# Annual meeting of the Coordinated Action « Modelling infectious diseases »

## 24-25 October 2023

TUESDAY 24 OCT.

9:30-9:40 Opening talk

**Session on « Generic methods »**

9:40-10:15 Mircea Sofonea (PCCEI, U. Montpellier) - On airborne transmission: history, biophysics, epidemiology & modelling

10:15-10:40 Noémie Lefrancq (Cambridge U.) - Agnostic identification of pathogen lineages and estimation of fitness dynamics

10:40-11:05 Olivier Supplisson (CIRB, Collège de France) - Herpes-simplex virus 1 and 2, varicella-zoster virus, Epstein–Barr virus, and cytomegalovirus infection seroprevalence in France, between 2016 and 2023: a multilevel regression and post-stratification approach

11:05-11:35 *Coffee break*

**Session on « Contact networks and individual-based transmission models »**

11:35-12:00 Quentin Leclerc (Institut Pasteur/CNAM/UVSQ) - Using contact network dynamics to implement efficient interventions against pathogen spread in hospital settings

12:00-12:25 Paul Henriot (MESuRS, CNAM) - An agent-based model to simulate the transmission dynamics of bloodborne pathogens within hospitals

12:25-13:00 Presentation of the workgroups and calls for funding of the Coordinated Action

13:00-14:15 *Lunch break*

**Session on « COVID-19 »**

14:15-14:40 Benjamin Faucher (SUMO, iPLESP) - Drivers and impact of the early silent invasion of SARS-CoV-2 Alpha

14:40-15:05 Anthony Hauser (EPIcx, iPLESP) - Reproducing the change in contact patterns observed during the COVID-19 pandemic using mobility data

15:05-15:30 Sabira Smaili (Santé publique France) - The effect of social deprivation on hospitalisations, intensive care unit episodes and deaths among COVID-19 inpatients between January 2021 and August 2022 in metropolitan France

15:30-16:00 *Coffee break*

**Session on « IST/Mpox »**

16:00-16:25 Baptiste Elie (Collège de France/U. Montpellier) - Viral and immune kinetics of HPV genital infections in young adult women

16:25-16:50 Davide Maniscalco (EPIcx, iPLESP) - Behavioral changes in the 2022 Mpox epidemic in MSM in Île-de-France

16:50-17:15 Presentation of the ANRS-MIE Programme for young researchers by Zélie Godin and Inmaculada Ortega Perez (ANRS-MIE)

17:30-19:00 **Poster session**

WEDNESDAY 25 OCT.

**Session on « Within-Host dynamics »**

9:00-9:35 Rodolphe Thiébaut (SISTM, U. Bordeaux) - How gene expression can inform dynamical models?

9:35-10:00 Constanze Ciavarella (IDEA, Institut Pasteur) - Plotting a path through the P. vivax treatment dilemma: a modelling study integrating individual-level observations from primaquine trials and population-level treatment effects

10:00-10:25 Thomas Cortier (MMMI, Institut Pasteur) - Modeling L. monocytogenes within-host infection using genetic tags to decipher the under-lying mechanisms of virulence and its fitness advantage.

10:25-10:50 Mathilde Grimée (IDEA, Institut Pasteur) - Modelling P. vivax and P. falciparum co-infections with heterogeneity in mosquito biting exposure

10.50-11.20 *Coffee break*

**Session on « Community Dynamics »**

11:20-11:55 Pauline Ezanno (DYNAMO, BIOEPAR, INRAE) & Madeleine Kubasch (INRAE/Ecole Polytechnique) - Tribute to Eliza Vergu

11:55-12:20 Eve Rahbe (EMAE, Institut Pasteur) - A data-driven multi-country mathematical model of antibiotic resistant *Escherichia coli* transmission to explore worldwide emergence spread at the populational level.

12:20-12:45 Carlos Olivares (IAME, INSERM) - Impact of beta lactam antibiotics on the gut microbiota: a modeling analysis

12:45-13:10 Noé Ochida (MMMI, Institut Pasteur) - Modelling approach to optimize release strategies for establishing Wolbachia within the Aedes aegypti population in Nouméa

13:10-14:15 *Lunch break*

End at 14:15

# Plotting a path through the P. vivax treatment dilemma: a modelling study integrating individual-level observations from primaquine trials and population-level treatment effects

Constanze Ciavarella[1], Thomas Obadia[1], Michael White[1]

**1 :** Infectious Disease Epidemiology and Analytics
*Institut Pasteur de Paris*

**Background**
Upon primary infection, some *Plasmodium vivax* (*Pv*) parasites develop into hypnozoites that lie dormant in the liver for weeks to months before reactivating to cause relapses. Treatment of *Pv* thus calls for radical cure, a type of therapy that clears parasites in both blood flow and the liver. The effectiveness of liver stage drugs primaquine (PQ) and tafenoquine (TQ) has been compared in several randomised control trials (RCTs). However, the individual-level efficacy of radical cure has never been formally estimated since hypnozoites are not directly observable. Moreover, the population-level impact of radical cure regimens still must be evaluated in cluster randomised trials. Such trials are necessary to measure the non-linear effects on transmission due to lower, heterogeneous *Pv* circulation and decreased population immunity.
**Methods & results**
We developed a compartmental model of *Pv* infection and fit it to data from several radical cure RCTs, assuming relapse and biting rates to be location-specific, but drug efficacy to remain constant across locations. The efficacies estimated from IMPROV trial data of 7- and 14-day high-dose PQ regimens (7 mg/kg total) were of 92% (95%CI: 87%-97%) and 97% (95%CI: 92%-100%), respectively. Pooled data from various RCTs yielded efficacy estimates of 70% (95%CI: 66%-74%) for low-dose PQ regimens (3.5 mg/kg total), and 93% (95%CI: 76%-100%) for high-dose TQ regimens (7.5 mg/kg total). Next, we estimated the population-level impact of introducing radical cure in case management using an existing individual-based model of Pv transmission. We tested several radical cure regimens (varying dosage and duration of administration) under various transmission scenarios (varying transmission intensity, seasonality, Pv relapse rates and care-seeking behaviour). Introducing radical cure may make elimination feasible where transmission is already low (<2% PCR-prevalence). As transmission intensity increases, the efficacy of radical cure is vastly reduced and differences between regimens even out.
**Implications**
To date PQ and TQ have been tested under trial conditions, while real-world implementations introduce many constraints that hamper their population-level impact. Rather than focusing on optimal dose and duration of administration, it might thus be more effective to increase adherence and care-seeking rates, and to widen eligibility criteria.

