Peut-on anticiper le devenir d'une épidémie?

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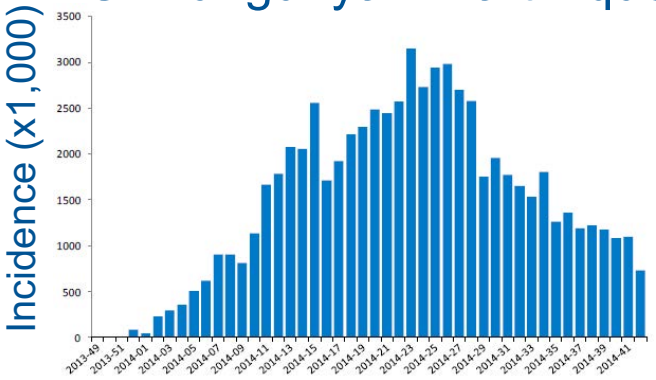
Situation awareness and decision making during epidemics

- Epidemics :
  - ➢ Emerging or reemerging: SARS, pandemic influenza, Ebola, …
  - ➢ Seasonal or endemic: dengue, influenza…
- Key needs for evidence-based policy making:
  - ➢ Assess the epidemiological situation:
    - ✓ Now-casting vs forecasting.
  - ➢ Characterize the threat:
    - ✓Mechanisms of spread?
    - ✓ Transmission risk factors?
    - ✓ Impact of interventions?
  - ➢ Extrapolate / predict:
    - ✓ What should be expected?
    - ✓ What should be done?

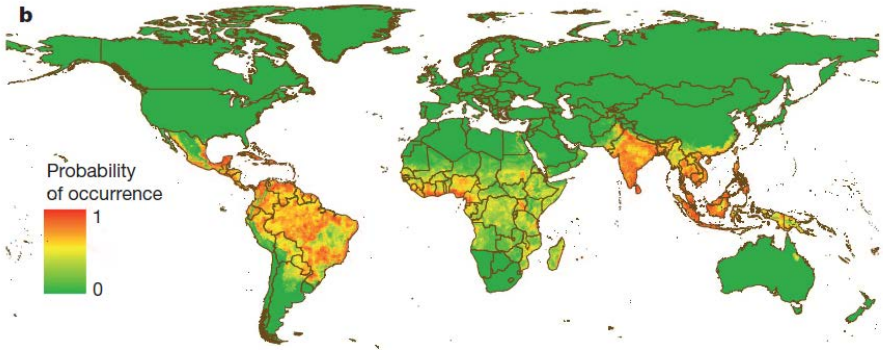
Chikungunya - Martinique



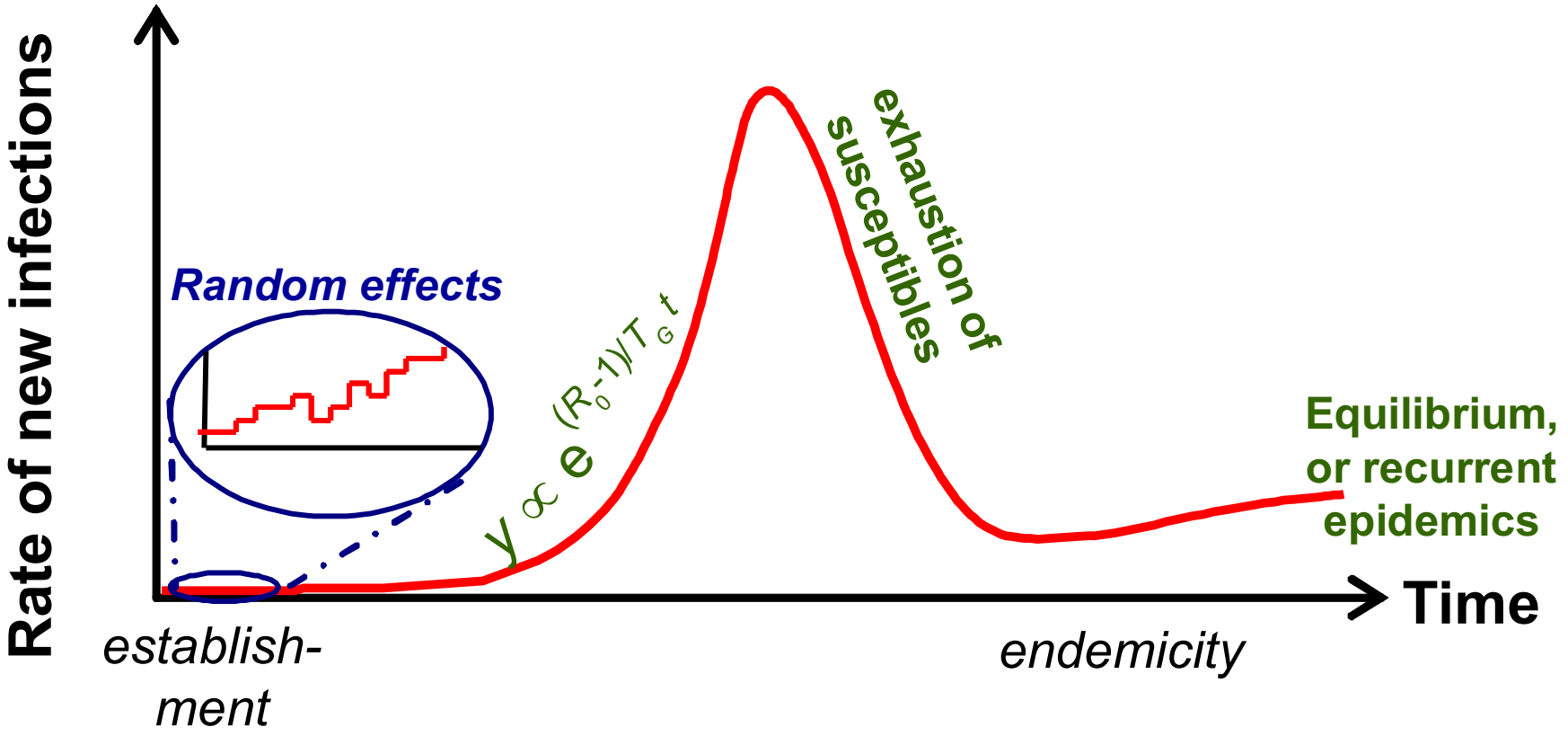
Zika – the Americas

Ebola – West Africa

Dengue – World



Epidemic dynamics



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Anticipating what may happen at different stages of the epidemic process

- At the stage of emergence
  - ➢ A novel swine influenza virus
- Once a known virus reaches a new location
  - ➢ Dengue in Reunion Island
- For viruses causing seasonal epidemics locally
  - ➢ Influenza in France

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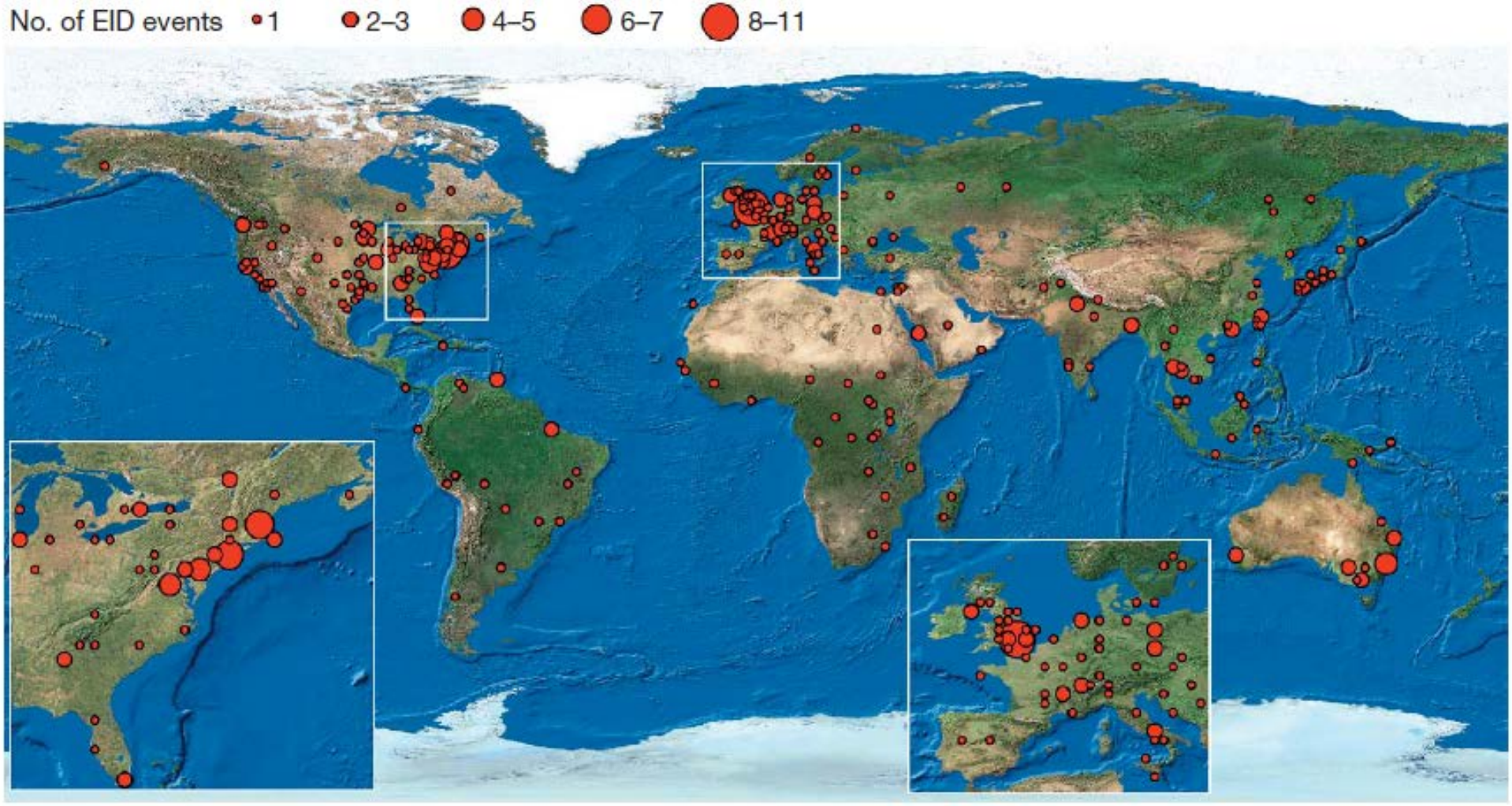
Emerging Infectious Diseases

>330 EID events reported since 1940 across the world



[Jones et al, Nature 2008]

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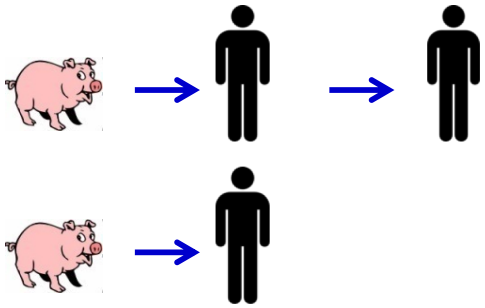
EIDs – What is the risk of a worldwide pandemic?

- Motivating example:
  - In 2011, emergence of a swine-origin triple reassortant influenza A(H3N2) variant (H3N2v) virus in the US with matrix gene from the H1N1pdm09 virus.
  - 12 human cases (6 exposed to pigs, 6 human-to-human infections).

- Question:
  - Is it the start of a worldwide pandemic?



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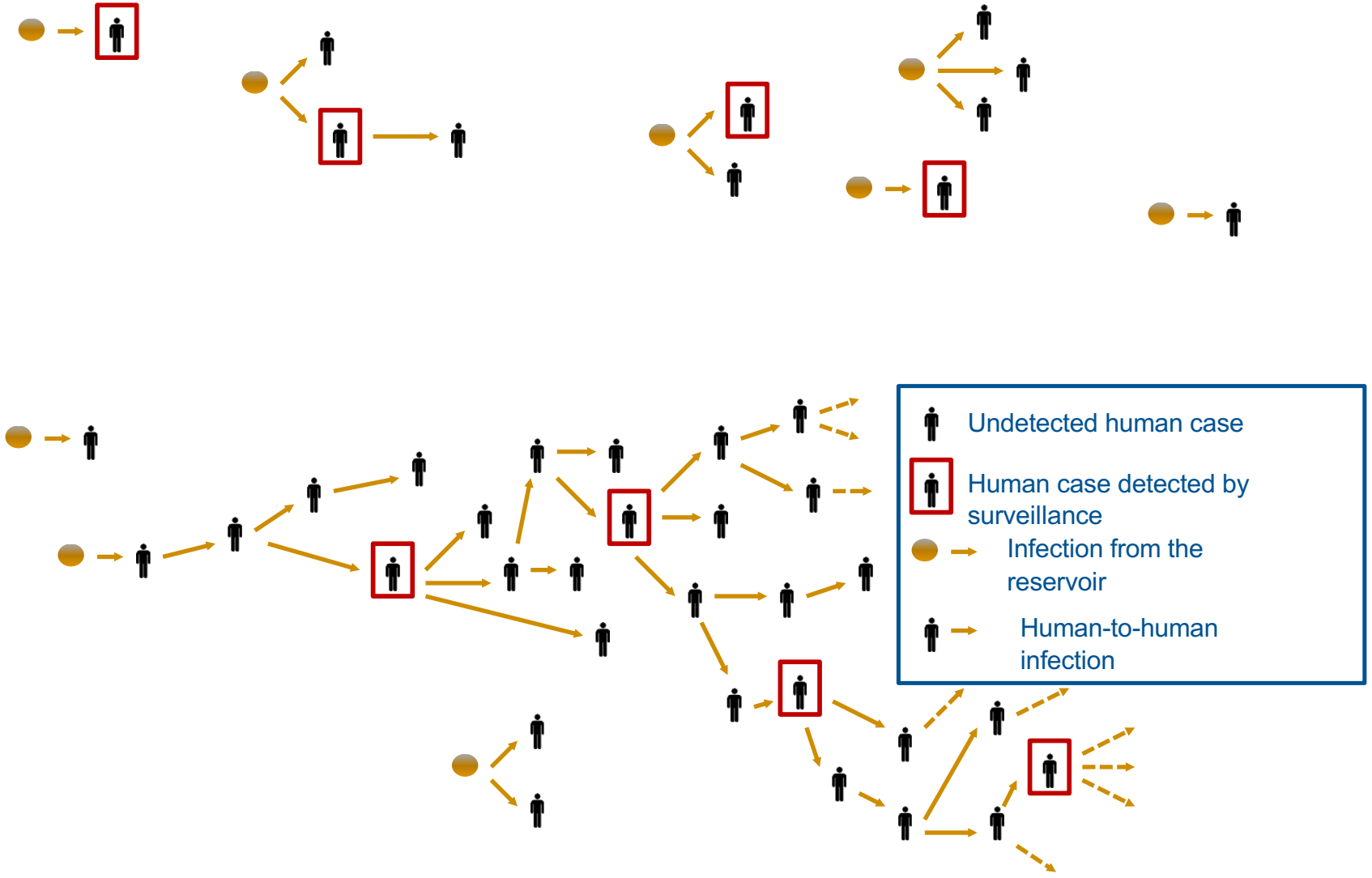
What underlying transmission dynamics?

