Phenomenological and theoretical approaches of the Covid-19 outbreak dynamics

with history and some recent improvements

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UGA & IUF

Teamwork

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Teamwork

* **S. Soubeyrand, J. Demongeot & L. Roques** Towards unified and real-time analyses of outbreaks at country-level during pandemics. *One Health* (2020), **11**, doi: 10.1016/j.onehlt.2020.100187

* **J. Gaudart, J. Landier, L. Huiart, E. Legendre, L. Lehot, M.K. Bendiane, L. Chiche, A. Petitjean, E. Mosnier, F. Kirakoya-Samadoulougou, J. Demongeot, R. Piarroux & S. Rebaudet** Factors associated with spatial heterogeneity of Covid-19 in France: a nationwide ecological study. *MedRxiv*, doi.org/10.1101/2020.09.17.20196360doi (2020). *The Lancet Public Health*, doi.org/10.1016/S2468-2667(21)00006-2 (2021).

* **J. Demongeot, K. Oshinubi, H. Seligmann & F.Thuderoz** Estimation of Daily Reproduction Rates in COVID-19 Outbreak. *IJERPH* (in revision). *MedRxiv*, doi.org/ 10.1101/2020.12.30.20249010 (2021).

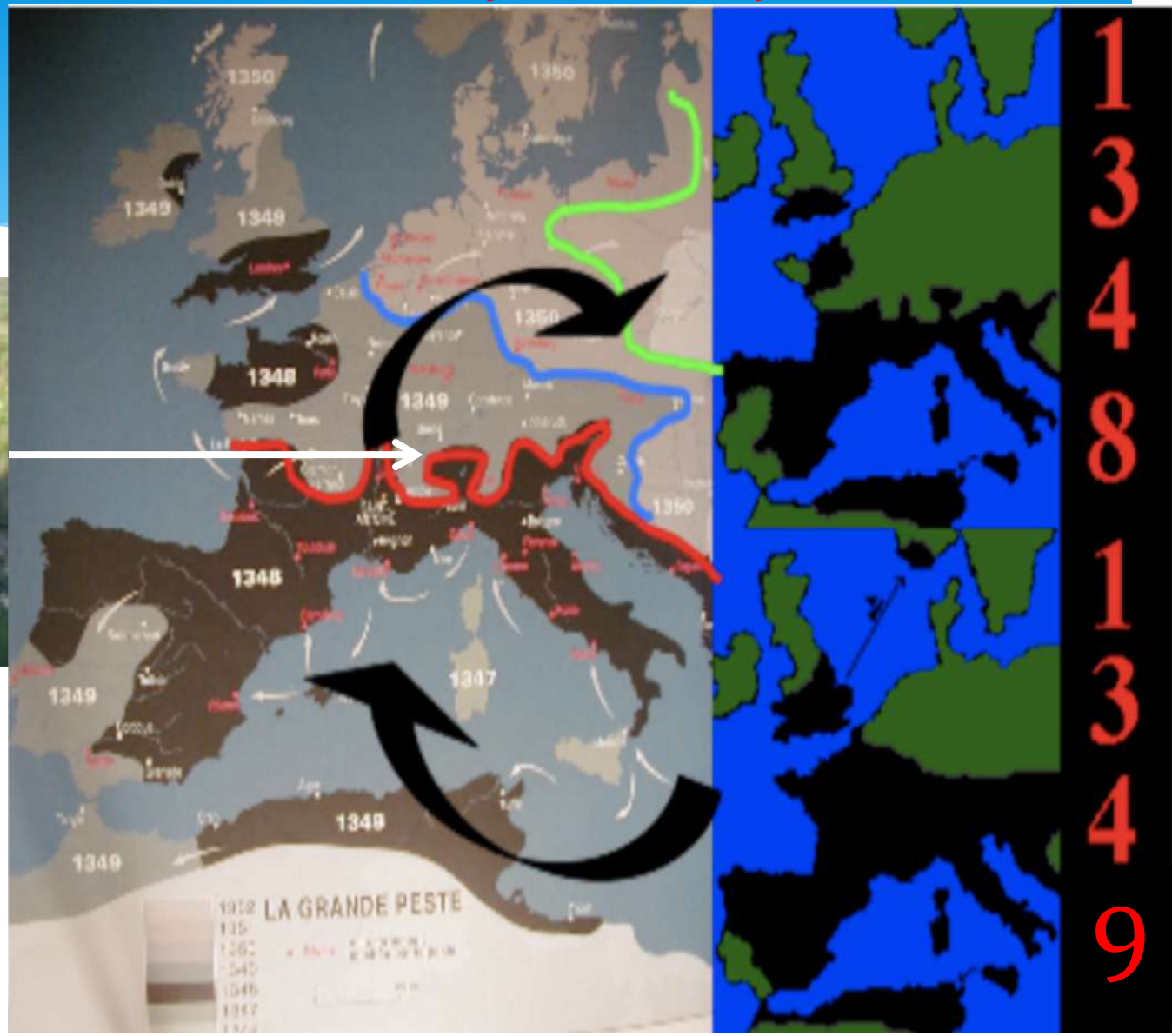
* **H. Seligmann, N. Vuillerme & J. Demongeot** Do confinements hasten viral evolution for greater contagiousness? *Biology* (in revision).

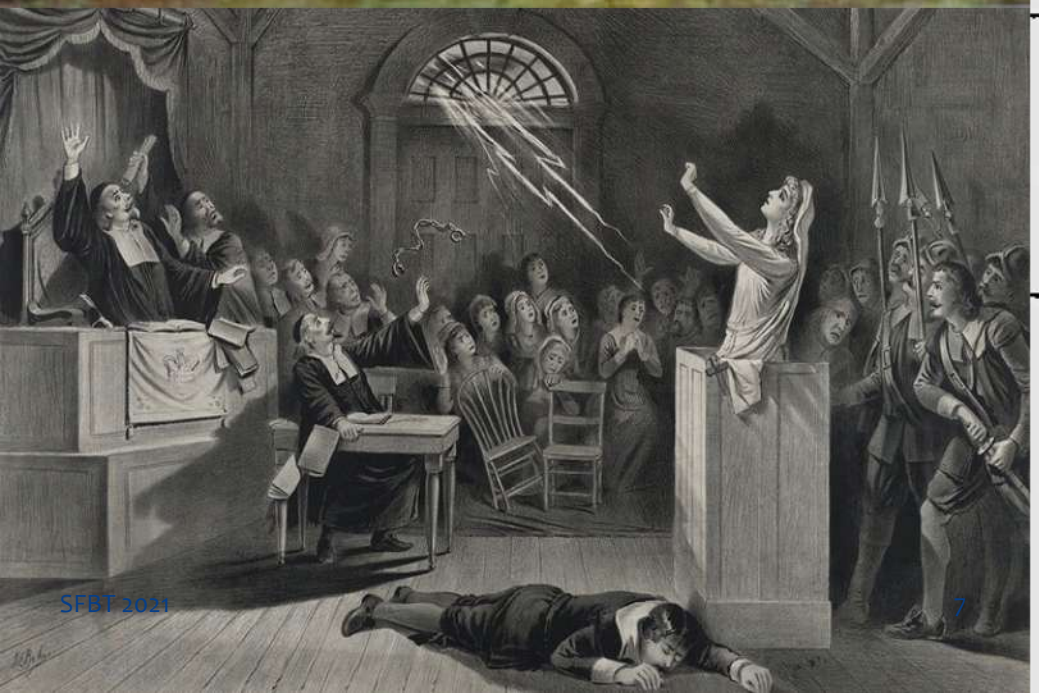
* **Q. Griette, J. Demongeot & P. Magal** A robust phenomenological approach to investigate COVID-19 data for France. *One Health* (submitted). *MedRxiv* doi: https://doi.org/10.1101/2021.02.10.21251500 (2021).

Phenomenological approach

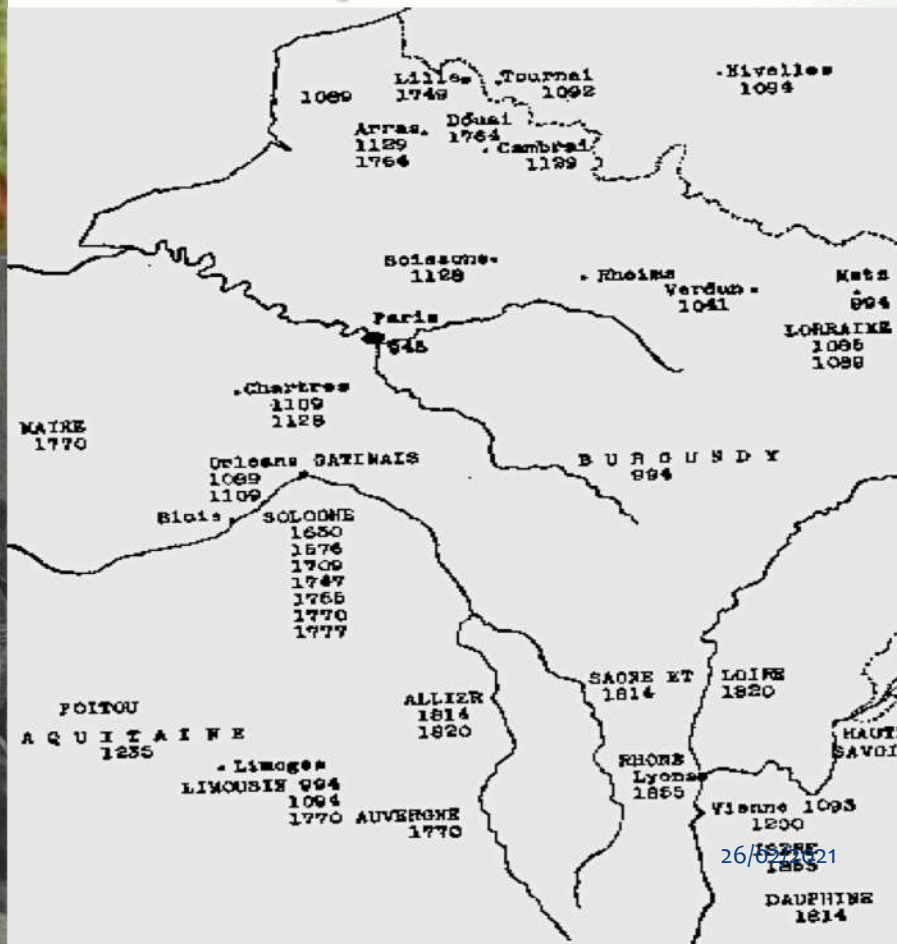
Plague propagation and the St Anthony monastery near Grenoble

St Anthony





St Anthony's fire



SMALLPOX SPREADING

- Smallpox virus was transmitted via the respiratory tract. Case fatality was increasing over the centuries and peaked in the 18th century (death of king of France Louis XV in 1774).
- In 1721 a method of smallpox inoculation (variolation) was introduced from Turkey into England by Lady Mary W. Montagu, the wife of the English Ambassador to Constantinople.
- Inoculation was even attempted against measles and plague before cow pox vaccination by E. Jenner in 1796.

Lady Mary W. Montagu
1689-1762

COVER UP!

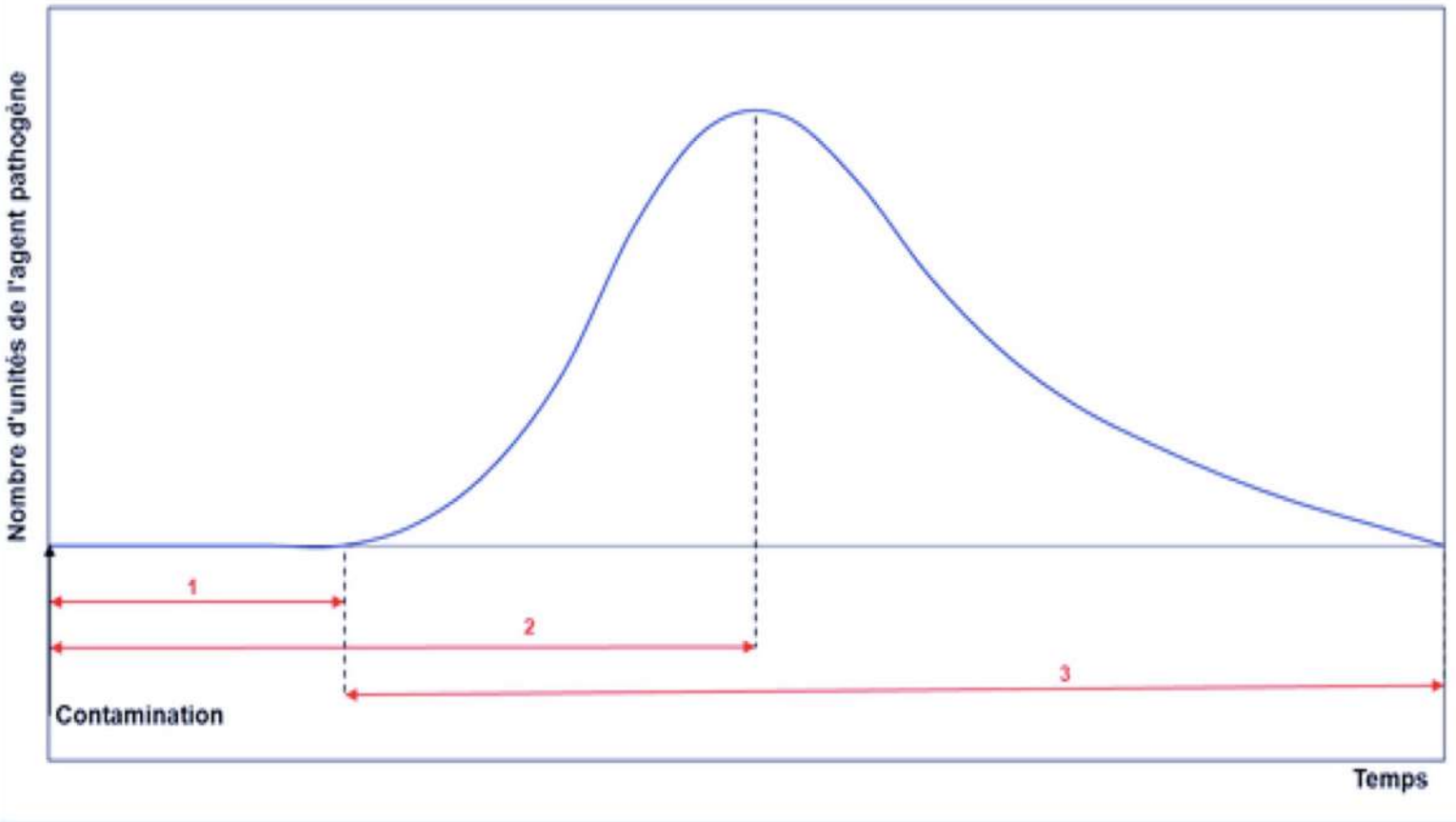
YOUR COUGHS AND SNEEZES

SPRAY SPREADS

COLDS · FLU · TUBERCULOSIS

THE ANNUAL SALE OF Christmas Seals MADE THIS POSTER POSSIBLE

Phenomenologic approach



La même figure peut servir pour définir les périodes de contagiosité (maladie contagieuse) ou d'infectiosité (maladie transmissible non contagieuse).

1 : délai de contagiosité (ou délai d'infectiosité)

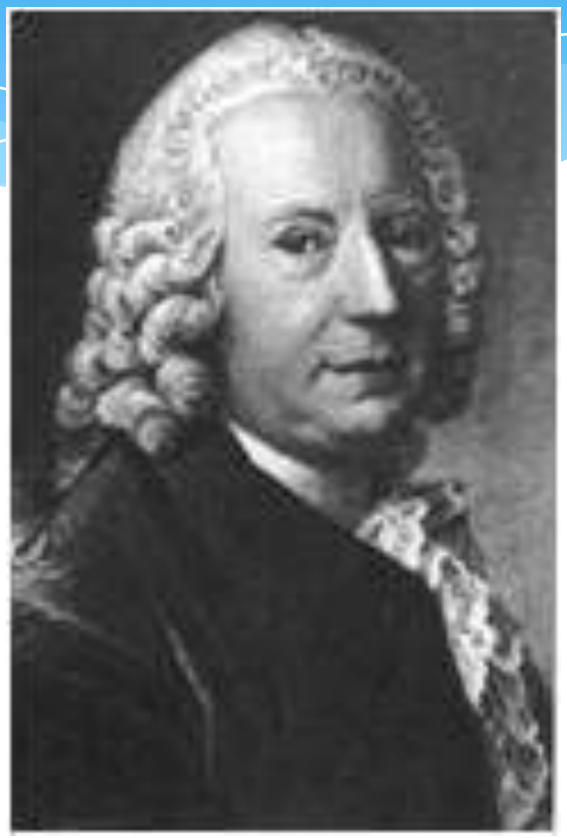
2 : délai de contagiosité maximale (ou délai d'infectiosité maximale)

3 : période de contagiosité (ou période d'infectiosité)

Daniel Bernoulli's life

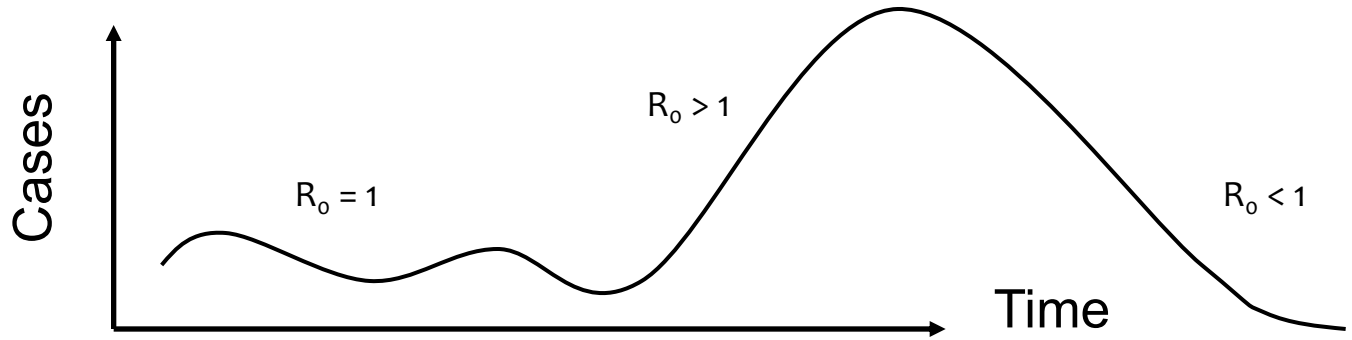
February 9th 1700 (Groningue, NL) – March 17th 1782 (Bâle, Switzerland)

* Learning differential calculus of Leibnitz, with his father , and his brother (Nicolas).
* Receiving a M.D. degree (1721), after studying philosophy, logic, and medicine at the universities of Heidelberg, Strasbourg, and Basel.
* Lecturing in St Petersburg until 1732, in medicine, mechanics, and physics
* Returning to University of Basel, and accepting a post in anatomy and botany.



§. 115. Notre méthode ſert encore à éclaircir une objection que quelques Médecins ſe ſont aviſés de faire contre l'Inoculation : elle conſiſte dans la contagion qu'on répand d'une maladie qui auroit pu demeurer dans l'inaction pendant pluſieurs années de ſuite ; ils pouſſent cette objection juſqu'à dire qu'un ſeul inoculé pourra donner la petite vérole à dix autres, chacun de ces dix encore à dix, & forment ainſi une progreſſion géométrique, dont le ſeul douzième terme ſurpaſſe de beaucoup le nombre de tous les hommes qui ont exiſté depuis la création du monde. On pourroit d'abord répondre à cela, que peut-être l'humanité s'en trouveroit mieux ſi la maladie en queſtion devenoit endémique & qu'elle exerçât ſon activité uniformément ſans la ſuſpendre : peut-être que le retour d'une épidémie long-temps ſuſpendue, fait un ravage plus terrible dans une ſeule année qu'une endémie uniformé

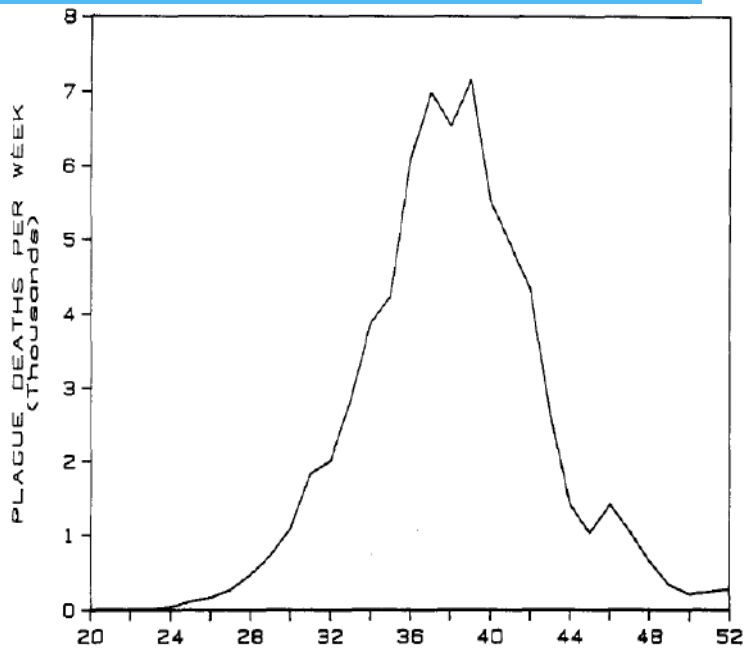
Endemic - Epidemic - Pandemic



- **Endemic**
  - **Transmission occur, but the number of cases remains constant**
- **Epidemic**
  - **The number of cases increases**
- **Pandemic**
  - **When epidemics occur at several continents – global epidemic**

Controversy about epidemic shapes

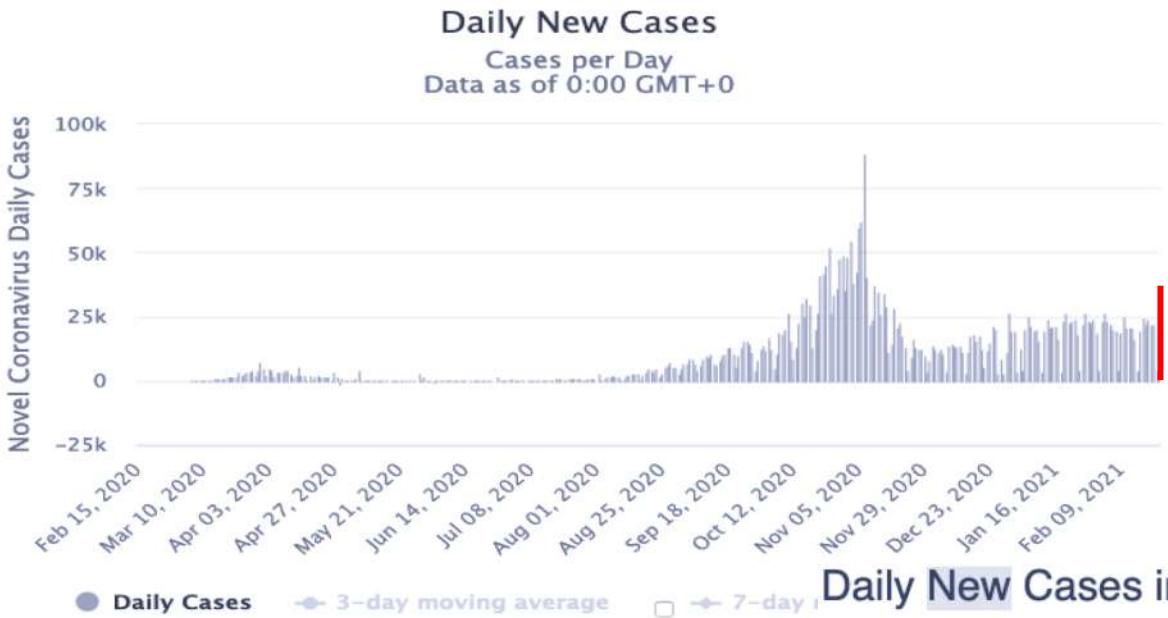
* In 1927 the "bell shaped geometry" of the epidemic curve was well understood but a controversy occurred on factors that determined both the magnitude of the epidemic and its termination within a given population.
* Two explanations, for the termination of an epidemic, were most in favour amongst medical circles at that time, namely:
  * (1) that the supply of susceptible people had been exhausted, and,
  * (2) that during the course of the epidemic the virulence of the infectious agent had gradually (or rapidly) decreased.



The 1665 Plague epidemic in London. Weekly reports of deaths due to the plague are recorded in Daniel Defoe's journal (Brayley, 1722).

