AMR project:

The emergence of antimicrobial resistance (AMR) is a complex phenomenon which has several causes including human behaviour at many levels of society. Its consequences are affecting everybody in the world and all experts expect the problem to become worse in the coming 20 or 30 years. Efforts have been made to understand all potential causes of antibiotic resistance and to devise new interventions needed to delay if not solve the risk of running out of effective antibiotics [1]. Antibiotics were instrumental for the development of modern medicine and still are a crucial component of modern healthcare [2]. Major surgeries, organ transplantations, and cancer chemotherapy, would not be possible without effective treatment for bacterial infections. In fact, it is not surprising that the issue of AMR has its hotspot in nosocomial care, especially in intensive care units (ICU) where the spread of resistant bacteria is a major issue. AMR develops when a micro-organism (bacteria, fungus, virus or parasite) is no longer susceptible to a drug to which it was originally susceptible. This means that standard treatments become ineffective; infections are more difficult or impossible to treat; the risk of the spread of infection to others is increased; illness and hospital stays are prolonged, with added economic and social burden; and the risk of death is greater—in some cases, twice that of patients who have infections caused by susceptible bacteria.

Increased awareness about resistant microorganisms is propelled by the increasing prevalence of extensively drug-resistant tuberculosis, recent reports about AMR in common bacteria such as Neisseria gonorrhoeae (the cause of gonorrhea), and the rise of so-called “superbugs”, bacteria that are circulating in hospitals around the world, which have become resistant to all available antimicrobial drugs.

Estimates have indicated that by 2050, 10 million lives a year and a cumulative 100 trillion USD of economic output may be at risk due to the rise of drug-resistant infections if we do not find solutions to slow down the rise of drug resistance proactively and immediately. Even today 700,000 people die of drug resistant infections every year. Most of the direct and much of the indirect impact of AMR falls on low and middle-income countries [3].

**PROJECT 1**

The first project aims at studying the emergence and spread of AMR as an eco-evolutionary process, in which bacteria with genes resistant to the actions of antimicrobial drugs are selected by the antibiotic usage. In this project you will develop a simple computer simulation model to evaluate the impact of resistance management strategies on the spread of AMR in different countries. An important factor that may be playing a central role in recent patterns of AMR spread is the naturally high prevalence of mix-infection in human populations [1,2]. Potentially this may be leading to the spread AMR as a secondary effect, in pathogens that were not the original target of treatment. This is particularly relevant in cases of: i) antigenically diverse pathogens, like **gonorrhoeae** [3], which characteristically create reservoirs of asymptomatic infection in the human population [4]; ii) cases of “competitive release” between coinfection pathogens where the burden of one infectious agent is suppressed in the presence of the other [2,5], and iii), horizontal gene transfer between bacteria of different species which enables AMR to emerge even in bacteria that are not directly treated with a specific antibiotic [6].

**Background**

There is growing awareness that infections frequently consist not of one, but rather of multiple pathogen genomes of different pathogen species and multiple strains of the same species. This phenomenon is prevalent in all disease-causing protozoa, helminths, bacteria, fungi, and viruses [1][2]. There is growing concern on how mixed-infections may be impacting the spread of drug resistance. From an evolutionary perspective, the stronger the strength of selection through drug use, the more rapid is the spread of resistance. Hence, aggressive use of **broad-spectrum antibiotics**, for example, is likely to introduce selection that favors resistance not only on the infectious agent causing clinical manifestations, but also on other co-infecting pathogens sensitive to these antimicrobials. Indeed, it is common to find many infectious agents in an **asymptomatic** state, i.e., where the person carrying them experiences no clinical symptoms and has no awareness of their presence. This is characteristic for antigenically diverse pathogens, such as **gonorrhoeae,** where people may be carriers but show no symptoms [4]. This is also a common phenomenon of mixed infections in general, where the burden of one infectious agent may be suppressed because of direct or indirect interactions with another co-infecting agents, leading to alterations in human pathology, pathogen transmission and virulence evolution. The phenomenon of mixed-infection therefore may be a key factor in the accelerating spread of antimicrobial resistance. **An understanding of eco-evolutionary processes could greatly benefit clinical medicine and public health policies**. To address this requires combined consideration of both within host as well as between host effects.

