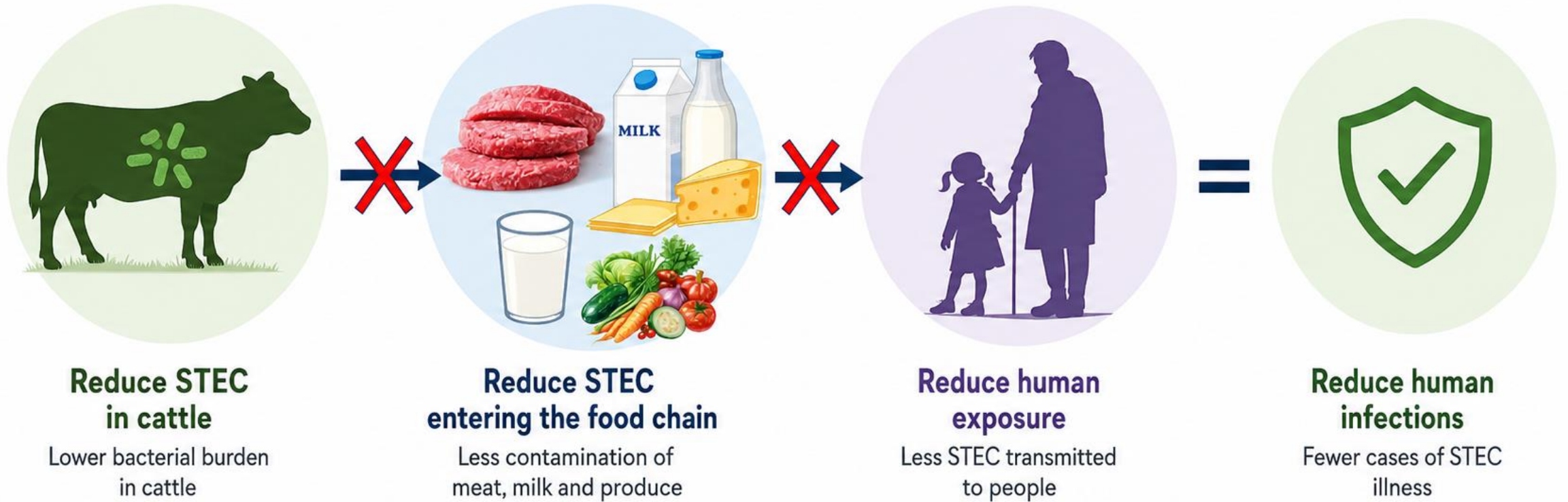


STEC management strategies

Advancing phage-based interventions for cattle
colonised with *Escherichia coli* O157:H7