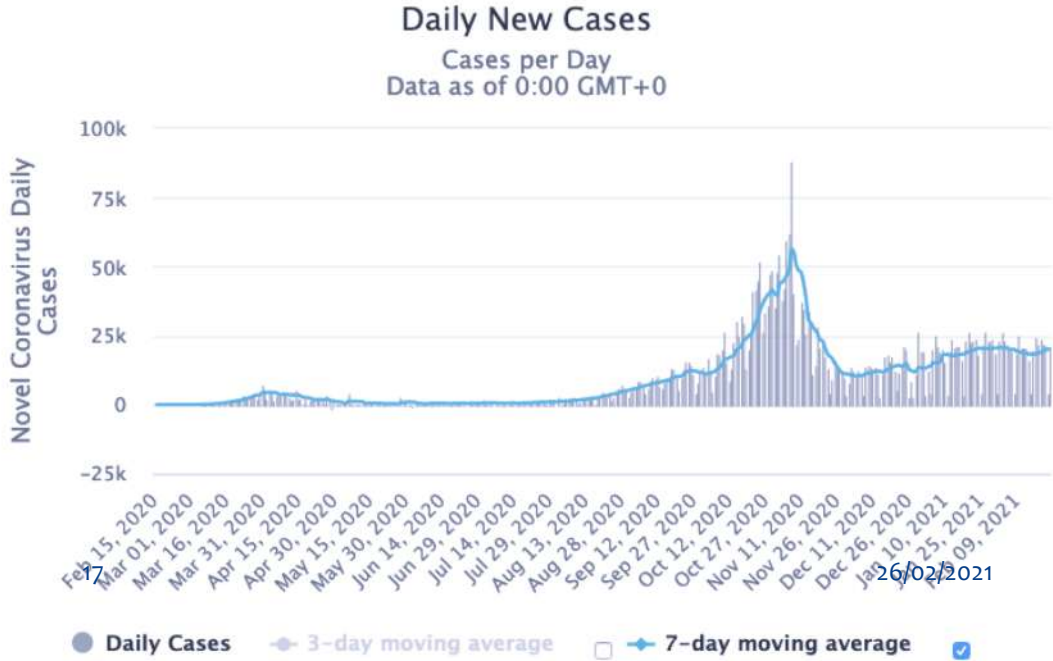
Screening data

Daily New Cases in France

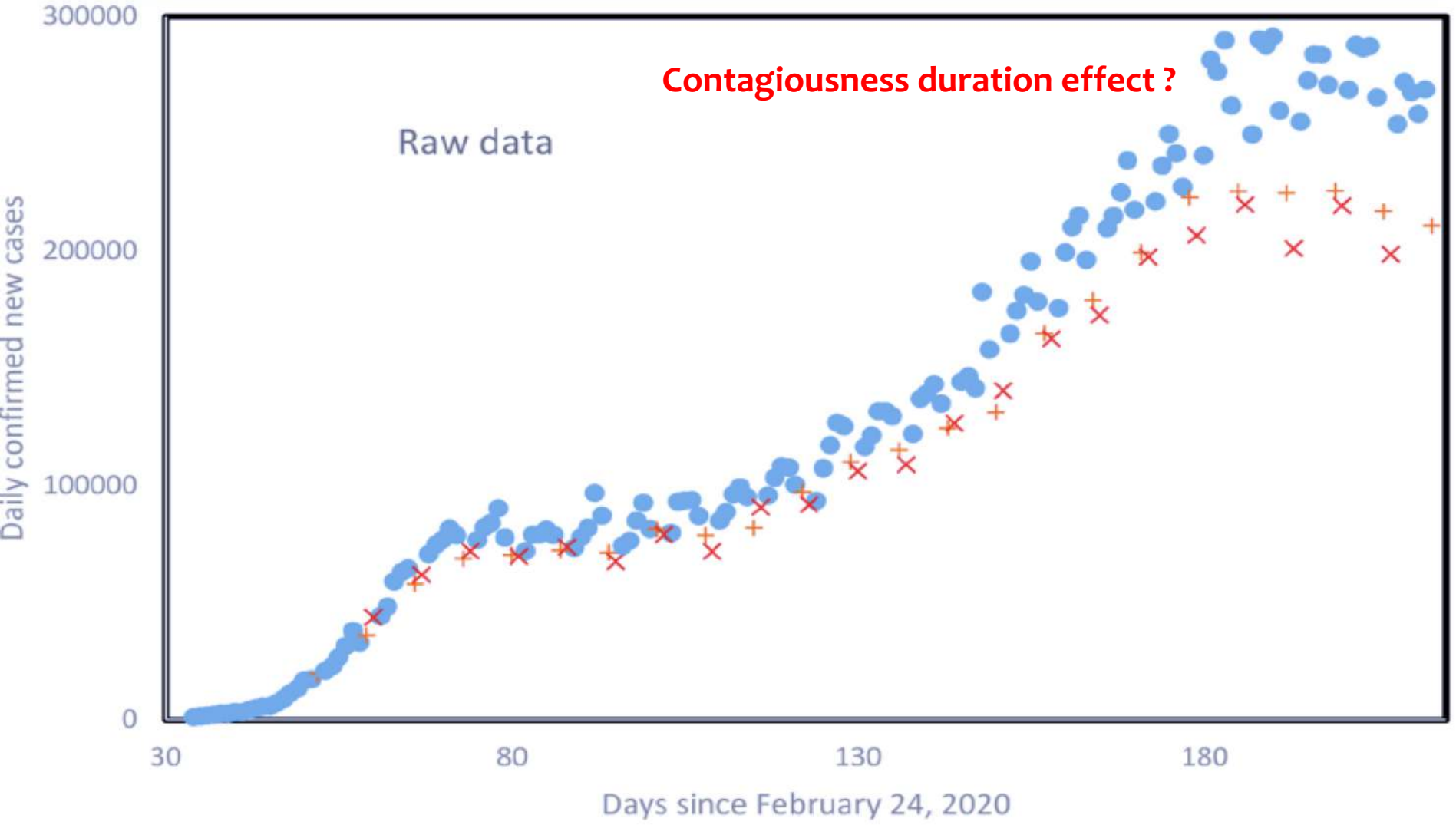


France
Covid-19

Daily New Cases in France



Week-end effect on data collecting

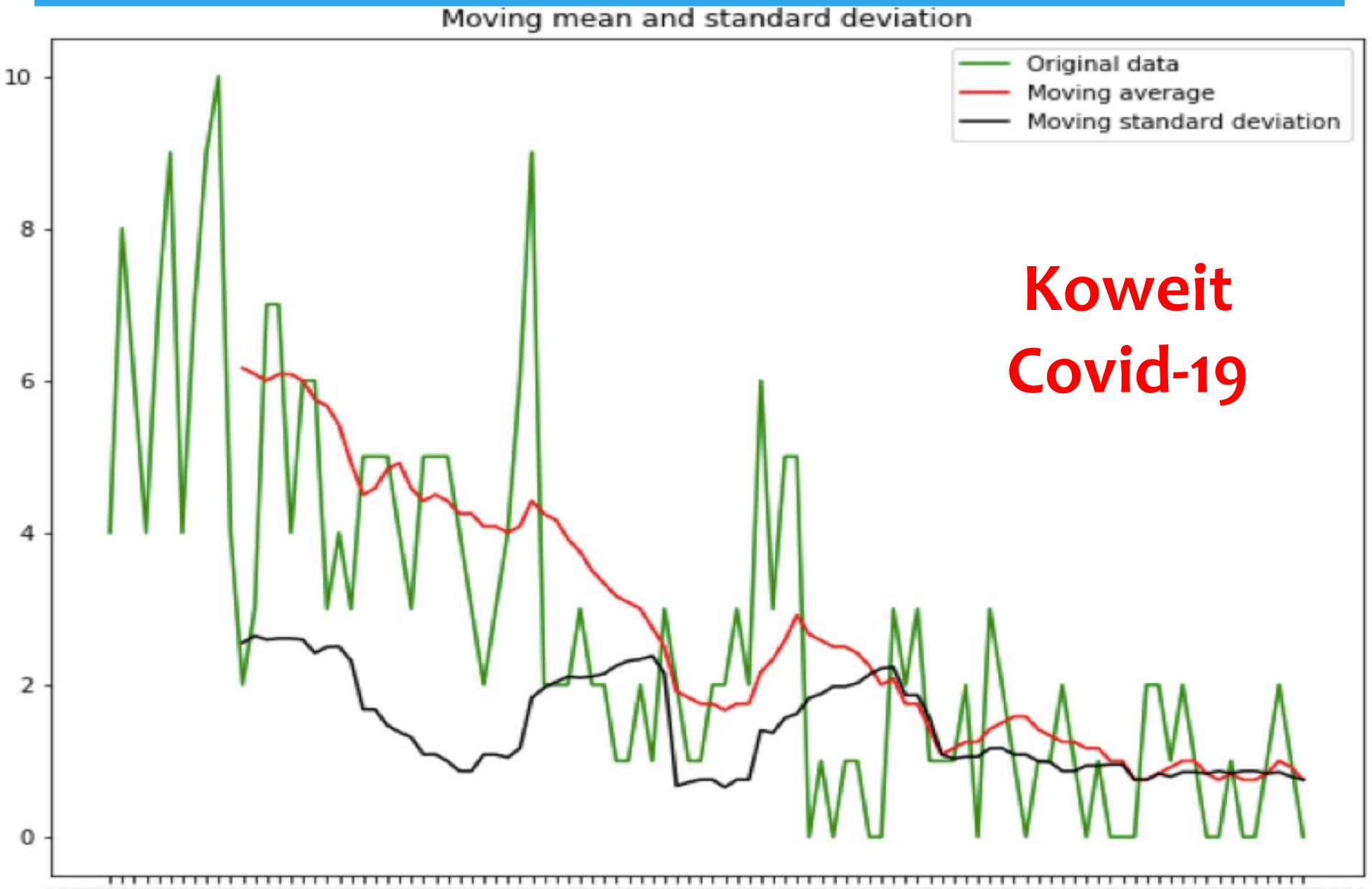


ARIMA description

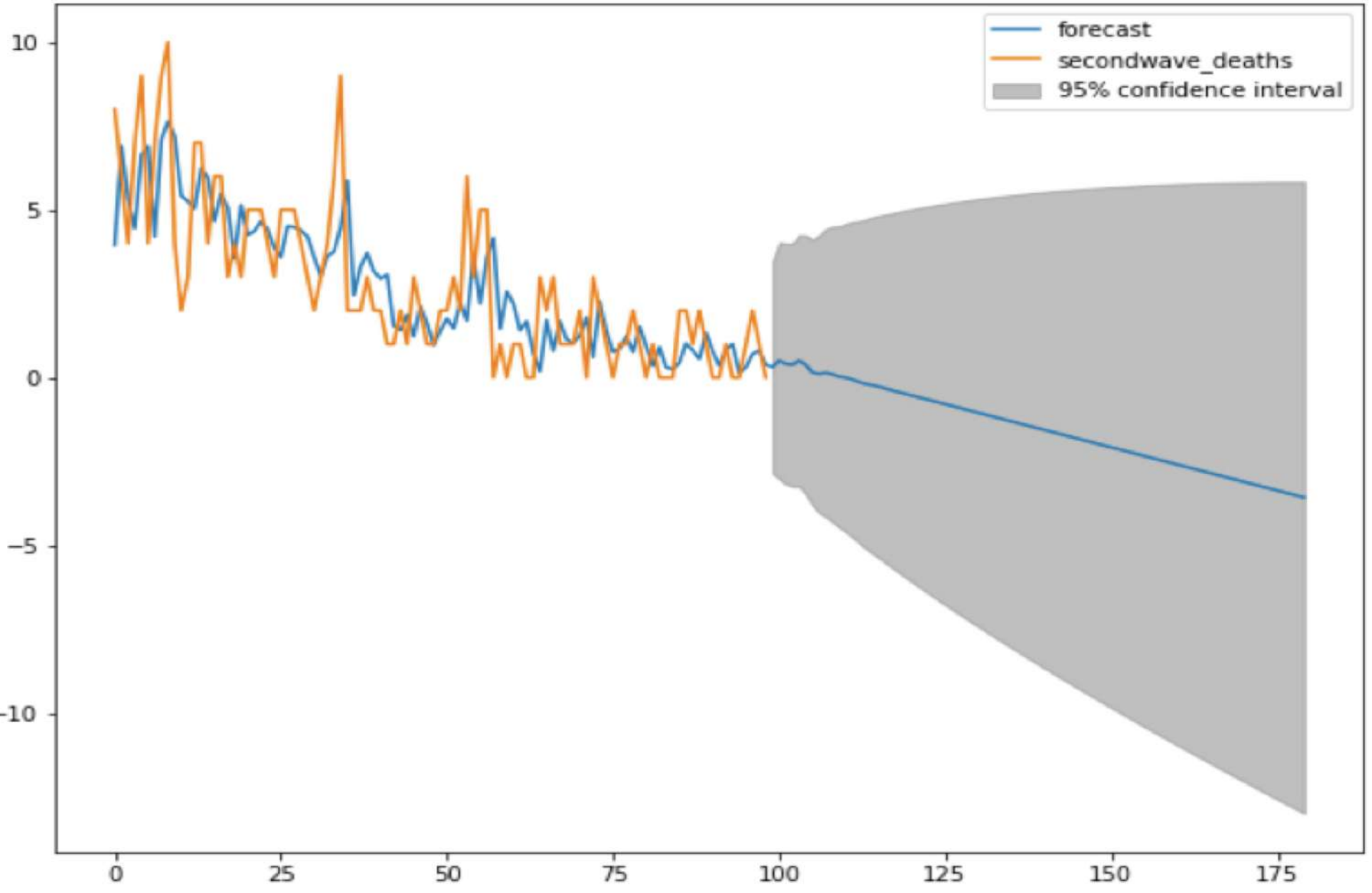
$$X_j = \Sigma_{k=1,r}\, a_k X_{j-k} + W_j$$

After stationarizing the X's (substracting trend and cyclic component)

ARIMA


Moving mean and standard deviation
Original data
Moving average
Moving standard deviation
10
8
6
4
2
0
Koweit
Covid-19

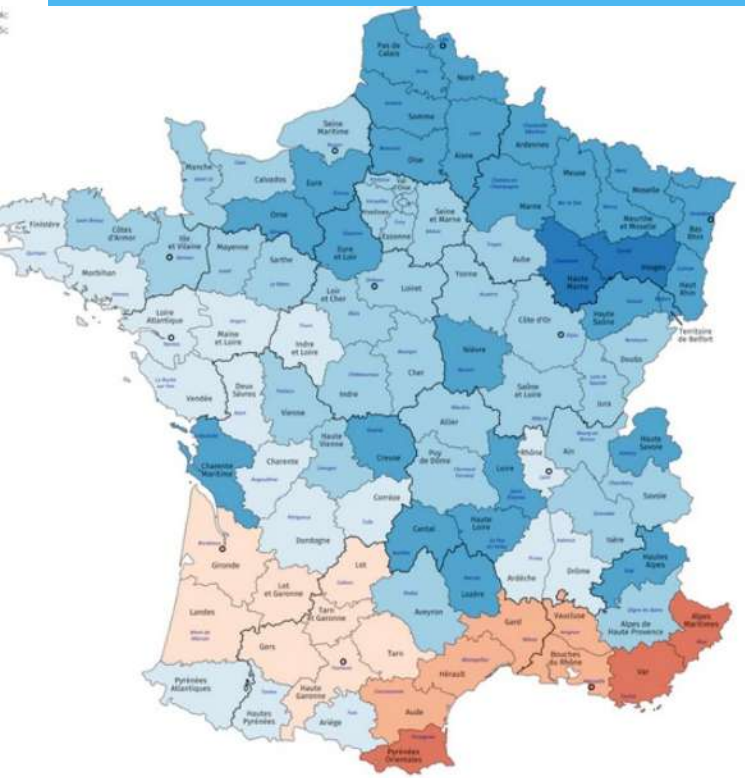
ARIMA

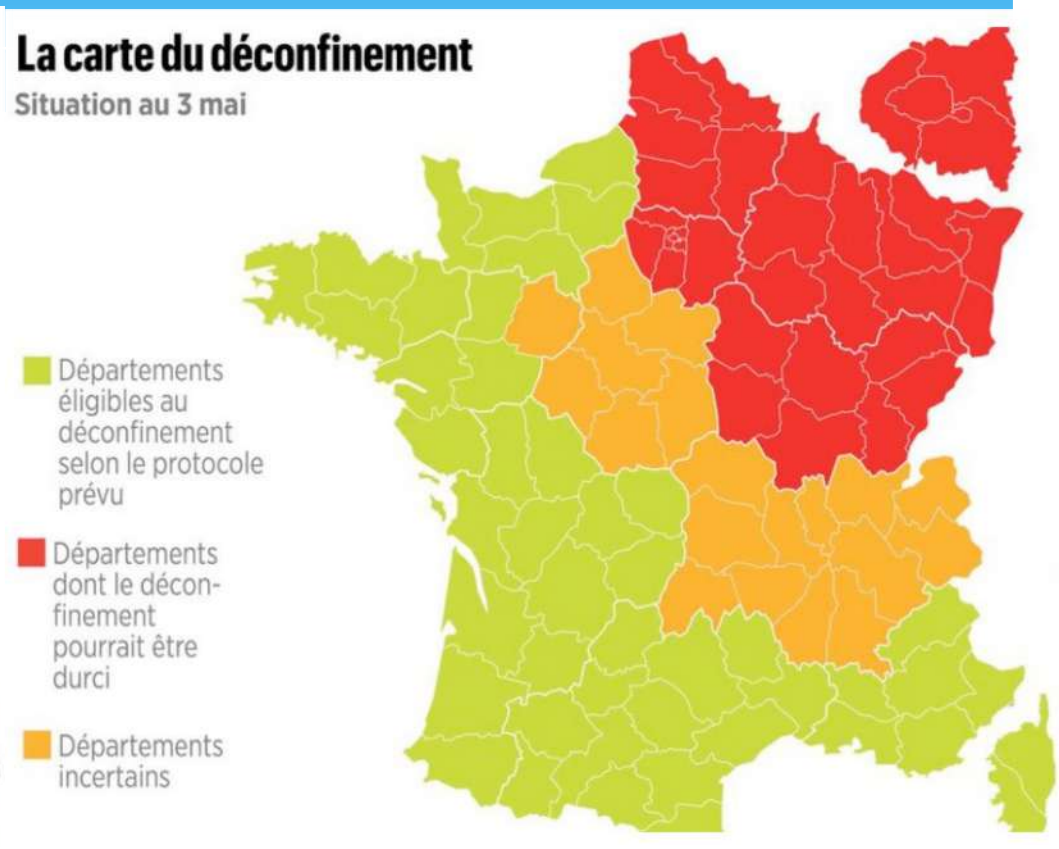

forecast
secondwave_deaths
95% confidence interval
10
5
0
−5
−10
0
25
50
75
100
125
150
175

Dependence on geoclimatic factors (e.g., air ambiant temperature)

Mean temperature in France

covid-19 spread





https://www.reddit.com/r/MapPorn/comments/7rq6uh/average_annual_temperature_in_departments_of/

http://www.leparisien.fr/societe/coronavirus-135-deces-en-24-heures-une-nouvelle-carte-de-deconfinement-03-05-2020-8310096.php

French Regions		2020	New Cases vs. Previous Day						
	Temp	4III	5III	6III	7III	10III	15III	23III	25III
Auvergne-Rhône-Alpes	11.00	49	15	11	27	49.0	54.8	150.9	181.5
Bourgogne-Franche-Comté	10.00	16	23	39	51	-2.0	67.6	110.8	111.0
Bretagne	11.53	23	6	3	8	14.3	27.0	34.0	56.5
Centre-Val de Loire	10.73	0	2	9	5	1.0	14.0	34.0	100.0
Corse	14.13	0	3	0	2	12.3	14.6	9.9	15.5
Grand Est	9.00	38	39	59	114	79.7	201.4	345.0	611.5
Hauts de France	10.40	65	9	23	76	25.3	58.0	91.3	242.0
Ile de France	10.80	55	21	13	15	121.3	275.6	545.6	724.5
Normandie	10.53	2	4	5	0	9.7	21.6	45.4	88.5
Nouvelle-Aquitaine	13.40	5	3	3	6	13.3	19.0	65.5	118.0
Occitanie	12.60	9	2	7	18	11.3	36.0	64.6	157.5
Pays de la Loire	11.40	7	1	8	2	4.3	15.4	23.1	37.5
Provence-Alpes-Côte d'Azur	11.80	13	5	8	12	24.0	56.2	139.9	208.5
Pearson Rx100		-48.95	-68.34	-74.73	-65.17	-34.3	-48.1	-43.5	-43.8

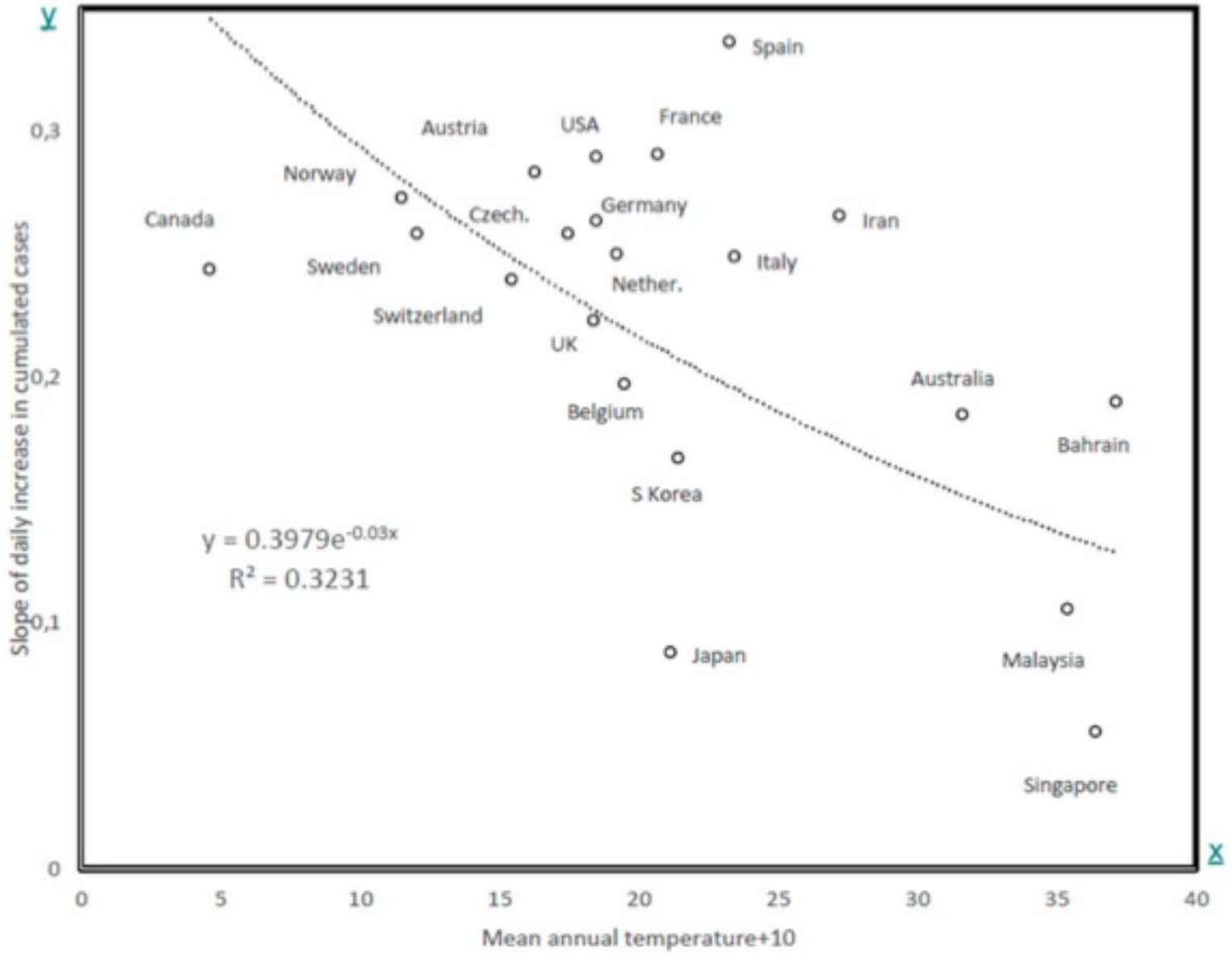
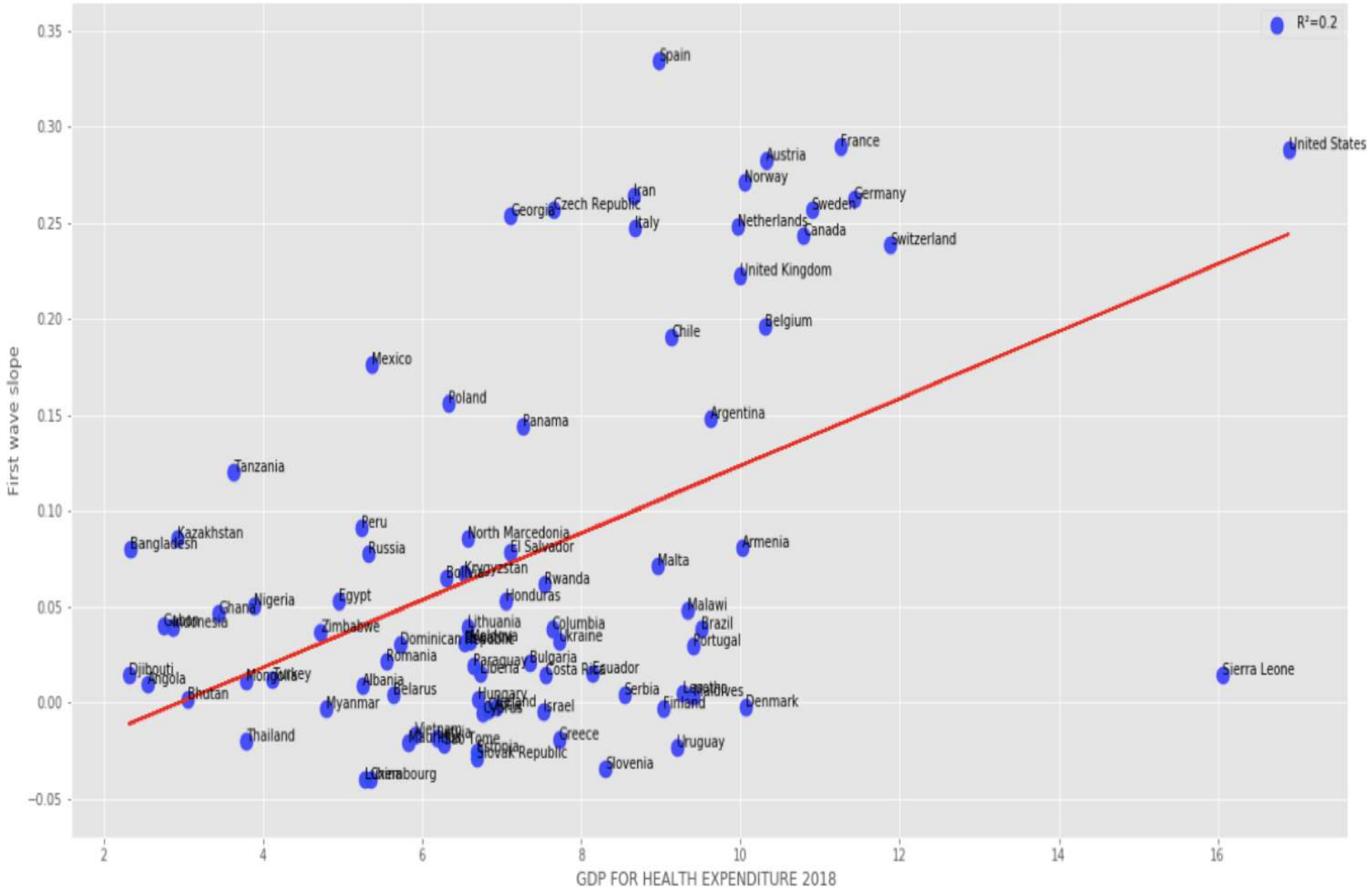


Figure 4. Slope of exponential model fitted to data in Table 3 as a function of mean annual temperature in that country. The Pearson correlation coefficient is R = −0.568, one-tailed $p = 0.0036$.

