Virtual Training 12 - Focus on the Agents of Whooping Cough

Global Spatial Dynamics and Vaccine-Induced Fitness Changes in *B. pertussis*

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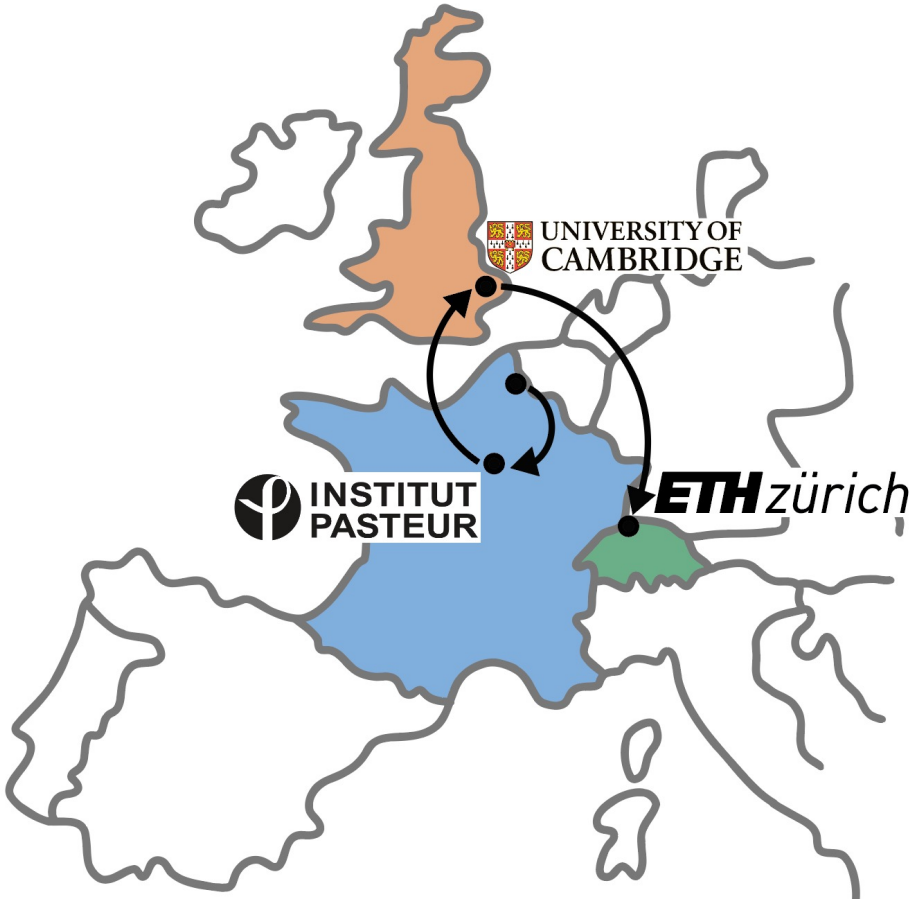
Noémie Lefrancq

Background:

- Undergraduate in Biology
- Master in Mathematics of Modelling
- PhD at the University of Cambridge in Infectious disease modelling

Worked at Institut Pasteur Paris

Currently: Postdoctoral fellow at ETH Zürich, Switzerland



Intended Learning Objectives

Specific objectives of this session:

1. Learn about **spatial dynamics** of *Bordetella pertussis*
2. Learn about the **fitness changes** of *Bordetella pertussis* and relation with vaccine types

Outline

This session consists of the following elements:

Introduction to the session

Part I: Global spatial spread of *B. pertussis*
1.1. *B. pertussis* clustering within locations
1.2. Spatial spread of *B. pertussis* within countries and across continents

Part II: Vaccine-Induced Fitness Changes in *B. pertussis*
2.1. Methods to estimate changes in fitness
2.2. Impact of vaccine type change on Bp genotypes' fitness

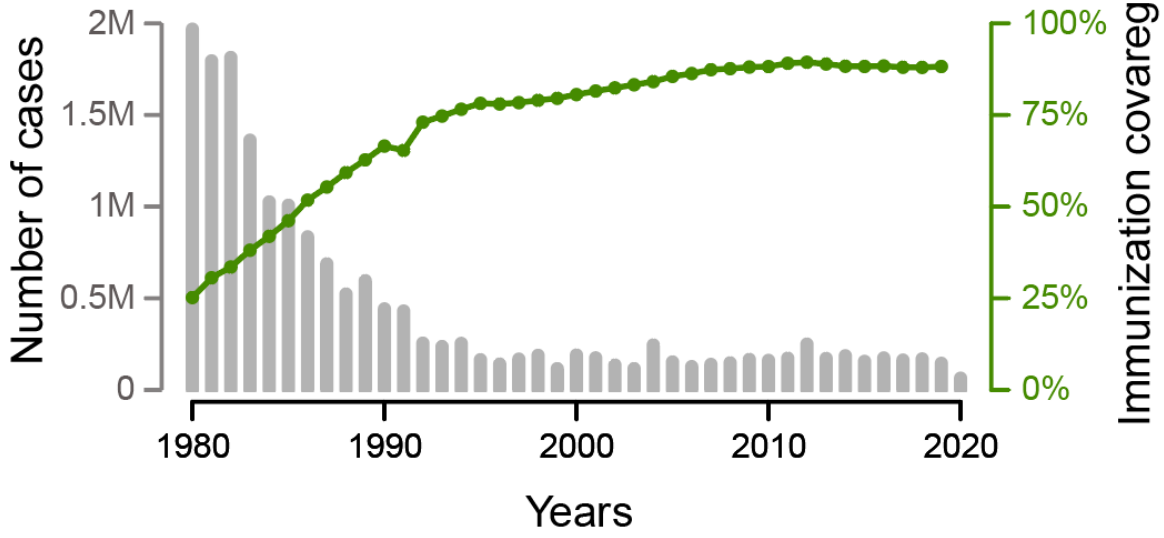
Introduction

B. pertussis global epidemiology

- Incidence greatly reduced since 1980s.
- Vaccination levels are typically high (>90%)
- However, persistent transmission is still observed[1].
- Reasons for persistence are still unclear[2]
  - Pathogen adaptation?
  - Acellular vaccines waning

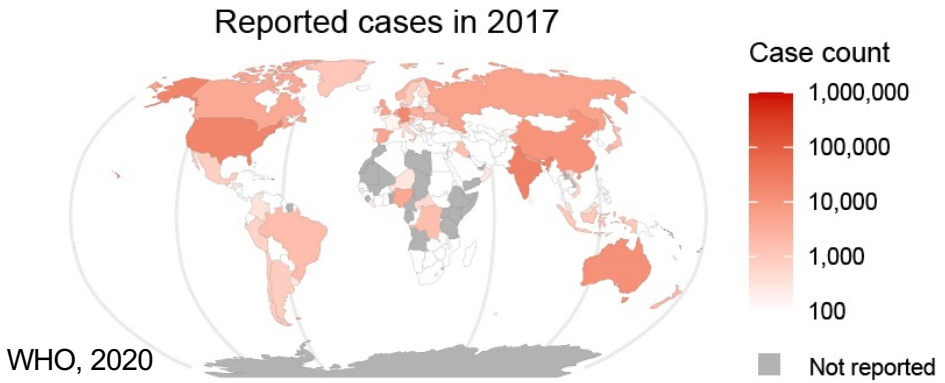
  and asymptomatic carriage?

Yearly number of cases & immunisation coverage
Source: WHO data[3]



1: Yeung *et al.,* 2017, 2: Jackson and Rohani, 2014, 3: WHO, 2020

Country-specific situation



Historical vaccine:
Whole-cell (WCV)

Recent vaccine:
Acellular (ACV), containing:

- Pertussis toxin (PT)
- Fimbria 2 & 3 (fim2 & 3)
- Pertactin (PRN)
- Filamentous Haemagglutinin (FHA)

- Persistent transmission observed[3] in all countries.
- Different vaccines exist.

3: WHO, 2020, 4: Lefrancq & Bouchez *et al.,* 2022

slido

Please download and install the Slido app on all computers you use

Do you think pertussis is mostly endemic, or spreads across locations?

ⓘ Start presenting to display the poll results on this slide.

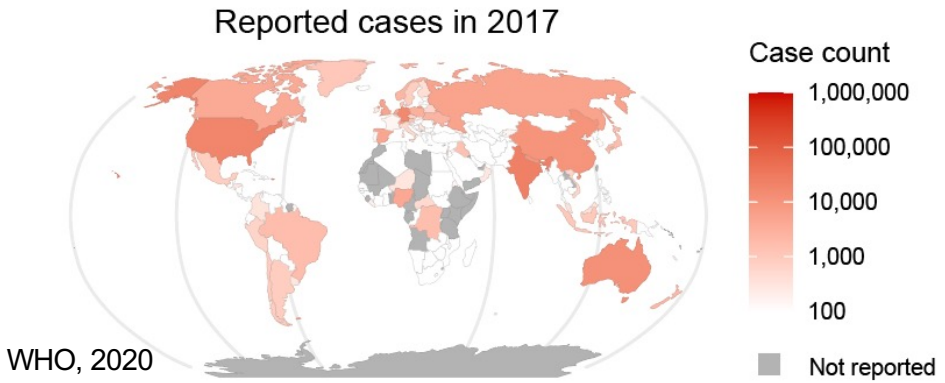
slido

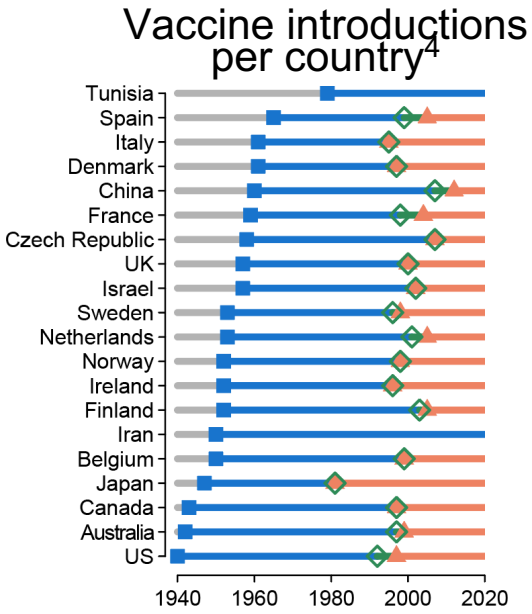
Please download and install the Slido app on all computers you use

What type of pertussis vaccine in implemented in your country?