Alison Low

Overall Ambition

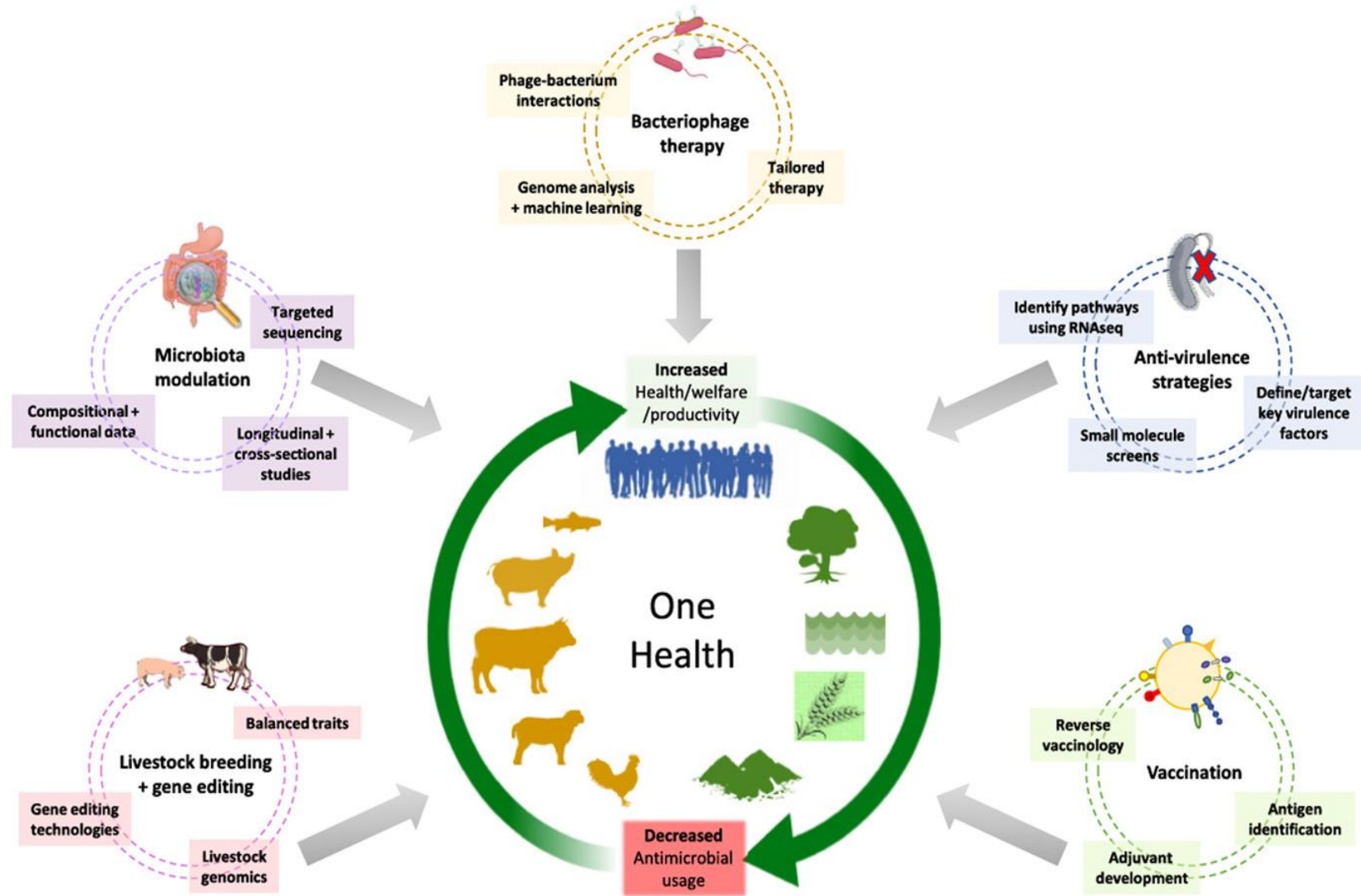


Infectious disease management strategies

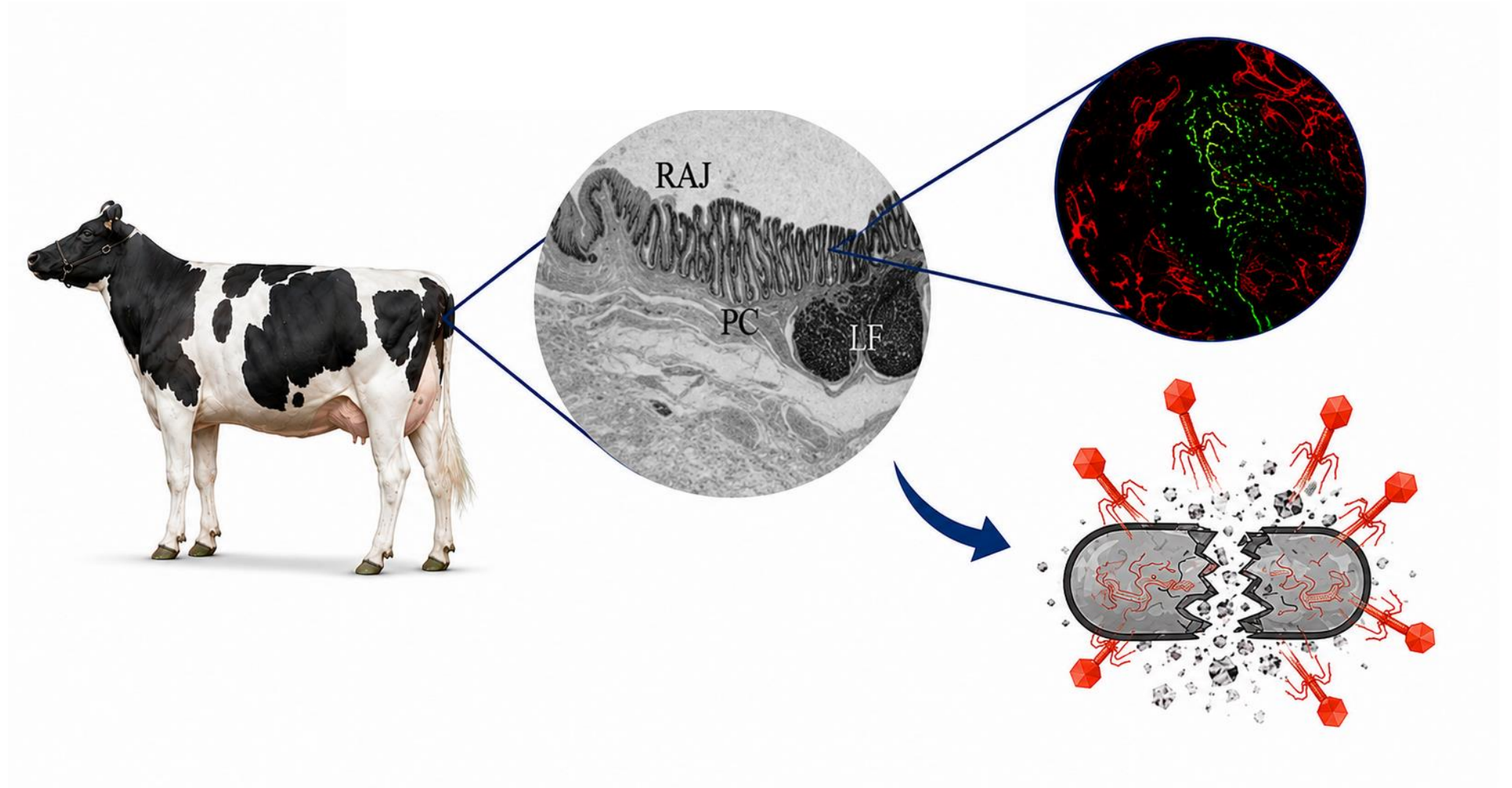


Antibiotics

One Health
alternatives to
antibiotics



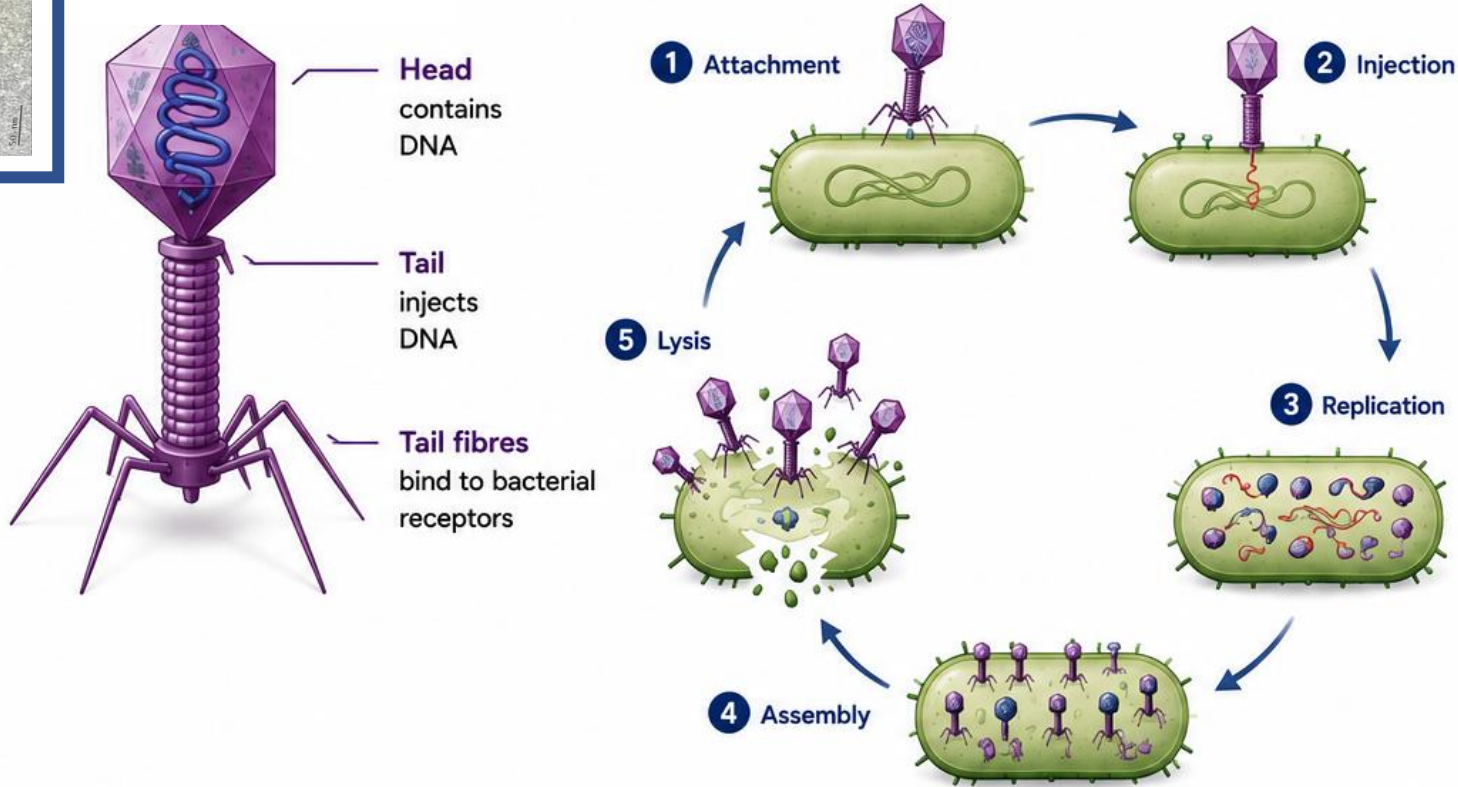
Phage interventions



Can we use phage to reduce O157:H7 in cattle?

Phages are natural viruses that infect bacteria.
