MATHEMATICAL MODELS OF THE DYNAMICS OF INTERACTING PATHOGENS IN HUMAN POPULATIONS: OPPORTUNITIES AND CHALLENGES

L u l l a   O p a t o w s k i

Université de Versailles Saint Quentin
UMR1018, Inserm/UVSQ/Paris Saclay
Epidemiology and Modelling of Antibacterial Evasion, Institut Pasteur
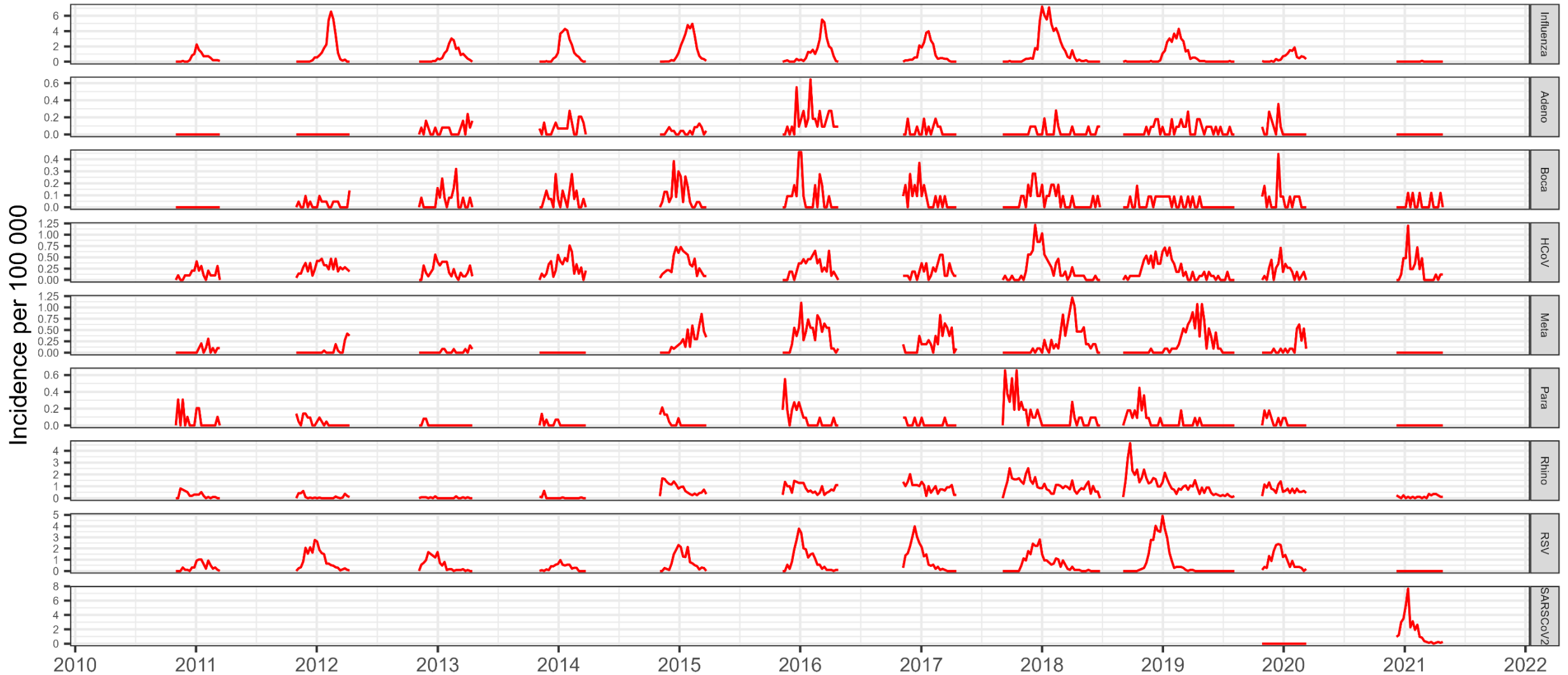
Nordita Workshop, Stockholm, June 2023

INFECTIOUS DISEASE EPIDEMIOLOGY

- Most classically, epidemiological studies and public health policies
  - focus on one pathogen at the time
  - trends, burden, interventions

ECDC
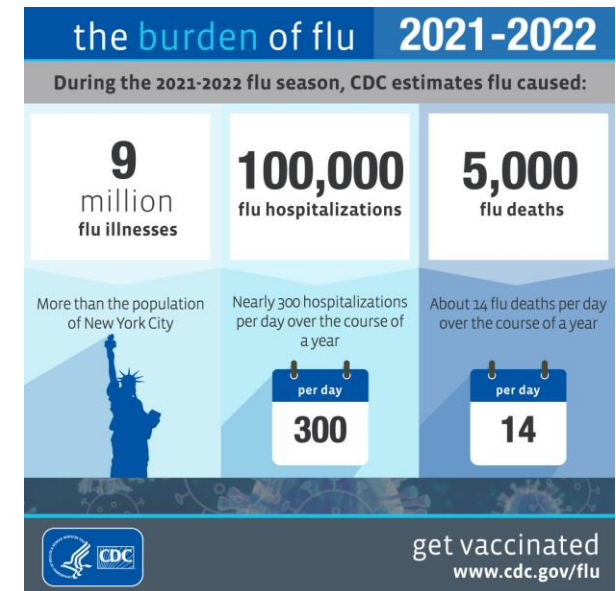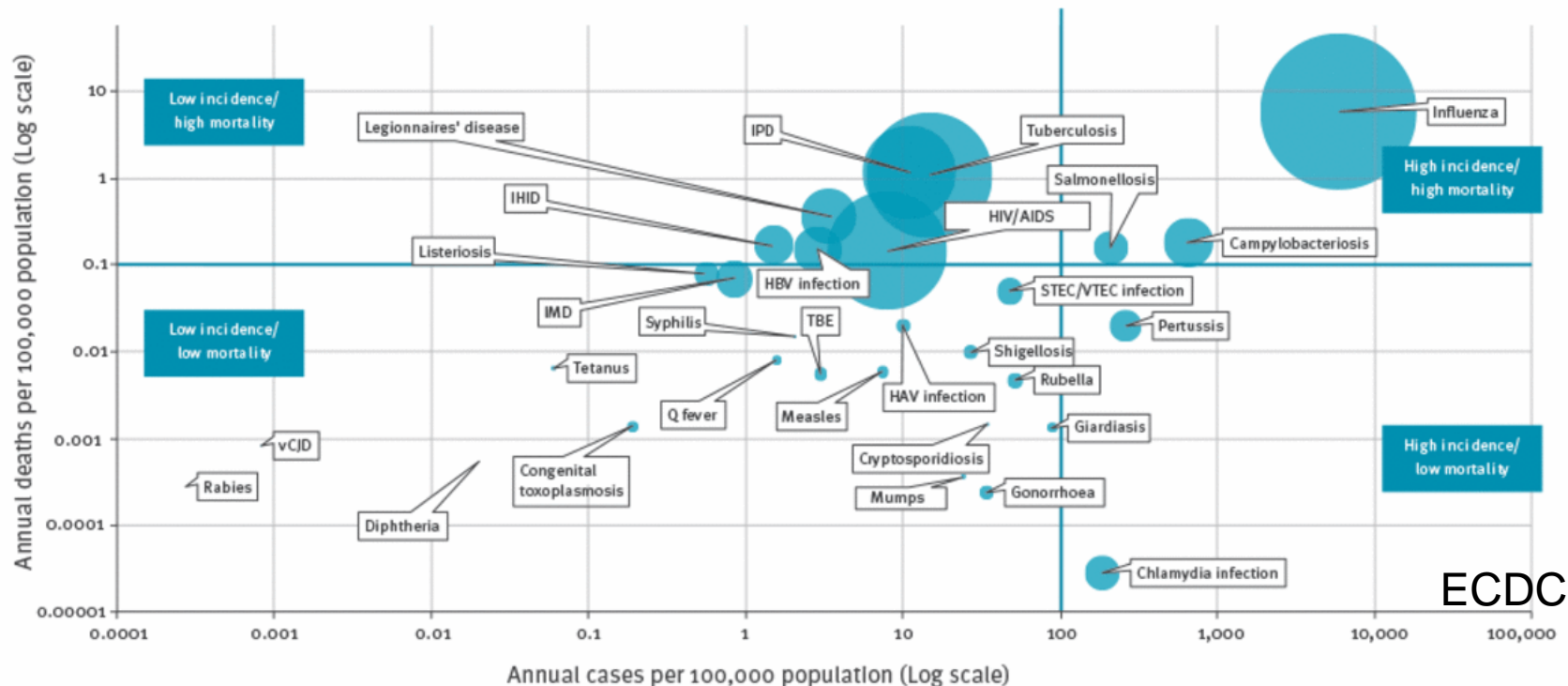
REALITY : RESPIRATORY VIRUSES

Positive cases from multiplex PCR in hospitalized patients, Valencia Community, Spain

Shirreff et al, in preparation

CO-CIRCULATION & INTERACTIONS

- Simultaneous co-circulation of many pathogens
  - Possible interactions in the environment and within hosts

- The presence of other microorganisms may alter the intrinsic properties of a given host-pathogen interaction
  - Transmission
  - Infection, replication
  - Evolution
  - Severity of infection / pathogenicity
  - Duration of infection

POTENTIAL BIOLOGICAL MECHANISMS
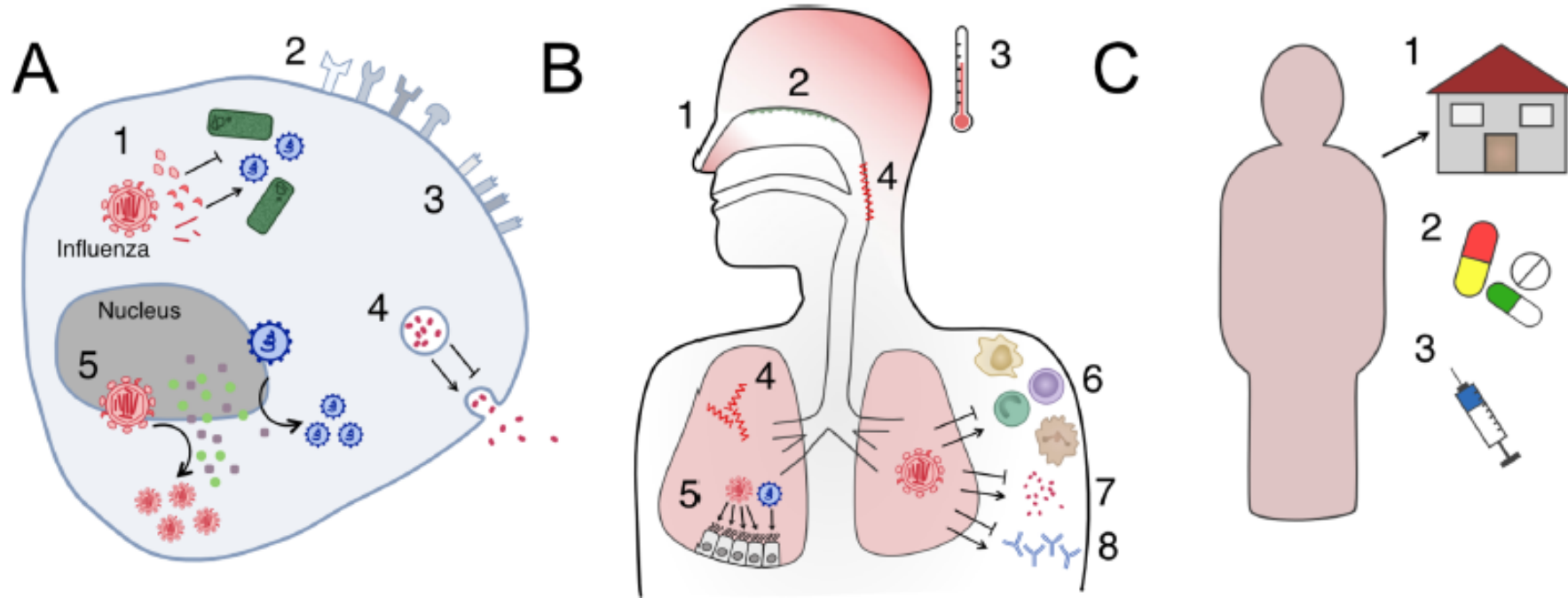
At the cellular-level
1: interactions between viral products
2: altered receptor presentation
3: cell damage (eg. receptor)
4: modification of immune system mediators
5: competition for ressources

