Biostatistics in a post-pandemic era: lessons learned for research, public health, drug and vaccine development, policy advice, and communication

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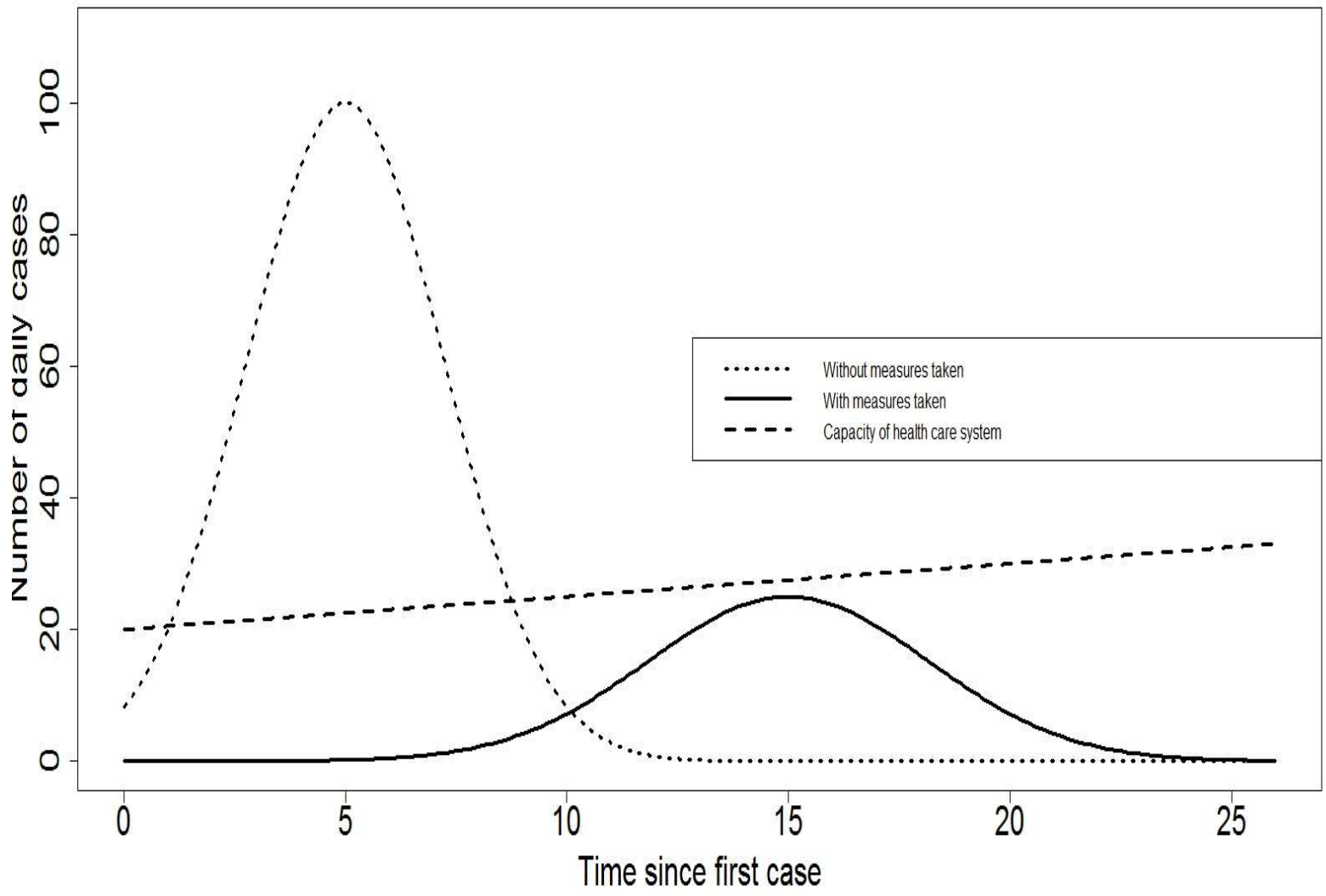
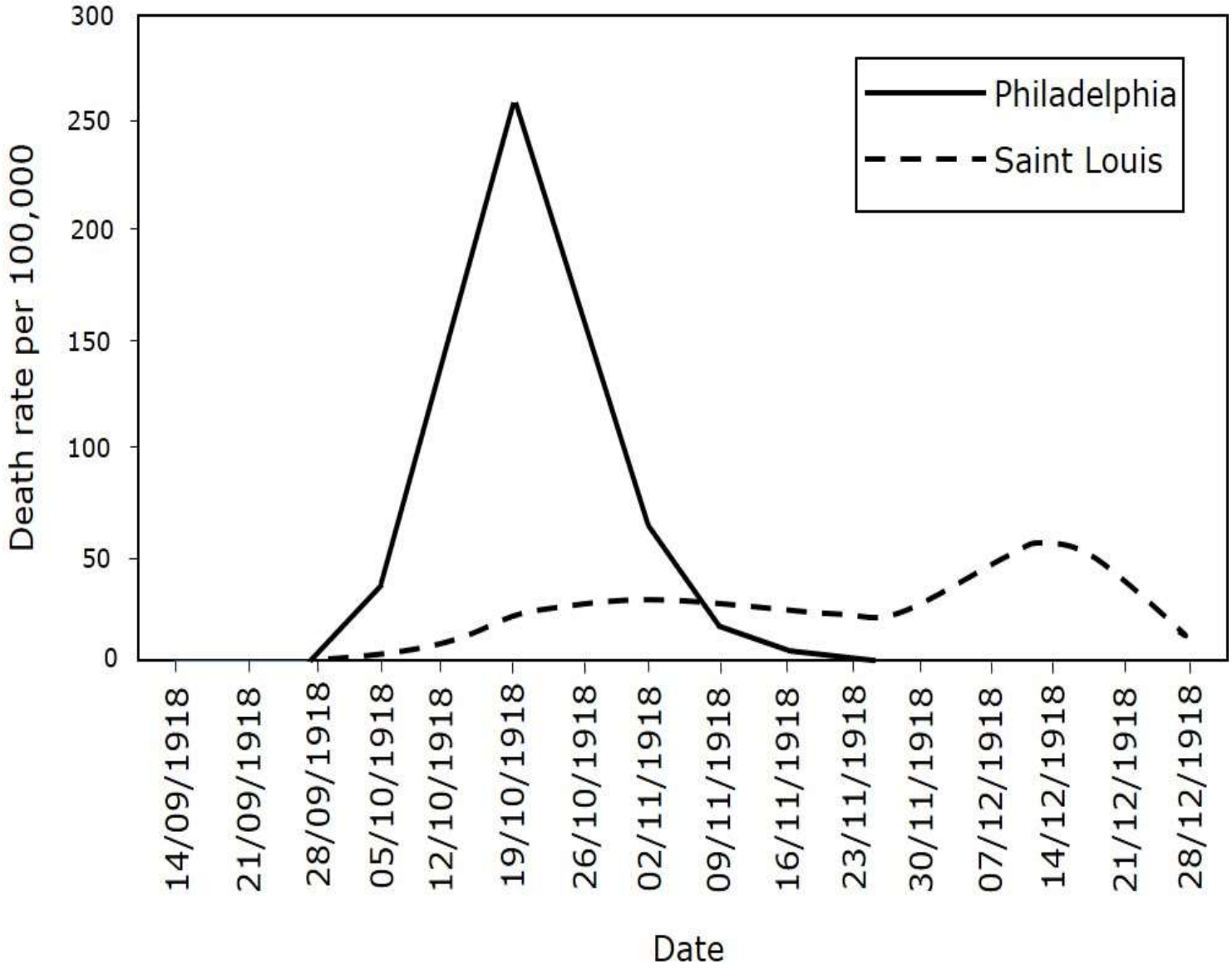
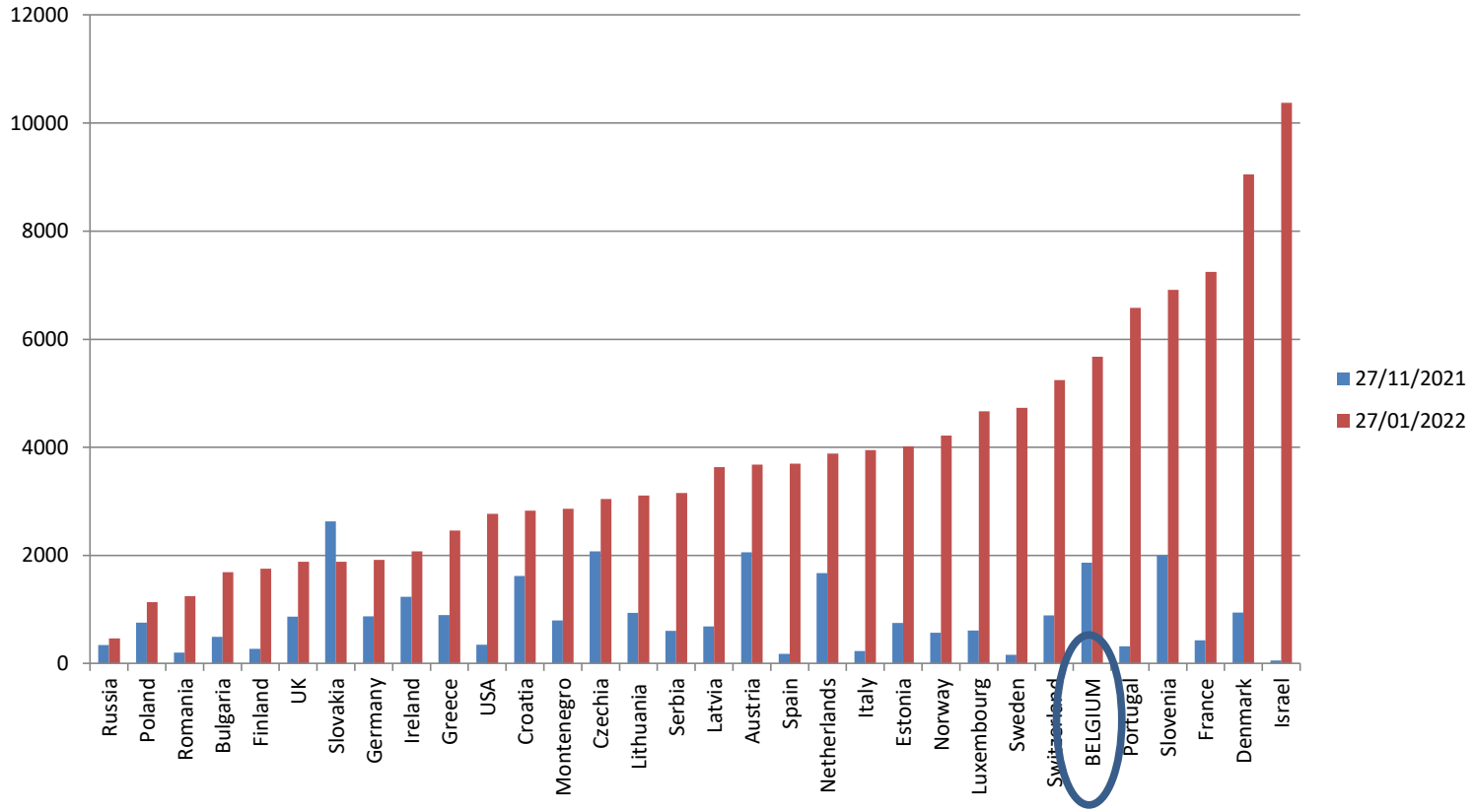
PSI, Amsterdam, 17 June 2024

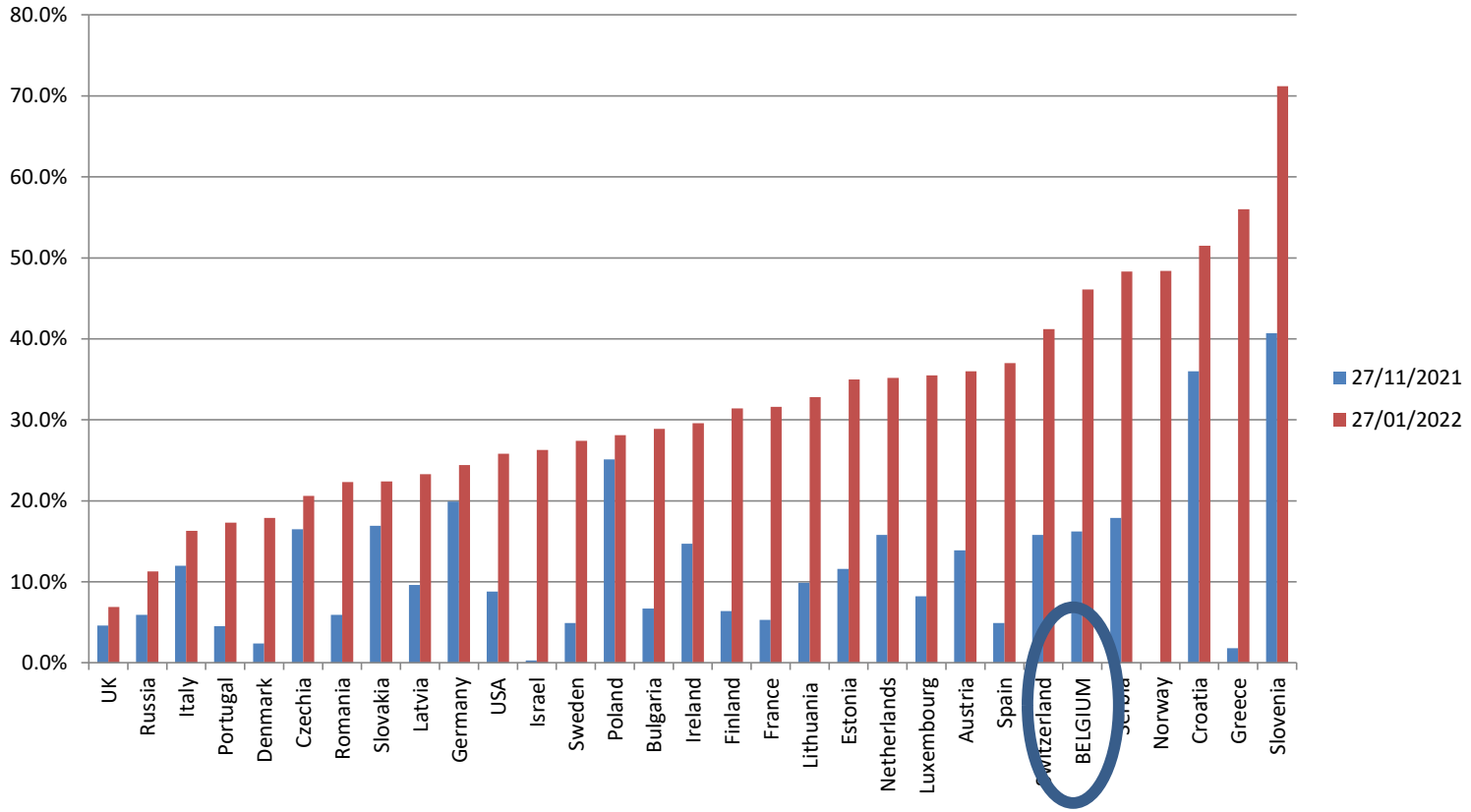

The effect of flattening the curve
Number of daily cases
0
20
40
60
80
100
0
5
10
15
20
25
Time since first case
Without measures taken
With measures taken
Capacity of health care system


Philadelphia
Saint Louis
Death rate per 100,000
300
250
200
150
100
50
0
14/09/1918
21/09/1918
28/09/1918
05/10/1918
12/10/1918
19/10/1918
26/10/1918
02/11/1918
09/11/1918
16/11/1918
23/11/1918
30/11/1918
07/12/1918
14/12/1918
21/12/1918
28/12/1918
Date

