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## ANTIMICROBIAL RESISTANCE (AMR)

### 1 The problem

Existing antibiotics are stopping to work

Causing globally ~ 10 million deaths and £66 trillion by 2050

### 2 The challenge

Antimicrobial resistance cannot be prevented

Developing new antimicrobials

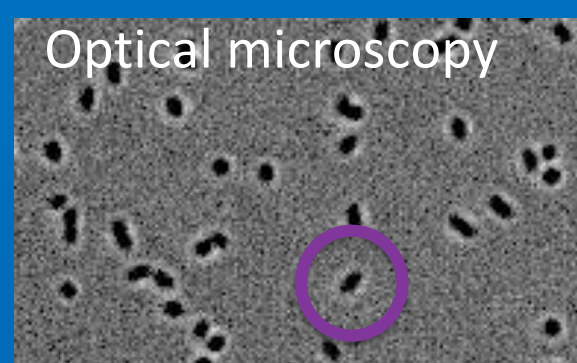
### 3 Our approach

Understanding key mechanisms underlying AMR

Resolve the outer membrane of bacteria at the nanoscale

## UNDERSTANDING HOW THE IMMUNE SYSTEM FIGHTS BACTERIA

### A Grow bacteria culture

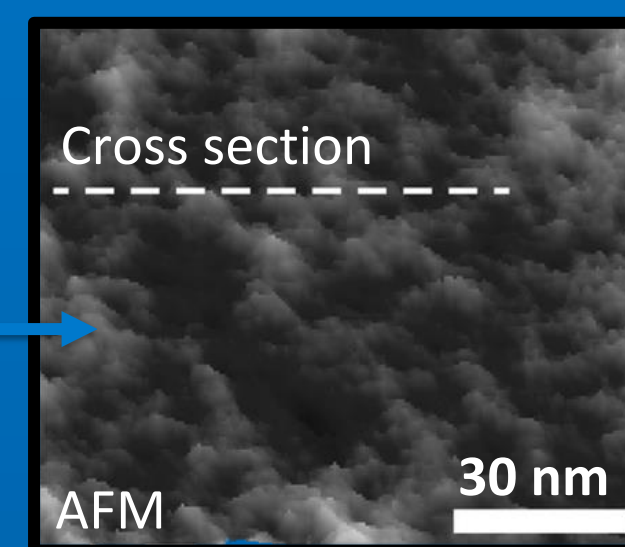


Atomic force microscopy (AFM) image of live *E. coli* (most common cause of bacterial infection in the UK)

