Phage Therapy - A tale of bacteria and viruses

HTGAA Bootcamp

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A killer is living amongst us

Trillions of kills per day

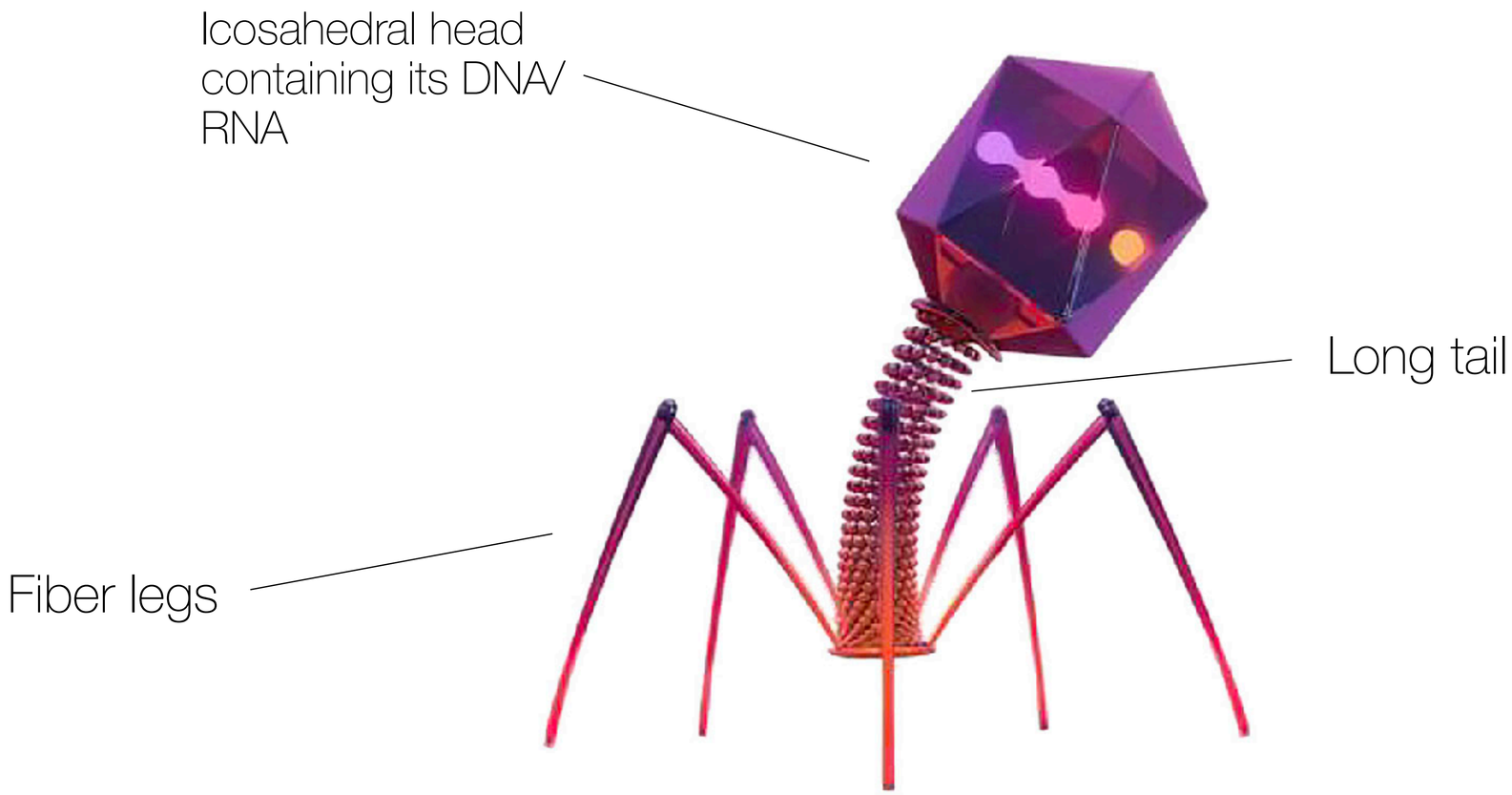
Source: https://www.poultryworld.net/health-nutrition/