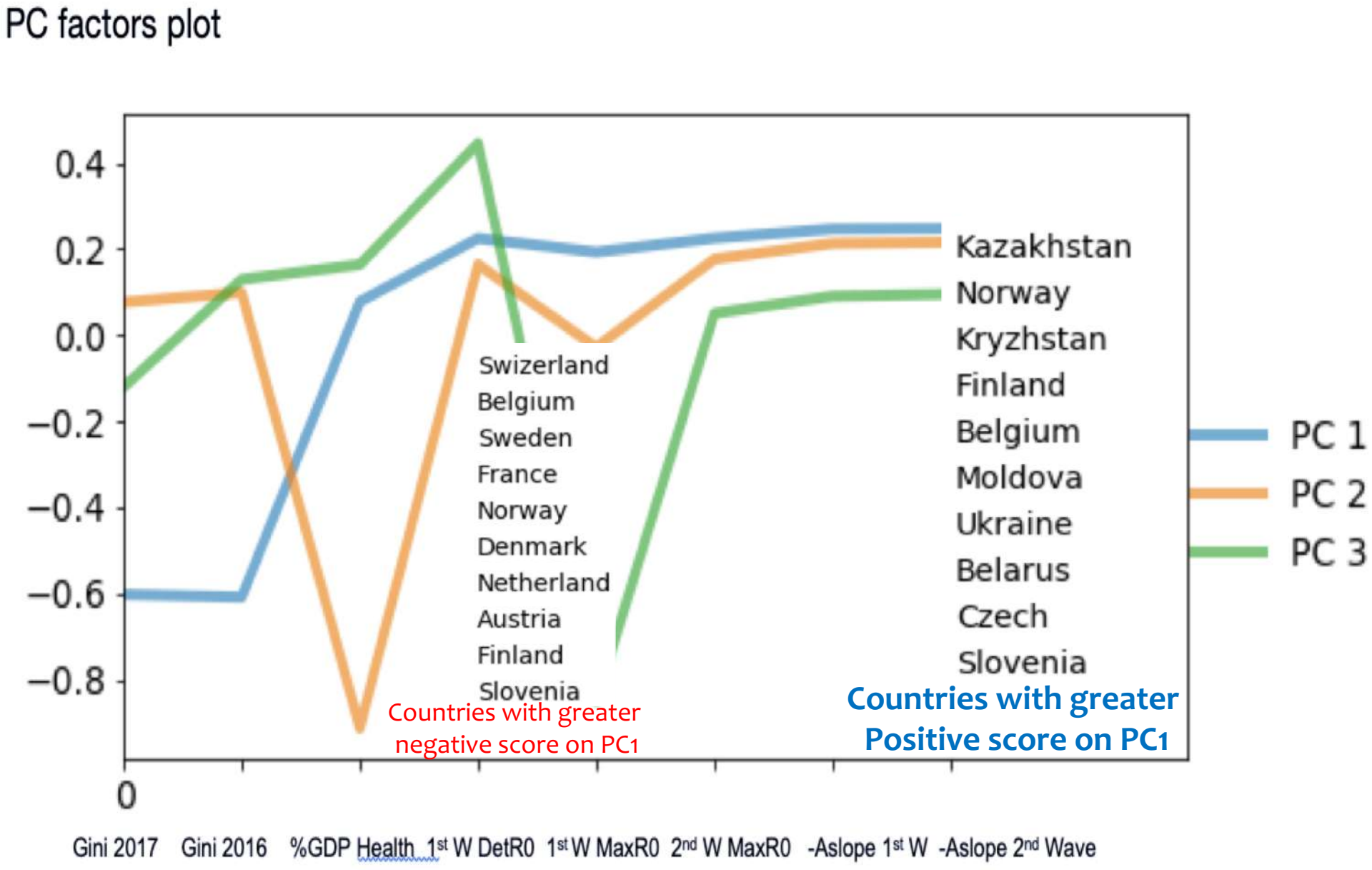
Dependence on socio-economic factors (e.g., % GDP for health expenditures)

Autocorrelation slope



PCA

FOR 91 COUNTRIES WITH SIMILAR SOCIO ECONOMY FEATURES (GINI INDEX AND GDP HEALTH)



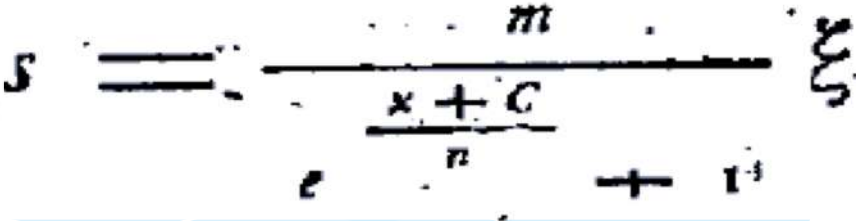
Phenomenological modeling

The Bernoulli-Verhulst logistic

J. Bernoulli

$$I = \frac{1}{\left(1 - \frac{1}{N}\right) e^{-\beta N t} + 1/N} = \frac{N}{(N-1)e^{-\beta N t} + 1}$$

N. Bernoulli



Bernoulli, 1760
d'Alembert, 1761
Lambert, 1772

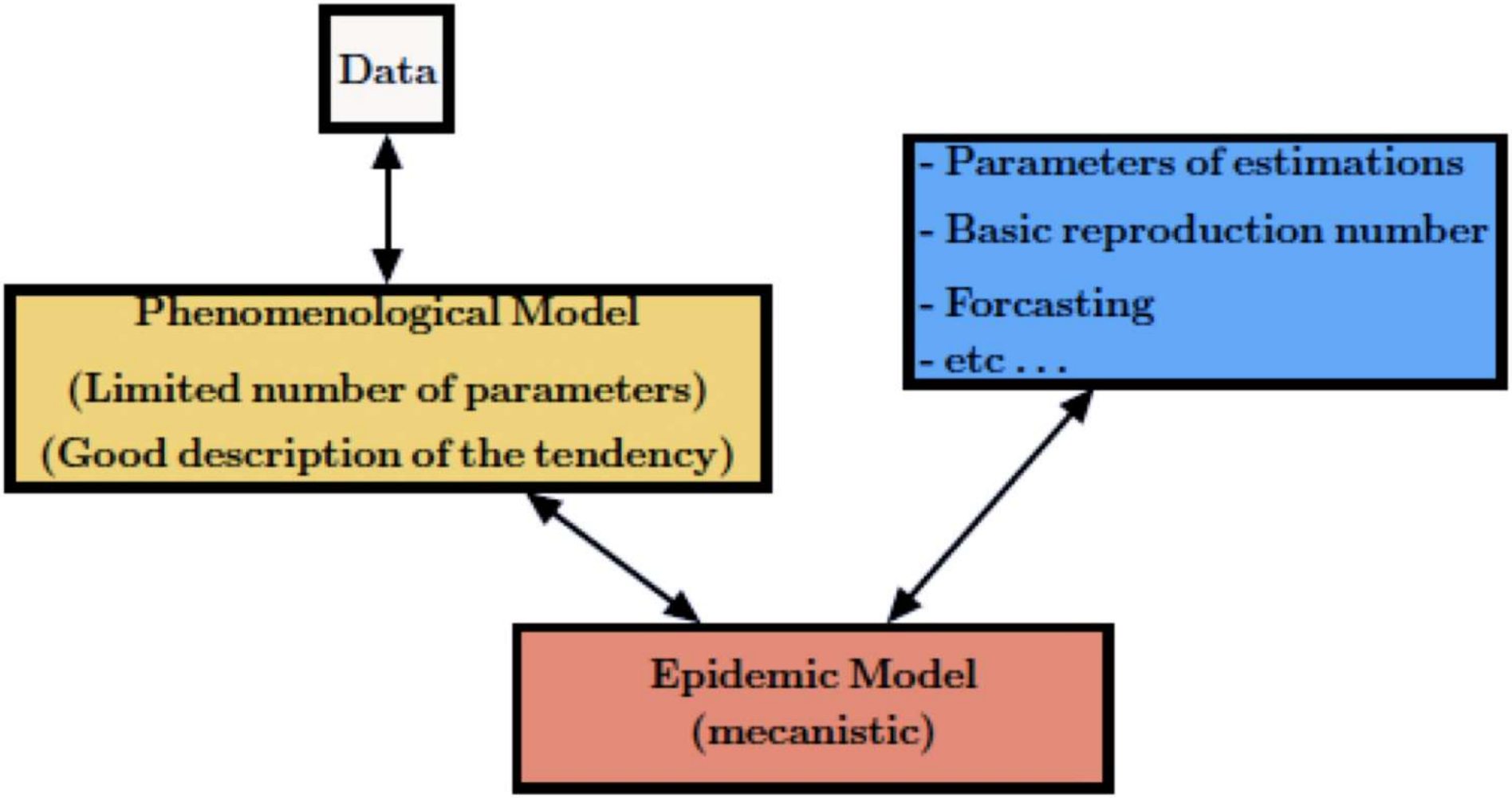
Verhulst, 1838
Hamer, 1906
Ronald Ross, 1916
McKendrick, 1925

Delbrück, 1940, Bartholomay, 1958,
McQuarrie, 1967 & Gillespie, 1970

Multi-agent or IBM discrete models

Fisher & KPP, 1937
Demetrius, 1974

PDE or Markov continuous models



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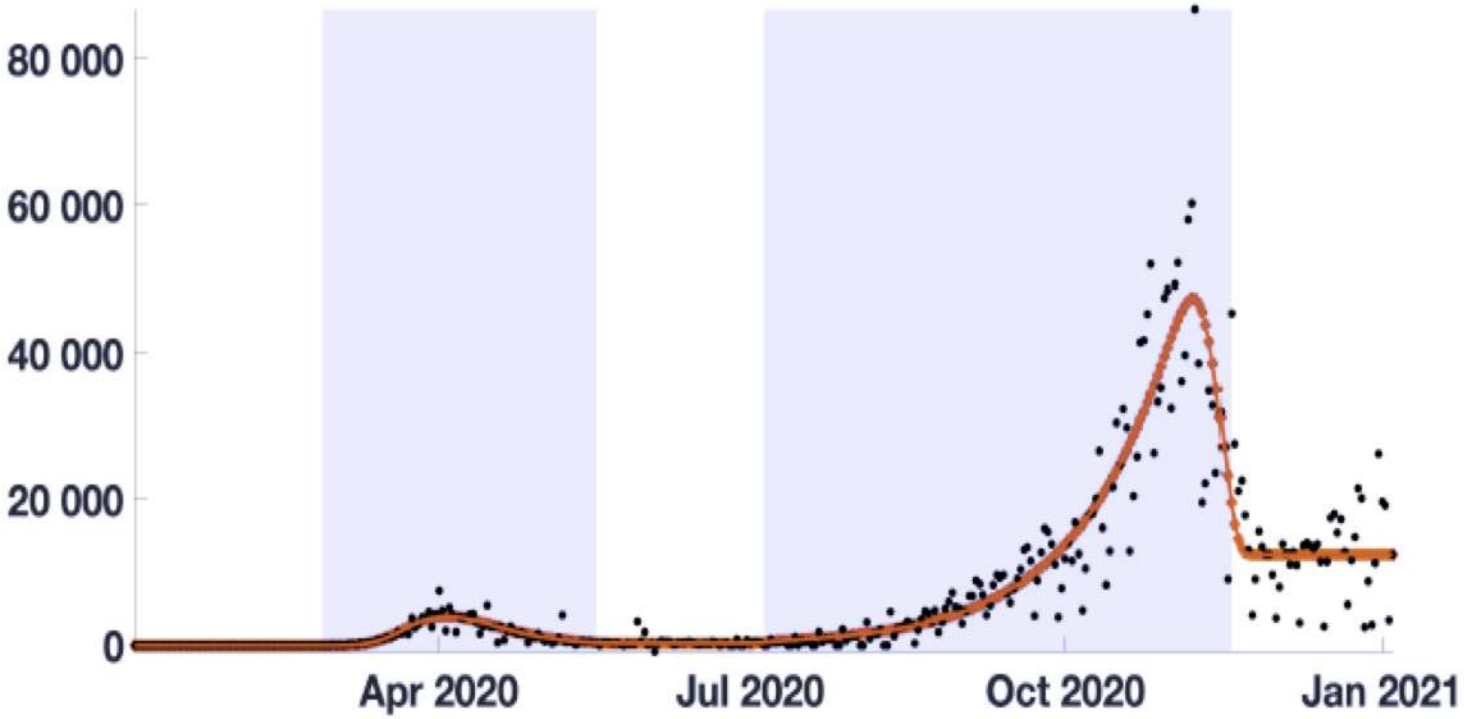


Figure 4: *The red curve corresponds to the first derivative of the phenomenological model and the black dots correspond to daily number of new reported cases in France.*

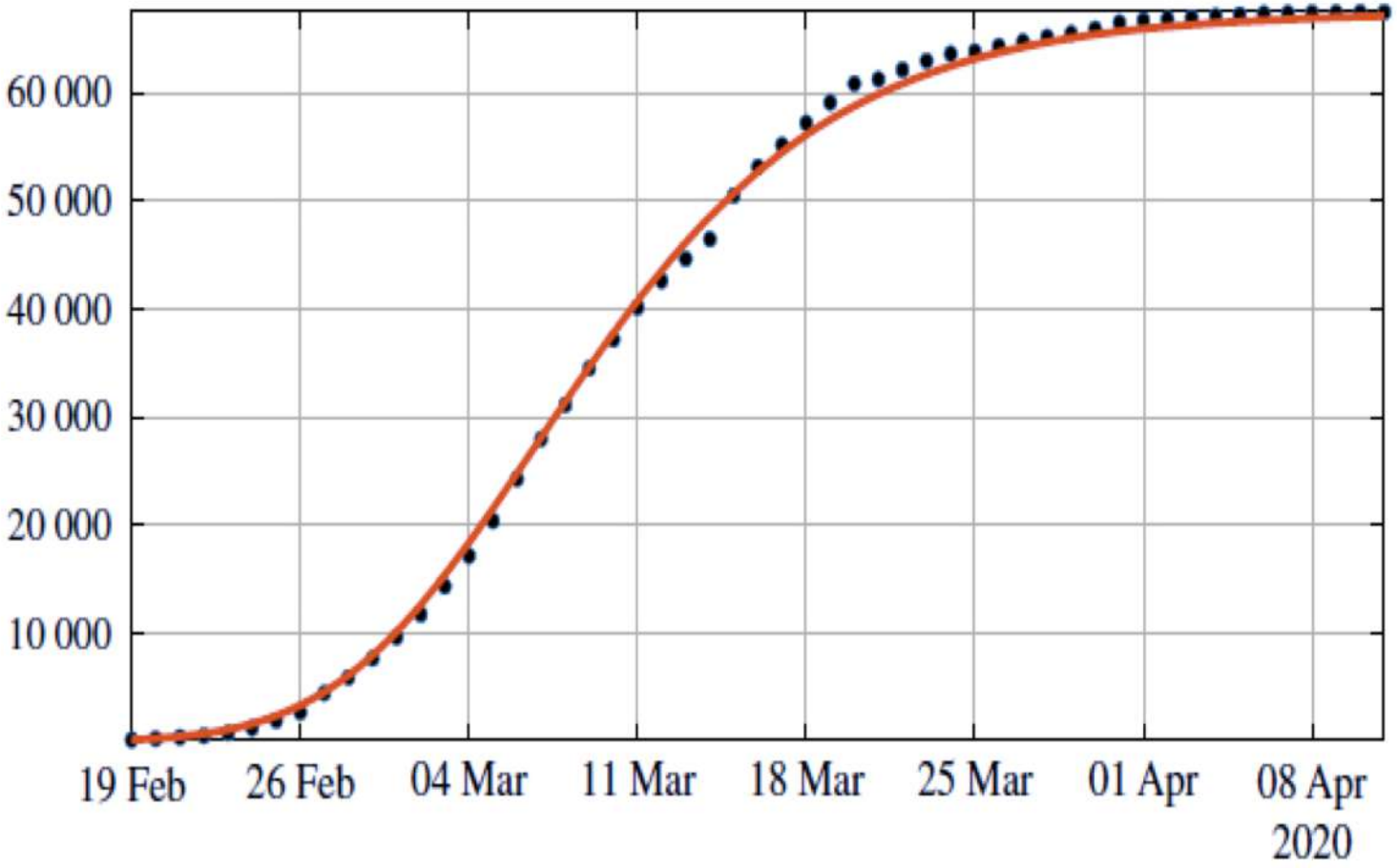


Figure 3. In this figure, we plot the best fit of the Bernoulli–Verhulst model to the cumulative number of reported cases of COVID-19 in China. We obtain $\chi_2 = 0.66$ and $\theta = 0.22$. The black dots correspond to data for the cumulative number of reported cases and the red curve corresponds to the model.

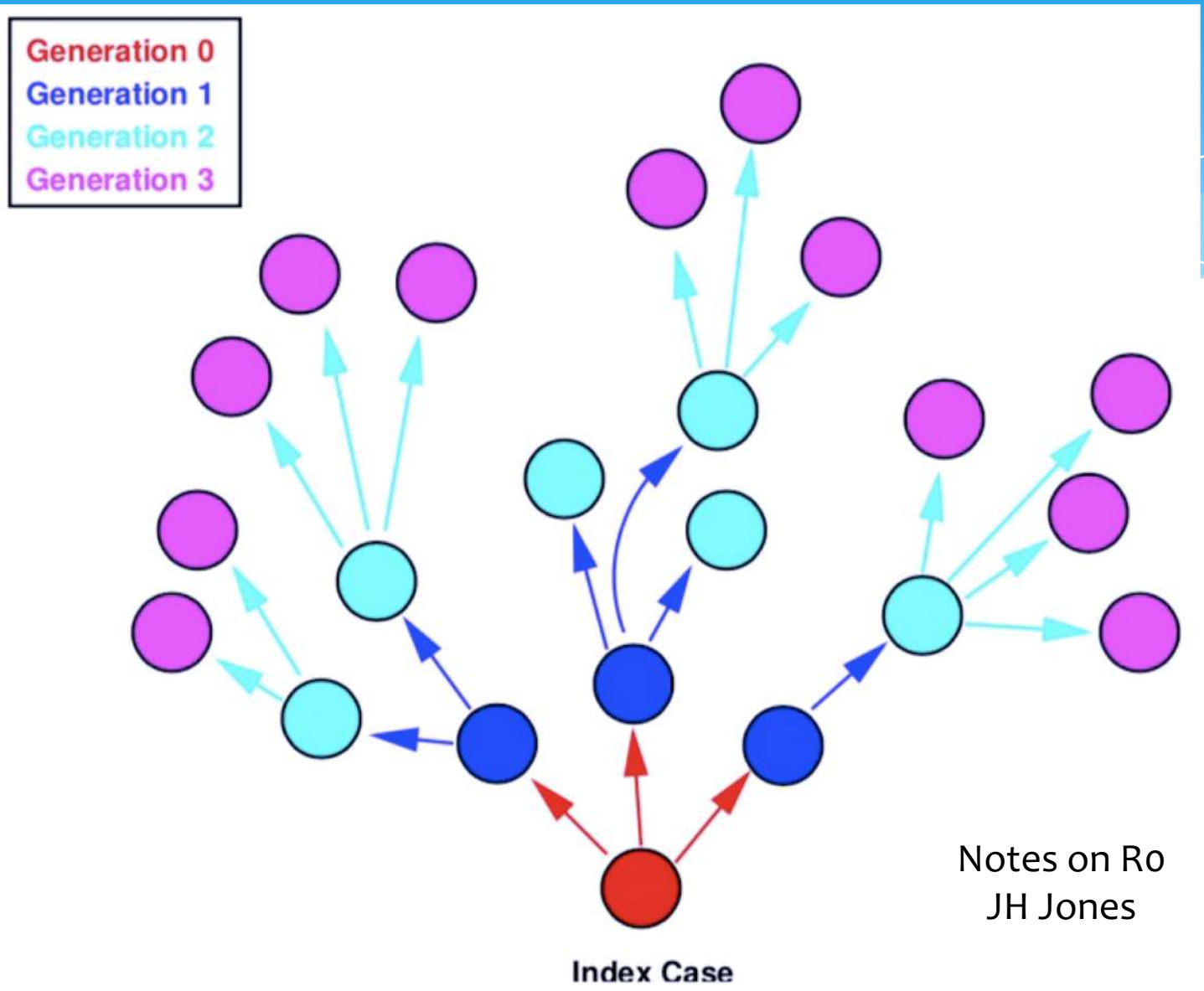
Demongeot, J.; Griette, Q.; Magal, P. Computations of the transmission rates in SI epidemic model applied to COVID-19 data in mainland China. *Royal Society Open Science* **2020**, *7*, 201878.

Theoretical approach

Discrete modeling

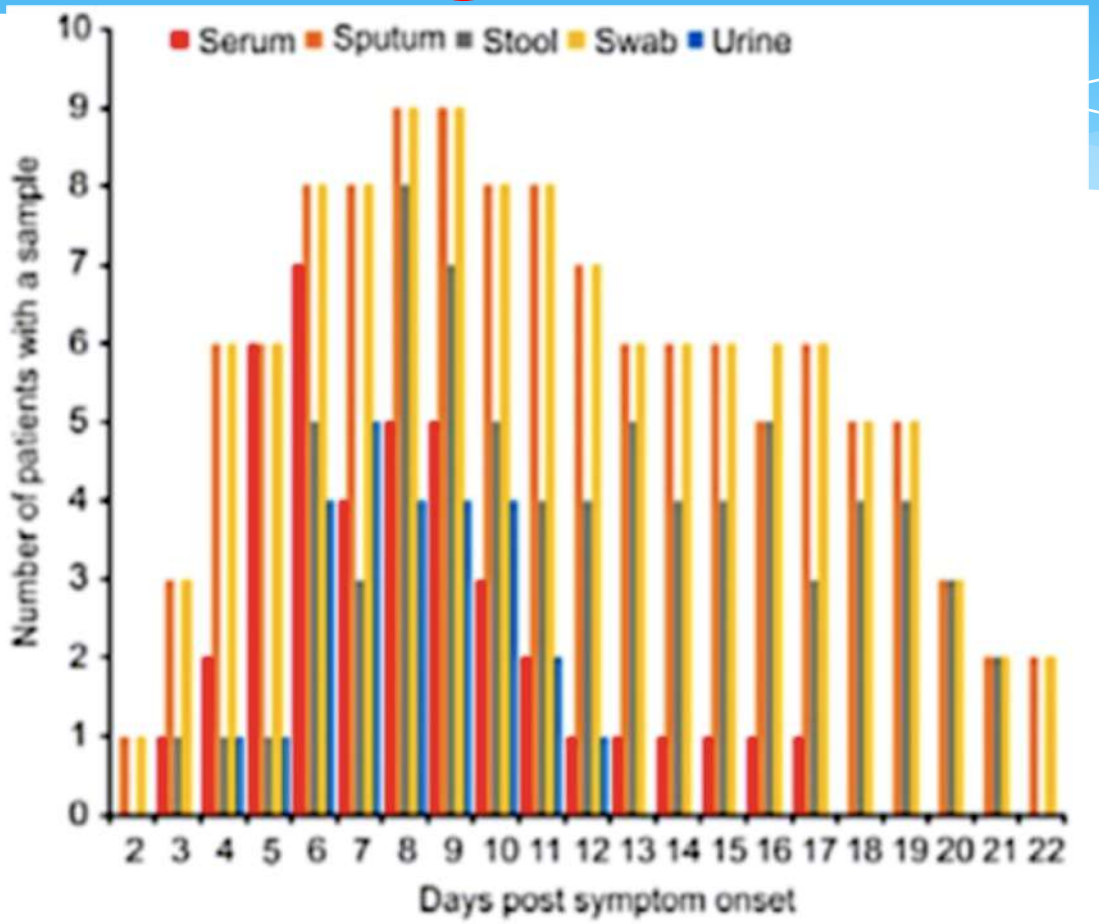
The daily reproduction numbers

Ro



Notes on Ro
JH Jones

R_0 depends on the day of the contagion period



J. DEMONGEOT, Y. FLET-BERLIAC & H. SELIGMANN Temperature decreases spread parameters of the new covid-19 cases dynamics. *Biology (Basel)*, **9,** 94 (2020).

