Programme des Journées plénières, 21-22 Novembre 2022

Agora, Site Haut-carré, Université de bordeaux, Campus Talence.

LUNDI 21 NOVEMBRE 2022

09:15-10:00	**Accueil café**
10:00-10:05	**Discours d'ouverture**
10:05-10:15	***Présentation Groupe de Travail « Intra-hôtes »***
	Session Intra-hôtes (10:15-11:30)
10:15-10:40	Modeling the temporal evolution of the neutralizing activity against SARS-CoV-2 variants after several administration of Bnt162b2 **Quentin Clairon** (University of Bordeaux, Inria Bordeaux Sud-Ouest)
10:40-11:05	Modelling the impact of antiviral treatment against SARS-CoV-2 in households **Hind Zaaraoui** (IAME, Inserm)
11:05-11:30	Using Plasmodium vivax genetic data to estimate the cause of recurrent vivax malaria **Aimee Taylor** (IDEA, Institut Pasteur)
11:30-11:35	***Pause***
11:35-11:45	***Présentation Groupe de Travail « Echelles mésoscopiques »***
	Session Interventions spécifiques à des lieux (11:45-12:50)
11:45-12:10	Monkeypox spread among Parisian venues **Mattia Mazzoli** (IPLESP, Inserm, Sorbonne Université)
12:10-12:30	Twenty years of modelling of school-based interventions: Applications to influenza and COVID19 **Simon Cauchemez** (Modélisation Mathématique des Maladies Infectieuses, Institut Pasteur)
12:30-12:40	COVID-19 transmission in schools **Vittoria Colizza** (IPLESP, Inserm, Sorbonne Université)
12:40-12:50	Discussion : risque épidémique et interventions dans les écoles
12:50-14:05	***Déjeuner***
	Session Phylodynamique et évolution (14:05-15:45)
14:05-14:30	Quantifying transmission dynamics of acute hepatitis C virus infections in a heterogeneous population using sequence data **Samuel Alizon** (EEH, CIRB, Paris)
14:30-14:55	Assessing sampling bias impact in phylodynamic inferences **Gonché Danesh** (Evolution Théorique et Expérimentale)
14:55-15:20	Fast approaches for phylodynamic model resolution uncover the epidemiological dynamics of outbreaks

	Anna Zhukova (Epidemiology and Modelling of Antibacterial Evasion, Institut Pasteur)
15:20-15:45	Mapping SARS-CoV-2 adaptation **Sylvain Gandon** (Centre d'Ecologie Fonctionnelle et Evolutive, CNRS)
15:45-16:15	**Pause**
	Session Réseaux de contact (16:15-17:30)
16:15-16:40	Evolution of social contacts patterns in France over the SARS-CoV-2 pandemic: results from the SocialCov survey **Paolo Bosetti** (Mathematical Modelling of Infectious Diseases Unit, Institut Pasteur)
16:40-17:05	The epidemic footprint of contact structures **Madeleine Kubasch** (MAIAGE, INRAE)
17:05-17:30	Synthetic school populations for epidemic models **Giulia Bassignana** (IPLESP, Inserm, Sorbonne Université)
17:40-19:15	**Session posters et drinks**
20:30 -***	*Diner Restaurant Café Français 5 Pl. Pey Berland, 33000 Bordeaux*

MARDI 22 NOVEMBRE 2022

09:00-09:10	***Présentation du Groupe de Travail « Comportements »***
09:10-10:25	***Session COVID et autres infections***
09:10-09:35	Using a dynamic transmission model to produce influenza activity scenarios for the winter of 2022/23: France, Germany, Italy, Spain and the United Kingdom **Pascal Crépey** (Université de Rennes, EHESP, CNRS, Inserm, Arènes - UMR 6051)
09:35-10:00	Global patterns and drivers of influenza decline during the COVID-19 pandemic **Francesco Bonacina** (IPLESP, Inserm, Sorbonne Université)
10:00-10:25	Modelling the impact of COVID-19 pandemic responses on the transmission and selection of antibiotic resistance in the community and hospitals **Aleksandra Kovacevic** (Epidemiology and Modelling of Antibacterial Evasion, Institut Pasteur)
10:25-10:50	**Pause**
10:50-11:00	***Présentation Groupe de Travail « COVID »***
11:00-11:10	***Présentation Groupe de Travail « RETEX »***
11:10-12:30	***Session COVID***
11:10-11:35	Estimating the date of emergence of an epidemic from detection data: Applications to COVID-19 **Sofía Jijón** (Institut d'écologie et des sciences de l'environnement de Paris, CNRS)
11:35-12:00	Non-Markovian modelling and COVID-19 epidemic **Bastien Reyné** (MIVEGEC, Université Montpellier II)
12:00-12:15	Impact of non-pharmaceutical interventions, weather, vaccination, and variants on COVID-19 transmission across departments in France **Juliette Paireau** (Modélisation Mathématique des Maladies Infectieuses, Institut Pasteur)
12:15-12:30	Estimation of the effect of non-pharmaceutical interventions and vaccination against COVID-19 in France using dynamical models **Iris Ganser** (SISTM Team , Univ. Bordeaux, Inserm)