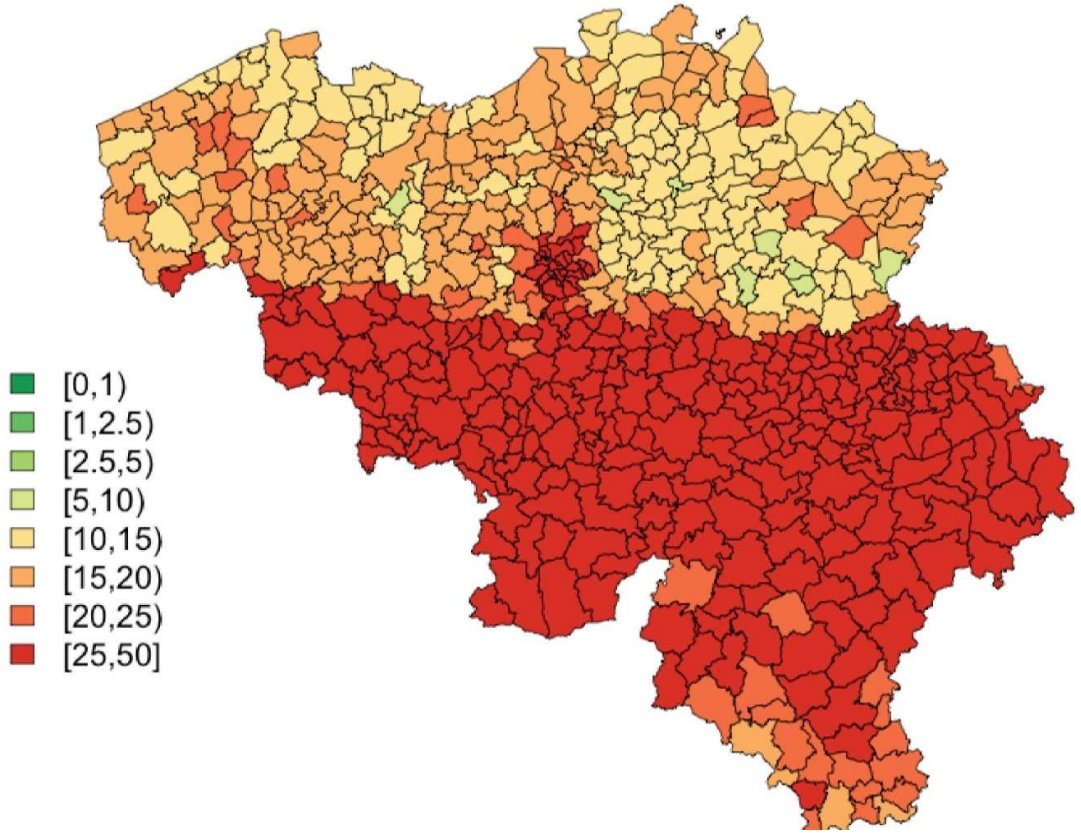
14-day incidence (based on OWID data)



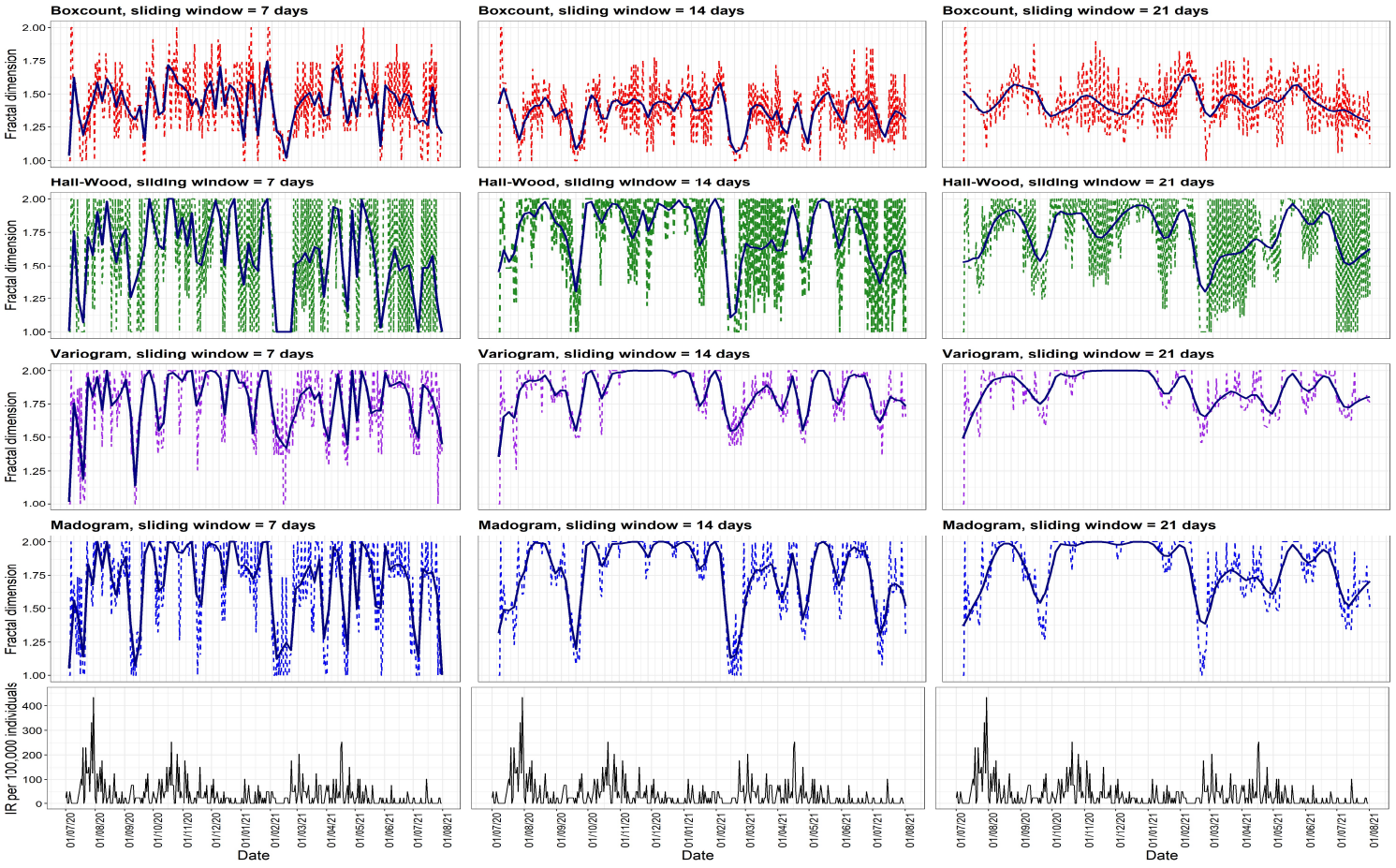
Positivity


80.0%
70.0%
60.0%
50.0%
40.0%
30.0%
20.0%
10.0%
0.0%
UK
Russia
Italy
Portugal
Denmark
Czechia
Romania
Slovakia
Latvia
Germany
USA
Israel
Sweden
Poland
Bulgaria
Ireland
Finland
France
Lithuania
Estonia
Netherlands
Luxembourg
Austria
Spain
Switzerland
BELGIUM
Norway
Croatia
Greece
Slovenia
27/11/2021
27/01/2022

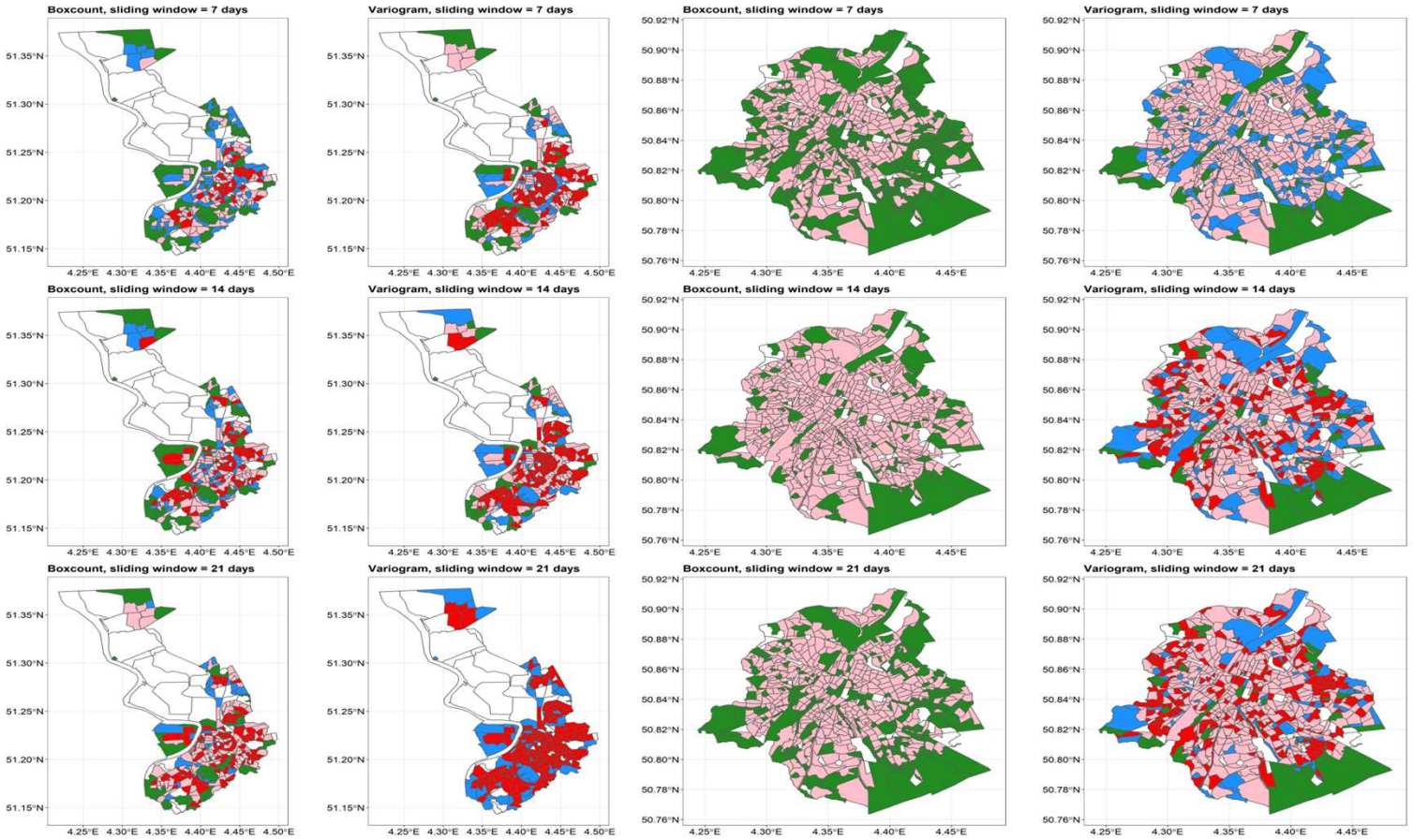
Understand population dynamics: Positivity Map, 11 November 2020



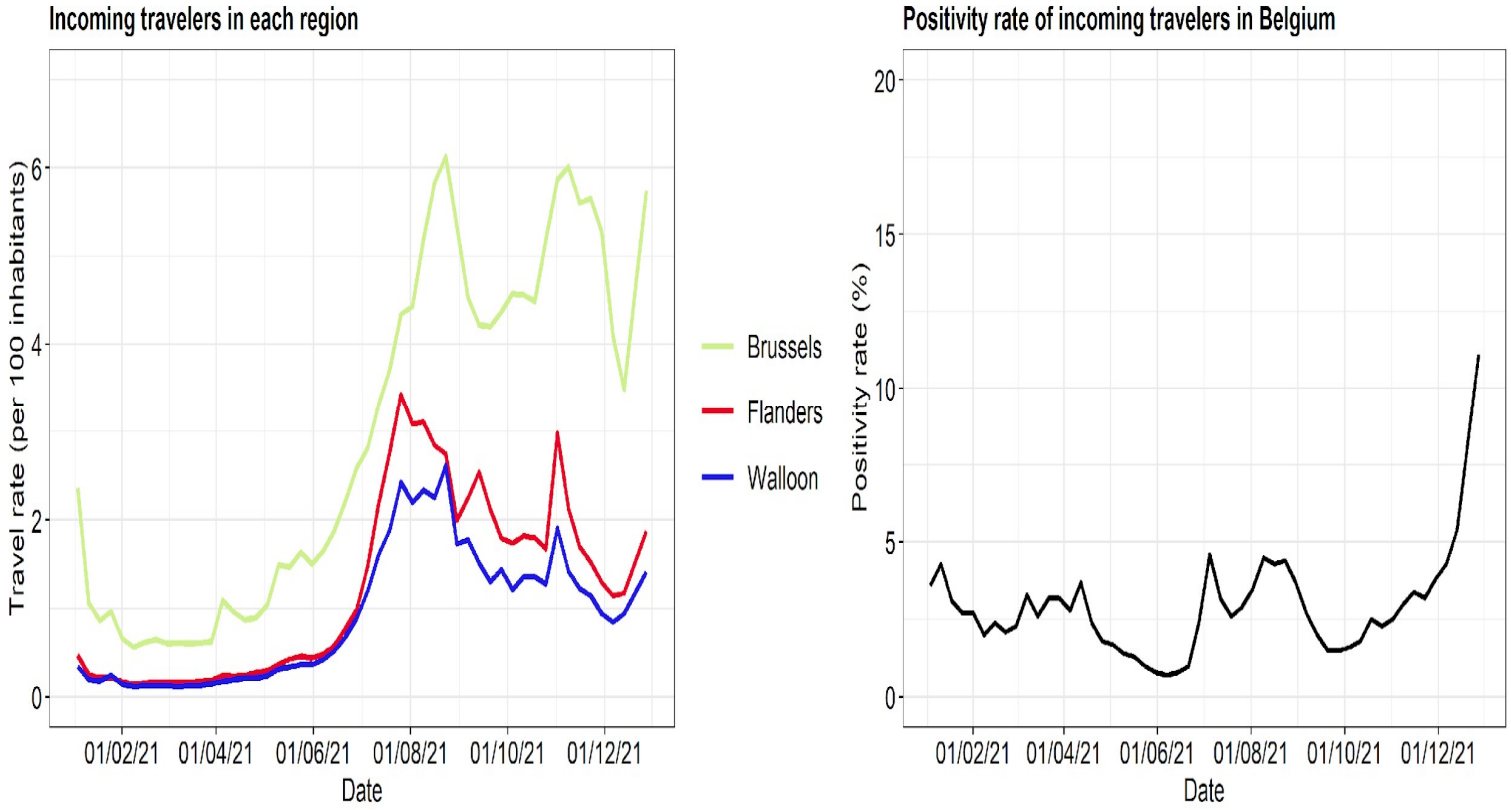
Vlaamse Controletoren: Fractal dimension