# Modeling L. monocytogenes within-host infection using genetic tags to decipher the underlying mechanisms of virulence and its fitness advantage.

Thomas Cortier[1], Julien Gaillard, Marc Lecuit, Simon Cauchemez

**1 :** Modélisation mathématique des maladies infectieuses - Mathematical modelling of Infectious Diseases
*Institut Pasteur [Paris], Centre National de la Recherche Scientifique : UMR2000, Université Paris Cité*

*L. monocytogenes* is a foodborne pathogen that infects humans and can be lethal, especially for immunocompromised individuals. It serves as an important model for studying the mechanisms of bacterial infections and their genetic determinants. The virulence genes of *L. monocytogenes* play a crucial role in binding to and crossing the epithelial barrier of the digestive tract, leading to systemic infections. By using mathematical models, we aim to characterize the infection caused by a virulent strain, to quantify and understand the different pathways and sites of bacterial proliferation-loops involved.

In recent years, sequence tag-based analysis of microbial populations (STAMP) has been employed to study bacterial population dynamics, including bottleneck and founding populations events. Marc Lecuit's laboratory has collected such data in mice infected with both Internalin-A active and mutated strains.

On the computational side, likelihood-free inference methods, such as ABC, have been developed to tackle complex models with intractable likelihoods. Integration of multi-dimensional systems of stochastic differential equations has been optimized to model complex systems of interconnected populations.

By combining these tools, we have developed a flexible modeling framework that utilizes compartmental models and time- and age-dependent stochastic dynamics to describe the number of bacteria with different genetic tags in each organ over time. This modeling framework allows us to test various models to characterize the infection process.

Using these models, we can infer the probability densities of various bacterial events (transfers, replication, death, average time to death). One key finding is that considering the organization of bacterial foci within tissues is essential for explaining the population data. We also discovered a new phenotype for these bacteria, which involves hiding and proliferating in the epithelium before re-entering the digestive tract and eventually returning to the environment. While the existing paradigm was that the virulent genes were selected to reach the gallbladder and proliferate there, this novel phenotype could be the principal fitness advantage conferred by the virulence genes as it occurs for all infections. Our study showcases the insights mathematical models can provide to the analyze complex microbiological data and decipher the dynamics of within-host infection.

# Viral and immune kinetics of HPV genital infections in young adult women

Nicolas Tessandier [1], Baptiste Elie [1, 2], Ignacio Bravo [3], Samuel Alizon [1]

**1 :** Centre interdisciplinaire de recherche en biologie
*Labex MemoLife, Collège de France, Institut National de la Santé et de la Recherche Médicale, Centre National de la Recherche Scientifique*
**2 :** Evolution Théorique et Expérimentale (MIVEGEC-ETE)
*Perturbations, Evolution, Virulence*
*Montpellier - France*
**3 :** Virostyle
*Perturbations, Evolution, Virulence*

**Background and aims of the study**

Human papillomaviruses (HPVs) are among the most prevalent sexually transmitted infections. While most of the skin and mucosal infections they cause are asymptomatic or benign and resolve within 6 to 18 months, some can become chronic and progress to cancerous lesions, particularly in the cervix. The factors governing infection clearance or chronicity remain poorly understood, in part because of the absence of an animal model. Our study sought to characterise the course of HPV genital infections and their control by the immune response.

**Methods and results**

We established the PAPCLEAR cohort, a longitudinal study involving 149 women aged 18 to 25 in Montpellier, France. These women were followed every two months through on-site visits, until HPV infection clearance or for up to 24 months. In this analysis, we focused on 75 participants infected with at least one HPV genotype. We examined HPV viral load, flow cytometry data from cervical smears, local cytokine concentration, and circulating antibody titers. We utilized Bayesian non-linear hierarchical models to compare viral dynamics and immune responses.

**Implications**

Our study provides pioneering quantitative analyses of highly oncogenic viruses within the host, revealing a consistent virus load pattern with a prolonged plateau phase. This finding has implications for virus load-based screening policies. We also investigate the role of specific mucosal immunity actors, such as lymphocytes TCRγδ, in shaping infection kinetics, leading to potential innovative treatment approaches. Additionally, we gain insights into the impact of natural immune memory on milder infections, refining epidemiological models.

# Drivers and impact of the early silent invasion of SARS-CoV-2 Alpha

Benjamin Faucher [1], Chiara Sabbatini [1], Peter Czuppon [2], Moritz Kraemer [3, 4], Phillipe Lemey [5], Vittoria Colizza [1], François Blanquart [6], Pierre-Yves Boelle [1], Chiara Poletto [7]

**1 :** Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique (IPLESP), F75012, France
*Sorbonne Université, INSERM U1136, Institut Pierre Louis d'Epidémiologie et de Santé Publique (IPLESP)*
**2 :** Institute for Evolution and Biodiversity, University of Münster, Münster 48149, Germany
**3 :** Department of Biology, University of Oxford, Oxford, UK
**4 :** Pandemic Sciences Institute, University of Oxford, UK
**5 :** Department of Microbiology, Immunology and Transplantation, Rega Institute, Laboratory for Clinical and Epidemiological Virology, KU Leuven, Leuven, Belgium
**6 :** Center for Interdisciplinary Research in Biology, CNRS, Collège de France, PSL Research University, Paris 75005, France
*Center for Interdisciplinary Research in Biology, Collège de France*
**7 :** Department of Molecular Medicine, University of Padova, 35121 Padova, Italy

**Background & aims of study :** SARS-CoV-2 variants of concern circulated unnoticed for some time before being recognized as a threat, delaying appropriate interventions. Better understanding the drivers of such silent spread and its impact on the epidemic is critical to inform future response. Here, we reconstructed the first three months of global Alpha dissemination and quantified Alpha silent spread while accounting for spatiotemporal heterogeneity in sequencing coverage, local epidemic growth, and international travel.

