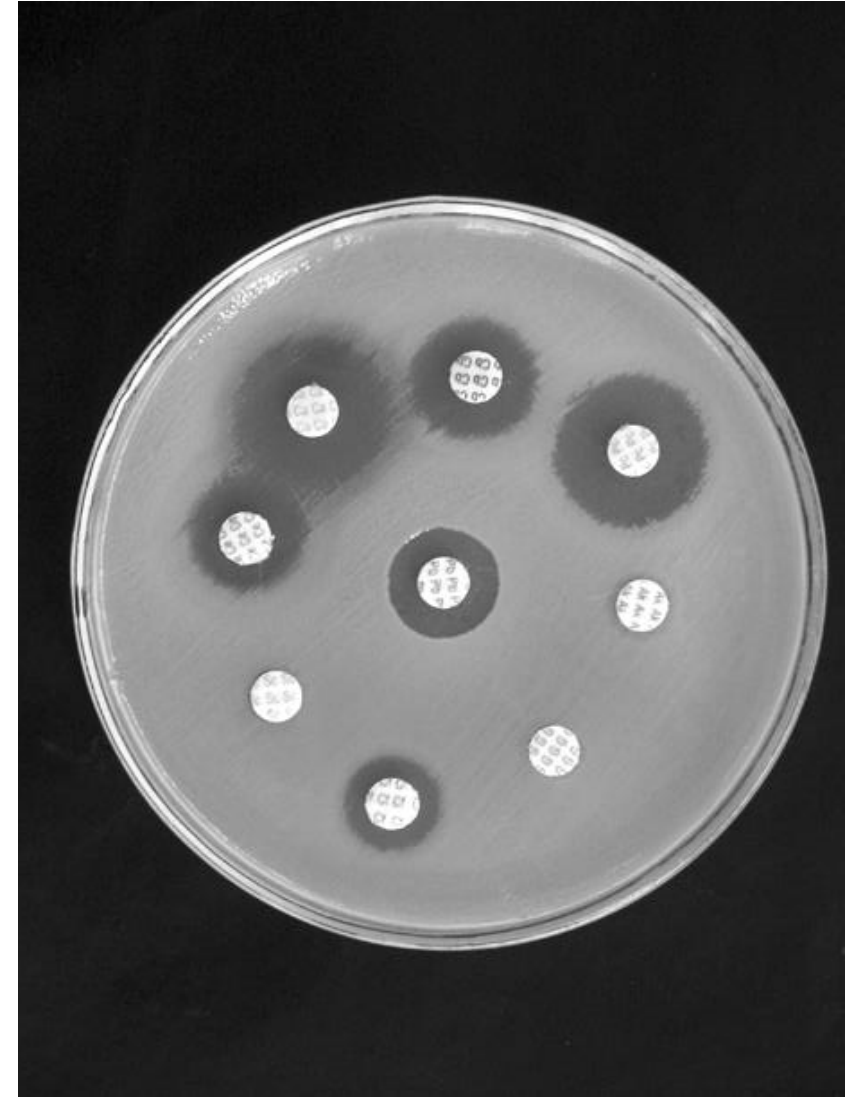


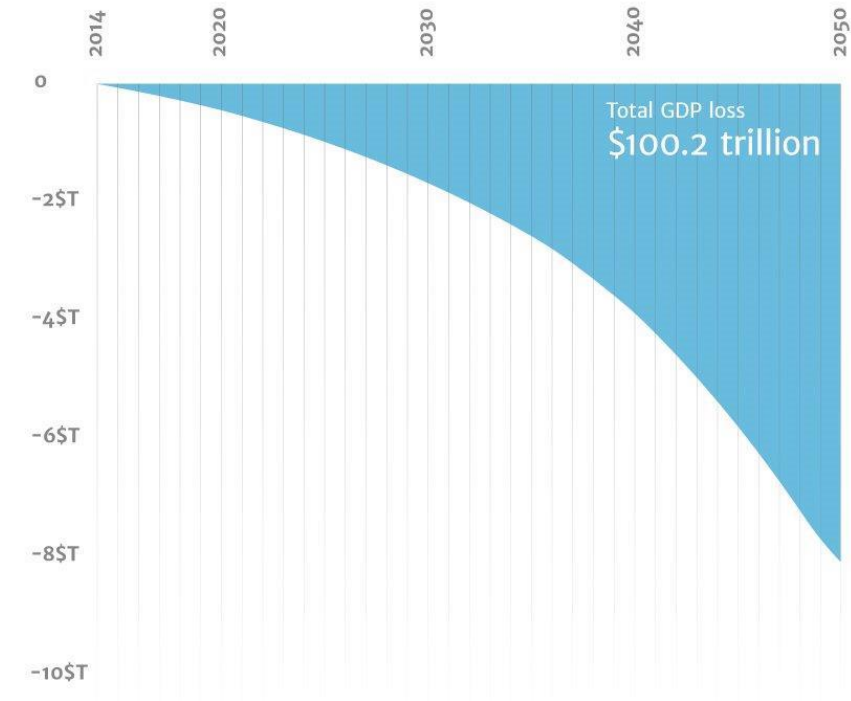
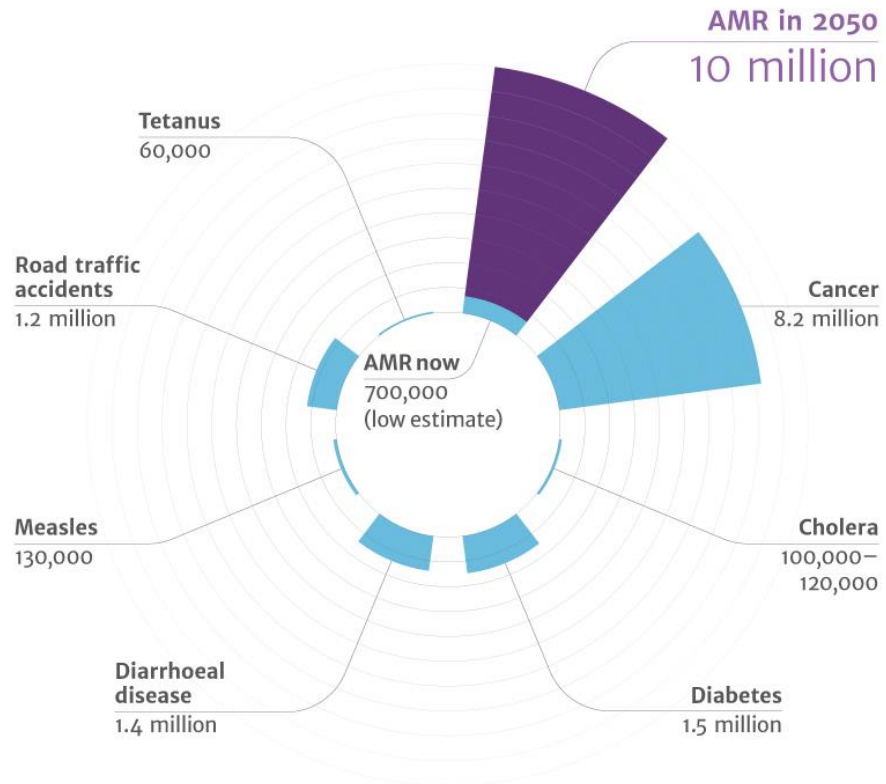
CRISPR-Cas: A Novel Solution to Antimicrobial Resistance in Agriculture

Joss Lazenby

- Antimicrobial resistance (AMR) is the evolution of microorganisms to survive exposure to previously effective compounds
- Drug-resistant pathogens are already estimated to cause 700,000 deaths a year
- Antibiotic resistance is especially concerning as certain bacterial pathogens approach pan-drug-resistance
- The continued rise of antibiotic resistance is potentially the biggest public health challenge of the 21st century