ⓘ Start presenting to display the poll results on this slide.

Country-specific situation





Historical vaccine:
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Recent vaccine:
Acellular (ACV), containing:

- Pertussis toxin (PT)
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- Pertactin (PRN)
- Filamentous Haemagglutinin (FHA)

- Persistent transmission observed[3].

How fast is Pertussis spreading across spatial scales?

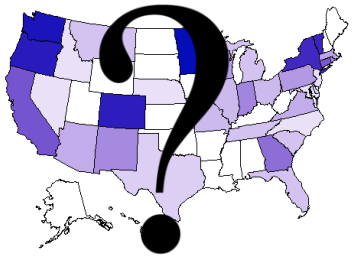
- Heterogeneity in timing of introductions and vaccine types.

How are vaccines impacting Pertussis strains at the population level?

3: WHO, 2020, 4: Lefrancq & Bouchez *et al.*, 2022

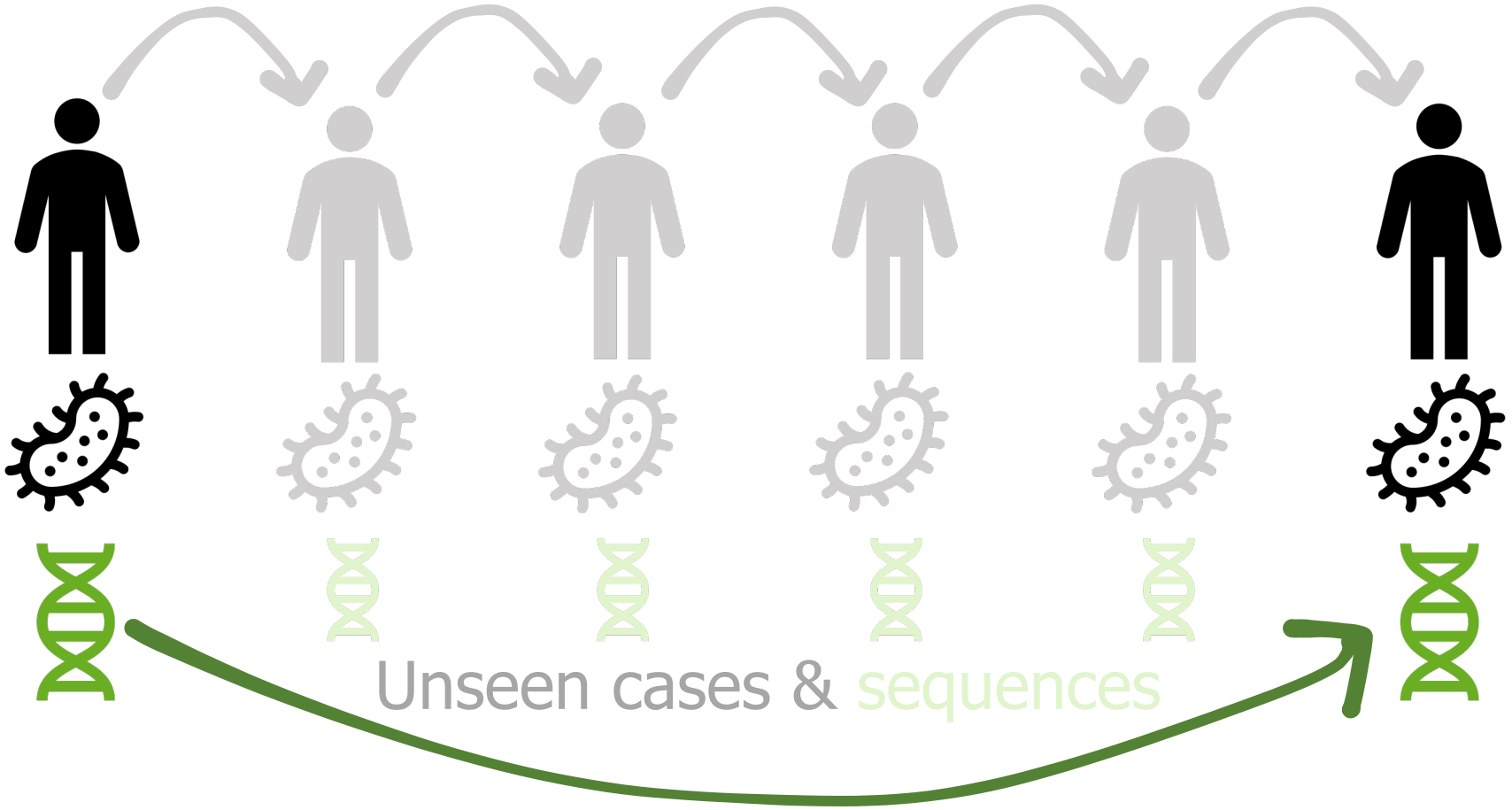
Key questions

Part 1: How fast is Pertussis spreading across spatial scales?



Part 2: How are vaccines impacting circulating strains?

Genetic epidemiology can help



Genetic epidemiology can help

By combining information of:

where people live

when they get sick

the bacterial genomes

- We can answer these key questions on pertussis circulation

Global genomics project

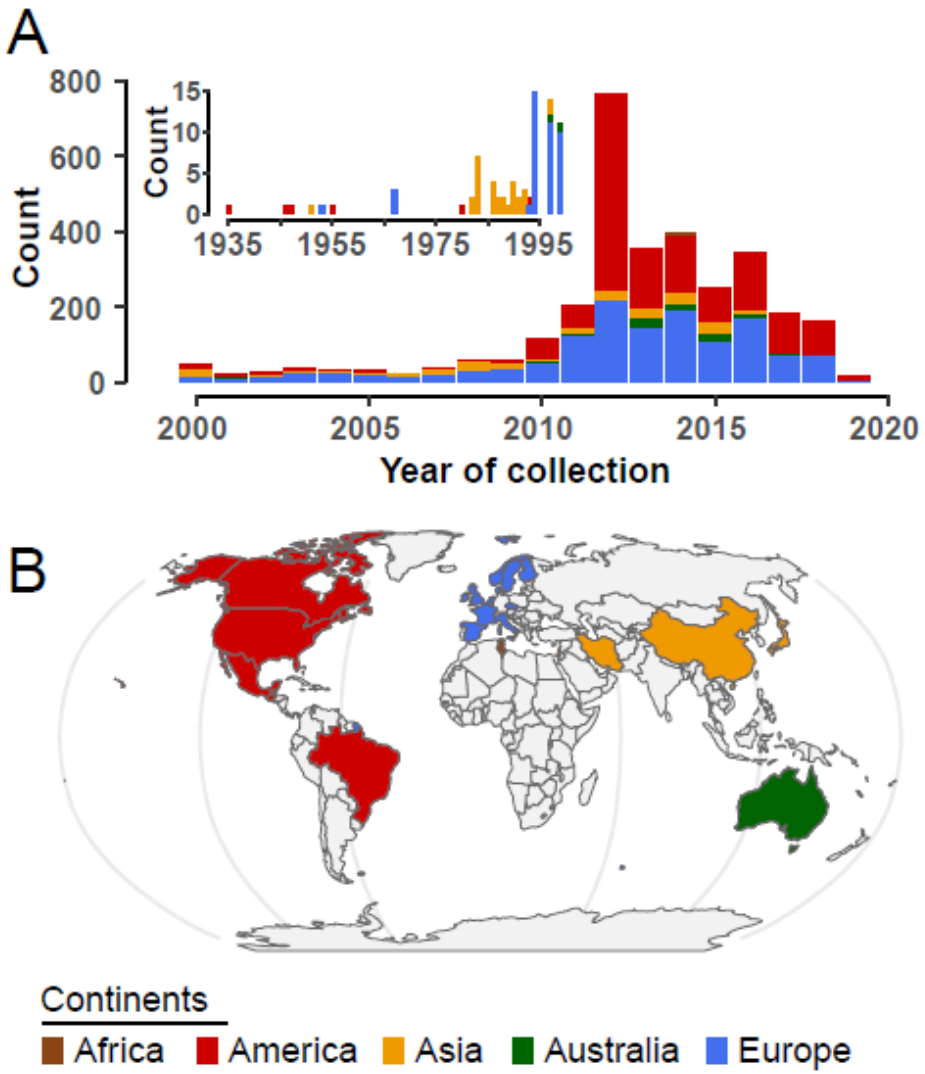
Joint work with Institut Pasteur Paris

3343 whole genomes from 1935 to 2019, from 23 countries:

- **1012 from France**
- **320 sequences from Europe**: Belgium, Czech Republic, Denmark, Spain, Finland, Italy, Ireland, The Netherlands, Norway, Sweden and The UK.
- **2012 from GenBank**

For each isolate, we have:

- **Date** of sampling (year)
- **Location** of sampling



Lefrancq & Bouchez *et al.*, 2022

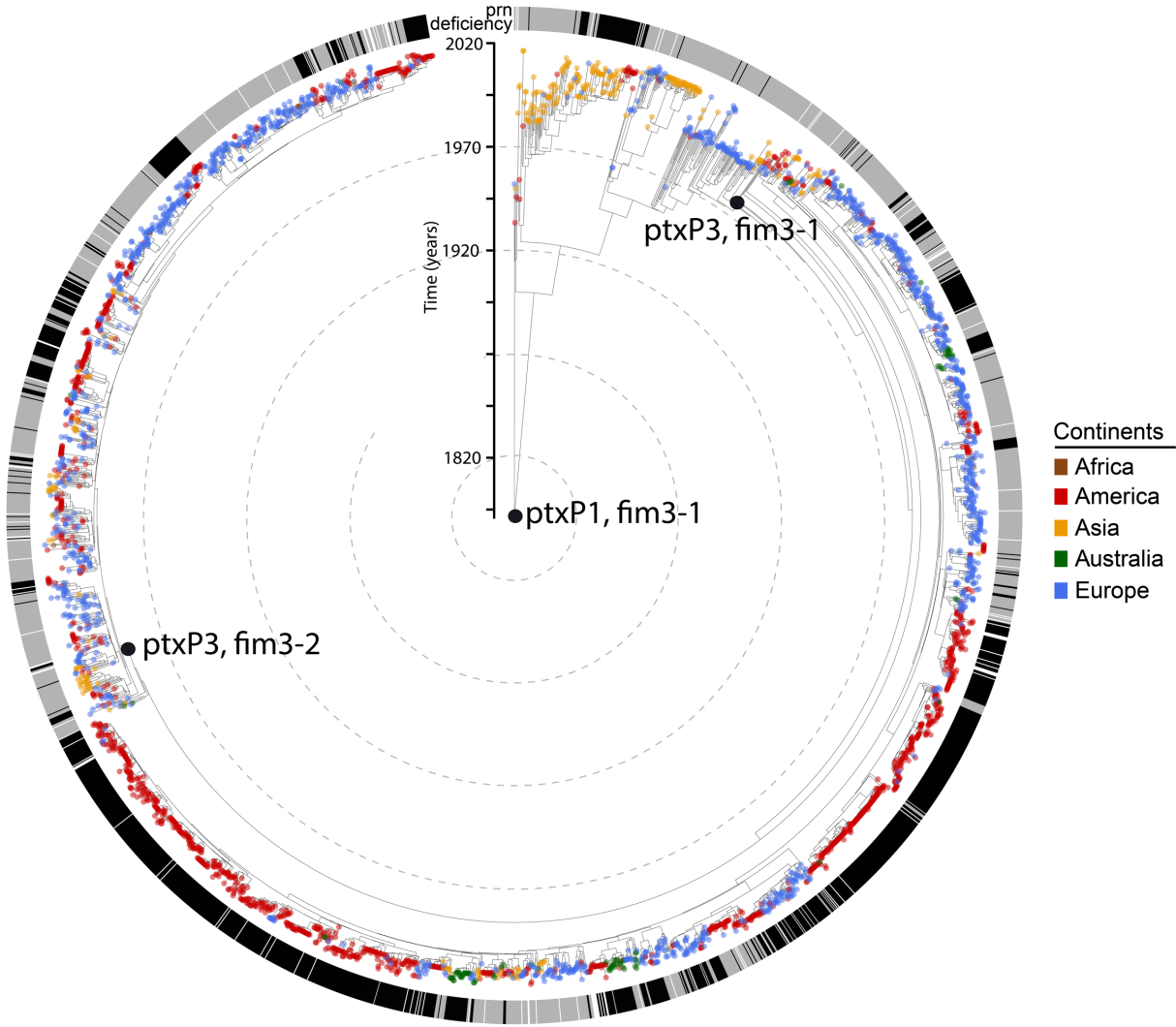
Timed-tree reconstruction

- We used genome-wide single nucleotide polymorphism variation (SNPs) to reconstruct tree with BEAST.

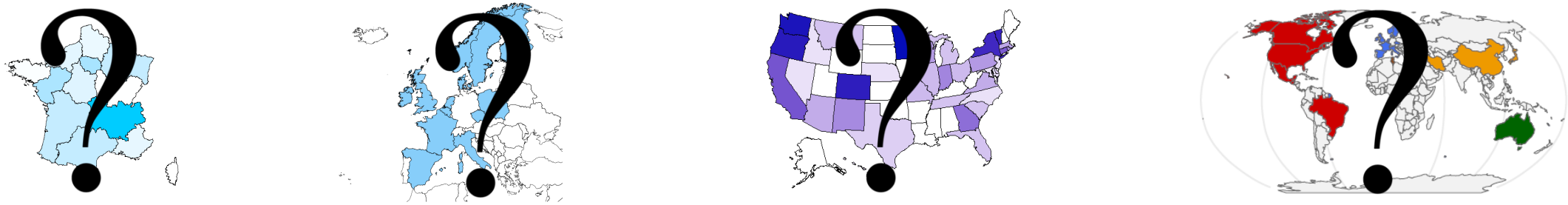
Initial observations

- Little diversity, only a few key changes
- Lots of mixing across continents

- **However, looking at trees can only tell us so much:**
  - **Not quantitative descriptions**
  - **Biased by when and where sequences were isolated**