**Methods & results :** We designed an international dissemination model for the date of first submission and associated date of collection of an Alpha sample in each country before 31 Dec 2020. We assumed that the date of first submission in a country other than the UK resulted from the epidemic growth in the UK, the outflow of travelers from the UK to the country, the sequencing coverage in this country, and the collection-submission delay. The model was fitted to GISAID data and was then used to predict the date of the first Alpha introduction in each country. We found that Alpha was likely spreading in ~65 countries before 31 Dec 2020, compared with the 24 that reported it. Silent spread - the delay from introduction to the collection of the first submitted sequence - lasted from days to months and was logarithmically associated with sequencing coverage. We then modeled Alpha local epidemics in six countries where a national virological investigation was conducted in January, assuming Alpha transmission was seeded by the flow of introductions as predicted by the international dissemination model. We recovered the trend of empirical estimates, which provided support for the predictions of international dissemination. By investigating the time of successful seeding of transmission chains in those countries vs. the time of first introduction we found that a low reproductive ratio at destination due to interventions delayed the epidemic seeding up to weeks.

**Implications :** Strong spatiotemporal heterogeneities in surveillance during Alpha emergence provided a major obstacle to data interpretation and anticipation. Lessons from the Alpha experience show the importance of local mitigation at the destination in case of emerging events.

# Modelling P. vivax and P. falciparum co-infections with heterogeneity in mosquito biting exposure

Mathilde Grimée [1], Michael White [1], Aimee Taylor [1]

**1 :** Infectious Disease Epidemiology and Analytics
*Institut Pasteur de Paris*

*Plasmodium vivax* and *Plasmodium falciparum*, two of the parasites causing human malaria, co-circulate in regions of Southeast Asia, Eastern Africa, and south and central America. As anti-malaria efforts in the past decades primarily have targeted *P. falciparum*, the more resilient *P. vivax* has taken over as the predominant parasite. In the affected regions of the world, research is now focusing on identifying effective anti-*vivax* strategies. Modelling can help us identify and explore how both parasites interact on an epidemiological level and how this can impact the effect of these anti-malaria interventions.

We developed a compartmental model of coinfection between *P. vivax* and *P. falciparum* in humans and mosquitos. Key biological differences between both parasites are considered in the model. Notably, after an individual is first infected with *P. vivax*, they can host dormant parasites in their liver – hypnozoites – that will reinvade the blood stream and cause disease relapse after a certain time. This is a feature unique to *P. vivax* and is explicitly considered in the model with dormant compartments.

A possible route of interaction between both parasites on an epidemiological level, is heterogeneity in mosquito biting exposure, which has been shown to occur in low-incidence settings, causing infections to cluster in on small parts of the population. The more heterogeneity, the more infections are forced into certain individuals, leading to higher rates of coinfection. We present simulations of different levels of heterogeneity and its effect on coinfection prevalence.

Another mechanism of interaction occurs via treatment. Both blood-stage infections with *P. vivax* and *P. falciparum* are treated with the same drug regimen.This could lead to fewer coinfections as expected in settings where high levels of clinical infections.

As the model is not yet fitted to data, simulations so far are performed with parameters informed from the literature. However, we show results from a systematic review collecting data on coinfection prevalence, which will ultimately be used to inform model updating and calibration.

# Reproducing the change in contact patterns observed during the COVID-19 pandemic using mobility data

Anthony Hauser[1], Laura Di Domenico[1], Vittoria Colizza[1]

**1 :** INSERM
*Sorbonne Université, INSERM U1136, Institut Pierre Louis d'Epidémiologie et de Santé Publique (IPLESP)*

Social contact data are key to model the spread of an epidemic over the different strata (e.g., age) of a population. During the COVID-19 pandemic, the CoMix study gathered valuable data on age-stratified contact patterns over time, carrying out contact surveys in 20 European countries. These studies are rather expensive and time-consuming, raising the need for alternative approaches to rapidly assess the potential epidemic impact of a novel virus in absence of real-time contact data. Here we use real-time data on mobility in specific settings to generate synthetic contact matrices over time accounting for changes in social activities.
We focused on the contact data collected in the Netherlands from 5,965 participants of the CoMix study over 28 survey waves between April 2020 and September 2021, using four age classes (0-10, 11-18, 19-64, 65+). We designed a statistical model able to analyse and reproduce the observed change in contact patterns using Google mobility data. We used a zero-inflated Poisson model, which summarized contact patterns for each age class over time through two variables: 1) the proportion of individuals having contacts and 2) the conditional mean number of contacts. The model also corrected for the survey fatigue in both variables. The mobility was regressed on both variables - the proportion of individuals having contacts and the conditional mean number. Two parameters - one for each variable - summarised the impact of mobility on the two variables, with a value of 0 indicating no effect of mobility, and a value of 1 showing a linear effect.
Model estimates yield 0.95 (95% credible interval [0.78-1.1]) for the probability of having contact at work, indicating that the proportion of people having contacts at work is strongly associated with their underlying mobility. We obtained an estimate of 0.55 (95% credible interval [0.44-0.66]) for the conditional mean number of contacts. Distinctly above 0, this estimate suggests that contact rates in the workplace are at least partially density-dependent.
Our findings show the potential of mobility data to reproduce the change in contact patterns over time, and their value for real-time response to epidemic outbreaks.

# An agent-based model to simulate the transmission dynamics of bloodborne pathogens within hospitals

Paul Henriot [1, 2], Mohammed El Kassas [3], Wagida Anwar [4], Samia Abdou [5], Kévin Jean [1, 2], Laura Temime [1, 2]

**1 :** Laboratoire Modélisation, Epidemiologie et surveillance des risques sanitaires
*Conservatoire National des Arts et Métiers (CNAM)*
**2 :** Pasteur-Cnam Risques infectieux et émergents
*Institut Pasteur [Paris], Conservatoire National des Arts et Métiers [CNAM]*
**3 :** Endemic Medicine Department, Faculty of Medicine, Helwan University
**4 :** Department of Community, Environmental and Occupational Medicine, Faculty of Medicine, Ain Shams University
**5 :** Department of Clinical Pathology, Faculty of Medicine, Ain Shams University

