ECOLE DOCTORALE PIERRE LOUIS DE SANTE PUBLIQUE A PARIS
EPIDEMIOLOGIE ET SCIENCES DE L'INFORMATION BIOMEDICALE

Directeur : Pierre-Yves Boëlle
Responsable pour Université de Paris : Isabelle Boutron

PROPOSITION DE SUJET DE THESE

SIGLE ET NOM DU LABORATOIRE : INSTITUT PIERRE LOUIS D'EPIDEMIOLOGIE ET DE SANTE PUBLIQUE, IPLESP, UMR S 1136, INSERM AND SORBONNE UNIVERSITÉ
NOM DE L'EQUIPE : EQUIPE 1, SURVEILLANCE ET MODELISATION DES MALADIES TRANSMISSIBLES

DIRECTEUR DE THESE : PIERRE-YVES BOËLLE AND CHIARA POLETTO
ADRESSE : 27 RUE DE CHALIGNY 75012 PARIS

TITRE DE LA THESE : IMPACT OF HOST POPULATION STRUCTURE ON THE ECOLOGY OF PATHOGEN STRAINS

CO-ENCADRANT EVENTUEL :
EQUIPE DU CO-ENCADRANT :
LABORATOIRE :

PRESENTATION DU SUJET

Contexte scientifique du projet
The increasing availability of virological data makes it possible to describe the ecology of viral populations at high resolution, revealing the patterns of virus phylogenies and variants' extinction/dominance. These patterns are complex and difficult to interpret in many cases because of relationships with host and environmental factors.

Influenza provides a paradigmatic example. Subtype co-circulation shows a marked geographical pattern that may be the result of the forces governing influenza circulation – e.g. seasonality, age structure, and international mobility [1]. Understanding these patterns is essential to anticipate influenza epidemics and aid the design of vaccines.

SARS-CoV-2 pandemic has prompted an unprecedented sequencing effort, that is enabling the real-time monitoring of new variants' emergence, co-circulation and dominance. Still, the mechanisms driving variants' interaction are largely unknown and predicting the traits (i.e. increase in transmissibility or immune escape) that enable a strain to raise to dominance is very hard [2].

Questions posées
The student will address the complex interdependence between host-population structure and pathogen ecology by focusing on two specific problems in influenza and SARS-CoV-2.

Influenza: Despite extensive surveillance efforts to track seasonal influenza epidemics, it still remains unclear how factors acting at different scales (e.g. local epidemics at the community level vs. international coupling due to travels) drive influenza subtypes' co-circulation. An integrative approach merging multi-scale epidemiological

models and multi-strain interaction, by pulling information from multiple sources, would improve our understanding on pluriannual influenza circulation.

SARS-CoV-2: The emergence of SARS-CoV-2 variants of concern (VOCs) has made the course of the COVID-19 pandemic unpredictable. VOCs are characterized by increase in transmissibility and/or potential to re-infect hosts. During 2021 emerging VOCs have become dominant in many cases or, in other cases, they have cocirculated with previously existing variants affecting only a proportion of the population. Often, the outcome of emergence has been heterogenous across countries or regions. For instance, the Beta variant became dominant in South Africa where it was originally identified, while it co-circulated with the Alpha variant in European countries. Population structure and environmental features may alter strain interaction dynamics and could be at the origin of such a heterogeneous outcome. Importantly, social contacts display a fat tail distribution. This feature was suggested to be the main driver of super-spreading events, that were frequently reported during the COVID-19 epidemic [3]. It was found also to alter new strain emergence and the co-existence between co-circulating strains [4,5]. Still the impact of the contact distribution on the selective advantage of the enhancement in transmissibility vs. the immune evasion remains unclear.

Sources de données qui seront utilisées

- Worldwide population distribution obtained from SEDAC, Columbia University[6].
- International Air-transportation data from IATA[7], accounting for the 99 % of the global commercial traffic.
- Statistics on household size and composition, for France (source INSEE, https://www.insee.fr/en/accueil).
- FluNet data. FluNet is a web based data collection reporting tool of the GISRS[8]. For each country, data available are weekly number of specimens tested for IV and the number testing positive subdivided in A/H1N1pdm, A/H3N2, A/H1N1 (previous pandemic period), A/H5N1, A (non subtyped), B/Victoria, B/Yamagata, B (lineage not determined). Countries currently represented in the dataset are around 150[9].
- SARS-CoV2 VOCs frequencies by country in Europe (https://www.ecdc.europa.eu/en/covid-19/situation-updates/variants-dashboard).

Méthodes

The student will develop computational models integrating data on human demography, mobility and behavior at different scales to simulate epidemic scenarios and understand the role of different factors in epidemic propagation and viral ecology.

SARS-CoV-2: The student will develop a multi-strain model describing the emergence of two SARS-CoV-2 variants, one with increased transmissibility and the other with immune escape. The interaction between the two emerging variants will be studied in varying the following factors:

- variants epidemiological traits – i.e. transmissibility of the historical variant, extent of the enhancement in transmissibility and the immune escape for the two emerging variants
- distribution of contacts mediating transmission, comparing different contact statistics to reproduce the different stages of the COVID-19 outbreak – e.g. baseline levels of contacts and their dispersion, and lower level of social interaction together with more limited variability, as registered during the periods of social restriction
- different level of incidence and population immunity due to the historical variant.