They are the most abundant biological entities on Earth.

PHAGE LIFE CYCLE



WHY PHAGES?



Highly specific



Natural & abundant



Self-amplifying



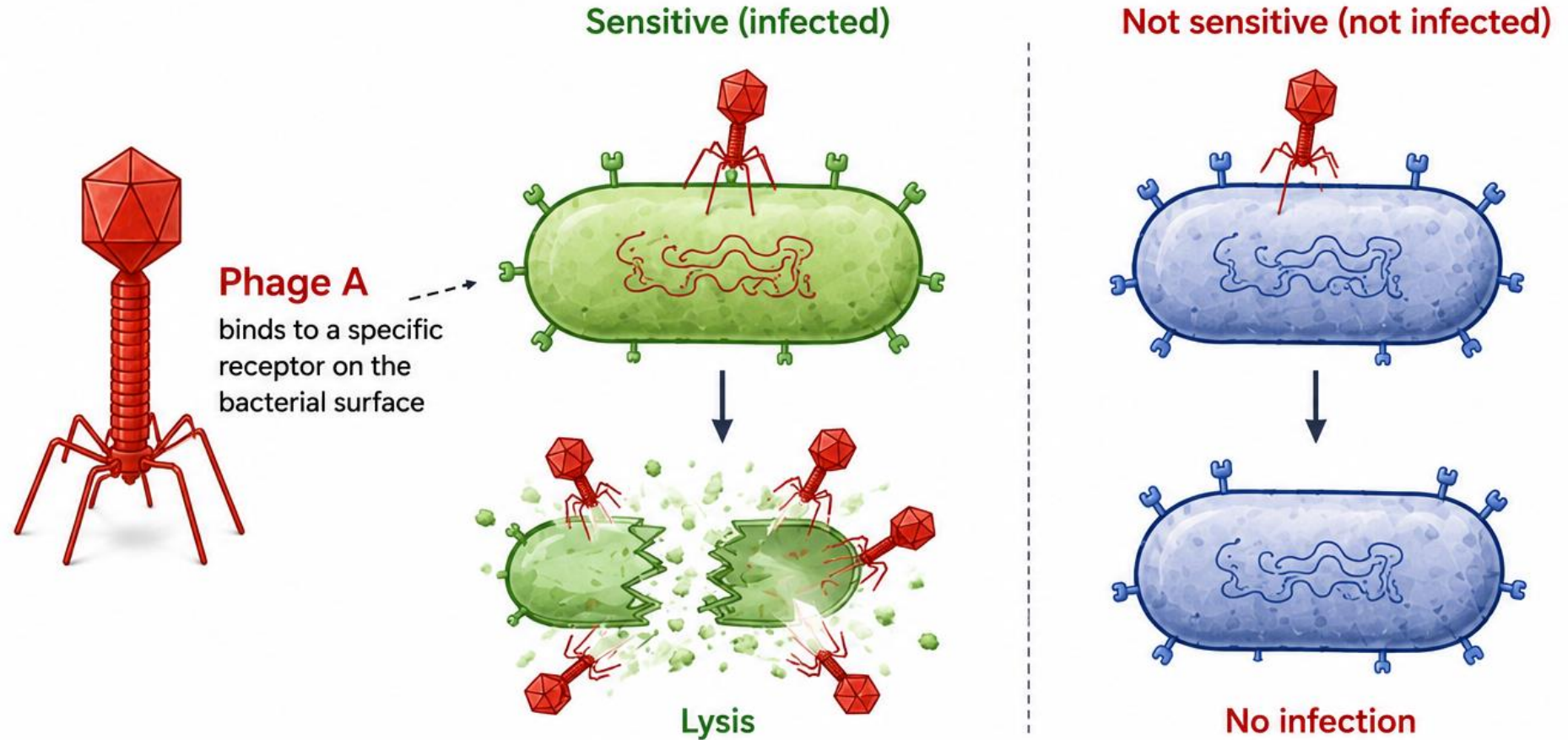
Active against
antibiotic-resistant
bacteria



Phages are nature's bacterial predators –
precise, powerful and promising tools for a future beyond antibiotics.