At the host-level
1: symtoms =>change of transmissibility
2: variation in commensal microbiota
3: symptomatic response to infection
4: tissue dammage (eg. nasopharynx, lung)
5: competition for ressources
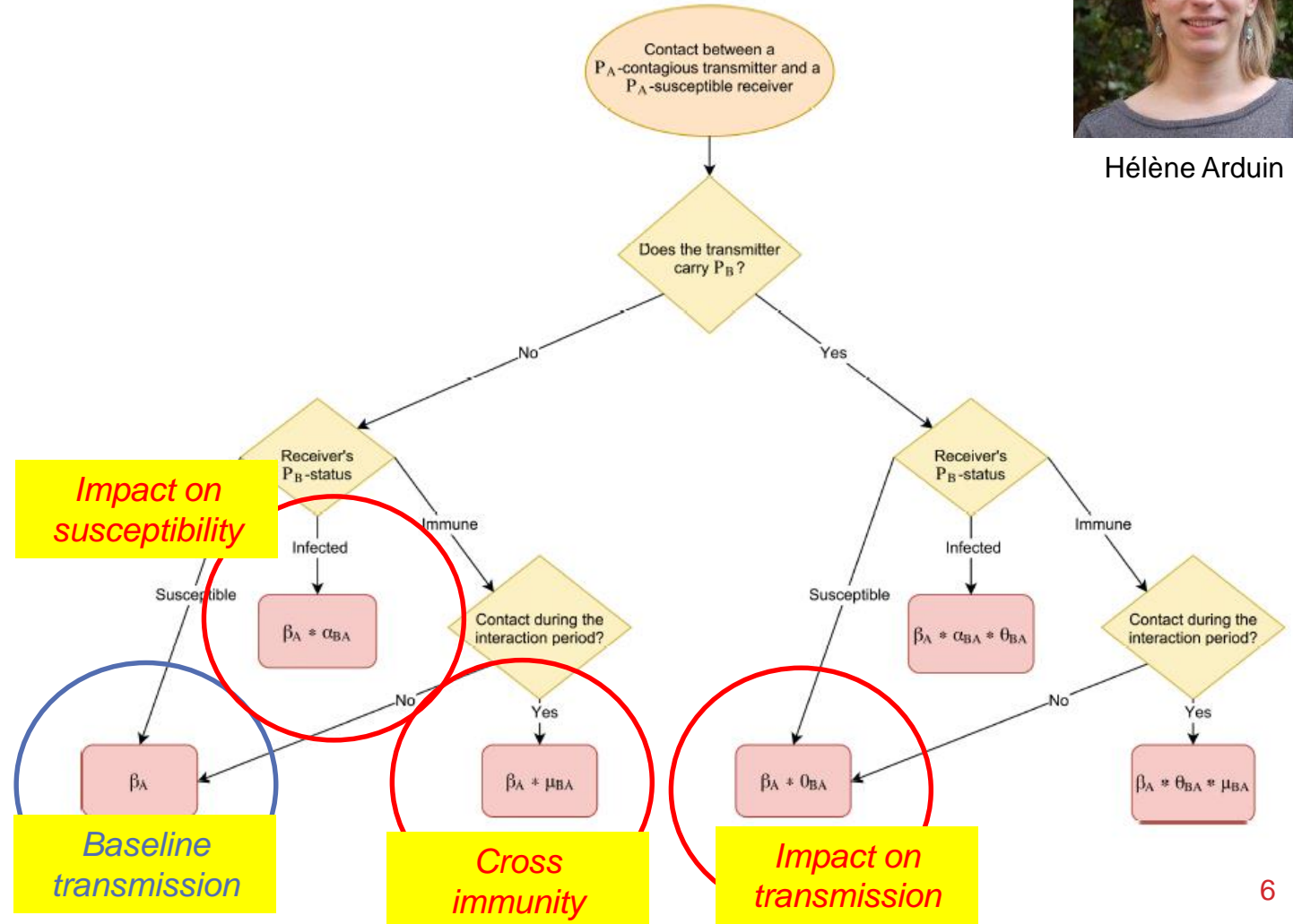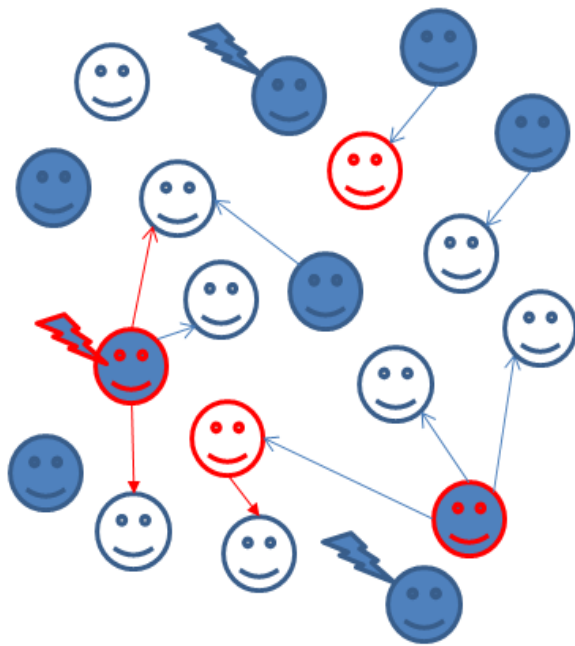6,7: immune reponse (cell- or antibody-mediated

At the population-level
1: behavioural response to disease
2: medication use
3: vaccination behaviour

5

AN INDIVIDUAL-BASED MODEL OF TWO PATHOGENS IN INTERACTIONS

- Individual-based model
- 2 pathogens P_A and P_B

Hélène Arduin

[Arduin et al, PAAMS 2018]

EXPECTED TRENDS FOR VIRUS-VIRUS
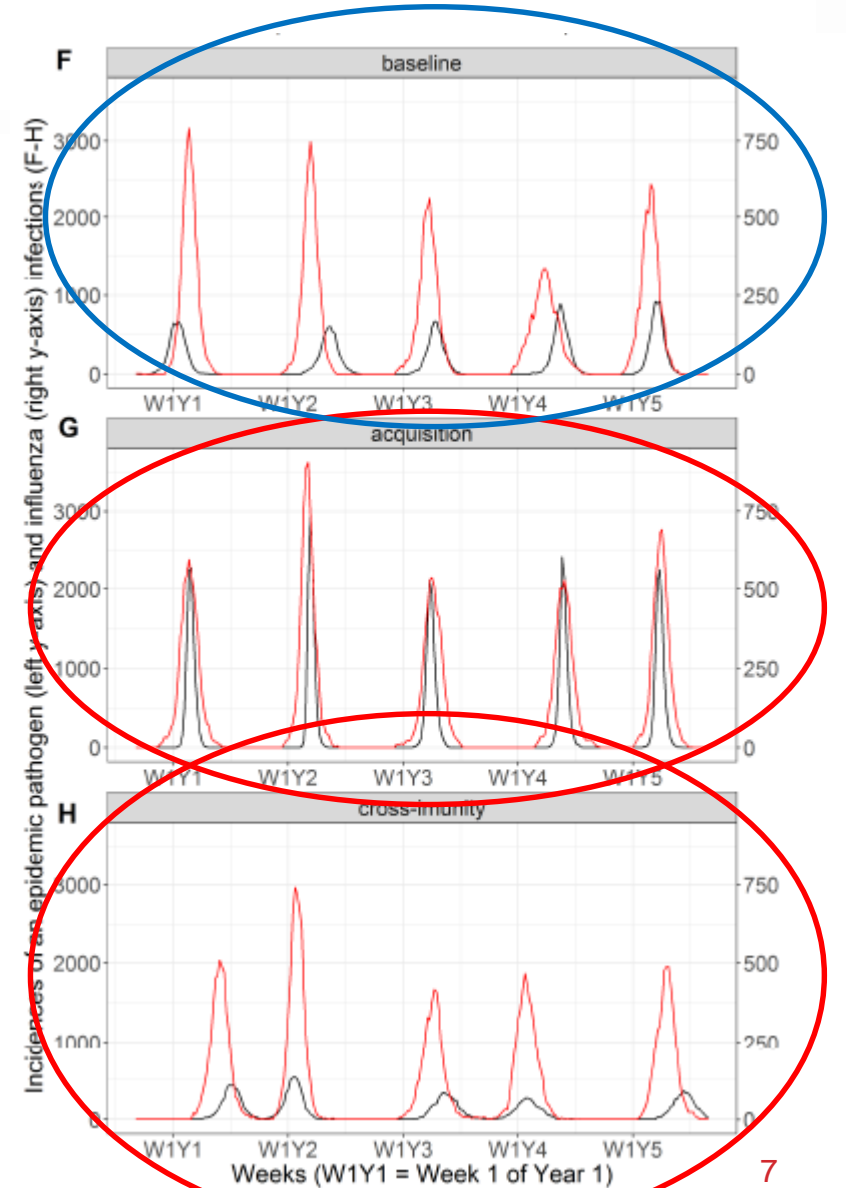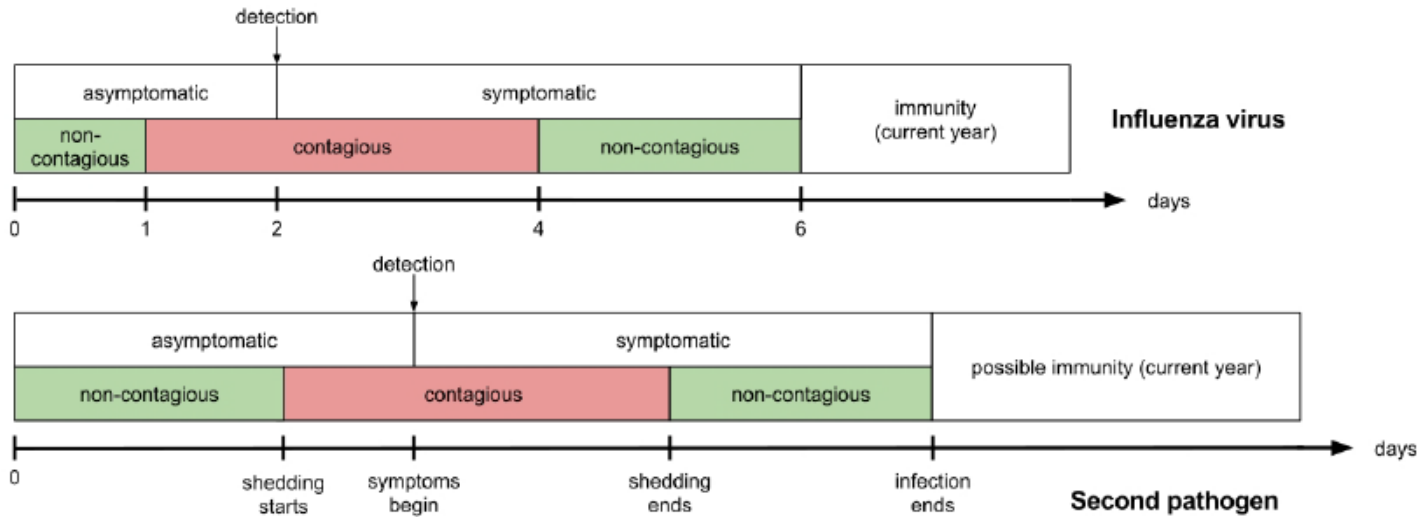
EXPECTED TRENDS FOR (COMMENSAL) BACTERIA

[Arduin et al, BMC infectious diseases 2017]
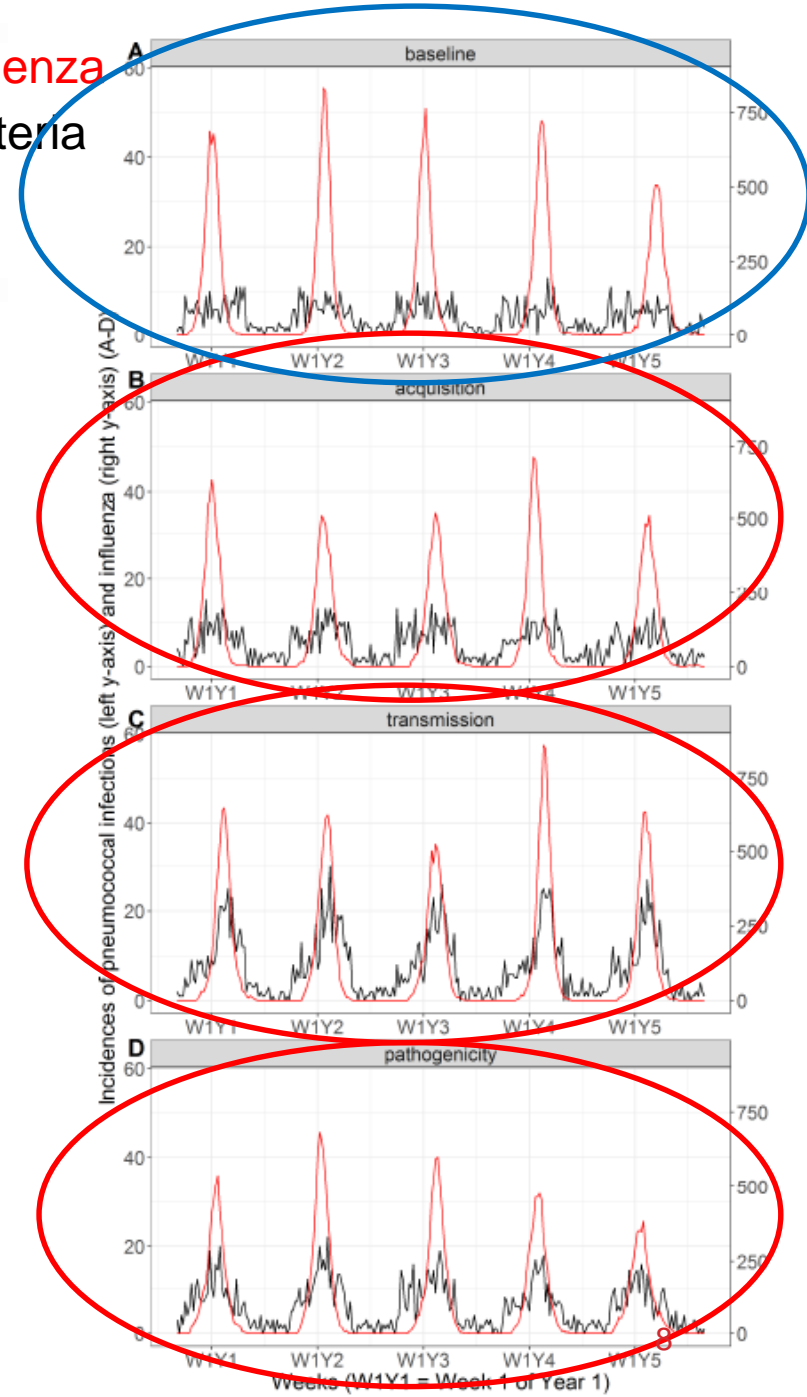
4 STORIES
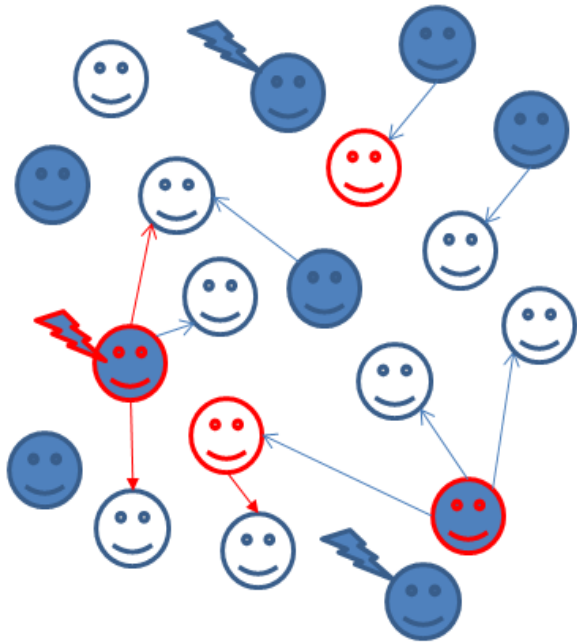
1. Virus – Bacteria
2. Virus – Virus
3. Microbiota - pathogen
4. Virus, interventions, surveillance

1: (RESPI) VIRUS-BACTERIA ?

