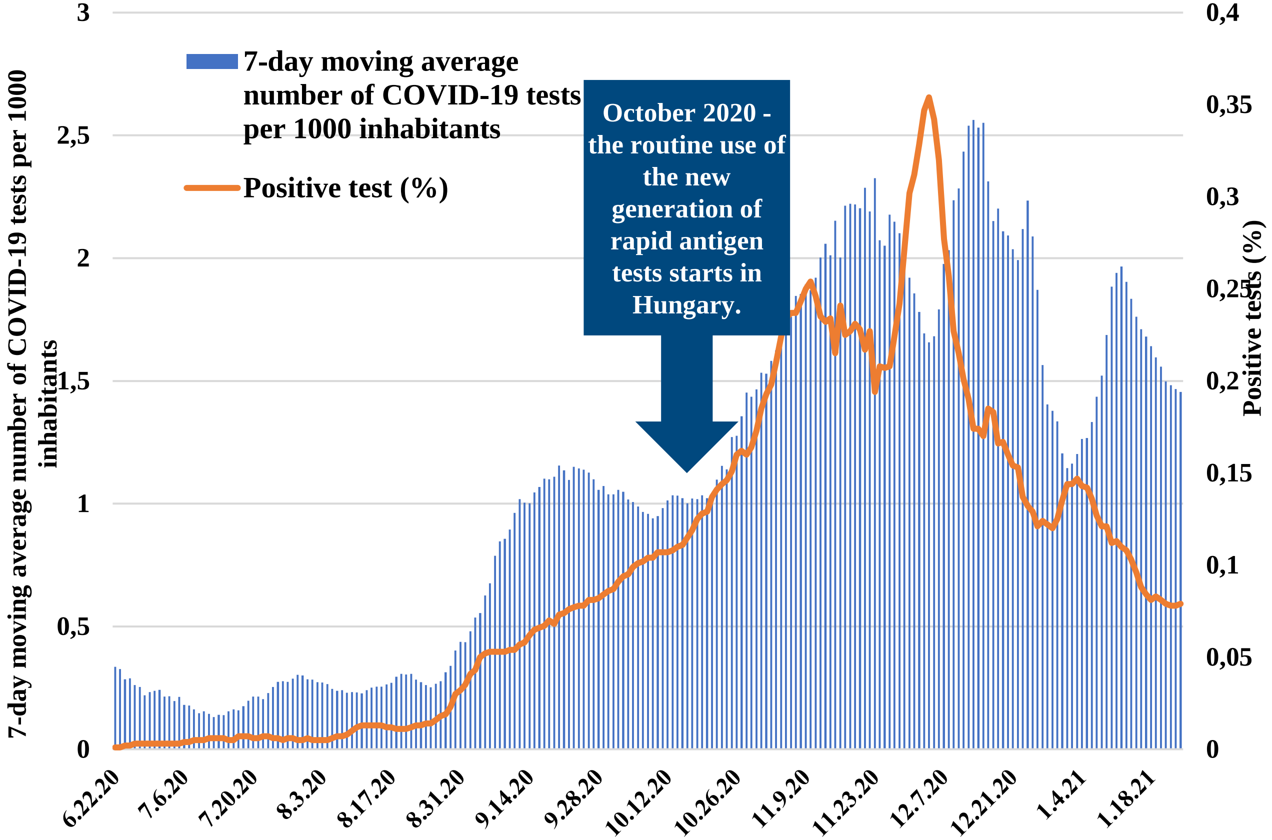


Average number of days between release of laboratory results and sampling.