Phage Specificity



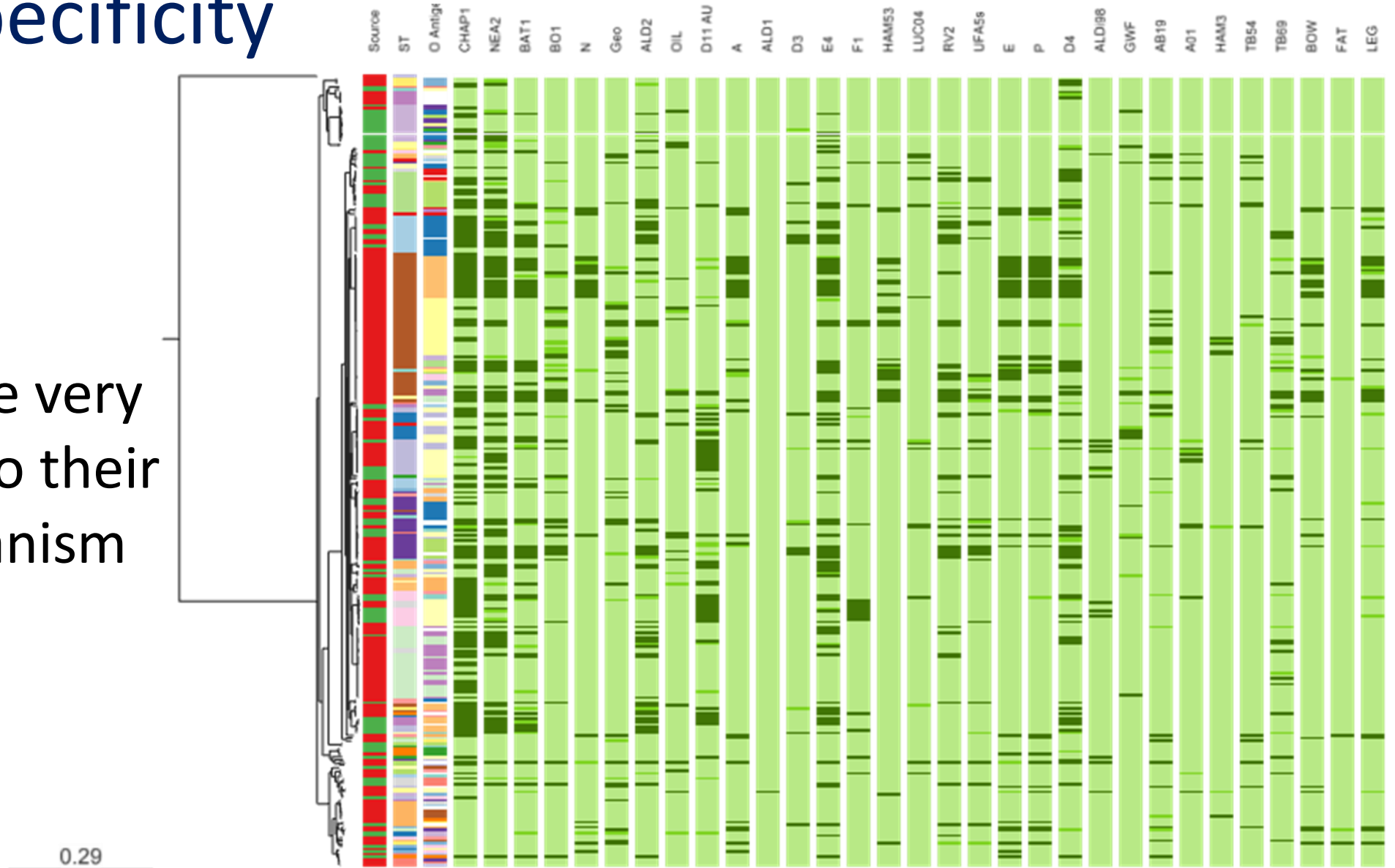
Matching receptor
Phage can bind and infect



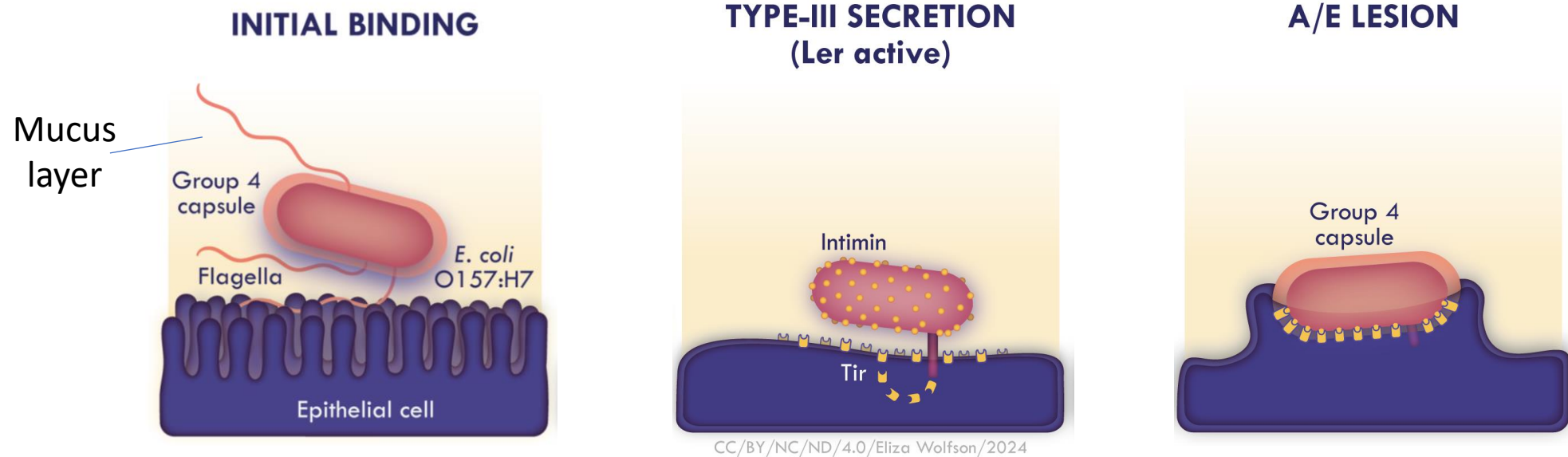
Different receptor
Phage cannot bind – no infection

Phage Specificity

Phage are very specific to their host organism

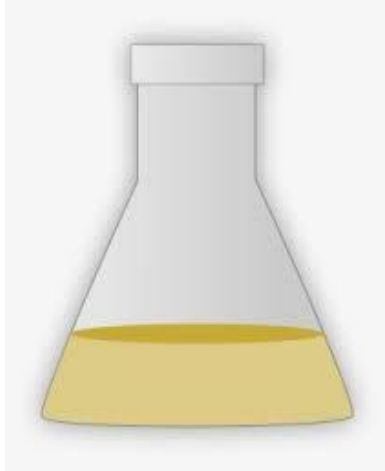


Bacterial sub populations

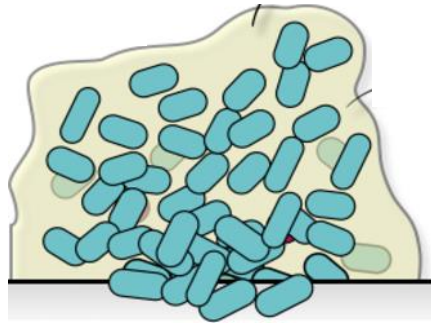


For successful phage therapy we need to eliminate multiple sub populations of bacteria.