Bloodborne pathogens are a major public health concern as they can lead to a variety of medical conditions, including cirrhosis and cancers with significant mortality and morbidity. Three viruses are of major concern: HCV, HBV and HIV. Their transmission is mostly community-associated but the iatrogenic risk of infection is not negligible, even today. Multiple recent studies have shown that hospitals are still playing an important role in the HCV transmission dynamics in patients during invasive procedures (Caminada *et al.*, 2023; Henriot *et al.*, 2022). Mathematical models are widely used to describe and assess pathogens transmission, within communities and hospitals. Nevertheless, few are focusing on the transmission of pathogens through blood and even fewer on their transmission within hospital as they usually study the risk of community-associated infection in vulnerable populations such as MSM or drug users (Cousien *et al.*, 2015). Herein, we propose an agent-based SEI (Susceptible-Exposed-Infected) model to explore the transmission dynamics of bloodborne pathogens within hospitals. This model simulates the dynamics of patients between hospital wards, from their admission to discharge, as well as the dynamics of the equipment used during at-risk invasive procedures, considering that patient contamination occurs after exposure to a contaminated equipment. Multiple parameters of the model, such as HCV prevalence, transition probabilities between wards or ward-specific probabilities of undergoing different invasive procedures, were informed with data collected in the University Hospital of Ain Shams in Cairo, Egypt in 2017 (IMMHoTHep project, ANRS-12377; Anwar *et al.*, 2021). We explored the effect of equipment shortage as well as the effect of random and systematic screening with associated modification in disinfection practices on the risk of infection for patients. By modifying some parameters of the model, we then explored the case of HBV in Ethiopia. In the future, this model could be used to assess the risk of transmission of other bloodborne pathogens in other contexts.

# Using contact network dynamics to implement efficient interventions against pathogen spread in hospital settings

Quentin Leclerc [1, 2, 3], Audrey Duval [1], Didier Guillemot [1, 3], Lulla Opatowski [1, 3], Laura Temime [2]

**1 :** Epidémiologie et modélisation de la résistance aux antimicrobiens - Epidemiology and modelling of bacterial escape to antimicrobials
*Institut Pasteur [Paris], Université Paris Cité*
**2 :** Laboratoire Modélisation, épidémiologie et surveillance des risques sanitaires
*Conservatoire National des Arts et Métiers [CNAM]*
**3 :** Centre de recherche en épidémiologie et santé des populations, UMR U1018
*Université de Versailles Saint-Quentin-en-Yvelines, Institut National de la Santé et de la Recherche Médicale, Université Paris-Saclay*

Long-term care facilities (LTCF) are a hotspot for pathogen transmission. Here, we show how taking into consideration the contact network between patients and staff is essential to implement effective interventions reducing the incidence of methicillin-resistant *S. aureus* (MRSA) colonisation.

We constructed a detailed contact network with more than 2.5 million close-proximity interactions between individuals recorded in a LTCF during the i-Bird study. We built an individual-based model to reproduce MRSA colonisation dynamics over this network. We examined the potential impact of three network-based interventions to reduce colonisation incidence: 1) staff reallocation reducing the number of unique contacts per staff, 2) staff reinforced contact precautions reducing the risk of patient-to-staff and staff-to-patient transmission, and 3) vaccination partially protecting those vaccinated against acquisition from any other colonised individual.

The effectiveness of reallocation depended on the staff categories targeted. The highest benefit when reallocating only one staff category was for healthcare assistants (median reduction: 13%), while the benefit did not exceed 8% for other categories. Contact precautions of nurses or healthcare assistants reduced incidence between 10-20%, and was therefore as or more effective than reallocation of these categories. Vaccination for these staff categories was less effective, reducing incidence by up to 12% only. Meanwhile, contact precautions or vaccination targeting other staff categories did not have a substantial impact. The benefit of these interventions can be optimised by targeting individuals in the studied network with most contacts (“frequency-based supercontactors”) or with the longest cumulative time spent in contact (“duration-based supercontactors”). With contact precautions, targeting 60 frequency-based supercontactors amongst staff led to a higher incidence reduction (13%) compared to randomly targeting 60 staff (9%). Vaccinating 60 duration-based patient supercontactors was more effective (22% reduction, highest of all the scenarios tested) than vaccinating 60 staff supercontactors (7%), or even 60 randomly selected patients (13%).

Identifying and targeting supercontactors increases the effectiveness of interventions against pathogen spread in LTCF. The nature of these supercontactors will likely vary depending on the organisational structure and type of healthcare institution and possibly the pathogen. Both staff and patients can be supercontactors, highlighting the importance of including patients in measures to prevent pathogen transmission in LTCF. Our analysis demonstrates the value of collecting and analysing contact data in healthcare settings to inform intervention implementation.

# Agnostic identification of pathogen lineages and estimation of fitness dynamics

Noémie Lefrancq[1], Loréna Duret [1], Julian Parkhill[1], Henrik Salje[1]

**1 :** University of Cambridge

Background & aims

A major challenge to public health is quantifying the underlying fitness of pathogen strains. Changing genetic diversity and population immunity, among other factors, mean that strain fitness is fundamentally dynamic, however, existing methods largely rely on a priori lineage definitions based on arbitrary definitions, with unclear links to fitness estimates. Here we present a novel agnostic framework that summarises the changes in population composition in phylogenetic trees through time, allowing for the automatic detection of circulating lineages based on differences in fitness, which we quantify and link back to specific amino acid changes. We apply this approach to SARS-CoV-2, influenza, dengue and Bordetella pertussis. We selected these pathogens as they present both viruses and bacteria, and include both well-studied and understudied threats to human health.

Methods & results

We use a genetic distance-based index that measures the epidemic success of each tip and node in a time-resolved tree. This measure is based on the expectation that tips and nodes sampled from an emerging successful lineage will be phylogenetically closer than the rest of the population at that time. We develop a tree partitioning algorithm using a generalised additive model that finds the set of lineages that best explains the index dynamics. Using simulated data, we show this index is robust to changes in sampling intensity and extreme sampling bias. We next apply our methods to time-resolved phylogenies of SARS-CoV-2 (N=3129 genomes, 2020-2023), H3N2 Influenza (N=1476 genomes, 2005-2023), dengue virus (N=2721 genomes, 1960-2017) and Bordetella pertussis (N=1248 genomes, 1953-2022). We recover the main known circulating lineages for each pathogen, including all the SARS-CoV-2 variants of interest, and influenza antigenic clusters. We also recover amino acid changes previously shown to be associated with fitness changes. In addition, for dengue and Bordetella pertussis, we detect the presence of multiple co-circulating lineages with underlying differences in fitness, none of which have been previously identified.

Implications

This framework provides an exciting avenue to identify pathogen lineages from phylogenetic trees, without relying on a priori lineage definitions, and explore fitness drivers at the population level.