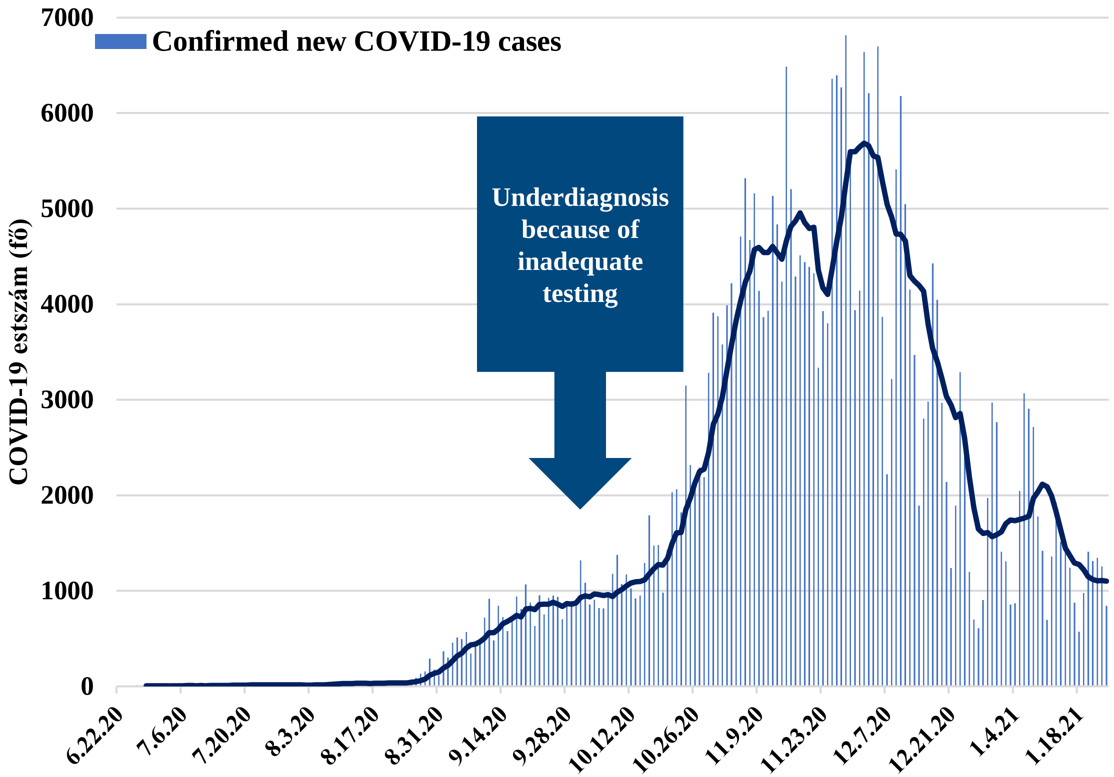
A turnaround time of more than one day indicates laboratory overload, lack of capacity and this may cause bias in surveillance data.

Example: changing testing methods, inadequate testing
Are these data suitable for trend analysis, R-estimation or model fitting?