Daily Reproduction numbers R_j

Let consider the classical reproduction rate R_o. If the model is deterministic, if X_j denotes the number of new cases at day j, and the contagious period is made of r consecutive days, with R_k the marginal reproduction rate at day k of the contagious period, we have:

$$X_j = \sum_{k=1,r} R_k X_{j-k} \tag{1}$$

which can be written as $X = MR$, hence giving:

$$R = M^{-1}X \tag{2}$$

Some Results-Nigeria

We have:

$$M^{-1} = \begin{bmatrix} 164 & 161 & 133 \\ 161 & 133 & 149 \\ 133 & 149 & 141 \end{bmatrix}^{-1} = \begin{bmatrix} 0.01796807 & 0.01502897 & -0.0328302 \\ 0.01502897 & -0.02832263 & 0.01575332 \\ -0.03283028 & 0.01575332 & 0.02141264 \end{bmatrix}$$

Daily Reproduction numbers R_j

After deconvolution, we get:

$$R = \begin{bmatrix} 0.16177513 \\ 0.38618314 \\ 0.58115333 \end{bmatrix}$$

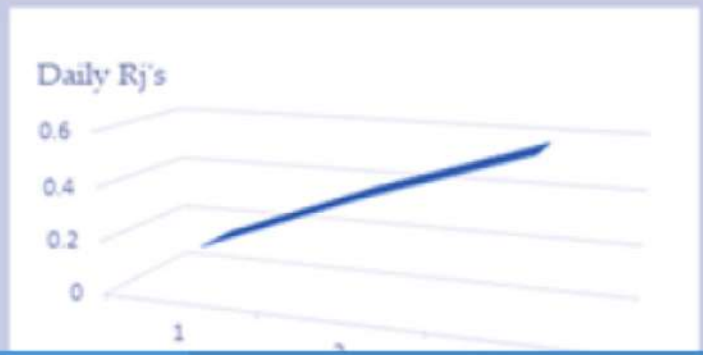
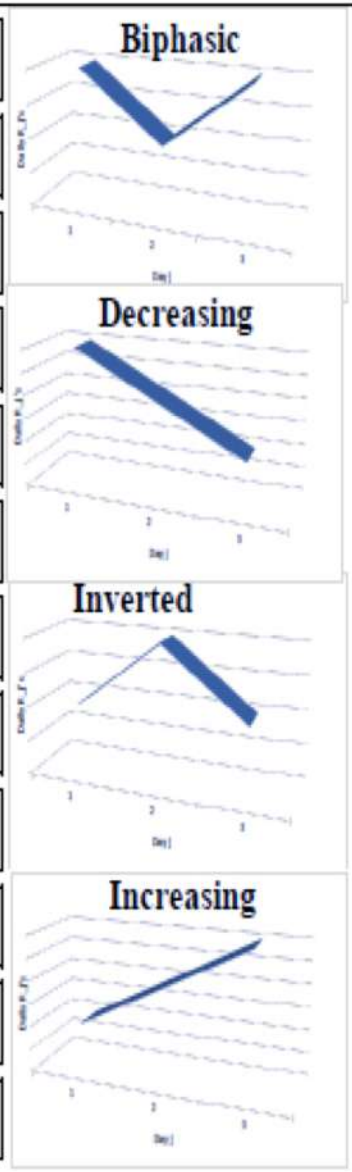


Table 2. Calculation of the daily R_j's for all countries and for the two first waves.

All countries		First wave		Second wave		
Country Name	**R0**	**R_j's**	**Biphasic**	**R0**	**R_j's**	**Biphasic**
AFGHANISTAN	0.65	0.17;0.09;0.39	YES	0.04	-1.38; -0.36; 1.78	INCR
ALGERIA	1.25	3.93;-6.21;3.53	YES	0.91	1.28;-1.06;0.69	YES
ARUBA	5.46	10.31;-39.32;34.47	YES	1.10	1.54;-1.60;1.16	YES
ANDORRA	1.36	1.00;0.79;-0.43	DECR	0.12	4.34;-1.63;-2.59	DECR
ANGOLA	0.63	0.33;1.42;-1.12	INV	1.70	9.22;-1.58;-5.94	DECR
ANTIGUA	1.92	0.00;1.25;0.67	INV	2.13	-0.40;1.33;1.20	INV
ALBANIA	0.96	0.48;0.50;-0.02	INV	0.66	1.98;-0.56;-0.76	DECR
ARGENTINA	0.73	0.57;-1.28;1.44	YES	0.36	1.27;0.75;-1.66	DECR
ARMENIA	4.43	17.99;-36.99;23.43	YES	0.86	1.41;-0.97;0.42	YES
AUSTRALIA	2.79	-1.02;3.47;0.34	YES	1.50	-0.88;0.68;1.70	INCR
AUSTRIA	1.17	-1.78;-0.05;3.00	INCR	2.08	0.62;-3.55;5.01	YES



Daily Reproduction numbers R_j

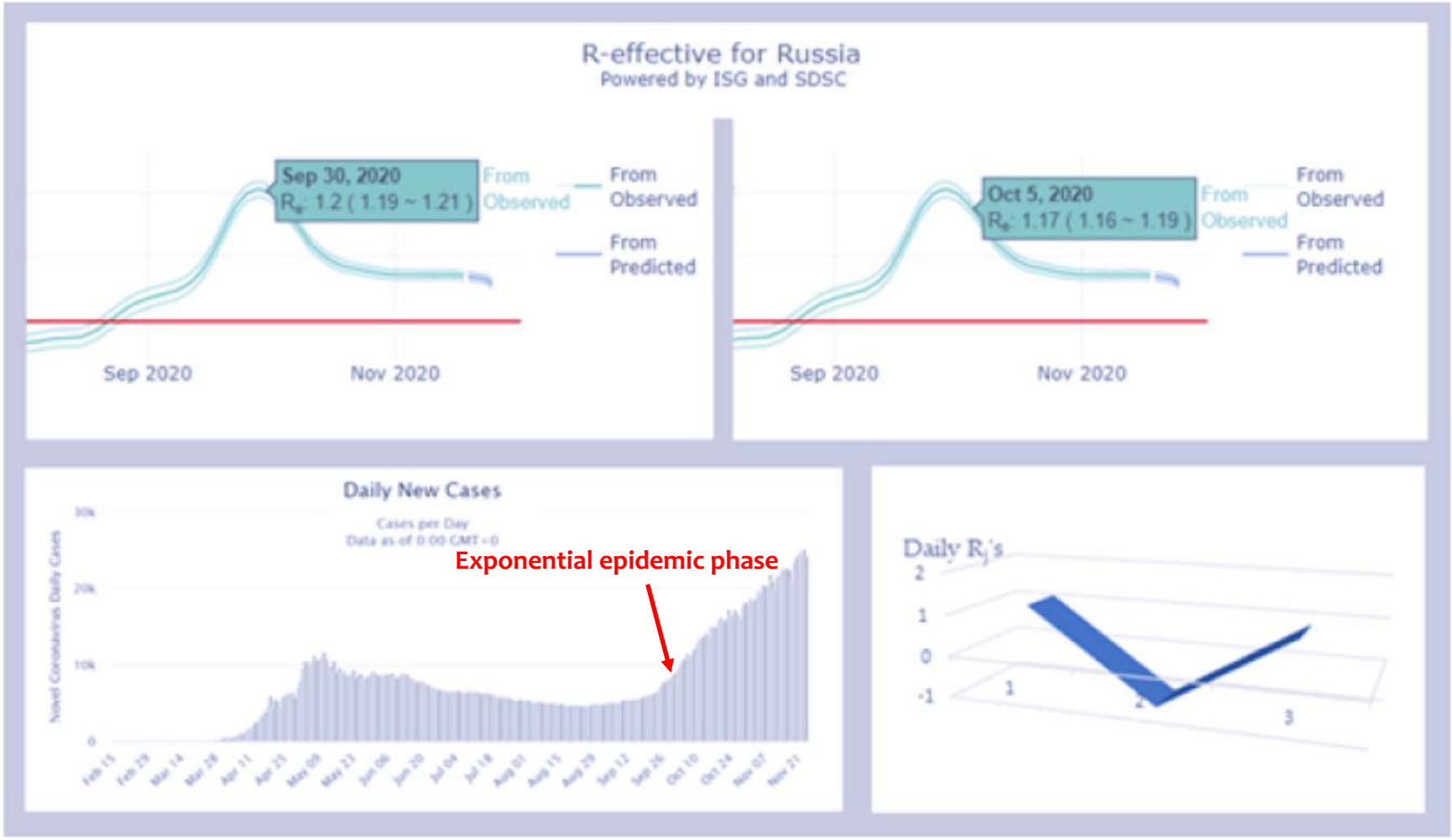
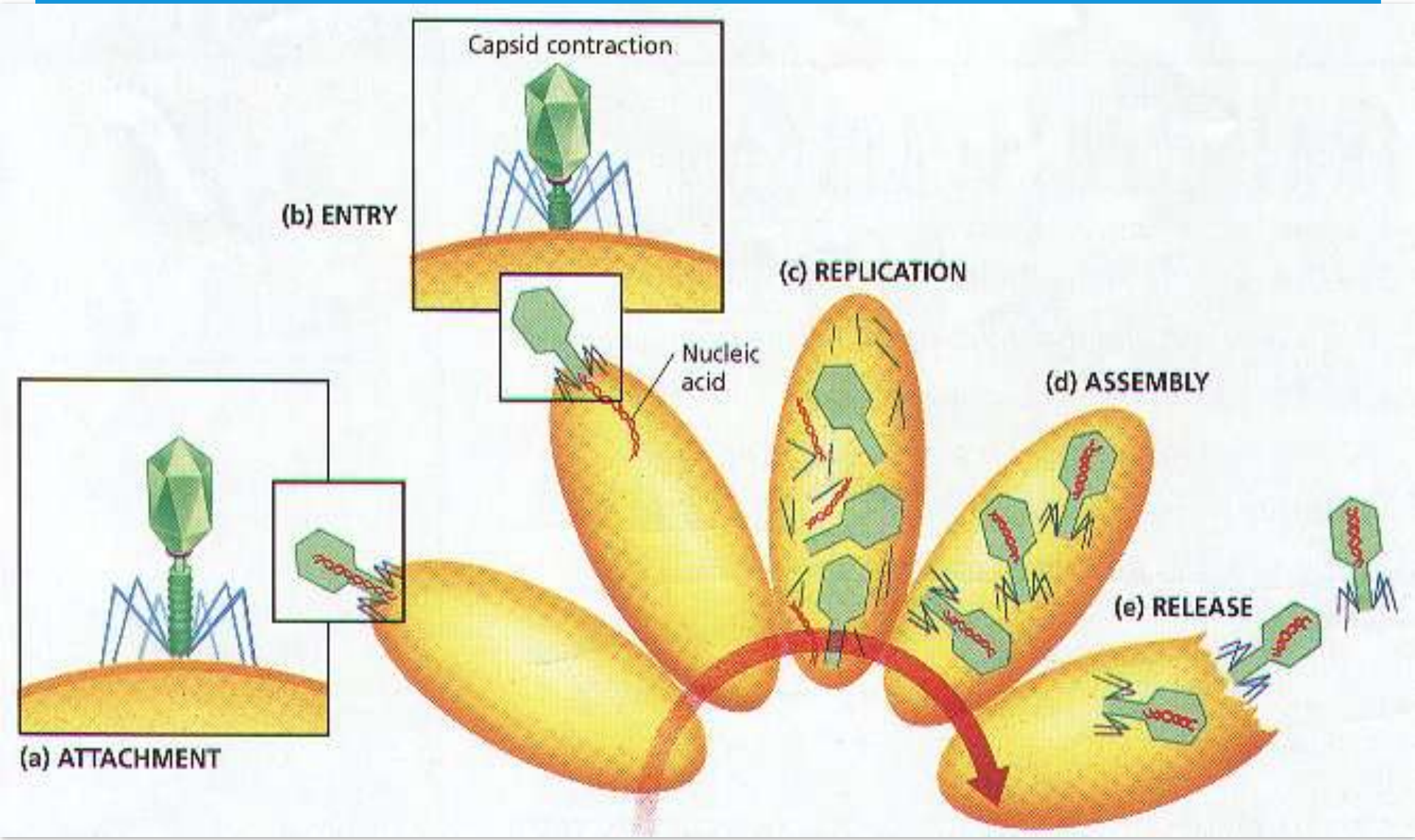


Figure: Top: estimation of the average transmission rate R_o for the 30th September and the 5th October 2020. Bottom left: Daily new cases in Russia between September 30 and October 5. Bottom right: V-shape of the evolution

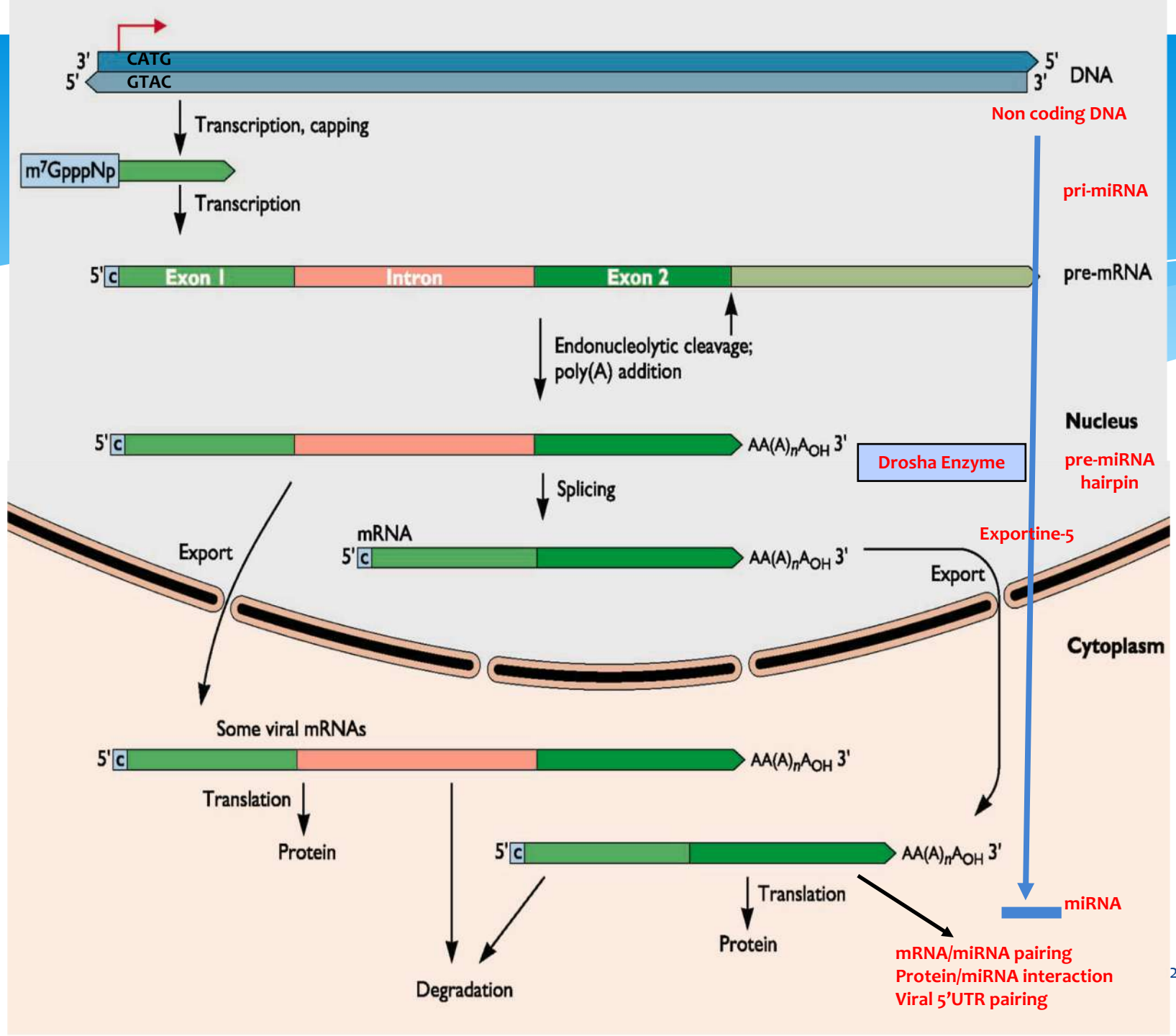
Mechanistic modelling

The µRNA-like model
(cluster bomb with cluster munitions)


Capsid contraction
(b) ENTRY
(c) REPLICATION
Nucleic acid
(d) ASSEMBLY
(e) RELEASE
(a) ATTACHMENT

Genomic

* Les bactériophages attaquent les bactéries (procaryotes)
* Les virus attaquent les cellules eucaryotes
* Tous deux utilisent la machinerie cellulaire pour fabriquer leurs macromolécules
* Dans l'hôte, ils provoquent soit un cycle lytique parasite, détruisant la cellule
* soit un cycle lysogénique commensal


3'
5'
CATG
GTAC
5'
3'
DNA
Non coding DNA
Transcription, capping
m7GpppNp
Transcription
pri-miRNA
5'
c
Exon 1
Intron
Exon 2
pre-mRNA
Endonucleolytic cleavage;
poly(A) addition
Nucleus
5'
c
AA(A)nAOH 3'
Drosha Enzyme
pre-miRNA
hairpin
Splicing
Exportine-5
Export
mRNA
5'
c
AA(A)nAOH 3'
Export
Cytoplasm
Some viral mRNAs
5'
c
AA(A)nAOH 3'
Translation
Protein
5'
c
AA(A)nAOH 3'
Translation
Protein
miRNA
Degradation
mRNA/miRNA pairing
Protein/miRNA interaction
Viral 5'UTR pairing

Homo sapiens hemoglobin subunit beta (HBB), mRNA NCBI Reference Sequence: NM_000518.5

ACATTTGCTTCTGACACAACTGTGTTCACTAGCAACCTCAAACAGACACCATGGTGCATCTGACTCCTGA

GGAGAAGTCTGCCGTTACTGCCCTGTGGGGCAAGGTGAACGTGGATGAAGTTGGTGGTGAGGCCCTGGGC

TGGGAGCAGCAAGAGAACCGT mir-451b

AGGCTGCTGGTGGTCTACCCTTGGACCCAGAGGTTCTTTGAGTCCTTTGGGGATCTGTCCACTCCTGATG

TACAGTATAGATGATGTACT miR-144-3p

CTGTTATGGGCAACCCTAAGGTGAAGGCTCATGGCAAGAAAGTGCTCGGTGCCTTTAGTGATGGCCTGGC

TCACCTGGACAACCTCAAGGGCACCTTTGCCACACTGAGTGAGCTGCACTGTGACAAGCTGCACGTGGAT

AAACCGTTACCATTAC

CCTGAGAACTTCAGGCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCATCACTTTGGCAAAGAATTCA

TGAGTT mir-451a TATTGCACTTGTCCCGGCCTGT miR-92a-3p

CCCCACCAGTGCAGGCTGCCTATCAGAAAGTGGTGGCTGGTGTGGCTAATGCCCTGGCCCACAAGTATCA

5′-TTTTCACCTTTACTACGCC-3′ Protein S Covid-19

CTAAGCTCGCTTTCTTGCTGTCCAATTTCTATTAAAGGTTCCTTTGTTCCCTAAGTCCAACTACTAAACT

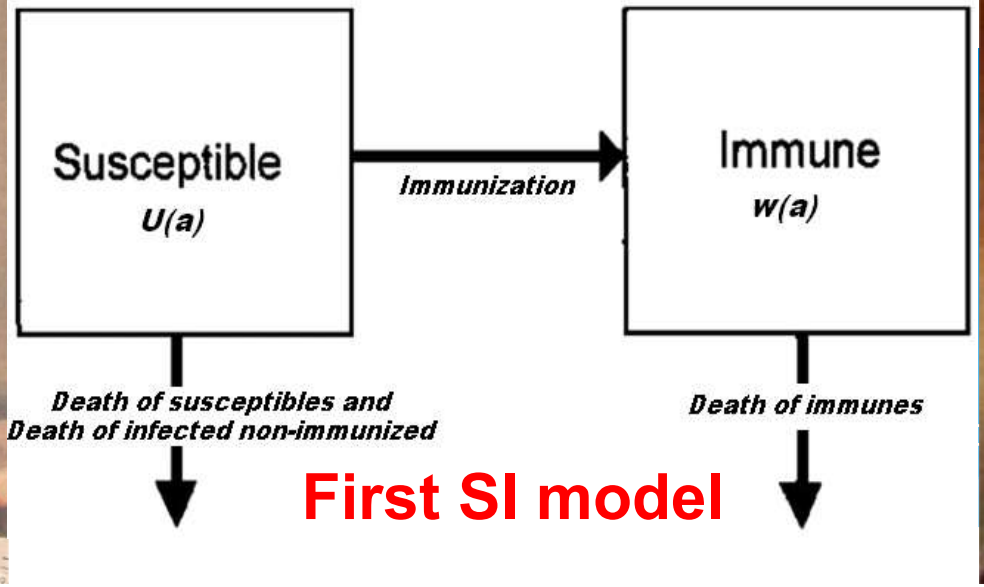
AGGTTGGGATCGGTTGCAATG miR-92a-1-5p

GGGGGATATTATGAAGGGCCTTGAGCATCTGGATTCTGCCTAATAAAAAACATTTATTTTCATTGCAA

Figure 2. Human beta-globin gene [24] potentially targeted by a subsequence from Covid-19 protein S [23] (in blue), by microRNA miR-93a known for inhibiting its translation [25] (in green) and by microRNAs involved in erythrocyte maturation [26-31] (in red).

Continuous modelling

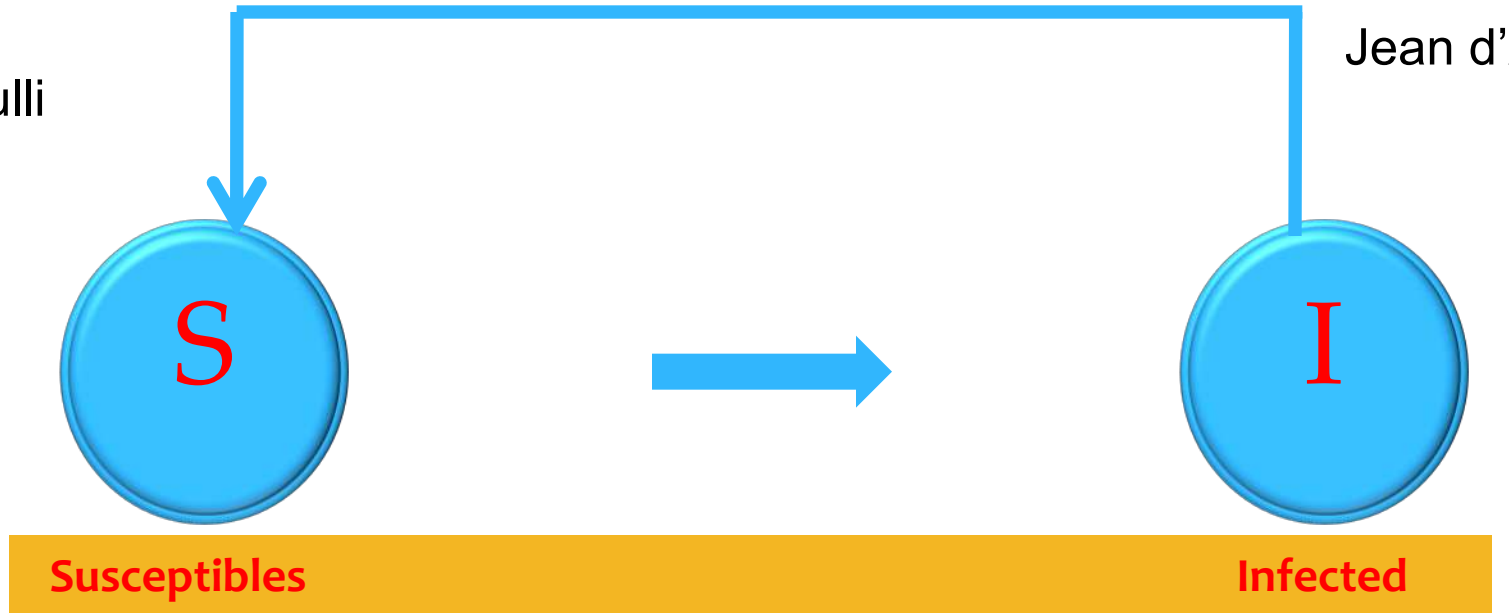
The SIR model



First SI model

Daniel Bernoulli

Jean d'Alembert



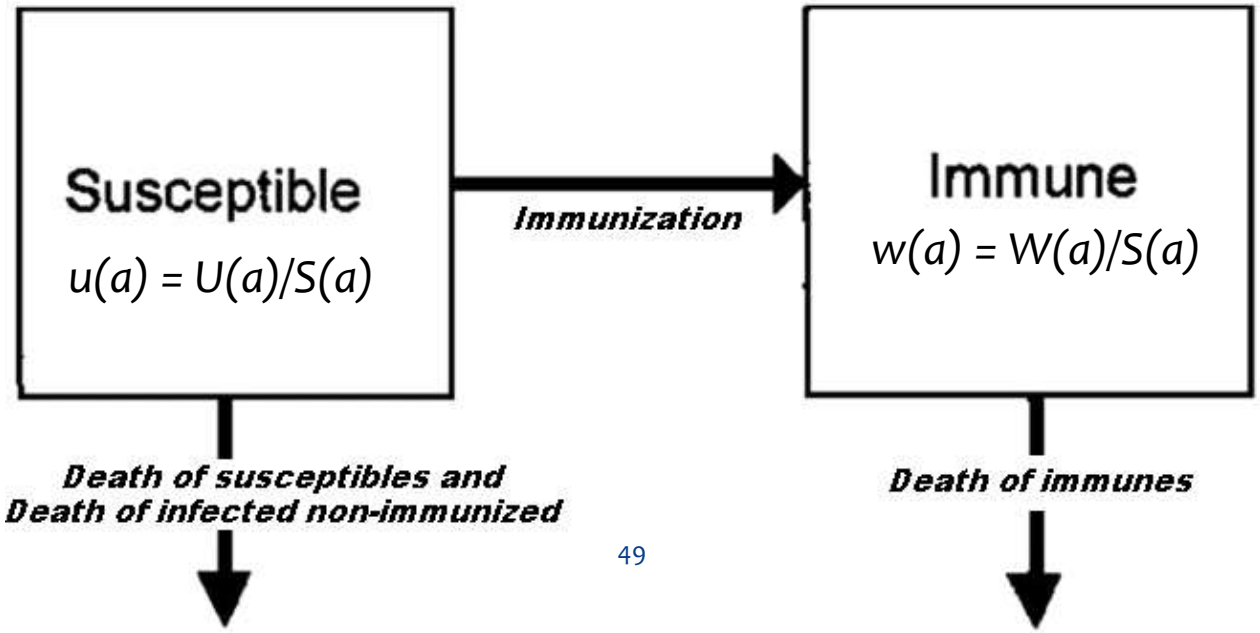
* This model assumes there is no immunity.