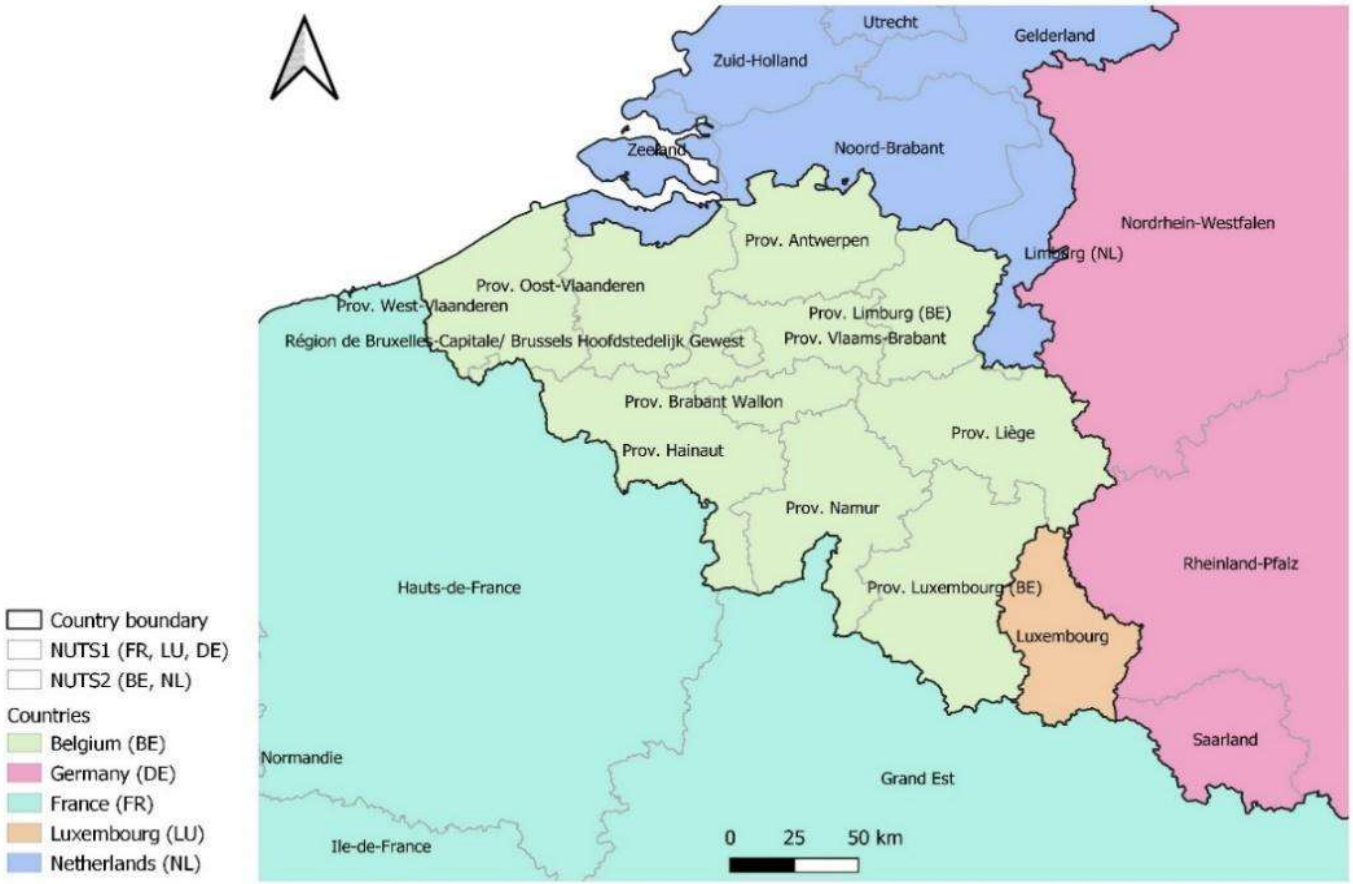
Fractal dimension



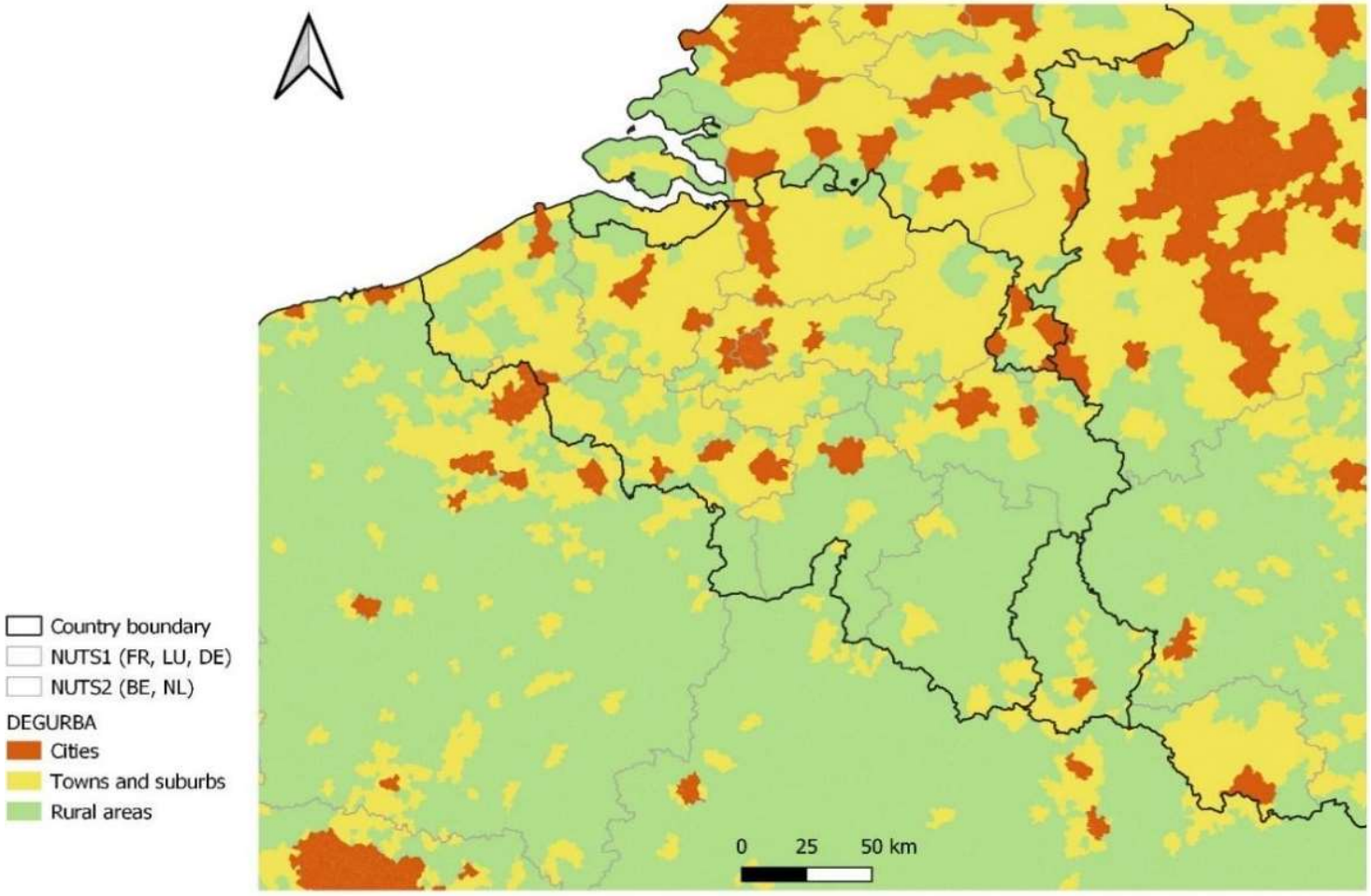
International perspective: Incoming travelers