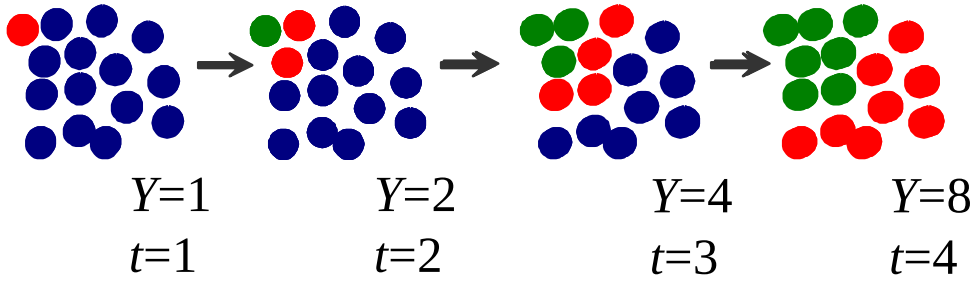
A. Spill-over events from the reservoir

B. Sustained transmission in humans



Quantifying the transmissibility of an infectious disease

Reproduction number R - mean number of cases generated by a case.



A major self-sustaining epidemic can occur only if the reproduction number R is >1.

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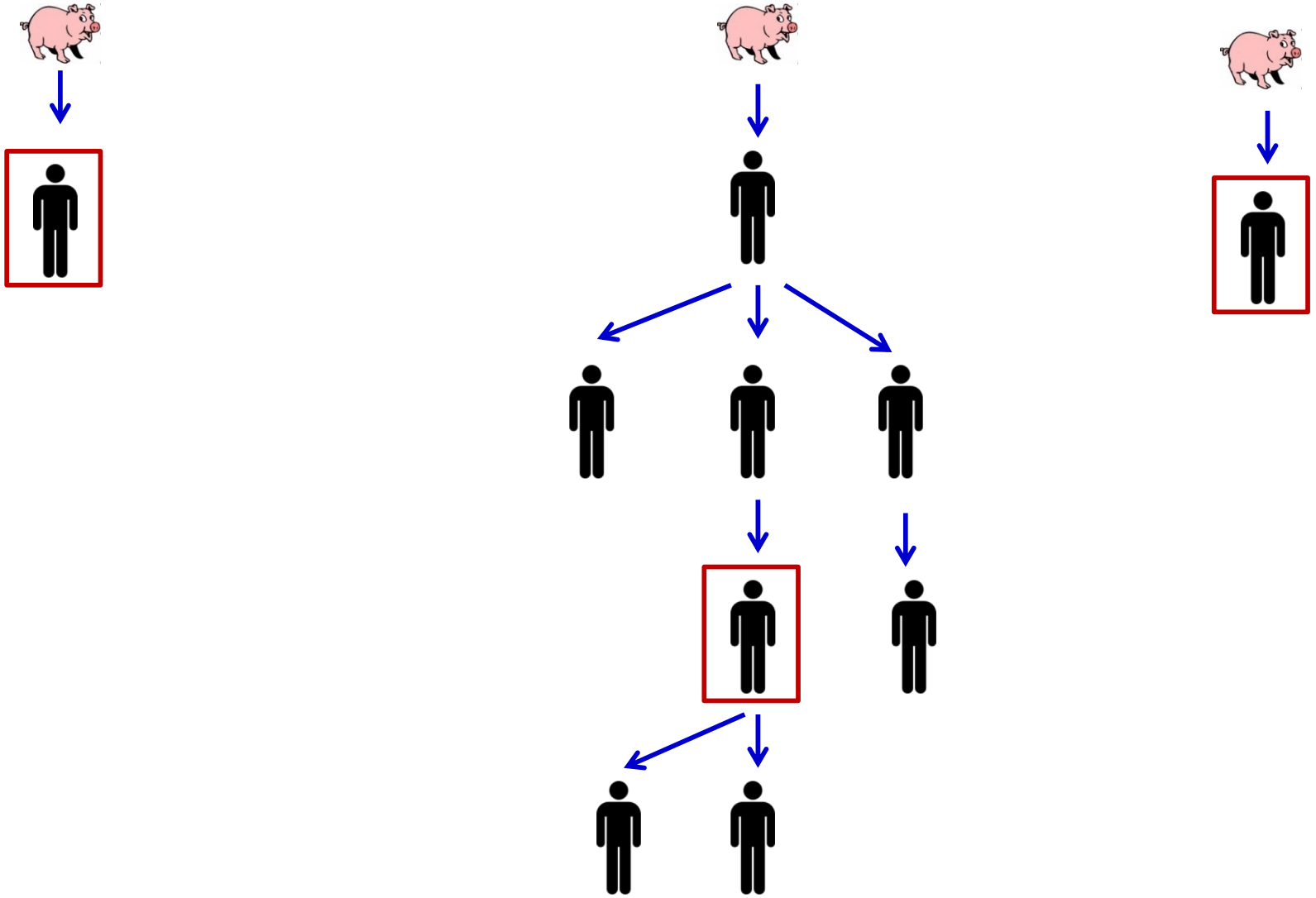
How to estimate *R* for zoonoses?



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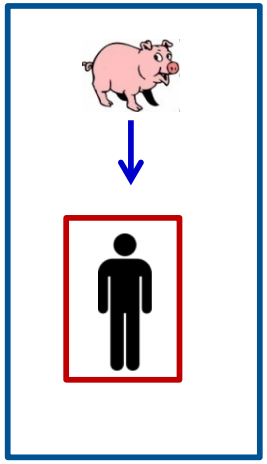
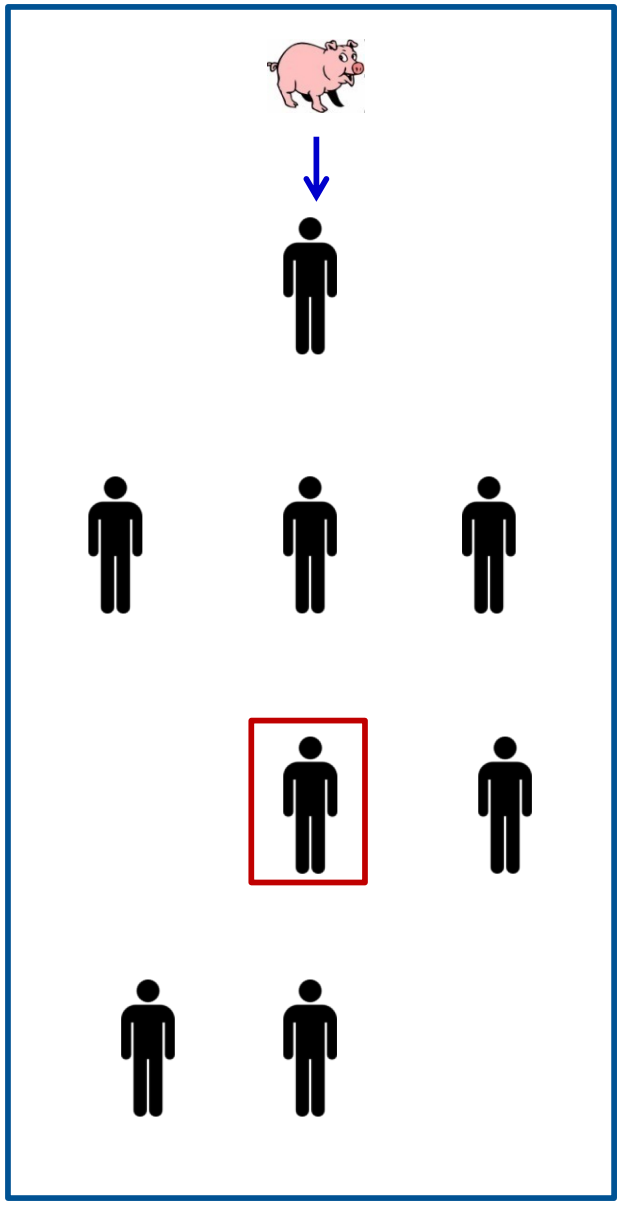
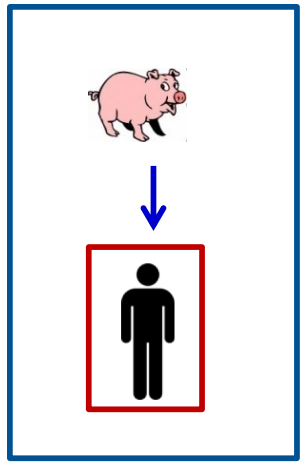
But chains of transmission are often imperfectly observed…



N=1



N=8



N=1

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Inference from cluster size

Expected number of cases at different generations

Gen. 1	Gen. 2	Gen. 3	Gen. 4 …
1	R	R^2	R^3

Average cluster size= $1 + R + R^2 + R^3 + R^4 \ldots$

Average cluster size= $\frac{1}{1-R}$

R=1-Average cluster size

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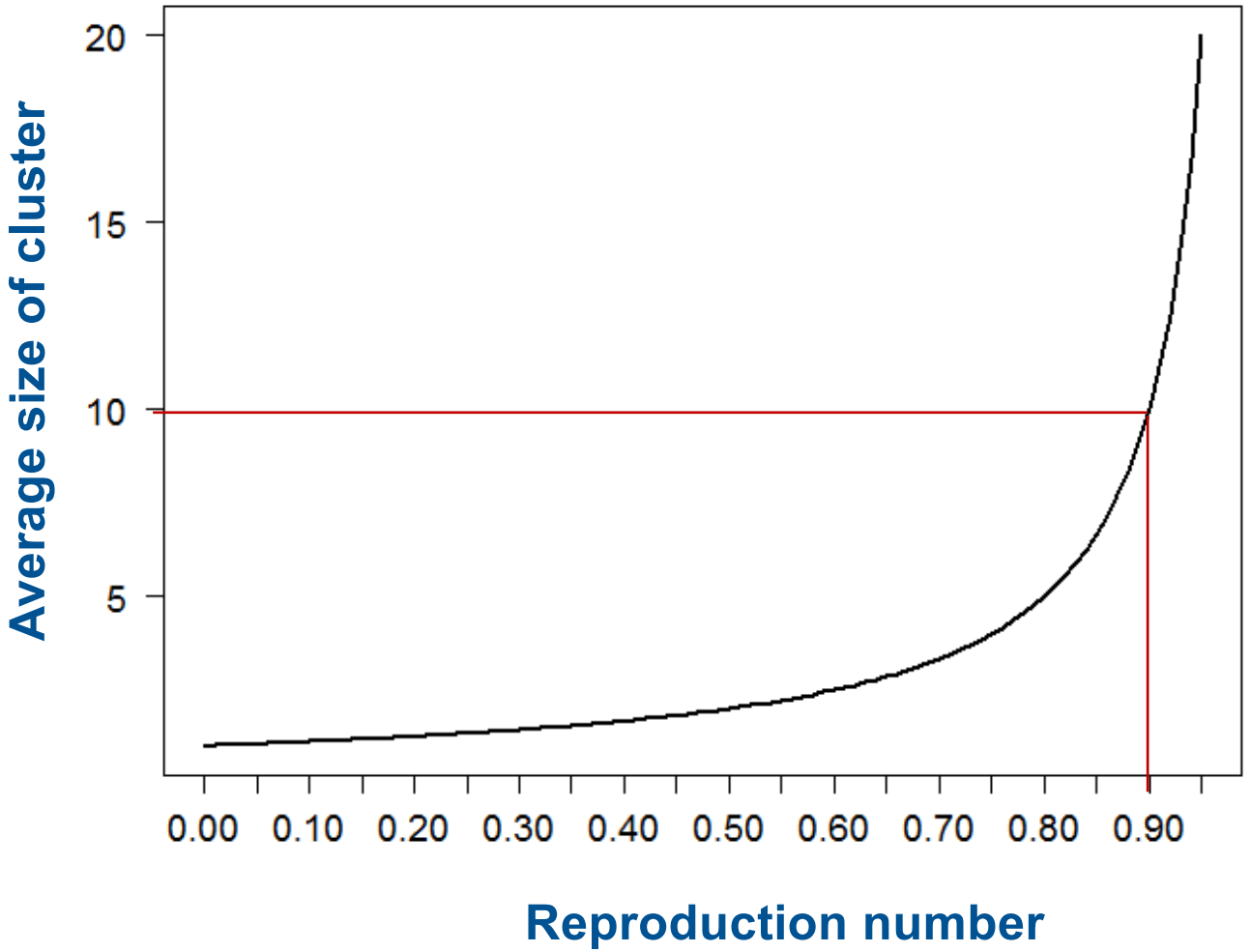
Relationship between the average cluster size and the reproduction number