# Behavioral changes in the 2022 MPOX epidemic in MSM in Île-de-France

Davide Maniscalco[1], Mattia Mazzoli[1], Olivier Robineau[2,3], Pierre-Yves Boelle[1], Anne-Sophie Barret[4], Emilie Chazelle[4], Alexandra Mailles[4], Harold Noël[4], Arnaud Tarantola[5], Annie Velter[6], Laura Zanetti[7], Vittoria Colizza[8]

**1 :** Sorbonne Université, INSERM, Institut Pierre Louis d'Épidémiologie et de Santé Publique, IPLESP, Paris, France
*umrs1136*
**2 :** Sorbonne Université, INSERM, Institut Pierre Louis d'Épidémiologie et de Santé Publique, IPLESP, Paris, France
**3 :** Université Lille, Centre Hospitalier de Tourcoing, ULR 2694-METRICS: Évaluation des technologies de santé et des pratiques médicales, Lille, France
**4 :** Santé publique France, Saint Maurice, France
**5 :** Santé publique France Regional Office, Saint-Denis, Île-de-France, France
**6 :** Santé publique France, Saint Maurice, France
**7 :** Haute Autorité de Santé, Saint-Denis, France
**8 :** Sorbonne Université, INSERM, Institut Pierre Louis d'Épidémiologie et de Santé Publique, IPLESP, Paris, France
*umrs1136*

The first case of mpox in the Île-de-France, the region of Paris, was confirmed on May 19 2022, then leading to a growing epidemic. Most of the cases were among men who have sex with men (MSM), the majority of whom having multiple sexual partners. The outbreak started declining at the end of June, before the mpox vaccination campaign was launched. We investigated whether the decline was attributed to the dwindling of susceptible MSM, to behavioral changes that may have occurred in response to the outbreak, or to the post-exposure prophylaxis (PEP) vaccination campaign for at-risk contact-persons.
Using survey data on Parisian MSM sexual habits, we built a temporal sexual contact network and informed an agent-based model for mpox transmission. We fitted the model to the data on mpox cases in Île-de-France. We included the effect of prior immunity from smallpox vaccine, of the PEP vaccination campaign, and of behavioral changes with the reduction of sexual activity due to risk awareness. We showed that PEP vaccination had no effect in curbing the wave. The dwindling of susceptible individuals cannot explain the decline alone. Considering a detection rate of 50% of the cases, the decline is explained by 13% high-risk MSM progressively stopping their sexual activity from mid-June to mid-July. This percentage is estimated to be higher (35%) if the change of sexual behavior occurred randomly among MSM, independently of their activity. The rapid decline of the mpox wave in Île-de-France observed in July 2022 was likely favored by behavioral changes in the MSM population driven by risk awareness, combined with building immunity in the population.

# Modelling approach to optimize release strategies for establishing Wolbachia within the Aedes aegypti population in Nouméa

Noé Ochida[1,2,3], Nicolas Pocquet [4], Nadège Rossi [5], Cameron Simmons [6], Christophe Menkes [7], Morgan Mangeas [7], Myrielle Dupont-Rouzeyrol [8],

**1 :** Institut Pasteur [Paris]
*Mathematical Modelling of Infectious Diseases Unit, Institut Pasteur, Université Paris Cité, UMR2000, CNRS, Paris, France*
**2 :** URE Dengue and Arboviruses, Institut Pasteur de Nouvelle-Calédonie, Pasteur Network, 98845, Nouméa, New Caledonia
**3 :** UMR ENTROPIE, IRD/Univ. Réunion/IFREMER/Univ. de Nouvelle-Calédonie/CNRS, Nouméa, New Caledonia
**4 :** URE Medical Entomology, Institut Pasteur de Nouvelle-Calédonie, Pasteur Network, Nouméa, New Caledonia
**5 :** World Mosquito Program, Institut Pasteur de Nouvelle-Calédonie, Pasteur Network, Nouméa, New Caledonia
**6 :** World Mosquito Program, Institute of Vector-Borne Disease, Monash University, Melbourne, Victoria, Australia
**7 :** UMR ENTROPIE, IRD/Univ. Réunion/IFREMER/Univ. de Nouvelle-Calédonie/CNRS, Nouméa, New Caledonia
**8 :** URE Dengue and Arboviruses, Institut Pasteur de Nouvelle-Calédonie, Pasteur Network, 98845, Nouméa, New Caledonia

Dengue fever is the most prevalent arbovirus in the world, potentially affecting an even larger population in the future. Its control historically relies on traditional anti-vector measures but the emergence of insecticide resistance in vector populations and the unproven efficacy of these methods for epidemic prevention necessitate the exploration of new approaches. We focus on the deployment of the promising *Wolbachia* strategy in New Caledonia, its obstacles and consider how to optimize the release strategy.

We developed a population dynamic model of *Aedes aegypti* integrating *w*Mel-infected mosquito populations, aiming to identify the factors for successful *w*Mel establishment in New Caledonia. Recommendations for optimizing release strategies were formulated, considering the impact of climate on mosquito life traits.

We estimated a 22% reduction of fecundity in *w*Mel-infected *Ae. aegypti*. To minimize the total number of mosquitoes released, we have identified two contrasting strategies: one involves short campaigns with a large number of individuals released per week, while the other spans over a longer duration with fewer mosquitoes released per week. The establishment speed of *w*Mel is primarily driven by the prevalence of *w*Mel within the population at the end of the campaign. Short, high intensity campaigns are more suited to winter and were overall the best strategy, as they facilitate achieving a high frequency of *w*Mel at the end of the campaign. At the end of the campaigns, thanks to a temperature dependent R0, we estimated a 95% reduction in dengue risk across most reporting areas in Nouméa.

# Impact of beta lactam Antibiotics On the Gut Microbiota: a modeling analysis

Carlos Olivares[1], Jean De Gunzburg[2], Etienne Ruppe [1], Tanguy Corbel[2], Stéphanie Ferreira[2], Jérémie Guedj [1], Charles Burdet[1]

**1 :** Université Paris Cité, IAME, Inserm, F-75018, Paris, France
*INSERM, IAME, UMR 1137*
**2 :** Da Volterra
*Da Volterra*

Antibiotic (AB) treatments shift the composition of the gut microbiota according to their spectrum of activity, posology and intestinal excretion rate. We aimed to build a comprehensive mathematical model to evaluate the ecological impact of AB exposure on gut microbiota [1,2].

