PI profile

## Katrina Lythgoe

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|   | **Dr. Katrina Lythgoe****Titles**: Group Leader**Location**: Big Data Institute**Department**: Nuffield Department of Medicine **Group**: Evolutionary Epidemiology of Viruses**Webpage**: https://www.bdi.ox.ac.uk/Team/katrina-lythgoe**Email**: katrina.lythgoe@bdi.ox.ac.uk |

### GMS themes:

* Genomic and –omic technologies
* Genome biology (genomes and genetic variation)
* Genomics of disease
* Genomic analysis (bioinformatics and statistical genetics)

### Research Overview

In our group, we are interested in the evolutionary epidemiology of viral infections, including HIV, Hepatitis C and Hepatitis B. More recently, we have also been working on the within-host evolution and transmission of SARS-CoV-2.

We use a combination of approaches, including population genetics, deterministic and stochastic modelling, and the evolutionary analysis of viral sequence data. More specifically, we are interested in evolutionary and ecological processes operating at different ecological scales (e.g. within- and between-host), to assess the impact this integration of scales has on our understanding of the evolution and epidemiology of infectious disease. Our ultimate aim is to produce better predictive models of the consequences of interventions, including the spread of transmitted drug resistance, changing levels of viral virulence, and adaptation of viruses to host immunological backgrounds.

Project areas: Viral Evolution, Evolutionary Epidemiology, Analysis of next generation sequencing data, Mathematical Modelling, Genomics, Phylogenetics, Population Genetics.

### Specific project proposals:

* Unravelling the role of transmission on SARS-CoV-2 evolutionary dynamics and vaccine escape
* Characterising the within-host compartmentalisation of Hepatitis C Virus
* Determining the role of Hepatitis C virus cccDNA transcriptional activity in increasing the lifespan of episomal cccDNA

Please contact directly for further information.

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Project proposal 1

# **Title: Unravelling the role of transmission on SARS-CoV-2 evolutionary dynamics and vaccine escape**

Supervisors: Dr Katrina Lythgoe and Professor Christophe Fraser

Wet/dry lab mix (approx): 100% dry lab

### Description:

SARS-Cov-2 has had a devastating effect on public health and economies globally. With the arrival of effective vaccines we are about to enter a different phase of the pandemic. What this looks like will depend on whether, or to what degree, vaccines block transmission, how vaccines are rolled out, and the evolution of vaccine escape. Although we should remain ambitious, eradication seems unlikely, and therefore SARS-Cov-2 is likely to remain endemic, at least in the medium term.

 Evolution of vaccine escape mutations requires their emergence within an individual, successful transmission, followed by ongoing chains of transmission. The level of SARS-Cov-2 sequencing (including in Oxford) and sharing of this data is unprecedented, enabling a unique insight into the evolution and transmission of this pathogen. We have shown that the virus has low levels of within-host diversity, is under strong evolutionary constraint, and that only one or a few variants are transmitted; this resulted in our assertion that vaccine escape is unlikely (*Lythgoe & Hall et al., Science 2021)*. This contrasts with subsequent rapid emergence of variants of concern that have large numbers of mutations that could move the virus significantly closer to vaccine escape. It has been hypothesised that these variants evolved in individuals who remained chronically infected for months.

**Overarching aim:**

The overarching aim of this project, if taken to DPhil, is to model and predict the evolution of vaccine escape, and to design optimal vaccination strategies that are ‘evolution-proof’. This will involve the development of models of SARS-CoV-2 evolution that include within- and between- host processes, and that are informed by, and fitted to, within-host whole-genome deep-sequencing data, estimates of transmission bottleneck size, and between-host phylogenies. We are part of the Office of National Statistics Covid-19 infection survey, and this project will give you access to >100,000 sequenced samples (and growing) plus metadata.

**During the rotation project you will:**

1. Perform a literature review.

2. Develop a model of within-host SARS-CoV-2 evolution and transmission, informed using within-host deep-sequencing data, and calculate the likelihood that and escape mutation will emerge and spread. This could use a branching-process type approach.

3. Write up.

 **This could form the foundation of a DPhil, which could help inform future vaccine development and roll-out.**

### Training Opportunities:

* During this DPhil you will learn how to analyse next-generation viral whole-genome sequencing (WGS) data
* Develop viral transmission models, including phylodynamic models, and test these using WGS data
* You will be given the opportunity to attend a specialised course on viral phylogenetics, and to audit the Health Data Science CDT lectures, particularly those on the dynamics and evolution of infectious disease.

### Background reading / references:

* Lythgoe & Hall et al., Science 2021, “SARS-CoV-2 within-host diversity and transmission”
* Rambaut et al., Virologcal 2020, “Preliminary genomic characterisation of an emergent SARS-CoV-2 lineage in the UK defined by a novel set of spike mutations” (virological.org)
* Antia et al., Nature 2003, “The role of evolution in the emergence of infectious diseases”
* Lythgoe, Pellis & Fraser, Evolution 2013, “Is HIV short-sighted? Insights from a multistrain nested model”

**Project proposal 2**

**Title: Characterising the within-host compartmentalisation of Hepatitis C Virus**

**Supervisors:** Dr Katrina Lythgoe, Professor Oliver Pybus and Professor Jane A. McKeating

**Wet/d**ry lab mix (approx): 100% dry lab

### Description:

Hepatitis C virus (HCV) is characterized by high mutation and evolutionary rates, often with long durations of infection between transmission events. Fundamentally, the evolution and epidemiology of this virus at the epidemiological scale cannot be properly elucidated without a detailed understanding of the link between within-host evolutionary dynamics and transmission. Mathematical modeling and evolutionary analysis of genetic data, particularly HIV, has helped answer key questions, including whether HIV continues to replicate whilst on treatment, how many HIV variants are transmitted among individuals, and how HIV spreads within and among population. However, similar work on HCV is in its infancy.