Modeling the temporal evolution of the neutralizing activity against SARS-CoV-2 variants after several administration of Bnt162b2

Quentin Clairon*[1,2,3], Mélanie Prague[1,3,4], Timothé Bruel[3,5], Delphine Planas[6,3], Schwartz Olivier[6,3], Rodolphe Thiébaut[1,2,3], and Jérémie Guedj[7]

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Résumé

The establishment of a response to vaccination is a complex immunological process. The relationship between the concentration of antibodies and their neutralizing capacity against different VoCs has not yet been described mechanistically. We use a mathematical model to characterize in detail the humoral response of 26 individuals after vaccination who received up to three doses of Bnt162b2 (Pfizer-BioNTech). Thanks to our modeling strategy, we were able to confirm the role of repeated injections as the main factor in the acquired long-term neutralizing activity through two mechanisms: increasing the pool of memory B cells and enhancing the neutralizing capacities of antibodies. We also pointed out the significant differences between VoCs in relative acquired neutralization from one injection to the next. Specifically, we noted the benefit of a booster dose for neutralization of Omicron (BA.1, BA.2, and BA.5 strains) compared with a two-dose vaccination regimen, consistent with results found in observational studies. Using Monte Carlo simulations, we quantify the duration of neutralization by evaluating how long it can remain above a certain threshold in a vaccinated population of individuals. These predictions highlight the dramatic differences between VoCs in the persistence of acquired neutralisation.

*Intervenant

Modelling the impact of antiviral treatment against SARS-CoV-2 in households

Hind Zaaraoui*[1]

[1]IAME – Institut National de la Santé et de la Recherche Médicale - INSERM – France

Résumé

One of the highest attack rates of SARS-CoV-2 is within households which could lead to a high viral burden inside homes but also a high risk of transmission and viral propagation outside.
The introduction of an antiviral treatment may be an important component to fight COVID-19 in different scales with households. It may prevent disease progression within hosts but may also prevent the virus transmission to the uninfected individuals. The effect of antiviral treatment depends highly on their efficacy, on the treatment initiation time and also on the individual characteristics such as the age and other risk factors.
The objective of this study is to determine the effect of the antiviral treatments within households through a multi-scale model that brings at the same time the within host and the between infected individual and susceptible one scales. A detailed understanding of the treatment efficacy requires to develop a time model that captures the complex interaction between the viral load kinetics thanks to the viral dynamic's models, the risk of disease transmission, the treatment efficacy and the timing of treatment initiation.

*Intervenant

Using Plasmodium vivax genetic data to estimate the cause of recurrent vivax malaria

Aimee Taylor*[1]

[1]IDEA – Institut Pasteur de Paris – France

Résumé

Malaria infects hundreds of millions of people year on year. The WHO is committed to a world ultimately free of malaria. Of the two most important causes of malaria, *Plasmodium vivax* is the most difficult to eliminate largely because it has the capacity to relapse: cause recurrent malaria via the activation of latent liver-stage parasites. Recurrent malaria can also be caused by the failure to treat a previous episode (recrudescence) and, in endemic settings, by a new infectious mosquito bite (reinfection). Knowing the cause of recurrent malaria is key to understanding malaria epidemiology and to providing efficacious treatment. For example, to evaluate the efficacy of a drug designed to kill *P. vivax* liver-stage parasites in an endemic setting, reinfections and recrudescence must be separated from relapses. However, there are no direct ways to unambiguously diagnose the cause of recurrent malaria. To address this problem, I am building a statistical model (Pv3R) that uses Plasmodium vivax genetic data to infer the probability of Relapse, Recrudescence and Reinfection. The likelihood of the model sums over various ways to phase/deconvolute genetic data from a pool of parasites. It also sums over graphs of relationships between malaria parasite genotypes and identity-by-descent partitions, which partition genotypes, locus-by-locus, into identical-by-descent clusters. I will describe these elements of the model in more detail, highlighting recent developments and future directions, namely model implementation using MCMC, and data application.