Average size	R
2	0.5
3	0.66
4	0.75
5	0.8
10	0.9
20	0.95



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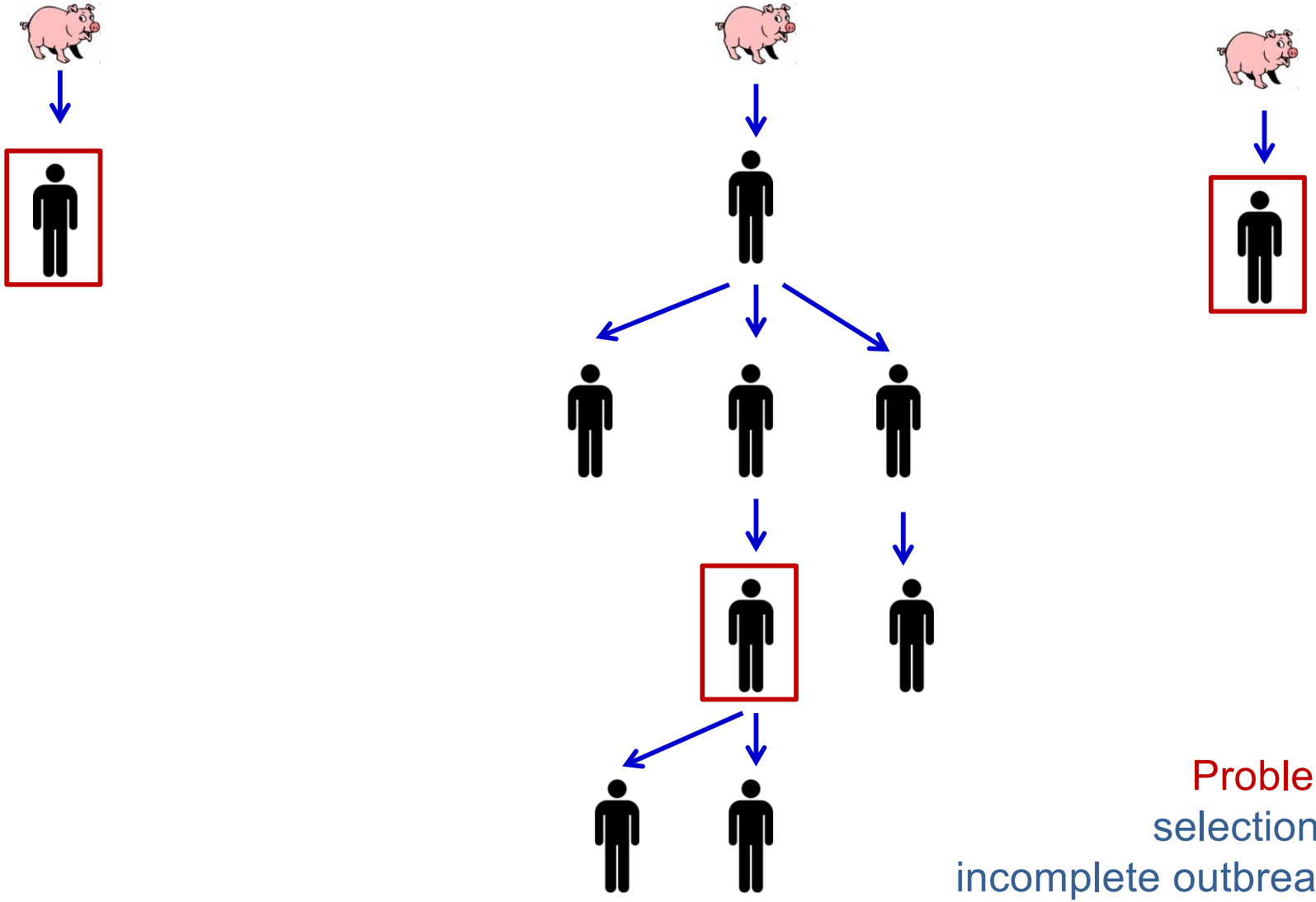
How to estimate *R* for zoonoses?



Problems
selection bias
incomplete outbreak investigations
low detection rate

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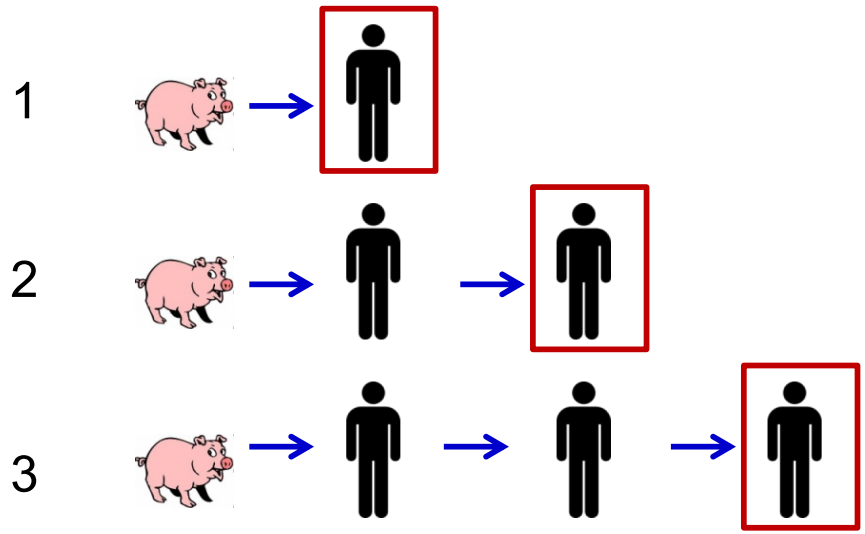
Probability *F* that first detected case was infected by reservoir

Length of the chain of transmission

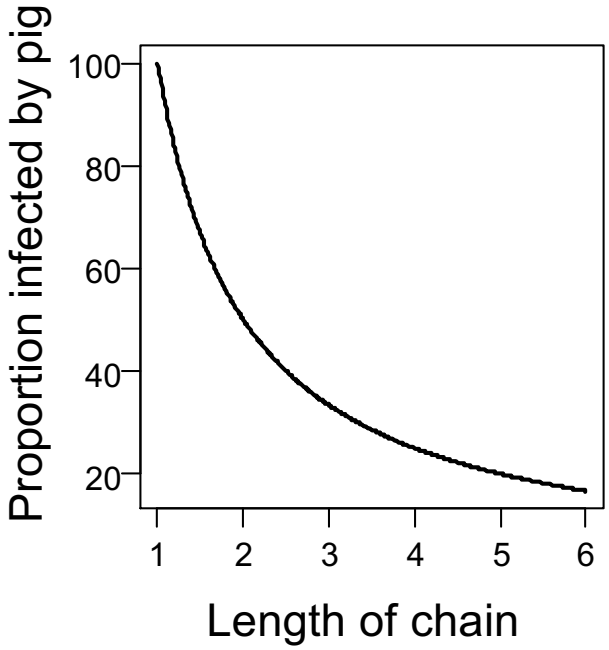


Proportion F of first detected cases infected by swine

1/1=100%

1/2=50%

1/3=33%



- From proportion, can estimate length of chain;
- From length of chain, can estimate the reproduction number.

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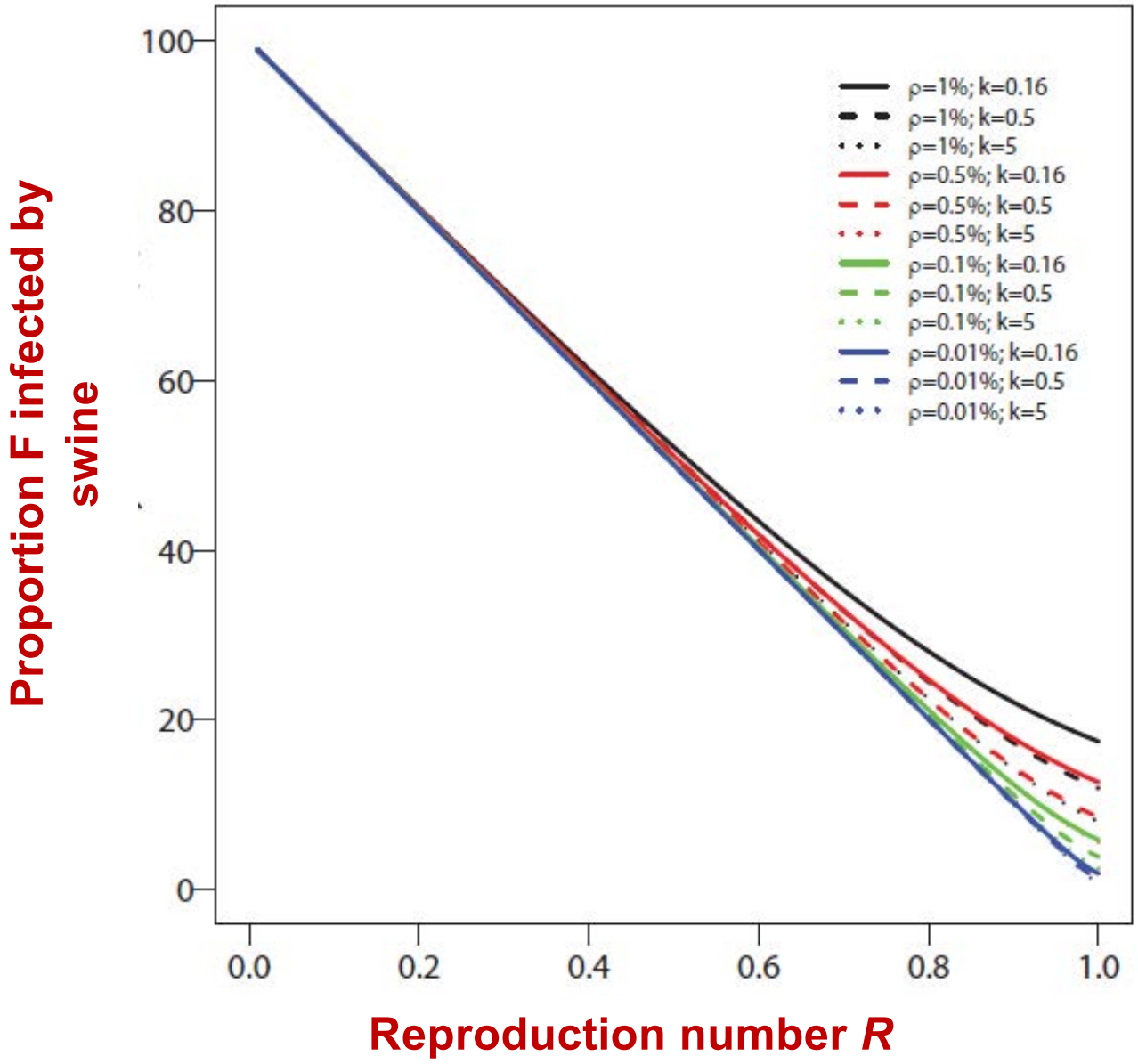
Inferring R



Case detection rate
0.01%-1%

Overdispersion k
0.16 (SARS)
0.5 (Measles)
5 (Ebola)

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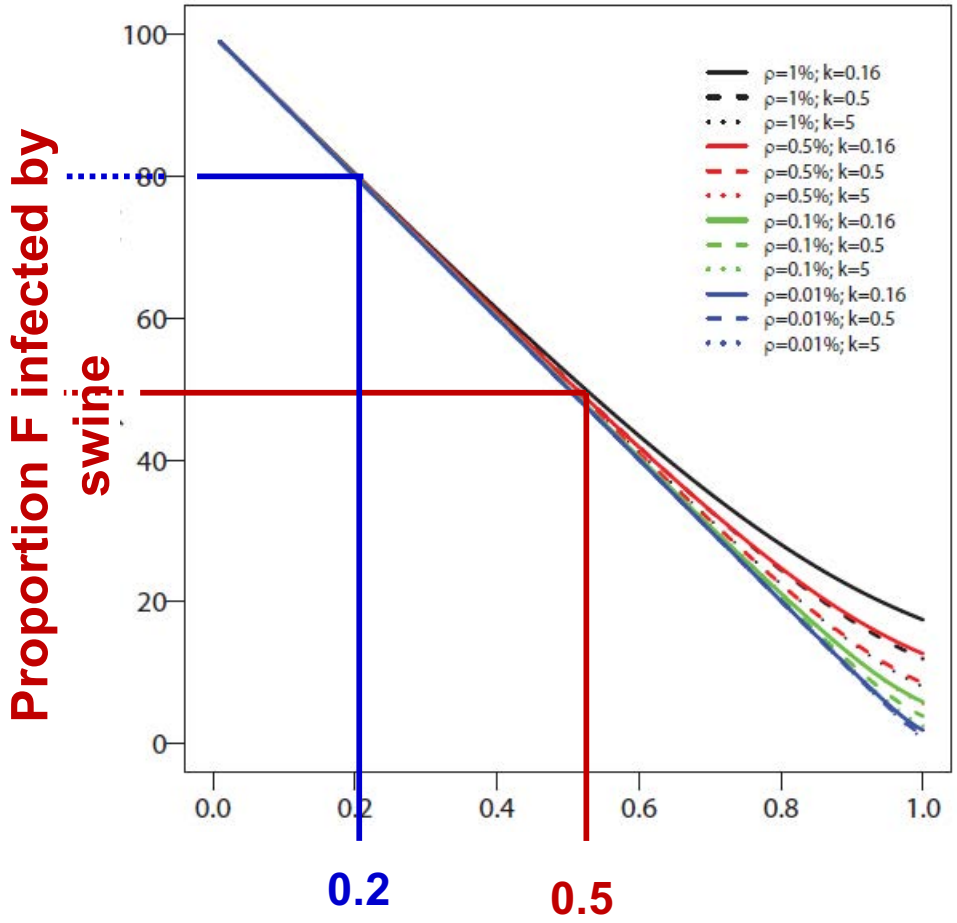
R for H3N2v and for other variants

Other variants: 81% (17/21) infected by swine
R=0.2 (95%CI: 0.1,0.4)

H3N2v: 50% (3/6) infected by swine
R=0.5 (95%CI: 0.2,0.8)



We concluded that H3N2v threat did not pose a pandemic threat!

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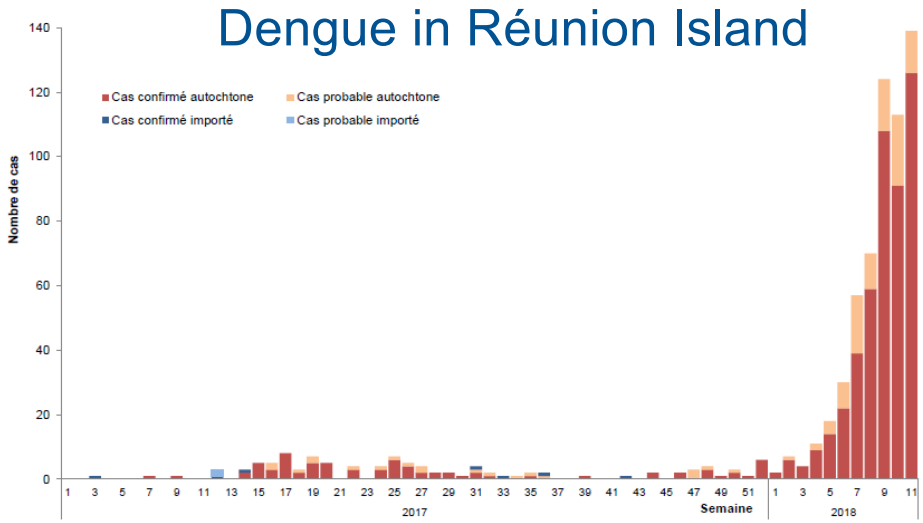
Will there be a large dengue epidemic in Réunion island in 2019?