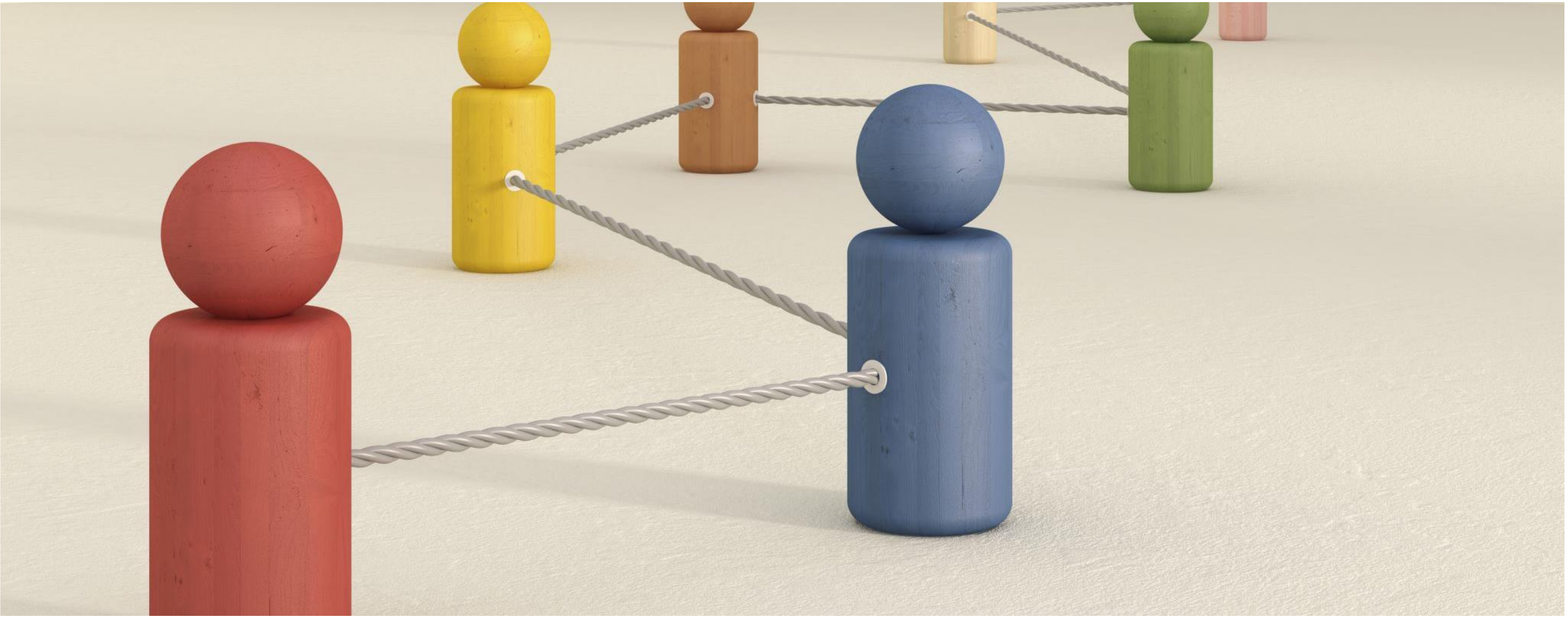
Testing coverage and test positivity



Confirmed COVID-19 cases (based on date of confirmation of infection)



Social dimensions



Epidemic modelling requires empathy and attention!

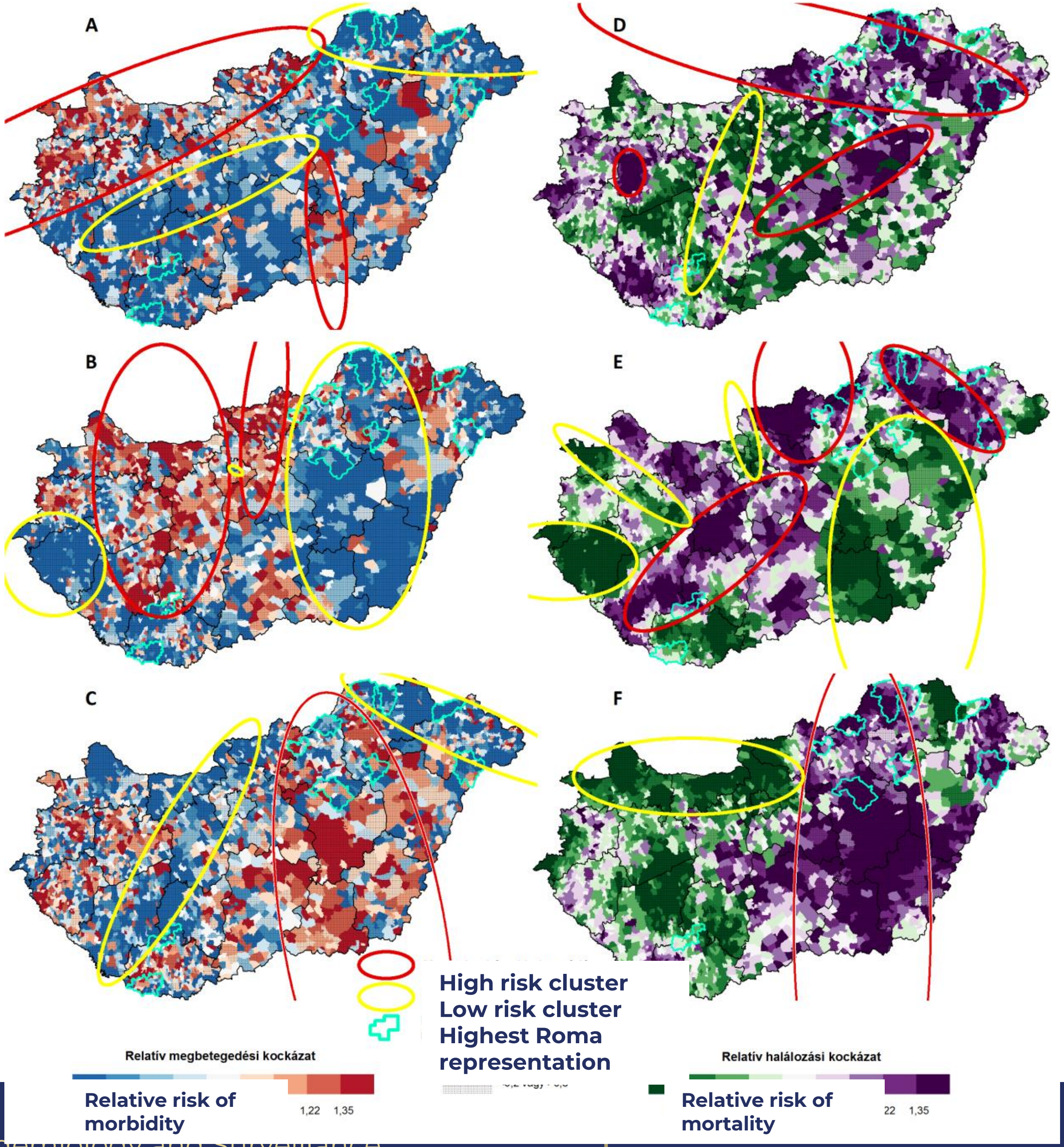
What is really happening in the population?