INTERACTIONS

INFLUENZA & BACTERIAL INFECTIONS
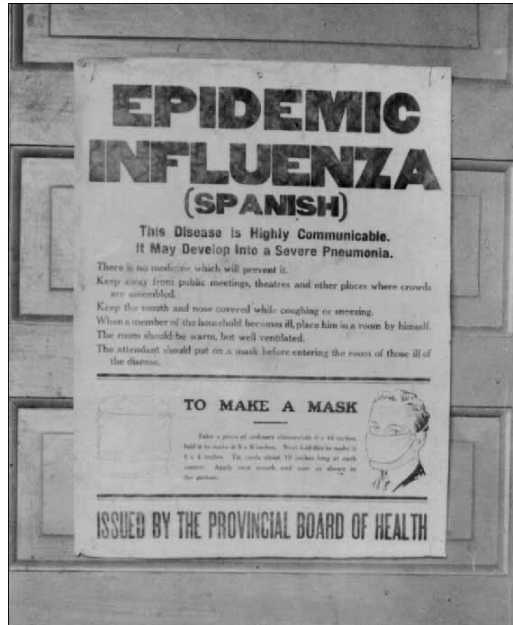
In flu pandemics most fatalities were due to a secondary bacterial infection : *S. pneumoniae*, *S. aureus, H. Influenzae or N. meningitidis*

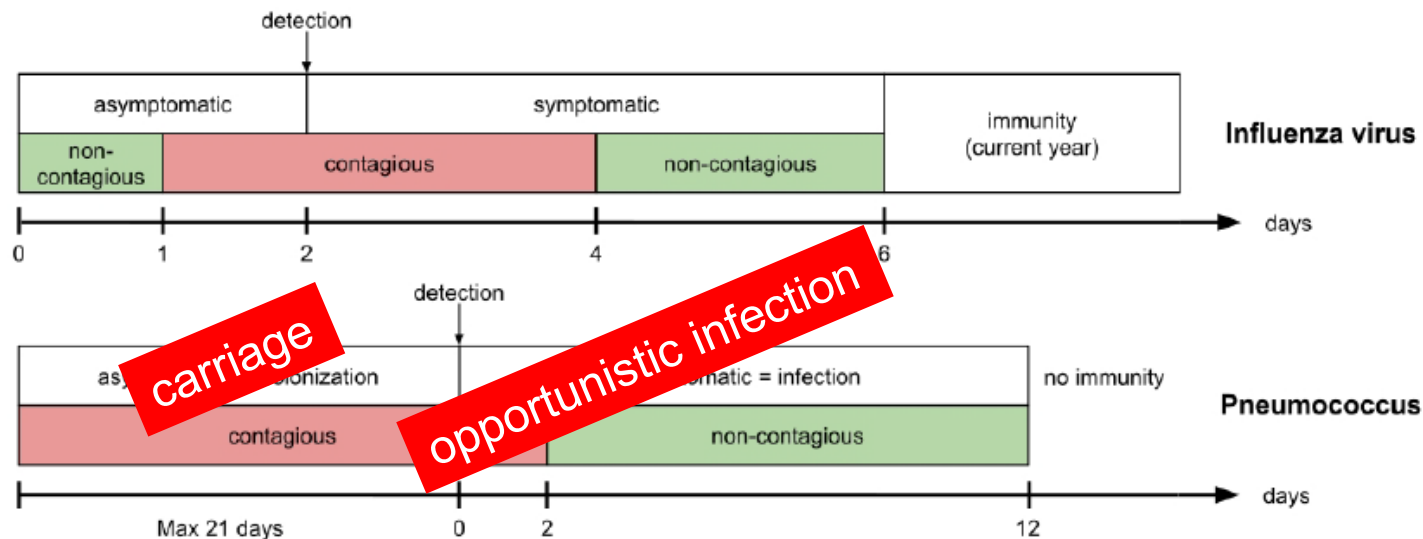Evidence of interactions from animal models: influenza infection predisposes to bacterial colonisation and infection

(Mc Cullers 2006; Short 2012; Lee J Infect Dis 2010; Smith 2013; Wolf 2014; Siegel 2014; McCullers 2010; Ghoneim 2013; Peltola 2006)
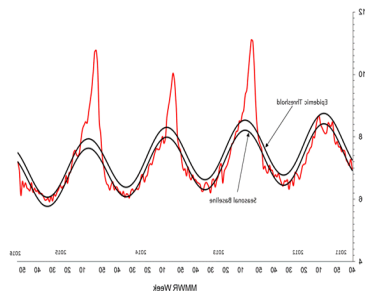
Inconsistent results in epidemiological studies

(Kuster 2011; Nicoli 2013; Murdoch 2009)

TRENDS OF INVASIVE PNEUMOCOCCAL DISEASES

A)

IPD in Ile de France region, 2000-2014

Matthieu Domenech
de Cellès
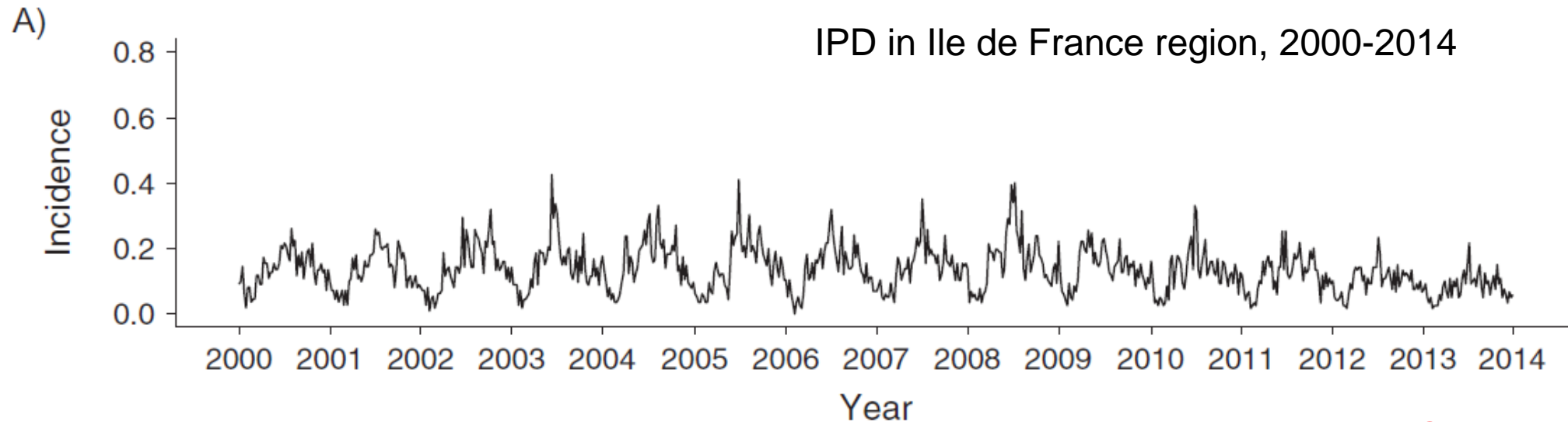
Strong seasonality
Winter peak

What is the contribution of respiratory viruses in observed trends of pneumococcal epidemiology?

[Domenech et al, Am Journal of Epidemiology 2017]

WEEKLY DATA IN FRANCE OVER 2000-2010

IPD
Hospital-based surveillance
(Epibac, Santé Publique France)

ILI
GPs network
(Sentinelles, Santé Publique France)

Climate
Temperature, Vapor pressure, Average humidity, and Sunshine duration
Meteo France

A — Invasive pneumococcal diseases

B — Influenza-like illnesses

C — PCA-transformed climate data

[Domenech de Celles et al., PNAS 2019]

[Domenech de Celles et al., PNAS 2019]
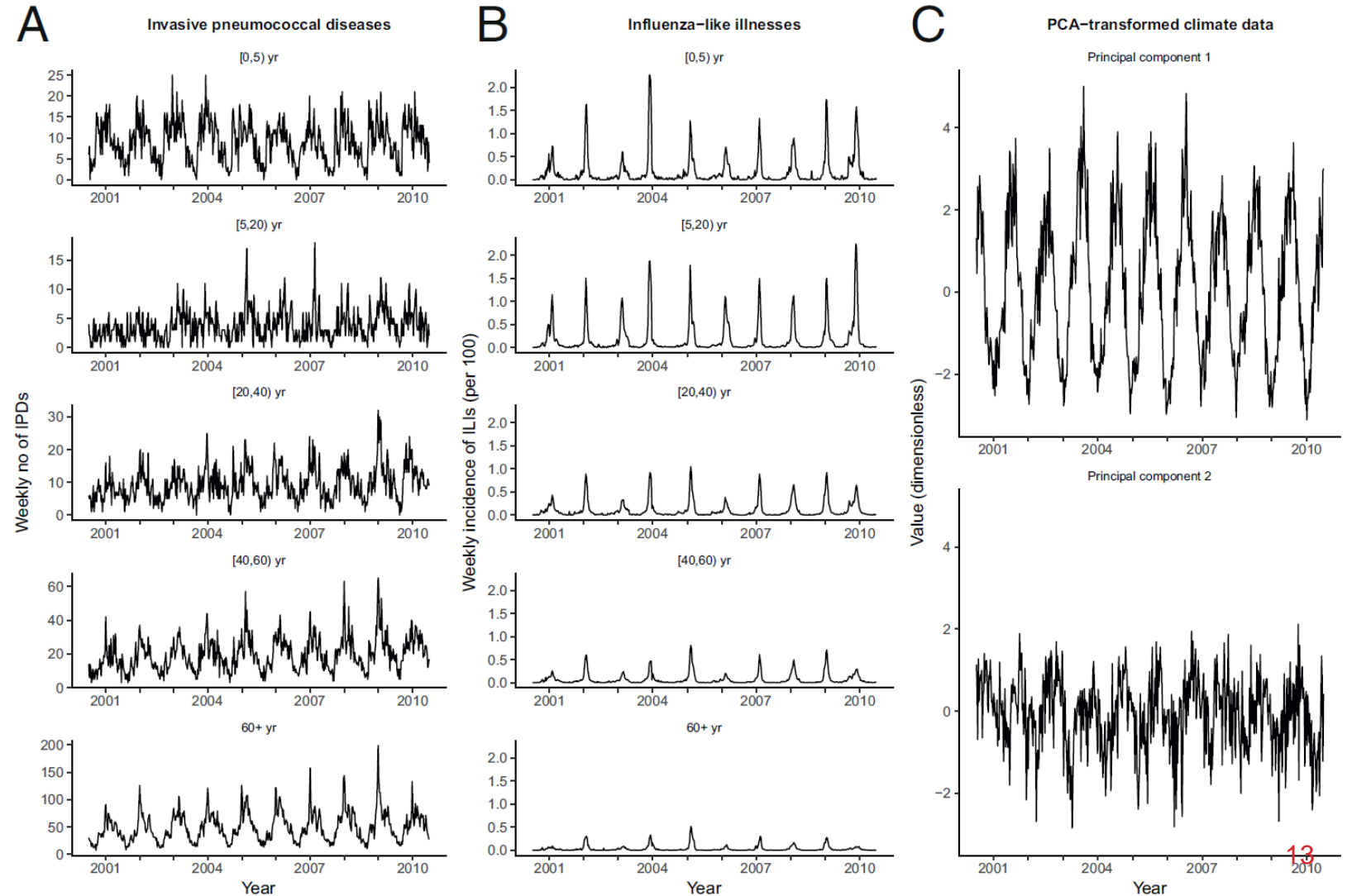
3 MECHANISMS OF INTERACTION MODELLED

3 mechanisms of interaction between pneumococcus and ILI:
- Transmission θ_β
- Acquisition θ_λ
- Invasiveness (pathogenicity) θ_α

IMPACT OF CLIMATE MODELLED
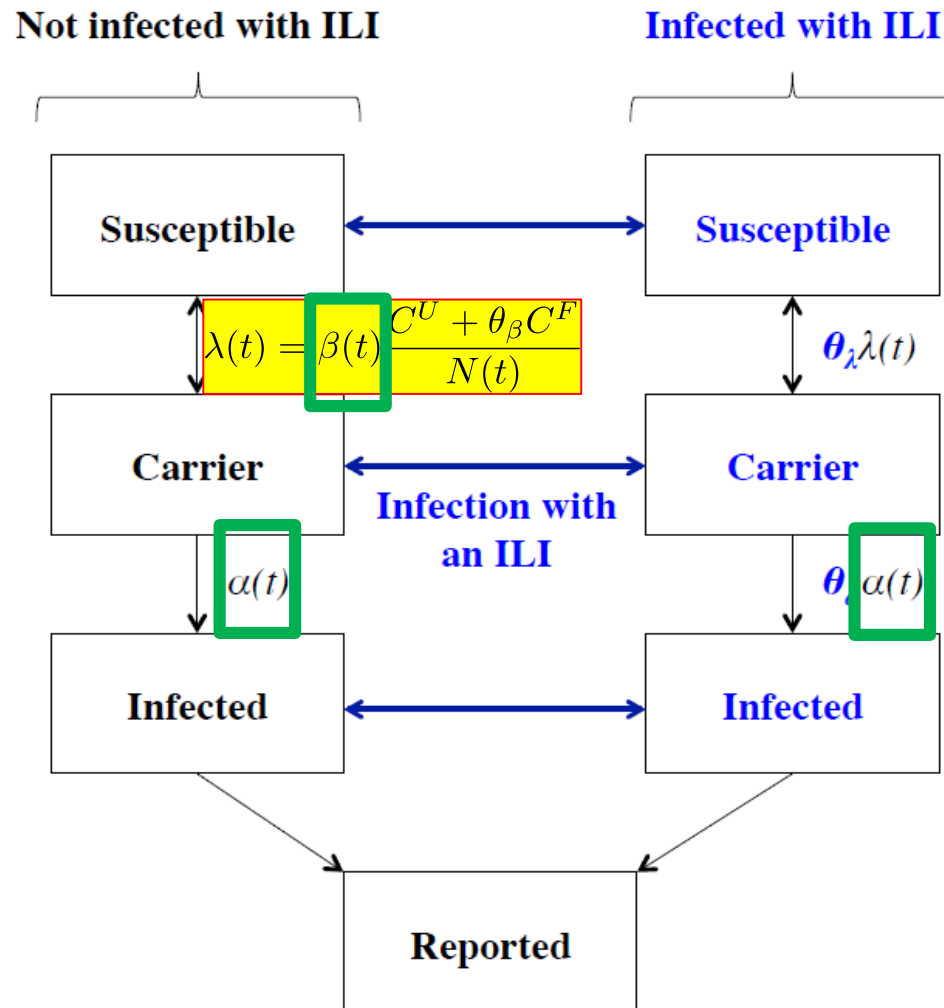
Climate modulating
background seasonality of
- Invasiveness α
- Transmission β