### C

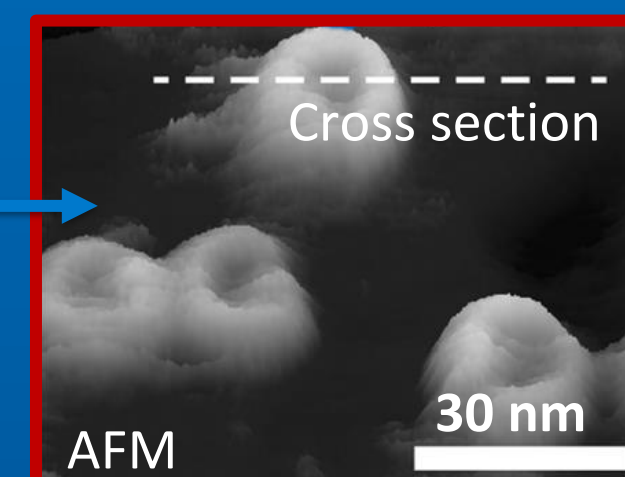


Nanoscale images of live bacteria



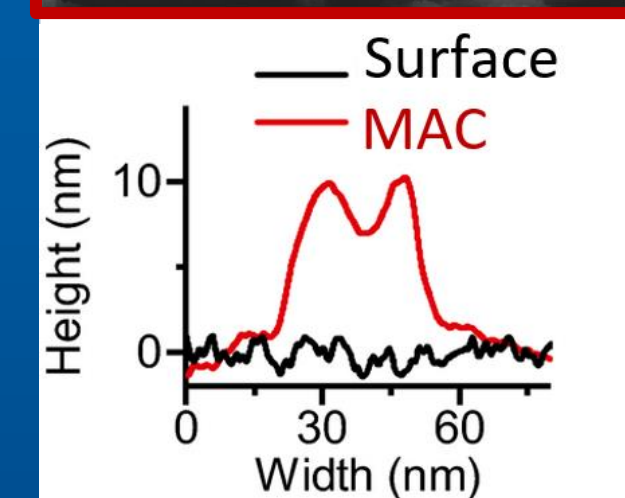
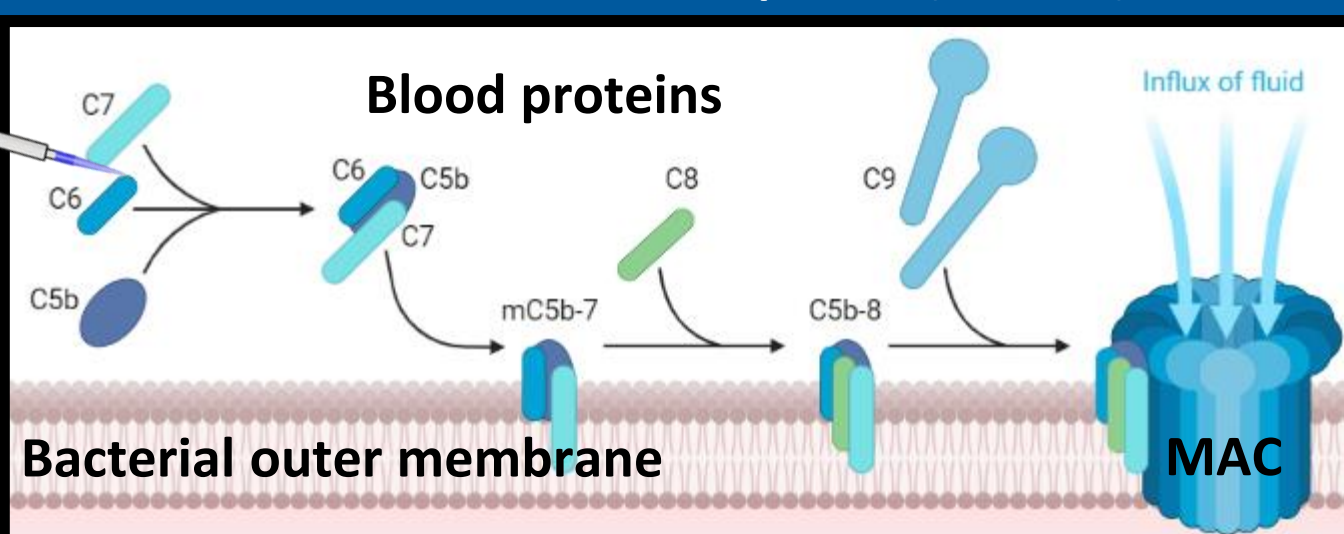
Protein assemblies imaged at high resolution