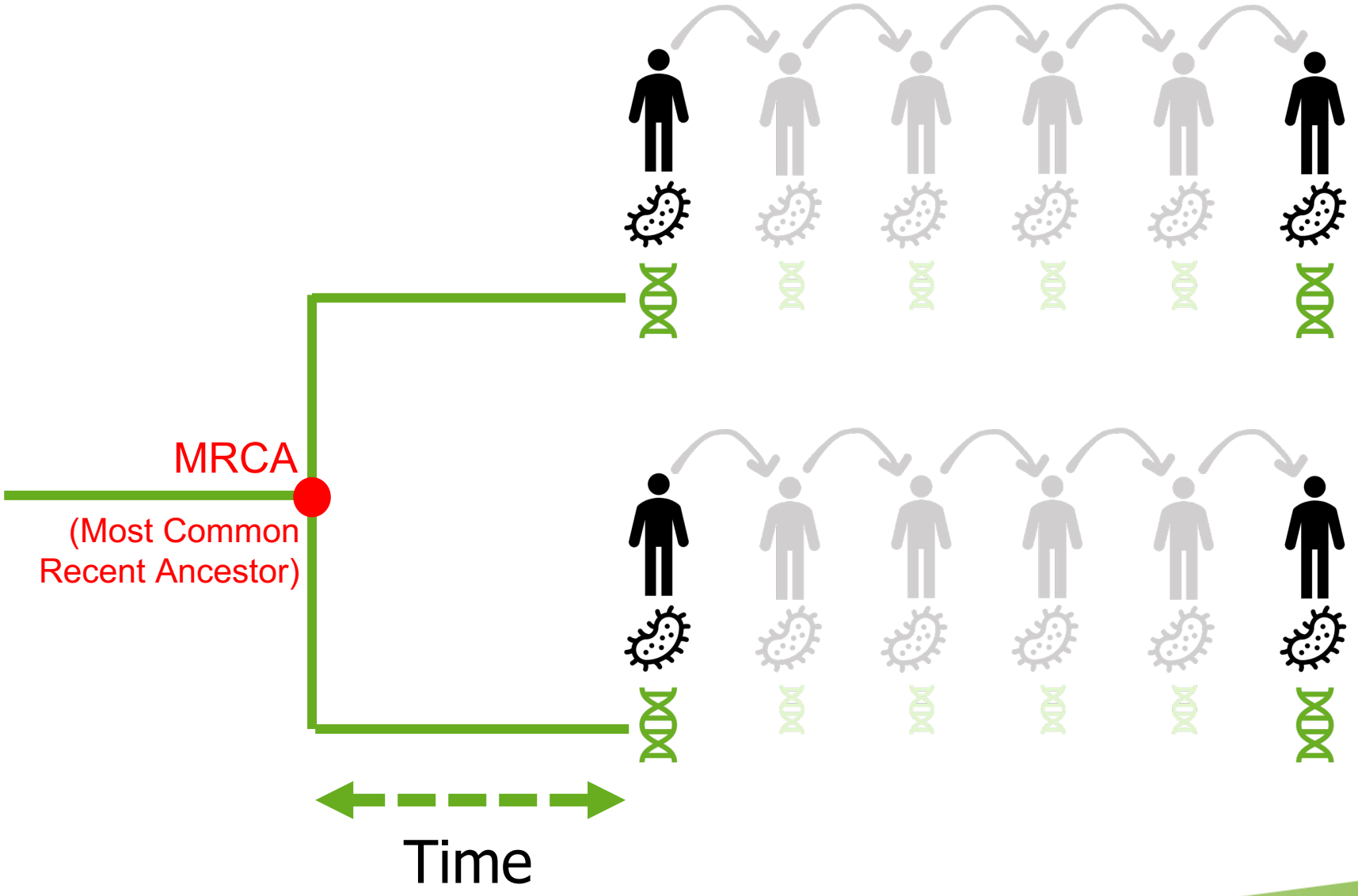
Lefrancq & Bouchez *et al.*, 2022



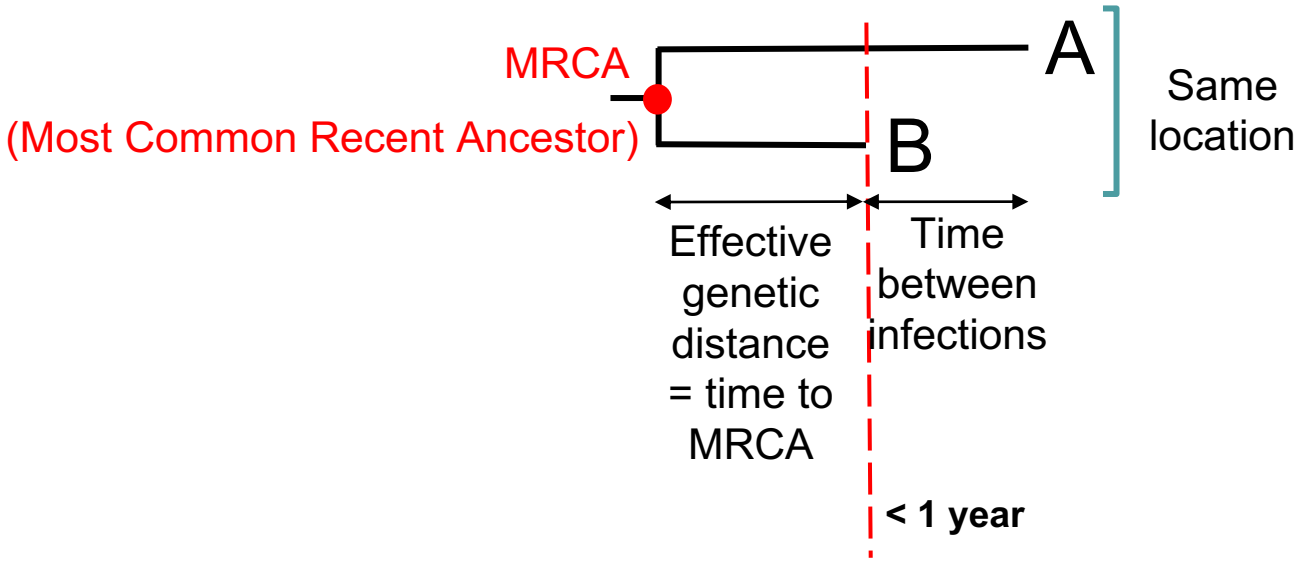
Part I: Global spatial spread of *B. pertussis*

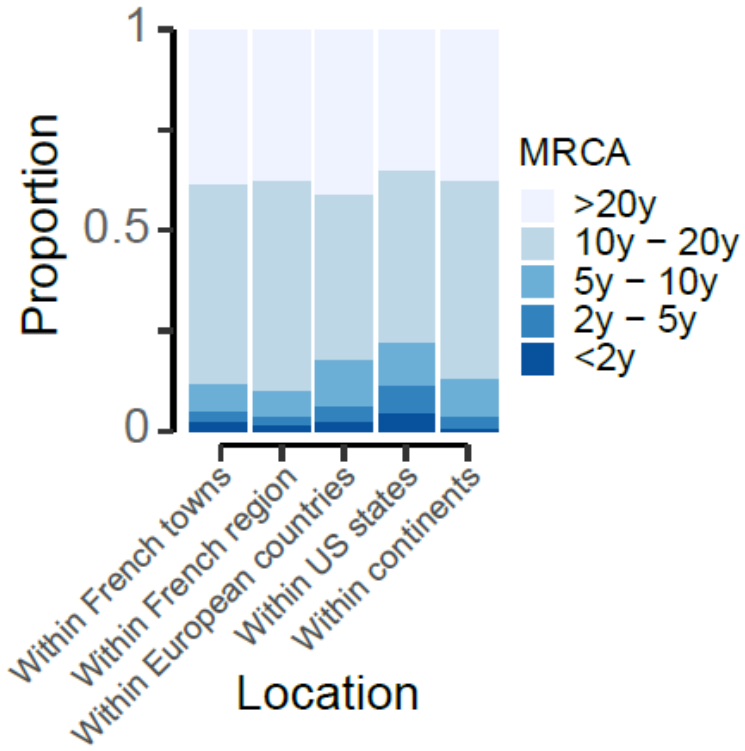
Lefrancq & Bouchez *et al.*, 2022

B. pertussis clustering within locations



B. pertussis clustering within locations

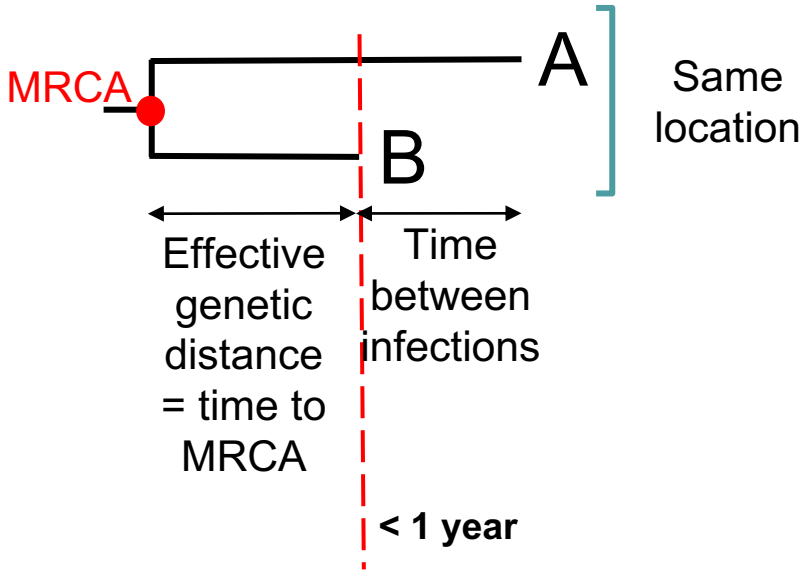




- Only 1-2% of pairs of cases from the same location and infected within the same year had closely related sequences (MRCA<2y).
- **Strong evidence that there are many independent co-circulating transmission chains consistent with a long-term endemic transmission.**

Lefrancq & Bouchez *et al.*, 2022

Investigating spatial spread of *B. pertussis*



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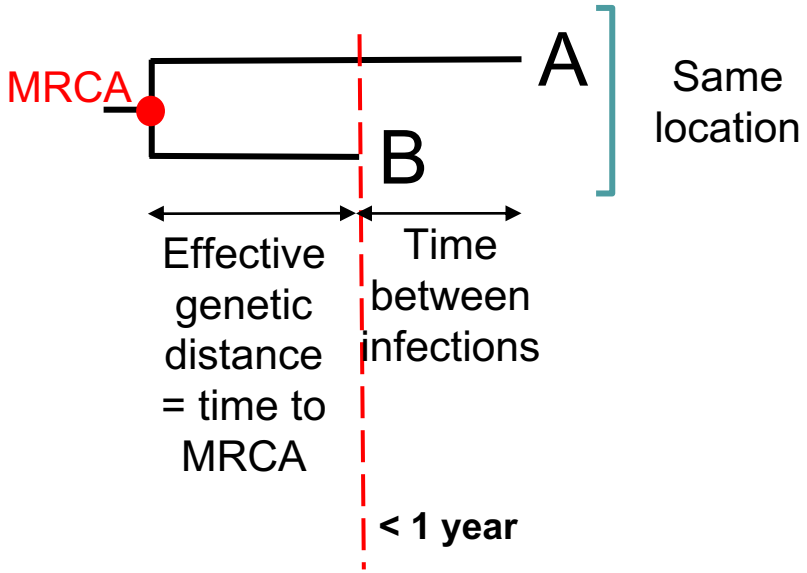


$$P_s = \frac{\#\, pairs\,\{MRCA \in window\ \&\ same\ year\ \&\ \boldsymbol{given\ location}\}}{\#\, \boldsymbol{pairs}\{\boldsymbol{same\ year}\ \&\ \boldsymbol{given\ location}\}}$$

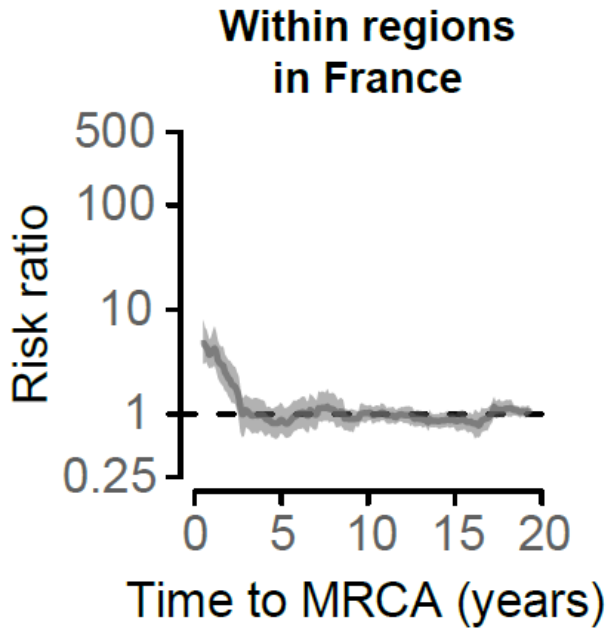
$$P_{ref} = \frac{\#\, pairs\{MRCA \in window\ \&\ same\ year\ \&\ \boldsymbol{diff\ location}\}}{\#\, \boldsymbol{pairs}\{\boldsymbol{same\ year}\ \&\ \boldsymbol{diff\ location}\}}$$

$$RR = \frac{P_s}{P_{ref}}$$

- By conditioning on spatial and temporal location of sequences, this approach **minimizes the impact of underlying sampling biases** with which cases were sequenced.