*Intervenant

Monkeypox spread among Parisian venues

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Résumé

The first case of the French monkeypox outbreak was detected on May 18, 2022. By the beginning of June, 72% of French cases had been detected in the Île-de-France region, primarily in Paris, and mainly among men-having-sex-with-men (MSM). Incidence rose rapidly with 440 confirmed cases by the end of June, of which 312 from Île-de-France. Using sexual behavioural data collected in the pre-epidemic period, we studied the early phase of the reported outbreak in Paris and investigated whether attendance to MSM commercial venues (e.g. saunas, backrooms, bars, etc.) fuelled the observed spread. Using the 1,089 respondents of the 2015 PREVAGAY survey in Paris, we built a bipartite network linking respondents to the MSM commercial venues they visited. We projected the data into the space of venues to build a network of venue co-visits, in which venues are nodes and links connect venues if they share co-visitors. Links were weighted by the number of co-visitors. We used outbreak data on the onset date from the post-infection survey answered by cases detected in Paris from the start of the outbreak till mid-July 2022 to determine the date of the first case in each commercial venue visited by cases in the 3 weeks prior to symptoms onset. We then fitted a mathematical model of transmission based on the empirical network of venue co-visits to the observed invasion times using Markov Chain Monte Carlo (MCMC) sampling. We repeated the estimation each time removing certain co-visits features from the network. We found that the original network of venue co-visits best reproduced the observed invasion dynamics among venues. Including information about the number of visits by each individual to each venue did not change the predictive accuracy of the model, suggesting that the existence of

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a co-visit is sufficient to predict the spread, irrespective of visit frequency. Our results also indicate that the first cases and the source venue likely went undetected.
Our findings indicate that the pattern of co-visits is a good predictor of spatial transmission among MSM venues in Paris. They underline the need for early intervention at co-visited sites and targeted information to users of co-visited sites to reduce the spread of monkeypox to yet unaffected venues or in the event of resurgence.

Twenty years of modelling of school-based interventions: Applications to influenza and COVID19

Simon Cauchemez*[1]

[1]Modélisation Mathématique des Maladies Infectieuses – Institut Pasteur de Paris – France

Résumé

In this presentation, I will discuss how the evaluation of control measures targetting schools has changed over the last 20 years, considering examples from influenza and COVID19 research. I will review the different types of data available to assess school-based interventions, identify their strengths and limits and discuss new opportunities and challenges.

*Intervenant

COVID-19 transmission in schools

Vittoria Colizza*[1]

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Résumé

School closures and distance learning have been extensively applied to control SARS-CoV-2 transmission in several countries. Through mathematical modeling and empirical data, I will present results on school transmission and review protocols to keep schools open in different phases of the pandemic.

*Intervenant

Quantifying transmission dynamics of acute hepatitis C virus infections in a heterogeneous population using sequence data

Gonché Danesh[1], Victor Virlogeux[2], Christophe Ramière[3], Caroline Charre[3], Laurent Cotte[4], and Samuel Alizon*[5]

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Résumé

Opioid substitution and syringes exchange programs have drastically reduced hepatitis C virus (HCV) spread in France but HCV sexual transmission in men having sex with men (MSM) has recently arisen as a significant public health concern. The fact that the virus is transmitting in a heterogeneous population, with different transmission routes, makes prevalence and incidence rates poorly informative. However, additional insights can be gained by analyzing virus phylogenies inferred from dated genetic sequence data. By combining a phylodynamics approach based on Approximate Bayesian Computation (ABC) and an original transmission model, we estimate key epidemiological parameters of an ongoing HCV epidemic among MSMs in Lyon (France). We show that this new epidemic is largely independent of the previously observed non-MSM HCV epidemics and that its doubling time is ten times lower (0.44 years versus 4.37 years). These results have practical implications for HCV control and illustrate the additional information provided by virus genomics in public health.

*Intervenant

Assessing sampling bias impact in phylodynamic inferences

Gonché Danesh*[1]

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Résumé

The phylodynamics research field hypothesizes that the way rapidly evolving viruses spread leaves 'footprints' in their genomes. This field has been blooming over the last decade and particularly with the COVID-19 pandemic and the rapidly-growing number of available genome data. Analyses of SARS-CoV-2 genomes have been performed to estimate the temporal reproduction number, the doubling time, and the date of the origin of the epidemic, using bayesian phylodynamic inference methods. These methods based on likelihood functions are the most commonly used but can be unsuitable for models with many parameters. A recent framework based on the Approximate Bayesian Computation (ABC) inference method that does not require a likelihood function has been developed, validated, and allowed to better understand an ongoing Hepatitis C virus epidemic in France. However, with the vast amount of publicly available sequence data, sampling is often highly biased which can impact estimates of epidemiological parameters. We study the effect of the sampling bias on parameter inferences using simulated phylogenies and different phylodynamic methods.