States variables

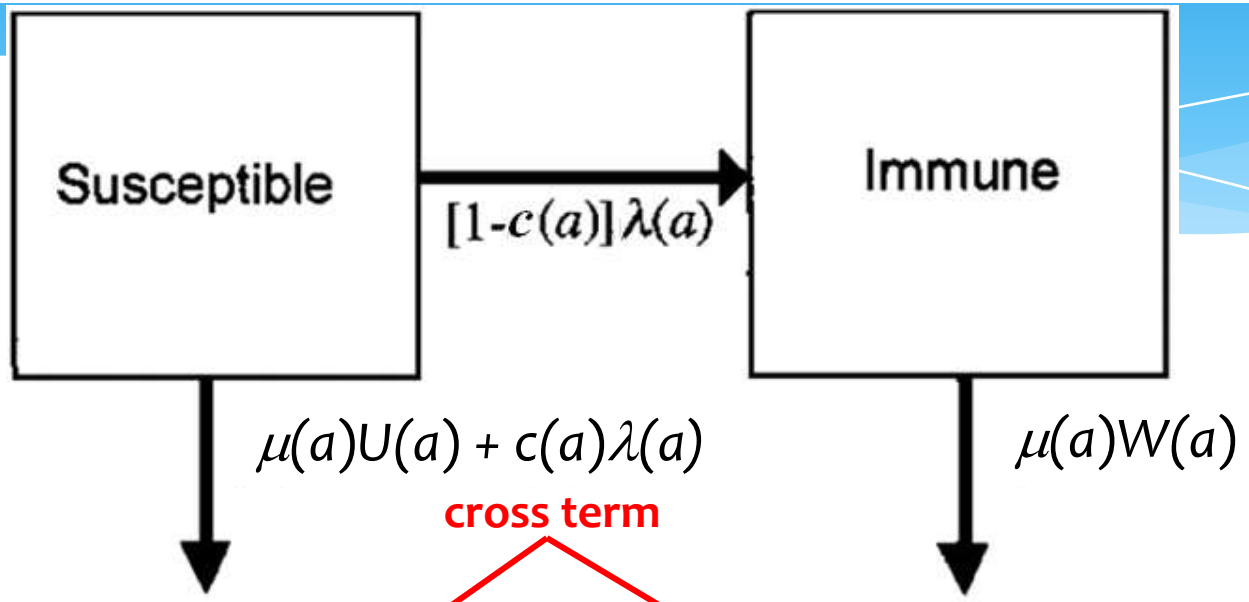
Population divided into: **susceptible**, *not yet been infected,* **infected** *and* **immune**, immunized *for the rest of their life after one infection.*

- ***u(a):*** *probability for a newborn individual to be susceptible (and alive) at age a.*
- ***w(a):*** *probability to be immune (and alive) at age a.*

$S(a) = U(a)+\lambda(a)+W(a)$



Differential equations



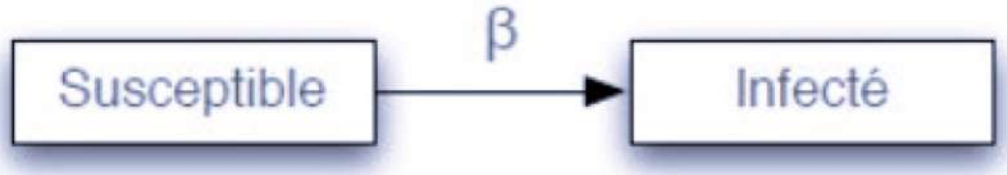
$$\frac{du}{da} = -[\lambda(a) + \mu(a)]u(a)$$

$$\frac{dw}{da} = [1 - c(a)]\lambda(a)u(a) - \mu(a)w(a)$$

After D. Bernoulli

* Hamer (1906) postulated that the course of an epidemic depends on the ***rate of contact between susceptibles and infectious individuals***. This notion has become one of the most important concepts in mathematical epidemiology:
* This so called "mass action" principle of transmission for directly transmitted viral and bacterial infections is based on the idea that the net rate of spread of infection is proportional to the product of the densities of susceptible and infectious persons. The idea was originally formulated in a discrete-time model.
* In 1908, Ronald Ross (celebrated as the discoverer of malaria transmission by mosquitoes) translated the problem into a continuous time framework in his pioneering work on the transmission dynamics of malaria (Ross, 1915; Ross and Hudson, 1917).
* Anderson G McKendrick (1927), extended and explored in more detail the ideas of Hamer and Ross.

Model SI Hamer (1906)

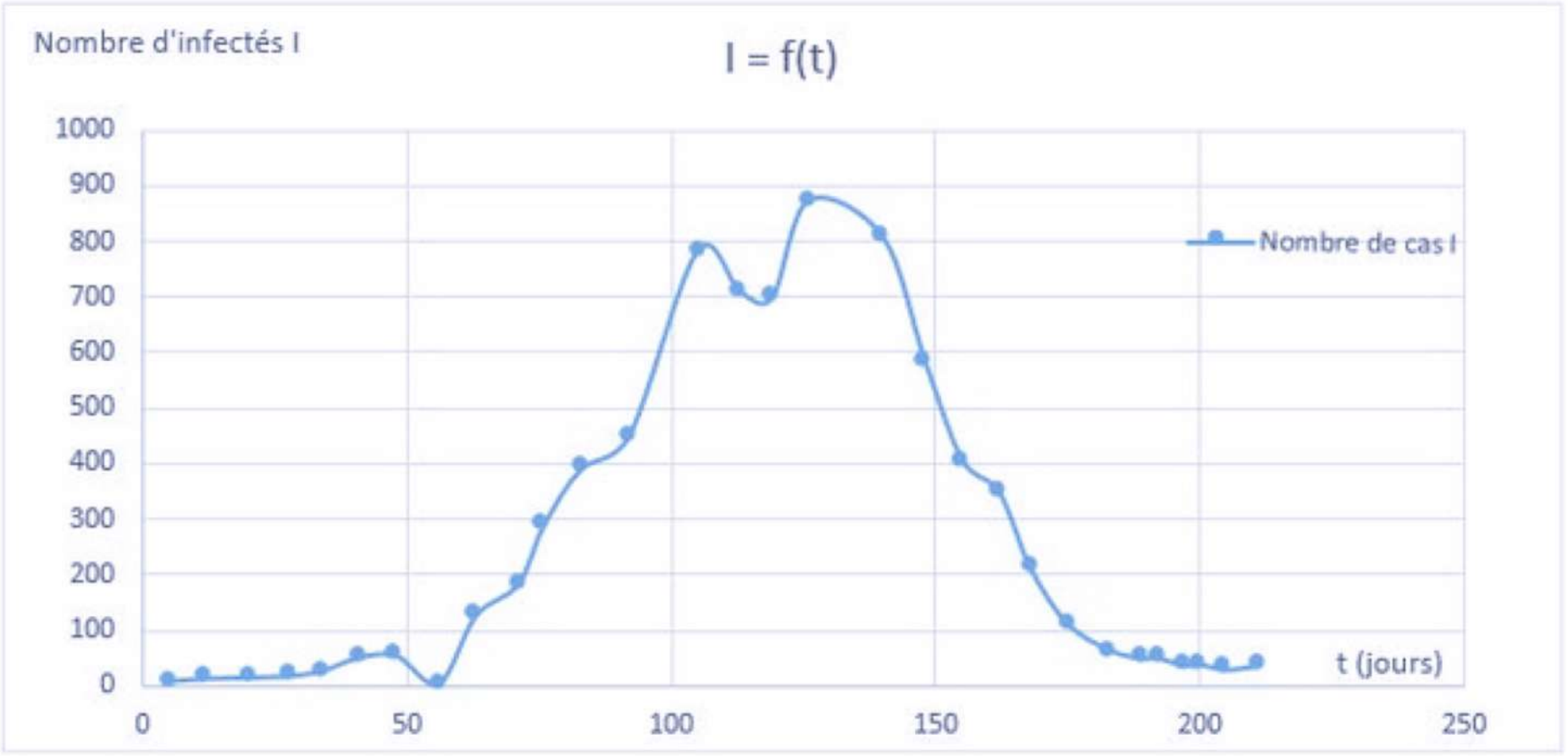


Et le système d'équations différentielles (A) à résoudre est :

$$\begin{cases} \frac{dS}{dt} = -\beta SI \\ \frac{dI}{dt} = \beta SI \end{cases}$$

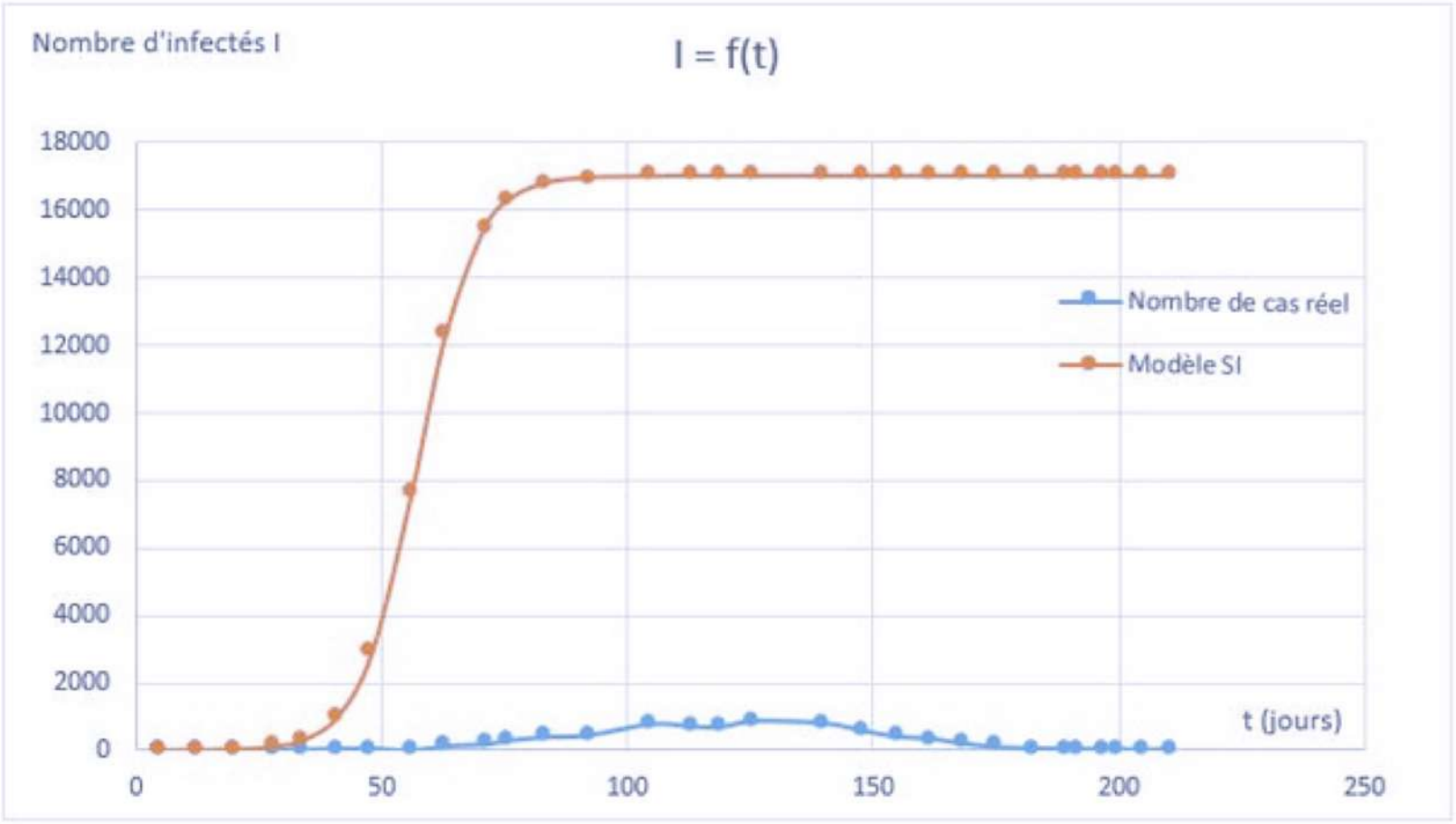
Jakob Bernoulli, uncle of Daniel

$$I = \frac{1}{\left(1 - \frac{1}{N}\right) e^{-\beta N t} + 1/N} = \frac{N}{(N-1)e^{-\beta N t} + 1}$$



Courbe 1 : Nombre d'infectés pendant l'année 1906 à Bombay

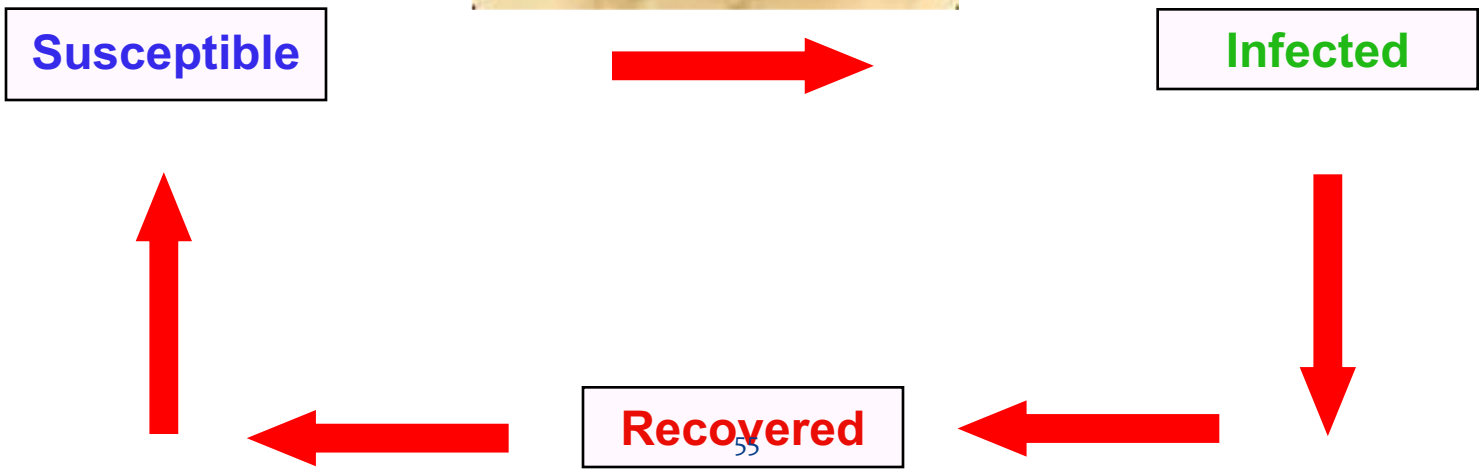
Superposons la courbe modèle avec un facteur β pas trop élevé (1 pour 100 000). Un membre du groupe I contaminera 1 membre du groupe S sur 100 000 chaque jour.



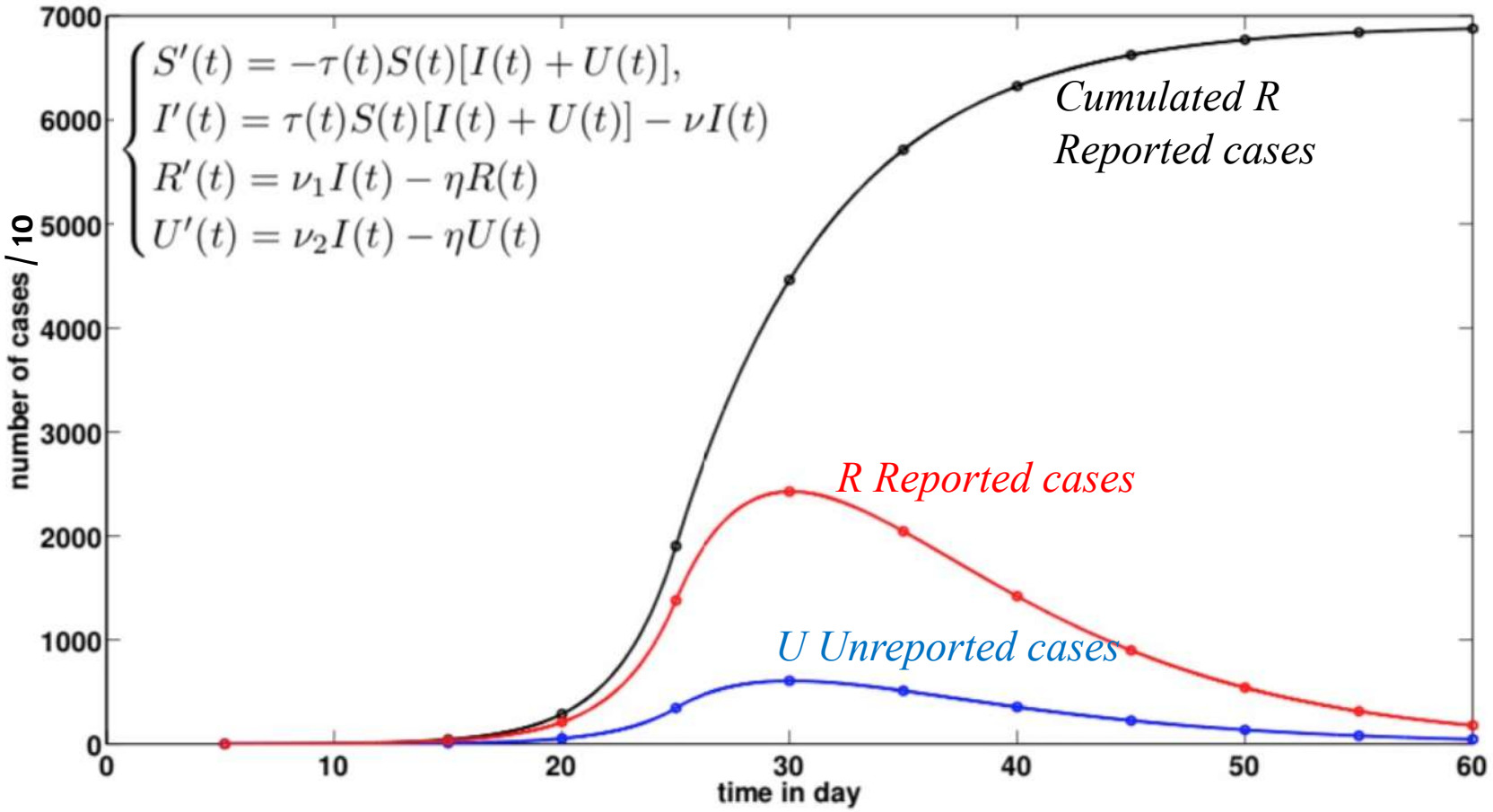
Courbe 2 : Modèle SI

SIRS model
Ross (1916) & McKendrick (1925)

Ronald Ross



Covid-19 dynamics



China 4/5/2020 Cases 82,880 New cases +3 Deaths 4,633

Liu, Z.; Magal, P.; Seydi, O.; Webb, G. Understanding Unreported Cases in the COVID-19 Epidemic Outbreak in Wuhan, China, and the Importance of Major Public Health Interventions. *Biology* 2020, 9, 50.

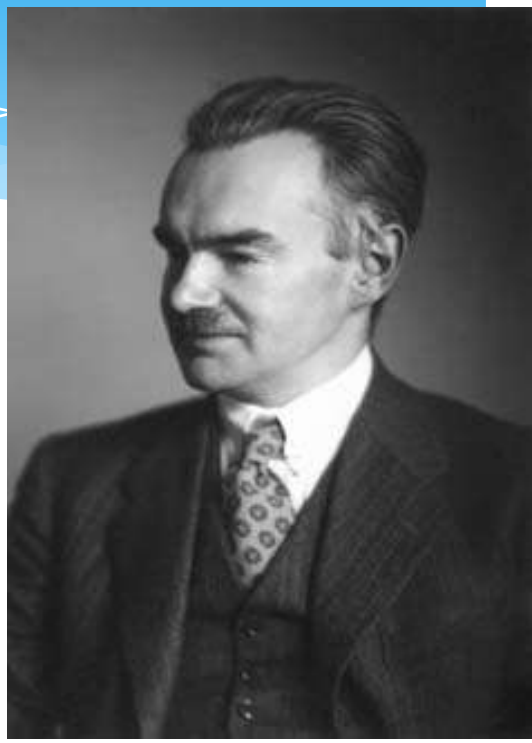
Many thanks for your attention !

NB

* Pierre Magal and myself are responsible of a peer-reviewed special issue on covid-19 modelling in *Biology*, Section Theoretical Biology in which you are invited to publish: www.mdpi.com/journal/biology/special_issues/COVID-19_Epidemic

Anderson G McKendrick's life

Edinburgh, September 8, 1876 - Edinburgh, May 30, 1943



* The fifth and last child of John Gray McKendrick FRS, a distinguished physiologist, trained as a doctor at the University of Glasgow, and joined the Indian Medical Service
* His primary interest was in research, and he became director of the Pasteur Institute at Kausali in the Punjab. He settled in 1920 in Edinburgh where he became Superintendent of the Laboratory of the Royal College of Physicians of Edinburgh for the rest of his life.
* McKendrick's career as a mathematical epidemiologist began in India. He worked with **Ronald Ross** and eventually would continue his work.

Hamer model with mortality

$$\frac{dS}{dt} = -rSI + \gamma I \qquad S(0) = S_0$$

$$\frac{dI}{dt} = rSI - \gamma I \qquad I(0) = I_0$$

* Note: S + I = N

The Steady State Equations

$$S_1 = N \qquad I_1 = 0$$

$$S_2 = \frac{\gamma}{r} \qquad I_2 = N - \frac{\gamma}{r}$$

There is in the population always the unstable steady state (S_1,I_1) "eradication" and the stable steady state (S_2,I_2) "disease endemic".