- Context
- Diversity
- Social differences
- Difficulties in understanding models and results

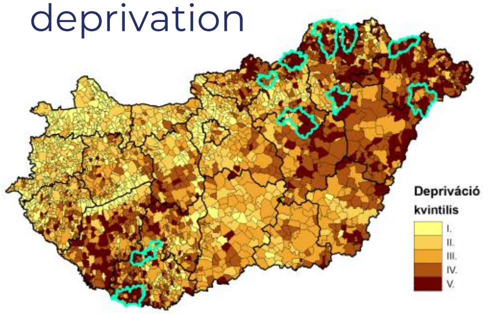
Example: spatial underdiagnosis of cases

Spatial distribution of the relative prevalence of

- registered COVID-19 morbidity (A, B, C) and
- COVID-19-related mortality (D, E, F) in Hungary at
  - PW 2 (A, D),
  - PW 3 (B, E) and
  - PW 4 (C, F)

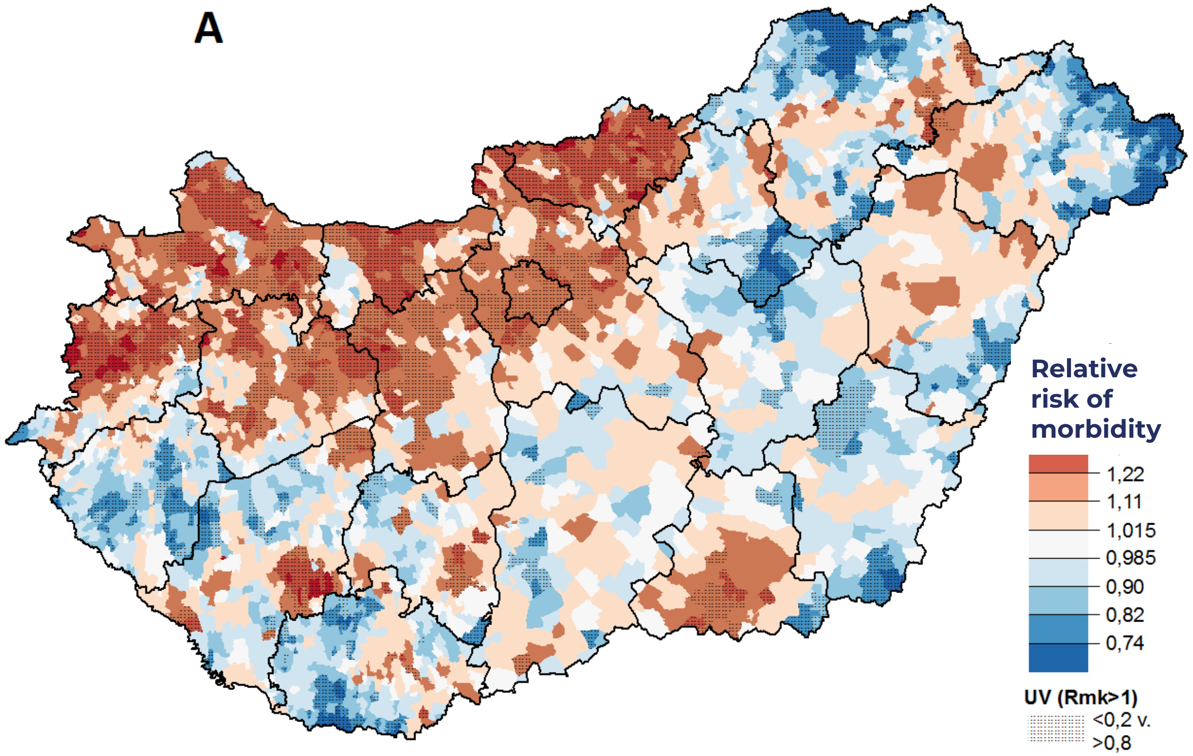


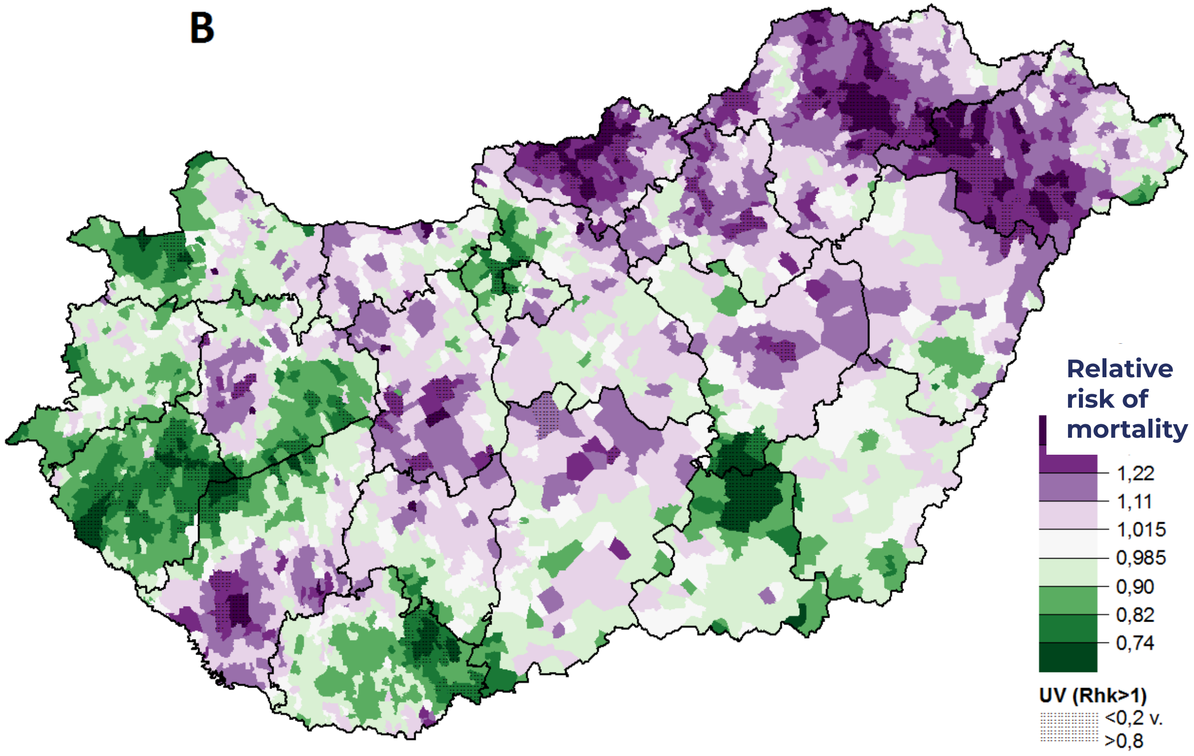
Social deprivation



Source: *Juhász et al., 2010,*

Example: the common components of the spatial distribution of the relative risk of morbidity (A) and mortality (B) of COVID-19 confirmed during pandemic waves 2 and 3 in Hungary





