# Drug Resistant *Mycobacterium tuberculosis:* Evaluating Macrophage Evasion Mechanisms as Potential Targets for Anti-Virulence Drugs

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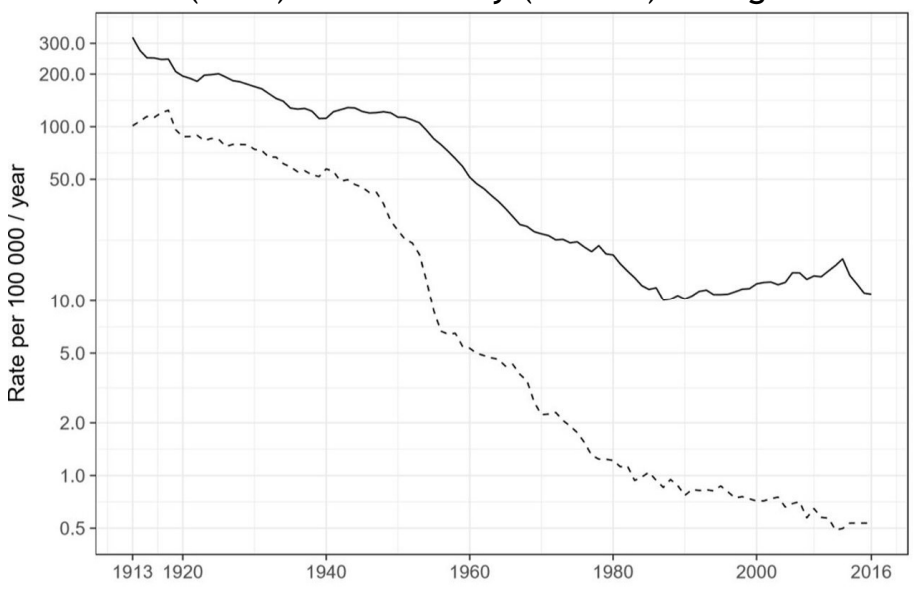
# *Mycobacterium tuberculosis: a Manageable Disease*

Incidence (Solid) and Mortality (Dashed) in England & Wales




**TB incidence (solid line) and mortality (dashed line) rates per 100 000 populations per year in England and Wales, 1913-2016.**

- Decline of tuberculosis cases over the years.
- Decreased percentage of cases ending fatally.
- Decline of cases caused by improved hygiene and preventative measures.
- Reduced fatalities caused by effective treatment using anti-microbials.

# Antibiotic Treatment

First Line Antibiotics:

- Highly effective against *M. tuberculosis* with minimal side-effects.
- Isoniazid, Rifampicin and Pyrazinamide.

Second Line Antibiotics

- More side effects, expensive and less effective at killing.
- Only used if resistant to first line drugs.
- Ofloxacin and Kanamycin.

# Treatment Duration


- *M. tuberculosis* is slow growing and has a long incubation time.
- Treatment over a long period of time is needed to kill all mycobacteria.

First Line

- **6 to 9 months**

Second Line

- **1 year+**

# Antibiotic Resistance

- Long treatment time more likely to cause missed doses or early stoppage.
- Allows for *M. tuberculosis* to survive and mutate to resist antimicrobials.
- Second line antimicrobials need to be used for a longer period of time.
- Leads to more missed doses etc. and gains more resistances.

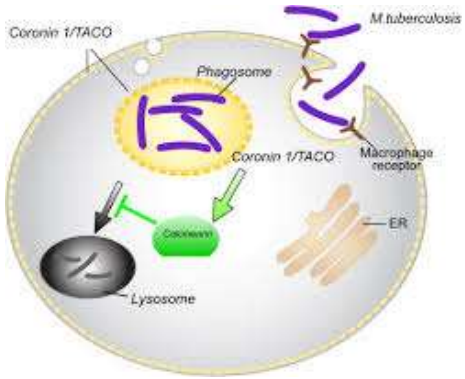
- **MDR-TB:** Multidrug Resistant Tuberculosis.
- **XDR-TB:** Extensively Drug Resistant TB.

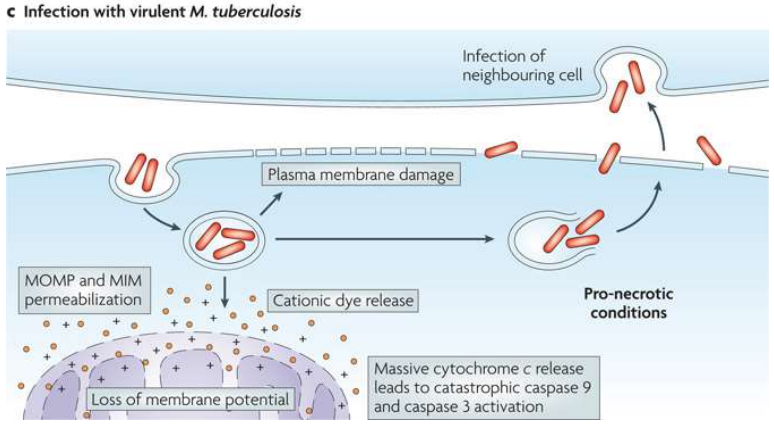
# Are antibiotics the only way to combat TB?

# Antivirulence Drugs for *M. tuberculosis*

- Designing drugs to target and block mechanisms of pathogenesis and disease.
- Aims to “disarm” the pathogen, not to kill it.
- “Evolution-Proof”: weaker selection pressure = less likely to acquire resistance.
- Can be designed to be species specific and not affect commensal bacteria.

# *M. tuberculosis:* Evasion of Macrophages




- Co-evolved with humans to evade immune system
- Prevents phagolysosome formation via coronin-1 recruitment.
- Escapes the phagosome via ESAT-6 membrane lysing activity.
- Induces cell death by inhibiting membrane repair mechanisms.

# Dissertation Overview

- Explain how drug resistance can be developed and its impact on modern medicine.
- Describe the antimicrobial processes of macrophages.
- Identify the mechanisms *M. tuberculosis* employs to evade these processes.
- Explain which mechanisms could be good targets for antivirulence drugs.
- Discuss the effectiveness of current antibiotic treatments for M. tuberculosis and possible anti-virulence drugs.
- Evaluate the challenges for discovering and introducing antivirulence drugs.

# THANK YOU