

**Title:** Reconstructing the life course epidemiology of influenza B using multi-strain serological data

**Description:** Viruses which undergo regular evolution in key antigenic proteins, such as SARS-CoV-2 and influenza, cause repeated infections in humans over the course of their lives due to their ability to escape host immunity. Influenza B is one of three main influenza subtypes (alongside A/H3N2 and A/H1N1) which contributes to the burden of seasonal influenza-like-illness, causing substantial severe disease, particularly in children. Despite accounting for almost a quarter of influenza cases annually, the long-term epidemiology of influenza B viruses are relatively understudied compared to influenza A.

Understanding the epidemiology of influenza is complicated, as repeated infection with different strains of influenza creates a heterogeneous immune landscape in the population. Each infection stimulates a mixture of new and cross-reactive memory immune responses, such that each individual's immune profile is a unique reflection of when and with which strains they were infected. This feedback between past exposures and immune responses to new strains leads to fascinating and epidemiologically important immune imprinting patterns. For example, there are observed differences in susceptibility to particular strains depending on birth year and differences in antibody responses from vaccination depending on an individual's pre-existing immunity.

To make sense of this complex immunological landscape, we developed a modelling tool, *serosolver*, which reconstructs individual-level lifetime infection histories using antibody data measured against multiple strains. By reconstructing these lifetime infection histories for many individuals we are able to reconstruct historical seasonal influenza patterns at the population level. We recently published our work applying this method to a large serological study of influenza A/H3N2, providing new insights into infection patterns over time, age and location.

This BSP project will extend this previous work to develop and apply custom mathematical models and Bayesian inference methods, linking immunological dynamics to population-level epidemiology for influenza B viruses. The aim of the work is to generate new insights into the long-term and spatial epidemiology and immunology of influenza B, as well as contribute to new tools for seroepidemiology.

The work of the project will comprise:

- 1) Undertaking a review to understand the currently existing serological models for influenza A and B
- 2) Learning how to use the *serosolver* R package with default data
- 3) Learning about the immunology and epidemiology of influenza A and B across settings
- 4) Developing and applying custom mathematical models and Bayesian inference methods to large cross-sectional dataset measuring antibody titers against multiple influenza B strains.
- 5) Adapting and fitting the *serosolver* R package to estimate which strains each individual was likely to have been infected.
- 6) Using statistical methods to understand how infection rates vary over time, between age groups and across settings.

There is a scope to change/adapt/extend the above points if there is a direction that the student is particularly interested in exploring. Please get in touch with Jasmina if this is the case.

## References:

1. Epidemiological background on Influenza immune escape under heterogeneous host immune histories. <https://doi.org/10.1016/j.tim.2021.05.009>
2. Immunological background on immune imprinting in early life shapes cross-reactivity to influenza B virus haemagglutinin. <https://doi.org/10.1038/s41564-024-01732-8>
3. Modelling background on reconstructed influenza A/H3N2 infection histories reveal variation in incidence and antibody dynamics over the life course. <https://doi.org/10.1101/2024.03.18.24304371>

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