*Intervenant

Fast approaches for phylodynamic model resolution uncover the epidemiological dynamics of outbreaks

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Résumé

Phylodynamics uses pathogen genomes as a source of information for epidemiological parameter inference. With constantly growing genome sequence availability, phylodynamics has a high potential for shedding light on epidemics, especially in the beginning, when classical epidemiological data (e.g. incidence curves) are yet limited. However due to the high complexity of differential equations used in phylodynamic models, current implementations suffer from numerical instability and are only applicable to datasets of limited size (< 500 sequences).

We solve this computational bottleneck in two ways: (1) via fine-tuned model-specific mathematical effort to improve likelihood computation for the Birth-Death Exposed-Infectious model, one of the most commonly used phylodynamic models, which targets pathogens featuring an incubation period (between the moment of infection and becoming infectious), such as Ebola and SARS-CoV2 ; and (2) via replacing a likelihood-based framework with a simulation-based (and therefore likelihood-free) deep learning approach for a larger spectrum of models. Our fast and accurate estimators are applicable to very large datasets (10 000 samples). This represents a crucial step in the field of phylodynamics, moving from proof of concept to analyses of large-scale real data, increasingly available today.

*Intervenant

Mapping SARS-CoV-2 adaptation

Sylvain Gandon*[1], François Blanquart[2], Sébastien Lion[3], David A Kennedy[4], Andrew F Read[4], and Troy Day[5]

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Résumé

The adaptation of SARS-CoV-2 to human populations is challenging our ability to control the on going pandemic. This adaptation involves several different phenotypic traits but it can be summarized on a map which gives the adaptation of the variants in naive hosts and immunized hosts. Here we show how to locate a new variant on this map of viral adaptation using four quantities: (i) the proportion of immunized hosts, (ii) the intensity of Non Pharmaceutical Interventions deployed to reduce transmission, (iii) the change in variant frequency across time, (iv) the difference in variant frequency across naive and immunized hosts. We use this approach to pinnpoint the location of the omicron variant on this map using data from France and Canada.

*Intervenant

Evolution of social contacts patterns in France over the SARS-CoV-2 pandemic: results from the SocialCov survey

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Résumé

Background. Several mitigation measures were implemented in France between 2020 and 2022 to limit the spread of the SARS-CoV-2 virus and reduce the burden on healthcare systems. Other than mitigation measures, several factors, such as individual protective behaviors or the emergence of a new more transmissible variant, may interact to modify the epidemic dynamics. To disentangle all of these various effects, it is critical to track social contacts in the population. Here, we present the analysis of data from the SocialCov survey that characterizes the evolution of contacts in France between December 2020 and May 2022.

Methods. The questionnaire was advertised on the governmental application TousAntiCovid over 6 campaigns. Participants were asked to report their contacts on the previous day, detailing characteristics such as age of the contacts, location and duration of contact and if the contact was physical or not. Participants living with children were also invited to fill the survey for one of their children.

Results. We gathered the answers of 44,396 participants who declared 287,738 contacts in total over six different recruitment campaigns. Reported contact patterns evolved over the study period, with changes based on age, but also holidays, weekend and easing of mitigation measures. The estimated average daily number of contacts in the French population increased from 5.3 in December 2020 to 9.7 in May 2022. Our survey also highlights some professional activities at much higher risk of having high levels of contacts: healthcare workers declared between 2 and 3 times more contacts than other workers during working days.

Conclusions. The SocialCov study provides unique data about the evolution of contacts over the years 2020-2022 in France. It highlights strong heterogeneities in the contact patterns according to age, employment and weekend/vacation periods that could be taken into account in a mathematical model for human-to-human transmission of the SARS-CoV-2 virus.