We used the data from the DAV-132-CL1006 clinical trial (sponsor Da Volterra), where 144 healthy volunteers (HV) were randomly assigned to receive a 5-day intravenous treatment with ceftriaxone (CRO,1 g once a day), ceftazidime/avibactam (CEF/AVI, 2g /0.5g every 8 hours (q8h)), piperacillin/tazobactam (PIP/TAZ, 4g /0.5g q8h) or to an untreated control group. Some antibiotic-treated subjects were also treated for 7 days with several doses of DAV132, a charcoal-based adsorbent that captures free antibiotics residuals in the late ileum and colon (7.5g or 12g q8h). Plasma and fecal concentrations of AB and betalactamase inhibitor (BI) were measured longitudinally. The composition of the gut microbiota was determined by 16S rRNA gene profiling, and quantitative 16S qPCR was used to estimate the total number of bacteria. A pharmacokinetic model previously developed [3] was adapted to predict plasma and feces exposure to AB over time, and a modified Lotka-Volterra model was used to characterize the effects of fecal drug exposure on the kinetics and the ecology of gut microbiota [4].

The median (min; max) time for antibiotic fecal concentrations to decrease below the limit of quantification after the last administration varied between antibiotic treatment groups: 4.3 [1.3, 11.7] for CRO, 4.6 [1.31, 20.3] for CEF, and 2.3 days [0.28, 17.3] for PIP.

Eleven bacterial families were significantly impacted by CRO (11 negatively), 10 by CEF/AVI (8 negatively), and 8 by PIP/TAZ (7 negatively) were used for modeling.
At day 16, 8/11 (72.7%) families returned to baseline abundance values following CRO administration, 8/10 (80%) for CEF/AVI, and 6/8 (75%) for PIP/TAZ. We are modelling bacterial families dynamics including pairwise interactions. This will establish a foundation of the interplay between AB and gut microbiota and help to optimize AB treatments, considering both pharmacokinetic and pharmacodynamic efficacy and unwanted effects on the gut microbiota.

[1] Palleja, A., Mikkelsen, K.H., Forslund, S.K. *et al.* Recovery of gut microbiota of healthy adults following antibiotic exposure. *Nat Microbiol* **3**, 1255–1265 (2018).
[2] Jean de Gunzburg and others, Protection of the Human Gut Microbiome From Antibiotics, *The Journal of Infectious Diseases*, Volume 217, Issue 4, 15 February 2018, Pages 628–636,
[3] Guk, J., Guedj, J., Burdet, C., Andremont, A., de Gunzburg, J., Ducher, A. and Mentré, F. (2021), Modeling the Effect of DAV132, a Novel Colon-Targeted Adsorbent, on Fecal Concentrations of Moxifloxacin and Gut Microbiota Diversity in Healthy Volunteers. Clin. Pharmacol. Ther., 109: 1045-1054.
[4] Guk, J, Bridier-Nahmias, A, Magnan, M, et al. Modeling the bacterial dynamics in the gut microbiota following an antibiotic-induced perturbation. *CPT Pharmacometrics Syst Pharmacol*. 2022; 11: 906- 918. doi: 10.1002/psp4.12806

# A data-driven multi-country mathematical model of antibiotic resistant Escherichia coli transmission to explore worldwide emergence spread at the populational level.

Eve Rahbe[1], Eugenio Valdano, Philippe Glaser, Lulla Opatowski

**1 :** Epidemiology and Modeling of Antimicrobials Escape
*Institut Pasteur de Paris*

Antibiotic resistance in commensal pathogenic Enterobacteriaceae is threatening global health. Resistance to -lactams, first detected in *Klebsiella pneumoniae* within hospitals, is now endemic worldwide and carried by *Escherichia coli* in the community. Recently, resistance to carbapenems emerged in *K. pneumoniae* within hospitals. Such resistance could also disseminate in the community through *E. coli* and become prevalent. To set up adapted control measures, it is crucial to understand dynamics of subsequent spread of an emerging resistance and optimize its surveillance. In that context, mathematical modeling is instrumental. Yet, few studies address the question of resistant Enterobacteriaceae community transmission. Here, we used modeling to understand the contribution of heterogeneous antibiotic use and worldwide travel to the global spread of an emergent resistance in the general population.

We developed a multi-country deterministic compartmental model tailored to *E. coli*, assuming a well-mixed population within a country and between-countries travel fluxes. The within-country model considers both bacterial colonization and infection. Antibiotic use selects for resistance during exposure and for a prolonged period due to microbiota perturbation. Acquisition of resistance happens through within-country contacts with individuals, and through travelers' contamination. First, the model is fitted to data of -lactams-resistant *E. coli* in countries across all continents (ATLAS) using Bayesian inference, accounting for antibiotic consumption variation over 2006-2019 (IQVIA). Next, the model is used to simulate and analyze dissemination scenarios of an emergent resistant *E. coli*, and to tailor surveillance.

Model calibration for 39 countries resulted in high heterogeneity in baseline transmission rates estimates, with medians ranging from 0.0067 (Belgium) to 0.0236 ind-1day-1 (Thailand). Progression-to-disease rates were more stable across countries: on average 1.2x10-6 infections carrier-1day-1. When simulating worldwide spread of carbapenem-resistant *E. coli*, we found that resistance prevalence depends on country of origin, within-country transmission rates and national antibiotic use rates.

Our model makes it possible to analyze global worldwide spread of an emerging resistant bacteria accounting for antibiotic exposure, microbiota dysbiosis and population mixing through travel fluxes. When tailored to specific bacteria, models represent a useful tool to explore scenarios for future resistance that emanate from hospitals and later spread in the community.