- Contacted in March 2018 by Santé Publique France because atypically large epidemic of dengue in Réunion Island.
- Modelling support to inform Public Health response.



- Questions:
  - What will happen during the austral winter? Will transmission persist?
  - What will happen in 2019?
- Challenges:
  - No major dengue epidemic in the island since the 70s.
  - But a lot of data documenting from other parts of the world.
  - Can we use these external data to train our models?

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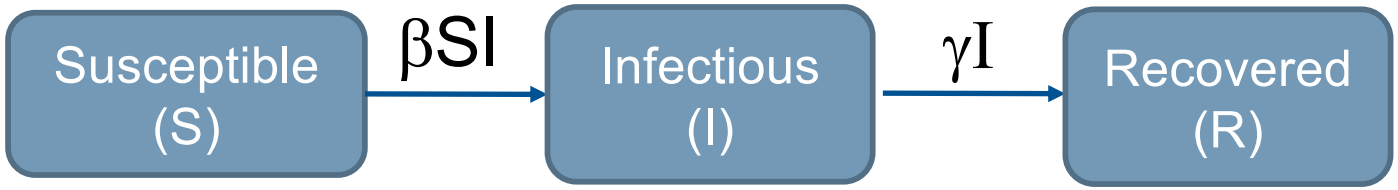
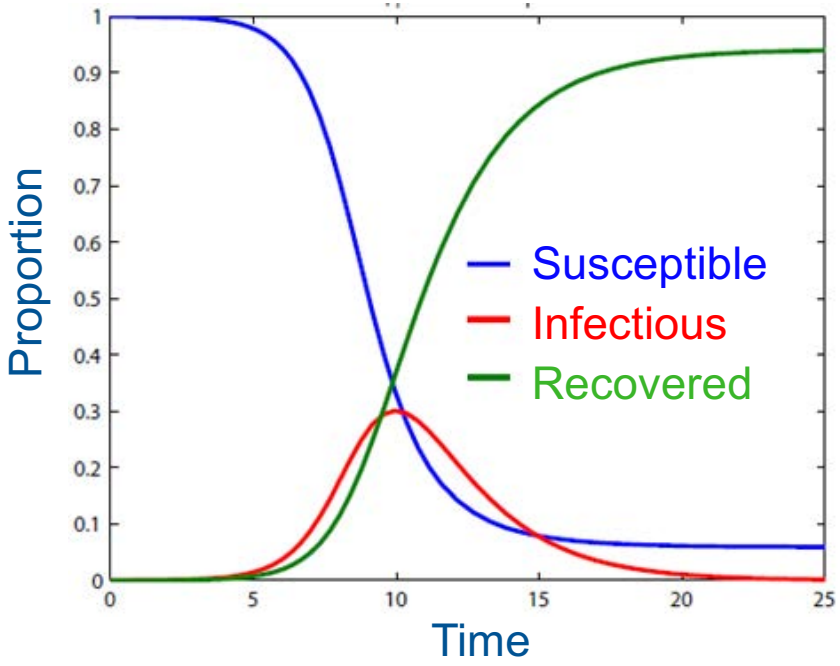
Compartmental models for epidemic processes



A set of ordinary differential equations

$$\begin{cases} \partial S/\partial t = -\beta.S.I \\ \partial I/\partial t = \beta.S.I - \gamma.I \\ \partial R/\partial t = \gamma.I \end{cases}$$



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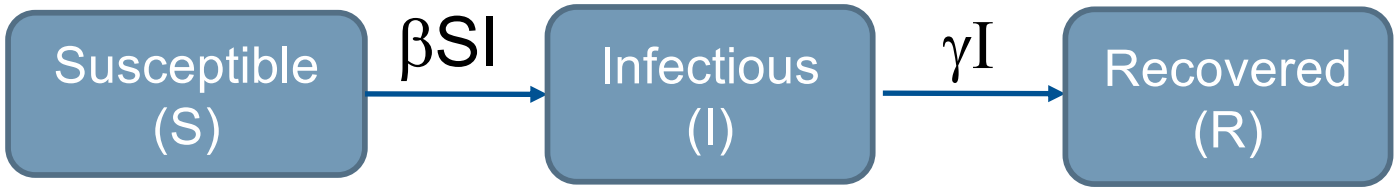
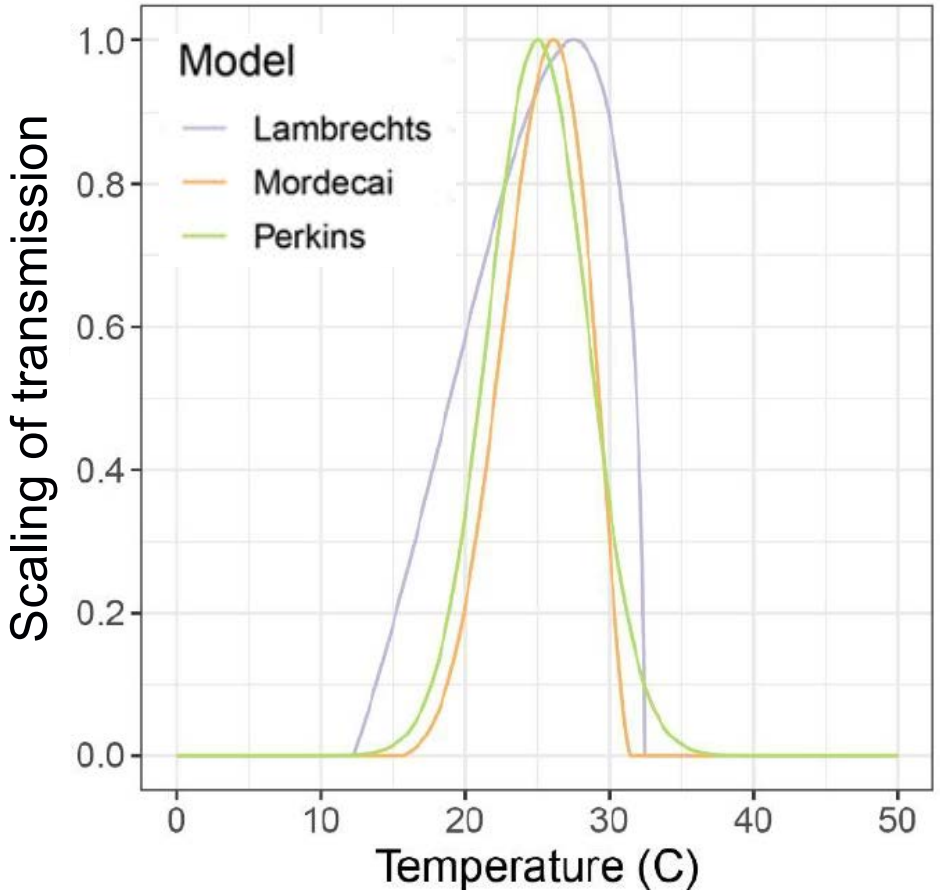
Modelling dengue epidemics in Réunion island



Transmission rate β modulated by climate variables

- **Lambrechts et al (PNAS 2011)**:
  - laboratory entomological data for *Ae. Aegypti*,
  - how probability of DENV transmission varies with temperature
- **Mordecai et al (Plos NTD 2017)**:
  - laboratory entomological data for *Ae. Aegypti* and *Ae. Albopictus*,
  - how mosquito lifecycle and probability of transmission affected by temperature for dengue, chikungunya, and zika viruses
- **Perkins et al (Plos Curr. 2015)**:
  - epidemiological case data collected during chikungunya outbreaks in the Americas



Different scenarios reflecting existing uncertainties

- **Model describing the association between climate and dengue transmission:** Lambrecht, Mordecai, Perkins
- **Scenarios for climate:** Average, Cold, Hot
- **Dengue generation interval:** 2-3 weeks
- **Detection probability ρ – probability that a person infected by dengue is detected by surveillance.** 10-40%

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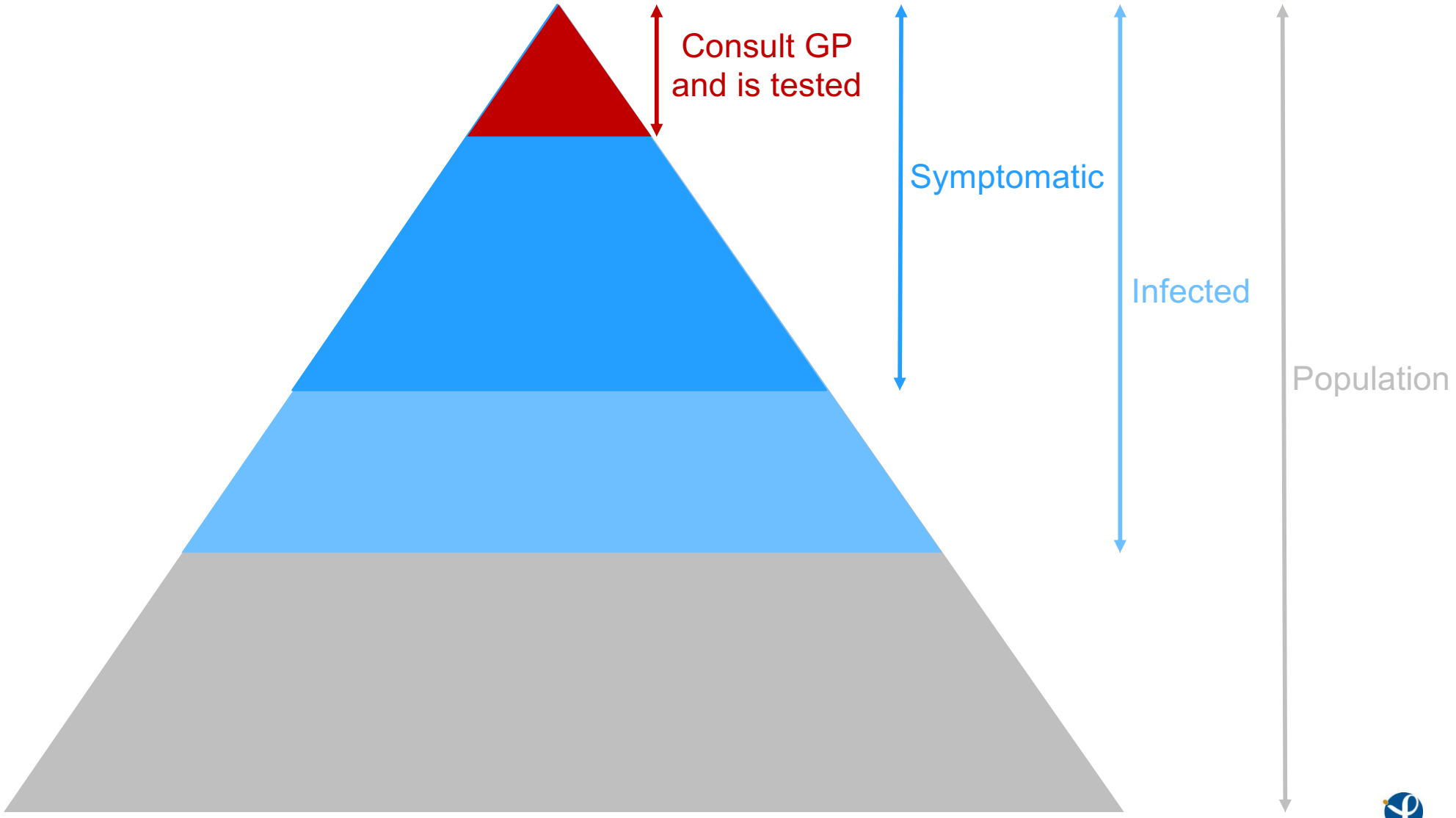
Detection probability ρ – why do we care?



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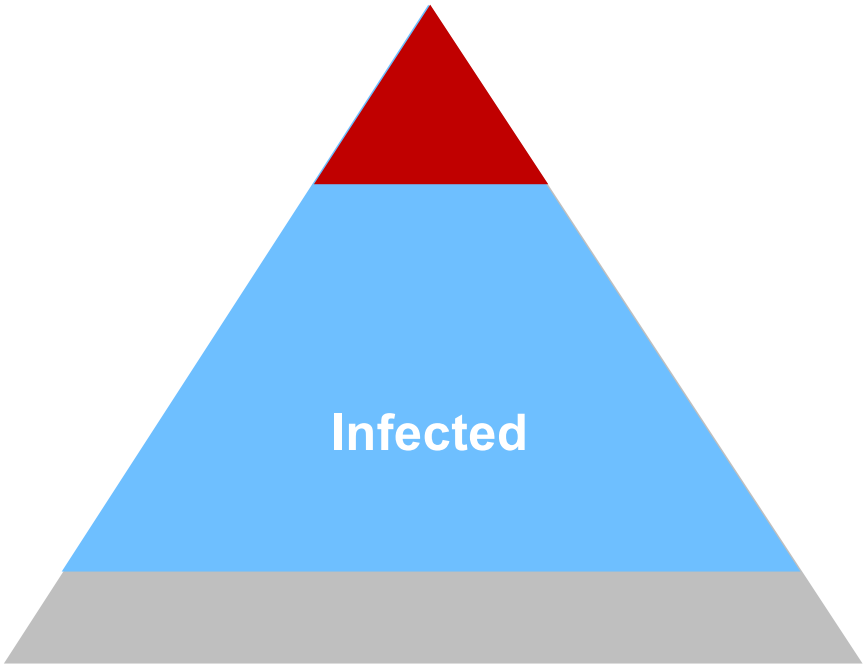
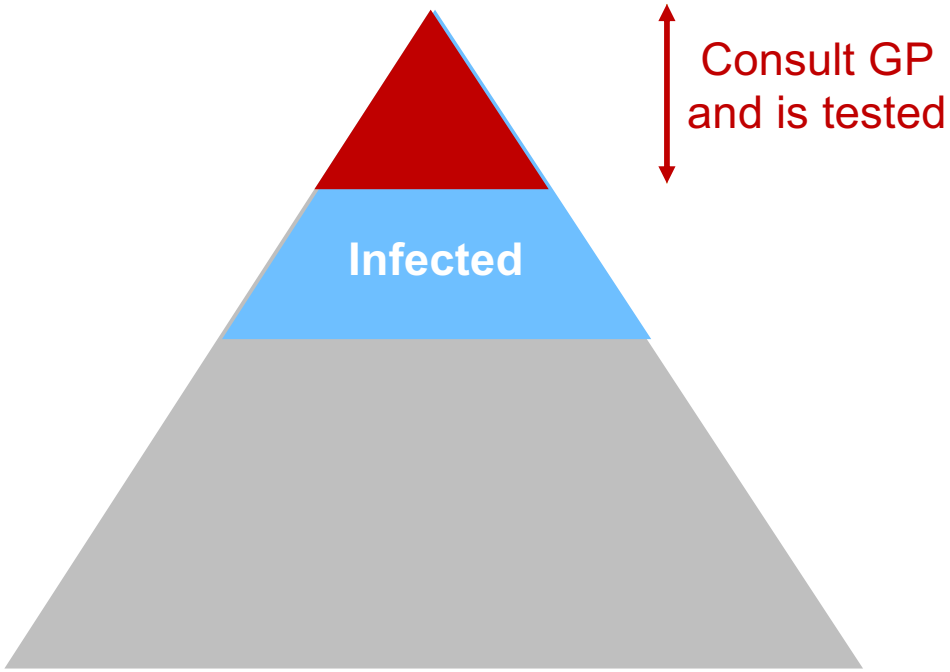
Detection probability ρ – why do we care?