Transnational perspective

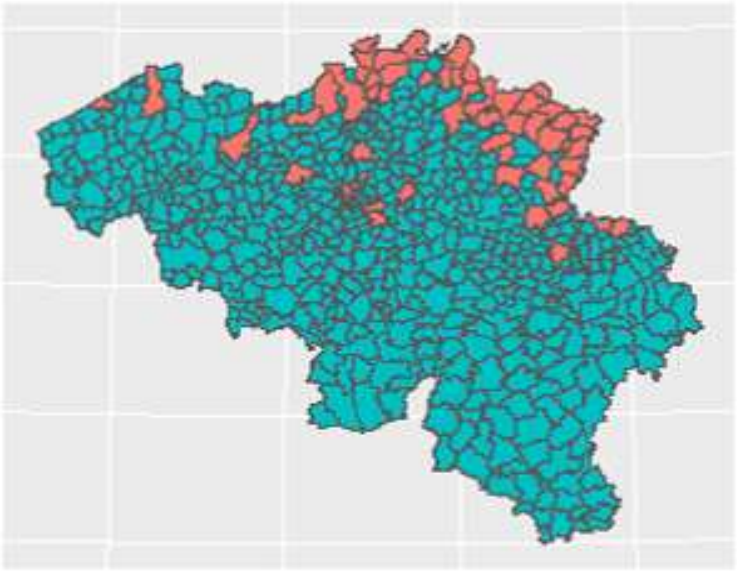


Degree of urbanization



Our neighbours

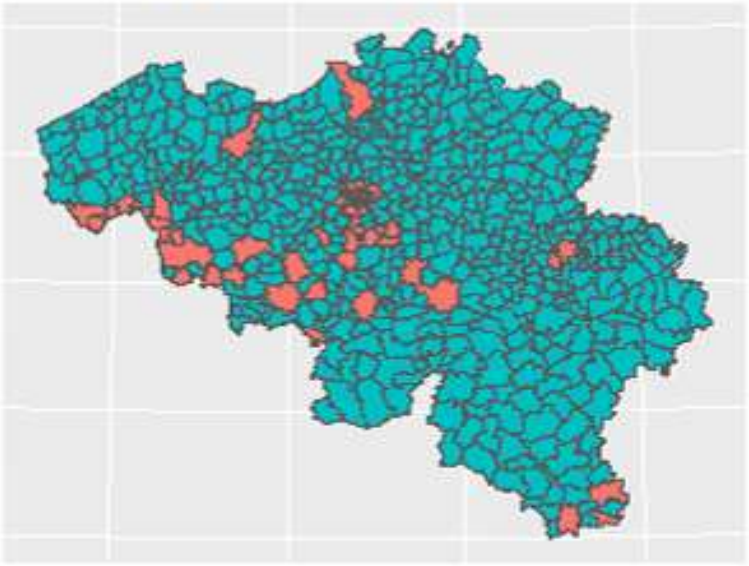
Dutch people in Belgium



10% highest proportion of Dutch inhabitants

Rest

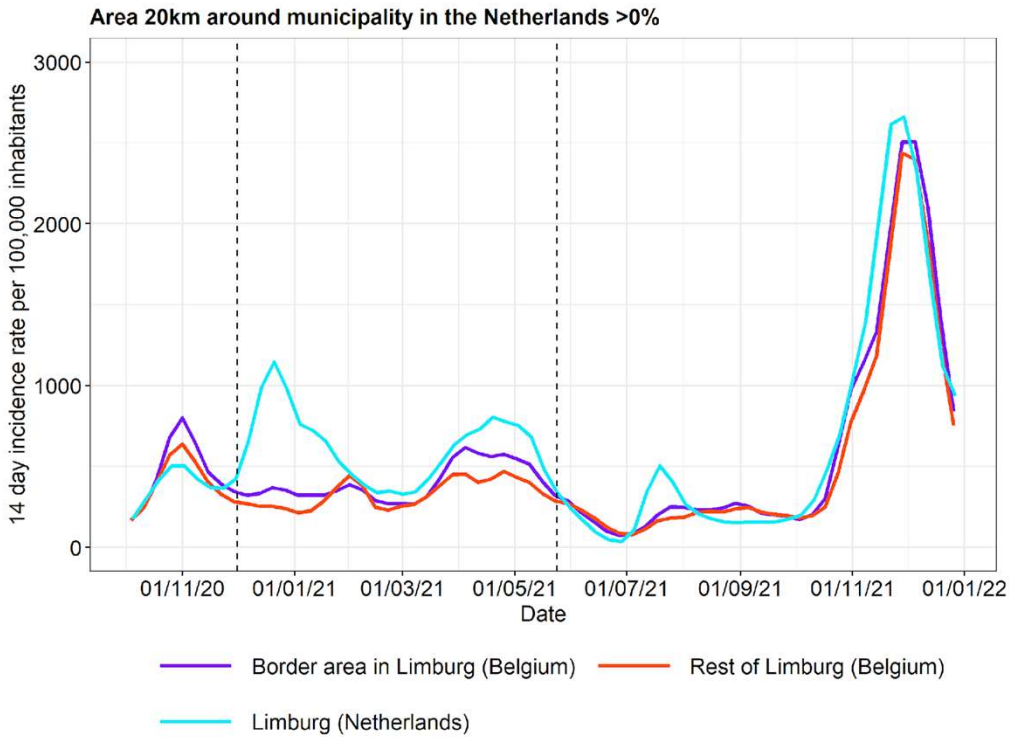
French people in Belgium

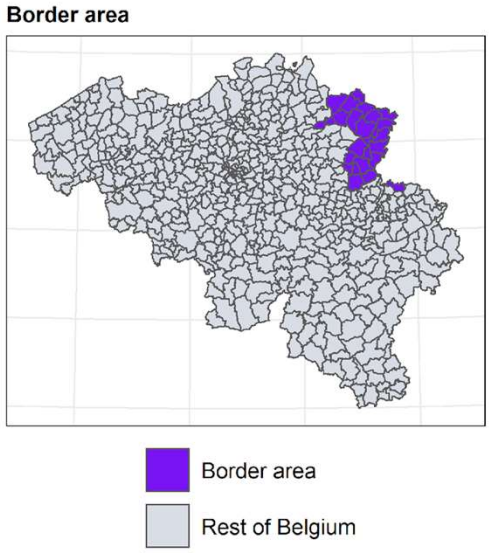


10% highest proportion of French inhabitants

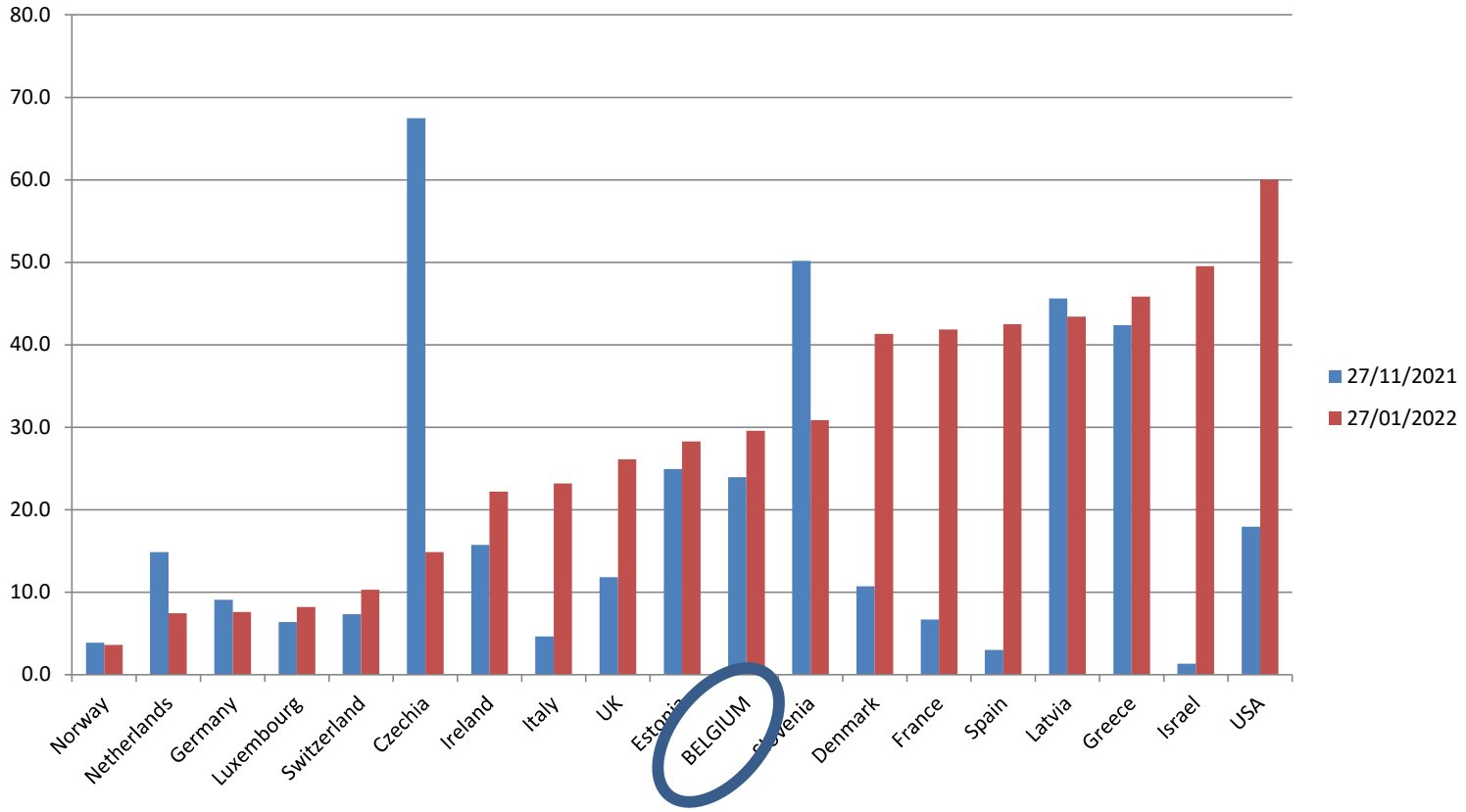
Rest

Border area Limburg

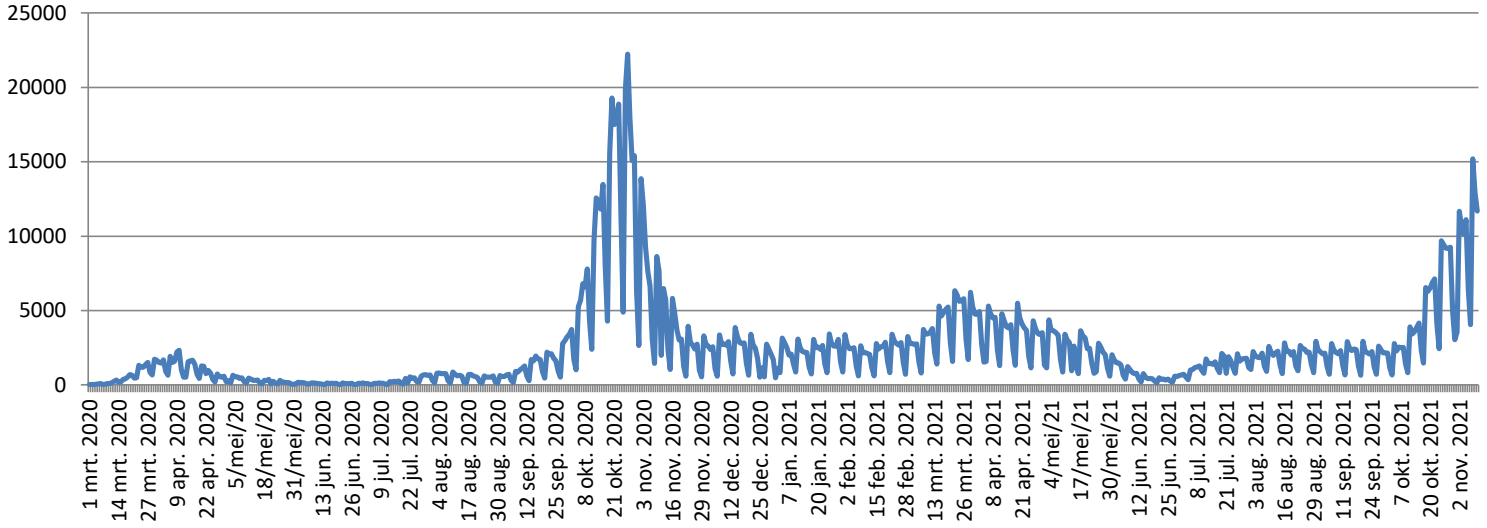




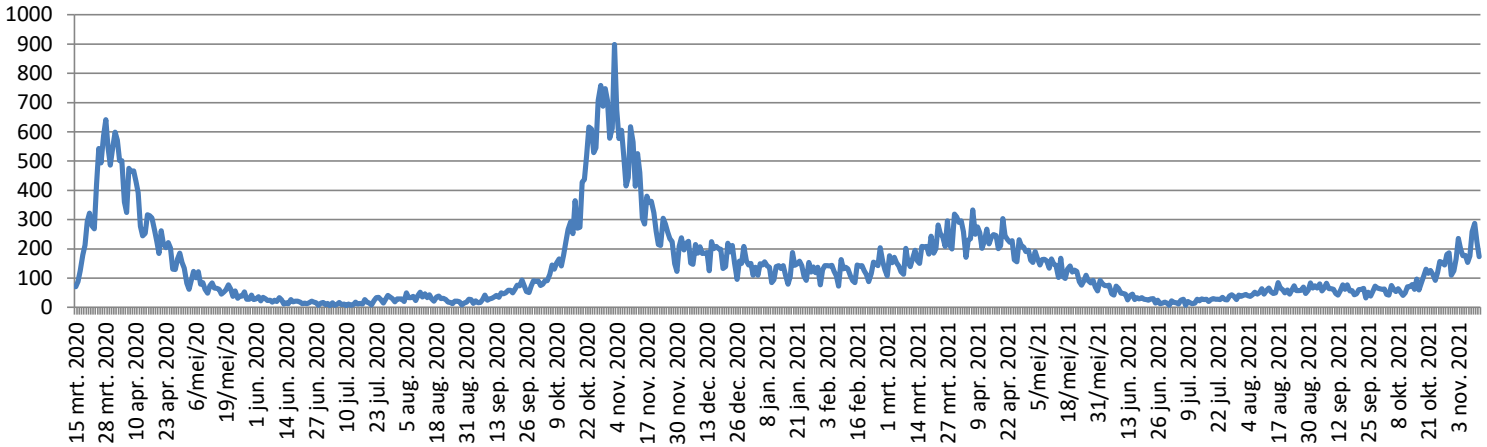
Hospitalisations per day per million



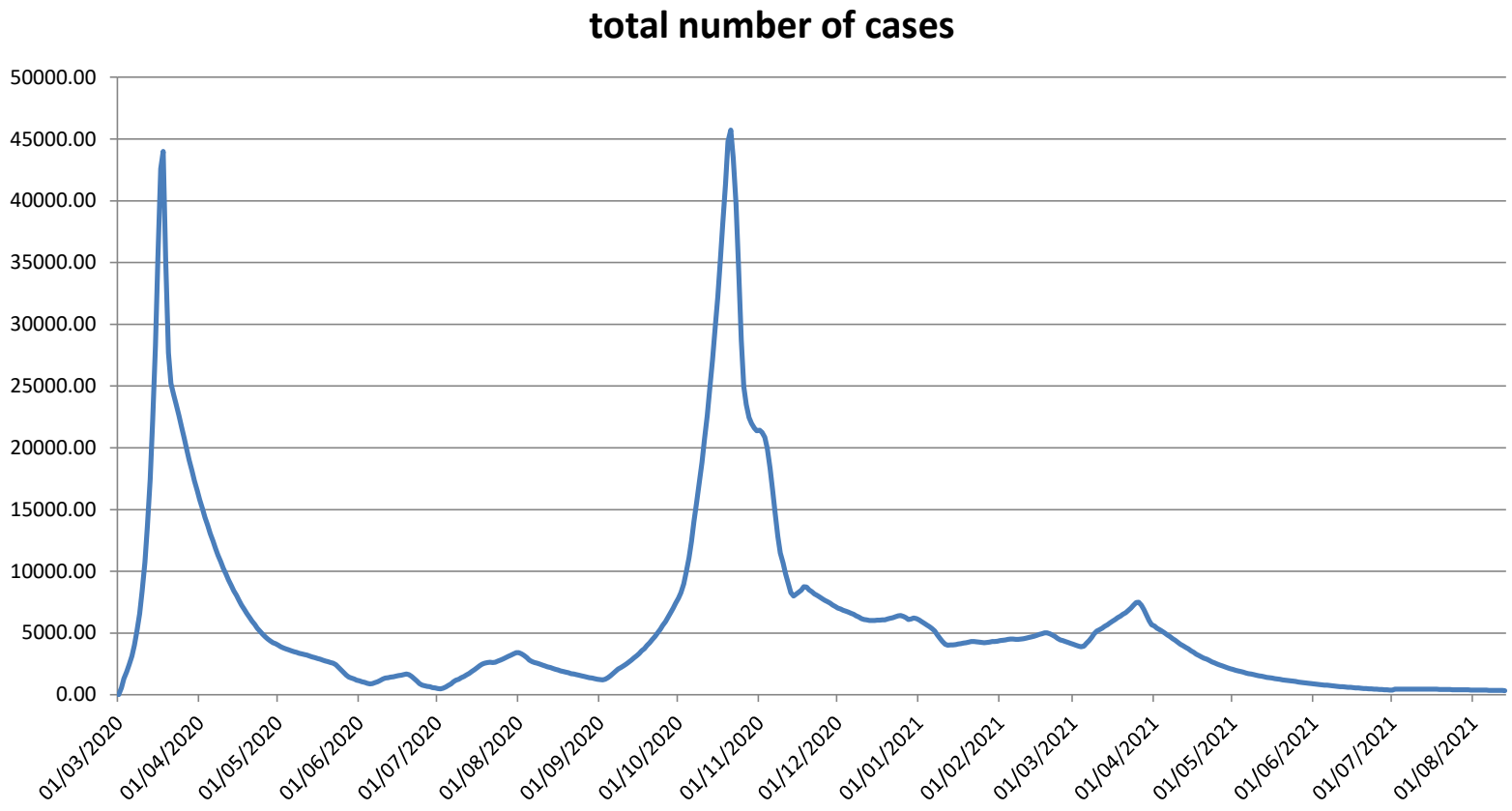
Confirmed Cases



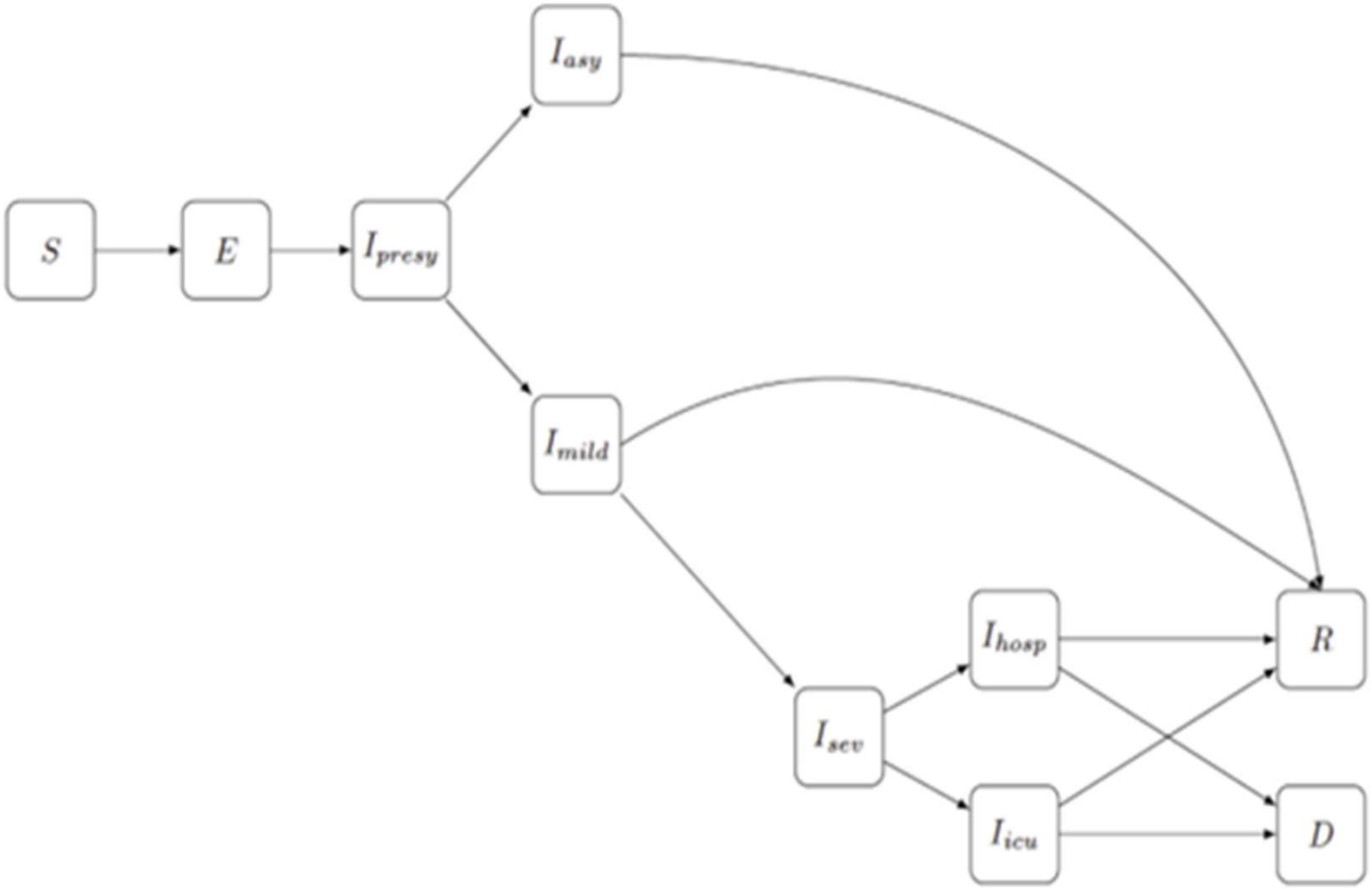
Hospital Admissions



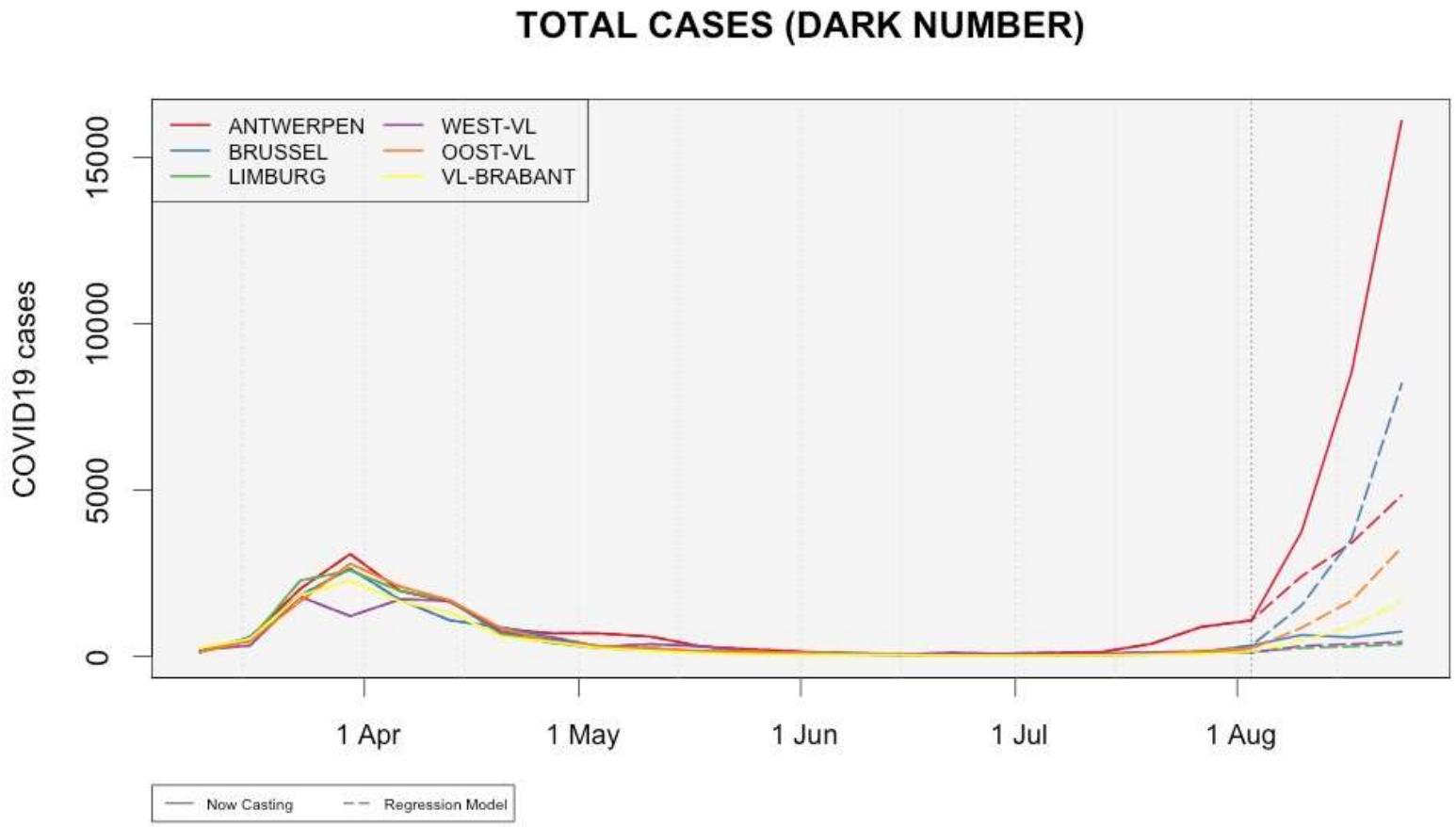
The dark number…



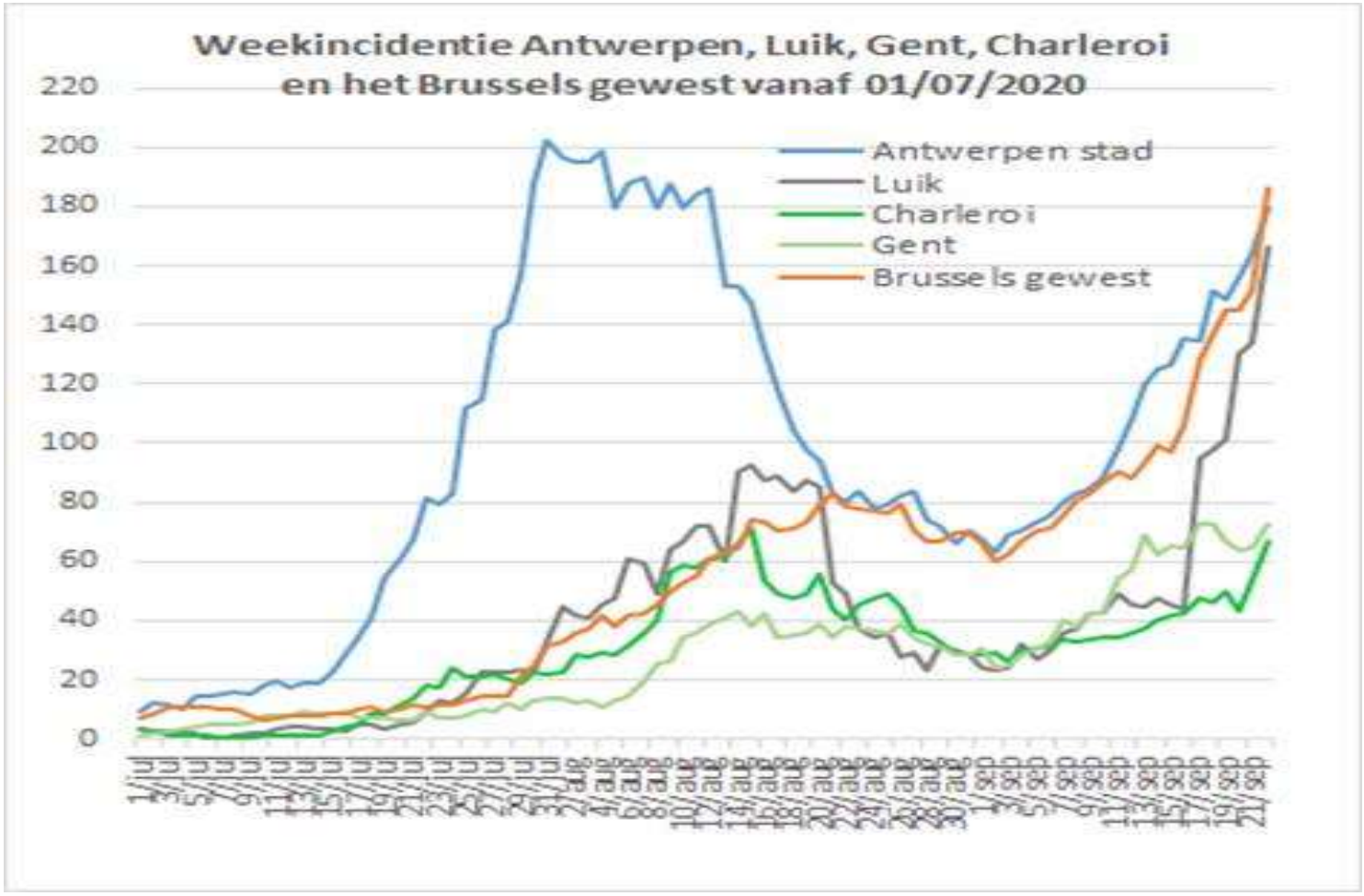
Stochastic model (Niel Hens)



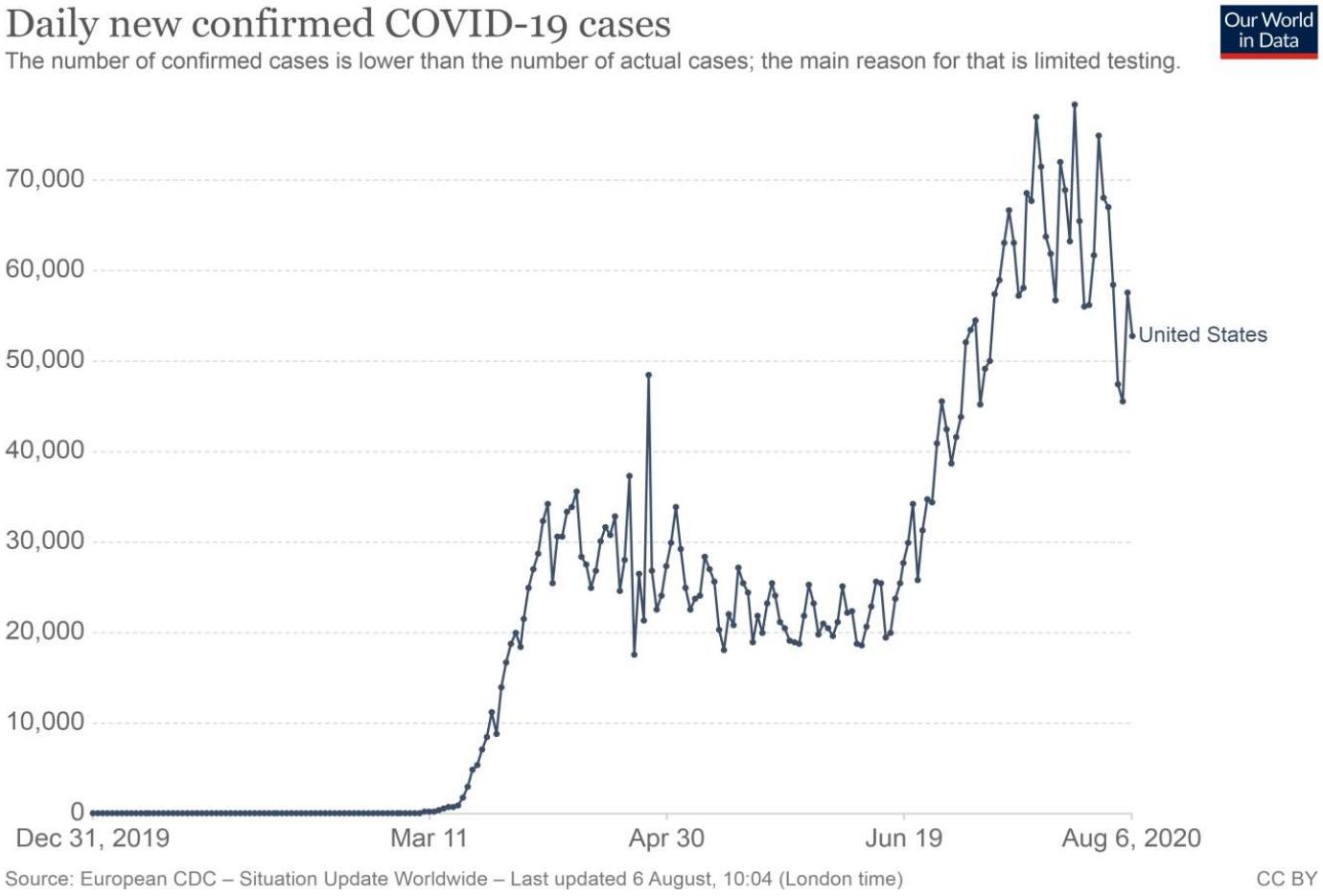
The power of scenarios: Summer 2020 in Antwerp



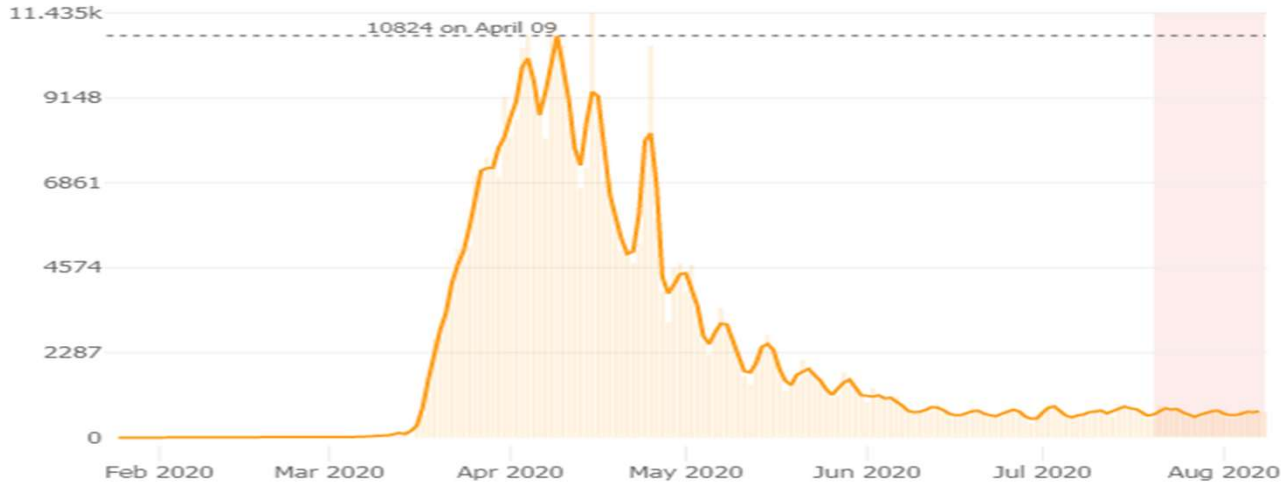
The Antwerp Curfew



Confirmed Cases in US



New York State & Texas