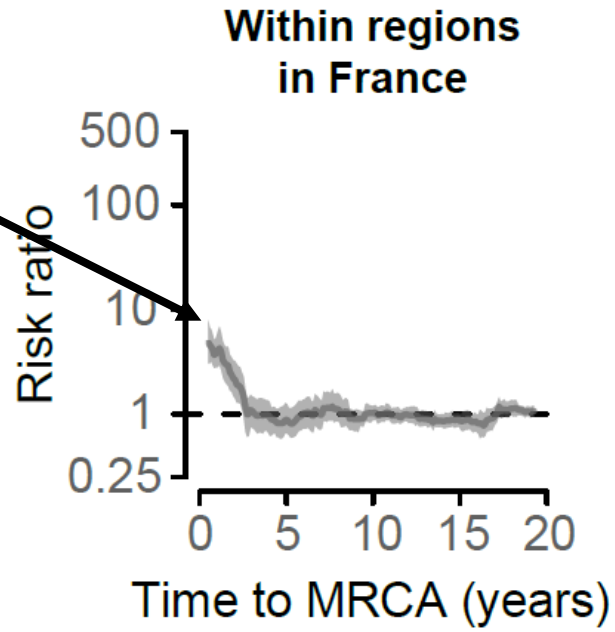
Salje et al., 2018

Investigating spatial spread of *B. pertussis*



Investigating spatial spread of *B. pertussis*

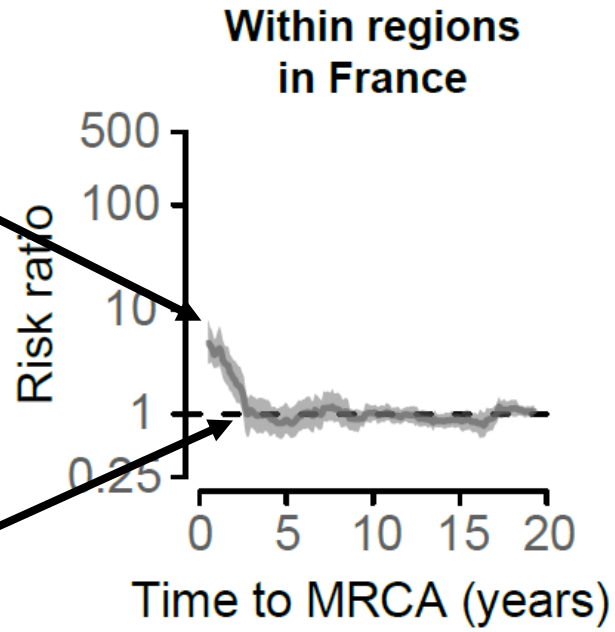
Spatial clustering of cases



Investigating spatial spread of *B. pertussis*

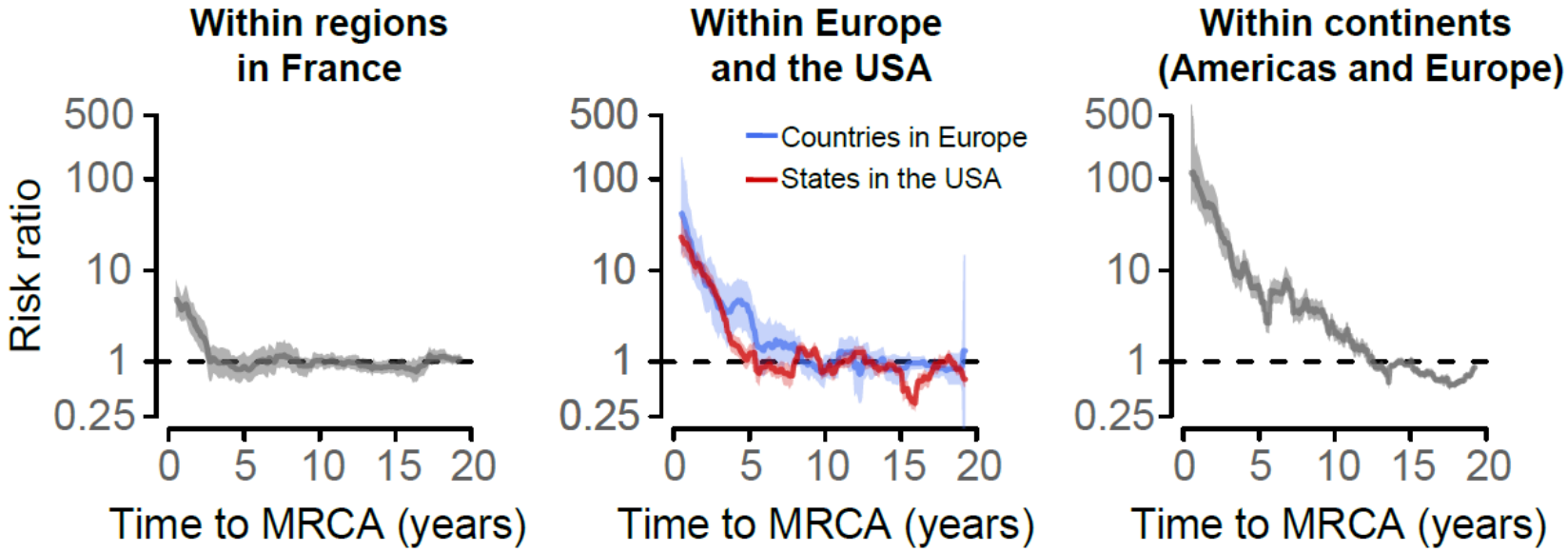
Spatial clustering of cases

Rate of spread across French regions



Lefrancq & Bouchez *et al.*, 2022

Investigating spatial spread of *B. pertussis*



- Clustering within US states is very similar to that observed within European countries.
- **It takes a few years for *B. pertussis* to be well mixed across France, Europe/US and continents.**

Lefrancq & Bouchez *et al.*, 2022

Questions?

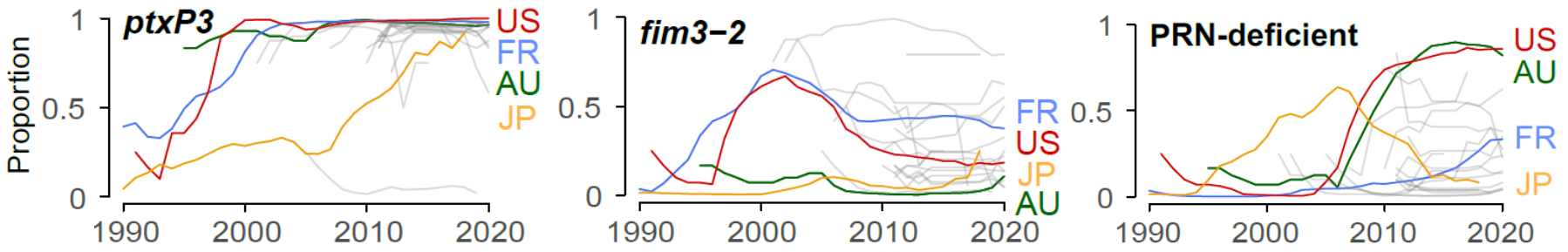
Part 2: Vaccine-Induced Fitness Changes of *B. pertussis*

