Antibiotic resistance is one of the largest global health challenges currently, and arises from interactions between antibiotic exposure, bacterial evolution, and genetic exchange within microbial communities. Resistance develops when bacteria gain mutations or resistance genes that allow them to survive antibiotic treatment. These traits can be spread through reproduction or horizontal gene transfer, enabling resistance to spread even when antibiotic pressure is reduced. Understanding the mechanism that drives this persistence is essential for predicting and controlling resistance dynamics.

Genetic Mechanisms: Antibiotics resistance arises through genetic changes that reduce or eliminate the effectiveness of antibiotics. These changes may occur through mutations or the acquisition of resistance genes from other bacteria. Once resistance genes are present, they can be spread through reproduction or horizontal gene transfer with other bacteria, allowing for resistance to spread rapidly in a bacterial population. These genetic mechanisms form the foundation upon which environmental and evolutionary pressures act, shaping resistance dynamics over time.

Antibiotic Use: Antibiotic overuse is one of the largest drivers of the evolution of resistance. Exposure to antibiotics creates strong selective pressure by inhibiting or killing susceptible bacteria while allowing resistant individuals to survive. Although mutations that lead to resistance often impose a fitness cost, these costs don't necessarily prevent resistant populations from persisting. Andersson and Hughes (2010) showed that compensatory evolution can offset fitness costs. Even without antibiotic use, bacteria can still gain resistance. Knoppel et al. (2017) found that after growing 500+ generations of E. coli and salmonella in four different growth medias without antibiotics, 3.5% of the bacteria gained mutations linked to resistance,

while only 0.6% became more susceptible to antibiotics, showing that resistance can arise and spread from anywhere, even areas that don't require it for survival.

Bacteriophages: In addition to antibiotic use, bacteriophages play a significant role in resistance dynamics. Bacteriophages are viruses that infect and kill bacteria for the purpose of reproduction. However, Calero-Caceres et al. (2019) demonstrated that phages can enable the movement of antibiotic resistance genes (ARGs) independently of antibiotic concentration. Because phages are abundant, environmentally persistent, and capable of long-term circulation in microbial ecosystems, they can sustain resistance even in environments with low antibiotic exposure. This persistence allows resistance genes to remain active in bacterial populations long after antibiotic pressure has decreased. Modeling and experimental studies further emphasize that phages are active drivers of resistance dynamics. A within-host model developed by Teytsa et al. (2024) shows that phage-bacteria interactions, particularly those involving lysogeny, strongly influence resistance persistence and bacterial survival thresholds. Their results highlight how prophage induction and phage absorption probabilities can determine whether resistant populations persist or collapse under antibiotic treatment. Environmental models also support how resistance doesn't necessarily arise from antibiotic use. Bechette et al. (2013) demonstrated that virus-bacteria dynamics in aquatic systems are strongly influenced by nutrient availability, suggesting that as long as there are sufficient nutrients, phage-mediated resistance gene transfer will persist.

Deterministic Modeling: Because antibiotic resistance arises from interacting biological and environmental processes, mathematical modeling provides a powerful framework for studying its dynamics. Deterministic models allow researchers to represent bacterial populations, antibiotic concentration, and genetic exchange processes in a quantitative way. For example,

Ibarguen-Mondragón et al. (2019) developed a system of ordinary differential equations to describe interactions between susceptible bacteria, resistant bacteria, plasmid concentration, and antibiotic concentration. Their analysis revealed multiple equilibrium states as well as oscillatory outcomes where bacterial populations wildly fluctuate, demonstrating that depending on initial conditions, resistance can be slowed or rapidly spread. These results are consistent with other deterministic modeling approaches that include additional biological processes. Bootsma et al. (2012) modeled non-inherited, physiological resistance by tracking intracellular antibiotic concentration and efflux pump regulation, showing that resistance can increase even in the absence of genetic mutation or horizontal gene transfer. Further complexity emerges when phage interactions are included.

Stochastic modeling: While deterministic models capture average system behavior, biological systems are inherently stochastic. Random events such as mutation, phage adsorption, infection, and gene transfer can substantially influence the trajectory of resistance populations, particularly in small populations. Merdan et al. (2017) found that stochastic resistance models produced more variable (sometimes up to 22.9% variance) and realistic outcomes than corresponding deterministic models. Similarly, Bogdanov et al. (2022) showed that stochastic branching-process models capture wide variability in bacterial survival under identical initial conditions, suggesting that chance events can determine whether resistance emerges or fails to establish.

Together, these studies show that antibiotic resistance emerges from the combined effects of selective pressure, physiological adaptation, and phage-mediated genetic exchange. While antibiotic concentration may initiate resistance, phage persistence, compensatory evolution, lysogeny, and randomness allow resistant populations to spread even as antibiotic usage

decreases. This project aims to model how antibiotics and bacteriophages jointly shape resistance dynamics. By integrating deterministic and stochastic approaches and incorporating phage-mediated processes, the project seeks to identify conditions under which resistance is amplified or suppressed and to inform strategies for limiting its spread.