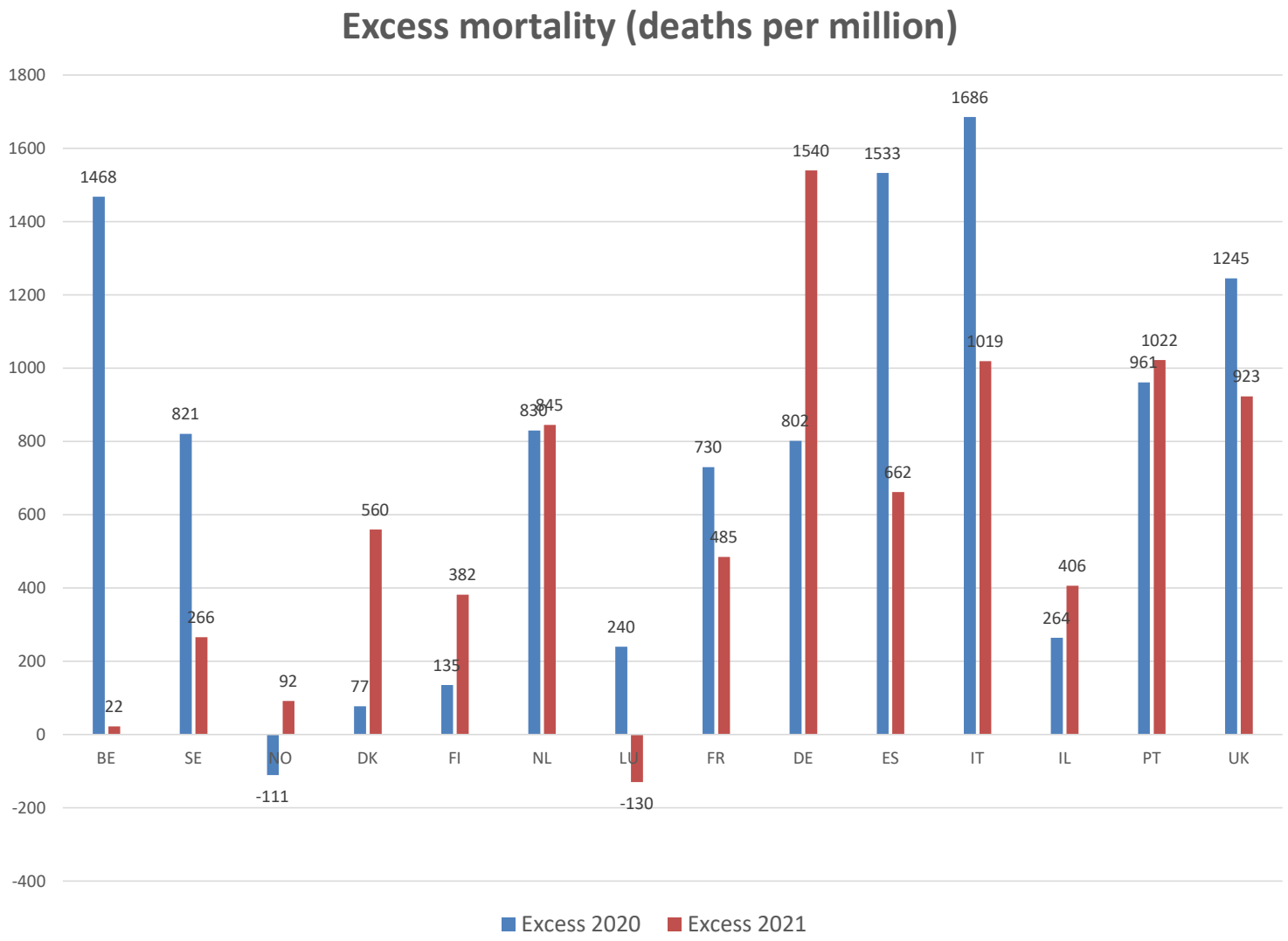
Deaths per million, July 31, 2020

Country	DPM	Country	DPM
New York City	2471	Luxembourg	182
New York State	1653	Germany	109
Spain	608 → 1013	Denmark	106
Italy	581 → 867	Argentina	73
United Kingdom	678 → 848	Finland	59
Belgium	849 → 772	Norway	47
Sweden	568 → 693	Greece	19
Netherlands	359 → 579	Uruguay	10
France	463 → 477	Cuba	8
United States	459	Australia	7
Brazil	429	New Zealand	5
Ireland	357	Madagascar	4

Mortality in 2020 - 2022

Year	Registered COVID deaths	Excess mortality (relative to 2017 – 2019)
2020	19,837	17,177
2021	8564	2616
2022	4981	6811

- Life expectancy decreases by 10 mts in 2020
- Excess mortality in 2020: older age groups
- Excess mortality in 2021: 65 – 74 years
- Excess mortality in 2022: 85+ years


Excess mortality (deaths per million)
1800
1600
1400
1200
1000
800
600
400
200
0
-200
-400
1468
22
821
266
-111
92
77
560
135
382
830
845
240
-130
730
485
802
1540
1533
662
1686
1019
264
406
961
1022
1245
923
BE
SE
NO
DK
FI
NL
LU
FR
DE
ES
IT
IL
PT
UK
Excess 2020
Excess 2021