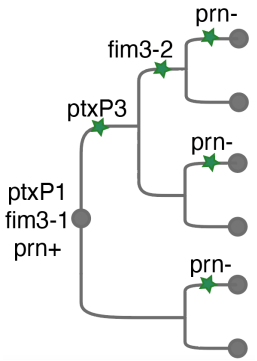
Lefrancq & Bouchez *et al.*, 2022

Fitness changes of *B. pertussis* genotypes

Genotypes based on virulence factors,

defined by the alleles of *ptxP*, *fim3* and expression of PRN





Fitness changes of *B. pertussis* genotypes

Genotypes based on virulence factors,

defined by the alleles of *ptxP*, *fim3* and expression of PRN

Proportion of strains by country

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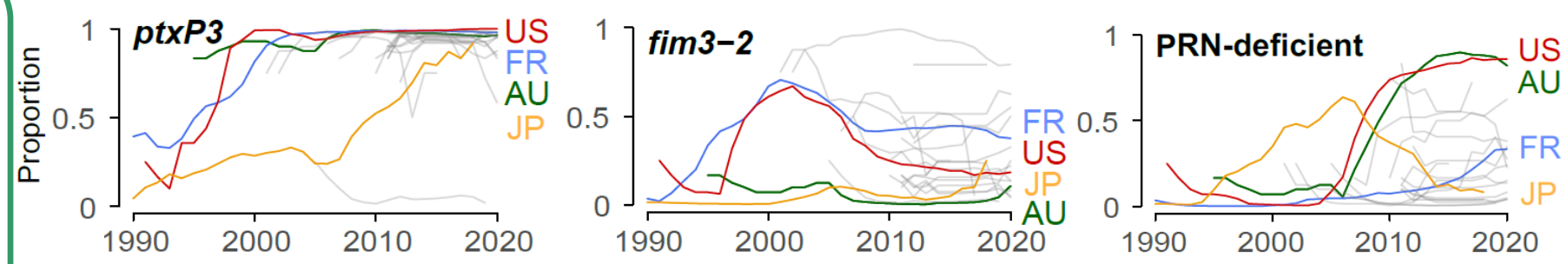
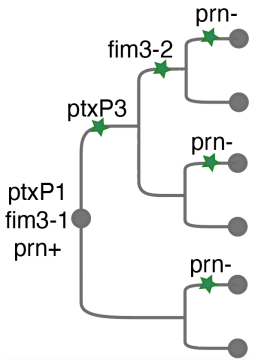
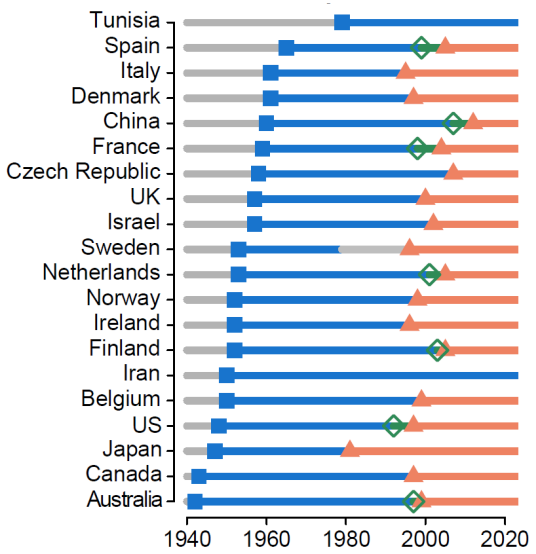
Vaccine implementations in each country





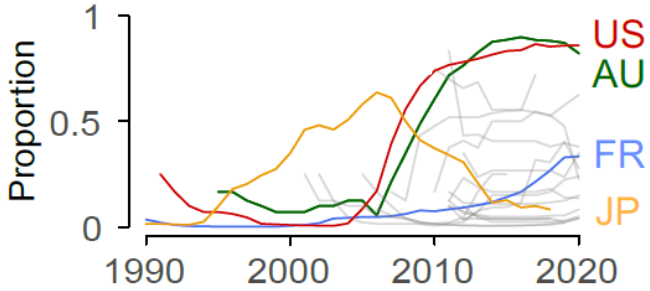


Historical vaccine:
Whole-cell

Recent vaccine:
Acellular

Investigating changes in *B. pertussis* fitness

Proportion of strains by country



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Vaccine implementations in each country

Historical vaccine:
Whole-cell (WCV)

Recent vaccine:
Acellular (ACV)

- We consider 6 different genotypes, based on the *ptxP*, *fim3* types and *prn* deficiency.

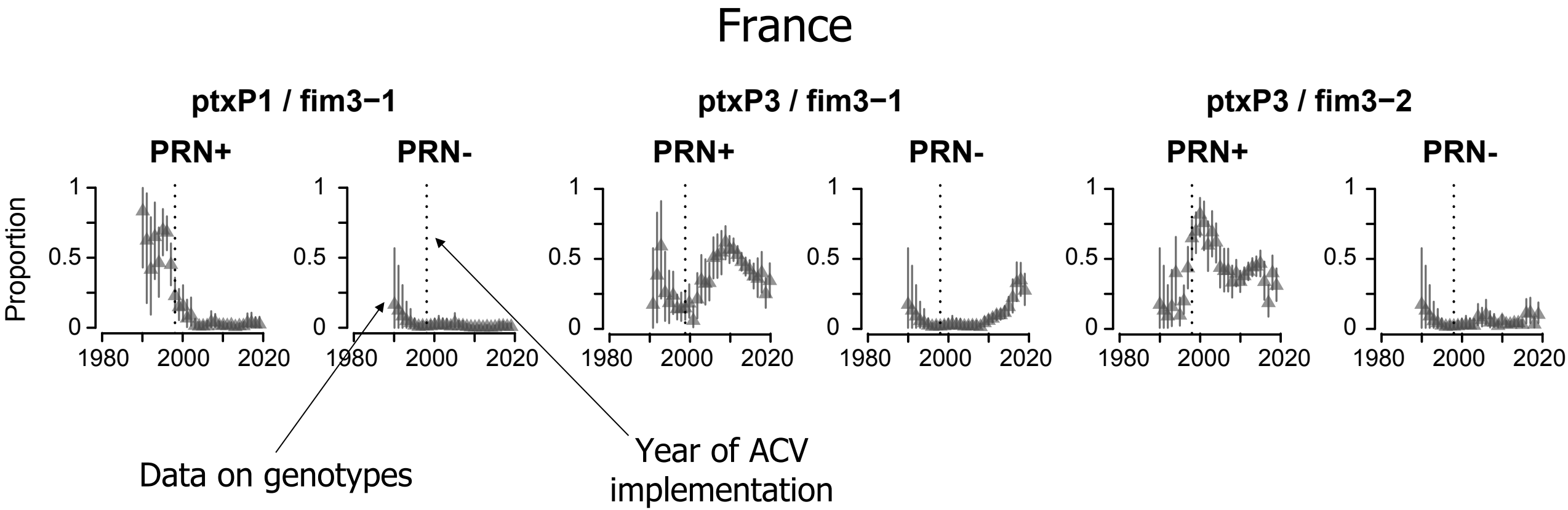
- Fit a logistic model to the relative abundance of each genotype i with respect to a chosen ref genotype

$$f_{i,ref}(t) = \frac{1}{1 + \left(\frac{1}{f_{i,ref,0}} - 1\right) e^{-r_i t}},$$
$$with\ i \in \{genotypes\} \setminus ref$$

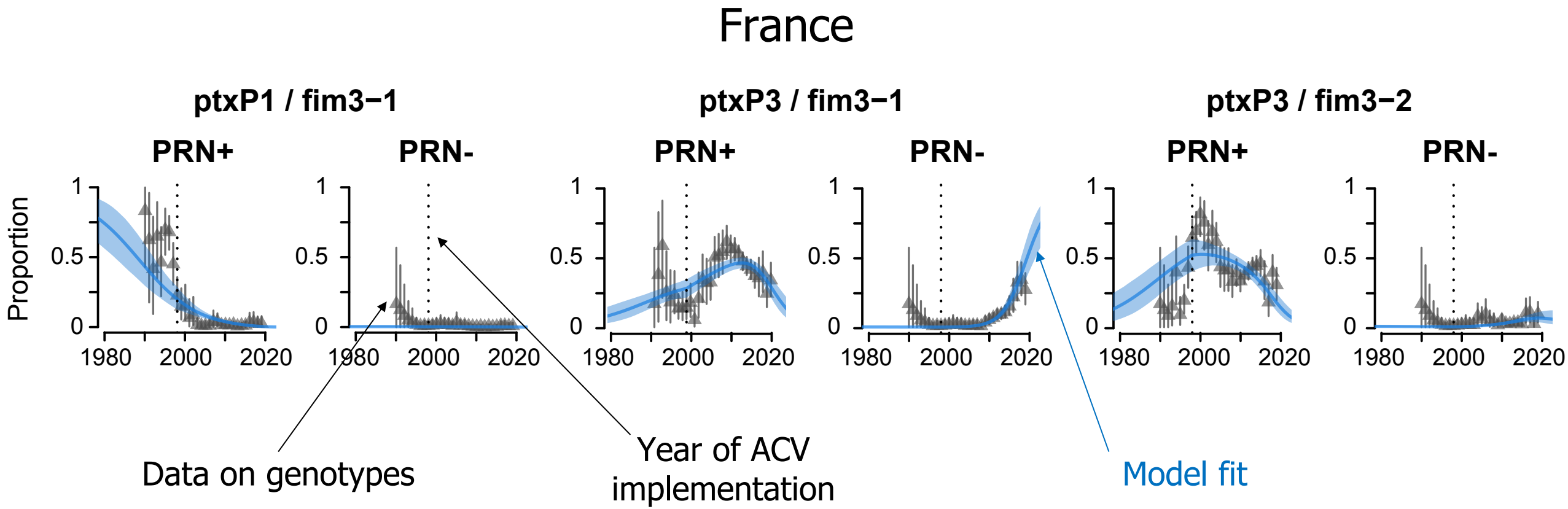
where $f_{i,ref,0}$ is the relative abundance of the genotype i compared to genotype ref at time 0

- We estimate the fitness advantage of each genotype:
  - **Same across all countries**
  - **Independently on the WCV and ACV eras**