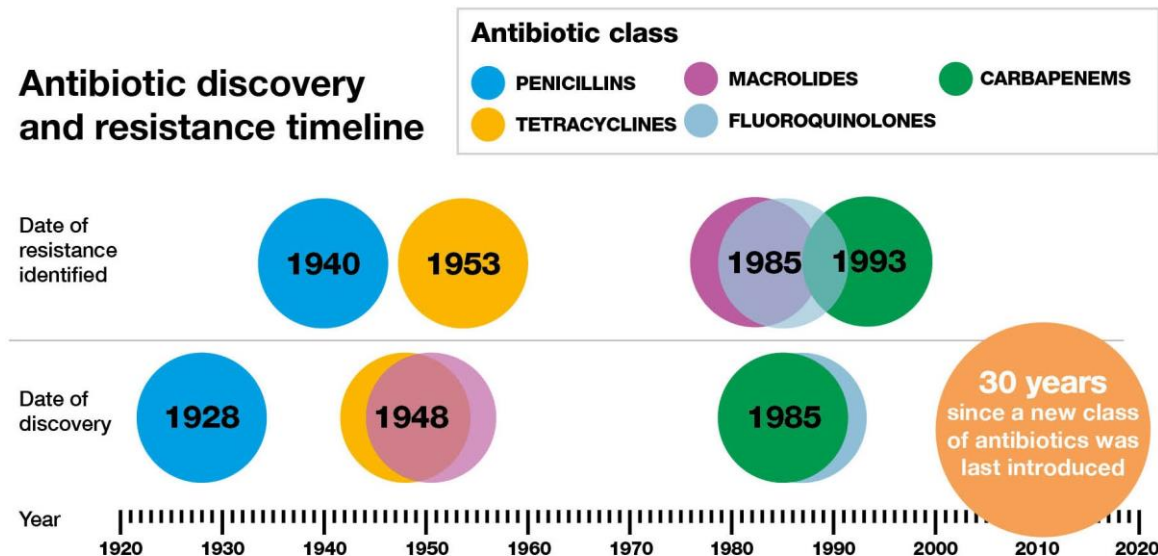


AMR: Global Impact



The antibiotic pipeline has run dry

- Despite urgent need for new treatments, the antibiotic pipeline has run dry
 - The last antibiotic class to enter clinical use did so more than 30 years ago
- Some hospital acquired infections have become exceptionally difficult to treat, such as MRSA



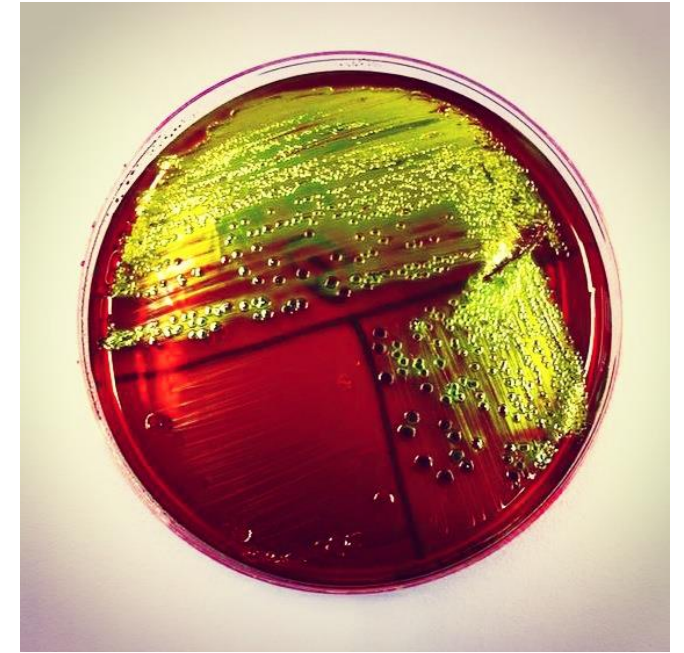
AMR is a One Health crisis

- Despite the importance of antibiotics in the clinic, the majority of produced antibiotics are used in agriculture
- They are used to treat infection amongst livestock, but in the past have also been used prophylactically or as growth promoters
- This usage has contributed to high levels of drug resistance in the microflora of food-producing animals