Low detection probability



Most of the population has already been infected and is immunized.

High detection probability



A large proportion of the population is still susceptible to infection.

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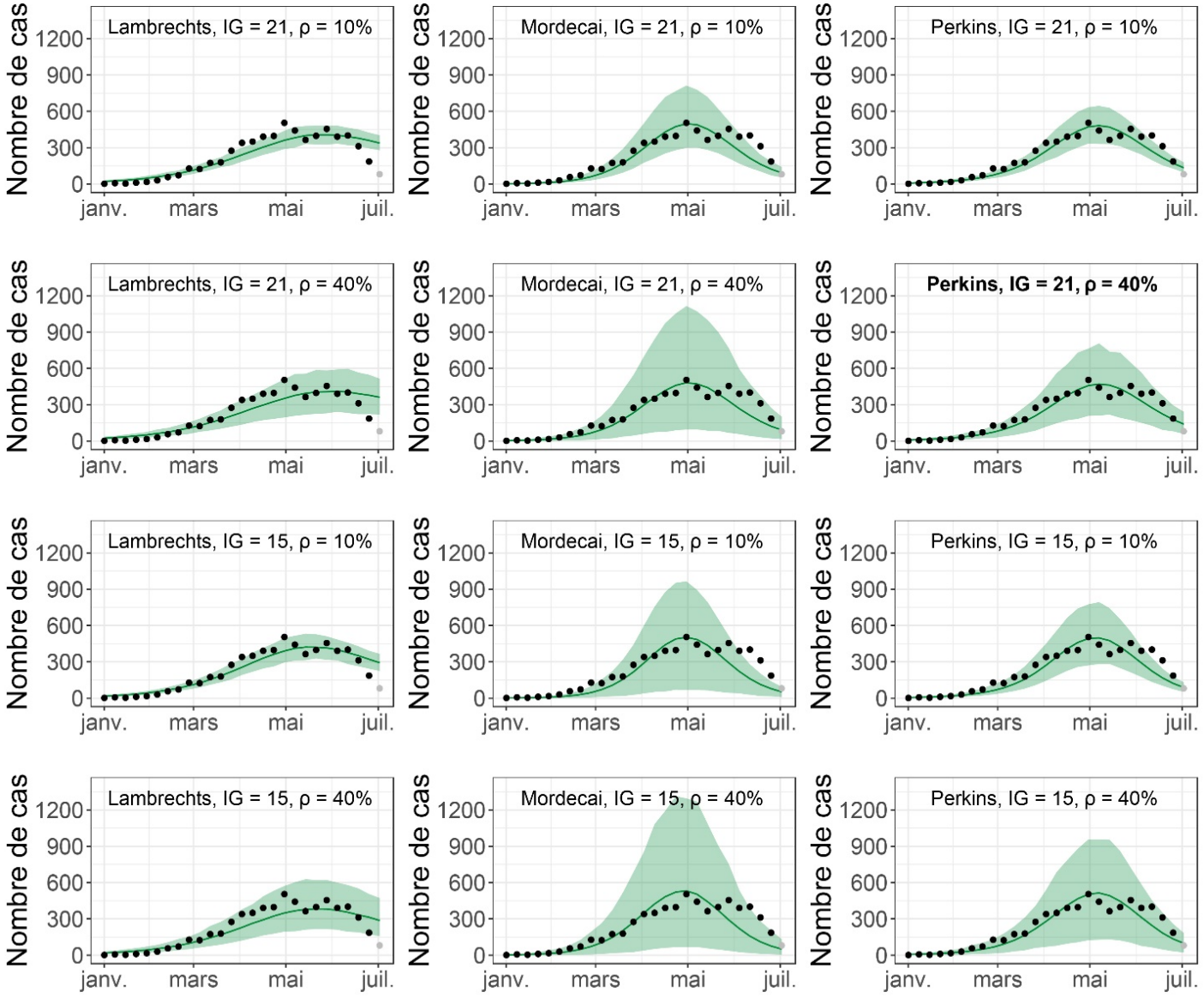
Assessment performed on 19th July 2018



Fitting the different models to latest available data with Markov chain Monte Carlo sampling.

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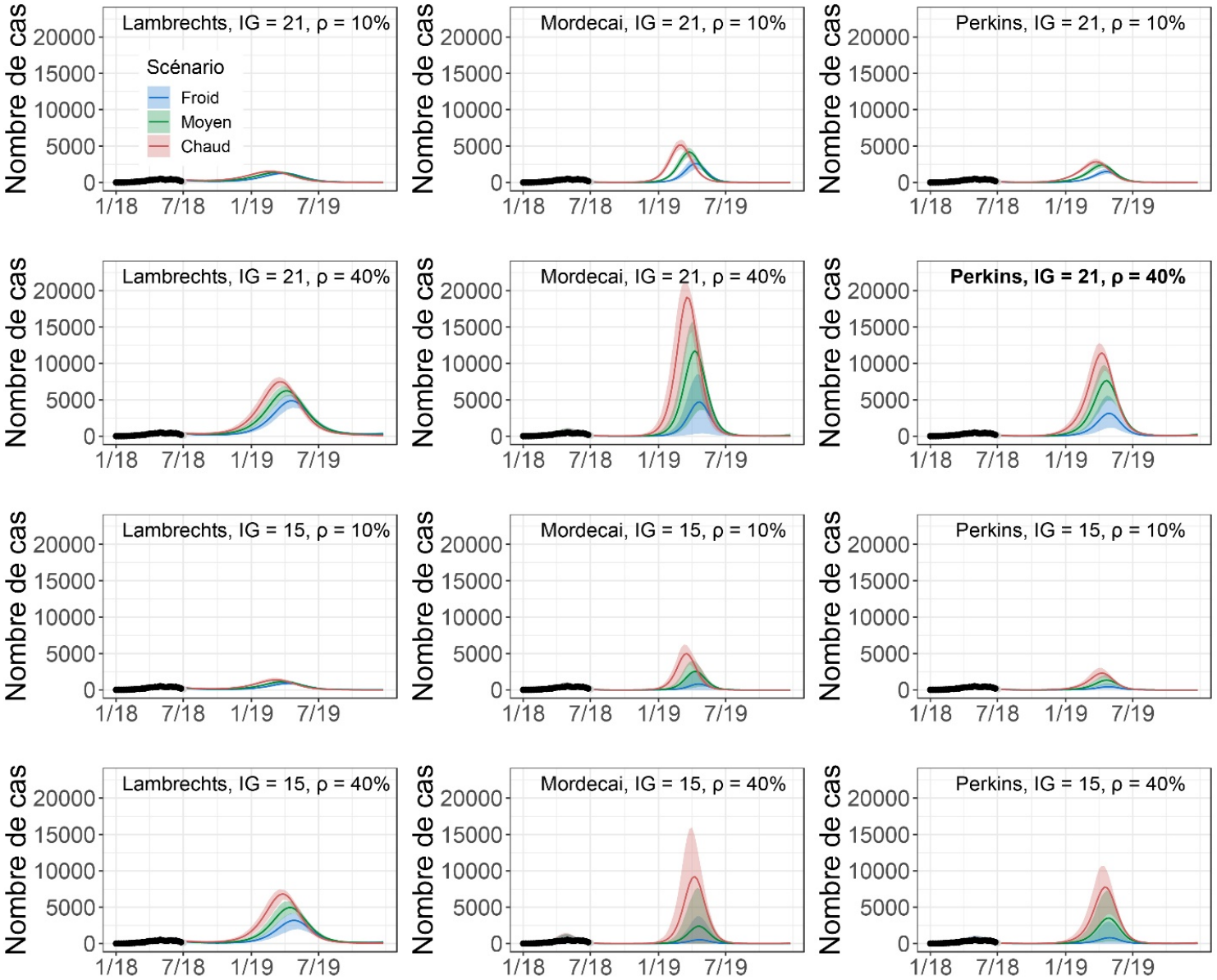
Assessment performed on 19th July 2018



Important heterogeneity but in all scenarios:

1) Persistance.
2) Second peak larger than first one.

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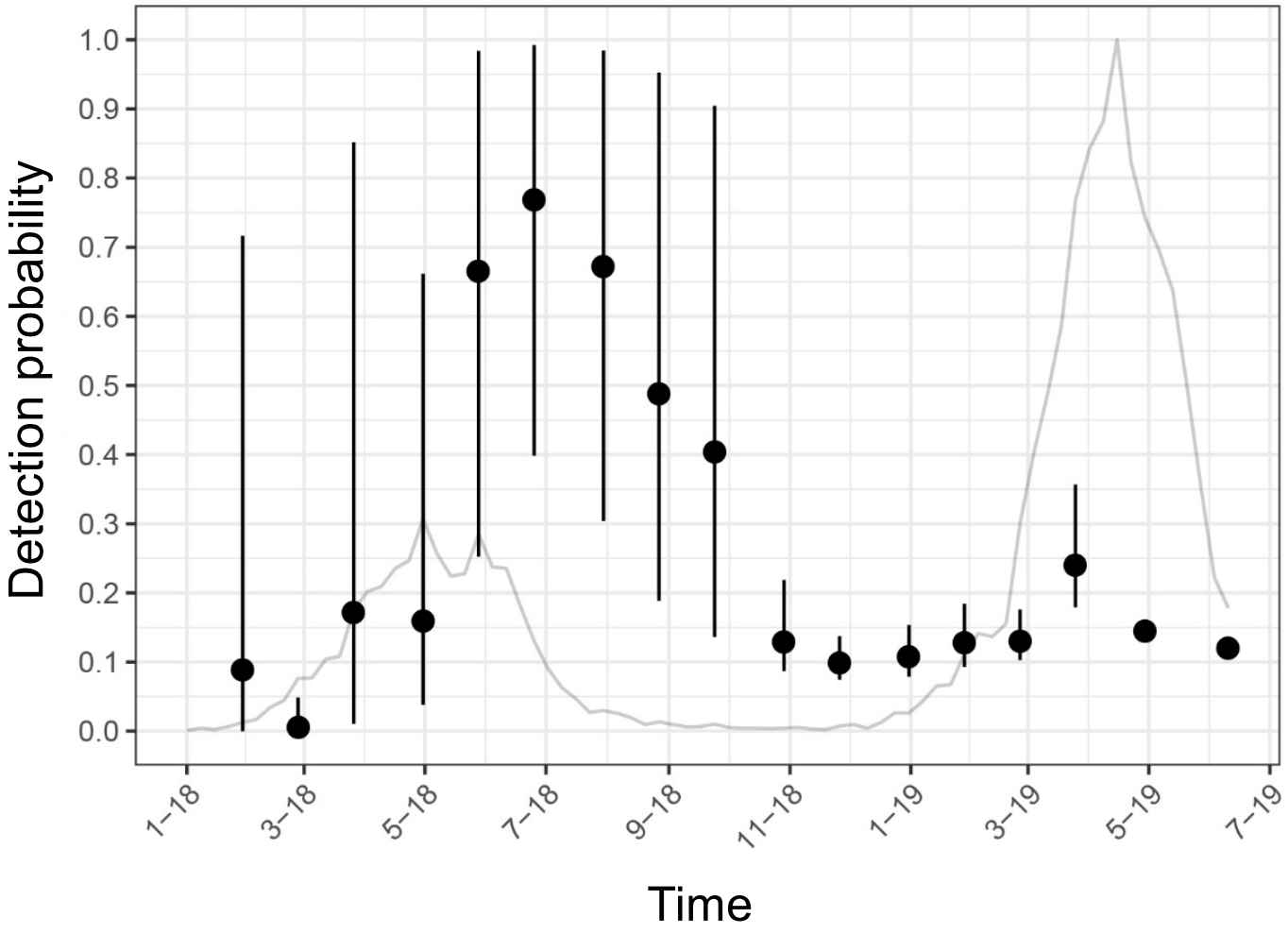
Estimates of the detection probability ρ



- Early on, data appear to be uninformative – we considered scenarios where detection probability ρ=10-40%.
- From start of second peak, signal that the detection probability was around 10%.
- Lobbying during the epidemic to collect serological data to estimate ρ independently.