# The effect of social deprivation on Hospitalisations, Intensive Care Unit episodes and Deaths among COVID-19 inpatients between January 2021 and August 2022 in metropolitan France

Sabira Smaili[1]

**1 :** Santé publique France - French National Public Health Agency [Saint-Maurice, France]
*DATA*

**Background**: While it has been established the COVID-19 pandemic has disproportionately affected socially disadvantaged populations, evidence on the dynamics of social inequalities throughout the history of the infection (from the risk of infection to disease evolution) remain sparse in France. This study examines the relationship between deprivation and three outcomes: hospitalisations, intensive care unit (ICU) episodes and deaths due to Covid-19 in metropolitan France during four epidemic waves (wave 3: 5th January -16th June 2021, wave 4: 23rd June-20th October, wave 5: 27th October-2th March 2022, wave 6: 9th March-31st August 2022).
**Methods:** This study uses the French national surveillance database for hospitalisations (SIVIC). For each outcome and for each epidemic wave: 1) the number of cases were aggregated at small area level (IRIS); 2) expected number of cases, standardized on age and sex were calculated using the population testing positive to COVID-19 as denominator recorded in the "SIDEP" information system. The social deprivation level of each patient was measured by the European Deprivation Index (EDI) calculated at the residential area level. The total number of cases by geographic area and wave was analysed in spatio-temporal bayesian Poisson regression models, with the expected number of cases as an offset, to estimate RR with 95% credible intervals (CI) of the association between outcomes and EDI in quintiles. Each model included a three-way interaction between EDI, population density (defined at municipality level as densely populated, moderately populated, sparsely populated) and wave, and an interaction between waves and spatially structured random effects at the department level.
**Results:** They were 305 203 hospitalisations recorded in the study period.Compared to the least deprived areas, people living in the most deprived areas, in densely populated municipalities had a higher risk of hospitalisations that increased over time from RR= 1.30 95%CI (1.26-1.34) (wave3) to 1.71(1.66-1.79) (wave 6). They had a higher risk of ICU episodes that increased from 1.43 (1.34-1.53) to 2.04(1.77-2,34), and of deaths that increased from 1.27(1.17-1,39) to 1.74(1,49-2.03). We found similar results in moderately populated municipalities for the three outcomes. Estimates were lower in sparsely populated municipalities but also increased over time for the three outcomes. We also found heterogeneity between departments and waves for the three outcomes.
**Conclusions**: Socially disadvantaged populations were more likely to develop severe forms of COVID-19 and to die. These inequalities increased over time despite the vaccination coverage progress. This result may suggest a lower vaccination coverage rate among disadvantaged populations but couldn't explain entirely the overall risk and the increase over time. Further investigations are necessary to understand these health inequalities. This study highlights the importance of considering the social position of individuals to manage the pandemic over time. The development of appropriate interventions towards disadvantaged populations are required to minimize health inequalities.

# On Airborne Transmission: history, biophysics, epidemiology & modelling

Mircea T. Sofonea[1]

**1 :** Pathogenesis and Control of Chronic and Emerging Infections
*Institut National de la Santé et de la Recherche Médicale, Université des Antilles, Etablissement français du don du sang [Montpellier], Université de Montpellier*

Airborne transmission was an emblematic point of tension during the COVID pandemic. From its identification to its prevention, it represents both a scientific and a health issue. In this lecture, I will draw on recent reviews and key works in the literature, while situating older sources in the evolution of points of view on the subject, in an attempt to summarise the main historical, biophysical and epidemiological elements relating to airborne transmission, with an emphasis on the contributions of modelling to the study of this subject, now a public health priority.

# Herpes-simplex virus 1 and 2, varicella zoster virus, Epstein–Barr virus, and cytomegalovirus infection seroprevalence in France, between 2016 and 2023: a multilevel regression and post-stratification approach

Olivier Supplisson[1], Benoit Visseaux, Samuel Alizon, Sonia Burrel, David Boutolleau, Stéphanie Boukobza, Mircea Sofonea

**1 :** Centre interdisciplinaire de recherche en biologie
*Labex MemoLife, Collège de France, Institut National de la Santé et de la Recherche Médicale, Centre National de la Recherche Scientifique*

**Context:** Serological data remain greatly underused in France. Information related to HSV-1, HSV-2, VZV, EBV, and CMV infection seroprevalence are either lacking, incomplete, or outdated.

**Method:** We used serological data collected from 2016 to 2022 by the leading French private network of medical biology centers with the aim of estimating strata-specific HSV-1, HSV-2, VZV, EBV, and CMV infection seroprevalence in France between 2016 and 2023. Strata were defined based on a grid of sex, age groups, district, and years. To account for our non-representative dataset and get predictions for sparsely sampled and non-sampled stratum, we relied on a full Bayesian modelling approach, which allowed us to use multilevel regression and post-stratification techniques combined with pseudo-Bayesian model averaging. For each virus, using a grid defined over a set of structured priors for the strata-varying effects, we first defined 72 possible models that we further combined using stacking weights defined as the linear combining weights maximizing the leave-group-out cross-validation log-score. The marginalisation of the posterior predictive distributions over some dimension of the grid allowed us to get seroprevalence estimates for various subpopulations (sex, sex-age), spatial scales (districts, regions, areas, whole country), and years.

**Results:** In total, the collected number of tests (number of positive tests) was 116,526 (75,000), 116,526 (19,861), 118,995 (109,414), 60,058 (50,343), and 37,565 (18,685), respectively for HSV-1, HSV-2, VZV, EBV, and CMV. Hence an observed infection seroprevalence of 64.36, 17.04, 91.95, 83.82, 49.74%, respectively. France as a whole had a model-based average [ETI95%] infection seroprevalence equal to 61.13 [60.48,62.08], 14.77 [14.16,15.53], 88.59 [87.97,89.16], 85.43 [84.33,86.15], and 50.78 [48.58,53.11]%, respectively for HSV-1, HSV-2, VZV, EBV, and CMV infections. For mainland France only, we found 60.79 [60.14,61.74], 14.4 [13.8,15.15], 88.83 [88.22,89.38], 85.58 [84.93,86.16], and 50.34 [48.38,52.6]%, respectively. We concluded to a likely positive difference in HSV-1 and HSV-2 infection seroprevalence between overseas territory and mainland France (16.85 [14.76,18.55] and 18.12 [16.06,22.79] percentage points, respectively). The seroprevalence was likely greater among females than males for all viruses, no matter the age. For HSV-2, the posterior predicted difference in infection seroprevalence was 5.95 [5.49,6.39] percentage points. We highlight a likely increase in seroprevalence with age but similar pattern for each sex. We notably concluded that EBV and VZV infection seroprevalence in mainland France reached as high as 90% among individuals aged (29,34]. Finally, we concluded to a high temporal stability of these infection seroprevalence over the study period.