Model results will be compared with variant frequencies to shed light on the mechanism underling the patterns observed in the data

Influenza: the student will develop a spatial epidemic model based on the metapopulation approach and integrating data on population distribution and air traveling. The metapopulation is used to model an epidemic propagation as the combination of a local transmission dynamics - modelled with the traditional mass-action equations and affected by local seasonality -, and a global infection diffusion - modelled by explicit accounting for the infectious individuals traveling along the links of the mobility network. The model for the transmission dynamics will account for the co-circulation between different influenza subtypes and their interaction through cross-immunity. The model output will be qualitatively compared with the empirical patterns recovered from FluNet data. Specifically, model parameter will be tuned to reproduce the frequency of subtypes dominance vs. co-existence events. The model will then provide an understanding on the role of the potential driving forces (among mobility, heterogenous local transmission specific to the climatic region, and subtype characteristics) on subtypes seasonal co-circulation patterns. In addition, we will model the emergence of a novel subtype, comparing scenarios with variable timing and location of emergence and variable viral characteristics of emerging subtypes. The goal is to understand how the emergence outcome varies in these scenarios, in terms of emergence/extinction of the emerging virus; extinction of previously circulating viruses and the possible presence of large pandemic wave(s) upon emergence.

Puissance de l'étude/nombre de sujets ;
The study will rely on stochastic numerical simulations. Stochastic effects will be handled carefully. A sufficient number of simulations will be performed. Numerical characterization of simulation output will be conducted with state-of-the-art data analysis approaches.

Calendrier prévisionnel
M0-M6: development of multi-strain model for SARS-CoV-2
M6-M12: use of the model to fit characterized emergence scenarios for SARS-CoV-2 VOCs
M12-M15: paper 1 writing
M15-M21: development of the metapopulation model of Flu circulation
M21-M24: analysis of scenarios for influenza spread
M24-M27: paper 2 writing
M 27-M36: papers' revisions, thesis writing, thesis review by the committee

Thème de chacun des articles prévus. Une proposition de sujet de thèse doit comporter au moins deux articles originaux.
Paper 1: one paper on the role of human contact network on the dynamics of VOCs emergence
Paper 2: one paper on the sub-types co-circulation of influenza

References
1. Bedford, T. *et al.* Global circulation patterns of seasonal influenza viruses vary with antigenic drift. *Nature* **523**, 217–220 (2015).
2. Bushman, M., Kahn, R., Taylor, B. P., Lipsitch, M. & Hanage, W. P. Population impact of SARS-CoV-2 variants with enhanced transmissibility and/or partial immune escape. *Cell* **184**, 6229-6242.e18 (2021).
3. Susswein, Z. & Bansal, S. Characterizing superspreading of SARS-CoV-2 : from mechanism to measurement. *medRxiv* 2020.12.08.20246082 (2020) doi:10.1101/2020.12.08.20246082.
4. Leventhal, G. E., Hill, A. L., Nowak, M. A. & Bonhoeffer, S. Evolution and emergence of infectious diseases in theoretical and real-world networks. *Nature Communications* **6**, 6101 (2015).
5. Pinotti, F., Fleury, É., Guillemot, D., Böelle, P.-Y. & Poletto, C. Host contact dynamics shapes richness and dominance of pathogen strains. *PLOS Computational Biology* **15**, e1006530 (2019).
6. Center for International Earth Science Information Network (CIESIN), Columbia University; and Centro Internacional de Agricultura Tropical (CIAT). The Gridded Population of the World Version 3 (GPWv3): Population Grids. Palisades, NY: Socioeconomic Data and Applications Center (SEDAC), Columbia University. *SEDAC* http://sedac.ciesin.columbia.edu/gpw.

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7. International Air Transport Association (IATA). http://www.iata.org.
8. National Influenza Centres (NICs) of the Global Influenza Surveillance and Response System (GISRS) and World Health OrganisationWHO. FluNet.
9. Alonso, W. J. *et al.* A global map of hemispheric influenza vaccine recommendations based on local patterns of viral circulation. *Scientific Reports* **5**, 17214 (2015).
10. Lemey, P. *et al.* Unifying Viral Genetics and Human Transportation Data to Predict the Global Transmission Dynamics of Human Influenza H3N2. *PLoS Pathog* **10**, e1003932 (2014).

PRÉREQUIS, FORMATION : quantitative science, such as applied mathematics, physics, statistics, computer science, quantitative epidemiology or any close related discipline

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SPECIALITE DE LA THESE

Santé publique - Epidémiologie	☐
Santé publique - Epidémiologie clinique	☐
Santé publique - Epidémiologie sociale	☐
Santé publique - Epidémiologie génétique	☐
Santé publique - Biostatistique	☐
Santé publique - Biomathématiques	☐
Santé publique - Biostatistique et Biomathématiques	☒
Santé publique - Informatique médicale	☐
Santé publique - Imagerie biomédicale	☐
Santé publique - Bioinformatique	☐
Santé publique - Recherches sur les services de santé	☐
Santé publique - Economie de la santé	☐
Santé publique - Science des données	☐
Santé publique – Prévention et promotion de la santé	☐

SIGNATURE DU. DE LA DIRECTEUR.TRICE DE THESE

VISA DU.DE LA DIRECTEUR.TRICE DU LABORATOIRE
(DEROGATION DE SIGNATURE NON ACCEPTEE)

AVIS FAVORABLE ☒

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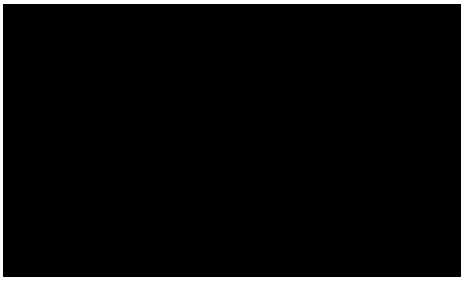

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