*Intervenant

The epidemic footprint of contact structures

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Résumé

The recent COVID epidemic has led to implementations of non-pharmaceutical interventions, among which teleworking strategies. This raises the question of the way these interventions impact the spread of an epidemic. Models with several levels of mixing (households, workplaces, etc) (1), as well as various formulations for R0 in such models (2) have been proposed in the epidemic modelling literature. However, little attention has been paid to the impact of the distribution of the population size within social structures (household model in (3)), effect that can help plan effective control strategies.
Since teleworking strategies consist in reshaping the distribution of workplace sizes, we focus on the influence of the latter on the model outcomes. We consider a simple model prone to exploring these issues, a stochastic SIR model with three levels of mixing, which takes into account a uniformly mixing general population, in addition to which each individual belongs to a household and a workplace. We show that the variance of workplace sizes appears to be a good proxy for the impact of the workplace size distribution on certain key parameters of the epidemic, such as epidemic size and peak. In particular, our findings also suggest that strategies where the proportion of teleworking individuals depends sublinearly on the size of the workplace consistently outperformed the strategy with the linear dependence, requiring a lower overall teleworking rate to bring R0 below 1.

However, one drawback of the model with three levels of mixing are the parameters involved, which may not be easily obtainable, raising interest in a reduced model. We propose a reduced unstructured SIR ODE-based model, explicitly taking into account social structure sizes. We show that this classical SIR model, sharing the same growth rate as the model with three levels of mixing, yields a generally satisfying approximation of the epidemic.

These results are very promising from the perspective of implementing effective strategies based on social distancing of specific contacts. Furthermore, they contribute to the effort of building relevant approximations of individual based model at intermediate scales.

(1) Ball, F. & Neal, P. (2002) A general model for stochastic SIR epidemics with two levels of mixing. Mathematical Biosciences 180 :73-102.

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(3) Becker, N.G & Dietz, K. (1995) The effect of household distribution on transmission and control of highly infectious diseases. Mathematical Biosciences 127:207-219.

*Intervenant

Synthetic school populations for epidemic models

Giulia Bassignana*[1], Elisabetta Colosi[1], Diego Andrés Contreras[2], Alain Barrat[2,3], and Vittoria Colizza[1,3]

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Résumé

Contact patterns among individuals are critical to study the potential transmission routes of infectious diseases. This is particularly important in schools, where a substantial amount of social mixing between individuals is expected. Networked wearable sensors can be used to assess with high spatial and temporal resolution the proximity of individuals, and their face-to-face interactions (1). These data can inform computational models, allowing the evaluation of strategies to mitigate the spread of infectious diseases, such as sanitary protocols in schools, and providing useful insights to applied public health. However, most datasets are only available for a small number of days, due to the resources required to run the studies for longer periods of time, and specific to the school under study. Additionally, the level of detail may vary in terms of aggregation over time and groups of individuals, depending on the data collection approach (e.g. surveys vs. sensors).

Here, we propose an algorithm to generate synthetic copies of an empirical contact network to extend the dataset in time (adding new time steps) and in size (adding new agents), considering both day-to-day variability of contacts and stable friendship relations. The algorithm we propose is able to reproduce the main features observed empirically such as class structure, within-class vs between-class links, contact duration heterogeneity, and similarity across days. Then, starting from high-resolution contact data, we use detailed to coarse data representations to inform a model of SARS-CoV-2 transmission and evaluate the impact of data representation on the predicted efficiency of different mitigation strategies. Results suggest that accounting for the variability of contacts has an important role in reproducing the final size of the epidemic, that could be underestimated by simpler procedures such as repeating the empirical dataset. We find that while the dynamics is different for different data representations, the ranking of protocols according to their efficiency remains coherent across representations. This ensures the consistency of model findings to inform public health advice (2). Our results can be used to generate realistic contact patterns in indoor environments where contacts between individuals are prolonged and in close proximity, such as schools and workplaces, for epidemic modeling purposes. These can help simulate a detailed description of disease transmission to aid the design of policies in these settings.

*Intervenant

References

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Using a dynamic transmission model to produce influenza activity scenarios for the winter of 2022/23: France, Germany, Italy, Spain and the United Kingdom

Pascal Crépey*[1], Laurent Coudeville[2], Meral Akçay[2], Clotilde El Guerche-Séblain[2], Bronke Boudewijns[3], Marco Del Riccio[3], and John Paget[3]

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Résumé

We applied a combined influenza and COVID-19 dynamic transmission model to assess reasonable future scenarios of influenza activity in France, Germany, Italy, Spain and the United Kingdom for 2022/23 winter.