WEEKLY DATA IN FRANCE OVER 2000-2010

IPD
Hospital-based surveillance
(Epibac, Santé Publique France)

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Temperature, Vapor pressure, Average humidity, and Sunshine duration
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A — Invasive pneumococcal diseases

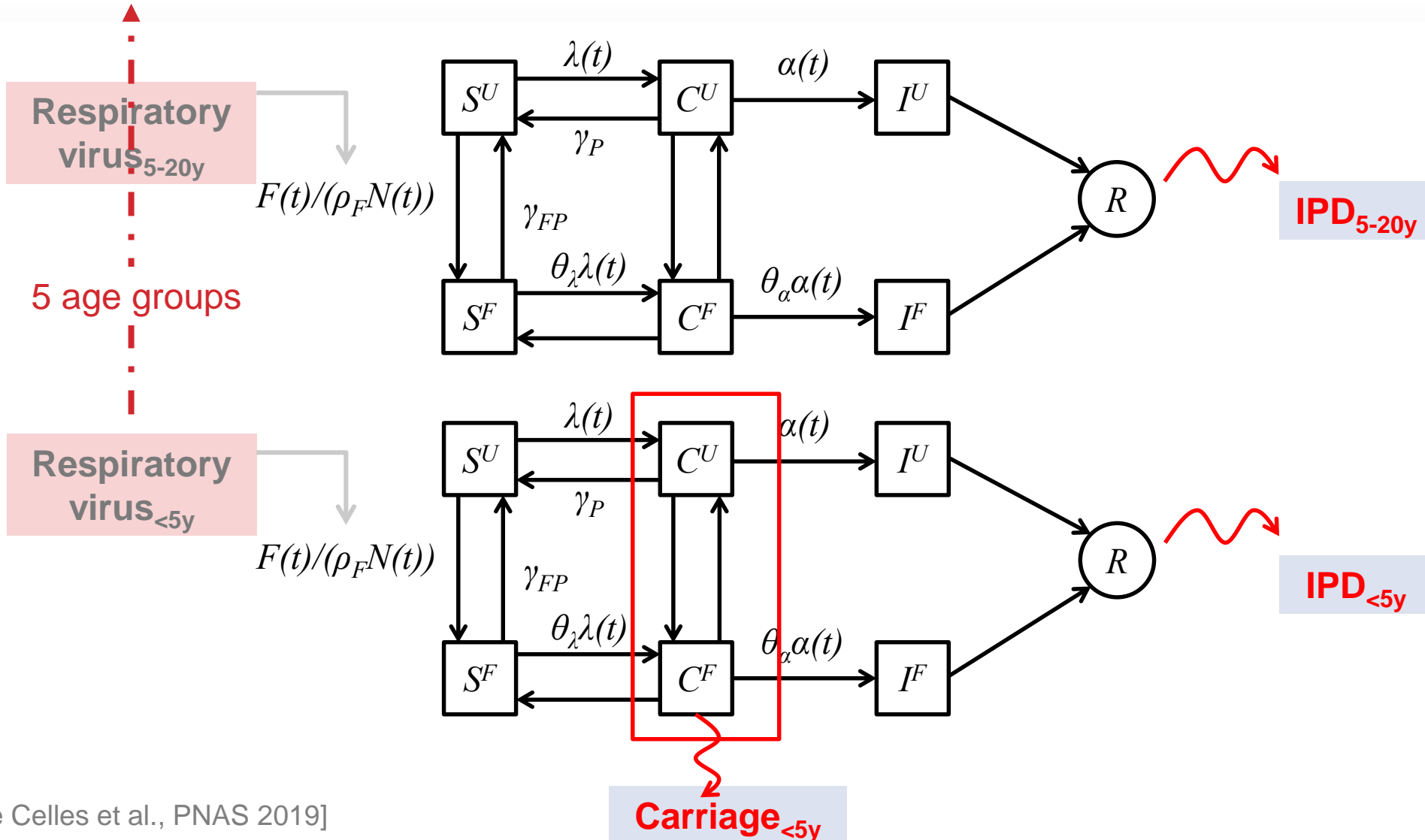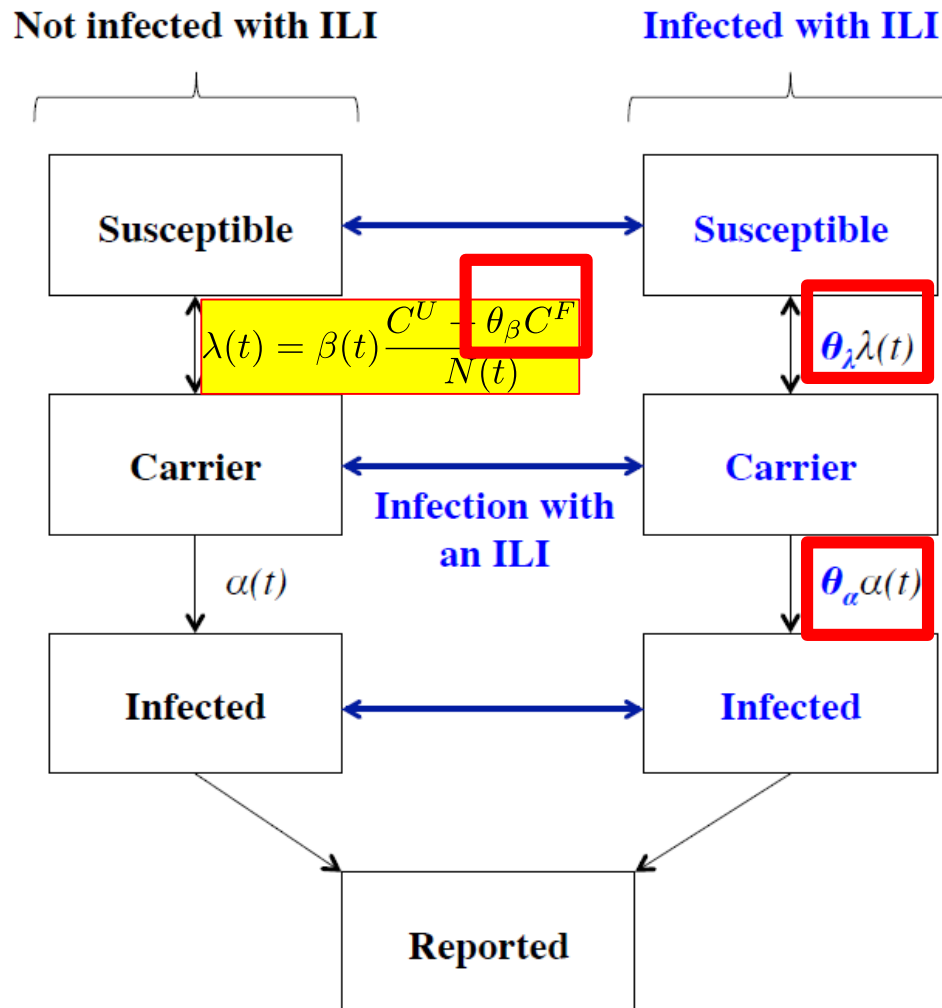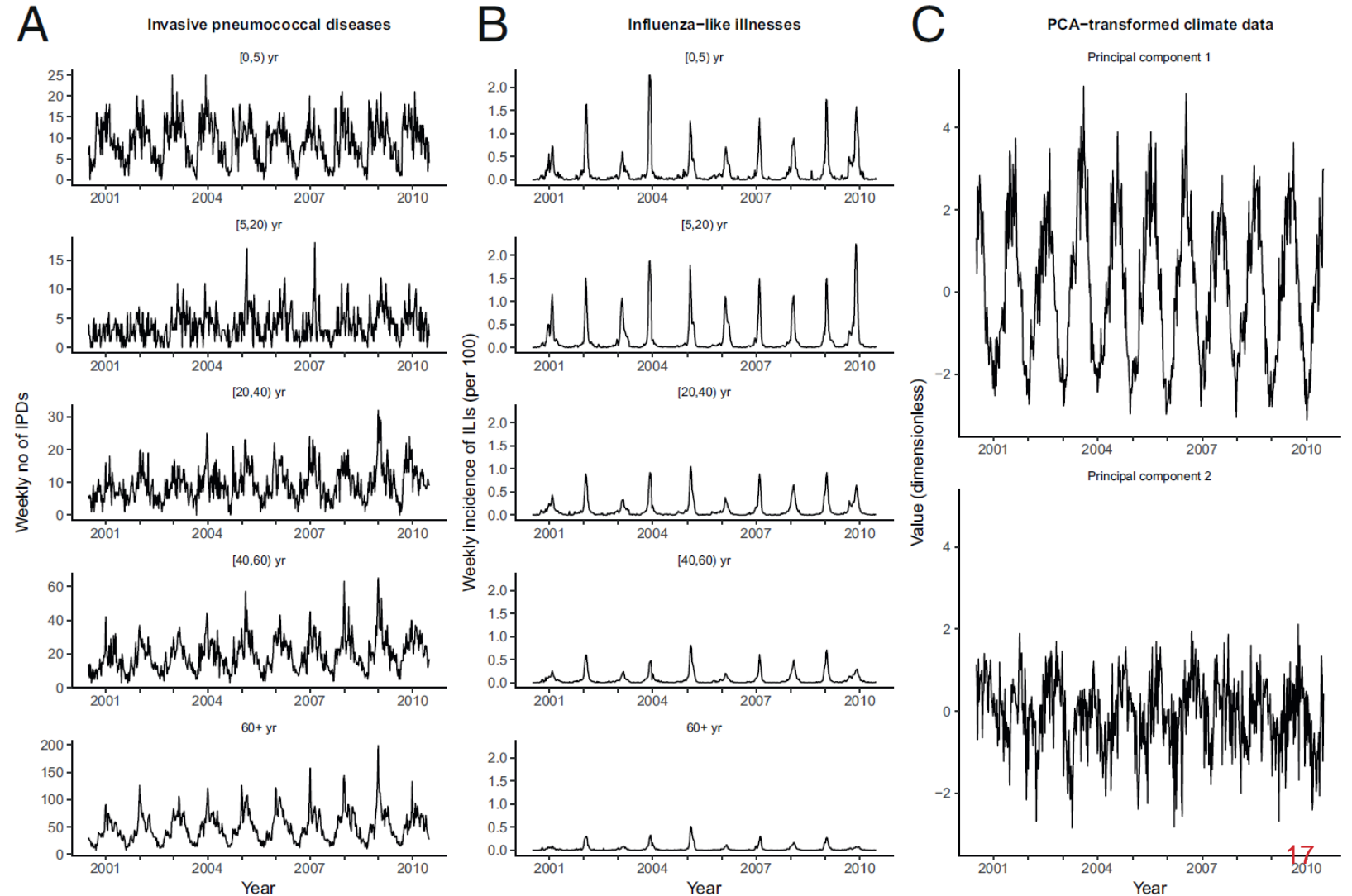B — Influenza-like illnesses

C — PCA-transformed climate data

[Domenech de Celles et al., PNAS 2019]

ANALYSIS OF FRENCH IPDs (2000-2010), MODEL COMPARISON

Hypothesis about source of seasonality			Seasonal covariates included							
		Climate	Ø	Lag 0	Lag −1	Lag −2	Lag −3	Lag −1	Lag −1	Lag −1
Acquisition rate	Invasion rate	ILIs	Ø	Ø	Ø	Ø	Ø	Lag −1	Lag 0	Lag 0
		ILI Interaction parameters	Ø	Ø	Ø	Ø	Ø	All	All	All, age-specific θ_α
Background seasonality	Ø	AIC	15252.1	15078.1	15112.7	15175.5	15207.5	—	—	—
		log L	−7612.1	−7523.1	−7540.4	−7571.8	−7592.7			
		n_θ	14	16	16	16	16			
		R^2	0.72	0.76	0.75	0.74	0.73			
Ø	Background seasonality	AIC	15211.2	15162.1	15079.9	15097.3	15172.9	14965.9	14917.5	**14890.2**
		log L	−7591.6	−7565.1	−7524.0	−7532.7	−7570.5	−7463.9	−7439.7	−7424.1
		n_θ	14	16	16	16	16	19	19	21
		R^2	0.72	0.74	0.76	0.75	0.73	0.76	0.77	0.78
Background seasonality	Background seasonality	AIC	15180.4	15079.4	15011.8	15049.9	15133.4	14900.2	14854.6	**14837.2**
		log L	−7575.2	−7522.7	−7488.9	−7508.0	−7549.7	−7430.1	−7407.3	−7396.6
		n_θ	15	17	17	17	17	20	20	22
		R^2	0.73	0.75	0.77	0.75	0.74	0.78	0.78	0.78
Term-time seasonality	Background seasonality	AIC	15145.5	15096.3	15010.0	15027.7	15105.5	14906.3	14858.6	**14826.6**
		log L	−7558.7	−7532.1	−7489.0	−7497.8	−7536.7	−7434.1	−7410.3	−7392.3
		n_θ	14	16	16	16	16	19	19	21
		R^2	0.73	0.74	0.76	0.75	0.74	0.77	0.78	0.78
Background and term-time seasonalities	Background seasonality	AIC	**15115.8**	**14996.8**	**14935.8**	**14981.1**	**15066.1**	**14835.3**	**14790.9**	**14773.6**
		log L	−7542.9	−7481.4	−7450.9	−7473.6	−7516.1	−7397.7	−7375.4	−7364.8
		n_θ	15	17	17	17	17	20	20	22
		R^2	0.73	0.76	0.77	0.76	0.74	0.78	0.79	0.79

ILIs lag

ILIs Interaction parameters

[Domenech de Celles et al., PNAS 2019]

ANALYSIS OF FRENCH IPDs (2000-2010), MODEL COMPARISON

Hypothesis about source of seasonality		Seasonal covariates included								
Acquisition rate	Invasion rate	Climate	Ø	Lag 0	Lag –1	Lag –2	Lag –3	Lag –1	Lag –1	Lag –1
		ILIs	Ø	Ø	Ø	Ø	Ø	Lag –1	Lag 0	Lag 0
		ILI Interaction	Ø	Ø	Ø	Ø	Ø	All	All	All, age-specific θ_α
			15207.5 −7592.7 16 0.73					—	—	—
			15172.9 −7570.5 16 0.73					14965.9 −7463.9 19 0.76	14917.5 −7439.7 19 0.77	**14890.2** −7424.1 21 0.78
			15133.4 −7549.7 17 0.74					14900.2 −7430.1 20 0.78	14854.6 −7407.3 20 0.78	**14837.2** −7396.6 22 0.78
			15105.5 −7536.7					14906.3 −7434.1	14858.6 −7410.3	**14826.6** −7392.3
seasonality	seasonality	n_θ R^2	14 0.73	16 0.74	16 0.76	16 0.75	16 0.74	19 0.77	19 0.78	21 0.78
Background and term-time seasonalities	Background seasonality	AIC log L n_θ R^2	**15115.8** −7542.9 15 0.73	**14996.8** −7481.4 17 0.76	**14935.8** −7450.9 17 0.77	**14981.1** −7473.6 17 0.76	**15066.1** −7516.1 17 0.74	**14835.3** −7397.7 20 0.78	**14790.9** −7375.4 20 0.79	**14773.6** −7364.8 22 0.79

Estimates:

- *ILI-associated increase of invasiveness:*
  - [0; 5yo[: Θ_α = 49 [30,68]
  - [5; 60yo[: Θ_α = 59 [40,72]
  - [60+[: Θ_α = 146 [89, 188]
- *ILI impact on acquisition:*
  - Θ_λ = 1.0[1.0,2.1]
- *ILI impact on transmission:*
  - Θ_β = 1.0 [1.0,3.3]

[Domenech de Celles et al., PNAS 2019]

PERSPECTIVES

- Evidence of interaction between Influenza and Pneumococcus, that depends on age
- Suggest that interventions targeting the virus can impact bacterial epidemiology
  - Currently working on investigating the impact of (antiviral) vaccine on IPDs and antibiotic resistance

CHALLENGE : DATA

- Limited to analysis of ecological data (incidence data)

- Still very little (no) data of co-carriage/infection available in populations
- New technologies allowing for testing several pathogens at the same time
  - Multiplex PCR that can test for >15-20 pathogens on a single test
  - Technologies for the detection and quantification of respiratory pathogens directly from clinical specimens
  - Metagenomics, microbiota

2: (RESPI) VIRUS-VIRUS ?

