RESIST2 :

Within-Host

The complex interactions between different species of bacteria, antibiotics and bacterial viruses within humans cannot be disentangled using lab data alone. What are the within-host dynamics before and during antibiotic exposure? What do we know about the dynamics of resistance movement and survival in these complex microbiomes that should inform mathematical models?

Modelling to reveal the joint effect of bacteriophages and antibiotics on AMR evolution

[Quentin Leclerc, PhD student, LSHTM]

Mathematical modelling can be used to look at AMR evolution, specifically the dynamics between bacteriophages and antibiotics.

- Bacteriophage ("phage") are bacterial viruses that can destroy bacteria but also spread resistance genes by a process called transduction
- Phage often present alongside antibiotics in environment and during phage therapy
- Varying reports of synergism/antagonism between phage and antibiotics
- Risk for transduction to create multidrug-resistant bacteria, then selected for by antibiotics
- Problem: conflicted evidence on interaction between phage and antibiotics, unknown consequences of transduction

Using mathematical modelling to infer dynamics
Multidrug resistant bacteria are being generated by transduction and then selected for by the antibiotics. These multiple processes can be explored in a model to capture AMR evolution.

Combining mathematical modelling and lab work

The role of modelling in this work and the use for policy.
- Lab work is essential, but can't tell the whole story
- Phage are powerful alternative to antibiotics but may increase AMR
- Mathematical modelling is a powerful tool to reveal the invisible

Within-population dynamics of (multi-)resistance evolution

[Danna R Gifford, Independent Research Fellow
MERMan Group, The University of Manchester]

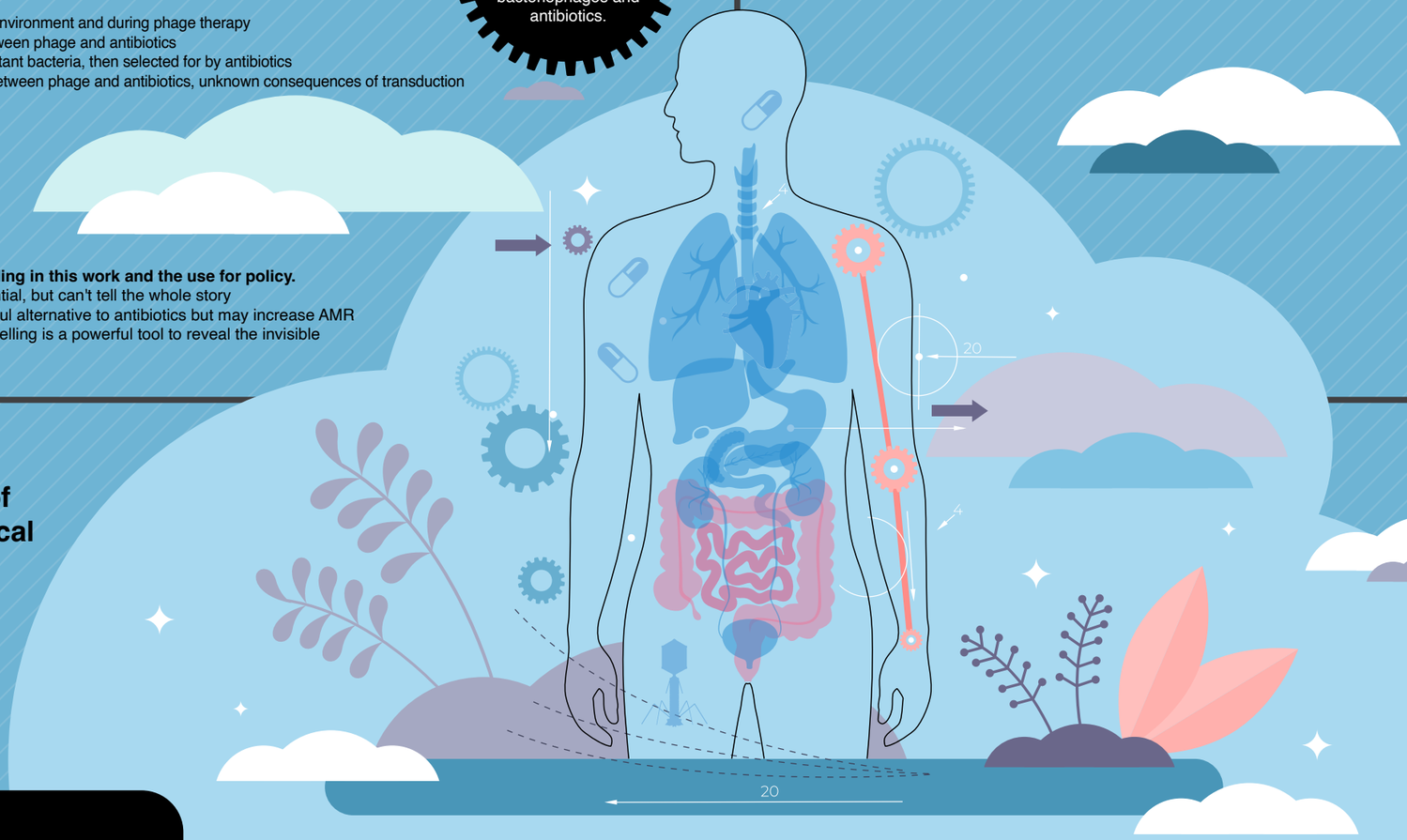
An experimental evolution technique was carried out in the lab to see if combinations of antibiotics are likely to suppress the evolution of resistance. Under some conditions involving high mutation rates, we do see multidrug resistance evolution occur. We can then use simple Lotka-Volterra models + mutations to predict resistance evolution within bacterial populations.