We used previously developed age-structured dynamic transmission models for COVID-19 and Influenza. The former was able to assess the level of necessary social distancing measure depending on COVID-19 activity, the latter accounted for impact of covid-related social distancing on influenza circulation. The models accounted for age-specific attack rate and hospitalizations rates since 2012 (Influenza), reported cases, hospitalizations, deaths, and variant distribution since 2020 (COVID-19), hospitalization and vaccination coverage rates by age, as well as country demographics. In the analyzed scenarios for the winter season 2022-2023: Influenza force of infection during the 2022-2023 season is like last pre-pandemic year (2019-2020), while COVID-19 is taken as either circulation of Omicron BA.5 like variant from August 2022 to July 2023, or emergence of a new variant in December 2022 with 25% immunity escape compared to Omicron BA.5.

Our results show that the limited influenza circulation in 2020-2022 could lead to a higher than usual influenza peak in 2022-2023 (compared to pre-COVID-19 period) due to loss of immunity. We also show that the combined number of hospitalizations for COVID-19 and influenza is expected to remain significant during the 2022-2023 winter season. Finally, from a public health perspective, we conclude that vaccination remains the best option to mitigate both COVID-19 and influenza epidemics and prevent further need for stringent social distancing measures.

*Intervenant

Global patterns and drivers of influenza decline during the COVID-19 pandemic

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Résumé

Influenza circulation declined during the COVID-19 pandemic. We quantified this decline globally by computing the change in influenza by country and trimester relative to 2014-2019 from the FluNet database. We used random forests and regression trees to identify and illustrate predictors of decline - using demographic, weather, pandemic preparedness, COVID-19 incidence, and pandemic response characteristics. We found that the decline in influenza during the COVID-19 pandemic was global but heterogeneous across space and time. COVID-19 incidence and pandemic preparedness were the two most important predictors of decline. Europe and North America initially showed limited decline despite high
COVID-19 restrictions; but strong decline afterwards as in most temperate countries where pandemic preparedness, COVID-19 incidence, and social restrictions were high; decline was limited in countries where these factors were low. The "zero COVID" countries experienced the greatest decline. These results set the stage for interpreting the resurgence of influenza worldwide.

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Modelling the impact of COVID-19 pandemic responses on the transmission and selection of antibiotic resistance in the community and hospitals

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Résumé

The COVID-19 pandemic pharmaceutical and non-pharmaceutical interventions dramatically modified the global ecological and epidemiological landscape of other infectious diseases. Specifically, the pandemic impacts on the spread of antibiotic-resistant bacteria both in the community and the hospital are poorly known with data either missing or being delayed. While the first wave of the pandemic may have exacerbated antimicrobial resistance (AMR) due to frequent administration of antibiotic prophylaxis to COVID-19 patients, the overall decrease in antibiotic use due to modified healthcare-seeking behaviour may have had the opposite effect in an early pandemic. To disentangle how different pandemic impacts may affect antibiotic-resistant bacteria, we propose specific drug-bug-setting mathematical models in which SARS-CoV-2 and the bacteria co-circulate within a population (community or hospital) to assess the effect of different control measures and antibiotic use scenarios on the trends of bacterial carriage prevalence, antibiotic resistance, and the incidence of antibiotic-resistant invasive bacterial disease (IBD). The models are applied to setting-specific pathogens: *Streptococcus pneumoniae*, a commensal community bacterium, and *Staphylococcus aureus* and *Escherichia coli*, common pathogens circulating in hospital populations.
A series of epidemiological scenarios reflecting impacts of SARS-CoV-2 on factors relevant for bacterial transmission in different settings are defined, implemented, and modelled through a modification of contact behaviour, hygiene, antibiotic prescribing, and population structure. Exploiting models for two specific settings (hospital and community) we used a simulation approach tailored to an early pandemic context to assess how surges in COVID-19 cases in the community may affect antibiotic-resistance selection and spread.

In the community model and scenarios, population-wide lockdown was associated with substantial reduction in *S. pneumoniae* colonization prevalence and IBD incidence regardless of the antibiotic resistance. In the absence of lockdown however, antibiotic prophylaxis led

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to increases of resistant IBD incidence while overall IBD incidence still decreased. We also found that within-host interactions, SARS-CoV-2 variants' reproductive numbers, and population immunization levels further affect the amplitude of effect on AMR spread in the community.