INTERACTIONS

INTERACTIONS IN INFLUENZA?

Table 2. Viruses that may be affected by interaction with influenza.

Virus	Study system	Effect	Illustrative publications
RSV	Population incidence	Competitive	Anestad 2007 [190]; Anestad 2009 [191]; Casalegno 2010 [77]; Anestad 1987 [192]; Yang 2012 [79]; Nishimura 2005 [193]; Glezen 1980 [76]; Pascalis 2012 [83]; Yang 2015 [67]; van Asten 2016 [194]; Meningher 2014 [195]; Velasco-Hernandez 2015 [117]
		Neutral	Navarro-Mari 2012 [68]
	Coinfection detection	Competitive	Greer 2009 [84]; Martin 2013 [196]
	Laboratory investigation	Competitive	Shinjoh 2000 [197]
Rhinovirus	Population incidence	Competitive	Casalegno 2010 [66]; Casalegno 2010 [77]; Pascalis 2012 [83]; Linde 2009 [198]; Anestad and Nordbo [199]; Cowling 2012 [65]; Yang 2015 [67]
		Neutral	Yang 2012 [79]; Navarro-Mari 2012 [68]; van Asten 2016 [194]
	Coinfection detection	Competitive	Tanner 2012 [200]; Mackay 2013 [201]; Nisi 2010 [86]; Greer 2009 [84]; Martin 2013 [196]
	Laboratory investigation	Competitive	Pinky and Dobrovolny 2016 [112]
Influenza	Population incidence	Competitive	van Asten 2016 [194]
	Coinfection detection	Competitive	Nisii 2010 [86]; Sonoguchi 1985 [56]
	Laboratory studies	Competitive	Easton 2011 [202]; Laurie 2015 [57]
HPIV	Population incidence	Competitive	Yang 2012 [67]; Anestad 1987 [192]; Yang 2015 [67]
		Neutral	Mak 2012 [78]
	Coinfection detection	Competitive	Pascalis 2012 [83]
		Neutral	Murphy 1975 [85]; Nisii 2010 [86]; Greer 2009 [84]; Martin 2013 [196]
	Laboratory investigation	Synergistic/Facilitating	Goto 2016 [203]

Abbreviations: HPIV, human parainfluenza virus; RSV, respiratory syncytial virus.

Opatowski et al., Plos Pathogens 2018

AND IN SARS-COV-2?

- Large heterogeneity across the studies reviewed
- Evidence that coinfection with IAV and SARS-CoV-2 causes more severe disease than monoinfection with either virus

Epi evidence :
- Coinfection prevalence is largely variable
- Influenza vaccines may be associated with reduced risk of SARS-CoV-2
- Earlier influenza infection may be associated with increased risk of SARS-CoV-2 infection and disease severity
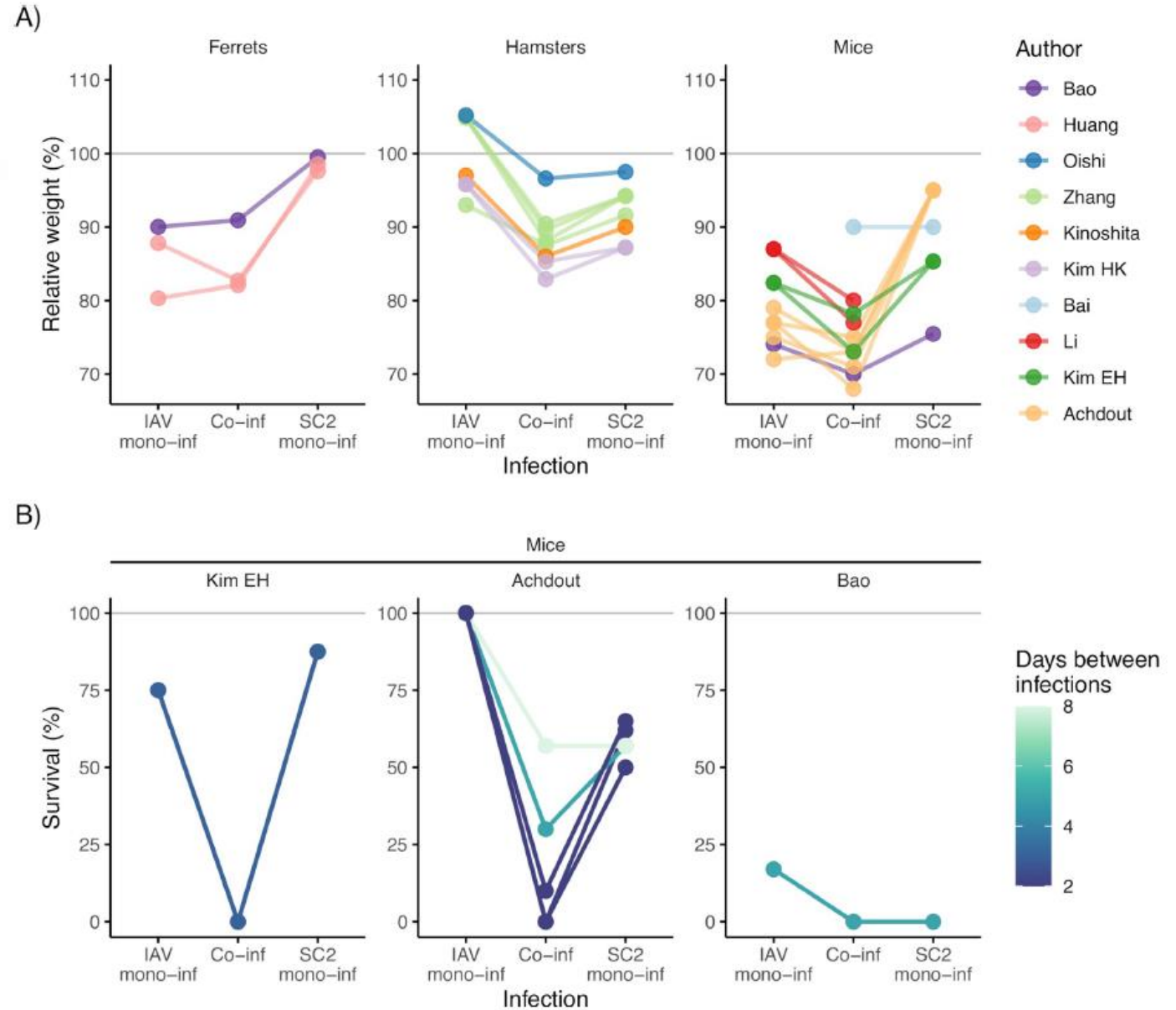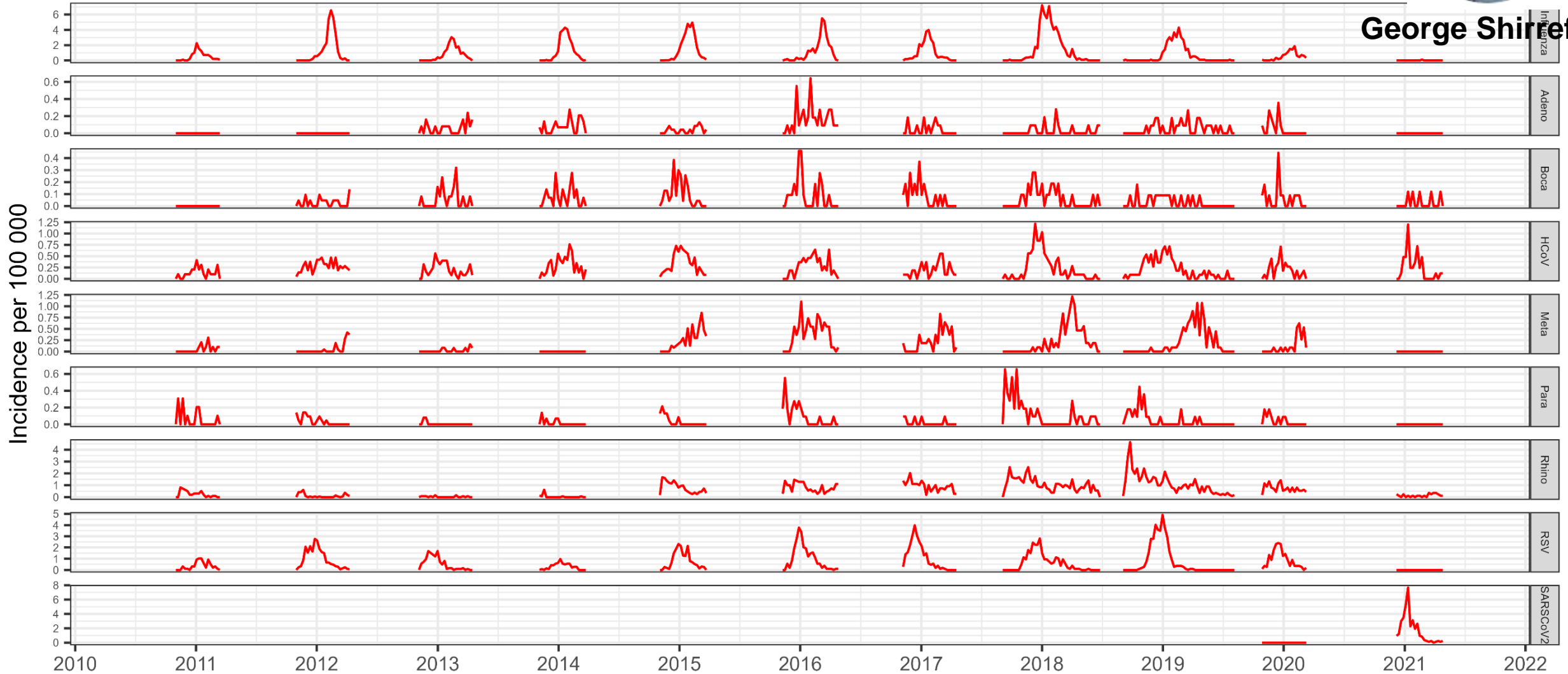

Fig 3. Summary results from animal studies assessing the effect of coinfection with SARS-CoV-2 and influenza A virus (IAV) on disease severity. [44–

Wong et al, Plos Pathogens 2023

INCIDENCE OF RESPIRATORY VIRUSES

Positive cases from multiplex PCR in hospitalized patients, Valencia Community, Spain

George Shirreff

Shirreff et al, in preparation

ESTIMATING THE IMPACT OF INFLUENZA ON SARS-COV-2 EPIDEMIOLOGY

Matthieu Domenech
de Cellès

- Early phase of the outbreak – overlap with the end of the flu epidemics in Europe