Probabilistic approach

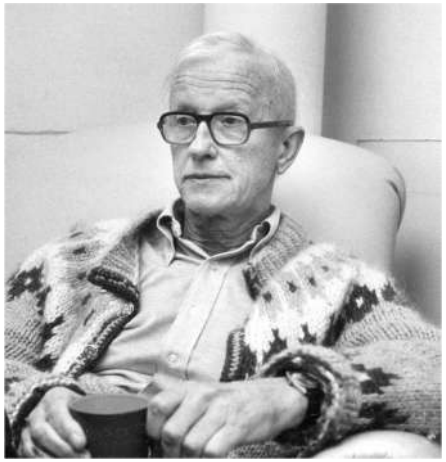
At least one event (contact ν, birth f, death μ) in $(t, t+dt)$, where $I=N-S$:

$$P(S(t+dt)=k) = (1-\nu(N-k)dt)\, P(S(t)=k) + f dt\, P(S(t)=k-1) - \mu dt\, P(S(t)=k+1)$$

By multipyling by s^k and summing over k, we prove **if *S* and *I* are independent**, that they are Poisson, whose parameter $E(S)$ verifies (by multiplying by k and summing):

$$dE(S)/dt \approx f\,E(S) - \nu\,E(SI) - \mu E(S)$$
$$\approx -\nu\,E(S)\,E(I), \text{ if } f = \mu$$

Stability parameter = KS evolutionary entropy of the corresponding Markov process



M. Delbrück 1940

M. DELBRÜCK. Statistical fluctuations in autocatalytic reactions. *Journal of Chemical Physics* **8,** 120–124 (1940)

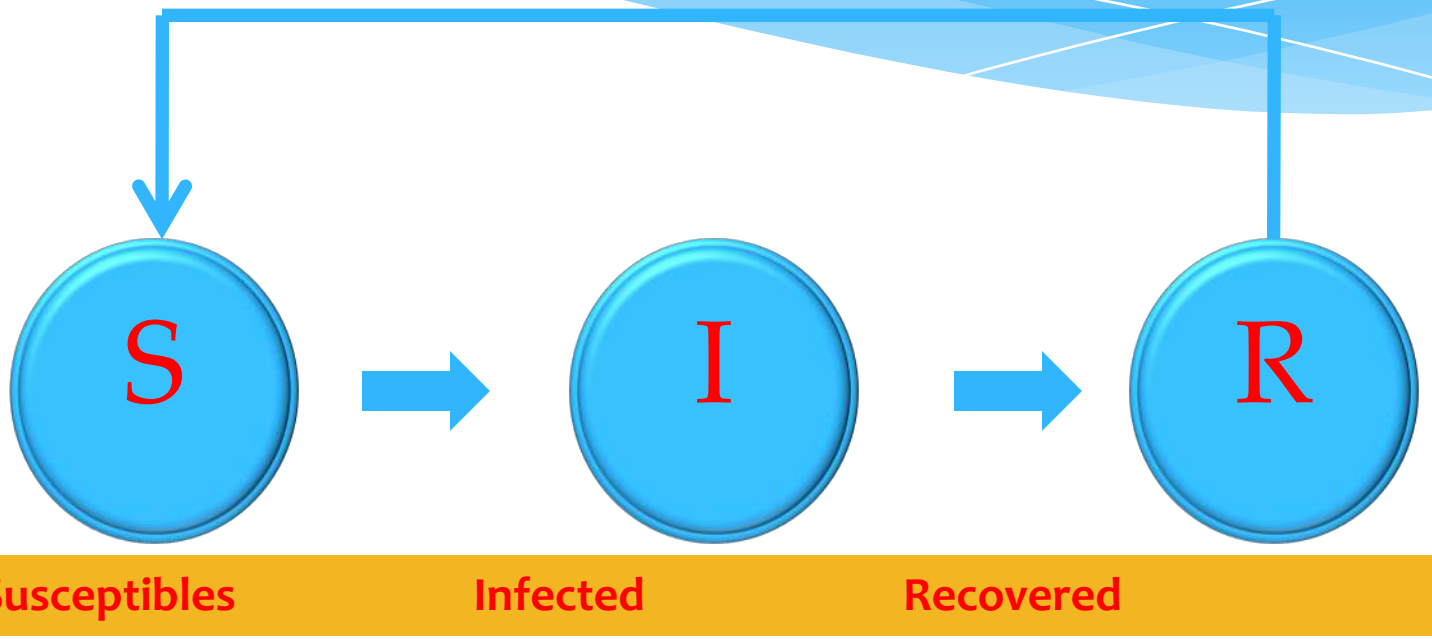
C.J. RHODES & L. DEMETRIUS. Evolutionary entropy determines invasion success in emergent epidemics. *PloS ONE*, **5,** e12951 (2010).

J. DEMONGEOT & L. DEMETRIUS. Complexity and Stability in Biological Systems. *Int. J. Bifurcation & Chaos*, **25,** 40013 (2015).

Applied mathematics

* In 1914 McKendrick published a paper in which he gave equations for the ***pure birth process*** and a particular ***birth-death process.***
* His 1925 paper, ***'Applications of mathematics to medical problems***' was particularly impressive. Some of its results for stochastic models of epidemics and population growth were rediscovered by William Feller in 1939. ***Feller*** remarks in his Introduction to the Theory of Probability & its Applications (3rd edition p. 450), "*It is unfortunate that this remarkable paper passed practically unnoticed*." The same paper is also the earliest reference in ***Dempster*** et al.'s 1977 paper that defined and popularized the EM algorithm (Expectation-maximization algorithm).
* In 1927 McKendrick began a collaboration with W. O. Kermack (1898 - 1970) which produced a notable series of papers. The first paper (1927) gave the differential equations for a ***deterministic general epidemic***.

The SIRS model



The SIRS model allows for a loss of immunity causing recovered individuals to become susceptible again.

The SIRS Model Equations

$$\frac{dS}{dt} = -rSI + \gamma R \qquad S(0) = S_0$$

$$\frac{dI}{dt} = rSI - aI \qquad I(0) = I_0$$

$$\frac{dR}{dt} = aI - \gamma R \qquad R(0) = 0$$

The Steady State Equations

$$S_1 = N \qquad I_1 = 0 \qquad R_1 = 0$$

$$S_2 = \frac{a}{r} \qquad I_2 = \gamma \frac{N - S_2}{a + \gamma}$$

$$R_2 = \frac{aI_2}{\gamma}$$

There is in the population always the steady state (S_1,I_1,R_1) "eradication" and if N>a/r, steady state (S_2,I_2,R_2) "disease endemic".

Threshold value

* The existence of a critical threshold density of susceptibles for the occurrence of a major epidemic can be deduced in a heuristic manner, via inspection of the right-hand side of equation.
* Following the introduction of a few infected into a susceptible population, a major epidemic is to occur, if the rate of increase in the density of infected is positive, ie the term $\beta X > v$. More formally, the critical density of susceptibles, $N\tau$, is given by:

$$N\tau = v/\beta$$

* No epidemic can occur unless the population of susceptibles exceeds this value (the recovery rate, v, divided by the transmission coefficient, β), and if it does exceed this value then the size of the epidemic (to a first approximation) is roughly equivalent to $2n$ times the degree to which the initial population density of susceptibles exceeds the critical value [$n = N(0) - N\tau$].
* Thus at the end of the epidemic the density of susceptibles will be as far below the threshold density, as initially it was above.

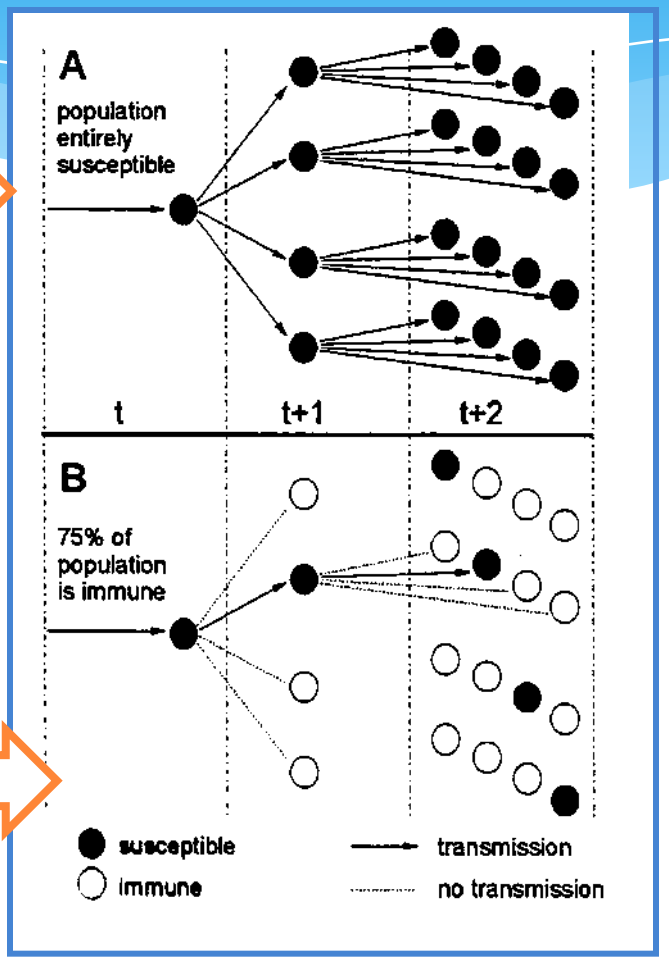
R_0 Basic reproductive number of infection

* Embodied within the threshold density concept, Kermack and McKendrick introduce the ***Ro*** parameter, in their analyses of the behaviour of the simple model.,
* ***Ro*** defined as ***Ro = βN/v;*** records the average number of secondary cases of infection produced by one primary case in a totally susceptible population.
* Kermack and McKendrick did not use the notion of a basic or case reproductive rate, analogous to Fisher's concept of a net reproductive rate, which is widely used in the disciplines of population genetics, ecology and demography (Fisher, 1930).
* For an infectious agent to spread in a population it is intuitively obvious that **Ro ≥1**. If this condition is not satisfied the infection will die out (see Ross, 1915; Macdonald, 1957).

Evaluation of the potential for spread of an infection

$R_0 = 4$
with whole population susceptible

$R_0 = 4$
with 75% population immune
(25% susceptible)



Duration of infection

* When both infectivity and recovery are functions of the duration of infection in an individual (e.g. distributed infectious and recovery rates). If we denote β and v as functions of the time s since infection then Ro is defined as:

$$R_0 = N \int_0^\infty \beta(s) \exp\left[-\int_0^s v(a)\, da \right] ds.$$

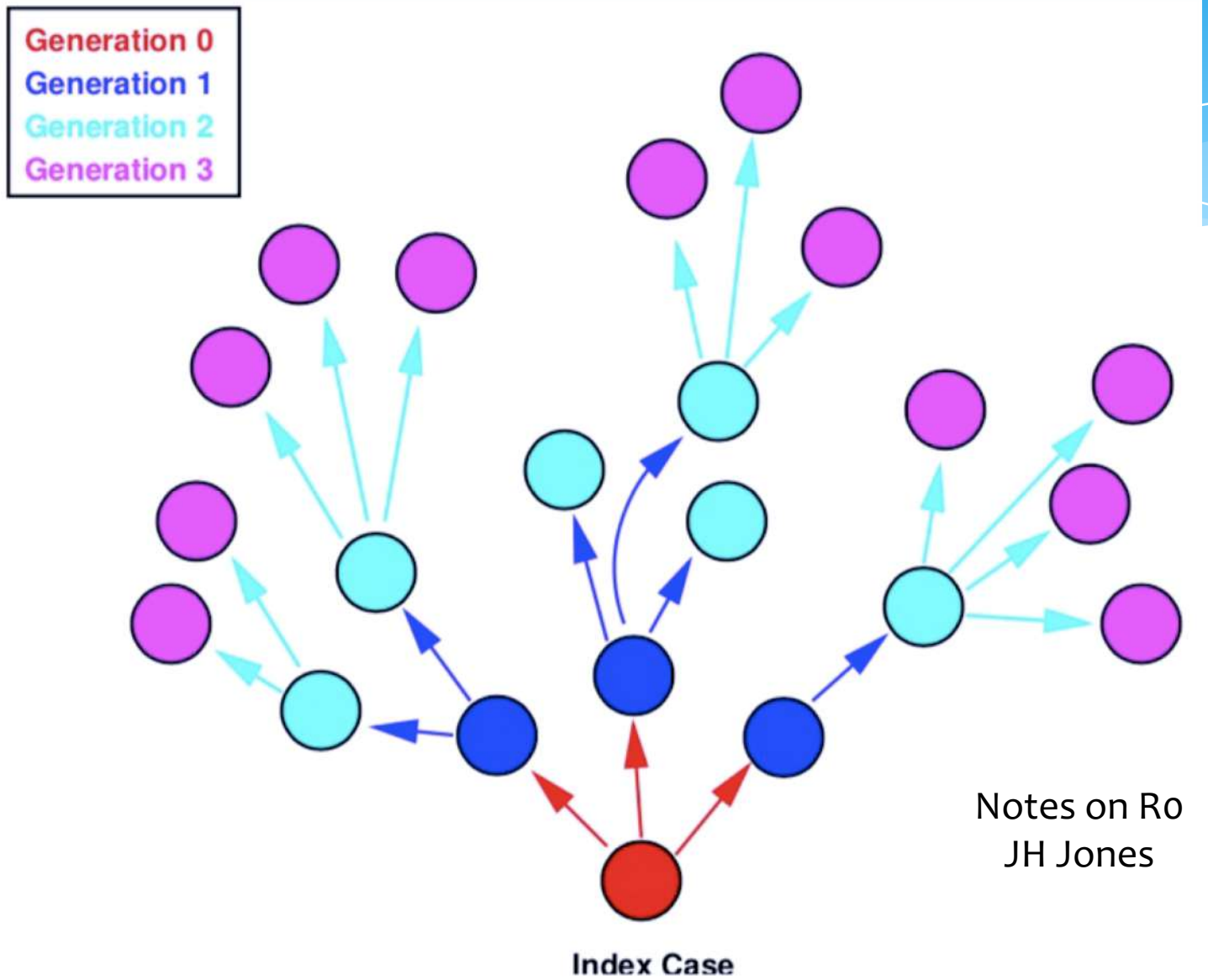
* Hence the threshold density, Nr, is given by

$$N_T = 1 / \left[\int_0^\infty \beta(s) \exp\left[-\int_0^s v(a)\, da \right] ds \right]$$

* A further problem addressed by Kermack and McKendrick was the issue of what fraction of the population will be infected during the course of an epidemic in a closed population. If we denote this fraction as I then in the general case, where a small fraction I(0) is infected at time t = 0.

$$I = 1 - (1 - I(0)) \exp(-R_0 I).$$

Ro



Notes on Ro
JH Jones

R_0

From The Editor

By Chris Evans, Editor

The best of *The Telegraph's* articles, sent by the Editor

Dear reader,

The Government's new "Stay Alert" message is now in full force and adverts are continually springing up to remind us of the importance of "controlling the R rate" to save lives. Sarah Knapton, our science editor, explains precisely what the R rate is in this excellent piece and analyses how reopening schools might impact on it.

R_0

The average number of secondary cases arising from an average primary case in an entirely susceptible population.

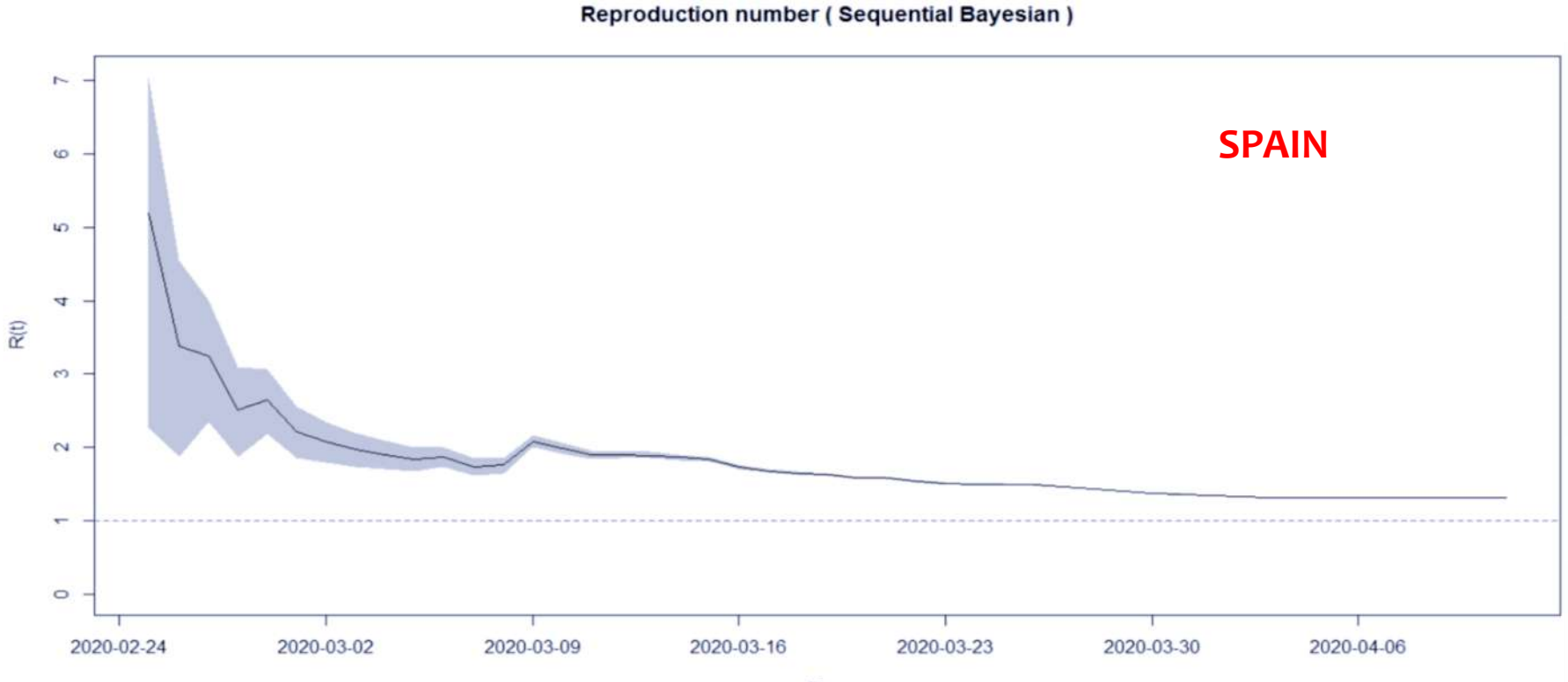
The basic reproduction number (basic reproductive rate, basic reproductive ratio R_0) of a contagious disease is the number of cases than a case of the disease generates (on an average) over the course of its infectious period in a susceptible population.

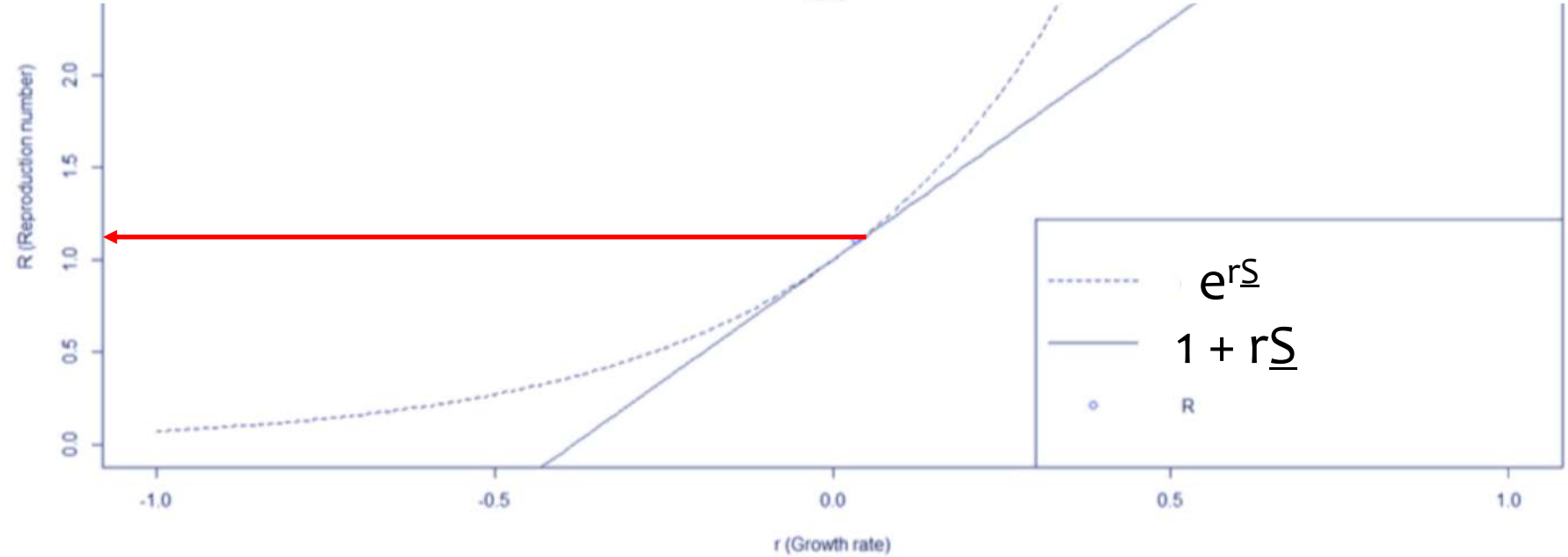
* If a<<1, then dI/dt = νSI, dLogI/dt = νS, and if I(0) = 1 and S is quasi-constant at start of the epidemic:

$$\mathrm{Log}(I(t)) = \nu \int_{[0,\tau]} S(\tau)d\tau \approx \nu \underline{S} t \ ,$$

if $\mathrm{Log}(I(t)) \approx \mathrm{Log}(R_0)t$, then

$$R_0 \approx e^{\nu \underline{S}} \approx 1+\nu \underline{S}, \text{ if } \nu \underline{S} << 1$$


Reproduction number (Sequential Bayesian)
SPAIN
R(t)
0
1
2
3
4
5
6
7
2020-02-24
2020-03-02
2020-03-09
2020-03-16
2020-03-23
2020-03-30
2020-04-06
Time


R (Reproduction number)
0.0
0.5
1.0
1.5
2.0
-1.0
-0.5
0.0
0.5
1.0
r (Growth rate)
e^{rS}
$1 + rS$
R

021

Restrictions :

- If S(0) is very large and I(0) small, then let use a saturation term rSI/(1+S)
- If the total population remains stable (f=μ), then S+I=N and S and I are not independent
- If the population is heterogeneous (e.g., if infectivity and susceptibility depends on age), then R_0 does not represent the initial exponential growth rate of infected

Modèle auto-régressif ARp

On dit que (X_t) est un processus **auto-régressif d'ordre** p (centré) s'il s'écrit

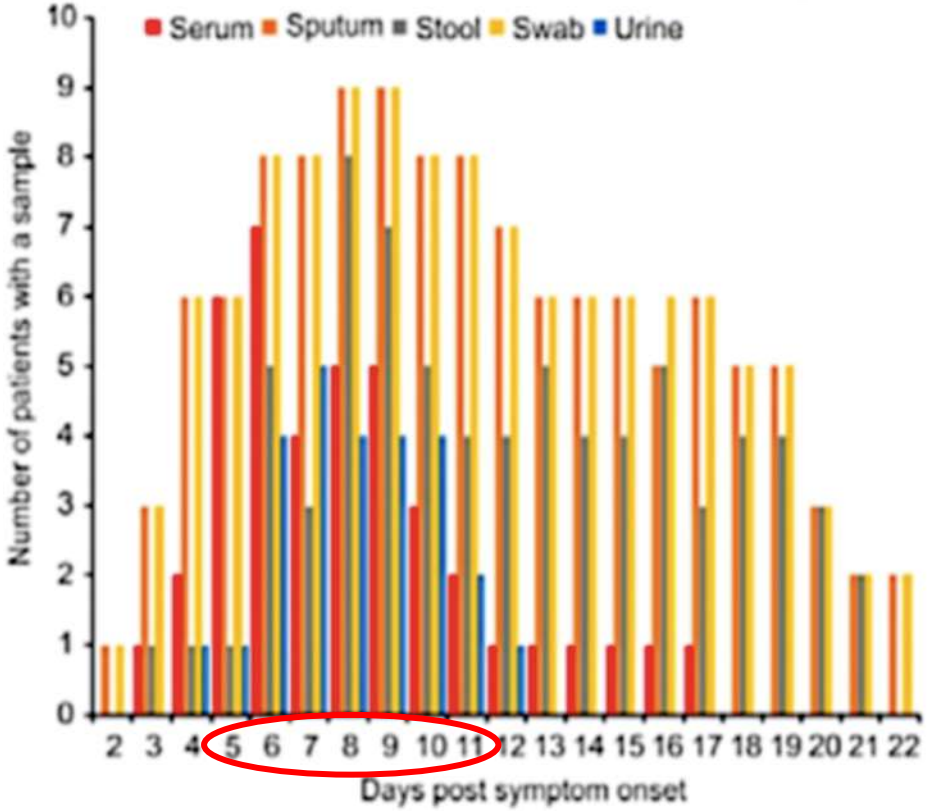
$$X_t = \epsilon_t + \sum_{j=1}^{p} a_j X_{t-j}, \tag{1}$$

où ϵ_t est un bruit blanc centré de variance σ^2.

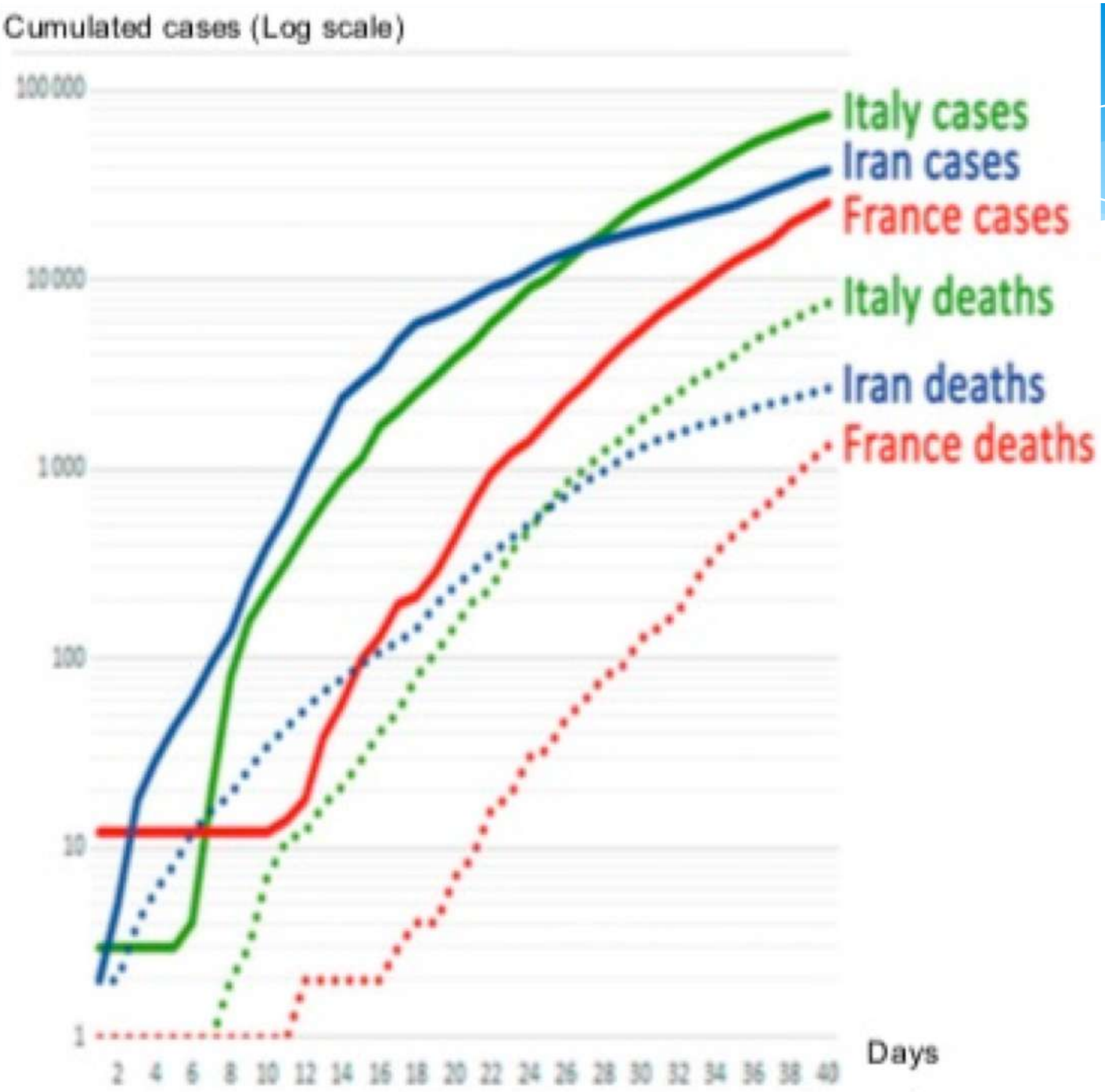
X_t est alors :

- la somme d'un choc aléatoire à l'instant t, ϵ_t, indépendant de l'historique
- d'une fonction linéaire de son passé $\sum_{j=1}^{p} a_j X_{t-j}$

Country	ARIMA (3,1,0) Residual STD	ARIMA (4,1,0) Residual STD	ARIMA (5,1,0) Residual STD	ARIMA (6,1,0) Residual STD	ARIMA (3,1,1) Residual STD
France	51.85	46.80	45.83	41.25	48.06
Italy	252.72	198.51		184.90	230.10
Germany	99.98	99.97	99.96	95.54	99.97
Chile	1.99	2.00		1.78	
China	361.52	344.30	343.50	342.61	349.15



J. DEMONGEOT, Y. FLET-BERLIAC & H. SELIGMANN Temperature decreases spread parameters of the new covid-19 cases dynamics. *Biology (Basel)*, **9,** 94 (2020).