Mortality risk higher for men

	Number of deaths			Percentage women versus men in DPM		
Age	**First half 2020**	**Second half 2020**	**2020**	**First half 2020**	**Second half 2020**	**2020**
0-24	1	7	8	(#DIV/0!)	(626)	(731)
25-44	42	47	89	83	68	75
45-64	537	611	1148	50	50	50
65-74	1119	1312	2431	51	48	50
75-84	2853	2894	5747	66	58	62
85+	5146	5200	10346	80	67	73
TOTAL	9698	10071	19769	109	93	101

Another counterintuitive result

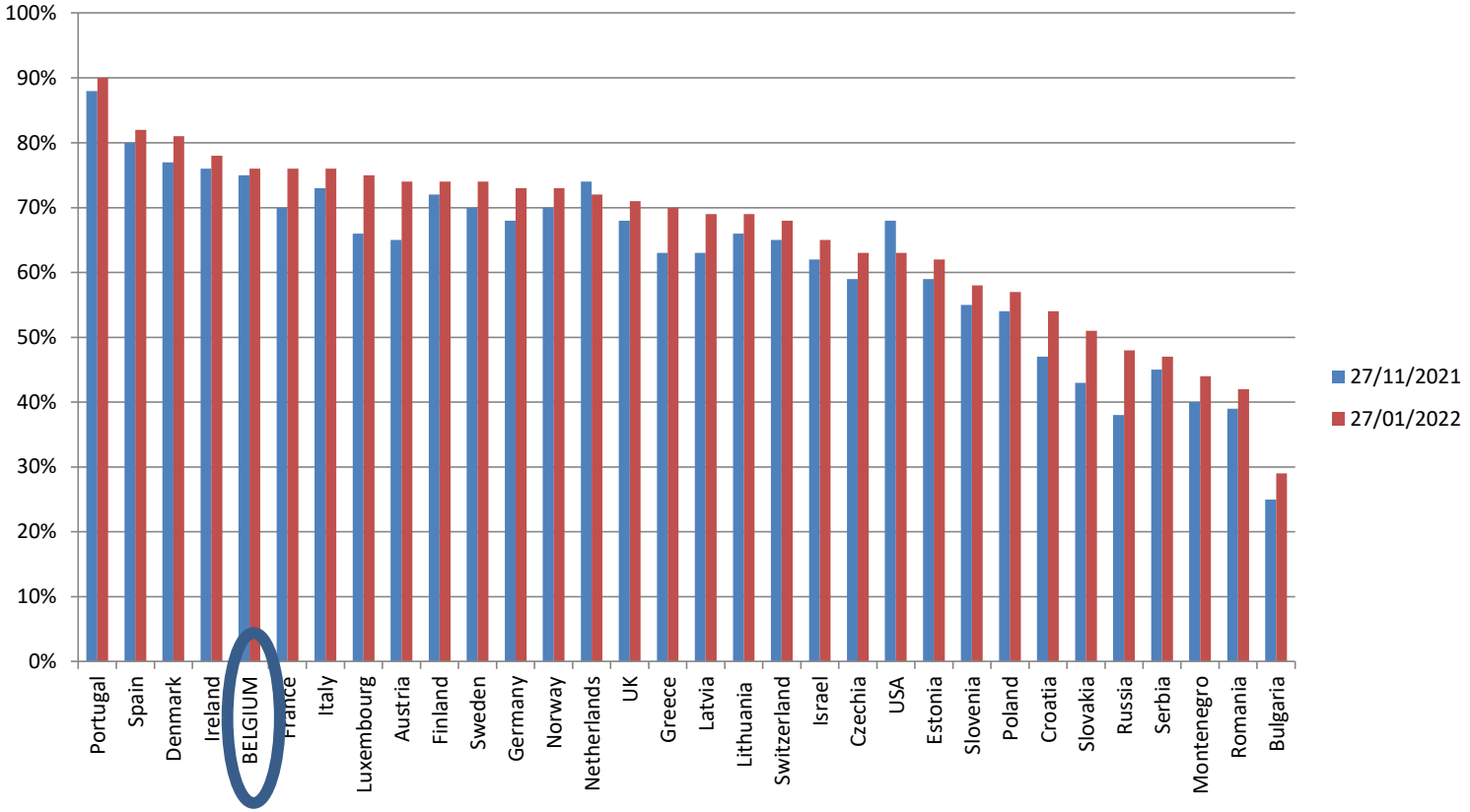
- Assume that 90% of population is vaccinated
- Assume that risk of ICU admission is 10 times higher for an unvaccinated person
- Assume that, overall, 0.8% of infections is admitted to ICU
- Then…

57% of ICU patients is vaccinated

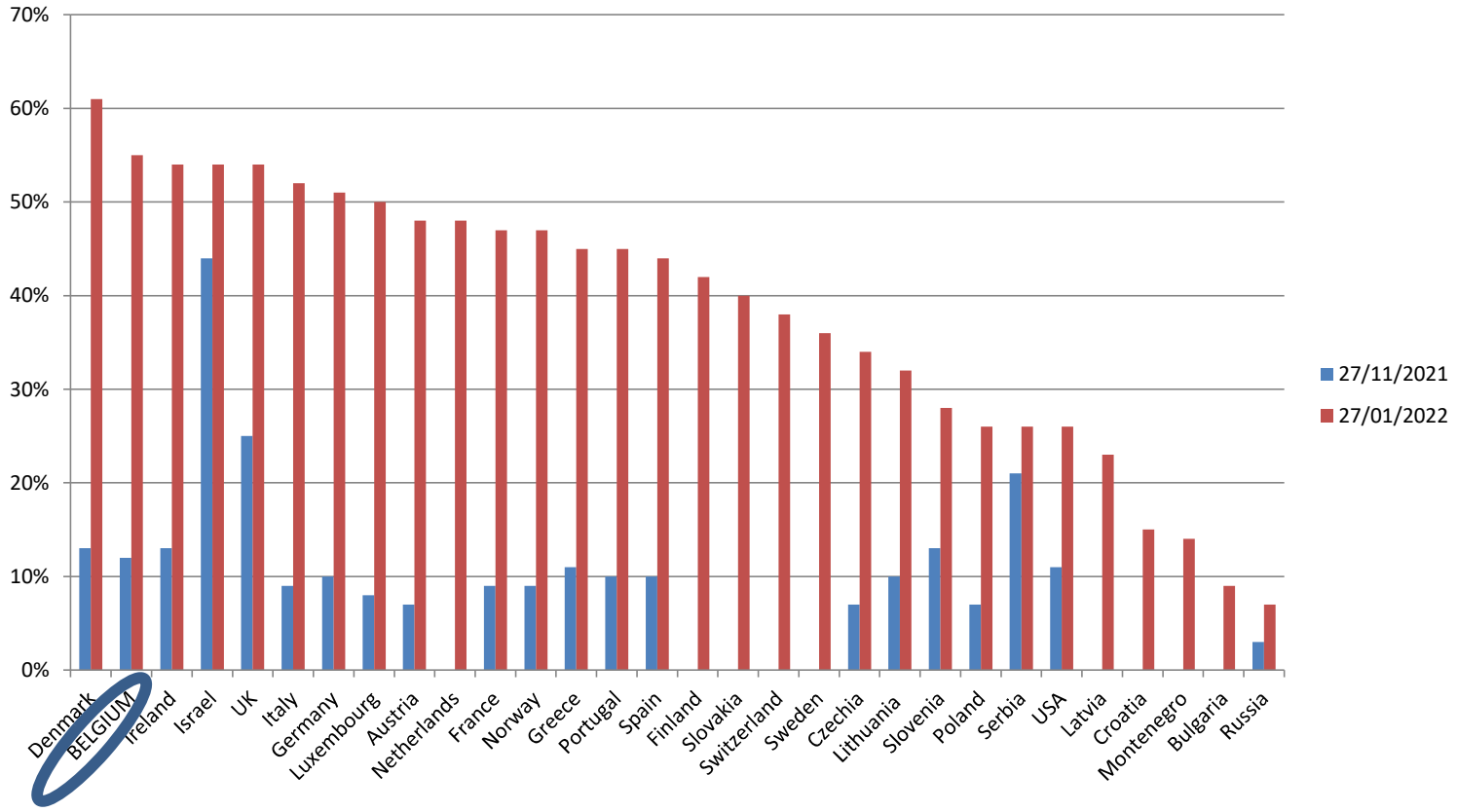
Explaining the strength of ‘the enemy’ The power of delta and omicron

Infection (start with 4 infected people)	R0	After 10 generations
Seasonal influenza	1.5	684
SARS-CoV-2 (Wuhan)	3.0	354.292
SARS-CoV-2 (Alpha)	5.0	48.828.124 (~50 million)
SARS-CoV-2 (Delta)	8.0	4.908.534.052 (~5 billion)
SARS-CoV-2 (Omicron)	2.0 (1/3 interval)	8.589.934.588 (~ 8.5 billion)

Full basic vaccination



Booster vaccination



Do vaccines work?

- *“They work or they do not work!”*

- A number of endpoints:

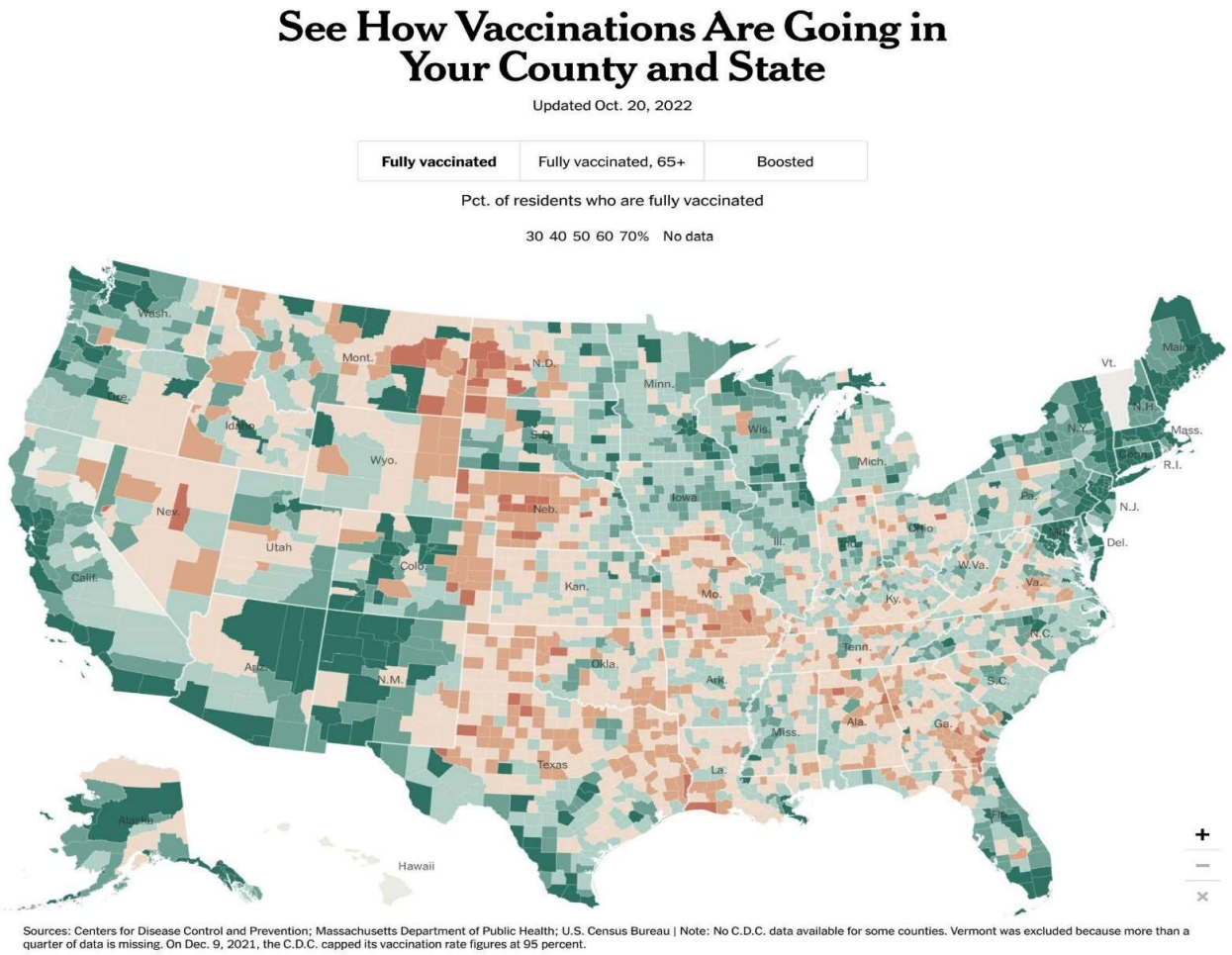
  - Transmission
  - Infection (including asymptomatic)
  - Symptomatic COVID
  - Severe COVID
  - Hospitalisation
  - ICU / mechanical ventilation
  - Mortality

Vaccines

- *Efficacy – effectiveness*
  - Surrogate / *Correlates-of-Protection*:
  - Humoral immunity
  - Cellular immunity
  - …
- A moving target …

W.T. → **α** → β → γ → **δ** → **o (BA.1 / 2 / 4&5)** → …

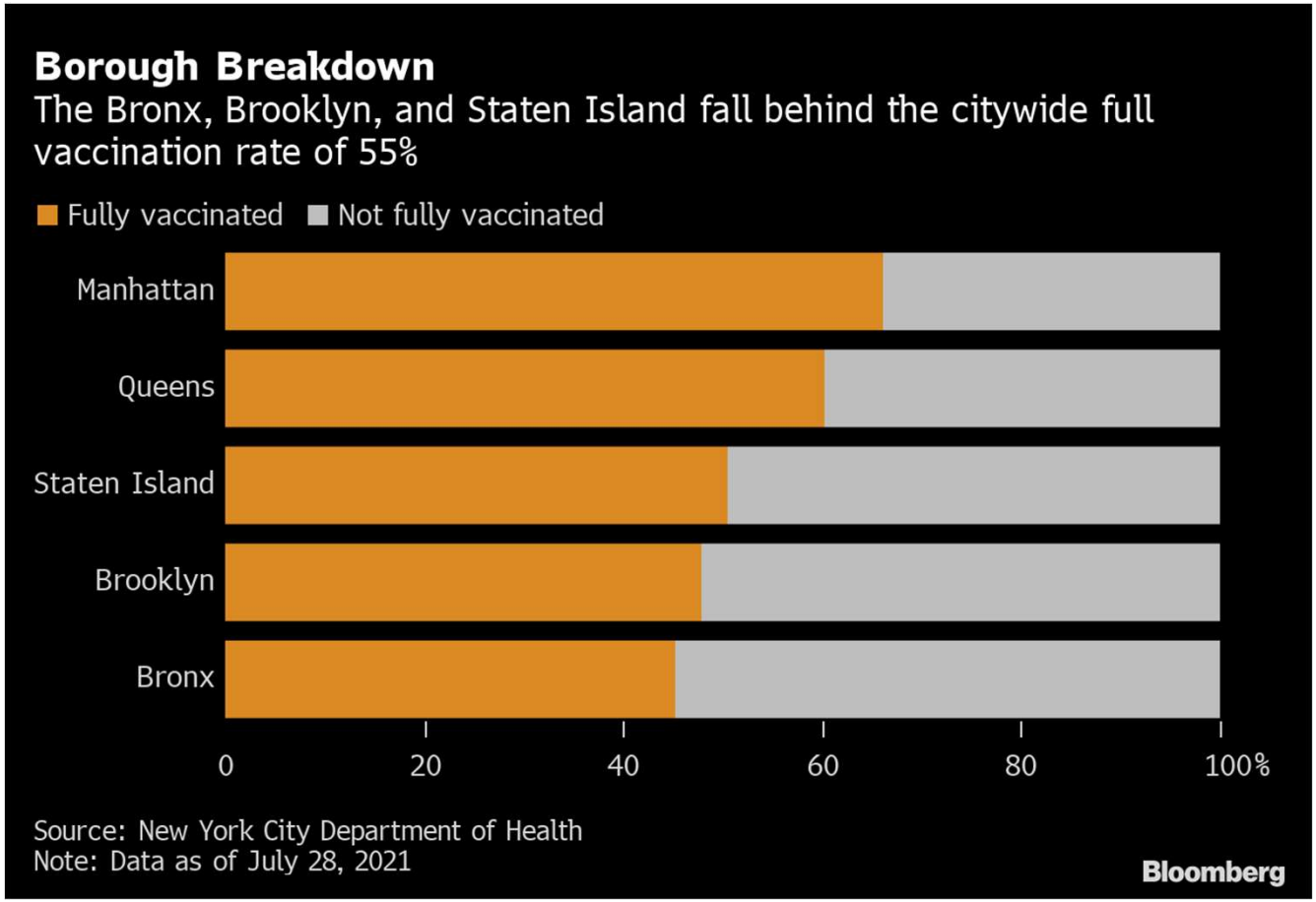
Vaccination in the USA (NYT)