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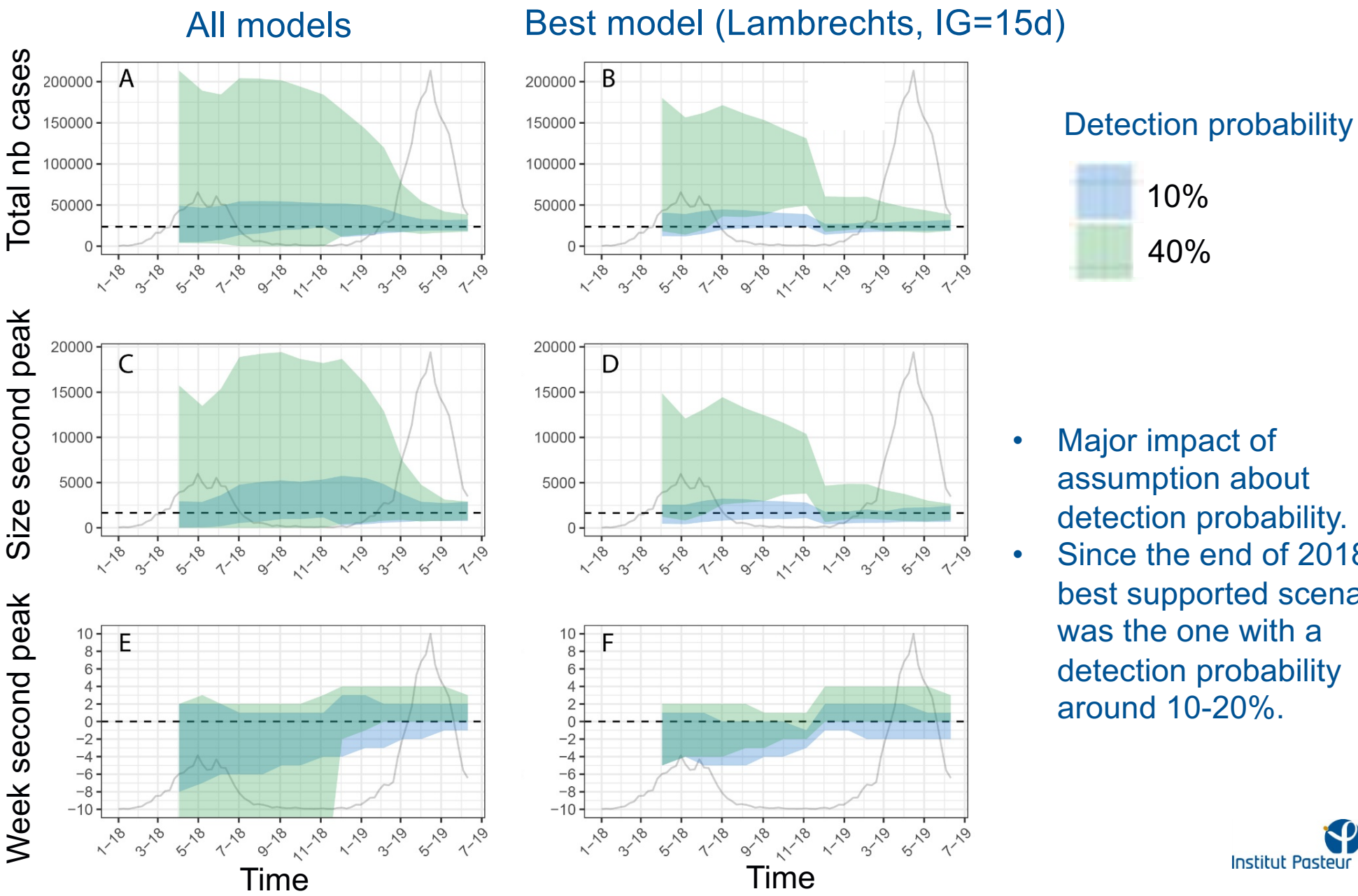
Performance of the models to predict the epidemic trajectory



- Major impact of assumption about detection probability.
- Since the end of 2018, best supported scenario was the one with a detection probability around 10-20%.

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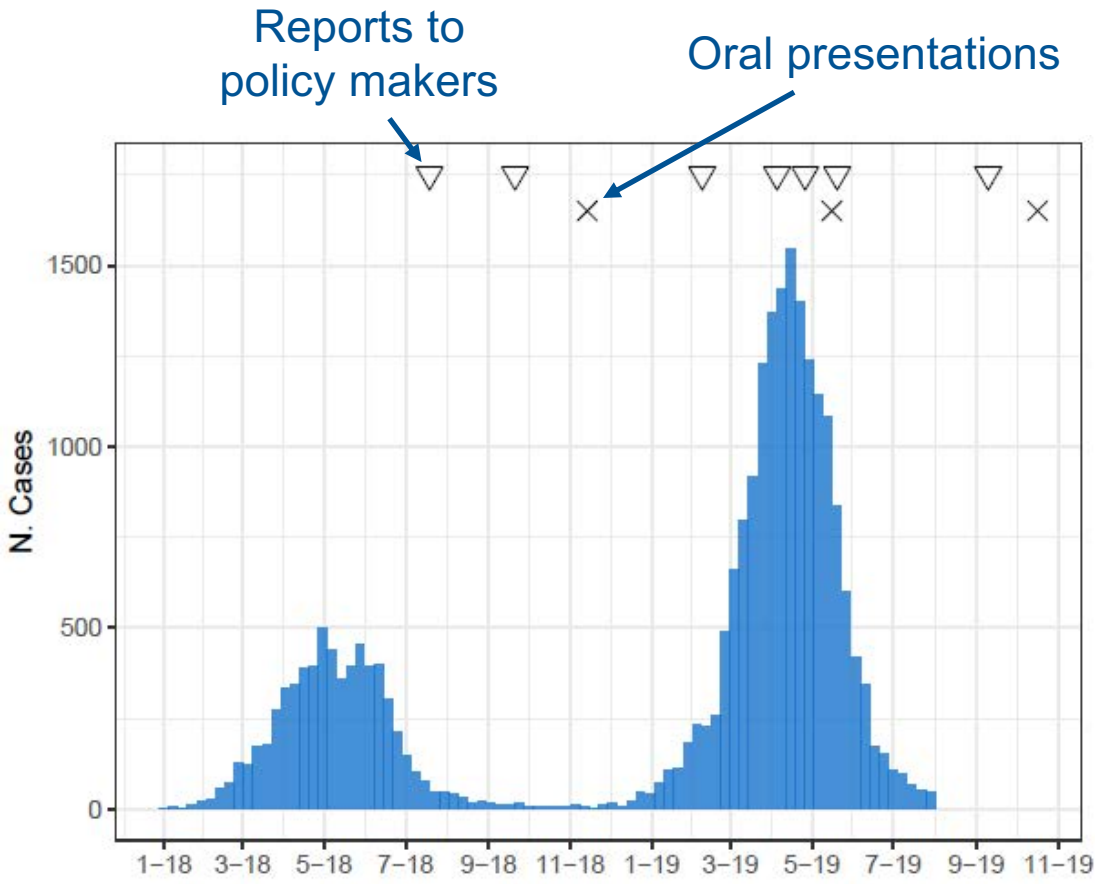
Communicating with Public Health officials and policy makers

- Very regular meetings with Public Health officials from Santé Publique France.
- 7 reports and 3 oral presentations for policy makers from the Ministry of Health and the local authorities from the island.



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How were modelling results used?

- Hospital physicians:
  - Anticipate hospitalizations for DENV.
  - Enrollment activities in ongoing clinical trial.
- Agence Régionale de Santé (ARS), i.e. the local health agency:
  - Plan response activities and resources.
  - February and April 2019 reports used to organize the reinforcement of different civilian defense actors and to strengthen vector control measures.
- Prefecture, which coordinates all the activities to control arboviruses:
  - Make sure that appropriate resources (e.g. firefighters) would be available in Réunion at the peak of the epidemic.

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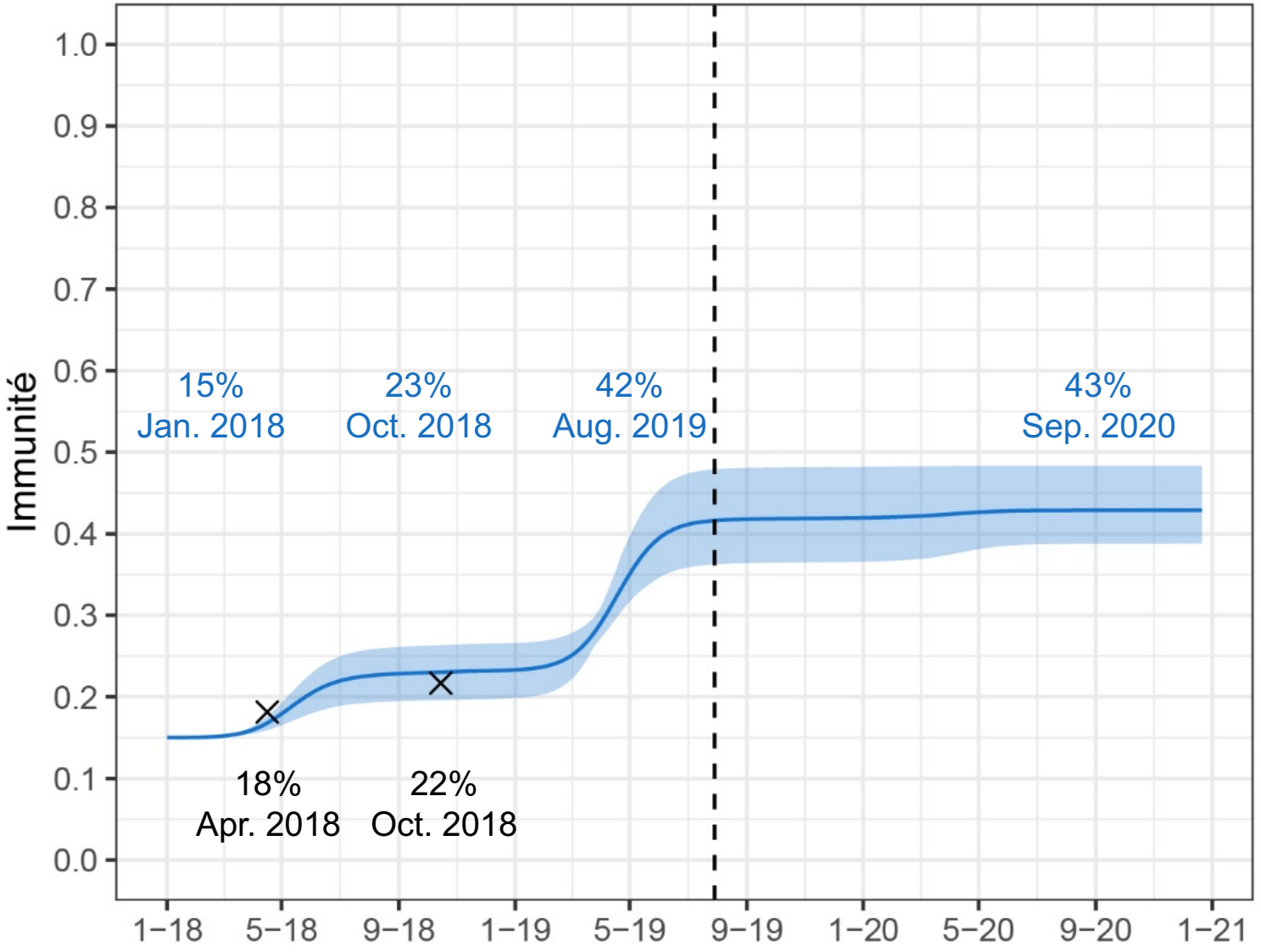
Current level of immunity in the population (DENV2)



Model

Serological data

19% immunised during 2nd wave

8% immunised during 1st wave

15% immunised before 1st wave

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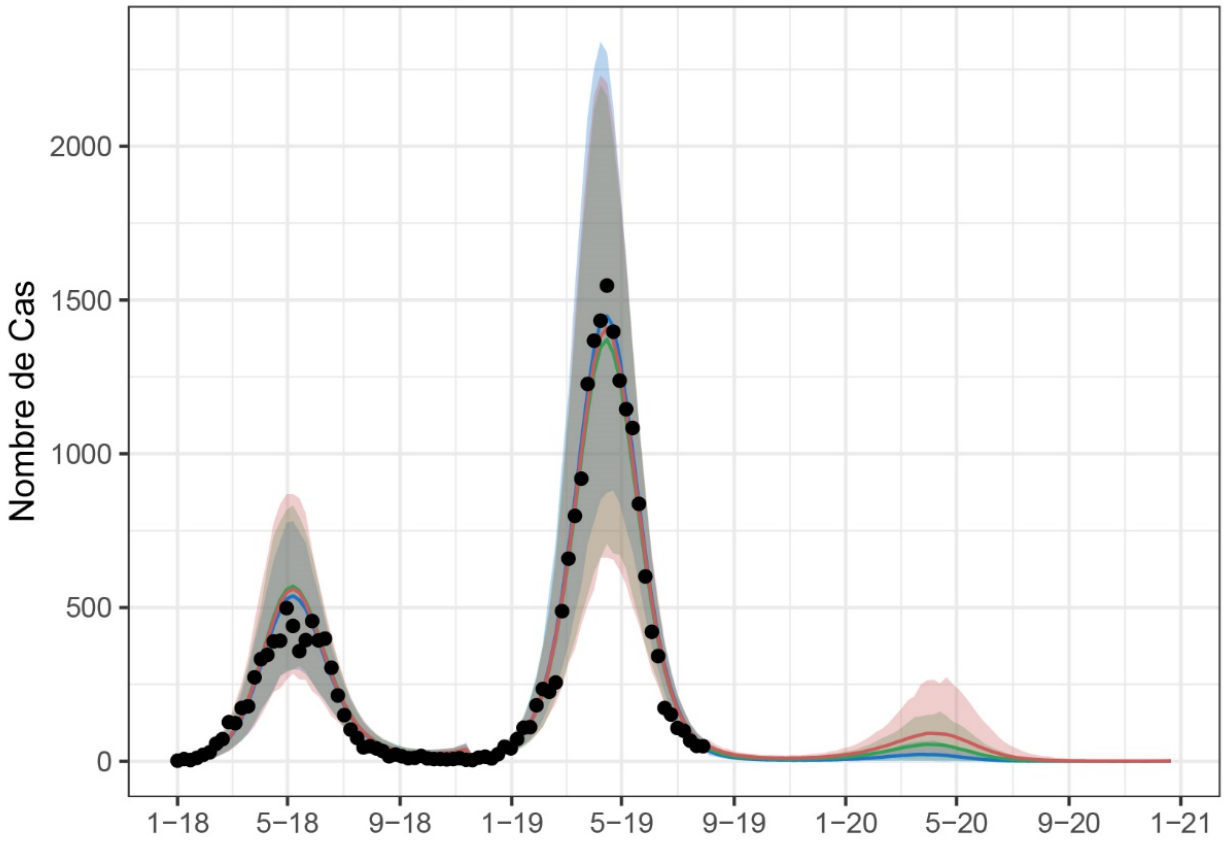
Risk of a third wave

Under assumption that 42% were immunized against DENV2

- No major 3rd wave expected if DENV2 remains the dominant serotype
- But possible if switch to DENV1.