AMR in poultry farming

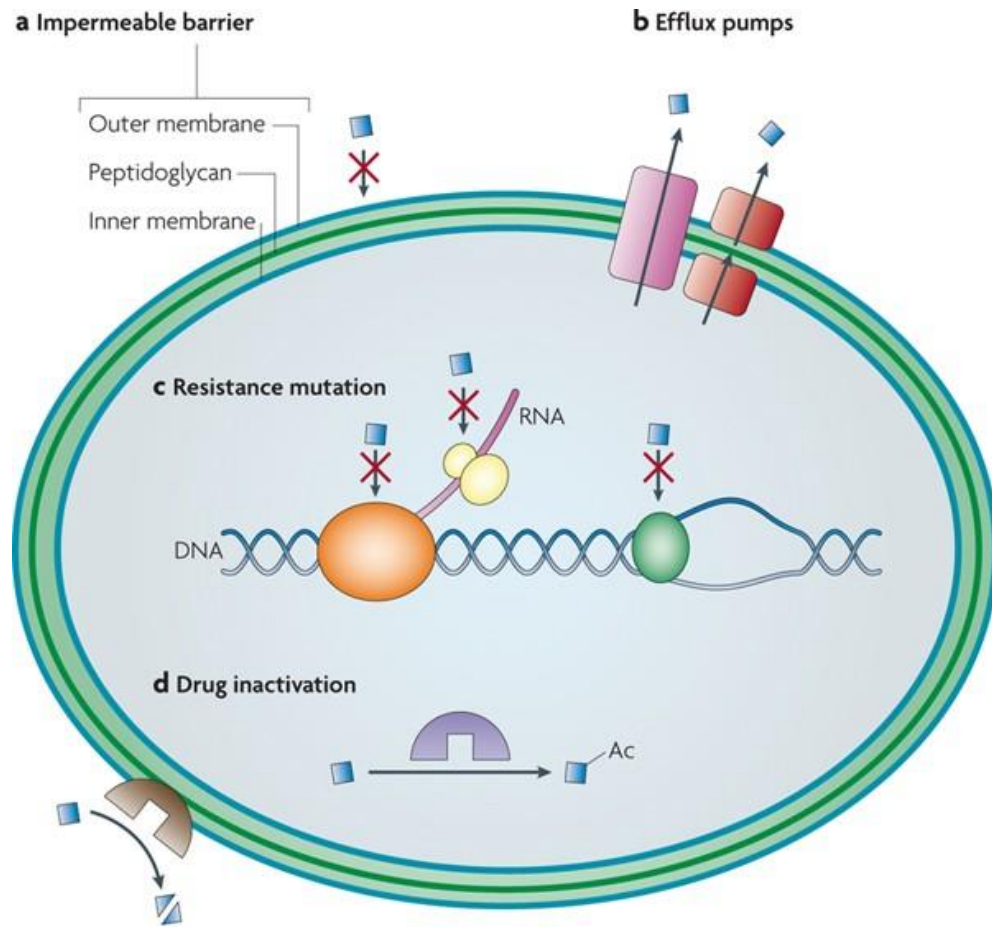
- AMR in the gut microbiota of food-producing is concerning
- Bacterial pathogens of chickens such as Avian Pathogenic *Escherichia coli* (APEC) are now widely resistant to antibiotics, limiting management options
- AMR may also transmit from animals to humans through foodborne pathogens such as *E. coli*, *Salmonella* or *Campylobacter*



Routes of AMR transmission

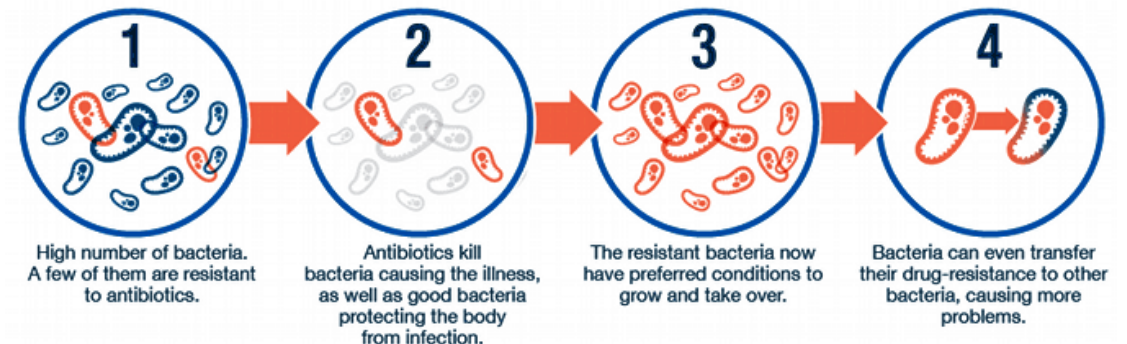


How do bacteria become resistant?



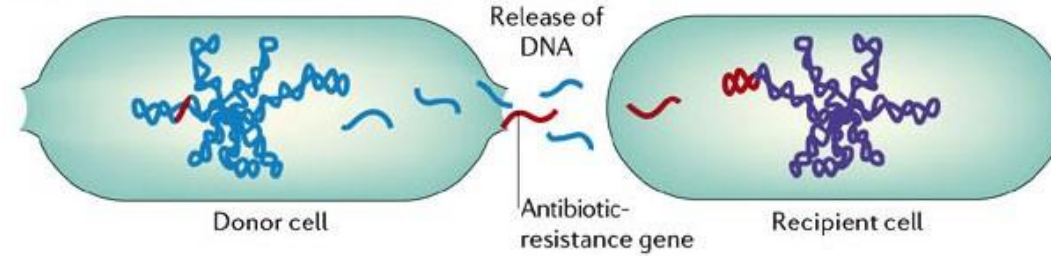
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How does antibiotic resistance occur?

