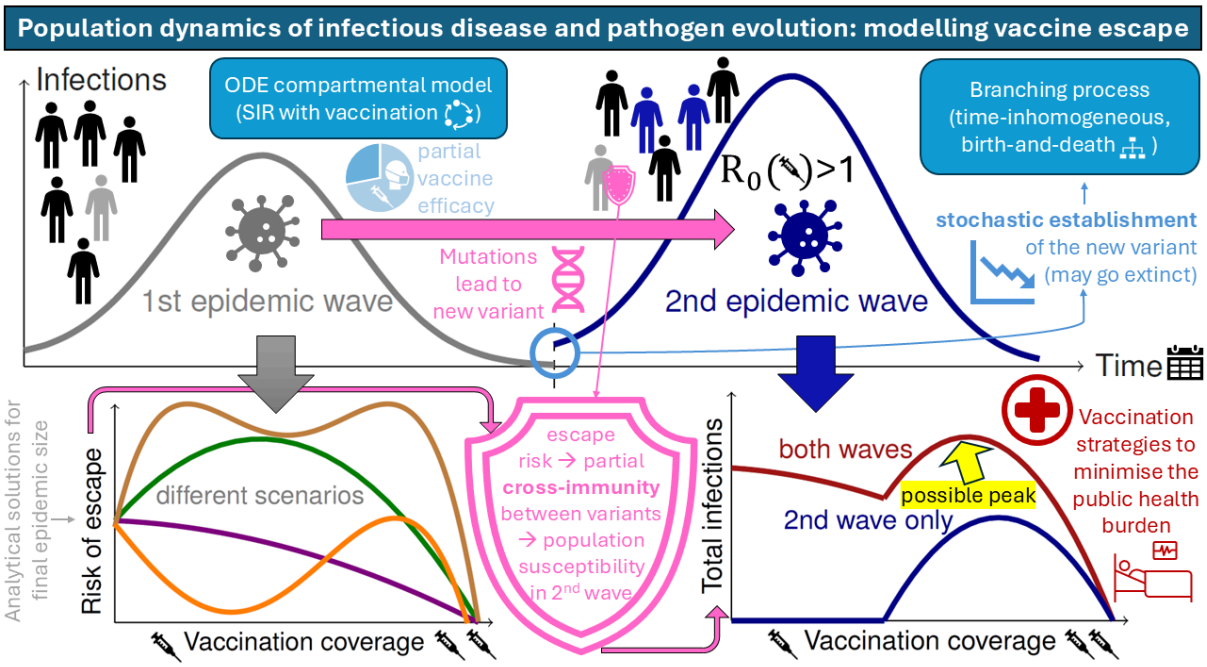
PhD thesis summary - M. A. Gutierrez



This thesis investigates **how the risk that an infectious pathogen evolves antigenically** (leading to pathogen strains that evade existing immunity) **depends on the vaccination coverage** of its host population. Deterministic compartmental models for epidemic dynamics are coupled with a parsimonious approach to pathogen evolution, capturing the selection pressure for immune escape. We study the qualitative patterns of this escape pressure—as a function of the vaccination coverage—and the epidemiological impact thereof, taking analytical approaches wherever possible.

Introduction

The ability to predict and control the spread of infectious diseases remains a great challenge for humanity. Fortunately, vaccination helps control many diseases. However, pathogen evolution can hinder controllability with vaccines or other interventions. For example, natural selection acting on pathogens sometimes produces new strains that escape existing immunity. These escape strains may increase the length and toll of an epidemic, because disease control—in terms of spreading and clinical outcomes—often relies on population immunity. Unfortunately, immunity itself can drive pathogen evolution towards immune escape. Hence, partial population immunity (induced by vaccination or infection) may be a double-edged sword for epidemic control.

Clinically safe vaccines are available against many pathogens. Most vaccines protect against severe symptoms of disease and often reduce host susceptibility or infectiousness, thus reducing disease prevalence. Notably, mass vaccination is responsible for the eradication of smallpox and the control of many childhood infections. The benefits of the initial COVID-19 vaccination campaigns were also immense. However, vaccine effectiveness may decrease due to pathogen evolution. Genetic mutations in SARS-CoV-2 (the

coronavirus that causes COVID-19) can lead to pathogen strains that evade vaccine-induced immunity, such as the Omicron variant. **Vaccine escape** also occurs in other viruses, including Influenza A and Hepatitis B, as well as in many bacteria. Some vaccine escape strains spread more easily in populations with high vaccination coverages. Moreover, vaccines themselves might facilitate the emergence of immune escape strains within individual hosts. Nonetheless, it is unclear how vaccination campaigns impact the overall risk of immune escape. This motivates the central question of this thesis: **how does the risk of immune escape during an epidemic depend on the vaccination coverage of the host population?**

Thesis aim and overview

This thesis aims to answer the following questions: In light of vaccine escape, under what circumstances are intermediate vaccination coverages the most risky (as suggested in the literature)? Which vaccination coverages are the least risky? More generally, how does the risk of vaccine escape depend on the vaccination coverage of the host population?