What do we know about the dynamics of resistance movement and survival in these complex microbiomes that should inform **mathematical models?**

What are the within-host dynamics before and during antibiotic exposure?

Key Challenges & Future Perspectives:

- AMR evolution is a multi-scale modelling problem, but what scales do resistance metacommunities operate on?
- How do organisms / populations / communities 'evolve' in situ?
- What parameters are important for resistance evolution? Rates of migration, mutation, horizontal gene transfer, fitness effects of resistance mutations
- How can we estimate relevant parameters under relevant conditions?



How do microbiome pathogen interactions drive the spread of resistance at the epidemiological level?

[David Smith, PhD, Institut Pasteur]

The within-host microbiome is a complex ecosystem of bacteria that acts as a reservoir for potential pathogens

Microbiome dysbiosis

After stable ecosystems undergo some sort of catastrophic event, there is typically a period of transient succession before that ecosystem regains stability. The common finding is that with increased biodiversity, we have increased resilience of these ecosystems. We see something similar with the gut microbiome - **Antibiotic Induced Microbiome dysbiosis** - which is increasingly recognised as a motivation for intervention, such as antibiotic stewardship, probiotics, and microbiome recovery therapy.

Modelling: How does dysbiosis affect epidemiological parameters of resistant bacteria (within-host growth, transmission rate, colonisation duration)?

Does dysbiosis affect the patient's risk of acquiring, carrying or spreading resistance? **We need more longitudinal data linking antibiotics to microbiome dysbiosis** and measures of dysbiosis like ecological diversity to subsequent colonisation risk. In order to be able to infer the strength of these microbiome pathogen interactions that seem to have a significant impact on the potential efficacy of control interventions.

Key Challenges & Future Perspectives:

- Lack of data and parameterisation - We don't often have enough data to actually make reliable predictions from our model
- Integrating infection models with immune response models
- Combination therapy development (inc. resistance minimisation)
- Understanding heterogeneity in infections

Infection modelling: countering resistance and virulence during infection

[Sara Jabbari, Reader in Mathematical Biology, University of Birmingham]

Three examples of **mathematical modelling** of infection processes:

1
Understanding Efflux
- Boolean modelling and efflux regulation
Mathematical modelling can generate hypotheses about heterogeneous single cell behaviour in an infection, which can be important when thinking about the evolution of resistance. It can take just one cell for antibiotic resistance to occur in a population.

2
Modelling a generic antiviral drug
Using simulations to combine antibiotics and antivirulence drugs. Mathematical modelling can be used to effectively design combination treatment strategies.

3
Anti-adhesion Treatment
Microbeads coated with MAM7 protein can prevent bacteria from binding to host cells. Binding is the crucial first stage in an infection. So if you can inhibit that, you can inhibit an infection. Mathematical modelling can be used for effective treatment design. But we need effective data to be able to work out which scenario we're in so that we can actually work out where/how we can improve those treatments.