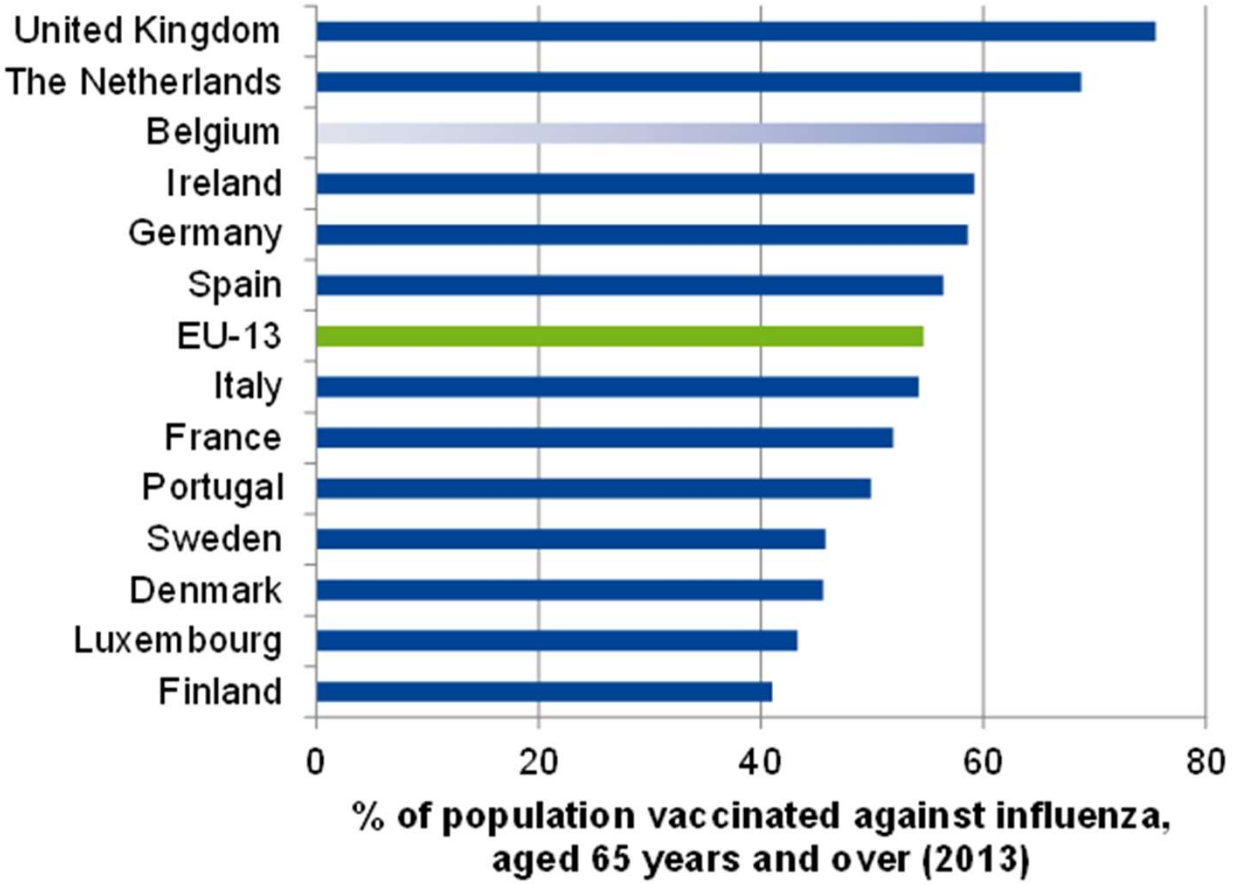
Heterogeneous Vaccine Coverage in Belgium

Category	Belgium	Flanders	Wallonia	Brussels
Full; entire population	74%	80%	70%	56%
Partial; entire population	75%	81%	71%	58%
Full; 65+	92%	95%	89%	82%
Partial; 12 - 17	75%	86%	67%	44%

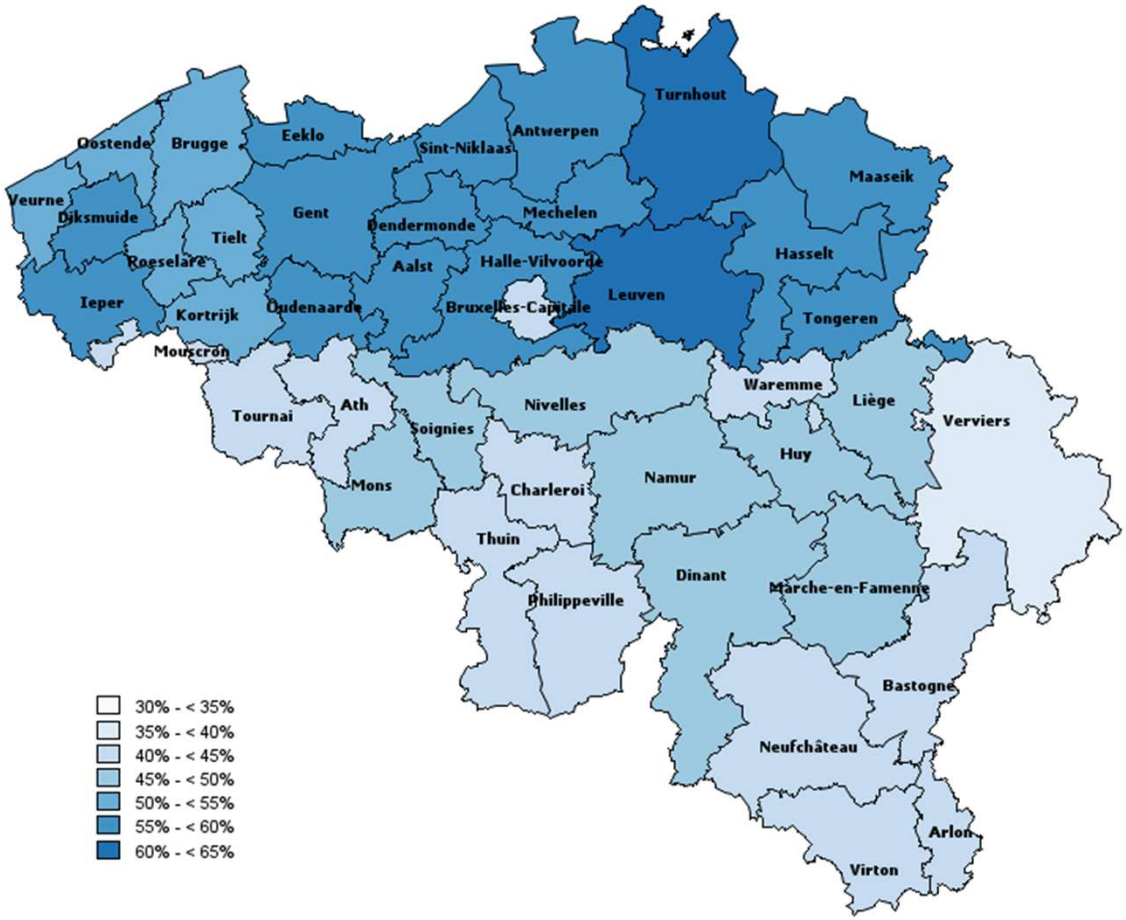
Intra-New York differences (COVID-19)



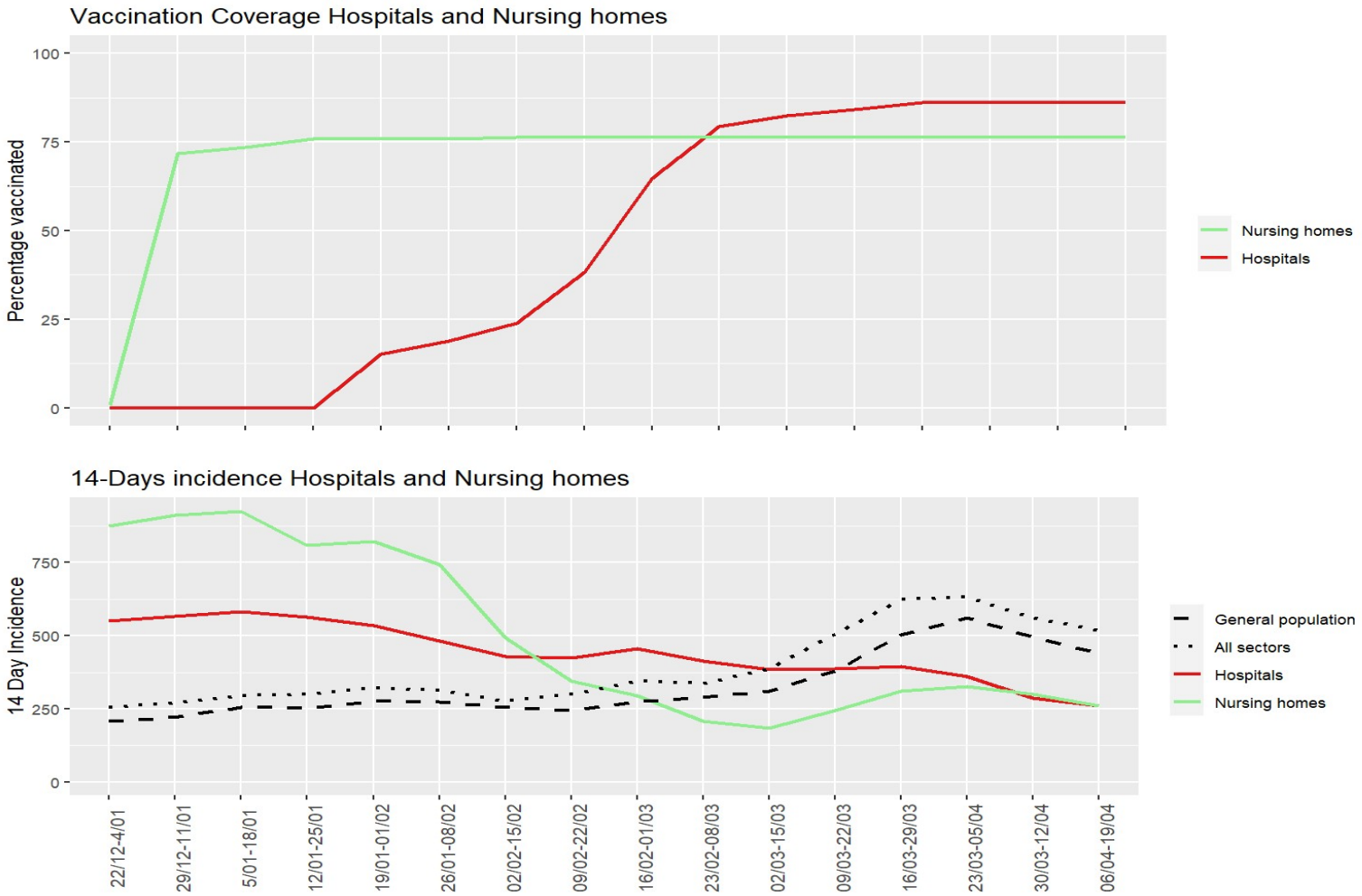
Regional differences, not just for COVID-19…



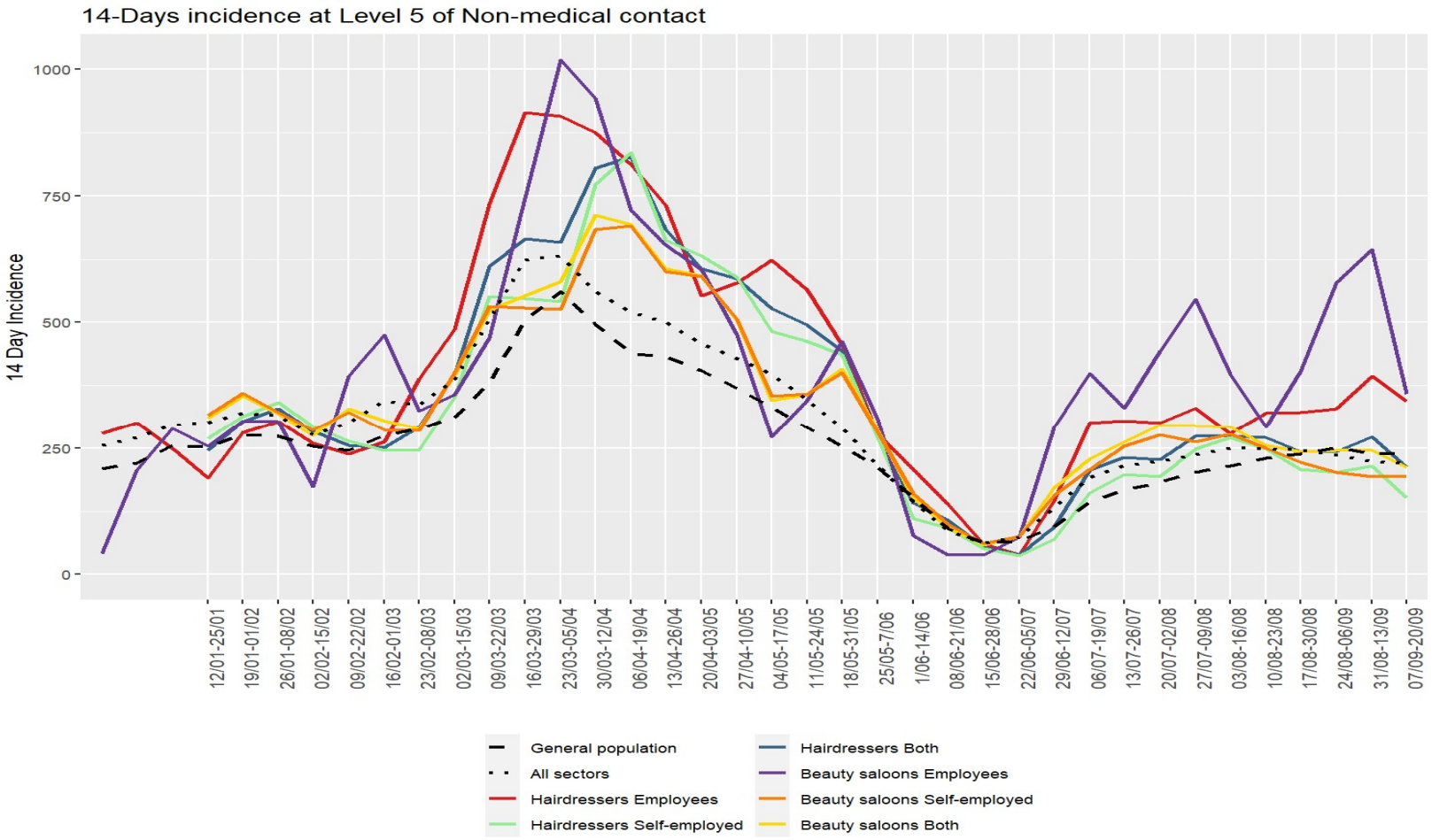
Intra-Belgium differences (influenza)