Chapters 2 to 4 show how different population and epidemiological factors affect the evolutionary pressure for vaccine escape (as a function of the vaccination coverage): **the escape pressure**. Chapters 5 and 6 instead consider the epidemiological impact of a mutant escape strain, weighted—through the escape pressure—by the risk that such an escape strain appears. Throughout the thesis, we derive population-level "phylodynamic" curves (similar to the adaptation rate in Grenfell *et al.* 2004, but in the context of vaccine escape) for the risk of immune escape as a function of the vaccination coverage. These curves describe **novel qualitative patterns** in the escape pressure. Many of these vaccine escape patterns reflect plausible scenarios in which intermediate vaccination coverages are *not* the worst option according to this approach (coupling evolution and epidemiology). Indeed, we find that, in some circumstances, intermediate vaccination coverages are the best strategy to minimise the risk and overall impact of vaccine escape. These findings contrast strongly with the results of other vaccine escape studies, which generally use narrower assumptions. Although this work is purely theoretical, SARS-CoV-2 and Influenza A motivate the research questions and methodological assumptions of this thesis.

Chapter 2: Basic model

*Summary: Chapter 2 varies the balance of the contributions to the escape pressure from infections in **unvaccinated and vaccinated hosts**. We use SIR-type models, for endemic disease and a transient epidemic wave. If within-host adaptation is substantially stronger in vaccinees, we find that the escape pressure follows a **unimodal pattern**: intermediate vaccination levels pose the greatest risk of escape. Otherwise, vaccination reduces the escape pressure.*

This chapter shows how the vaccination coverage in a population affects the potential for the appearance of vaccine escape strains. We measure this risk of vaccine escape through an escape pressure function. The escape pressure is a linear combination of the infections in vaccinated and unvaccinated individuals. The relative weight in the escape pressure of vaccine breakthrough infections is the relative net pathogen adaptation rate within

vaccinees. We find that this relative adaptation rate determines the shape of the escape pressure as a function of the vaccination coverage.

There are two possible patterns. On the one hand, if vaccination substantially increases the net pathogen adaptation at the host level, the population-level escape pressure is a unimodal function of the vaccination coverage. Thus, intermediate vaccination coverages maximise the risk of escape. On the other hand, if the relative net adaptation rate in vaccinees is not too high, there is a new vaccine escape pattern at the population level: the escape pressure is a monotonically decreasing function of the vaccination coverage. In general, the escape pressure also depends on the vaccine efficacies against infection and transmission, since a reduction in infections limits the opportunities for the pathogens to mutate.

Chapter 3: Population heterogeneity

*Summary: Chapter 3 extends the approach of Chapter 2 to heterogeneous populations. We account for differences in the pathogen adaptation rate within host types, such as i**mmunocompromised individuals**. We find that this novel form of heterogeneity may qualitatively change how the escape pressure depends on the vaccination coverage. In particular, for some parameters, the escape pressure has a **bimodal pattern**. We also analyse strategies for vaccine prioritisation.*

This chapter explores vaccine escape in heterogeneous populations, generalising the escape pressure of Chapter 2. We allow for infections in different host types to have different weights (which represent the rates of pathogen adaptation within each host type) in the escape pressure. We find that this new type of heterogeneity may lead to new qualitative patterns in the population-level escape pressure. We focus on a population split into mixers (with a higher contact rate) and immunocompromised/vulnerable hosts (with a higher pathogen adaptation rate), for which we study vaccine-prioritisation strategies.

If vaccination reduces the pathogen adaptation rate within each host, we find that vaccinating first the vulnerable minimises the escape pressure. For other parameter values, vaccinating first the hosts with more contacts—and, later, the vulnerable—minimises the escape pressure. With this mixers-first vaccination strategy, the escape pressure may be *lowest* at intermediate vaccination levels (e.g., with a bimodal pattern or a U-shape). With a vulnerable-first strategy, the escape pressure is always decreasing or unimodal. However, the vulnerable-first strategy is not always optimal to minimise the disease burden.

Chapter 4: Reinfections

*Summary: Chapter 4 extends the approach of Chapter 2 to account for a different pathogen adaptation rate during reinfections in **recovered hosts**. We derive the final size of an epidemic in which infections induce partial protection against reinfection. If vaccines induce stronger protection than past infections, we identify a new pattern: **vaccination always reduces the escape pressure**, regardless of the adaptation rate in hosts with prior immunity (acquired from infection, vaccination, or both).*

This chapter explores how vaccination affects the risk of antigenic escape during an epidemic of a pathogen capable of reinfecting hosts, generalising the escape pressure of Chapter 2. Obtaining final-size expressions of SIRI-type models, we study how the escape pressure depends on the relative net pathogen adaptation rate in hosts with prior immunity, the vaccination coverage of the population, and the partial immunity against infection. We allow vaccines and infections to induce different levels of protection.