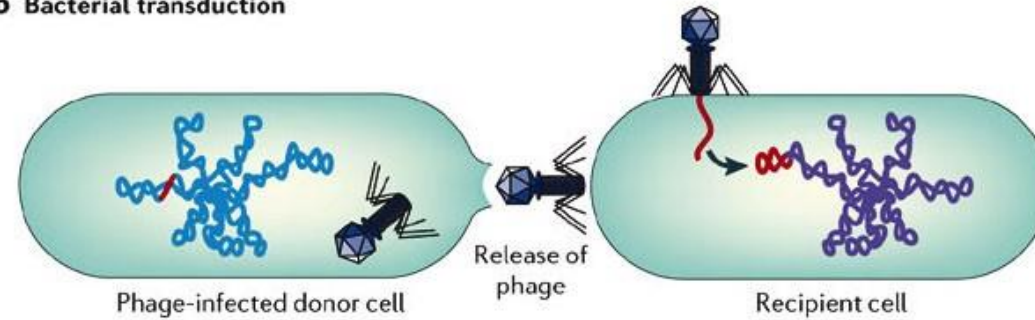


Horizontal Gene Transfer

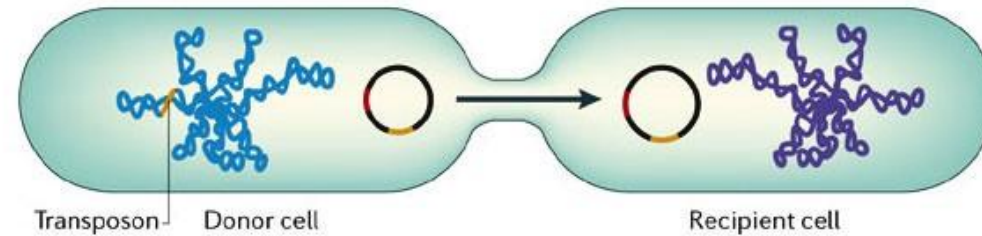
a Bacterial transformation



b Bacterial transduction



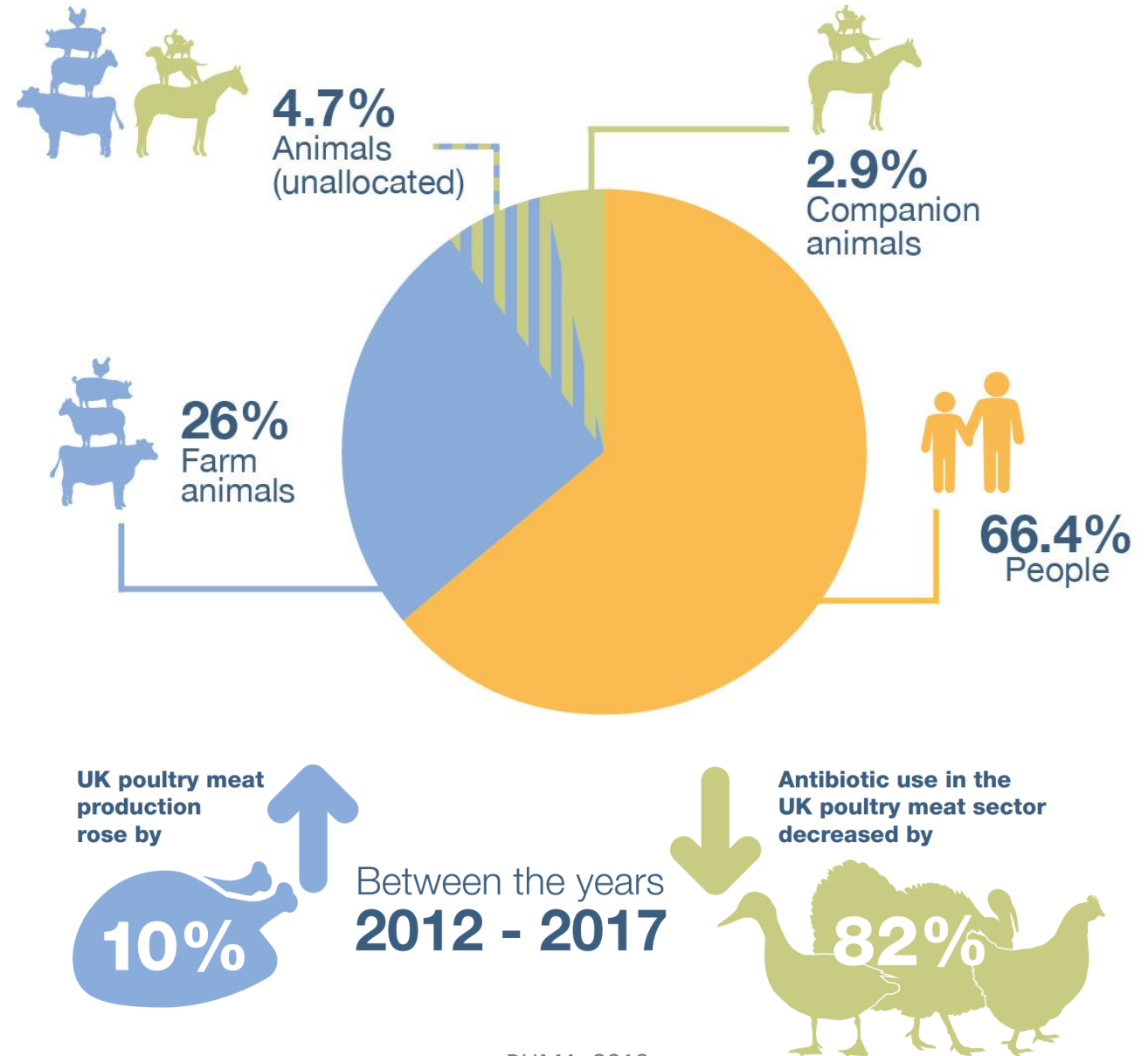
c Bacterial conjugation



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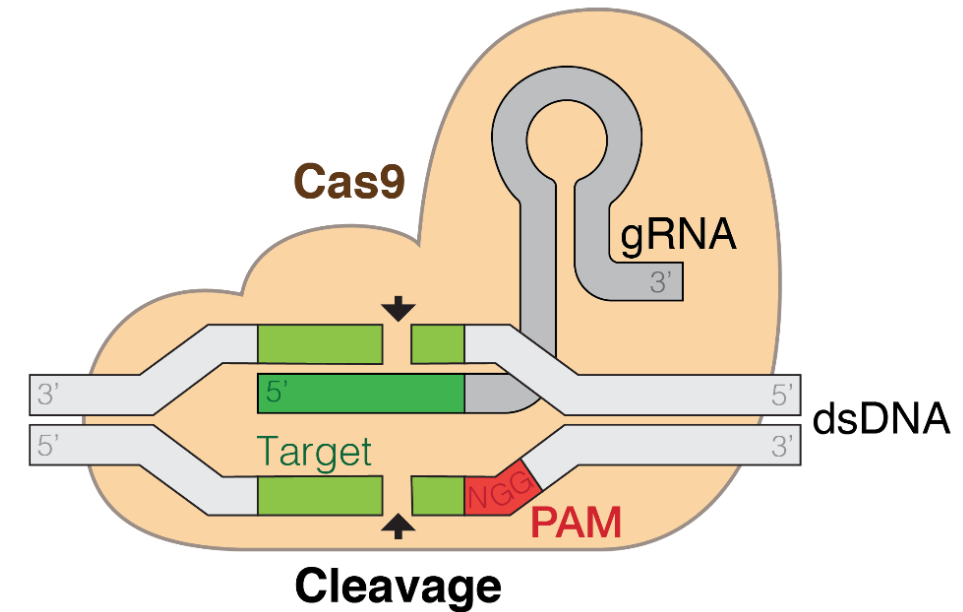
What is being done to combat AMR?

- Antibiotic stewardship programs have been implemented to prevent the spread of AMR
- In the UK, the poultry industry has nearly totally phased out the use of fluoroquinolones
- However, despite reduced use resistance persists in foodborne bacteria