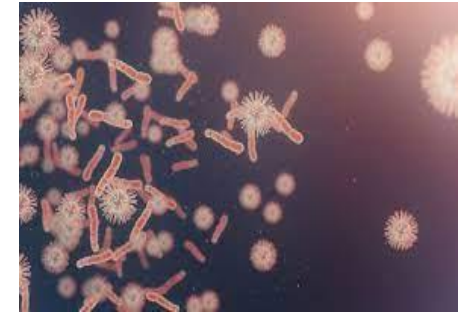
***In vitro* conditions**



***In vivo* conditions**



Attached to cells



Bacteria associated with mucus

Screening bacteriophage activity against *E. coli* under *in vivo*-like conditions

Cattle trials

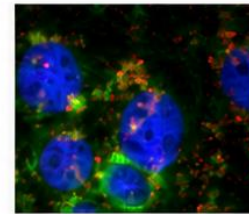
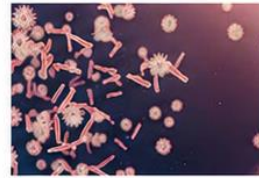
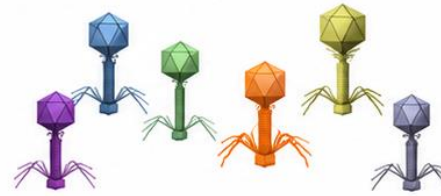
Understanding the
pathogen you want
to treat

USDA Feedlot O157 Strain

MARC: Clay
Center, Nebraska



National Animal
Disease
Center: Ames,
Iowa



UK PT 21 / 28 O157 strain



 Moredun

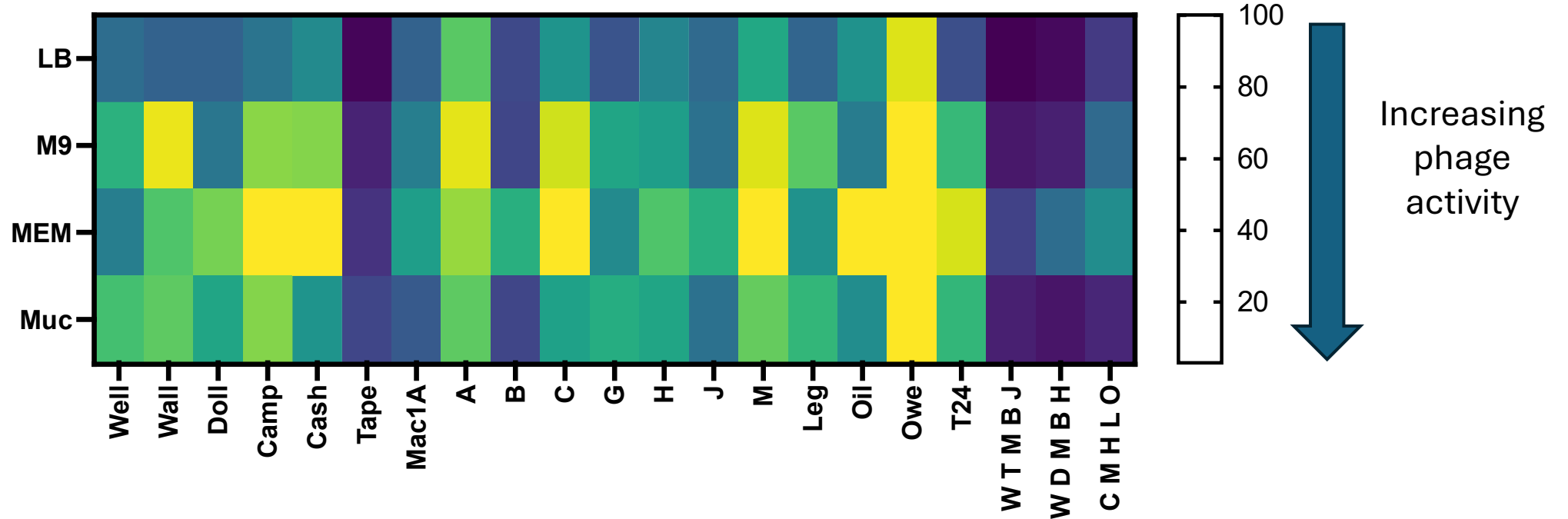
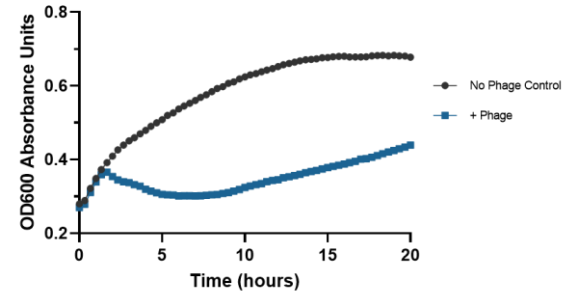
 ROSLIN