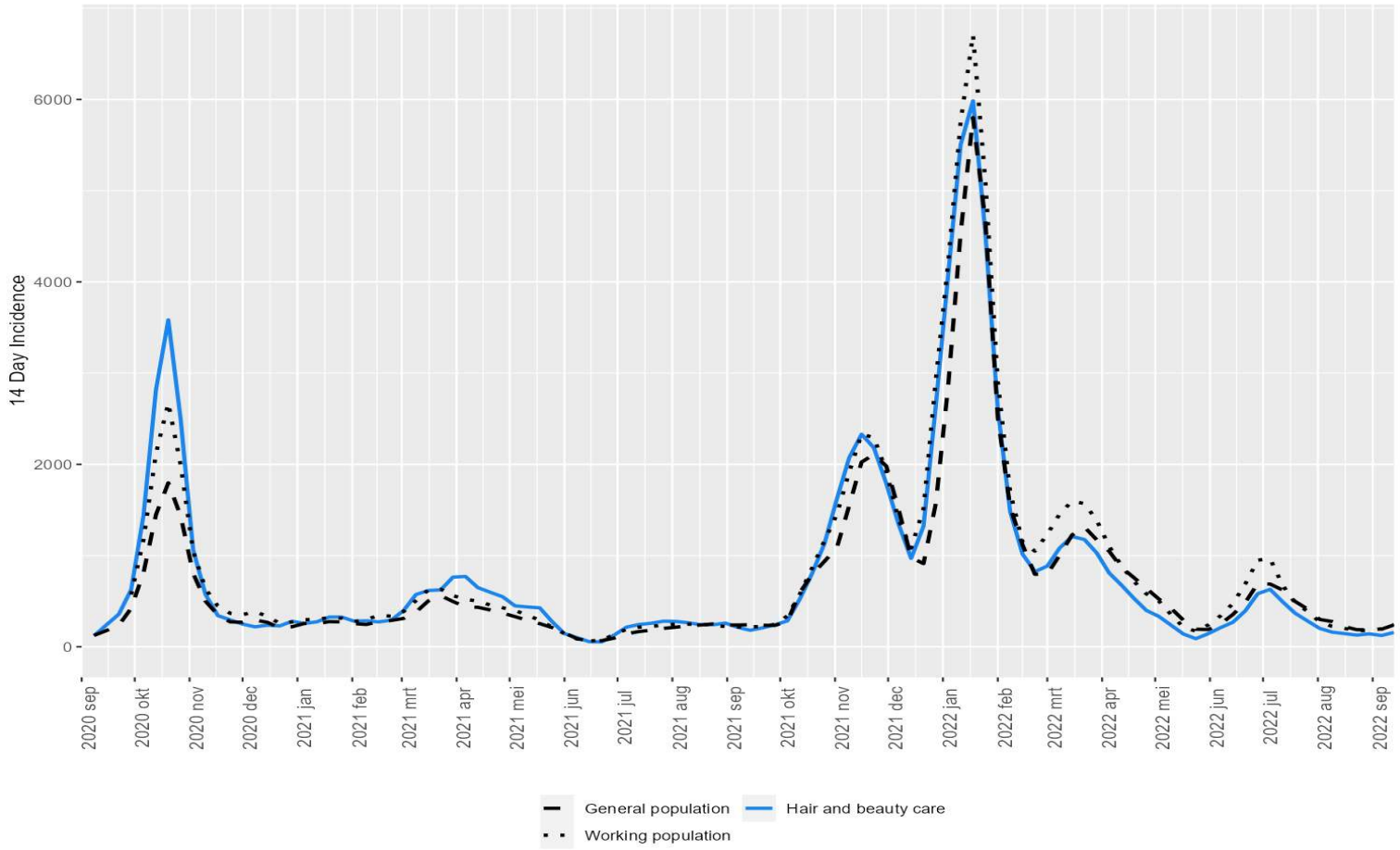
Health care workers early 2021



Non-medical contact professions



Non-medical contact professions



From a monolithic traditional RCT to a learning health system

- Adaptive platform trial
- Natural history data (e.g., serological survey,…)
- Real world (follow-up) data
- Surrogate markers, surrogate endpoints, correlates-of-protection
- Endpoint selection
- Safety evaluation (from APT & RWD)
- Input from mathematical modeling of infectious diseases to build and adapt the design
  - Benefit at individual level
  - Benefit at trial level

A Certain Amount of Flexibility

- Optimal design and adaption rules (may change dynamically)
- Change of allocation rules (e.g., response adaptive)
- Enrichment of certain populations
- Add/remove interventions along the way
- Sample size reassessment
- Mathematical modeling at design stage and during trial conduct
  - What (sentinel, epi) data are needed, alongside the trial?
- Proper quantification of risk/benefit – health economy

Surrogates / Correlates-of-protection

- Two levels of surrogacy:
  - At **individual level**: an endpoint that is able to predict a person's true endpoint, given their (vaccination) status
  - At **trial level**: and endpoint of which the treatment effect is able to predict the treatment effect on the true endpoint
- Candidates:
  - Humoral immunity measure(s)
  - Cellular immunity measure(s)
  - "Earlier" endpoint for "later" one
- But what is the true endpoint?
    - Infection, symptomatic infection, serious infection, hospitalization, ICU admission, mechanical ventilation, death
- As time goes by… key endpoints may change

Issues statisticians need to think about

- Role of simulation:
  - Clinical trial simulation (design stage / updating of trials)
  - Simulation towards input from epi and mathematical modeling
- Repurposing (vaccines, drugs)
- Dynamic evolution (time trends)
  - Historic controls remain useful, even when no new controls can be found (because very large exposure to pathogen and/or prior vaccination)
  - Old intervention arms may become new/additional control arms
  - Non-concurrent control arms
- Missing data
- Selective willingness of participants towards a set of vaccines
- Heterogeneity between centers and countries
- Interaction with policy makers
- Interaction with general public (understanding the paradigm):
  - Communication
  - Education

Lessons Learned During Pandemic

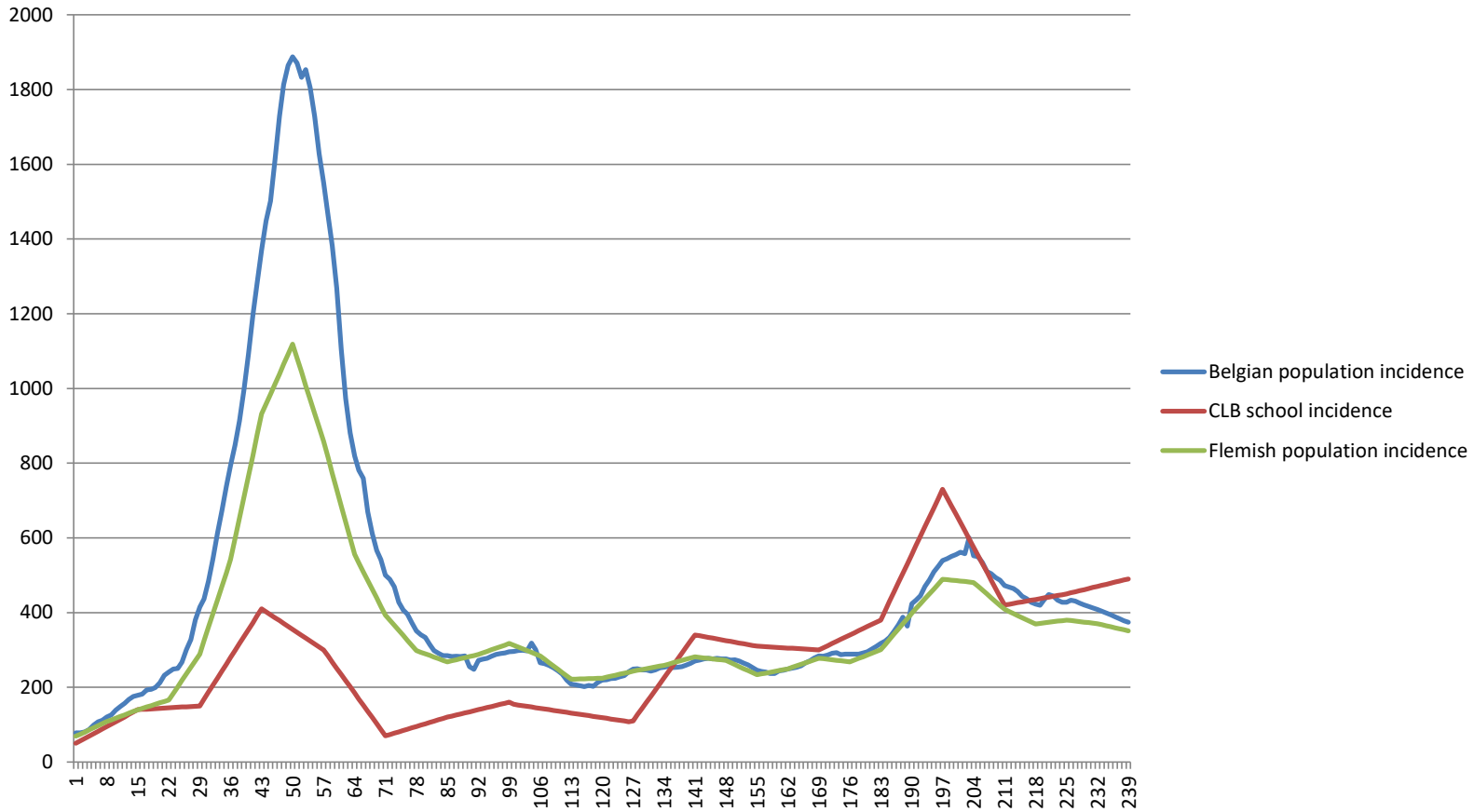
- Vaccines:
  - Interplay between RCTs, natural history data, RWE
- Other therapeutic indications – same story:
  - Rare diseases:
    - Large European projects (EJ PRD, ERDERA, RealiseD)
    - Sponsors – academia – regulatory/HTA – patients/parents
  - Neurodegenerative diseases:
    - Quest for early detection, surrogacy,…

Lessons Learned from the Past and From Now…

- HIV / AIDS
  - Surrogacy evaluation?
  - Survival / CD4 / VL / VL below detection limit
  - HAART ← Co-enrolment
- Therapeutic “accidentally” discovered

Incidence Flemish school system (2020-2021)

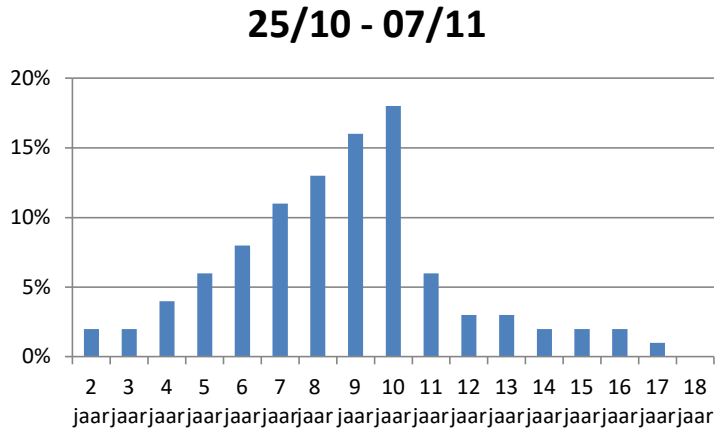
(Source: CLB)

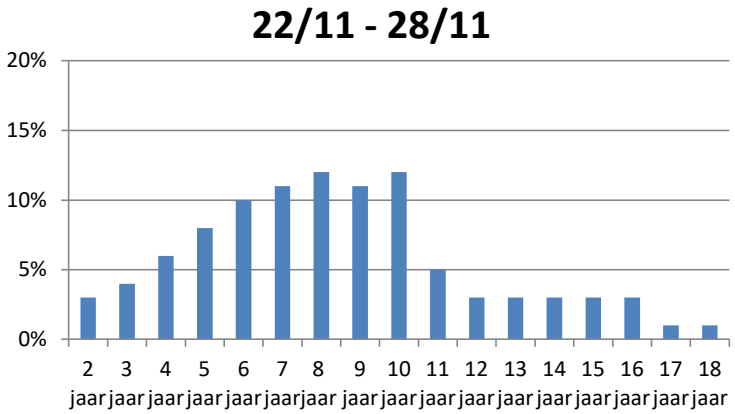


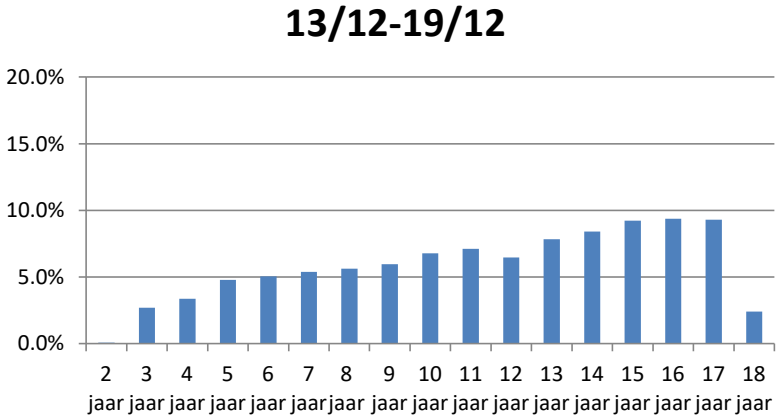
Heated debate: Role of schools

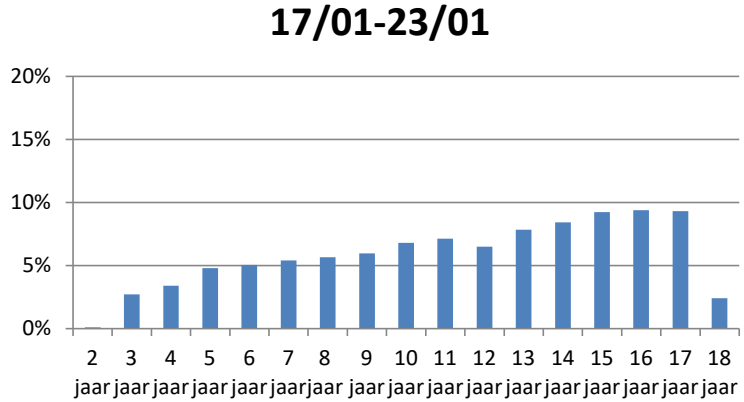
- Situation Spring 2020
- Fall 2020: Children are **not** the engine
- February 2021: Alpha is on the rise
- Measures needed:
  - Schools
  - Extra-scholarly activities
- The complexity of a federal country
- BUT: The role of **higher** education… in French speaking Belgium

Fractions infections Flemish schools









August – September 2020: Climate change

- Prevention paradox
- Media:
  - Paradigm shift: metaphor → scoop
- “Living with the virus”
- Advisory structure called into question
- Fall 2020 wave
- Remarkably under-exposed:
  - Role of Spanish variant…

Coronavirus *(De Morgen, 23 juli 2020)*

Epidemiologist Van Damme: ‘It is 5 past 12. I had expected robust measures’

‘Het is vijf na twaalf. Ik had kordate maatregelen verwacht.’ Dat heeft epidemioloog Pierre Van Damme (UAntwerpen) gezegd in *VTM Nieuws*, na afloop van de Nationale Veiligheidsraad. Ook viroloog Marc Van Ranst sprak bij de VRT van een gemiste kans.

Four experts receive police protection: “A bizarre fact”
(GVA, 20 September 2020)

Conclusion

- Pandemic preparedness
- Education
  - General public
  - Broad array of professionals
- Communication
  - Media
  - Policy makers
  - Scientists
  - General public