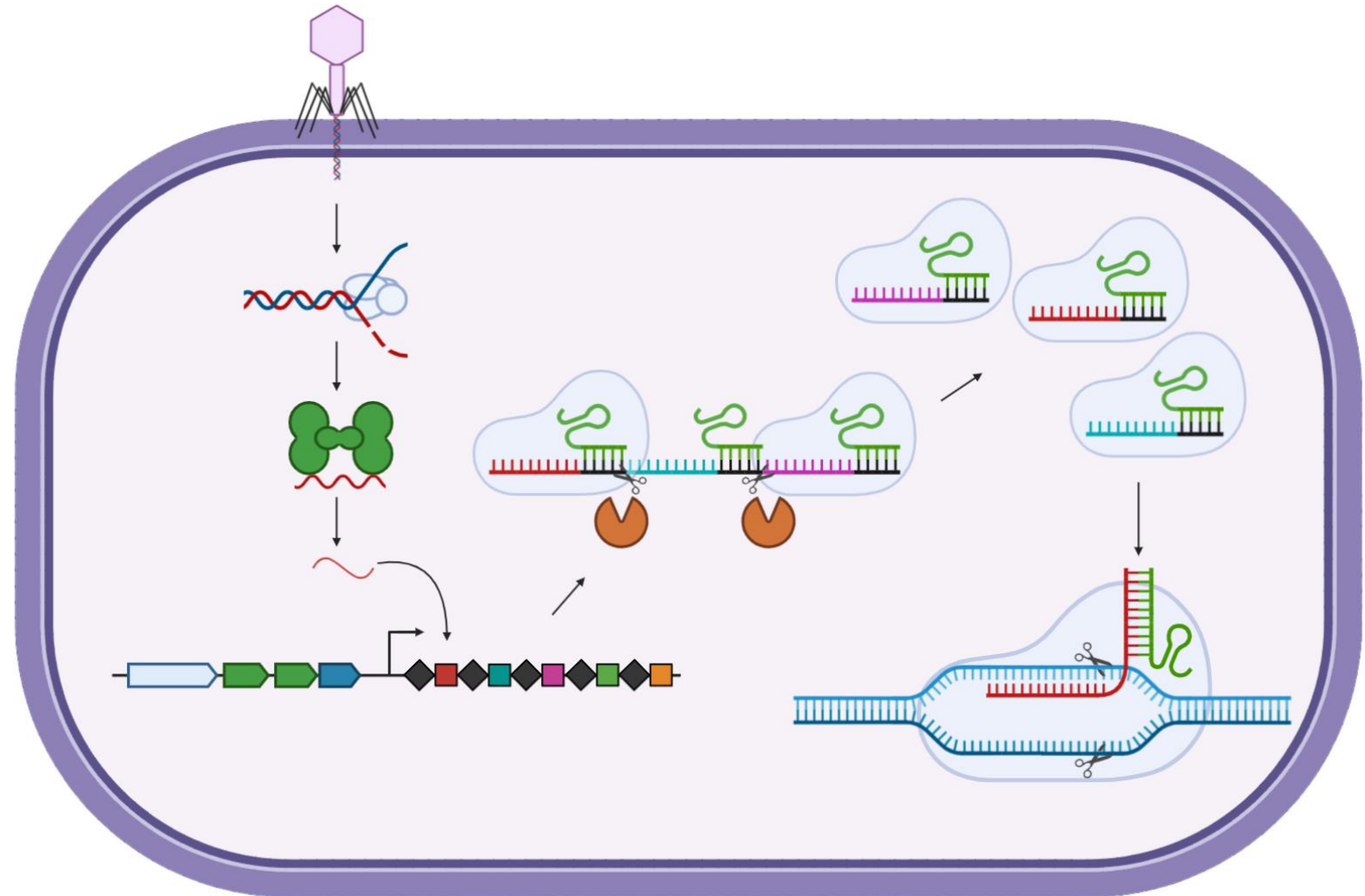
CRISPR-Cas9: a revolutionary technology

- CRISPR-Cas9 has become famous as a gene editing tool
- It has recently been utilised to cure the genetic disease beta-thalassemia in humans
- Using a guide RNA, complementary genomic DNA can be modified with very high accuracy
- The CRISPR-Cas9 systems used in biotechnology originate from *Streptococcus pyogenes*, where they function as an immune system against viruses



CRISPR-Cas: a bacterial immune system

- CRISPR-Cas is an adaptive immunity system in bacteria
- Invading DNA is recognised by Cas proteins and integrated into the CRISPR array
- Expressed CRISPR RNA complex with Cas proteins to cleave foreign DNA