Using a physiological relevant growth media for interactions

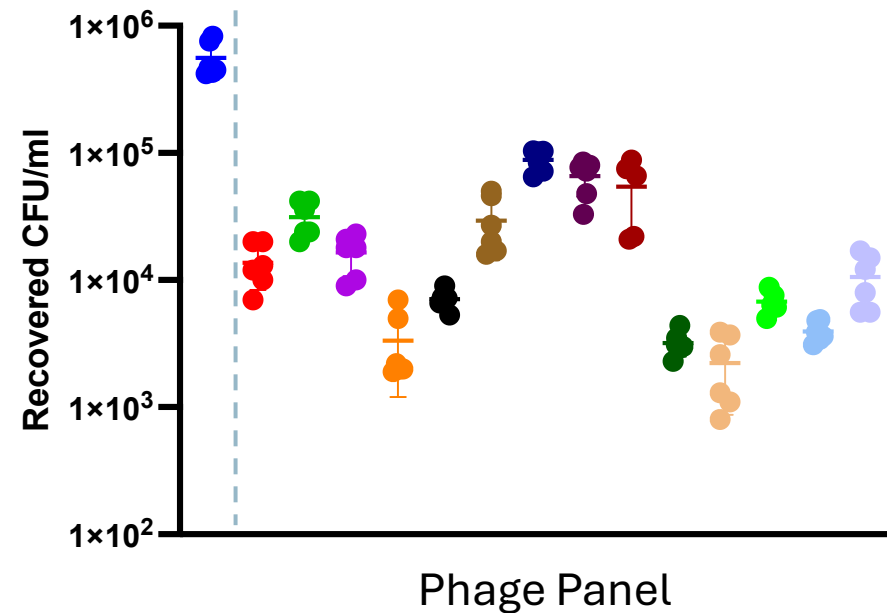
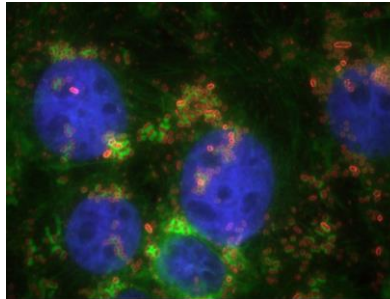
USDA Feedlot
O157 Strain

Phage activity screen in
different media

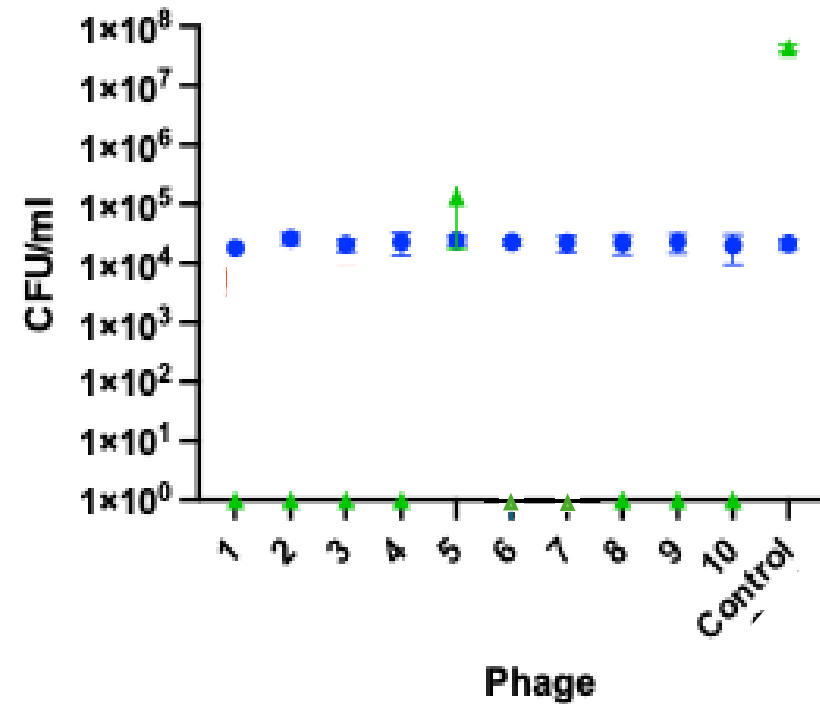
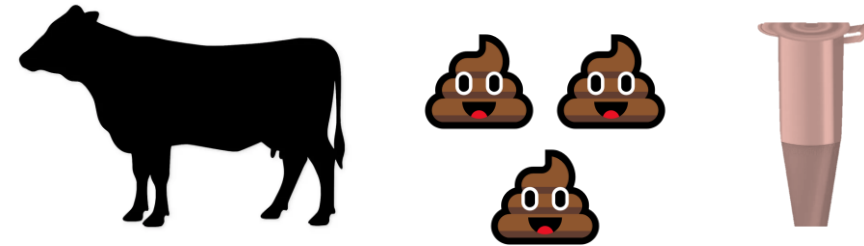