In hospital settings, simulations were conducted for two pathogens (methicillin-resistant *Staphylococcus aureus* and extended-spectrum beta-lactamase-producing *Escherichia coli)* in geriatric and paediatric hospital wards. Antibiotic resistance dynamics was found to be highly context-specific: SARS-CoV-2 outbreaks had significant impact on bacterial epidemiology only in facilities with high underlying risk of bacterial transmission. On the other hand, antibiotic resistance burden was reduced in facilities with timelier, and more effective implementation of COVID-19 control measures, which highlights the control of antibiotic resistance as an important collateral benefit of robust pandemic preparedness.
In this study we found that SARS-CoV-2 outbreaks are likely to drive antibiotic resistance but results strongly depend on the setting and bacterial species considered. In the community, impact on AMR is smaller with lockdown implementation. These findings are congruent with the recent global reports on 2019-2020 AMR trends. More data is needed to analyse trends and quantify these interactions.

Estimating the date of emergence of an epidemic from detection data: Applications to COVID-19

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Résumé

ABSTRACT

Background. While the first infection by an emerging disease is often unknown, information on early cases can be used to date it, which is of great interest to trace the disease's origin and understand early infection dynamics. For COVID-19, the date of the first human SARS-CoV-2 infection was estimated at mid-October/mid-November 2019 using a mathematical model for the epidemic spread coupled with genomic data tracing transmission at the individual level (1); these estimates were recently revised to late-October/early-December 2019 (2). Dating attempts can also be done for SARS-CoV-2 variants of concern, such as Alpha, whose date of emergence was estimated at early August 2020 using a stochastic model describing early epidemics dynamics (3) and which time of most recent common ancestor was estimated at late August 2020 (4). Stochastic approaches studying early dynamics are rarer than deterministic ones and thus methodological developments remain of great interest in the field of mathematical epidemiology.

Methods. We extended the model presented in (3) to estimate the time elapsed between emergence (i.e., first human infection with the focal disease, pathogen or variant) and the detection of the N-th case. We run numerical simulations of infectious disease spreading from a single infectious individual to obtain a time series of cases, calibrating our model using available data. We account for superspreading events by assuming the number of secondary cases follows a negative binomial distribution. The main outcome of our model is the expected time to the detection of N cases.

Findings. An early validation of our model was performed through its application to the context of the spread of the Alpha variant in the UK, where 406 detected cases were sequenced by November 11th, 2020 (5). Our preliminary results suggest a median (95% credibility interval, CrI) number of days between the first infection and the 406-th reported case of 113.61 (92.89–144.6), dating the first SARS-CoV-2 infection to July 21 (June 20 – August 11), 2020. These results thus fall within the emergence estimations reported in (3) while suggesting an earlier emergence than (4). Next, we parametrized the model to reproduce the dynamics of the early stages of the SARS-CoV- 2 and estimated a range of probable dates for the emergence of the COVID-19 pandemic. We used data on the date of symptom onset

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of the early confirmed cases of SARS-CoV-2 infection in Wuhan (up to the end of December, 2020). Our preliminary results yield a median (95%CrI) number of days between the first infection and the 174-th case of COVID-19 symptom onset of 37.92 (26.9–54.15), dating the first SARS-CoV-2 infection in Wuhan at November 24 (November 7 – December 5), 2019, falling within the estimates found in (2).

Conclusion. The main outcome of our model is the methodology to estimate the delay from the first infection to the N-th reported case of an emerging epidemic, as well as the simulation of time series of cases calibrated using early available data. Our results on the early COVID-19 cases fall within the ranges previously estimated, by using different methods. This modelling framework is generic and flexible, and thus can be applied to estimate the starting time of outbreaks, in contexts other than COVID-19, where some key parameters (such as transmission and detection rates) are known.

Keywords. Mathematical epidemiology; early epidemic dynamics; timing of detection; dating epidemic emergence; SARS-CoV-2.

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Non-Markovian modelling and COVID-19 epidemic

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Résumé

Classical ODEs-based models come with the tacit assumption that the time spent in each compartment for each individual is distributed exponentially. However, many biological processes are non-Markovian and depend on what already happened. A usual workaround is to chain various compartments representing a unique epidemiological reality (e.g. I1 -> I2 for infected individuals) to encapture the heterogeneity occurring in the biological processes. Such phenomena happened during the COVID-19 epidemic, e.g. among infected individuals where different events (infectiousness, hospital admission risk) might happen on different timescales, or later with the immunity waning. It led us to explore some alternative modelling formalism to better acknowledge those heterogeneities.

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Impact of non-pharmaceutical interventions, weather, vaccination, and variants on COVID-19 transmission across departments in France

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Résumé

Background: Multiple factors shape the temporal dynamics of the COVID-19 pandemic. Quantifying their relative contributions is key to guide future control strategies. Our objective was to disentangle the individual effects of non-pharmaceutical interventions (NPIs), weather, vaccination, and variants of concern (VOC) on local SARS-CoV-2 transmission.
Methods: We developed a log-linear model for the weekly reproduction number (R) of hospital admissions in 92 French metropolitan departments. We leveraged (i) the homogeneity in data collection and NPI definitions across departments, (ii) the spatial heterogeneity in the timing of NPIs, and (iii) an extensive observation period (14 months) covering different meteorological conditions, VOC proportions, and vaccine coverage levels.