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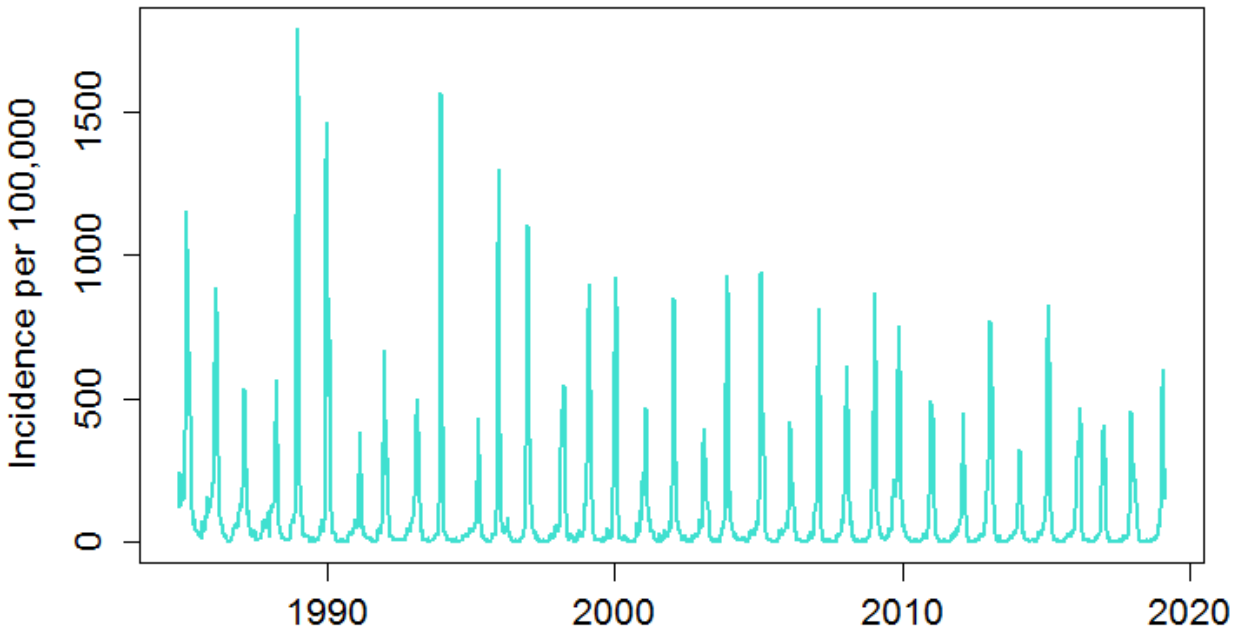
Predicting influenza epidemics in France

Sentinelles network

- Surveillance network of ~1300 general practitioners (GPs) (2% of the total GPs)
- Data since 1984
- Weekly incidence of influenza-like illness



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Forecasting challenges

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

FluSight: Flu Forecasting

Español

Research teams compete to predict epidemics:

- Influenza
- Dengue
- Chikungunya
- Ebola

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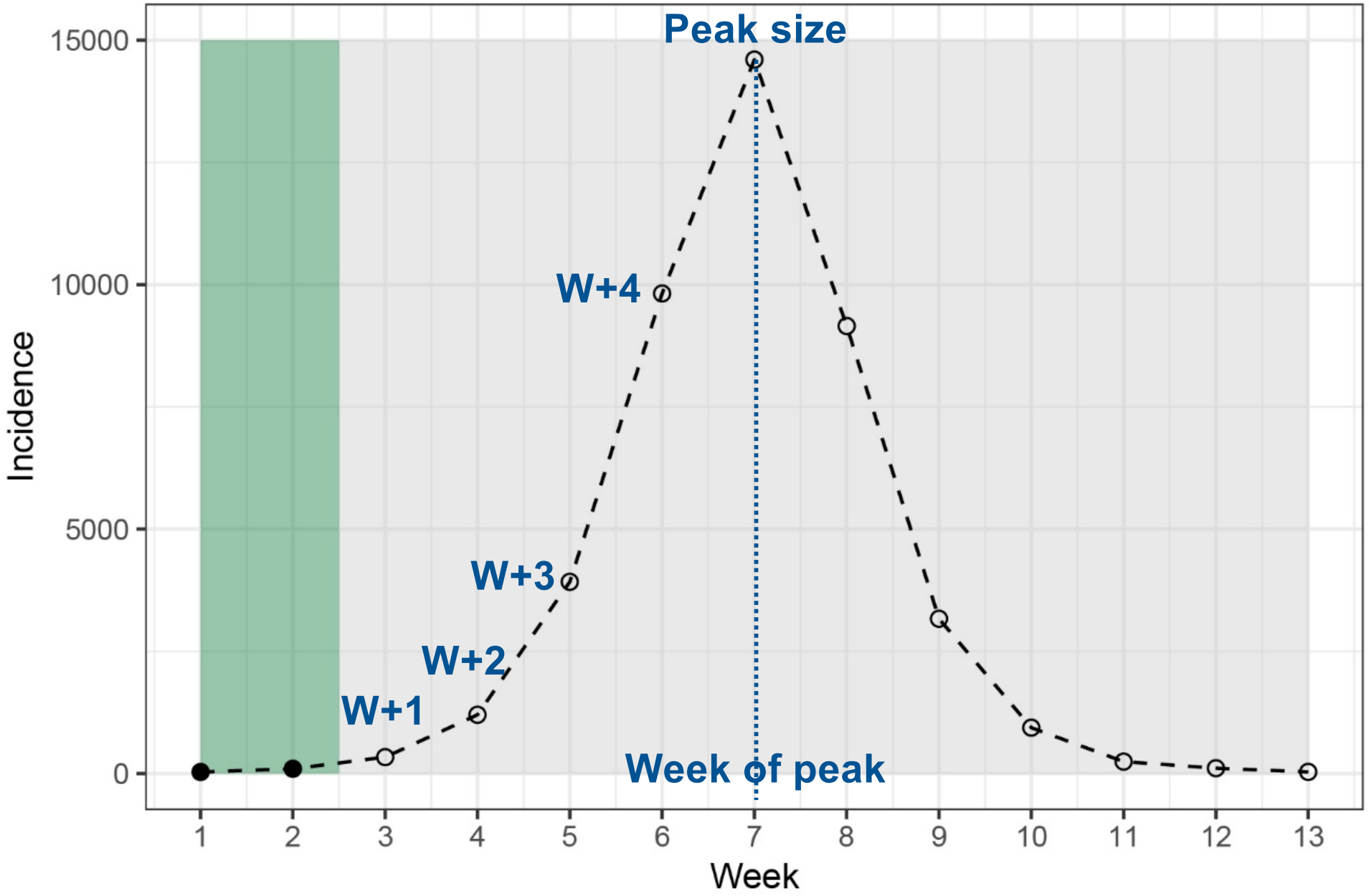
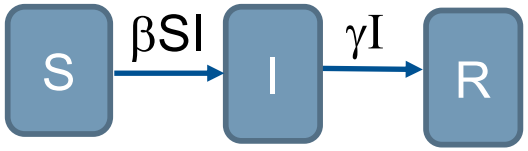
Forecasting targets



Different types of models

Mechanistic models



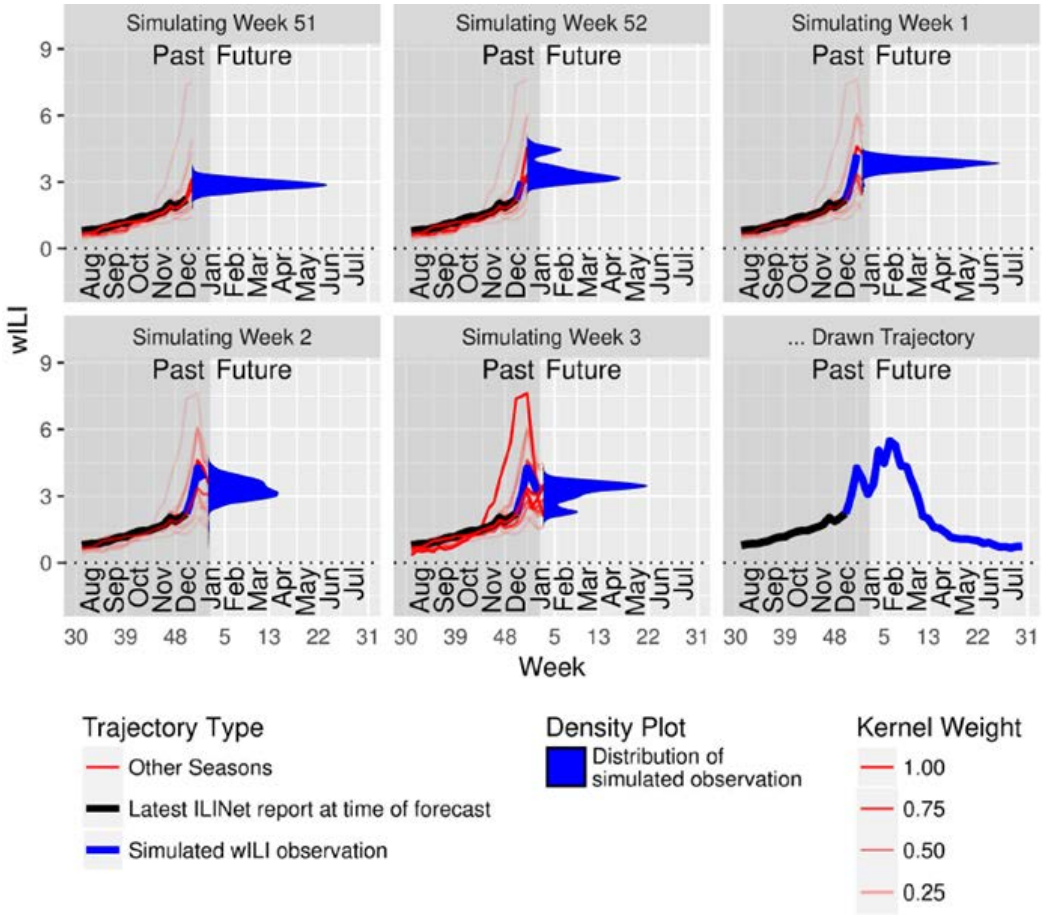
Calibration: Ensemble Kalman Filter, Adjusted Ensemble Kalman Filter, PMCMC, …

Time-series models

E.g. SARIMA (Seasonal Auto-Regressive Integrated Moving Average model)

$$\hat{y}_t = \underbrace{\mu}_{\text{constant}} + \underbrace{\phi_1 y_{t-1} + \ldots + \phi_p y_{t-p}}_{\text{AR terms (lagged values of } y)} \underbrace{- \theta_1 e_{t-1} \ldots - \theta_q e_{t-q}}_{\text{MA terms (lagged errors)}}$$

Statistical models



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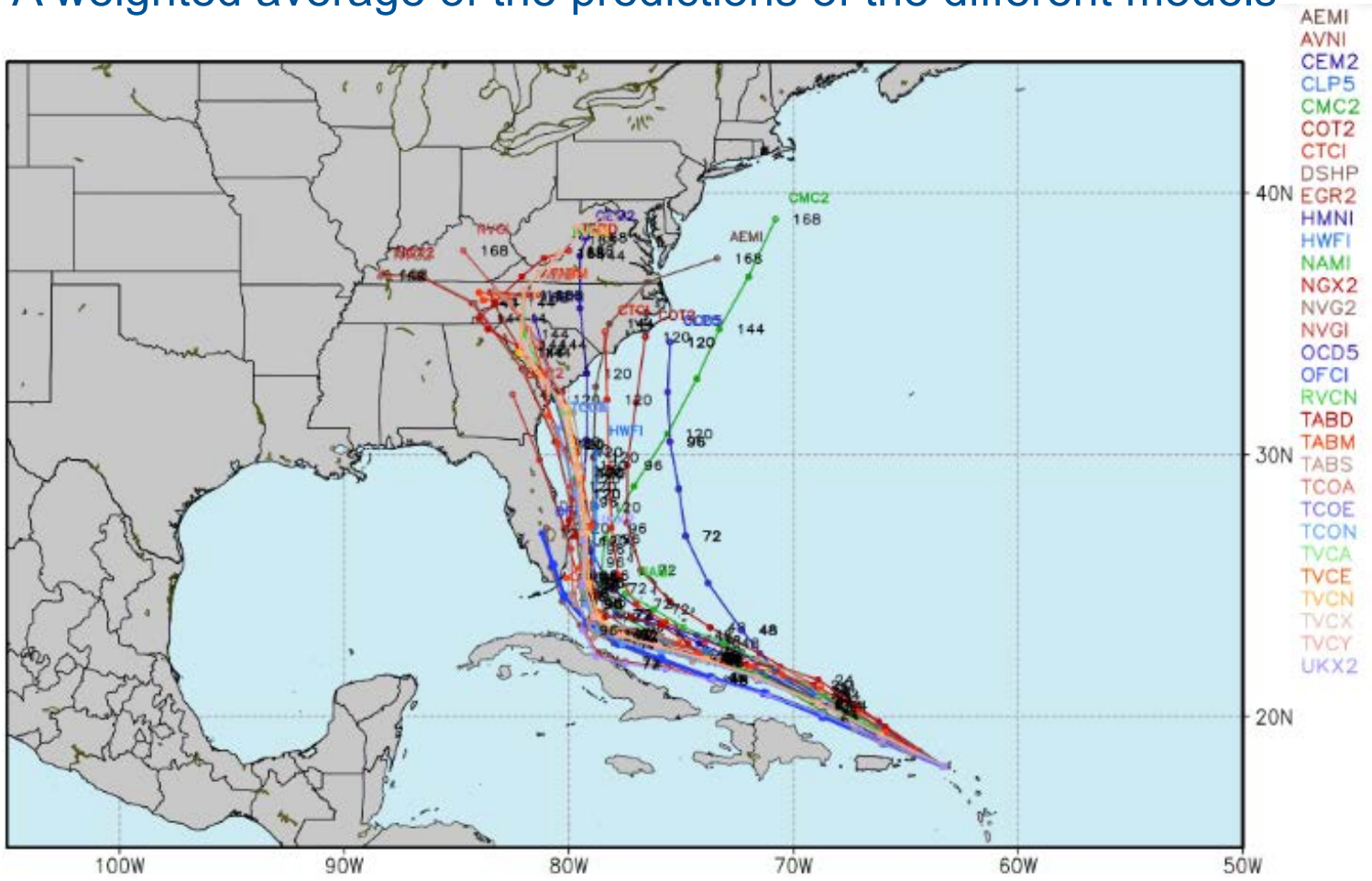
What is the best model? The Ensemble model

A weighted average of the predictions of the different models



20 different models used to predict influenza epidemics in France

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1985-1986
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2017-2018
2018-2019
2019-2020
...