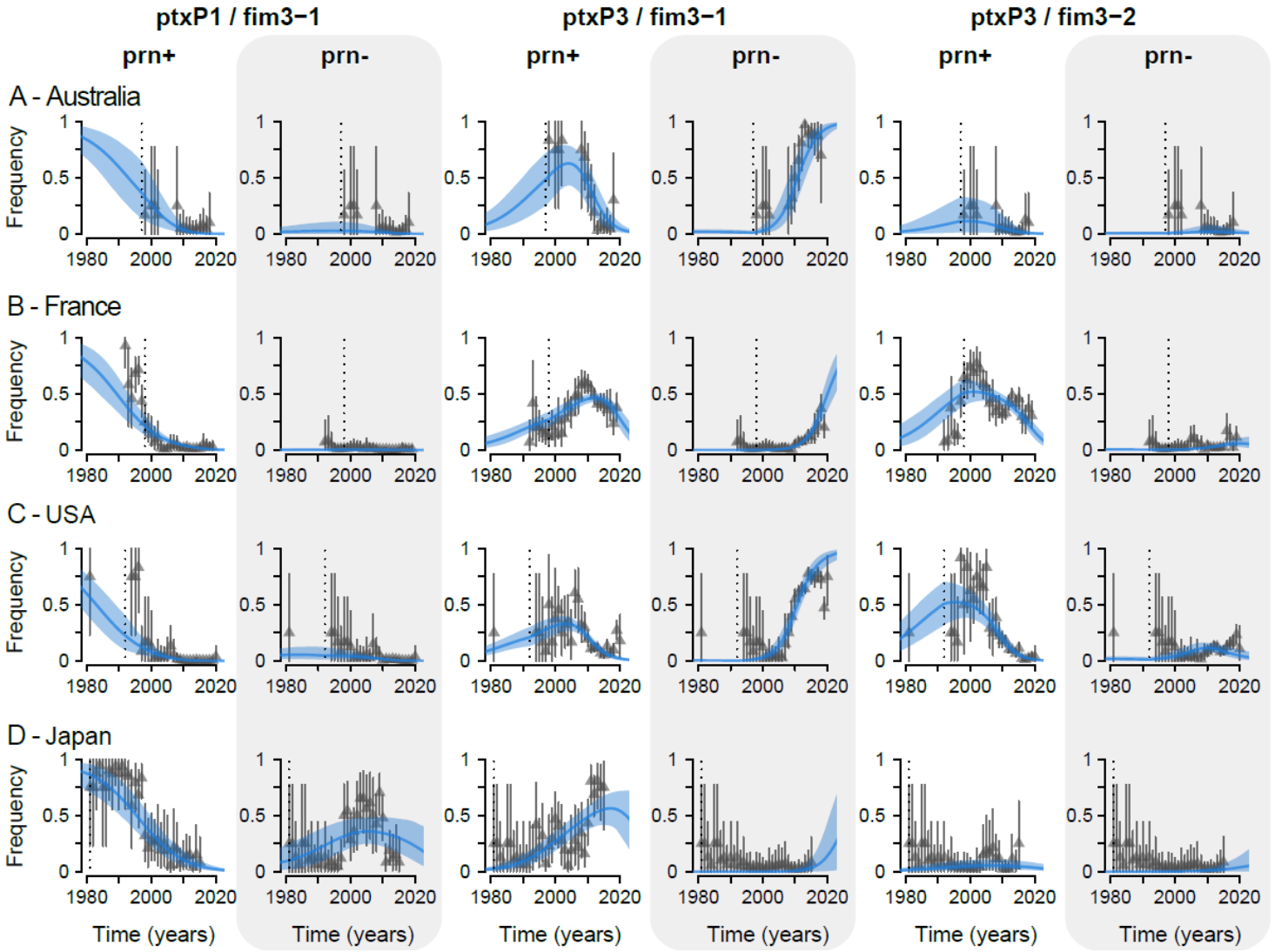
Example of fits obtained

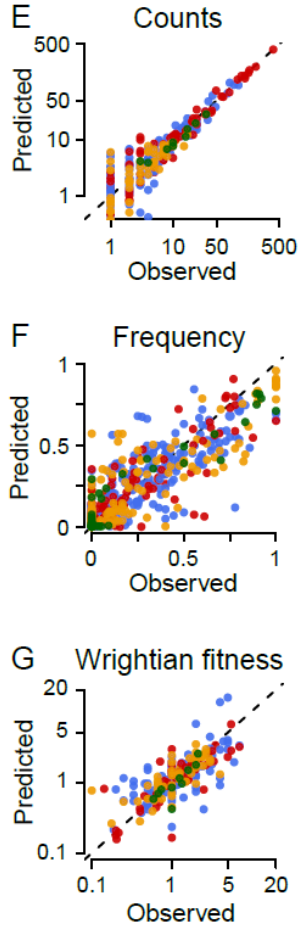


Example of fits obtained



Fits obtained across countries



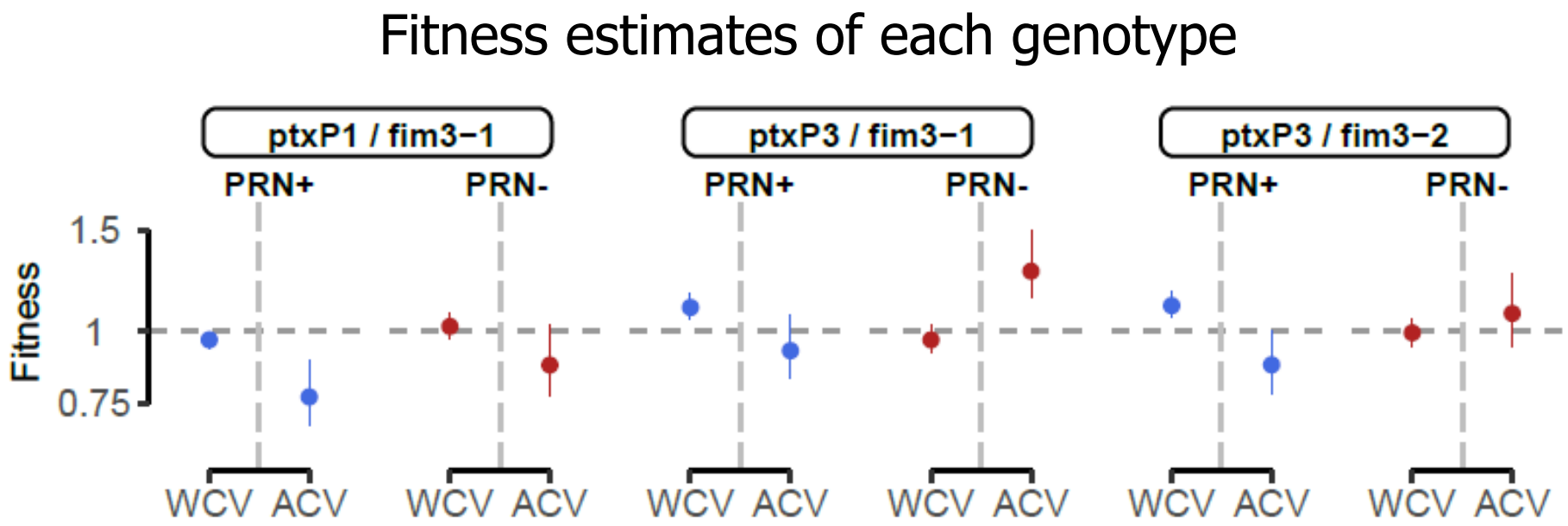


We fit to all 20 countries.

- Our simple model is able to capture the country-specific trends in frequencies.

Lefrancq & Bouchez *et al.*, 2022

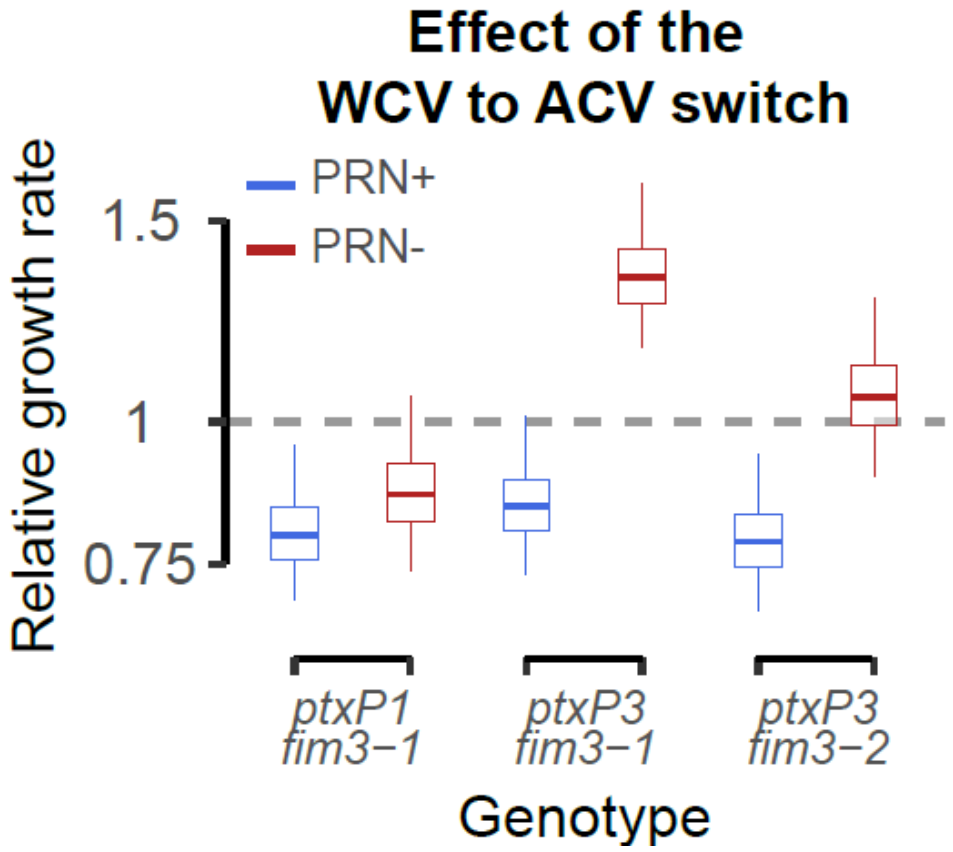
Fitness estimate of each genotype



- The ptxP3/fim3-1/PRN- genotype is the fittest in ACV era.
- **Vaccine switch (WCV to ACV) is associated with large changes of fitness.**