Broadly speaking, this inevitably raises question on what are the most suable **resistance management strategies** in light of mixed-infections? It has been argued for example that the policy of “aggressive chemotherapy” may be a double-edged sword for resistance management [4]. On the one hand, aggressive chemotherapy reduces the chances of the *de novo* formation of high-level resistance; yet aggressive chemotherapy also provides a significant evolutionary advantage to infections that already contain resistant parasites. It is very likely that effectible resistance management protocols will need to be tailored to particular drug-pathogen combinations in specific epidemiological conditions, and that patient treatment regimens may also need to be modified as resistance evolution proceeds. In this project students will:

1. Carry our data analysis to test for signatures of secondary effect of antimicrobial resistance.
2. Construct a computer simulation model to explore resistance management strategies.

References:  
[1] Balmer and Tanner, *Lancet Infect Dis*, 2011. Prevalence and implications of multiple-strain infections

[2] Cox, *Parasitology*, 1999. Concomitant infections, parasites and immune responses

[3] Harris et al, *Lancet Infect Dis*, 2018. Public health surveillance of multidrug-resistant clones of Neisseria gonorrhoeae in Europe- a genomic survey

[4] Chan et al, *Med Health R I,* 2013. Recommendations For the Diagnosis of Neisseria gonorrhoeae and Chlamydia trachomatis, Including Extra-Genital Sites

[5] Read, Day and Huijben, *PNAS*, 2011. The evolution of drug resistance and the curious orthodoxy of aggressive chemotherapy

[6] Wintersdorff et al, *Frontiers Microbiology*, 2016. Dissemination of Antimicrobial Resistance in Microbial Ecosystems through Horizontal Gene Transfer

Resources:

Data about antibiotic usage and antibiotic resistance is available [R1].

**PROJECT2:**

AMR in Gonorrhoea infections.

*Neisseria gonorrhoeae* is a sexually transmitted bacterium that developed resistance to all antibiotic classes that have been used for its treatment. As a result, strains resistant to multiple antibiotic classes are now being transmitted in two host populations: heterosexual men (HetM) and men who have sex with men (MSM). In many countries there is only one antibiotic remaining for *N. gonorrhoeae* treatment and strategies to manage its administration are necessary to prevent or at least slow down resistance spread. For this reason it is essential to understand the dynamics and drivers of resistance spread to provide insights for devising optimal antibiotic management strategies.

A recently published mathematical model indicates that the spread of resistant strains are mainly driven by antibiotic usage [5]. The spread of *N. gonorrhoeae* has also been modeled using a stochastic network simulations [6]. Aim of this project is to implement the emergence and spread of resistant strains in a sexual contacts network and compare the results with those of the mathematical model.

References

1. R. Laxminarayan et al., *Antibiotic resistance—the need for global solutions*, The Lancet Infectious Diseases, Volume 13, Issue 12, December 2013, Pages 1057-1098
2. 2. R. Bentley, J.W. Bennett, *What Is an Antibiotic? Revisited*, Advances in Applied Microbiology, Volume 52, 2003, Pages 303-331
3. The Review on Antimicrobial Resistance Chaired by Jim O’Neill, *Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations*, [LINK](#https://amr-review.org/sites/default/files/AMR%2520Review%2520Paper%2520-%2520Tackling%2520a%2520crisis%2520for%2520the%2520health%2520and%2520wealth%2520of%2520nations_1.pdf)
4. J. Bengtsson-Palme et al., *Environmental factors influencing the development and spread of antibiotic resistance*, FEMS Microbiology Reviews, Volume 42, Issue 1, 1 January 2018
5. S.M. Fingerhuth et al, *Antibiotic-Resistant Neisseria gonorrhoeae Spread Faster with More Treatment, Not More Sexual Partners*, PLoS Pathog 12(5): e1005611.
6. M. Kretzschmar et al., *Modeling Prevention Strategies for Gonorrhea and Chlamydia Using Stochastic Network Simulations*, Am J Epidemiol 1996;144:306-17

Resources:   
R1. <https://resistancemap.cddep.org/> (Data on antibiotic resistance and usage 2000-2015)