- Flu-SARS-CoV-2 transmission model including a range of assumptions about the impact of influenza, and accounting for interventions (stringency index)

| Quantity	Belgium	Italy	Norway	Spain
Study period (year 2020)	13 Feb–28 Jun	29 Jan–28 Jun	25 Feb–28 Jun	06 Feb–28 Jun
Log-likelihood (SE)	−383.2 (<0.1)	−669.1 (<0.1)	−160.8 (<0.1)	−558.8 (0.1)
Basic reproduction number (R_0)	3.3 (2.0, 4.0)	2.0 (2.0, 2.3)	2.3 (2.0, 2.7)	2.0 (2.0, 2.6)
Impact of control measures (b)	1.02 (0.90, 1.06)	0.76 (0.75, 0.81)	1.07 (0.94, 1.09)	0.89 (0.88, 0.96)
Average relative variation in SARS-CoV-2 transmission rate associated with influenza (e^{β_F})	1.9 (1.5, 2.8)	2.4 (2.2, 2.7)	2.1 (1.2, 2.8)	2.5 (2.1, 3.1)
Initial number exposed to SARS-CoV-2 ($E_1(0)$)	60 (10, 100)	40 (15, 85)	50 (80, 1550)	130 (45, 540)
Proportion infected, as of 4 May 2020 (%)	8.1 (6.1, 10.5)	6.1 (4.2, 8.3)	0.4 (0.3, 0.6)	5.5 (4.4, 6.6)
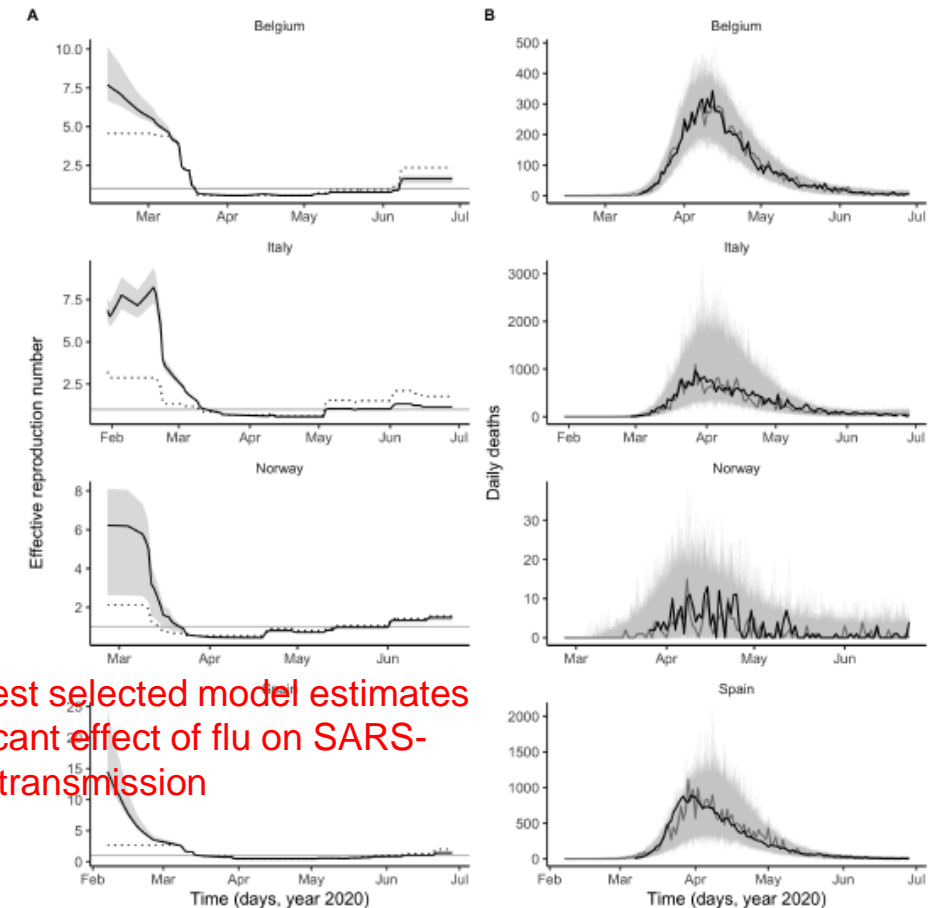
The best selected model estimates significant effect of flu on SARS-CoV2 transmission

[Domenech de Celles et al PeerJ 2021]
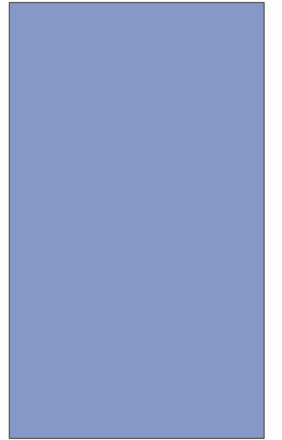
ANALYSE SIMULTANEOUSLY VIRUS TRENDS USING A 2-VIRUS MODEL

George Shirreff
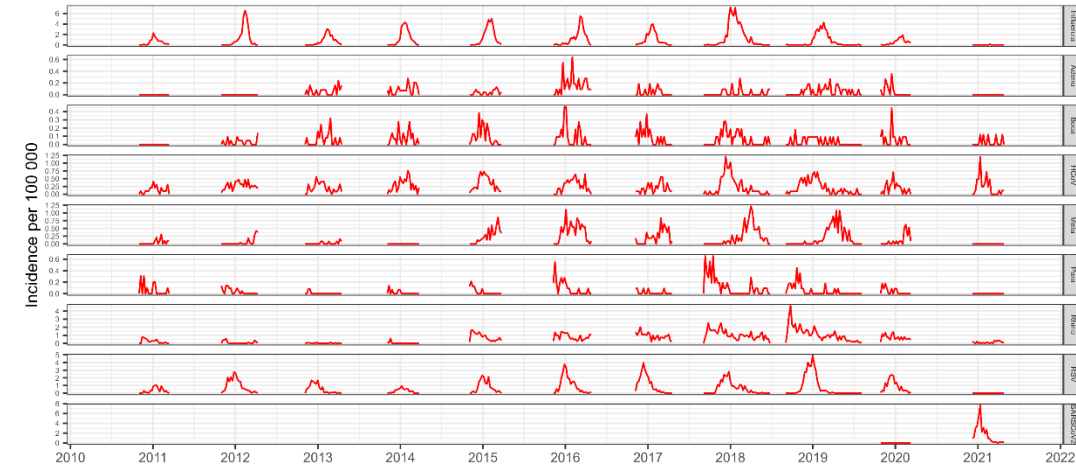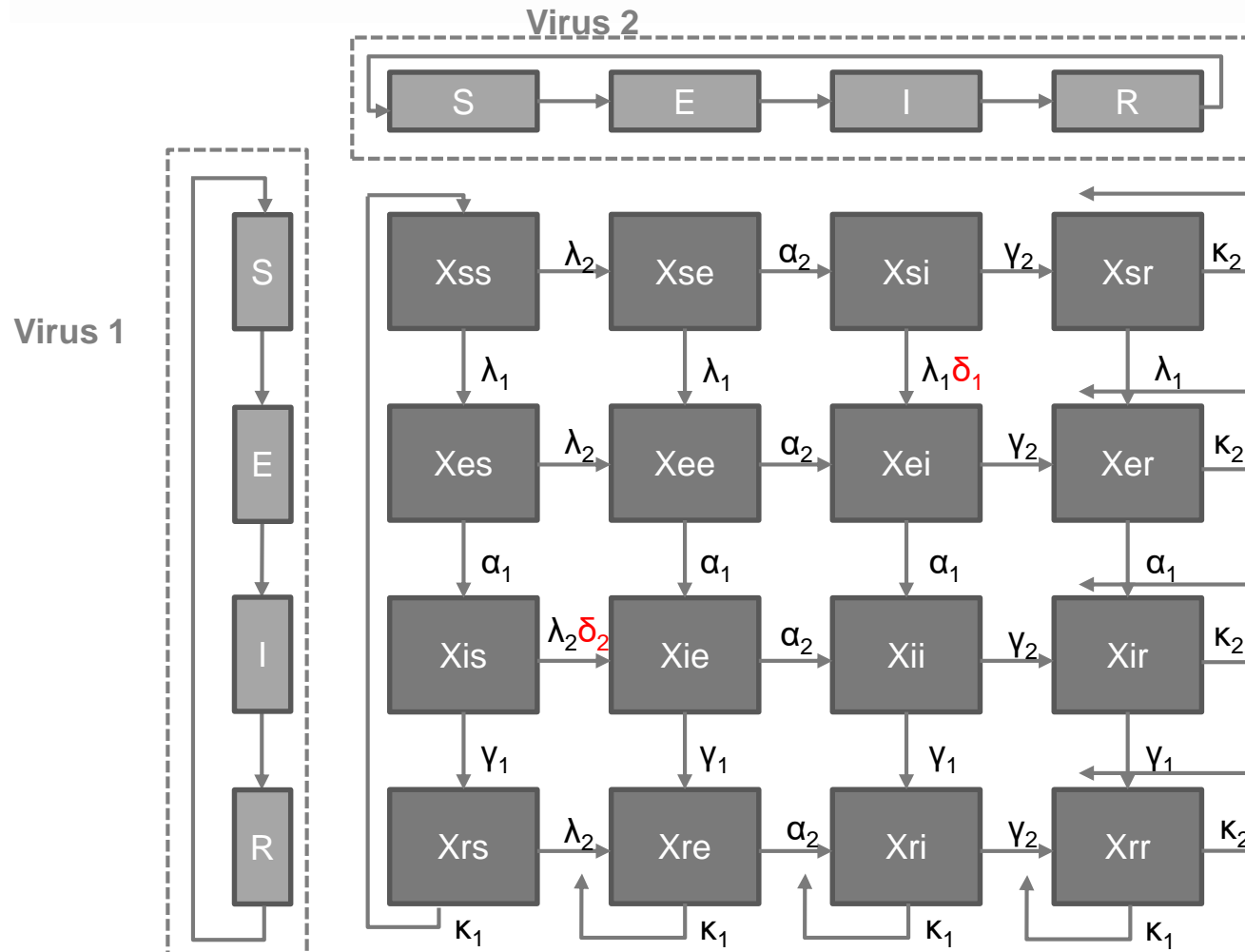
$$\lambda_1 = \beta_1 * (Xis + Xir + \sigma_1 * Xii + Xie)/N$$
$$\lambda_2 = \beta_2 * (Xsi + Xri + \sigma_2 * Xii + Xei)/N$$

δ_1 = factor of susceptibility to virus 1
if already infected with virus 2

σ_1 = factor of transmissibility of virus 1
if co-infected with virus 2

Shirreff et al, in preparation

3. MICROBIOTA'S IMPACT ON ACQUISITION

MECANISTIC HYPOTHESES (ON ANTIBIOTIC RESISTANT BACTERIA)

David Smith

1. Commensal bacteria can help / hinder acquisition / colonization dynamics of pathogens
2. Antibiotics and drugs in general can disrupt commensal flora, *by extension any interactions that occur between flora and pathogens*
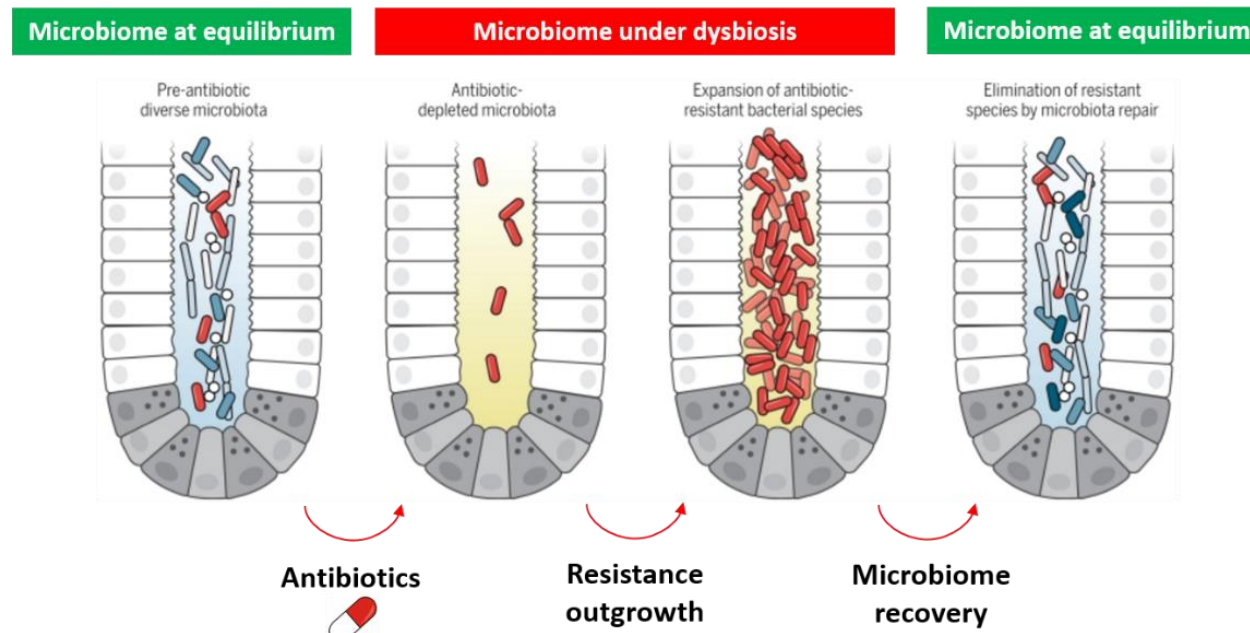
(Pamer, *Science* 2016)

A MODEL FOR MICROBIOME-PATHOGEN CO-COLONIZATION

- Compartmental ODE model
- Patient population in healthcare setting

- **Drug use (q_a)**
  - Proportion of patients receiving antibiotics
- **Drug resistance (q_r)**
  - Proportion of antibiotics against which pathogen resistant

Include interaction mechanisms

1. Microbiome dysbiosis (σ)
2. Microbiome recovery (δ)
3. Pathogen acquisition ($\beta + \alpha$)
4. Pathogen clearance ($\gamma + \sigma$)
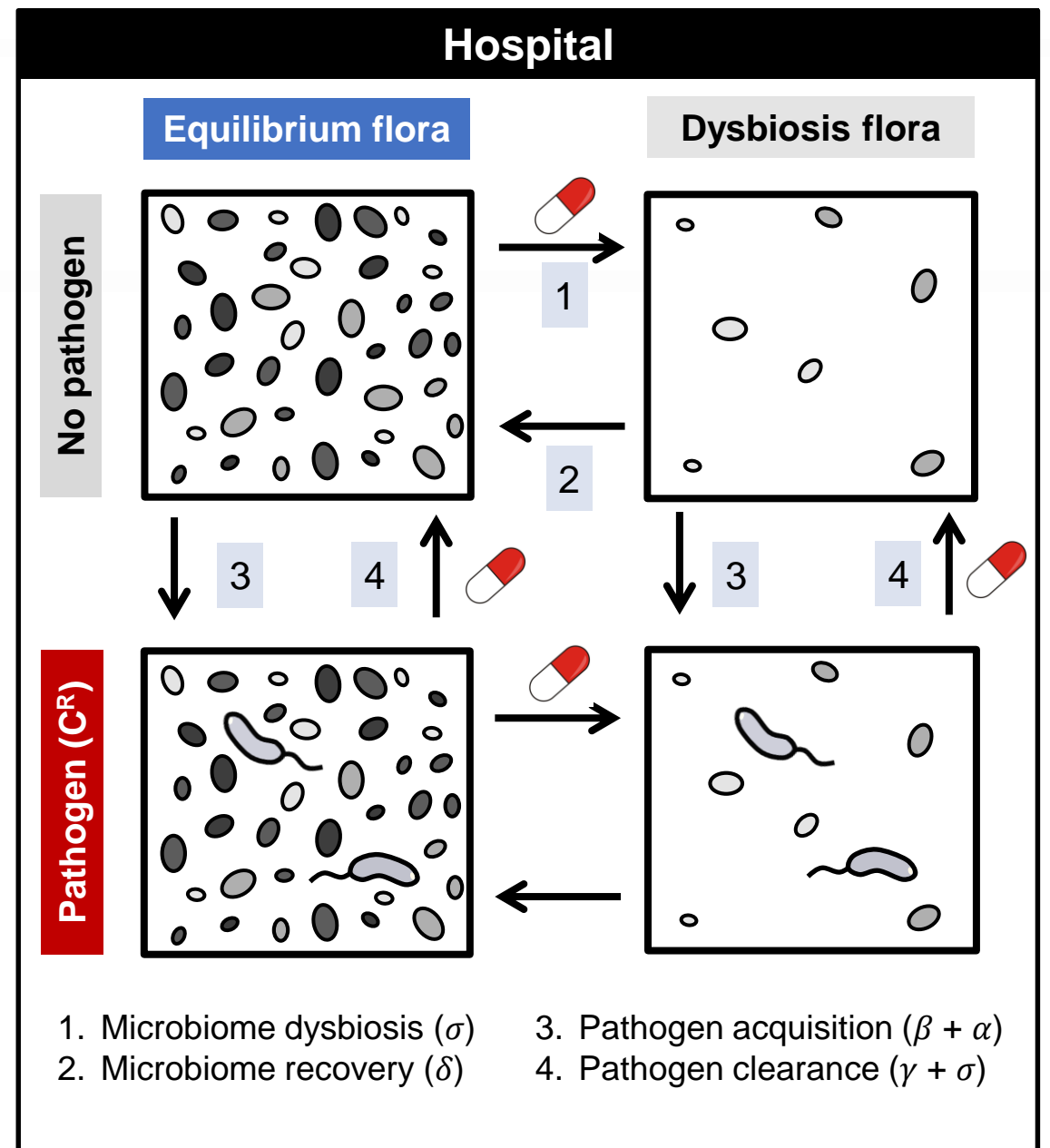
[Smith et al, eLIfe 2021]