**Limitations:** The targeted quantity of interest, namely the infection seroprevalence in the general population, being unobserved, any empirical assessment for our posterior prediction was impossible beyond posterior predictive check on the collected data. The modelling approach did not account for the tests' imperfect clinical performance.

**Implications:** The analysis highlights spatial and demographic patterns in HHVs infection seroprevalence that should be accounted for when designing public health policy aiming at decreasing their incidence.

# How gene expression can inform dynamical models?

Rodolphe Thiébaut[1,2]

**1 :** Vaccine Research Institute
*Université Paris-Est Créteil Val-de-Marne - Paris 12*
**2 :** Université de Bordeaux, Inserm U1219 BPH, Inria SISTM team, F-33000, Bordeaux
*Université de Bordeaux (Bordeaux, France), Univ. Bordeaux; Inserm U1219 BPH; Inria SISTM team; VRI;*

The value of viral and immune dynamics mathematical modeling largely depends on the capacity of estimating model parameters with data. These data are repeated measurements of viral or cellular concentrations in blood or other tissues. Unfortunately, these measurements are usually sparse, which poses a challenge for practical identifiability. This is particularly prevalent for cellular concentrations, as obtaining repeated venous sampling in substantial amount for flow cytometry is quite restrictive.
We propose a solution based on leveraging gene expression measurements in whole blood. Firstly, deconvolution algorithms can be used to predict the abundance of cell populations based on the whole blood gene expression. The underlying hypothesis is that the abundance of particular gene expressions in whole blood is mainly driven by the abundance of the cells expressing those genes, rather than by an increase in gene expression at the single cell level. Therefore, a reference matrix relating gene expression with various cell types can be used to predict the abundance of a specific cell type based on gene abundances measured in the whole blood. Secondly, whole blood gene expression can be measured using a finger prick test, which allow study participants to perform the sampling themselves in a minimally invasive way. This in turn unlocks the path to much more intensive and frequent sampling. Thirdly, the frequently predicted populations can be used in the observation model of a dynamical system. This approach helps overcome the challenges posed by sparse data and restricted venous sampling, leading to better estimates of model parameters and improved understanding of viral and immune dynamics.
We are illustrating the approach at each step by presenting results and obstacles from several published (Obermoser et al., 2013, Rinchai et al., 2022) and unpublished studies (clinicaltrials.gov NCT04356495).

**References**

Obermoser, G., Presnell, S., Domico, K., Xu, H., Wang, Y., Anguiano, E., Thompson-snipes, L., Ranganathan, R., Zeitner, B., Bjork, A., et al. (2013) Systems Scale Interactive Exploration Reveals Quantitative and Qualitative Differences in Response to Influenza and Pneumococcal Vaccines. Immunity 38, 831–844.
Rinchai D, Deola S, Zoppoli G, Kabeer BSA, Taleb S, Pavlovski I, Maacha S, Gentilcore G, Toufiq M, Mathew L, et al; PREDICT-19 Consortium; Chaussabel D. (2022) High-temporal resolution profiling reveals distinct immune trajectories following the first and second doses of COVID-19 mRNA vaccines. Sci Adv. 8:eabp9961.

POSTERS

Claudio Ascione (SUMO, IPLESP) – To quantify the impact of extreme weather events on the spread of infectious disease epidemics

Francesco Bonacina (SUMO/LPSM, Sorbonne U.) – Understanding the coupled dynamics of influenza (sub)types: a global analysis leveraging compositional data analysis

Paolo Bosetti (MMMI, Institut Pasteur) – Assessing the probability of sustained Mpox transmission since 2016 in Nigeria

Antoine Brault (MMMI, Institut Pasteur) – RSV epidemic in France

Kelly Charniga (MMMI, Institut Pasteur) – Updating reproduction number estimates for Mpox in the Democratic Republic of Congo using surveillance data

Sophie Chervet (Institut Pasteur/INSERM/UVSQ) – Impact of age and vaccination on the SARS-CoV-2 transmission in children from French households – comparison of alpha and omicron variants

Elisabeta Colosi (EPIcx, IPLESP) – Estimate of COVID-19 school transmission contribution during weekly screening in the Auvergne-Rhône-Alpes region, France, week 47, 2021 to week 06, 2022

Lina Cristancho-Fajardo (MMMI, Institut Pasteur) – Assessing bias when studying within-household pathogen transmission from household serosurveys

Wen Fu (SUMO, IPLESP) – Modelling the transmission of Lyme borreliosis in endemic regions of France, 2009 to 2021

Vincent Garot (CIRB, Collège de France) – Deep learning for phylodynamic

Younjung Kim (SUMO, IPLESP) – The importance of livestock movements in human RVF spatial spread in Mayotte: insights from two modelling studies

Maylis Layan (Institut Pasteur/CNAM/UVSQ) – Impact of the COVID-19 pandemic on the transmission of ESBL-producing enterobacteria among patients hospitalized in intensive care units in Guadeloupe

Aurélie Maurin (MESuRS, CNAM) – Evaluation of the transmission dynamics of S. pneumoniae in the French population: optimising amoxicilline prescriptions in a context of antibiotic shortage

Julie Muzzolon (UCBL/Santé publique France) – A comparison of methods for estimating the incidence of HIV in France

Tran Bach Nguyen (IAME, INSERM) – Antiviral efficacy of tecovirimat against Mpox: a translational and modeling study

Francesco Parino (EPIcx, IPLESP) – Integrating dynamical modeling and phylogeographic inference to characterize global influenza circulation

Charlotte Perlant (MMMI, Institut Pasteur) – Investigating spatial patterns of the 1892 Cholera epidemic in France

Albano Rikani (EPIcx, IPLESP) – Iterating short periods of non-pharmaceutical interventions reduces loss of adherence to restrictions

Matthew Shin (MMMI, Institut Pasteur) – Quantifying regularity of COVID-19 epidemic waves in France to assess predictability of future waves and improve forecasting

Olivier Supplisson (CIRB, Collège de France) – Age-sex patterns of herpes simplex virus 1 and 2, varicella-zoster virus, Epstein–Barr virus, and cytomegalovirus infections seroprevalence among hospitalised patients in Paris area, France, 2016 to 2022

Nicolas Tessandier (CIRB, Collège de France) – Exploring the origin of HPV virus load variations in genital infections in young women

Aurélien Velleret (MaIAGE, INRAE) – Individual based infection models on (not so) dense large random networks