Context must be taken into account

- Interventions (targeted or not)
- Compliance
- Local epidemiology - regional differences at high resolution
- Differences in access to and use of curative and preventive health care
- Data collection - how it is done, how well it reflects the real situation

Epidemiological modelling is multidisciplinary: it is based on the collaboration of mathematicians, physicians, epidemiologists, biostatisticians, virologists and sociologists.

Examples for model quantification – more challenges in parameter estimations

Model quantification – some examples for key parameters, which might be difficult to estimate

- Proportion of infected individuals who are properly tested and isolated and thus do not cause further infections
- Proportion of individuals vaccinated / immune
- Risk reduction provided by vaccination, against infection, hospitalisation and death
- Proportions of individuals comply with NPI-s

Vaccination

The long-term proportion of individuals who are susceptible in any given age group depends on:

Direct effect of vaccination

=> ↓ proportion susceptible

Indirect effect of vaccination

=> ↓ force of infection (infection risk)

=> ↑ proportion still susceptible by a given age

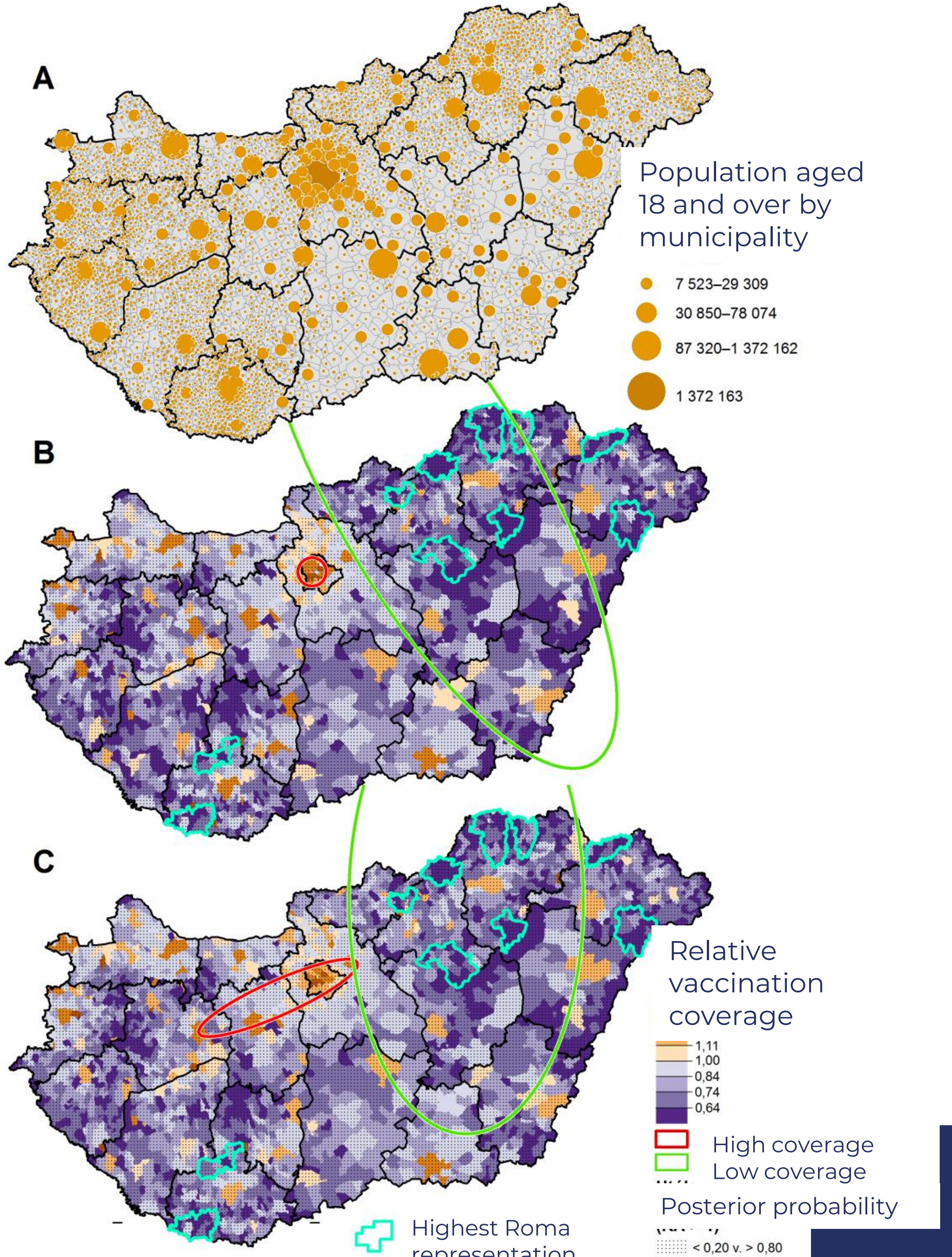
In the long-term:

- direct effect is the same for adults and children (the proportion vaccinated is identical)
- indirect effect is smaller for children than adults since children have fewer person years of exposure to the reduced force of infection than adults.

Example for spatial heterogeneity:

Spatial inequalities in population density in Hungary (A), relative COVID-19 vaccination coverage at the end of PW 3 (B) and PW 4 (C)

Source: Oroszi et al, BMJ Global Health, 2021, Oroszi et al J. Pers Med 2022



Epidemiological data should accurately reflect reality, without any systematic deviation that could introduce bias.

But the reality is often different.

In such cases it is all about “dirty hands but clear mind”.

The quality of epidemiological data may be questionable for a lot of reasons

Internal validity

Does the study/surveillance measures what it intends to measure?

Data management problems

1. Not clear and consistent data collection process
2. Not accurate data entry and verification
3. Inadequate data cleaning and normalization
4. Inadequate data analysis and reporting

Chance

Bias

Confounding

External validity

What is the degree to which the available epidemiological data can be generalized or applied to real–world settings beyond the specific study condition

Population

Temporal

Ecological

Cross-cultural

Measurement

What can be done if critical issues arise with epidemiological data?

- Elaborate methodologies to detect anomalies in the raw data,
- Report back and/or try to correct errors (if possible),
- Detect outliars
- Generate time-series with enhanced quality (data reconciliation, data fusion, data clustering etc.),
- Use real-time surveillance by monitoring mobility, survey social contact numbers, use social media to assess compliance with measures,
- Validate surveillance data with external data sources
- Be advocate of proactive testing, contact tracing, surveillance development,
- Perform sensitivity analysis.

Take home messages

- There is an increased risk and impact of emerging epidemics;
- There is an increased need for epidemiological modelling;
- Models are usually poorly understood, modellers and epidemiologists must be prepared to defend their models and results;
- Modelling can be part of decision making process, but decisions are not made by mathematicians and epidemiologists – this is called „evidence informed decision making";
- The research questions of modelling should be relevant;
- Models are necessarily simplified representations of reality;
- The main limitations come from the uncertainties and the assumptions upon which they are built;
- Estimation of parameters can be based on recent epidemiological data from the real world, which is certainly a better approach than estimating parameters at the theoretical level;
- However, epidemiological data may also be inaccurate or biased;
- Efforts should be made to check the validity of basic data and improve data quality together with epidemiologists;
- Caution must be taken in interpreting and implementing the models' results, together with the limitations, and ensuring that the critical variables are properly taken into account;
- **Despite all the difficulties, epidemiological modelling is a very nice intellectual challenge, very useful and fun.**

Thank you for your attention

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