MODELLED INTERACTIONS

1. Barrier protection (ε)
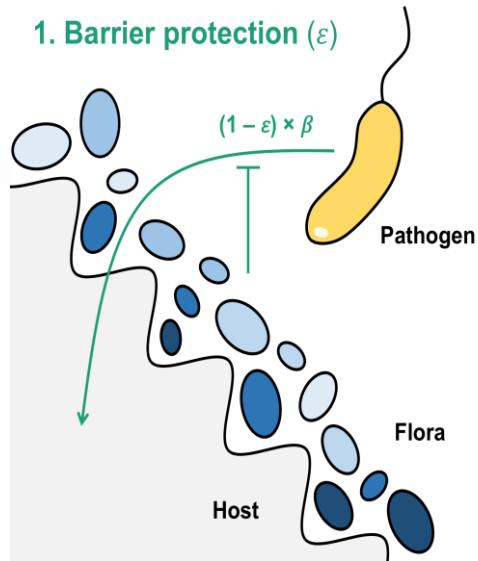
Reduced pathogen force of infection (λ)

Eg. Bifidobacteria bacteriocins inhibit *C. difficile* and *E. coli* colonization

Buffie & Pamer *Nat Rev Immunol* 2014

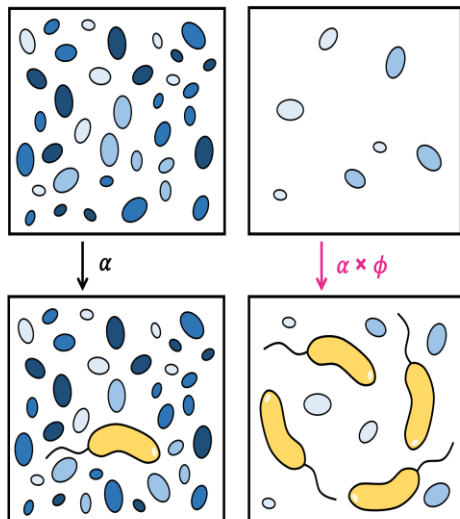## 2. Niche competition (η)   3. Niche cooperation (ζ)
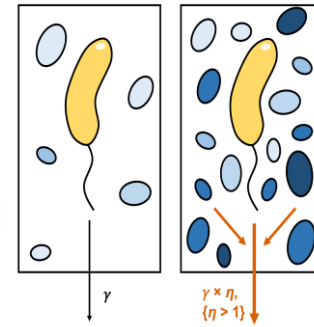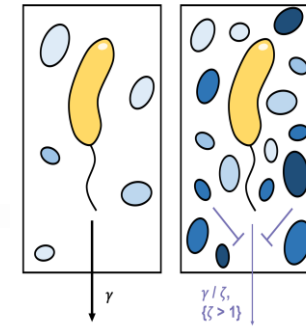
Affected pathogen clearance rate (γ)

Eg. Bacterioides bacteriocins reduce colonization duration in *E. faecalis, Listeria spp.;* Bacterioides metabolites enhance colonization duration in *E. coli*

Pacheco et al. *Nature* 2012   Kamada et al. *Nat Rev Immunol* 2013

4. Ecological Release (ϕ)

Enhanced endogenous acquisition rate (α)

Eg. *C. scindens* bile acids prevent outgrowth of subdominant *C. difficile* colonies
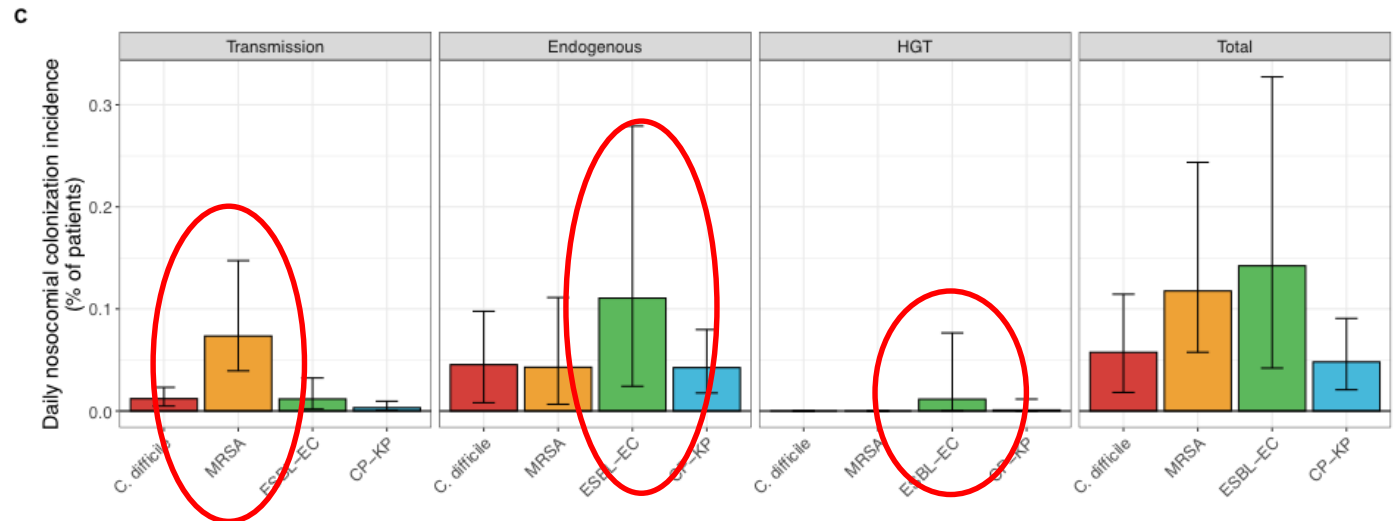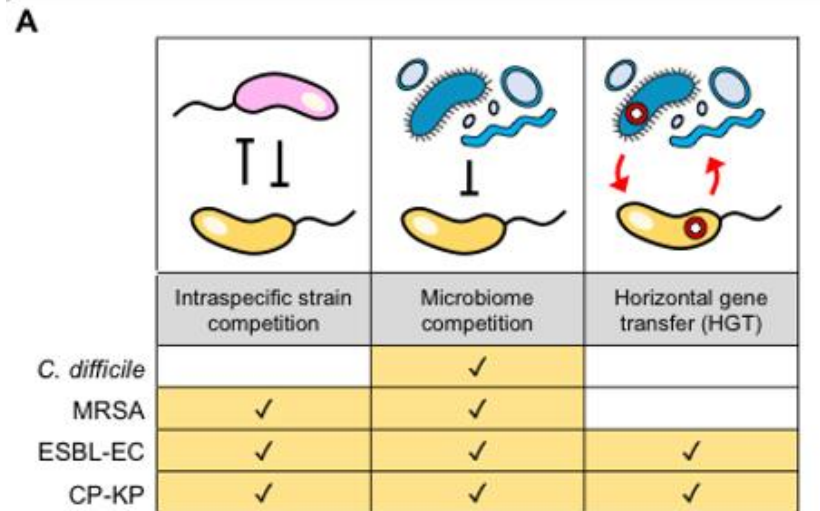
Buffie et al. *Nature* 2014

5.HORIZONTAL GENE TRANSFER (HGT)

HGT (χ)
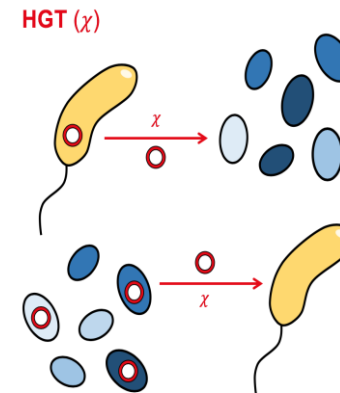
HGT especially important among Gram-negative pathogens (ESBL-Enterobacteria)

APPLICATION TO BACTERIAL SPECIES

Different types of ecological interactions, different colonisation dynamics

- **Between-host transmission:** MRSA

- **Endogenous acquisition:** enteric bacteria

- **HGT:** potentially important for Enterobacteria

[Smith et al, eLIfe 2021]

4: IMPACT OF MULTI-X IN TERMS OF PUBLIC HEALTH

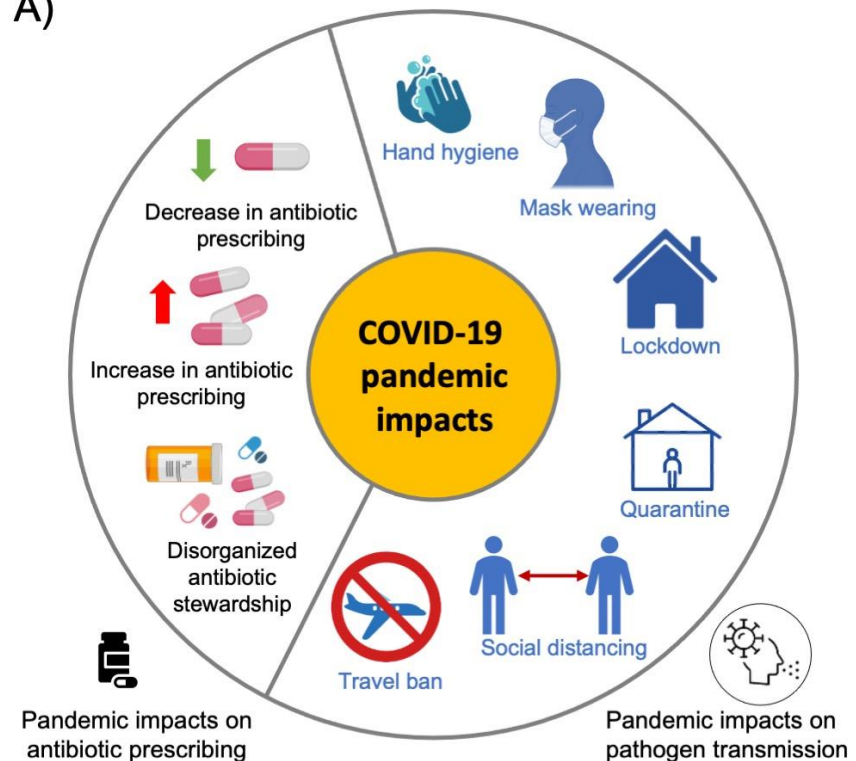INTERACTIONS & INTERVENTIONS

CO-CIRCULATION & PUBLIC HEALTH IMPACT

Impact on surveillance

- Surveillance disrupted
- Health care system saturated
- Change behaviours
  - Access to care
  - Drug exposure
  - Testing etc…

Indirect impact of interventions

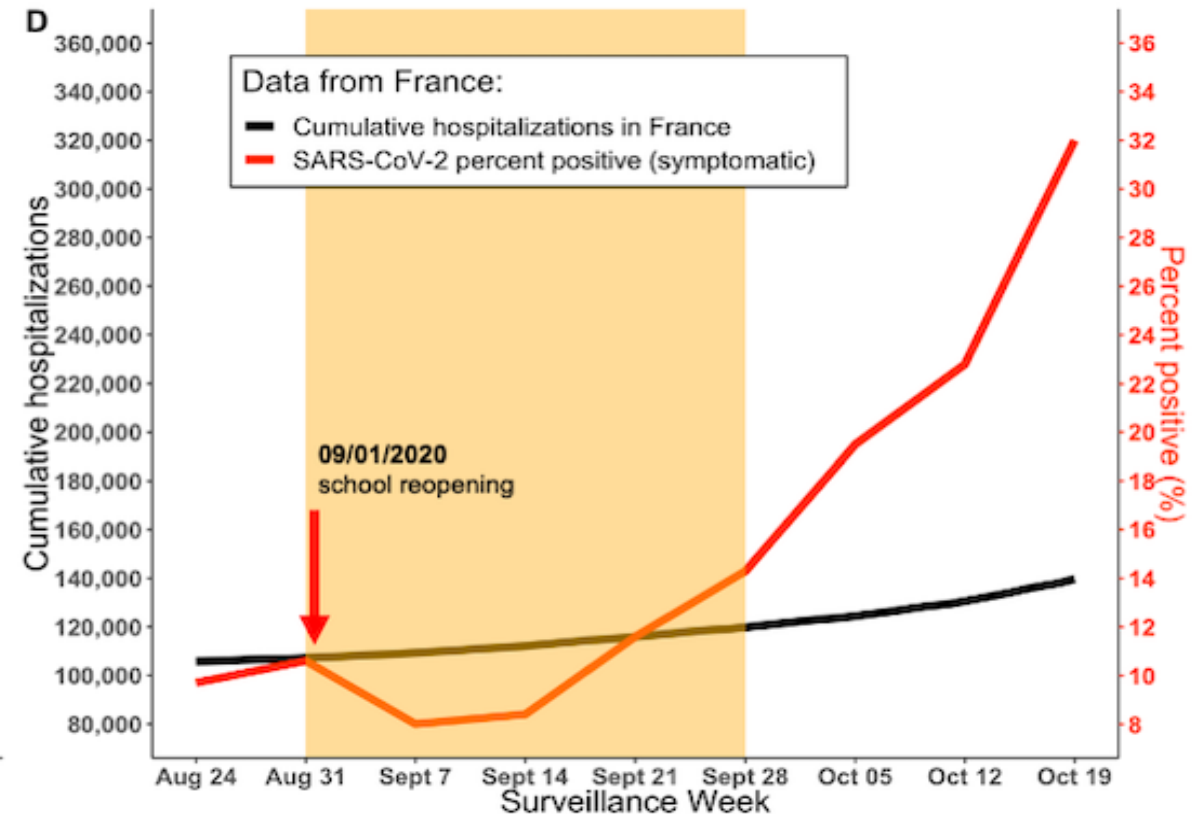- Interventions targeting one pathogen can modify transmission of others