If vaccines are not as protective as past infections, intermediate vaccination coverages can maximise the escape pressure. This unimodal pattern occurs if infections in partially immune hosts contribute sufficiently more to the escape pressure than infections in immunologically naïve hosts. However, a new pattern appears if vaccines protect against infection at least as much as a past infection: vaccination always reduces the escape pressure. With such effective vaccines, the escape pressure is a decreasing function of the vaccination level, regardless of the net adaptation rate in hosts with prior immunity.

Chapter 5: Stochastic establishment

Summary: Chapter 5 extends the deterministic escape pressure of Chapter 2 to consider the stochastic establishment of emerging immune escape strains. Using a ***time-inhomogeneous branching process****, we find that interference with the wildtype strain may substantially hinder the establishment probability of new strains, especially those emerging at late times. As a result, we find that new qualitative patterns appear in the escape pressure. Depending on the cross-reactivity of existing immunity,* ***intermediate vaccination coverages may lead to the lowest escape pressure****.*

This chapter shows how the vaccination coverage affects the overall potential for the appearance and stochastic establishment of immune escape strains. New infections with the wildtype strain reduce the pool of hosts susceptible to the mutant, thus decreasing its establishment probability. The partial cross-immunity between the strains determines the magnitude of this effect. In general, the overall escape pressure for the appearance *and* establishment of an escape strain has its maximum shortly before the peak prevalence of the wildtype strain.

We find that the vaccination coverage may affect the escape pressure through new qualitative patterns. If cross-immunity between strains is strong, mutant establishment is impossible, or only possible with high vaccination coverages in the population. With intermediate cross-immunity, mutant emergence—both appearance and establishment—is less likely at intermediate vaccination coverages. With weak cross-immunity, the overall escape pressure is a decreasing or unimodal function of the vaccination level (depending on the relative net pathogen adaptation within vaccinees, as in Chapter 2).

Chapter 6: Successive epidemic waves

Summary: Bringing together the preceding chapters, Chapter 6 balances the risks of vaccine escape with the ***epidemiological benefits of vaccination****. Here the escape pressure of Chapter 2 determines the cross-reactivity of existing immunity to an emerging strain, which*

*may cause a new, non-overlapping, epidemic wave. For this **second epidemic**, we again use a deterministic model. We find that it is theoretically possible for the **overall public health burden** to be highest at intermediate vaccination coverages, but only if the relative adaptation rate in vaccinees is very high. Otherwise, vaccination reduces the overall public health burden.*

This chapter shows how vaccination can have important indirect epidemiological consequences, through a second epidemic wave of a mutant escape strain. We assume that the escape pressure accumulated during the epidemic of a wildtype strain determines the cross-immunity of the mutant strain: the higher the escape pressure, the lower the cross-immunity. Intermediate vaccination coverages may increase the escape pressure (see Chapter 2). Thus, vaccination may reduce strain cross-immunity and allow the spread of the mutant strain. However, the net effect of vaccination is multifaceted, because vaccines reduce transmission of both strains (both through strain-specific and broad immunity).

Assuming (i) that the mutant outbreak begins after eradication of the wildtype and (ii) that wildtype infections elicit the same immune response against the mutant strain as vaccines, we find that it is theoretically possible for the overall incidence—of both strains combined—to be maximal at an intermediate vaccination coverage. However, this situation only occurs for a narrow range of parameter values. If the relative net adaptation rate in vaccinees is not very high or the rate of antigenic drift is either sufficiently low or sufficiently high, vaccination always reduces the overall public health burden.

Conclusion

This thesis has studied how the risk of antigenic escape depends on the vaccination coverage of the host population. We have shown that the overall selection pressure for escape is not always a unimodal function of the vaccination coverage. More generally, these results reveal **novel patterns for vaccine escape**: new shapes in a kind of population-level phylodynamic curve.

We find that **heterogeneities in the net pathogen within-host adaptation rate** across different types of infectees are key in shaping the escape pressure. Thus, it would be valuable to improve current understandings of how within-host escape evolution depends on host immune status (e.g., vaccinated, immunocompromised, recovered). We also identify other factors as important determinants of the patterns of vaccine escape: heterogeneous population structures (such as hosts with different contact rates) and the vaccination order of the population groups, the strength of vaccine-induced immunity (especially in comparison to infection-induced immunity), as well as the strain cross-immunity (which may cause—through susceptible depletion and stochastic effects—the loss of emerging strains).

This thesis also studied the epidemiological **impact of vaccine escape**. We have determined the balance between the immediate epidemiological benefits of vaccination and its potential unintended consequences due to pathogen evolution. Based on these results, we cannot rule out the possibility that, under certain conditions, some partial vaccination coverages may increase the overall public health burden.