Results: Three lockdowns reduced R by 72.9% (95%CI: 71.4-74.2), 70.4% (69.2-71.6) and 60.4% (56.1-64.3), respectively. Curfews implemented at 6/7pm and 8/9pm reduced R by 34.5% (28.1-40.4) and 18.4% (11.4-24.8), respectively. School closures reduced R by only 4.6% (1.6-7.4). We estimated that vaccination of the entire population would have reduced R by 74.0% (59.4-83.3), whereas the emergence of VOC (mainly Alpha during the study period) increased transmission by 46.9% (38.2-56.0) compared with the historical variant. Winter weather conditions (lower temperature and absolute humidity) increased R by 41.7% (37.0-46.7) compared to summer weather conditions. Additionally, we explored counterfactual scenarios (absence of VOC or vaccination) to assess their impact on hospital admissions.
Conclusions: Our study demonstrates the strong effectiveness of NPIs and vaccination and

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quantifies the role of meteorological factors while adjusting for other confounders. It highlights the importance of retrospective evaluation of interventions to inform future decision-making.

Estimation of the effect of non-pharmaceutical interventions and vaccination against COVID-19 in France using dynamical models

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Résumé

Background: The COVID-19 pandemic has caused substantial morbidity and mortality and taken a heavy toll on healthcare systems worldwide. In anticipation of exponential disease transmission and healthcare systems arriving at their limits, many governments enforced non-pharmaceutical interventions (NPIs) to curb viral transmission while waiting for an effective vaccine. Since their implementation, there has been much interest in determining the effectiveness of different NPIs, as well as estimating the effectiveness of vaccines after they became available. However, there is a need to further study NPI effects because i) data quality has improved significantly since the beginning of the pandemic; ii) the effectiveness of stringent lockdowns and vaccination have been disputed; and iii) many studies faced methodological challenges that could bias the magnitude and uncertainty of effect estimates. **Objectives:** We aimed to develop a single mathematical model to explicitly represent he effectiveness of individual NPIs on SARS-CoV-2 transmission in France and simultaneously estimate the effect of vaccines. Moreover, we aimed to quantify the number of lives saved and hospitalizations averted by NPIs and vaccinations, respectively.

Methods: We developed a multi-level, population-based disease transmission model of the COVID-19 pandemic in France from March 1st, 2020, until the emergence of omicron variant (Nov 1st, 2021). We created an extended SIR model, with observations being cases, deaths, hospital admissions, and hospital occupancy and random effects to account for inter-department variability. We estimated the time-varying transmission rate by an integrated regression model, depending on the effect of NPIs, while accounting for the apparition of viral variants of concern (VoCs), seasonal weather conditions, and vaccination.

Results: We show that NPIs implemented by the French government strongly decreased SARS-CoV-2 transmission. The first lockdown was estimated to reduce transmission by 90% (95% CI 85-95) and was more effective than the second and third lockdowns (reduction by 47% (95% CI 42-52) and 25% (20-29), respectively). The curfew at 6 pm was slightly more effective than the curfew at 8 pm (transmission reduction by 51% (49-54) vs. 46% (42-50)).

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School closures were estimated to have a smaller effect on transmission (15% reduction, 95% CI 5-22). We also observed a strong effect of weather on transmission, with an average reduction of 19% in summer and an average increase of 11% in winter conditions. Beyond NPI effectiveness, our mechanistic model using only epidemiological and vaccine coverage data demonstrated a large protective effect of the vaccine on hospitalization, and a smaller, but still significant, effect of the vaccine on transmission, depending on vaccine coverage and VoC presence in the population. At the end of the study period, the effective vaccine protection, taking into account population vaccine coverage and reduced effectiveness against VoCs, ranged between 72% - 95% against hospitalization and 35% - 49% against infection across departments.

Conclusion: The NPIs implemented by the French government had a strong effect on reducing viral transmission, hospitalizations, and deaths. Likewise, vaccination of the French population reduced transmission and strongly reduced hospitalization. Our results retrospectively emphasize the importance of stringent NPIs and a high vaccination rate to control the COVID-19 pandemic and prevent future epidemic resurgence.

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