A)

IMPACT ON SURVEILLANCE

The Impact of Cocirculating Pathogens on Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)/ Coronavirus Disease 2019 Surveillance: How Concurrent Epidemics May Introduce Bias and Decrease the Observed SARS-CoV-2 Percentage Positivity
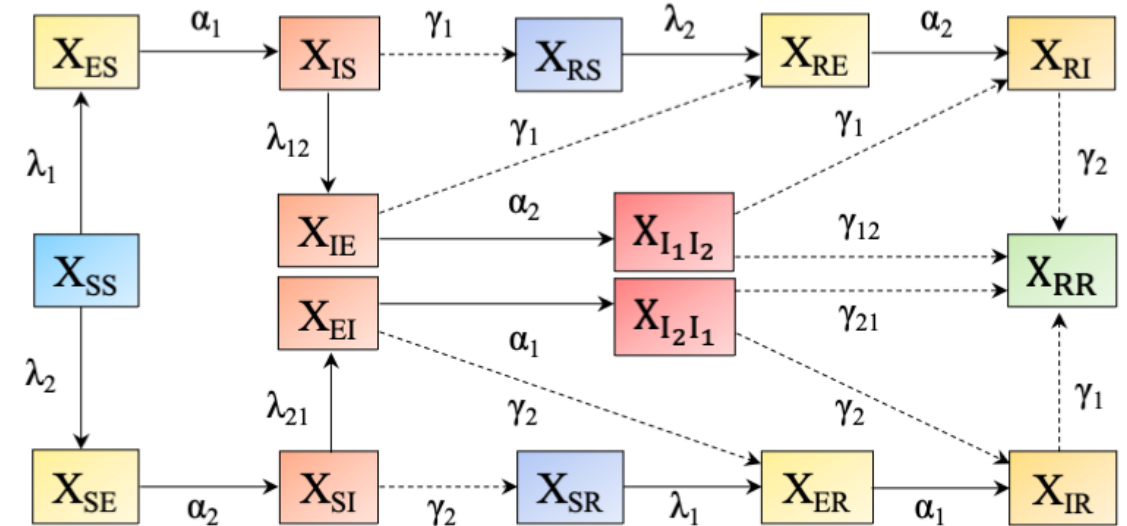
Aleksandra Kovacevic,[1,2] Rosalind M. Eggo,[3,4] Marc Baguelin,[3,4,5] Matthieu Domenech de Cellès,[6] and Lulla Opatowski[1,2]

[1]Epidemiology and Modelling of Antibiotic Evasion, Institut Pasteur, Paris, France, [2]Anti-infective Evasion and Pharmacoepidemiology Team, CESP, Université Paris-Saclay, Université de Versailles Saint-Quentin-en-Yvelines, INSERM U1018 Montigny-le-Bretonneux, France, [3]Centre for Mathematical Modelling of Infectious Diseases, London School of Hygiene and Tropical Medicine, London, United Kingdom, [4]Department of Infectious Disease Epidemiology, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, United Kingdom, [5]MRC Centre for Global Infectious Disease Analysis and the Department of Infectious Disease Epidemiology, Imperial College London, London, United Kingdom, and [6]Max Planck Institute for Infection Biology, Infectious Disease Epidemiology Group, Berlin, Germany

Aleksandra Kovacevic

- COVID-19 surveillance indicators may be impacted by increased co-circulation of other respiratory viruses delaying control measure implementation

- **Objective: assess impact on the monitoring of positivity rates of SARS-CoV-2 and interpretation of surveillance data**

TWO-VIRUS MODEL

- Neutral interaction assumed

- Testing model
  - Focus on symptomatic tests
  - Symptomatic individuals infected with SARS-CoV-2 (T_{COV})
  - Contact tracing - delay, d in days, ($T_{CONTACTS}$);
  - Symptomatic individuals infected with virus-2 (T_{V2});
  - Baseline number of symptomatic tests (T_b)

$$T(t) = T_b + T_{COV}(t) + T_{CONTACTS}(t-d) + T_{V2}(t)$$

- Testing strategies investigated
  - Standard SARS-CoV-2 RT-PCR (sensitivity s_{pcr})
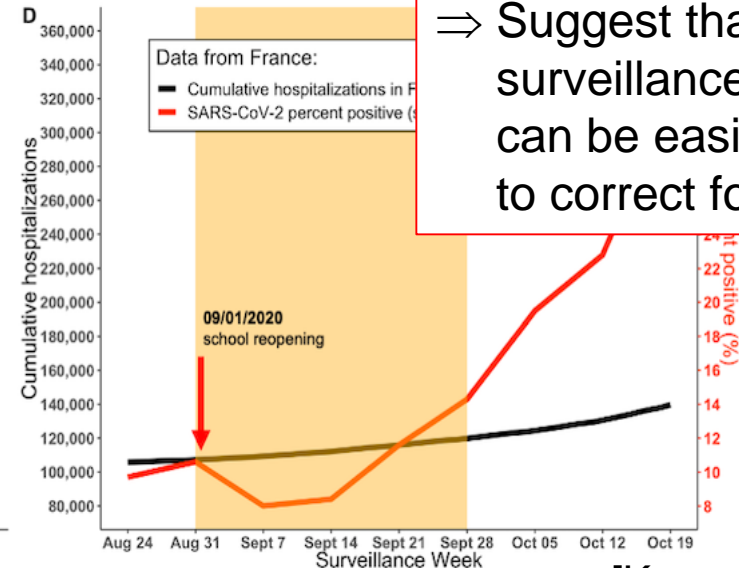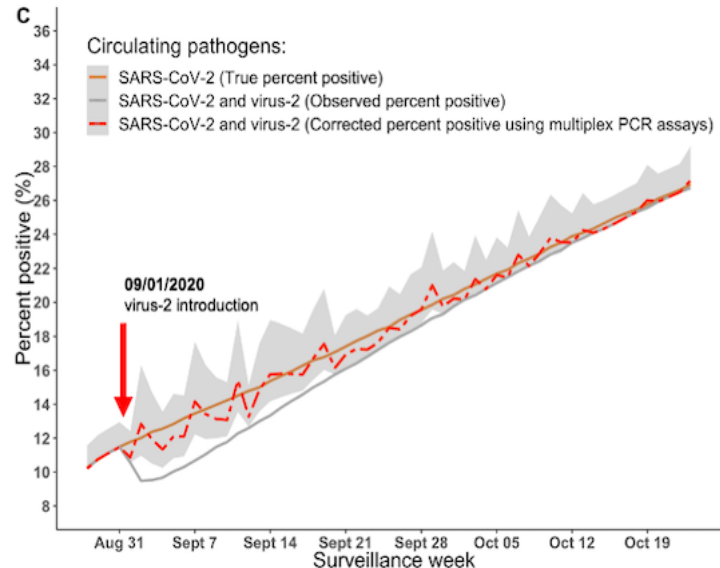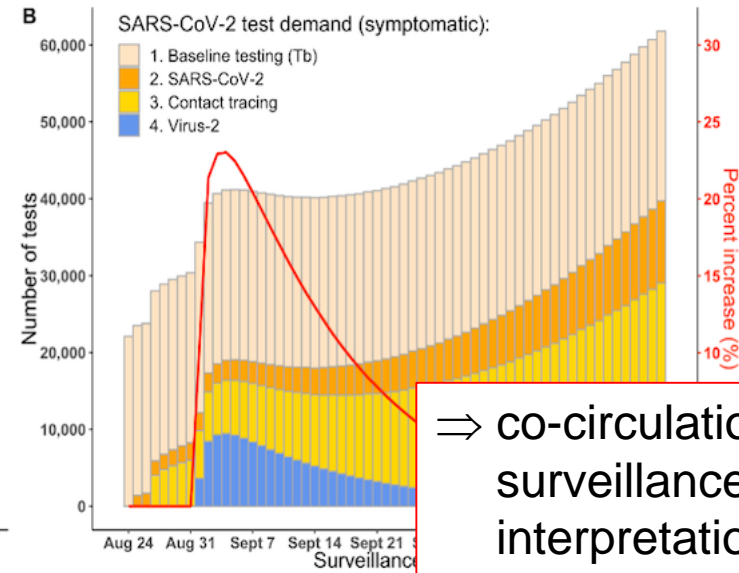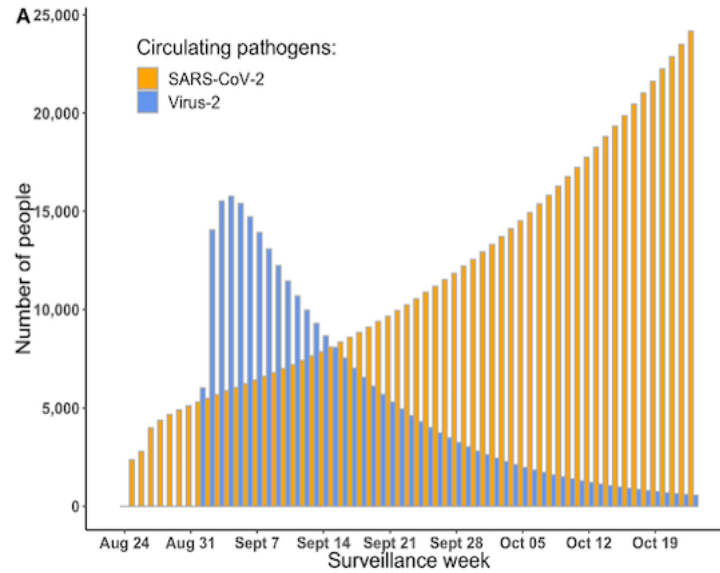 - Multiplex PCR (testing for virus2) in a subsample of individuals (sensitivity s_m)

SIMULATION STUDY AND CORRECTION

Multiplex testing can help correct surveillance data

m=0.1% = 1 multiplex test for every 1,000 symptomatic tests
=> correction that closely follows real percent positive of SARS-CoV-2

⇒ co-circulation can bias surveillance and interpretation
⇒ Suggest that surveillance system can be easily adapted to correct for it

[Kovacevic et al JID 2021]

SUMMARY OF RESULTS

- Interactions in cocirculating pathogens can alter the natural epidemiology of pathogens

  1. Evidence of interaction at the population level between Influenza and Pneumococcus, that depends on age

  2. Evidence of non neutral interaction between viruses – to be explored further

  3. Bystander impact of interventions – application to COVID19 pandemic

AND I DID NOT MENTION…
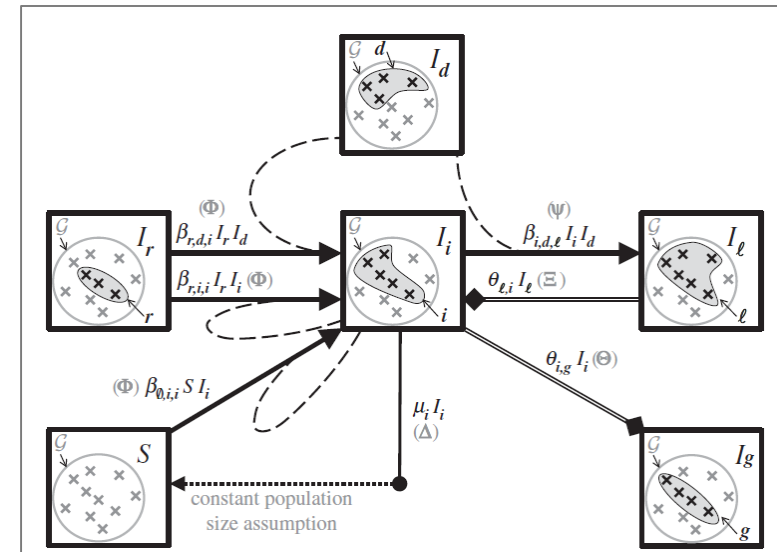
- Within-species diversity and interactions between subtypes, serotypes, genotypes etc…
    - Influenza
    - HPV
    - Pneumococci
    - Etc…

A MODELLING CHALLENGE: FORMALIZING MULTIPLE PATHOGENS IN INTERACTION

- Translating from a single host to population
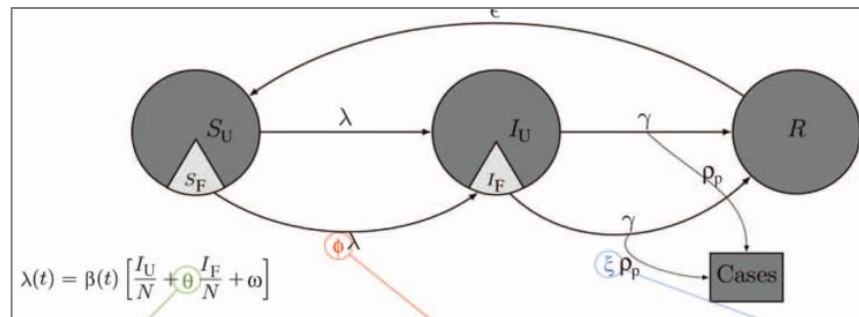
Model of pneumonia transmission by Shrestha et al, 2013

Model of multiple genotypes, coupling the within-host and between-host scales by Sofonea et al, 2015

OPPORTUNITY AND CHALLENGES

- Controlling one virus can affect the dynamics of circulating pathogen and lead to **beneficial / detrimental outcome**

- Considering interactions => better evaluation and anticipation global impact of public health measures

- **Challenges**
  - Better knowledge of interactions needed : identification, strength, excess cases
  - Complex models, inference questions
  - Needs for data !

COLLABORATORS

Institut Pasteur / UVSQ / INSERM:
Aleksandra Kovacevic
George Shirreff
Matthieu Domenech de Cellès
Hélène Arduin
David Smith, Laura Temime
Didier Guillemot
Laurence Watier

INSERM, Sentinelles:
Pierre-Yves Boëlle
Cécile Souty

London:
Marc Baguelin (Imperial College)
Roz Eggo (LSHTM)

CNR Pneumococcus:
Emmanuelle Varon
Marie-Cécile Ploy

CNR Influenza:
Sylvie van der Werf

Santé Publique France:
Daniel Levy-Bruhl

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Thank you!