Analysing 33 years of influenza surveillance

❶ 25 training seasons

❷ 7 validation seasons

❸ 1 test season

❹ Real-time predictions for coming season

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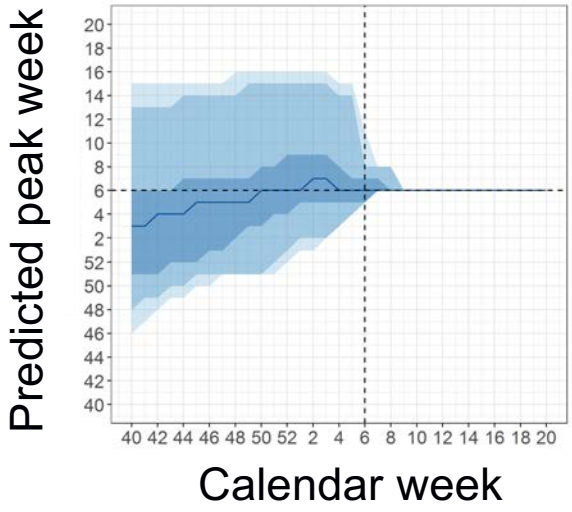
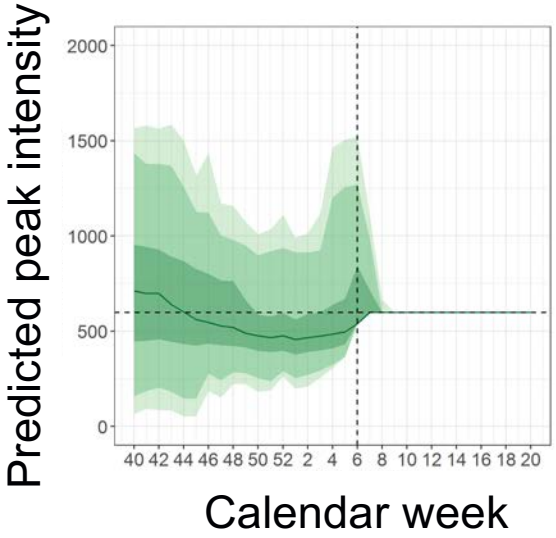
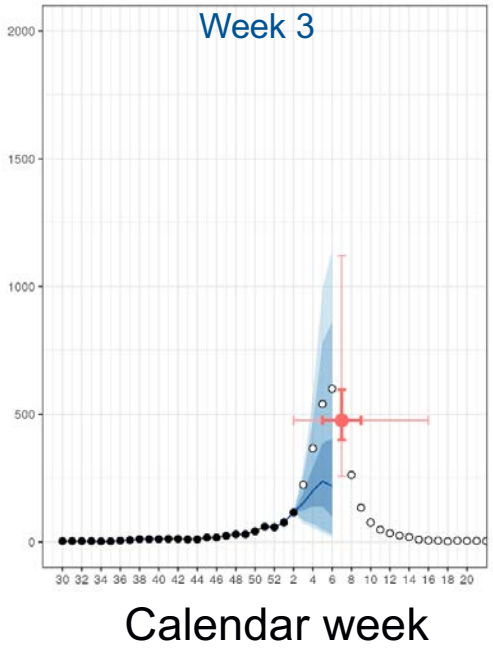
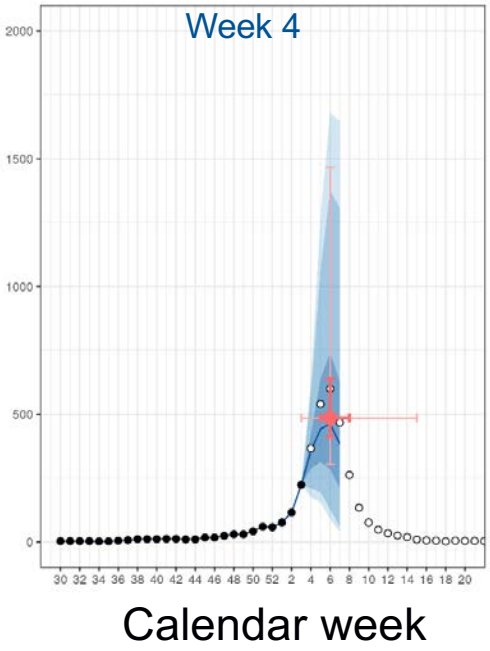
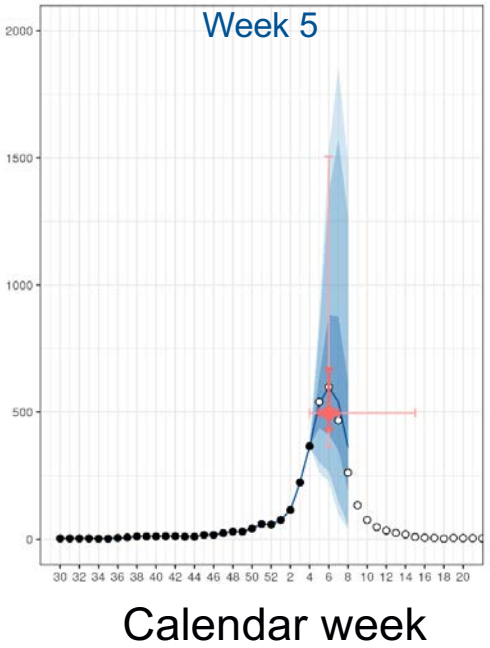
Results for test season 2018/2019

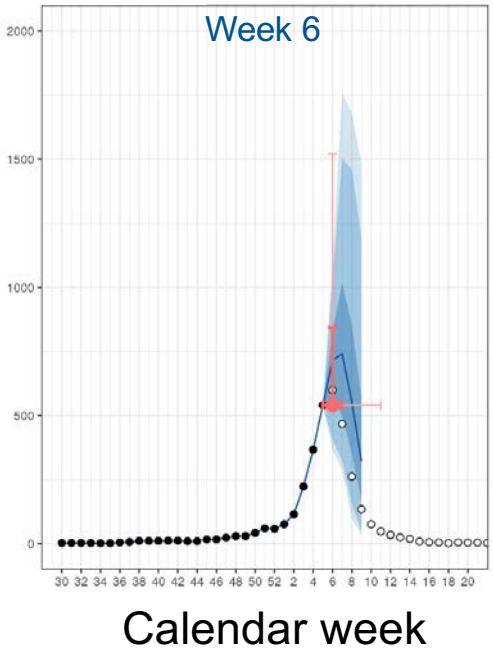












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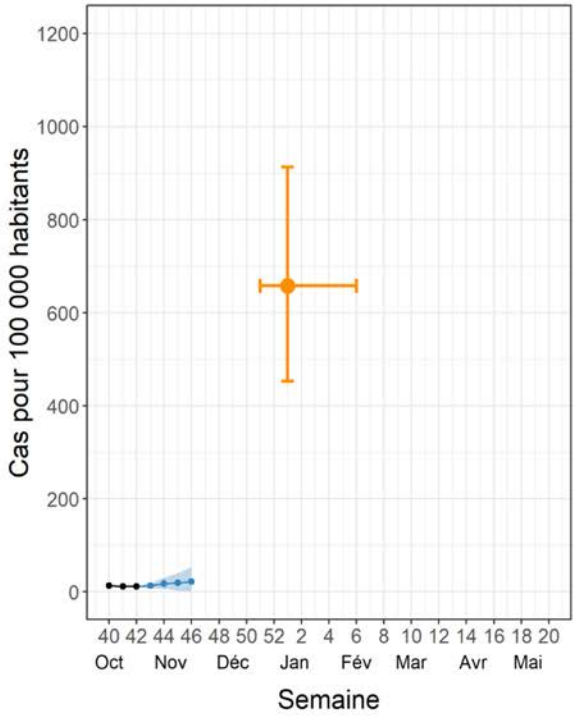
Real-time use during 2019-2020 influenza season

Saison grippale 2019/2020

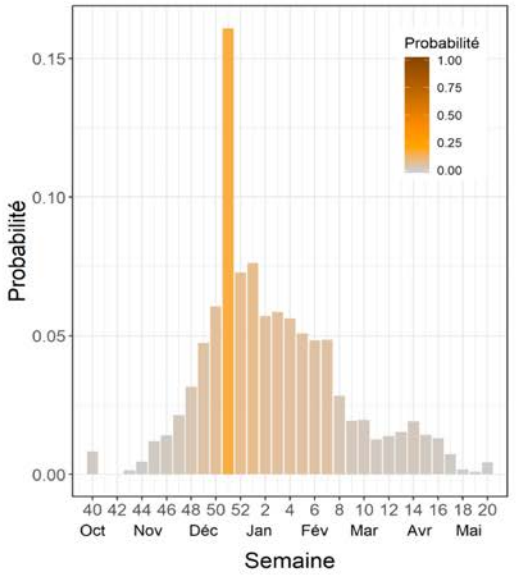
Prédictions du 23 octobre 2019 (mercredi de la semaine 43)

Le graphique ci-dessous montre les prédictions pour la saison grippale 2019-2020. Les données publiées à ce jour par le réseau Sentinelles sont représentées en noir. Les prédictions pour les 4 prochaines semaines sont représentées en bleu (médiane et écart inter-quartile). Les prédictions pour le pic (semaine et taille) sont représentées en orange (médiane et écart inter-quartile).



Prédictions du pic épidémique

Il y a 34% de chances que le pic épidémique ait lieu en décembre et 30% en janvier.



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Future improvements for influenza predictions

- Integration into decision making process and tools for Public Health planning.
- Regional versus national predictions.
- Information about circulating subtype.
- Accounting for antigenic distances between viruses.

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Conclusions

- Epidemic forecasting is an expending field.
- Performance depends on nature of the transmission process and quality of available data.
- A lot more efforts required for it to be properly integrated into decision making process.

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Acknowledgements

- **Institut Pasteur (France): Alessio Andronico, Juliette Paireau**, Q. ten Bosch, H. Salje.
- **Santé Publique France:** H. Noel, D. Levy Bruhl, D. Che, B. Coignard, H. de Valk, M.C. Pathy, Y. Lestrat, L. Menudier, P. Vilain.

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Funded by the National Institutes of Health

INVESTISSEMENTS D'AVENIR

Labex IBEID

Institut Pasteur

AXA Research Fund

HORIZON 2020

INCEPTION

Fondation de France

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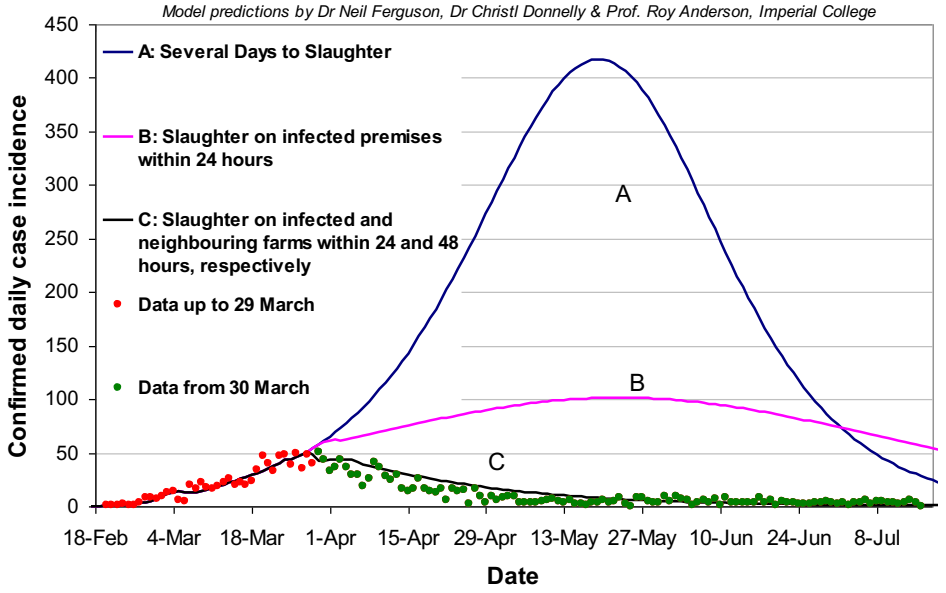
How good are we at predicting epidemics?

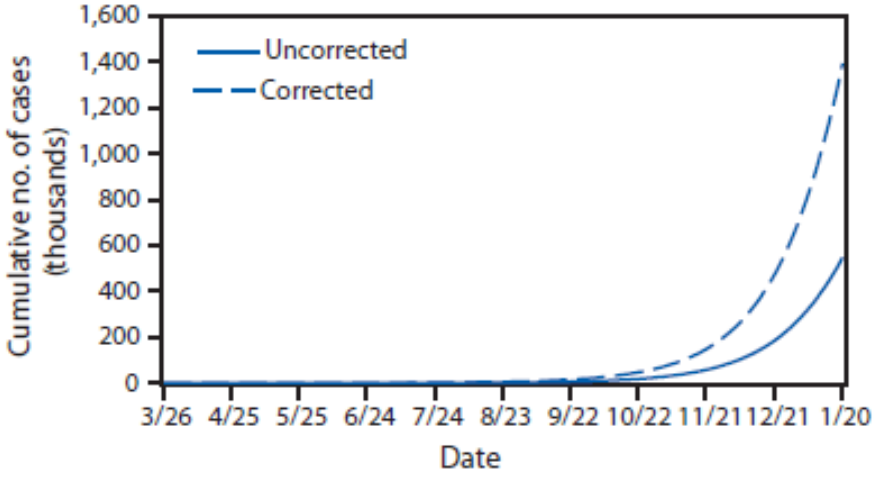
Foot-and-mouth disease epidemic in the UK in 2001

- Modelling decisively guided the response of the authorities.
- Excellent data, good understanding of underlying transmission process.



Ebola epidemic in West Africa in 2014-2016

- In Sept 2014, CDC modellers predicted 1.4 million cases within 5 months if nothing changed.
- Good to mobilize the Public Health community and funders, but what about the science?



Predictions rarely the most important insight for decision makers – Ebola [courtesy of N. Ferguson]

- ‘How many Ebola cases will be imported to the UK/US?’
- ‘What would the impact of border screening be?’
- ‘How long should suspect cases be isolated?’
- ‘How many cases will there be in 4 weeks time?’
- ‘How many cases are being missed?’
- ‘Why is the CFR different between the 3 countries?’
- ‘What proportion of cases are being hospitalised?’
- ‘How many beds will be needed to achieve control in SL?’
- ‘Where are the current hot-spots?’
- ‘Are women more at risk?’
- ‘What are the risk factors for transmission?’
- ‘What is the variation in CFR between hospitals?’

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