Cumulated cases (Log scale)
100 000
10 000
1 000
100
10
1
2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40
Days
Italy cases
Iran cases
France cases
Italy deaths
Iran deaths
France deaths

Linear prediction before and after inflexion

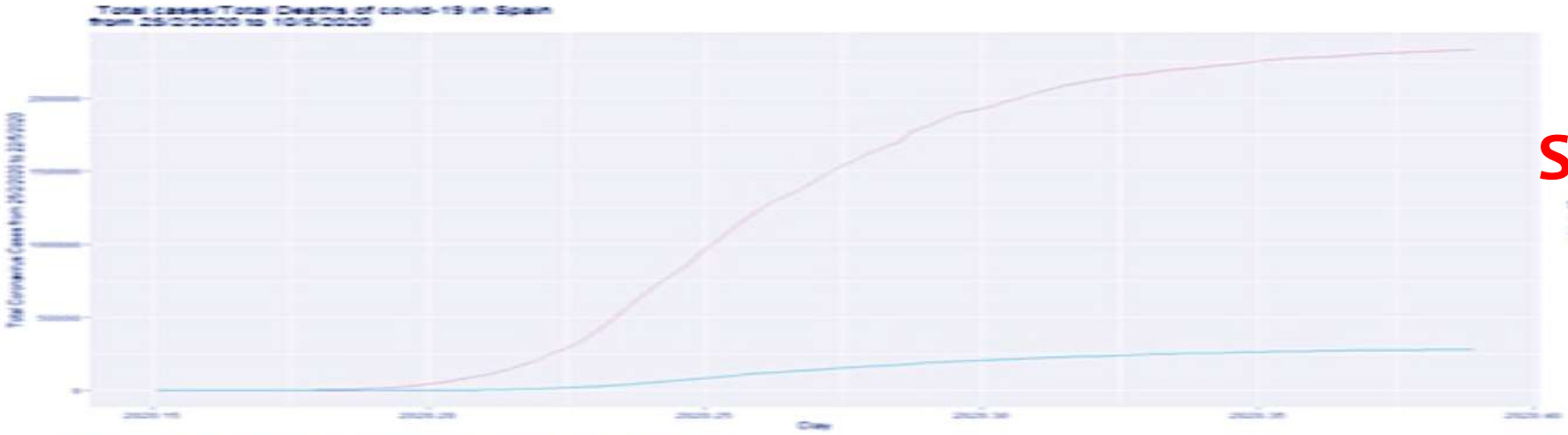
		Before resp. date (sd)		After resp.date (sd)	
Country	Trend change	Linear term	Quad. term	Linear term	Quad. term
Germany	2020-04-04	0.3860(0.0322)	-0.0051(0.0008)	-0.0638(0.0091)	3e-04(4e-04)
French	2020-04-01	0.4094(0.0238)	-0.0054(0.0006)	-0.0508(0.0220)	0(0)
Italy	2020-03-22	0.3410 (0.0205)	-0.0045 (0.0006)	-0.0090 (0.0049)	-5e-04 (2e-04)
Morocco	2020-04-17	0.1882(0.0382)	-0.0018(0.0011)	0.0025 (0.0254)	-6e-04(7e-04)
UK	2020-04-12	0.3403 (0.0169)	-0.0037 (0.0004)	0.0230 (0.0101)	-9e-04 (3e-04)
USA	2020-04-26	0.4489(0.0251)	-0.0048(0.0004)	-0.0092 (0.0217)	1e-04 (8e-04)
Spain	2020-04-01	0.3957(0.0267)	-0.0051(0.0006)	-0.0639 (0.0131)	0 (3e-04)

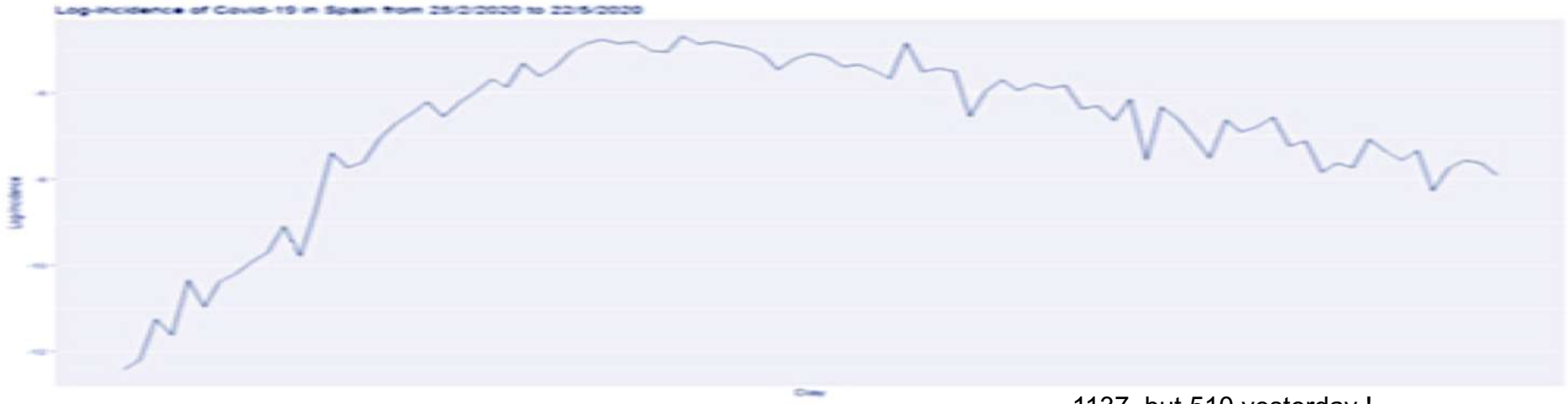
L. Hobbad, M. Alahiane, M. Rachdi, I. Ouassou

Now | Yesterday | 2 Days Ago | Columns | Search:

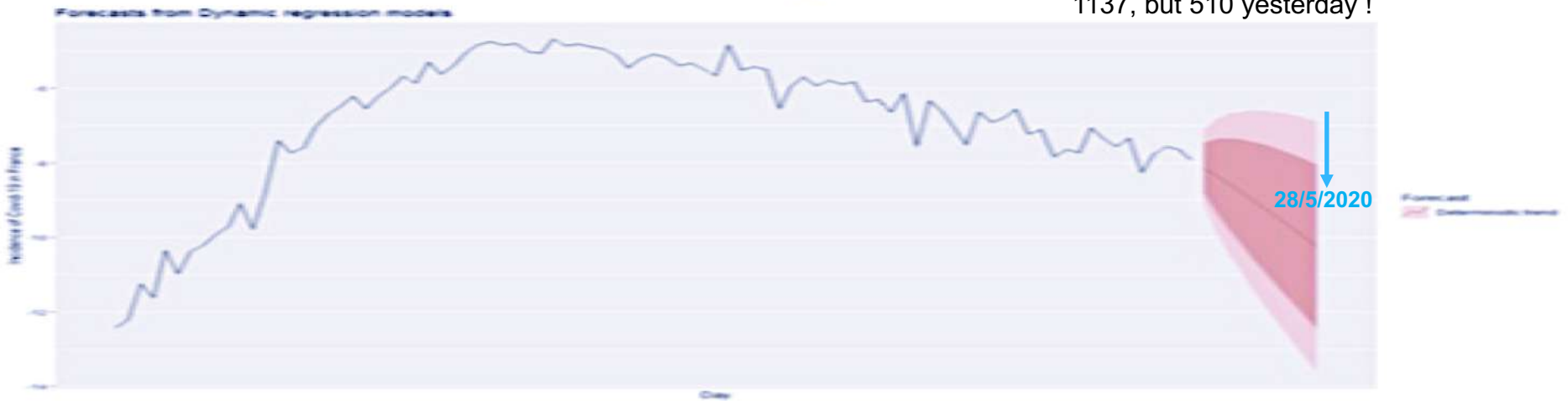
All | Europe | North America | Asia | South America | Africa | Oceania

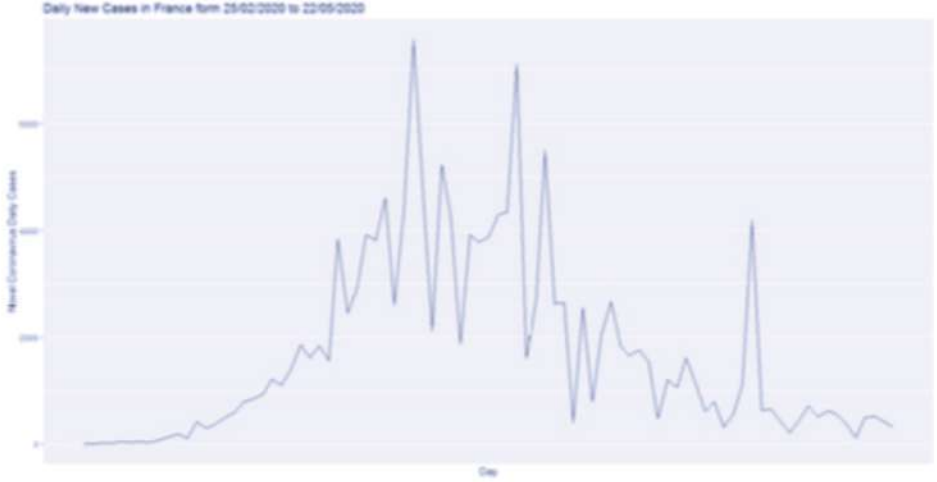
#	Country, Other	Total Cases	New Cases	Total Deaths	New Deaths	Total Recovered	Active Cases	Serious, Critical	Tot Cases/ 1M pop	Deaths/ 1M pop	Total Tests	Tests/ 1M pop	Population
	World	5,910,145	+9,238	362,114	+565	2,583,502	2,964,529	53,975	758	46.5			
1	USA	1,768,461		103,330		498,725	1,166,406	17,202	5,346	312	16,331,312	49,365	330,827,597
2	Brazil	438,812		26,764		193,181	218,867	8,318	2,066	126	871,839	4,104	212,422,152
3	Russia	379,051		4,142		150,993	223,916	2,300	2,598	28	9,701,280	66,479	145,928,996
4	Spain	284,986		27,119		196,958	60,909	854	6,096	580	3,556,567	76,071	46,753,197
5	UK	269,127		37,837		N/A	N/A	1,559	3,966	558	3,918,079	57,743	67,853,964
6	Italy	231,732		33,142		150,604	47,986	489	3,832	548	3,683,144	60,909	60,469,504
7	France	186,238		28,662		67,191	90,385	1,429	2,854	439	1,384,633	21,217	65,260,761
8	Germany	182,452		8,570		164,100	9,782	744	2,178	102	3,952,971	47,194	83,760,156
9	India	165,829	+443	4,713	+2	71,106	90,010	8,944	120	3	3,483,838	2,527	1,378,752,175
10	Turkey	160,979		4,461		124,369	32,149	683	1,911	53	1,928,209	22,885	84,254,857
11	Iran	143,849		7,627		112,988	23,234	2,543	1,715	91	876,492	10,448	83,892,015
12	Peru	141,779		4,099		59,442	78,238	926	4,306	124	928,797	28,207	32,928,451
13	Canada	88,512		6,877		46,840	34,795	1,613	2,347	182	1,585,235	42,036	37,711,800
14	Chile	86,943		890		36,150	49,903	1,289	4,552	47	530,173	27,756	19,101,165

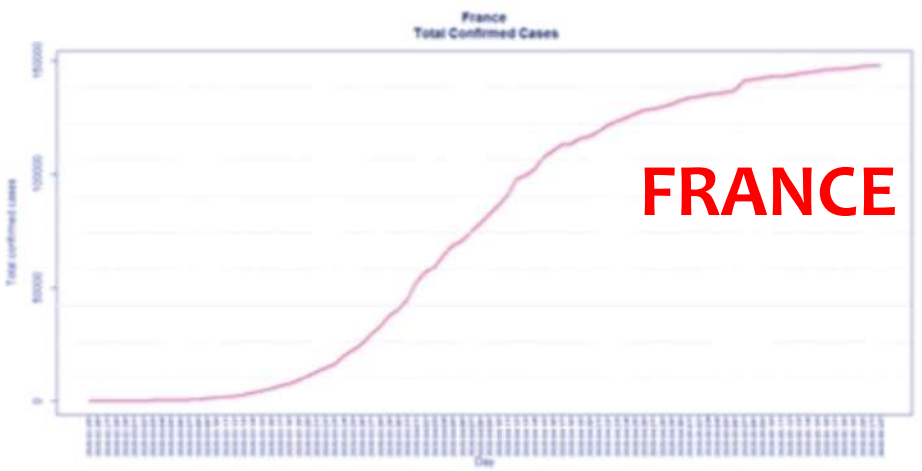


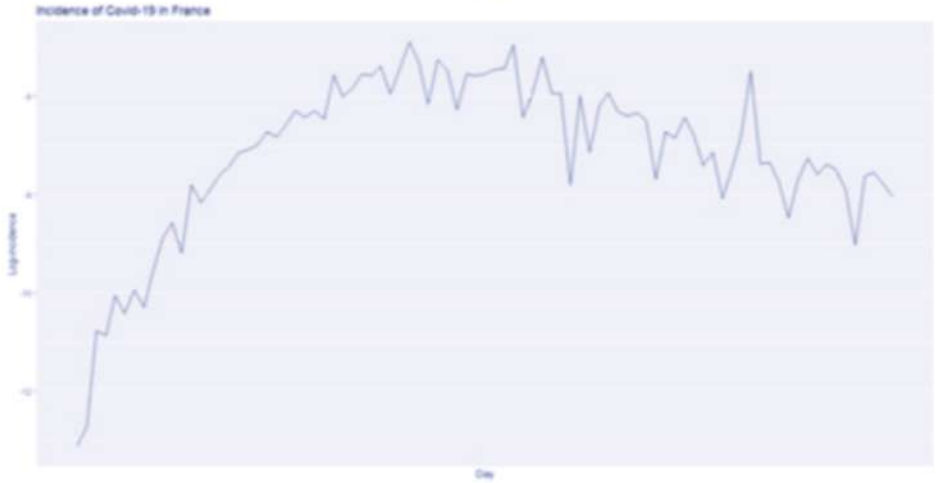


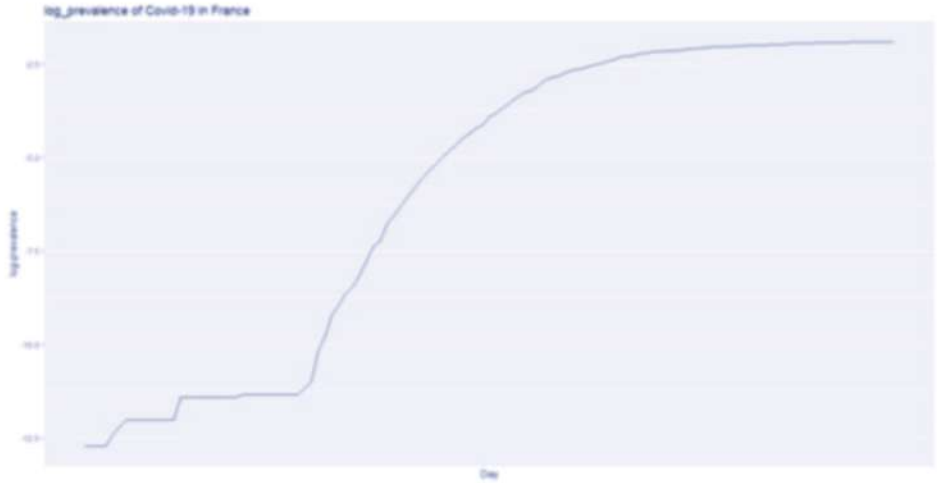
1137, but 510 yesterday !




Daily New Cases in France form 28/02/2020 to 22/05/2020

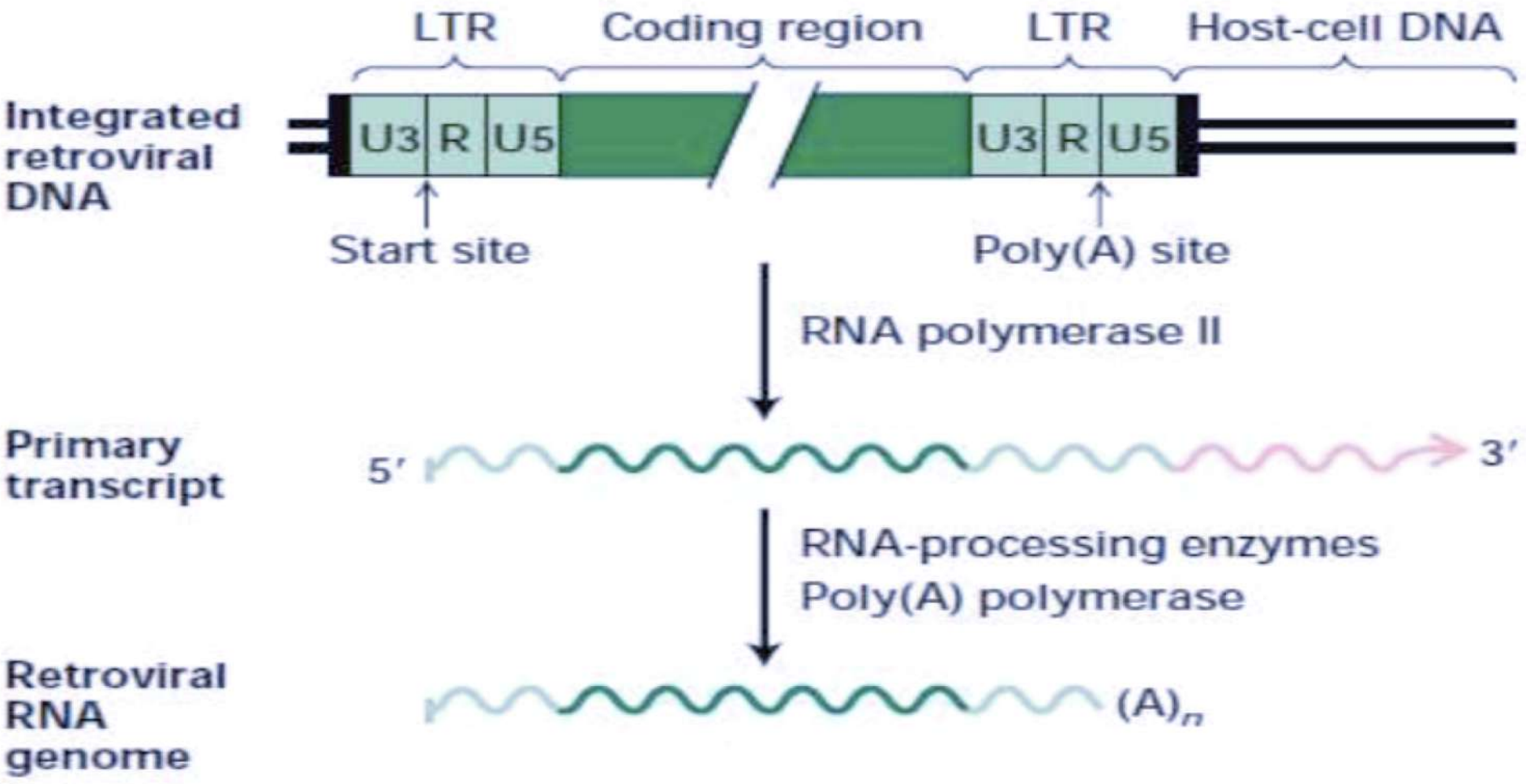

France
Total Confirmed Cases
FRANCE


Incidence of Covid-19 in France


log_prevalence of Covid-19 in France


Forecasts from Dynamic regression models
1325, but yesterday 191 !
29/05/2020

Generation of retroviral genomic RNA from integrated retroviral DNA



Ref: Molecular cell biology(lodish et all. 2008)

Beneficial Functions of HERVs

- Enhancement and promotion of gene expression
- HERV-E LTR
  - enhancer for endothelin B receptor and apolipoprotein C- I
- HERV-H LTR
  - enhancer activities in embryonic and hematopoietic cells
- Would be considered as "foreign"
- Could trigger B-cells to produce antibodies against them
- Cross-react with other proteins of our bodies
- Molecular mimicry mechanism

Homo sapiens endogenous retrovirus HERV-K102, complete sequence GenBank: AF164610.1: 1112-2596 Gag protein

ATGGGGCAAACTAAAAGTAAAATTAAAAGTAAATATGCCTCTTATCTCAGCTTTATTAAAATTCTTTTAA
AAAGAGGGGGAGTTAAAGTATCTACAAAAAATCTAATCAAGCTATTTCAAATAATAGAACAATTTTGCCC
ATGGTTTCCAGAACAAGGAACTTTAGATCTAAAAGATTGGAAAAGAATTGGTAAGGAACTAAAACAAGCA
GGTAGGAAGGGTAATATCATTCCACTTACAGTATGGAATGATTGGGCCATTATTAAAGCAGCTTTAGAAC
CATTTCAAACAGAAGAAGATAGCGTTTCAGTTTCTGATGCCCTTGGAAGCTGTATAATAGATTGTAATGA
AAACACAAGGAAAAAATCCCAGAAAGAAACGGAAGGTTTACATTGCGAATATGTAGCAGAGCCGGTAATG
GCTCAGTCAACGCAAAATGTTGACTATAATCAATTACAGGAGGTGATATATCCTGAAACGTTAAAATTAG
AAGGAAAAGGTCCAGAATTAGTGGGGCCATCAGAGTCTAAACCACGAGGCACAAGTCATCTTCCAGCAGG
TCAGGTGCCCGTAACATTACAACCTCAAAAGCAGGTTAAAGAAAATAAGACCCAACCGCCAGTAGCCTAT
CAATACTGGCCTCCGGCTGAACTTCAGTATCGGCCACCCCCAGAAAGTCAGTATGGATATCCAGGAATGC
CCCCAGCACCACAGGGCAGGGCGCCATACCCTCAGCCGCCCACTAGGAGACTTAATCCTACGGCACCACC
TAGTAGACAGGGTAGTGAATTACATGAAATTATTGATAAATCAAGAAAGGAAGGAGATACTGAGGCATGG
CAATTCCCAGTAACGTTAGAACCGATGCCACCTGGAGAAGGAGCCCAAGAGGGAGAGCCTCCCACAGTTG
AGGCCAGATACAAGTCTTTTTCGATAAAAATGCTAAAAGATATGAAAGAGGGAGTAAAACAGTATGGACC
CAACTCCCCTTATATGAGGACATTATTAGATTCCATTGCTCATGGACATAGACTCATTCCTTATGATTGG
GAGATTCTGGCAAAATCGTCTCTCTCACCCTCTCAATTTTTACAATTTAAGACTTGGTGGATTGATGGGG
TACAAGAACAGGTCCGAAGAAATAGGGCTGCCAATCCTCCAGTTAACATAGATGCAGATCAACTATTAGG
AATAGGTCAAAATTGGAGTACTATTAGTCAACAAGCATTAATGCAAAATGAGGCCATTGAGCAAGTTAGA
GCTATCTGCCTTAGAGCCTGGGAAAAAATCCAAGACCCAGGAAGTACCTGCCCCTCATTTAATACAGTAA
GACAAGGTTCAAAAGAGCCCTATCCTGATTTTGTGGCAAGGCTCCAAGATGTTGCTCAAAAGTCAATTGC
CGATGAAAAAGCCCGTAAGGTCATAGTGGAGTTGATGGCATATGAAAACGCCAATCCTGATGTCAATCAG
CCATTAAGCCATTAA

Observed 50 ancient pentamers (red) among 1481 possible = 3.4% (expected 2.1%±0.5%)

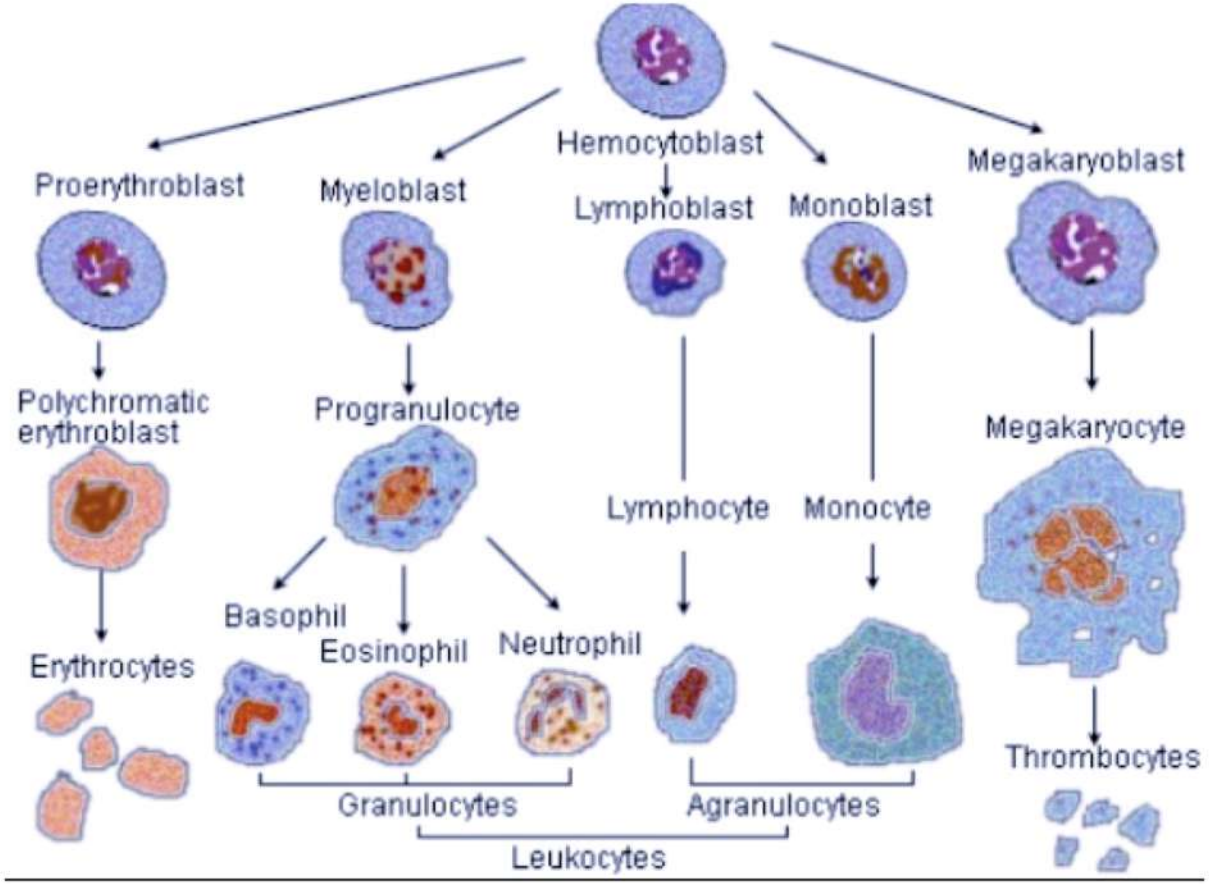
Figure 5. Complete RNA sequence of the Gag protein of the virus HERV-K102 [36]. The green subsequence of length 14 (271-285) is present in the RNA sequence of the protein S of the virus Covid-19 [22]. Red: pentamers belonging to ancient circular RNAs as measure of the genomic structure's age in evolution [7,8].