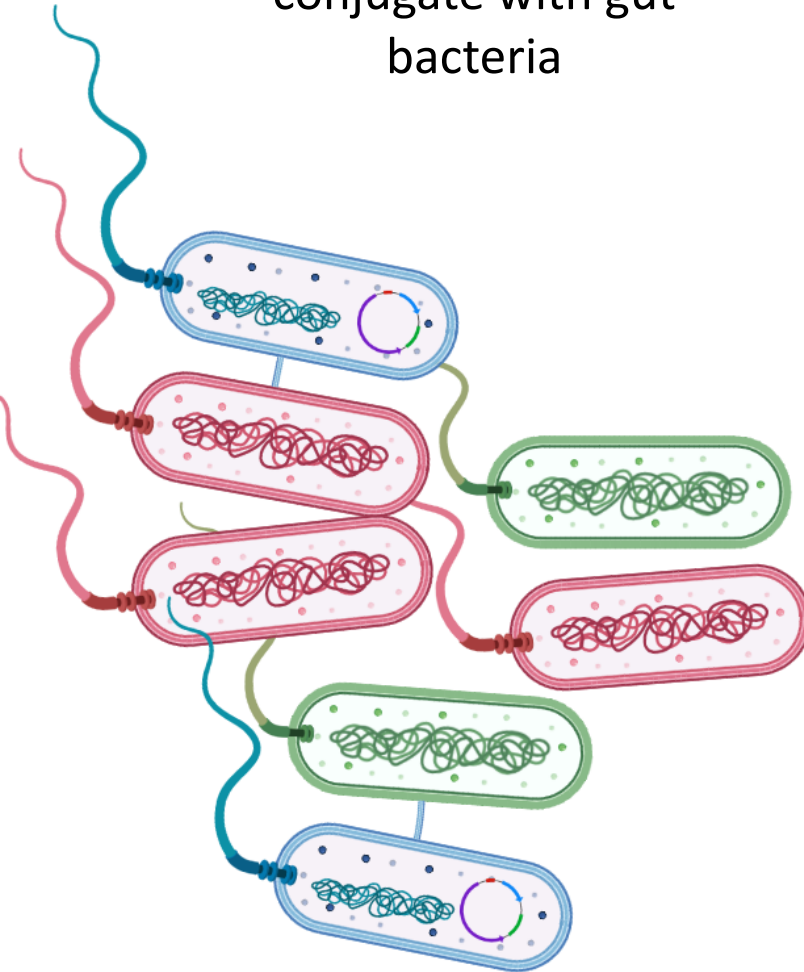
- Double-strand breaks induced by Cas proteins are fatal if the bacterial chromosome is targeted
- Prior research has shown that introduction of a CRISPR system can kill bacteria
- A CRISPR-Cas system can target antibiotic resistance genes, sensitising or killing resistant bacteria
- My project aims to design a probiotic that can transfer CRISPR-Cas system targeting resistance genes to the gut microbiota

Delivering CRISPR-Cas to the gut

Probiotics
conjugate with gut
bacteria

CRISPR-Cas kills resistant bacteria

Sensitive bacteria are
unaffected

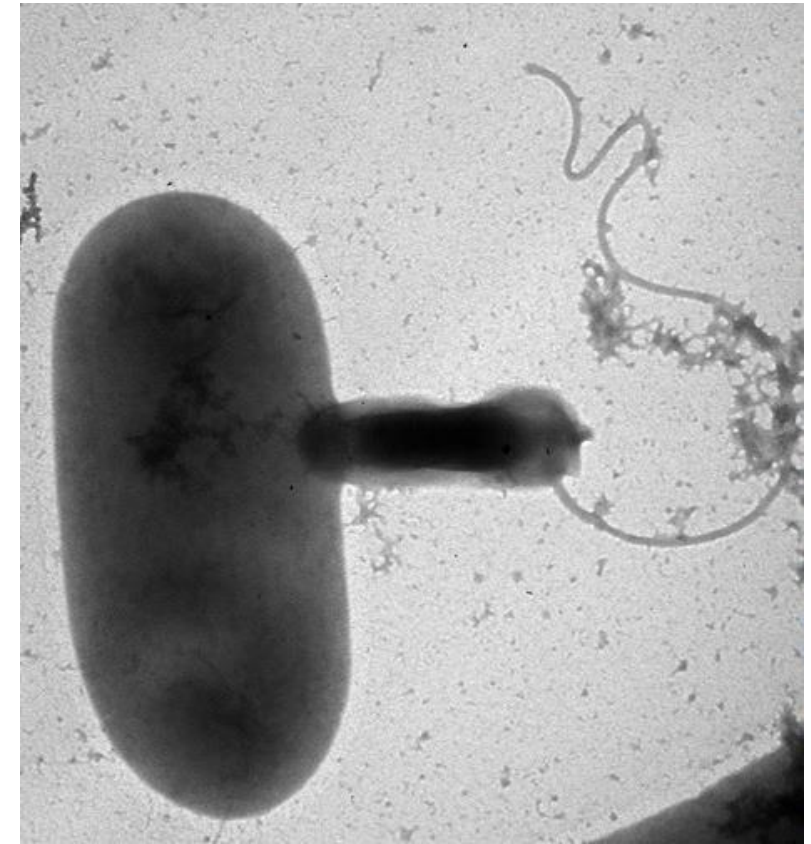


- Due to AMR, alternative strategies of infection control are being researched
- These include bacterial viruses (bacteriophages) and predatory bacteria

Bacteriophages



Bdellovibrio bacteriovorus



- AMR is potentially the greatest public health challenge post-COVID
- However, AMR is an environmental issue as well as a public health one
- Although stewardship and monitoring programs can only be beneficial to fighting AMR, persistent elements remain a challenge
- Novel strategies such as the use of CRISPR-Cas could potentially help the remediation of AMR from the environment
- Challenges remain, from delivery to anti-CRISPR systems present in bacteria

Thank you for listening!

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