Over 1.5 billion people are infected with parasitic helminths. For some hosts, the association with helminths is brief, as worms are quickly expelled; for others, the association is chronic, lasting months to years**.** Such variation in duration is observed for many infectious diseases, and has implications for individual and public health: duration is a key determinant of both the cumulative health cost of infection and the risk of onward transmission. **Despite these profound individual- and population-scale impacts, the within-host processes that drive infection duration are insufficiently known.**

For example, scientists do not fully understand the host-parasite interplays that drive the immune system (in the case of helminth infection) towards a clearance-promoting T-helper type 2 (Th2) immune response rather than a chronicity-promoting T-helper type 1 (Th1) or regulatory T cell response. **Genetic and environmental factors affect the immunological outcome, but their relative impacts are unknown, especially under natural environmental conditions.** We’ve shown that immune responses and duration of infection in mice kept outdoors differs qualitatively from those of siblings back in the lab, with rewilded mice showing higher Th1 activation, lower Th2 activation, and slower worm expulsion. We propose that by unpacking the **intricate, reciprocal ecological interactions between immune cells and parasites**, across host genotypes, among individuals of a given genotype, and across environments, we will be able to identify the processes that generate such variation in the rate at which worms are expelled.

We will deploy powerful mouse models from immunoparasitology in naturalized environments throughout this project. Drawing on theory from population ecology, we hypothesize that variation in the relative strengths of negative and positive within-host feedback loops drives variation in infection duration by generating ecological **Allee effects**, such that even subtle variation in parasite dose or the immune activation rate can lead to widely different infection durations. To test this, we will quantify within-host dynamics by integrating mathematical models with experimental manipulations of host genetics, immune response induction, and environment in the tractable system of laboratory mice (*Mus musculus)* infected by gastrointestinal nematodes *(Trichuris muris*). We will pursue the following Aims:

**Aim 1. Quantify the relative strength of chronicity- and clearance-promoting feedback loops across host strains and test whether this explains the variable response to dose.** Inoculating dose offers a powerful experimental probe of immune response induction, as theory predicts that the response of duration to dose variation depends on the strength of the feedback loops. We will naturalize the microbiota of strains of mice that differ in nematode susceptibility to better match cellular immune phenotypes of wild mammals. We will inoculate them with varied doses of *T. muris* andgenerate multivariate data on within-host dynamics. We will fit the data to mechanistic mathematical models to test whether reciprocal feedbacks do generate dynamical Allee effect “tipping points” – or whether other within-host ecology explains varied expulsion rates.

**Aim 2: Experimentally manipulate rates of immune induction and effector impacts to alter the relative strength of feedback loops.** Again working with partially-naturalized mice, we will manipulate the rates of immune response induction using knockout mice deficient in Th2 signaling or effector function, as well as “trickle infections” in which parasites are inoculated at realistically slow rates. These manipulations directly alter the strength of Th1 and Th2 immune feedbacks, allowing us to further test and extend our mathematical framework to reveal how these feedbacks drive variation in infection duration.

**Aim 3: Embed host strain-by-parasite dose interactions in a more realistic natural environment by rewilding mice and quantifying effects upon immune feedbacks and duration of infection.** We will further naturalize key strains of mice by taking some of our experiments outdoors each year. Theory suggests multiple ways real world exposure could alter duration of infection, from weakening clearance-promoting feedback mechanisms to biasing the immune response towards Th1. We will expose the rewilded mice to variable doses of *T. muris* and use the mathematical model to test how the natural environment alters the immunological processes governing T helper cell polarization and thus infection duration outdoors.

We will thus elucidate dynamic within-host processes that drive varied infection duration across genotypes and environments, in a model system of relevance to global health – arguably an improved model of chronic helminthiasis due to naturalized environment. We will also generate testable hypotheses for other systems.