Our previous work shows HCV infection is characterised by different subpopulations which are only intermittently observed in plasma. Consequently, virus sequenced from a single time point is unlikely to be representative of the viral diversity present in that individual, resulting in the potential to incorrectly infer transmission. However, poor resolution of phylogenetic trees using short/moderate reads make it difficult to test which processes generated these patterns.

We have developed a method to generate long-read within-host whole-genome sequence data in order to generate high-resolution next generation sequencing data from a large number individuals sampled over many years. Using this data you will ascertain whether multiple long-lived lineages of virus exist, and whether they are consistent across the whole genome. Further, you will test whether population subdivision is due to selective or non-selective processes, and whether it differs for cirrhotic and non-cirrhotic individuals. Finally, you will use this data to determine the consequences for determine who-infected-whom using genetic data. This is a crucial question for public health, as it will help determine where intervention efforts should be focussed.

**Training Opportunities:**

· During this DPhil you will learn how to analyse next-generation viral whole-genome sequencing (WGS) data

· Develop and use phylogenic models, including structured coalescent models, to determine the extent and tempo of within-host population turnover

· Develop viral transmission models to determine the effect of within-host population structure on between-host evolutionary dynamics

· You will be given the opportunity to attend a specialised course on viral phylogenetics, and to audit the Health Data Science CDT lectures, particularly those on the dynamics and evolution of infectious disease.

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**Background reading / references:**

· Pybus, O.G. & Rambaut, A. Evolutionary Analysis of the Dynamics of Viral Infectious Disease. Nature Reviews Genetics 2009. Doi:10.1038/nrg2583

· Raghwani J, Wu C, Ho CKY, Jong M De, Molenkamp R, Schinkel J, et al. High-Resolution Evolutionary Analysis of Within-Host Hepatitis C Virus Infection. 2019; 1–8. doi:10.1093/infdis/jiy747

· Rose R, Rodriguez C, Dollar JJ, Lamers SL, Massaccesi G, Osburn W, et al. Inconsistent temporal patterns of genetic variation of HCV among high-risk subjects may impact inference of transmission networks. Infect Genet Evol. Elsevier; 2019;71: 1–6. doi:10.1016/j.meegid.2019.02.025

**Project proposal 3**

**Title: Determining the role of Hepatitis B virus cccDNA transcriptional activity in increasing the lifespan of episomal cccDNA**

**Supervisors:** Dr Katrina Lythgoe and Professor Jane A. McKeating

**Wet/d**ry lab mix (approx): 100% dry lab

### Description:

Hepatitis B virus (HBV) infection is a major global health problem with over 240 million infected individuals at risk of developing progressive liver disease and hepatocellular carcinoma. HBV is an enveloped DNA virus that establishes its genome as an episomal, covalently closed circular DNA (cccDNA) in the nucleus of infected hepatocytes. Currently available standard-of-care treatments for chronic hepatitis B (CHB) include nucleos(t)ide analogues (NA) that suppress HBV replication but do not target the cccDNA and hence rarely cure infection. There is considerable interest in determining the lifespan of cccDNA molecules, and the mechanisms resulting in its longevity, to design and evaluate new curative treatments.

We previously reported an evolutionary mathematical model of cccDNA persistence (Lythgoe et al., 2021), based on within-host next-generation sequencing to data, to estimate cccDNA lifespan. However, our estimated values cannot explain the long-term persistence of cccDNA in most patients, suggesting that key processes are missing from our understanding. Working closely with the McKeating group, you will incorporate new data to refine these models, and to better understand the mechanisms regulating cccDNA half-life. This will include both the replenishment of cccDNA via pgRNA-rcDNA, where encapsidated genomes recycle to the nucleus, and the variation in cccDNA transcriptional activity over the course of infection. Specifically, you will test the hypothesis that HBV cccDNA transcriptional activity increases the lifespan of episomal genomes.

**Training Opportunities:**

* Development and analyse of evolutionary models of viral infection
* You will be given the opportunity to attend a specialised course on modelling of infectious disease, and to audit the Health Data Science CDT lectures, particularly those on the dynamics and evolution of infectious disease.
* Experience working in a collaborative team environment and presenting data at internal lab meetings, journal clubs and seminars.
* Contribute data towards publication in peer-peer reviewed journals

**Background reading / references:**

· Pybus, O.G. & Rambaut, A. Evolutionary Analysis of the Dynamics of Viral Infectious Disease. Nature Reviews Genetics 2009. Doi:10.1038/nrg2583

· Lythgoe et al. Estimating hepatitis B virus cccDNA persistence in chronic infection. Virus Evolution 2021. Doi:10.1093/ve/veaa063

· Testoni et al. Serum hepatitis B core-related antigen (HBcrAg) correlates with covalently closed circular DNA transcriptional activity in chronic hepatitis B patients. J Hepatol 2019. Doi:10.1016/j.hep.2018.11.030

· Bimodal distribution and set point HBV DNA viral loads in chronic infection: retrospective analysis of cohorts from the UK and South Africa. Wellcome Open Research 2020. Doi:10.12688/wellcomeopenres.15941.2