### B Add human serum (blood proteins)



Membrane attack complex (MAC) nanopores

### C The immune system responds: formation of membrane attack complex (MAC)

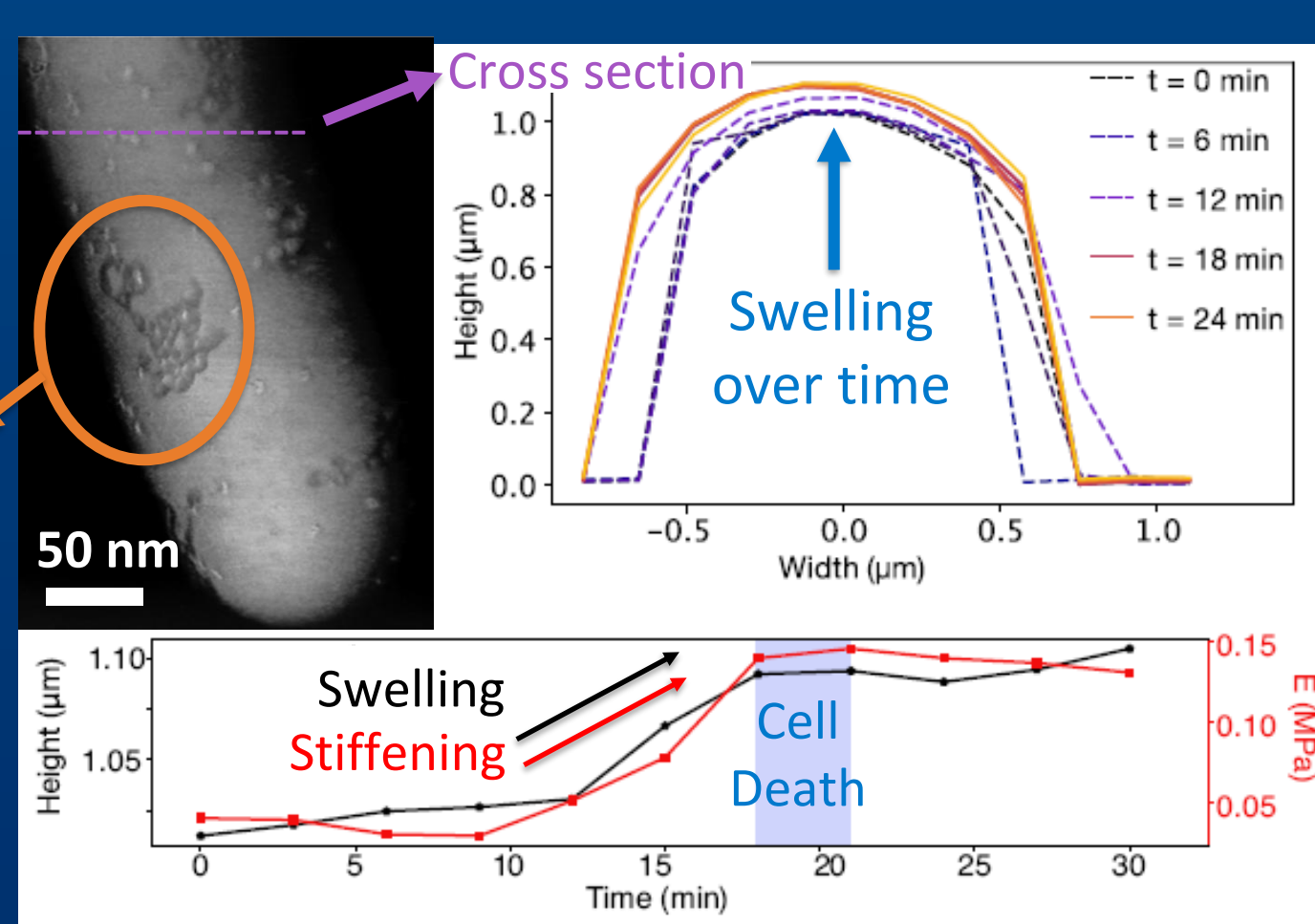
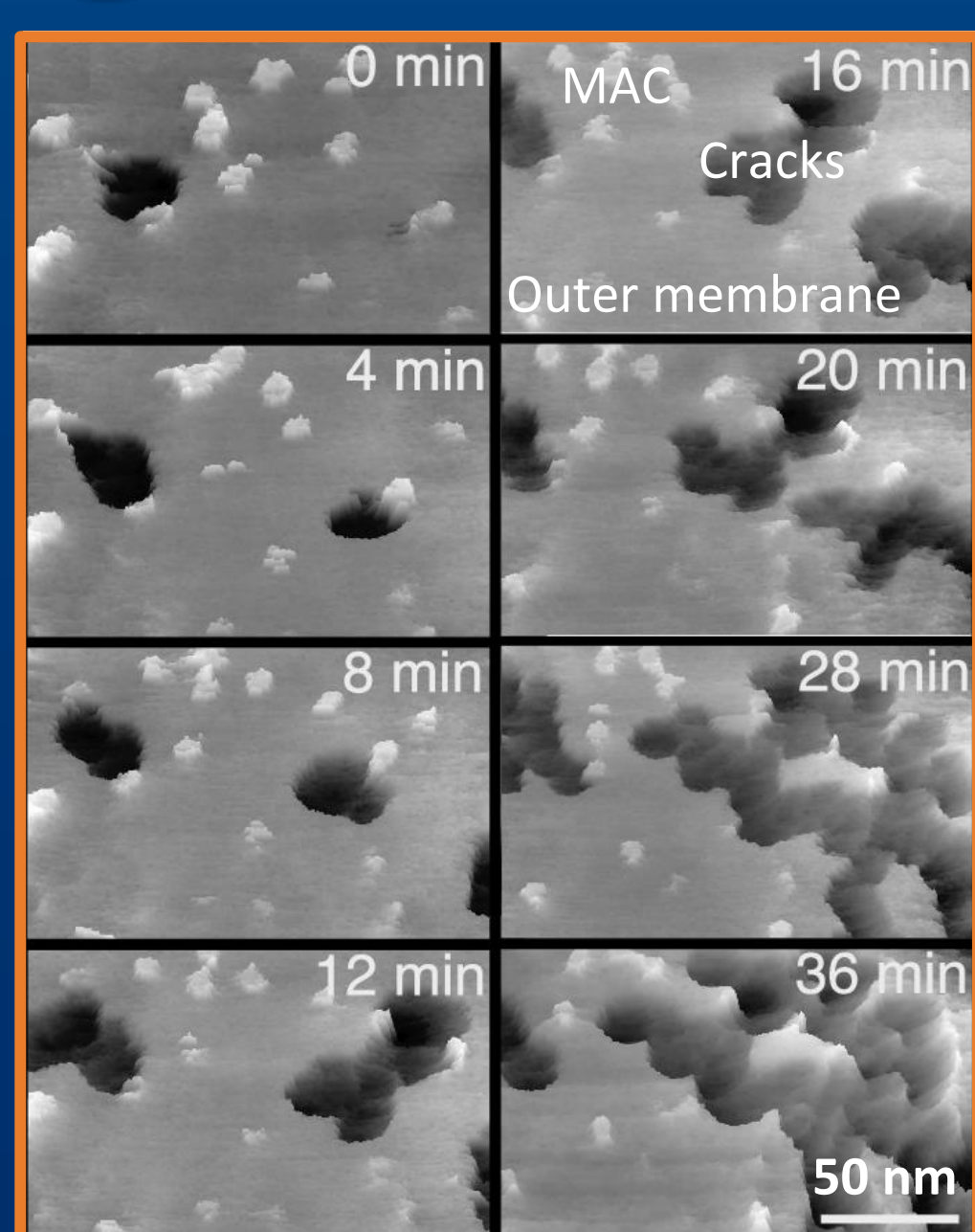


Each MAC pore is only 10 nm tall

MAC nanopores kill bacteria

## BACTERIA SWELL AND STIFFEN BEFORE DYING

### D Bacteria's outer membrane swells, stiffens and cracks over time



New mechanism of killing bacteria is revealed

## DEVELOPMENT OF NEW ANTIBIOTICS

The bacterial membrane plays a key role in antimicrobial resistance (AMR)

Our work shows how the MAC destabilises bacterial membranes and kills bacteria

This new understanding enables innovative antibiotics to be developed that will target this mode of killing bacteria

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#### References:

- 1) UK 5-year action plan for antimicrobial resistance 2024 to 2029, WHO
- 2) IHME Global Burden of Disease Study 2019 (GBD 2019)
- 3) Bortolini C., Benn G. *et al.*, EMBO J, 43:6152 - 6160 (2024)
- 4) Benn G., ..., Bortolini C. *et al* PNAS, 118(44) (2021)
- 5) Heesterbeek DA *et al.*, EMBO J, 38:e99852 (2019)