Covid-19 dynamics depends on genomic factors like retro-viruses

Homo sapiens microRNA let-7e (MIRLET7E), microRNA NCBI Reference Sequence: NR_029482.1

5′–**TGAGGTA**TT**GTG**AA**T**T**TT**CACC**TTTTA**–3′ **Protein S Covid-19**
3′–G**GCTTTATTCT**G**CAA**GCA**ATCAA**ATAAT–5′ **Homo sapiens HBG2**
5′–CCCGGGC**TGAGGTAGGAGGTTGTATAGTT**GAGGAGGACACCCAAGGAGATCACTATACG–3′

J. Demongeot, E. Drouet, A. Moreira, Y. Rechoum & S. Sené. Micro-RNAs: viral genome and robustness of the genes expression in host. *Phil. Trans. Royal Soc. A*, **367**, 4941-4965 (2009).
J. Demongeot & H. Seligmann. Covid-19 and miRNA-like inhibition power. *Biology* (submitted).



Homo sapiens erythropoietin (EPO), mRNA NCBI Reference Sequence: NM_000799.4

TTTTCACCTTTTACTACGCC Protein S Covid-19

CCTTTCCCAGATAGCACGCTCCGCCAGTCCCAAGGGTGCGCAACCGGCTGCACTCCCCTCCCGCGACCCA
GGGCCCGGGAGCAGCCCCCATGACCCACACGCACGTCTGCAGCAGCCCCGCTCACGCCCCGGCGAGCCTC
AACCCAGGCGTC**CTGCC**CCTGCTCTGACCCCGGGTGGCCCCTACCCCTGGCGACCCCTCACGCACACAGC
CTCTCCCCCACCCCCACCCGCGCACGCACACATGCAGATAACAGCCCCGACCCCCGGCCAGAGCCGCAGA

ACGGGCGGCTCCTCTTAATCAG Protein S Covid-19

GTCCCTGGGCCACCCCGGCCGCTCGCTGCGCTGCGCCGCACCGCGCTGTCCTCCCGGAGCCGGACCGGGG
CCACCGCGCCCGCTCTGCTCCGACACCGCGCCCCCTGGACAGCCGCCCTCTCCTCCAGGCCCGTGGGGCT
GGCCCTGCACCGCCGAGCTTCCCGG**GATGA**GGGCCCCCGGTGTGGTCACCCGGCGCGCCCCAGGTCGCTG

TTTTCACCTTTTACTACGCC Protein S Covid-19

AGGGACCCCGGCCAGGCGCGG**AGATG**GGGGTGCAC**GAATG**TC**CTGCC**TGGCTGTGGCTTCTCCTGTCCCT

First author (year)	Region	Study period	Sample size	Categorisation of haematological factors	Main findings
Guan (2020)[16]	552 hospitals in 30 provinces, autonomous regions, and municipalities in mainland China	December 11, 2019 - January 31, 2020	1099	Lymphocytopenia: lymphocyte count of less than 1500 cells/mm^3	Lymphocytopenia was present in 83.2% of patients on admission. 92.6% (50/54) of patients with the composite primary endpoint (admission to an intensive care unit, use of mechanical ventilation, or death) presented with lymphocytopenia vs. 82.5% (681/825) of patients without the primary endpoint (p=0.056[a]). Severe cases presented lymphocytopenia more frequently (96.1%, 147/153) vs. non-severe cases (80.4%, 584/726); p<0.001[a]
Huang (2020)[17]	Jinyintan Hospital, Wuhan, China	December 16, 2019, to January 2, 2020	41	Low lymphocyte count of <1.0 $x10^9$ lymphocytes per litre	85% (11/13) of patients needing ICU care presented low lymphocyte count vs. 54% (15/28) of patients that did not need ICU care (p=0.045).
Wang (2020)[19]	Zhongnan Hospital, Wuhan, China	January 1 to February 3, 2020	138	Lymphocytes treated as a continuous variable, $x10^9$ per L	ICU cases presented with lower lymphocyte count (median:0.8, IQR: 0.5-0.9) vs. non-ICU cases (median: 0.9, IQR: 0.6-1.2); p=0.03. Longitudinal decrease was noted in non-survivors.
Wu (2020)[20]	Jinyintan Hospital, Wuhan, China	December 25, 2019, to February 13, 2020	201	Lymphocytes treated as a continuous variable, $x10^9$ /mL in a bivariate Cox regression model	Lower lymphocyte count was associated with ARDS development (HR=0.37, 95%CI: 0.21-0.63, p<0.001 in the incremental model); the association with survival did not reach significance (HR=0.51, 95%CI: 0.22-1.17, p=0.11)
Young (2020)[21]	4 hospitals in Singapore	January 23 to February 3, 2020	18	Lymphocytes treated as a continuous variable, $x10^9$ per L; lymphopenia was defined as <1.1 $\times 10^9$/L.	Lymphopenia was present in 7 of 16 patients (39%). Median lymphocyte count was 1.1 (IQR: 0.8-1.7) in patients that required supplemental O_2 and 1.2 (IQR:0.8-1.6) in those that did not; no statistical comparison was undertaken.

Blood routine parameters of patients with COVID-19 on admission.

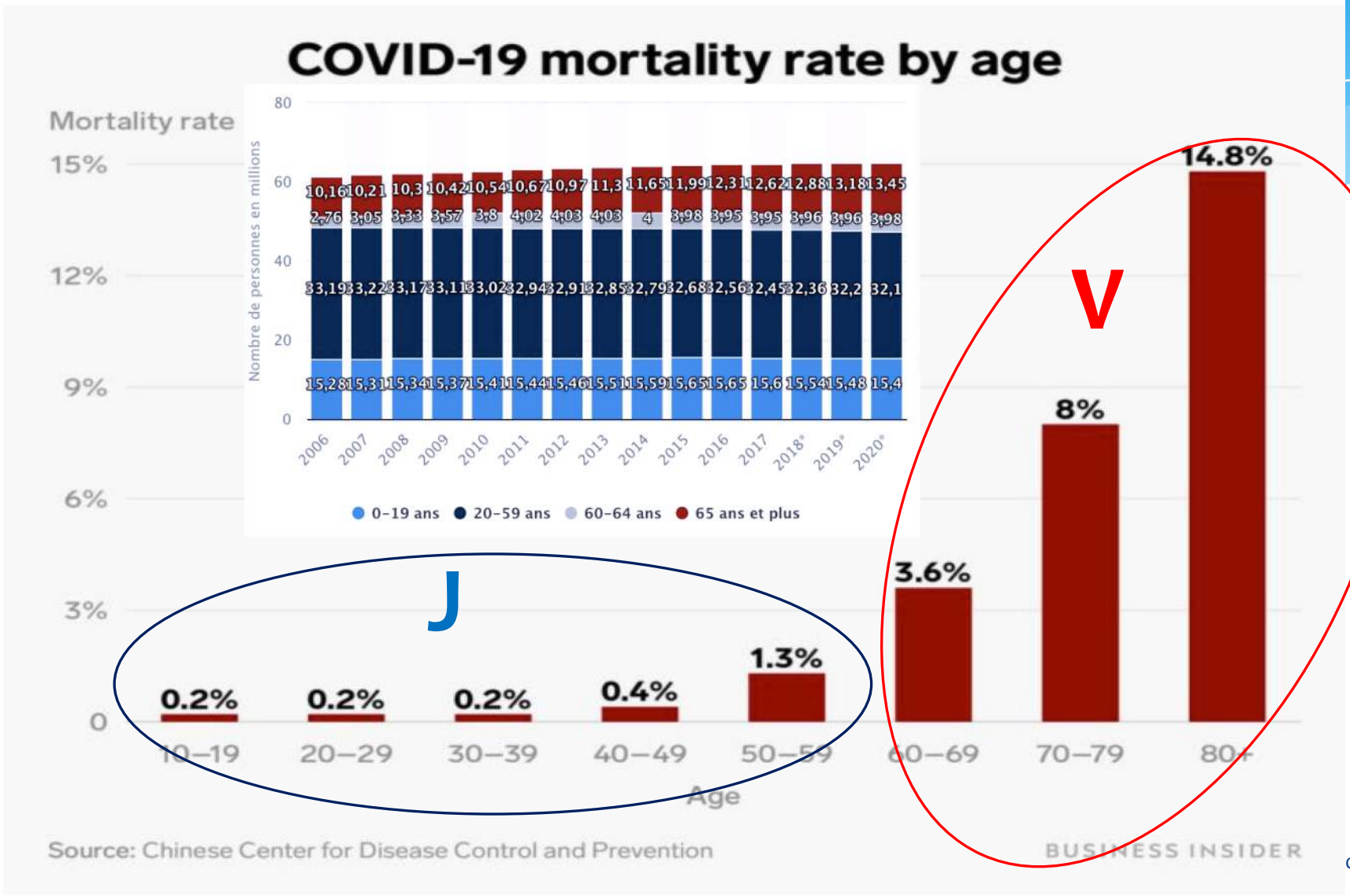
	Median (IQR)		
	All patients (n = 116)	Controls (n = 100)	*P* value
Age, Median(IQR),Range, years	50.0 (41.0–57.0), 20–93	48.5(37.3–59.8), 21–90	0.397
Sex			0.739
Male(%)	60 (51.7%)	53 (53.0%)	
Female(%)	56 (48.3%)	47 (47.0%)	
Blood routine			
Leucocytes($\times 10^9$ per L)	4.60 (3.76–6.40)	5.95 (5.13–6.88)	< 0.001
Neutrophils($\times 10^9$ per L)	3.10 (2.33–4.30)	3.20 (2.70–3.88)	0.456
Lymphocytes($\times 10^9$ per L)	1.00 (0.72–1.40)	2.10 (1.80–2.40)	< 0.001
Monocyte($\times 10^9$ per L)	0.39 (0.29–0.49)	0.40 (0.34–0.47)	0.372
Eosinophil($\times 10^9$ per L)	0.02 (0.01–0.05)	0.10 (0.06–0.16)	< 0.001
Hemoglobin(g/L)	132.5 (122.3–145.8)	146.5 (135.0–156.0)	< 0.001
Platelet($\times 10^9$ per L)	180.5 (145.5–229)	240.0 (202.8–274.8)	< 0.001
MLR	0.37 (0.27–0.56)	0.19 (0.17–0.23)	< 0.001
NLR	2.91 (1.87–4.83)	1.58 (1.34–1.98)	< 0.001
PLR	169.0 (123.5–245.6)	113.0 (95.1–138.2)	< 0.001

Le coronavirus isolé chez le pangolin est capable d'entrer dans les cellules humaines alors que celui isolé chez la chauve-souris *R. affinis* ne l'est pas. Par ailleurs, cela suggère que le virus SARS-Cov-2 est issu d'une recombinaison entre deux virus différents, l'un proche de RaTG13 et l'autre plus proche de celui du pangolin. En d'autres termes, il s'agit d'une chimère entre deux virus préexistants. Ce mécanisme de recombinaison avait déjà été décrit chez les coronavirus, notamment pour expliquer l'origine du SARS-Cov. Il est important de savoir qu'une recombinaison aboutit à un nouveau virus potentiellement capable d'infecter une nouvelle espèce hôte. Pour qu'une recombinaison se produise, il faut que les deux virus divergents aient infecté le même organisme de façon concomitante.
Deux questions restent en suspens : dans quel organisme a eu lieu cette recombinaison ? (une chauve-souris, un pangolin ou une autre espèce ?) Et surtout dans quelles conditions a eu lieu cette recombinaison ?

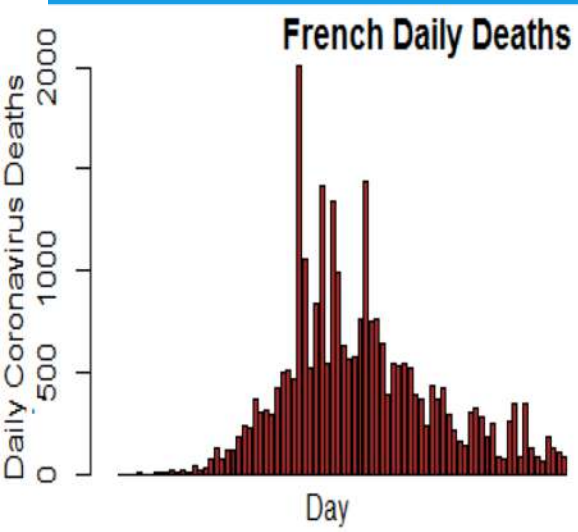
https://www.santemagazine.fr/actualites/actualites-sante/covid-19-lanalyse-des-genomes-revelerait-une-origine-double-du-virus-432862

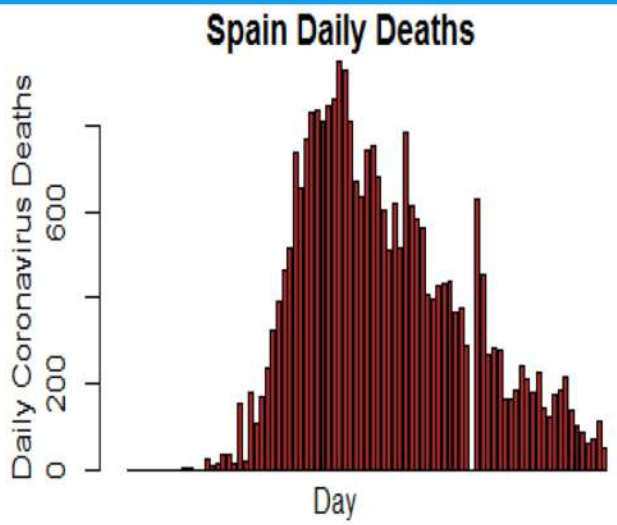
Dependence on age-structure of the susceptible population

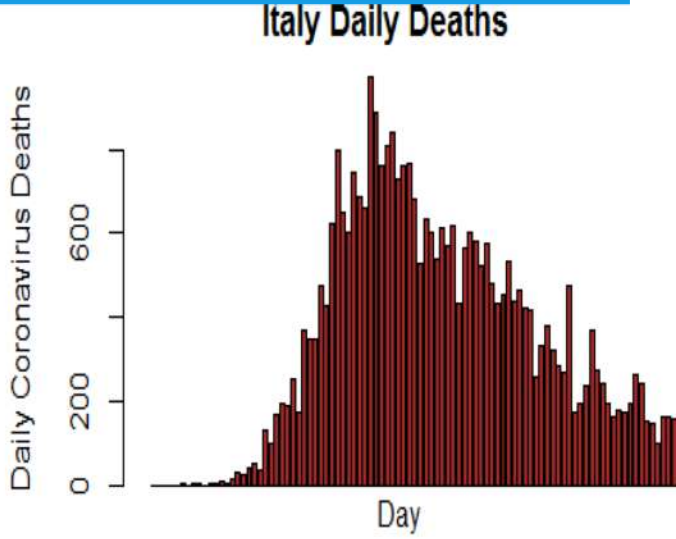
Covid-19 dynamics depends on age

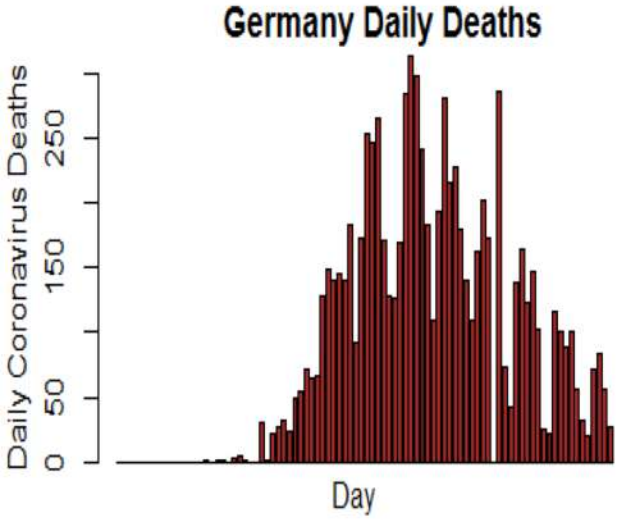


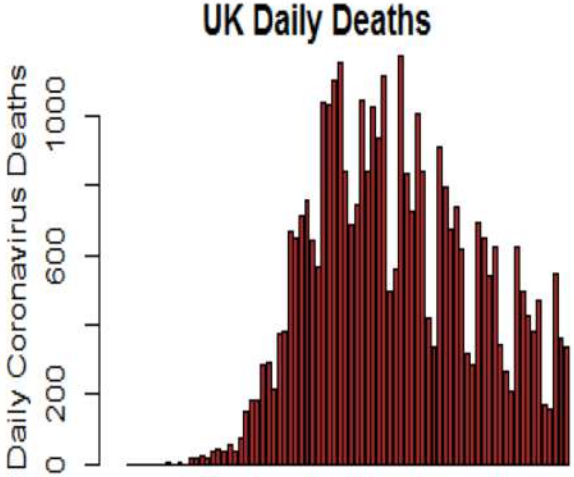
Shayanne Gal/Business Insider

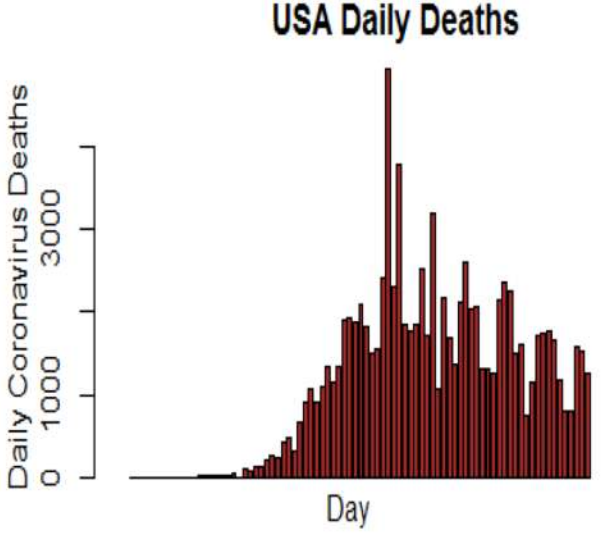

French Daily Deaths
Daily Coronavirus Deaths
0
500
1000
2000
Day

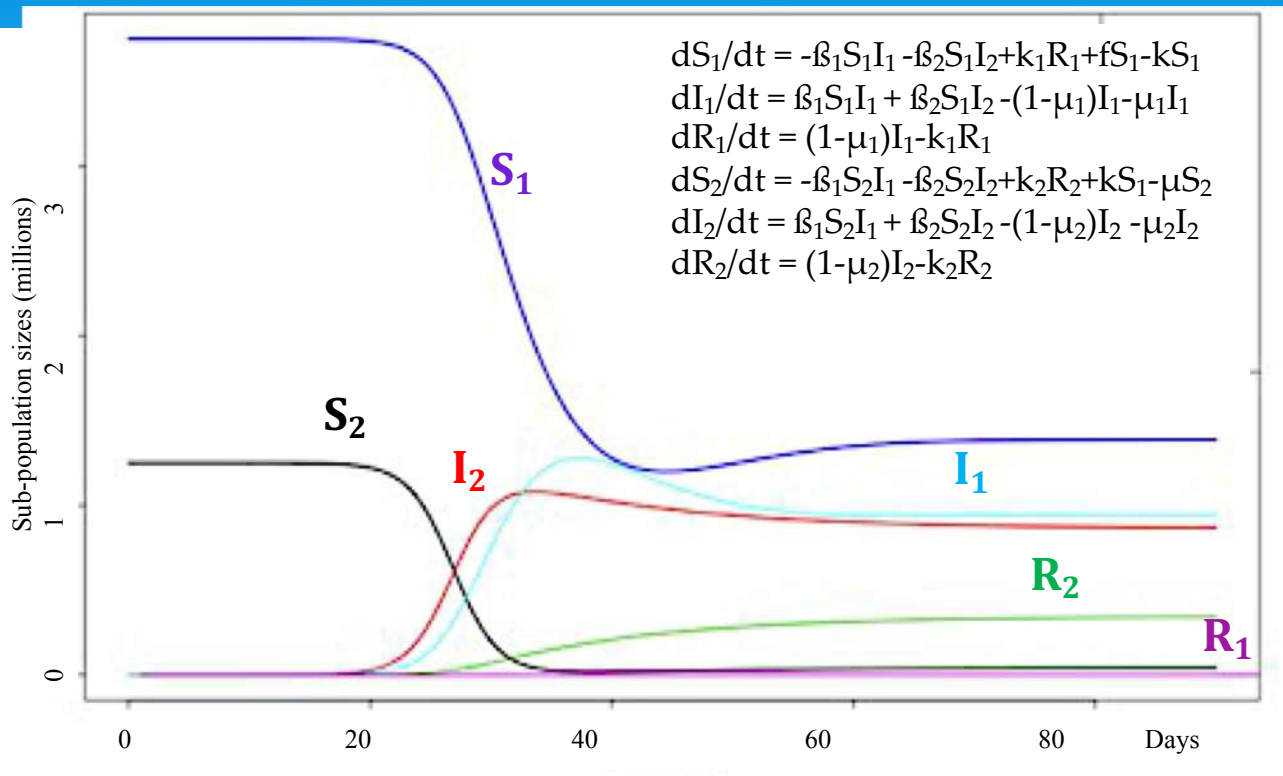

Spain Daily Deaths
Daily Coronavirus Deaths
0
200
600
Day


Italy Daily Deaths
Daily Coronavirus Deaths
0
200
600
Day


Germany Daily Deaths
Daily Coronavirus Deaths
0
50
150
250
Day


UK Daily Deaths
Daily Coronavirus Deaths
0
200
600
1000


USA Daily Deaths
Daily Coronavirus Deaths
0
1000
3000
Day



J. DEMONGEOT, O. HANSEN, H. HESSAMI, A.S. JANNOT, J. MINTSA, M. RACHDI & C. TARAMASCO Random modelling of contagious diseases. *Acta Biotheoretica*, **61**, 141-172 (2013).

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