Lefrancq & Bouchez *et al.*, 2022

Fitness estimate of each genotype



- **The PRN-deficient strains are on average 1.1 times more fit after the vaccine switch.**

Lefrancq & Bouchez *et al.*, 2022

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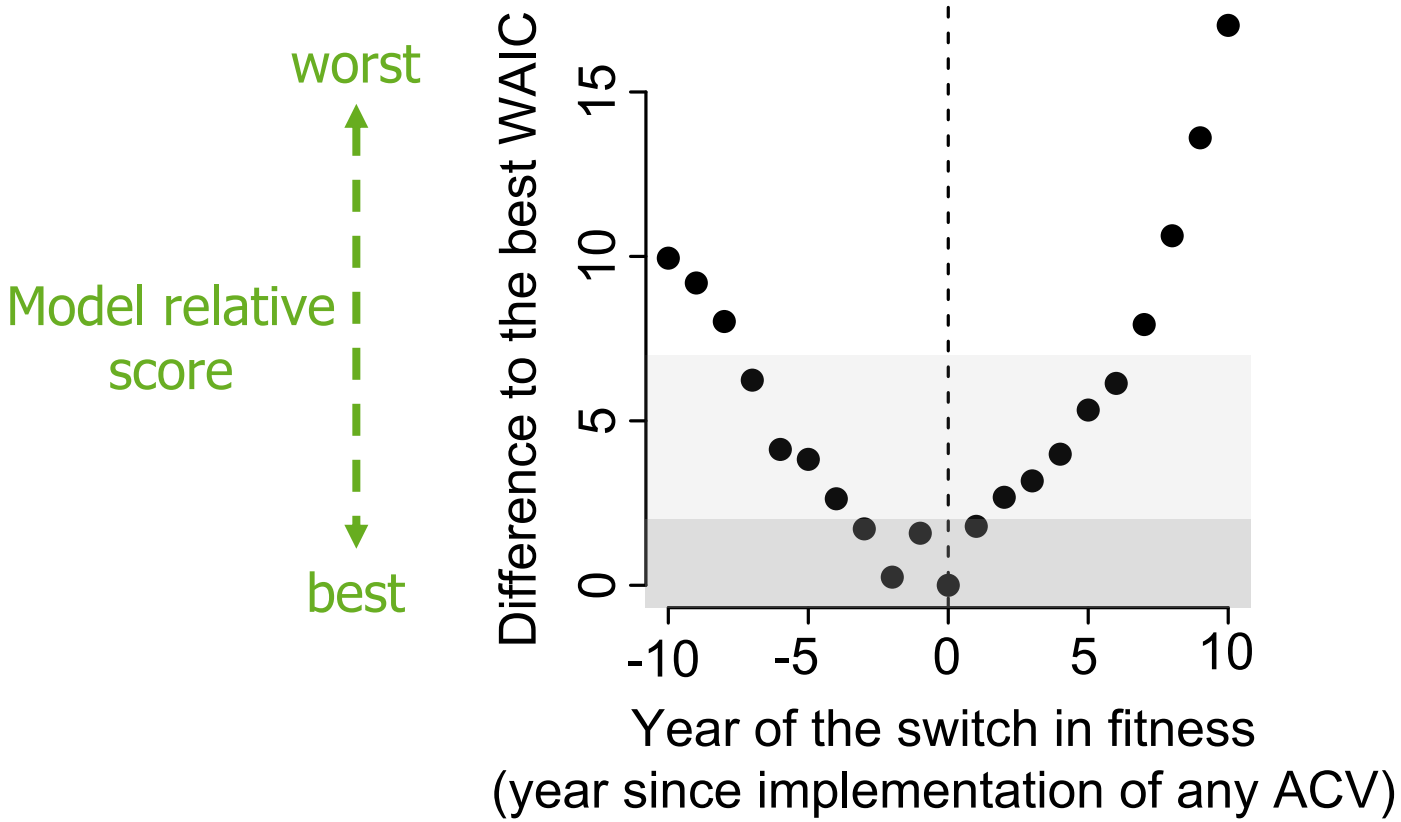
How long does it take for the vaccine switch to induce a fitness change?

ⓘ Start presenting to display the poll results on this slide.

Time it takes for the vaccine to change selection pressure

Model comparison to test different delays between vaccine implementation and change in fitness



In summary

List of learning points in this session:

Part I: Global spatial dynamics of *Bordetella pertussis*

Evidence of many independent co-circulating transmission chains within locations, consistent with a long-term endemic transmission.

Bp spreads both nationally and internationally in just a few years.

Part II: fitness of the different genotypes, and the effect of vaccine types

Genotypes have largely different fitness.

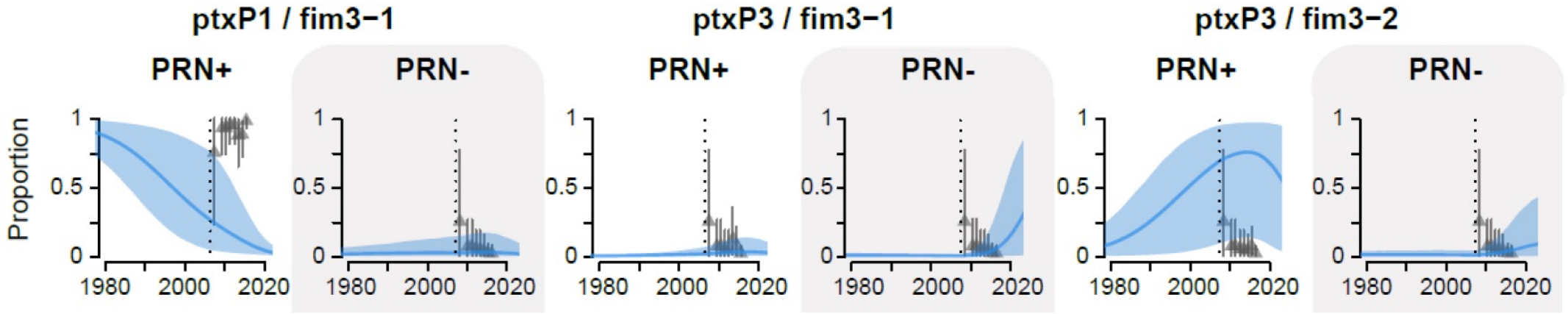
The implementation of ACV is associated with a fitness shift, especially of prn-deficient genotypes.

All in all, it suggests that **future work** needs to **reconcile the rapid spread** between countries **with the history of vaccination** to better understand maintenance of *B. pertussis.*

Limitations & perspectives

Biased sampling: sequences mostly from High Income Countries.

Unexplained dynamics: we cannot explain the dynamics in China.



Only 6 genotypes considered: we might be missing the true underlying causal variants.

Effect of the SARS-CoV-2 pandemic? This study was done on isolates up to 2019, but social distancing measures have had an effect on *Bp* spread and strain diversity.

Lefrancq & Bouchez *et al.*, 2022

Thank you for your attention!

Questions?

Further reading

More on this study (article): N. Lefrancq & V. Bouchez, *et al.* Global spatial dynamics and vaccine-induced fitness changes of Bordetella pertussis. Sci. Transl. Med. (2022)

More on *B. pertussis* epidemiology and evolution (book): Rohani, Pejman, and Samuel Scarpino (eds), Pertussis: Epidemiology, Immunology, and Evolution (Oxford, 2018)

More on general modelling infectious diseases (book): Keeling, Matt J., and Pejman Rohani. Modeling Infectious Diseases in Humans and Animals. Princeton University Press (2008)

References

1: K. H. T. Yeung, P. Duclos, E. A. S. Nelson, R. C. W. Hutubessy, An update of the global burden of pertussis in children younger than 5 years: A modelling study. *Lancet Infect. Dis.* 17, 974–980 (2017).

2: D. W. Jackson, P. Rohani, Perplexities of pertussis: Recent global epidemiological trends and their potential causes. *Epidemiol. Infect.* 142, 672–684 (2014).

3: WHO, Diphtheria tetanus toxoid and pertussis (DTP3) - Immunization coverage estimates by country

4: N. Lefrancq, V. Bouchez, N. Fernandes, A.-M. Barkoff, T. Bosch, T. Dalby, T. Åkerlund, J. Darenberg, K. Fabianova, D. F. Vestrheim, N. K. Fry, J. J. González-López, K. Gullsby, A. Habington, Q. He, D. Litt, H. Martini, D. Piérard, P. Stefanelli, M. Stegger, J. Zavadilova, N. Armatys, A. Landier, S. Guillot, S. L. Hong, P. Lemey, J. Parkhill, J. Toubiana, S. Cauchemez, H. Salje, S. Brisse, Global spatial dynamics and vaccine-induced fitness changes of Bordetella pertussis. Sci. Transl. Med. 14, eabn3253 (2022).

5: H. Salje, D. A. T. Cummings, I. Rodriguez-Barraquer, L. C. Katzelnick, J. Lessler, C. Klungthong, B. Thaisomboonsuk, A. Nisalak, A. Weg, D. Ellison, L. Macareo, I.-K. Yoon, R. Jarman, S. Thomas, A. L. Rothman, T. Endy, S. Cauchemez, Reconstruction of antibody dynamics and infection histories to evaluate dengue risk. Nature 557, 719–723 (2018).

Acknowledgements

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