Using a physiological relevant growth media for interactions

On cells



Ex vivo – bovine fecal samples



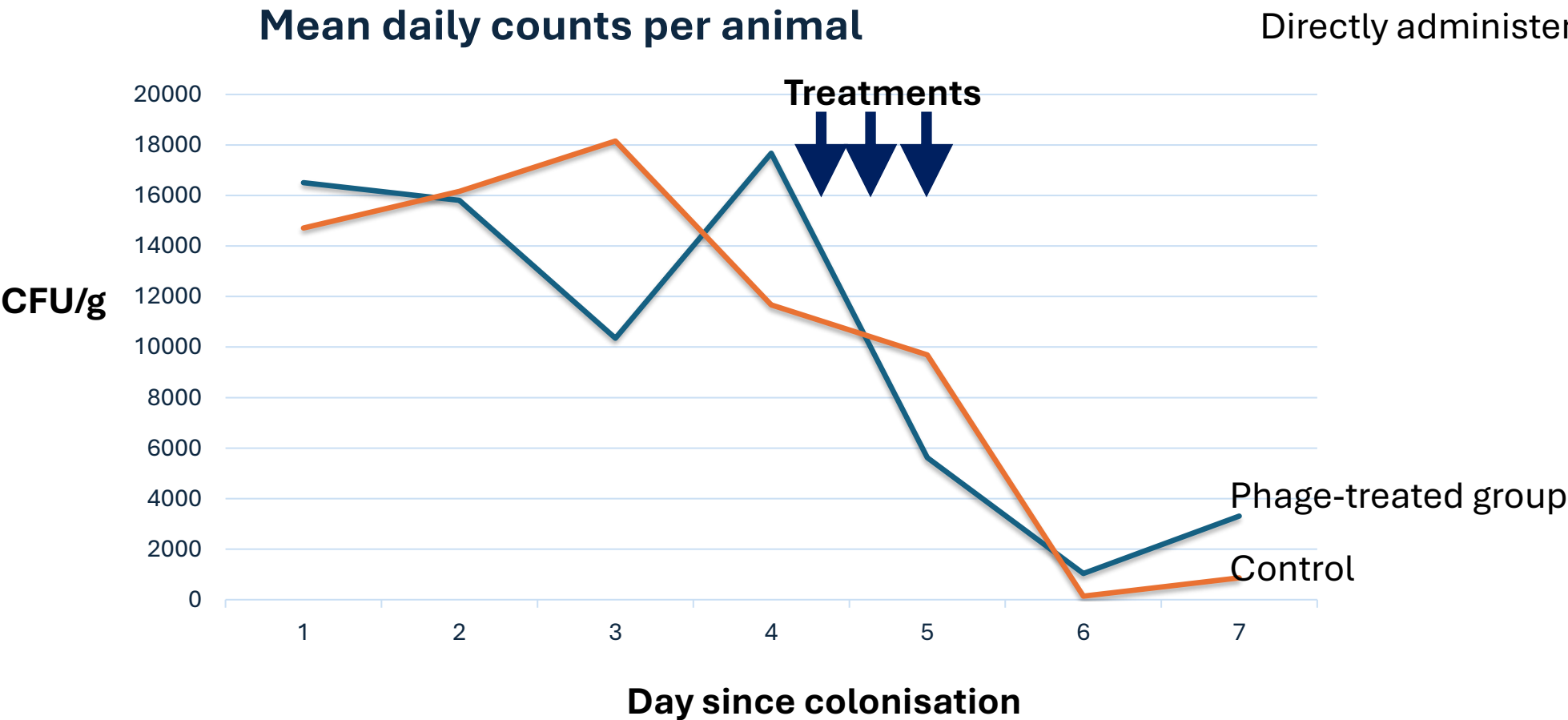
Phage efficacy cattle trial

16 animals

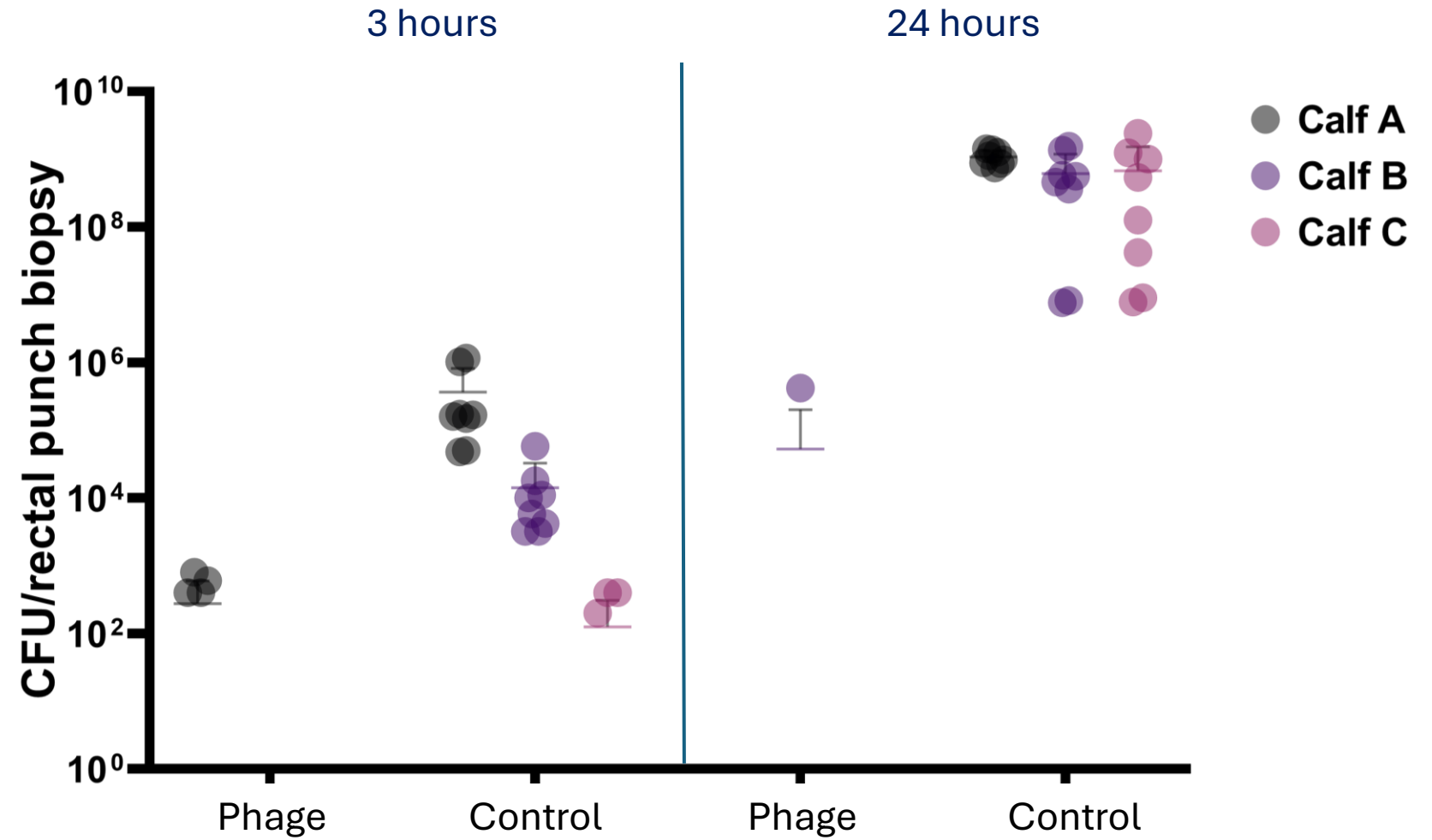
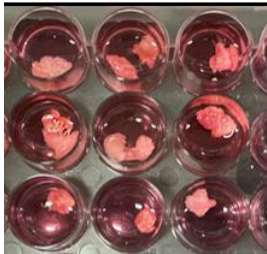
Phage treatment given to 8 animals on day 4 and 5

10^{11} PFU of phage cocktail

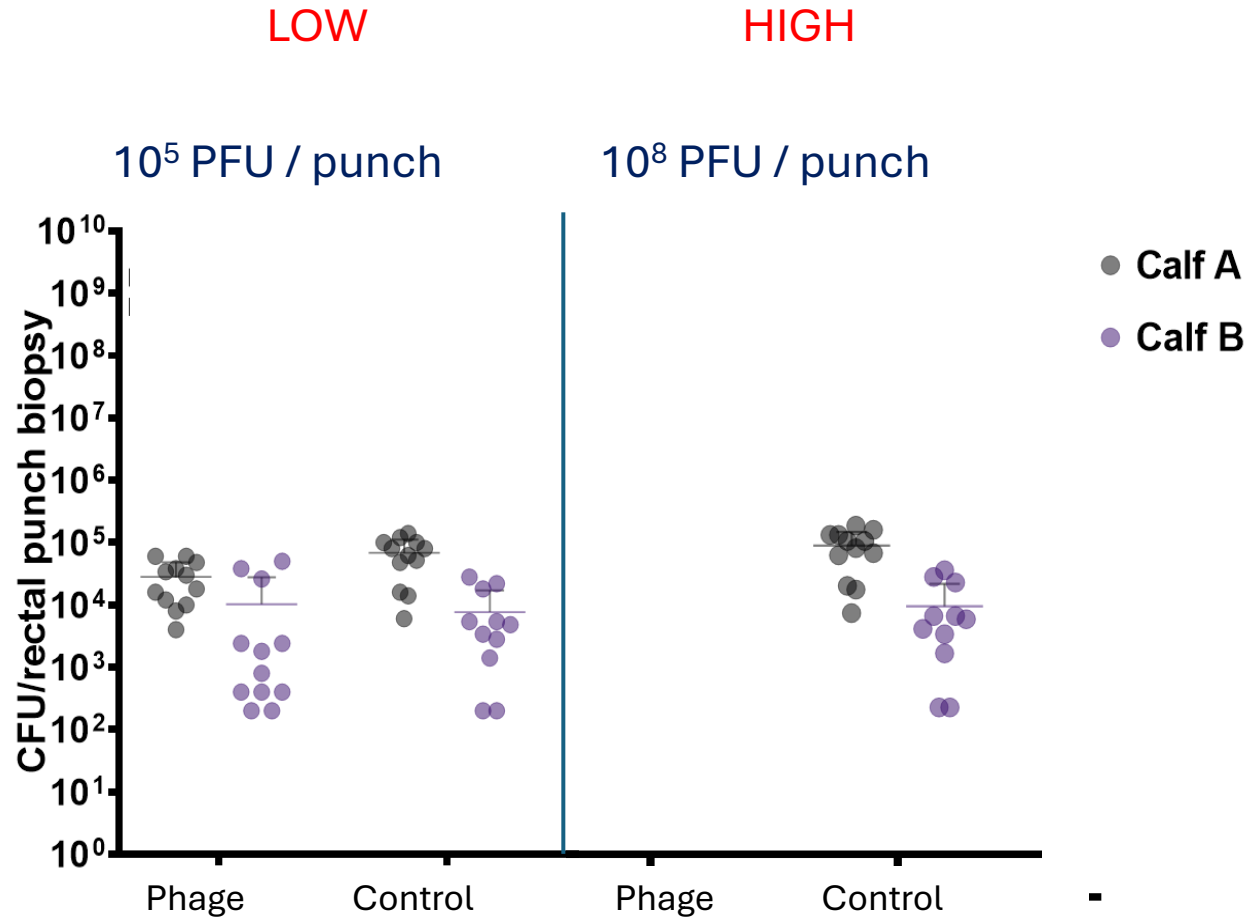
Directly administered



Further *ex vivo* work with UK PT21/28 strain



Number of phage really matters.....



Actually phage are
not the perfect
predator

Millions of years of
co-evolution

Understanding the
biology will be key
for successful
interventions

We need to deliver high numbers of phage to the site, and they need to stick

Deliver phage in a sticky gel

Add phage to a pluronic gel mix

Liquid at room temperature

Gels at body temperature

Mucoadhesive

Engineer phage to be muco-adhesive

Identify domains that naturally adhere to mucins

Engineer them into target phage

Deliver engineered phage

But could antibiotics work in STEC management in cattle...?

Paromomycin: a targeted option for STEC



Aminoglycoside
antibiotic



Already licensed
for use in calves



Not absorbed
from the gut



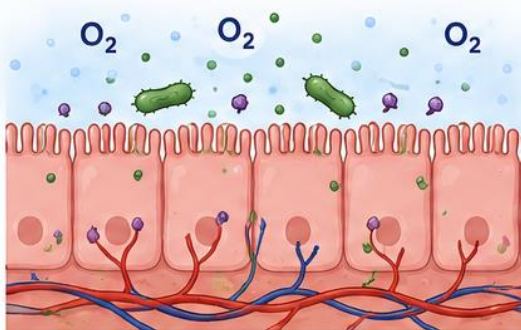
Will not contaminate
milk



Requires oxygen
to be active

Where it works

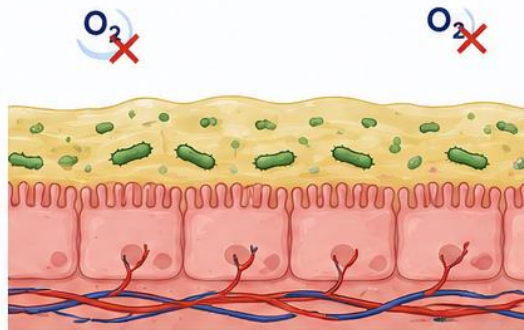
RAJ (Recto-Anal Junction)
(Oxygen present)



Paromomycin active → reduces STEC

Where it doesn't work

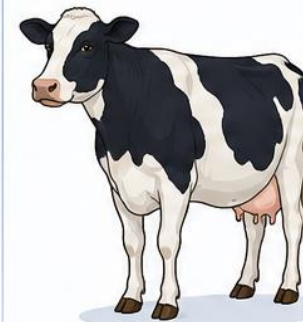
Other gut niches
(Low oxygen)



Paromomycin inactive → limited effect

If toxin is induced

Limited impact on the cow



- ✓ Minimal systemic absorption
- ✓ Low risk of clinical disease
- ✓ Cow wellbeing maintained

Watch this space.....

Conclusions

- We have good phage that can kill bacteria

in liquid media

in type III inducing conditions

in the presence of bovine rectal mucus

on bacteria attached to epithelial cells

in a fecal slurry

on *ex vivo* tissue punches with colonised bacteria

- Administering large numbers of phage directly into cattle rectum not effective
- Need a way to administer and **retain** phage direct to the site of colonisation
- There is potential for antibiotic treatment in targeted situations



Thank you



- David Gally
- Asim Ullah
- Sean McAteer
- Jess Parkin
- Gally Group



- Stephen Fitzgerald
- Tom McNeilly
- David Frew



- Jim Bono
- Crystal Loving
- Joel Maki