Living on our skin, in our intestine and all around us

One of the deadliest entities on our planet

Bacteriophage

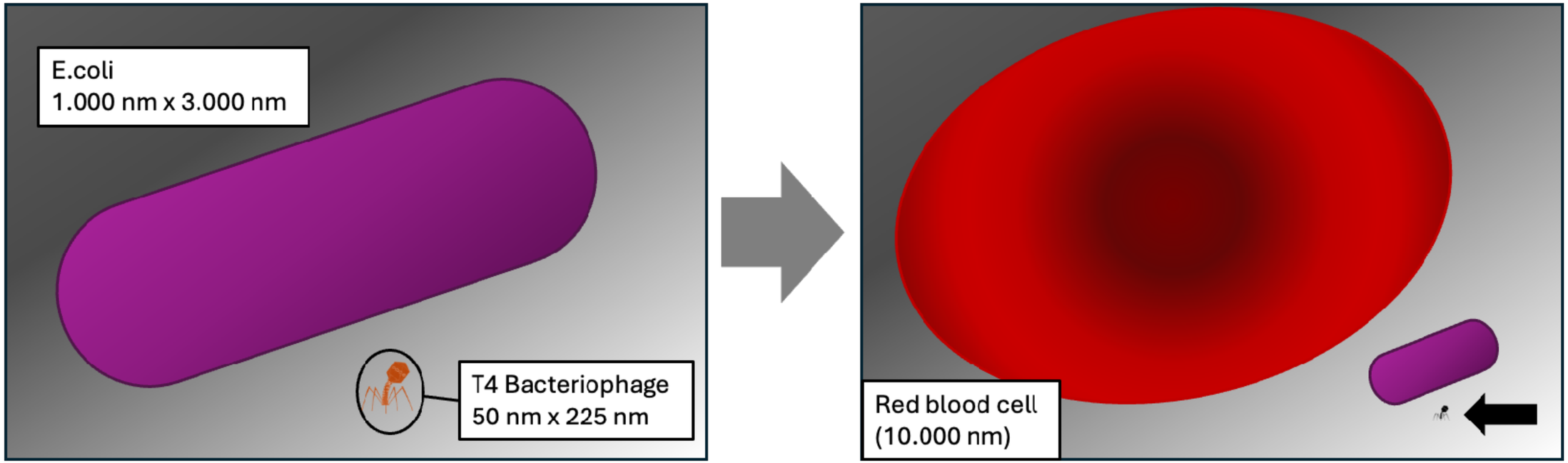
A killer is living amongst us - a virus



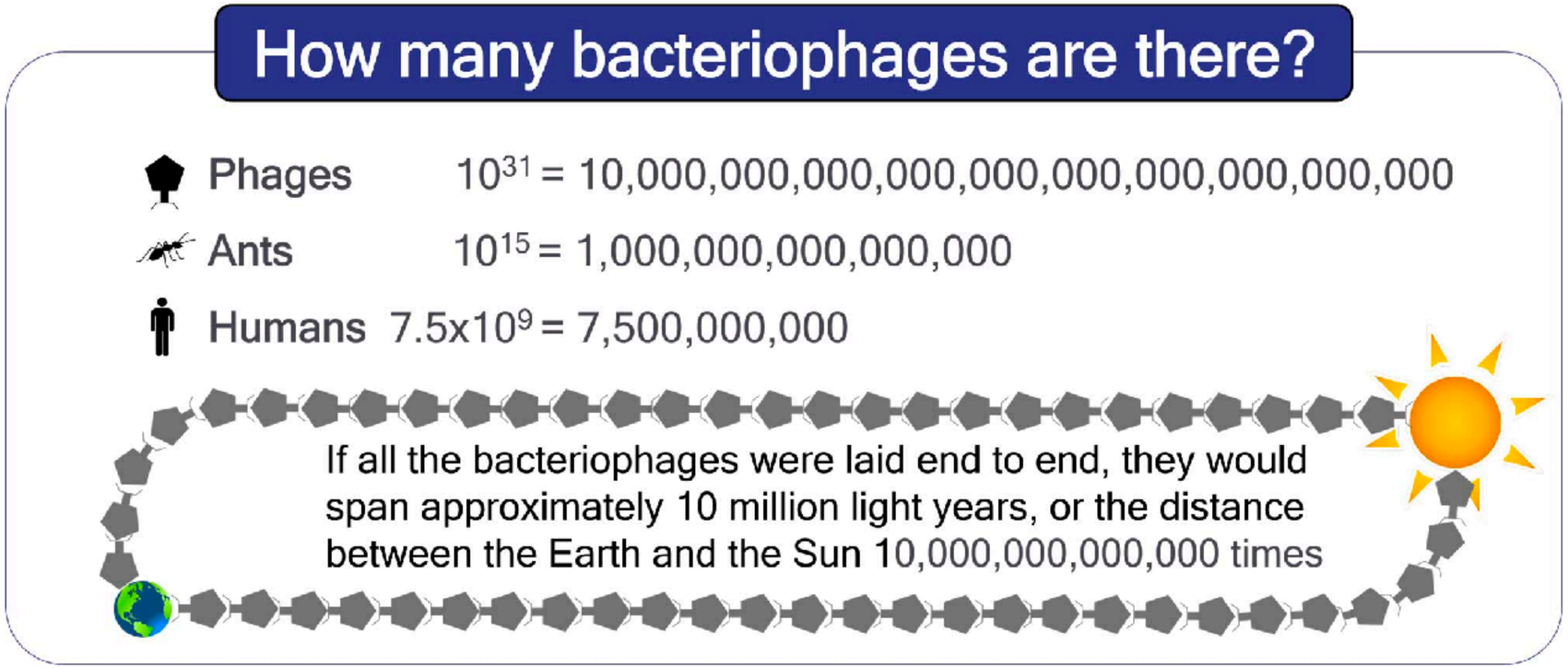
Source: https://www.poultryworld.net/health-nutrition/

Bacteriophage

Bacteriophages in scale



How many are there?



Source: https://sciencefest.indiana.edu/bacterial-viruses/

Omnipresent, where bacteria exist – including outside and inside a human!

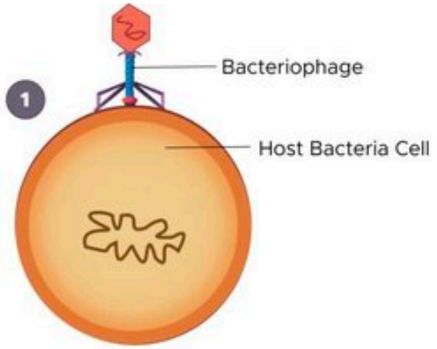
Soooo should I be worried?

No!

Source: https://www.discovermagazine.com/the-sciences/the-secret-cleaning-power-of-bacteria

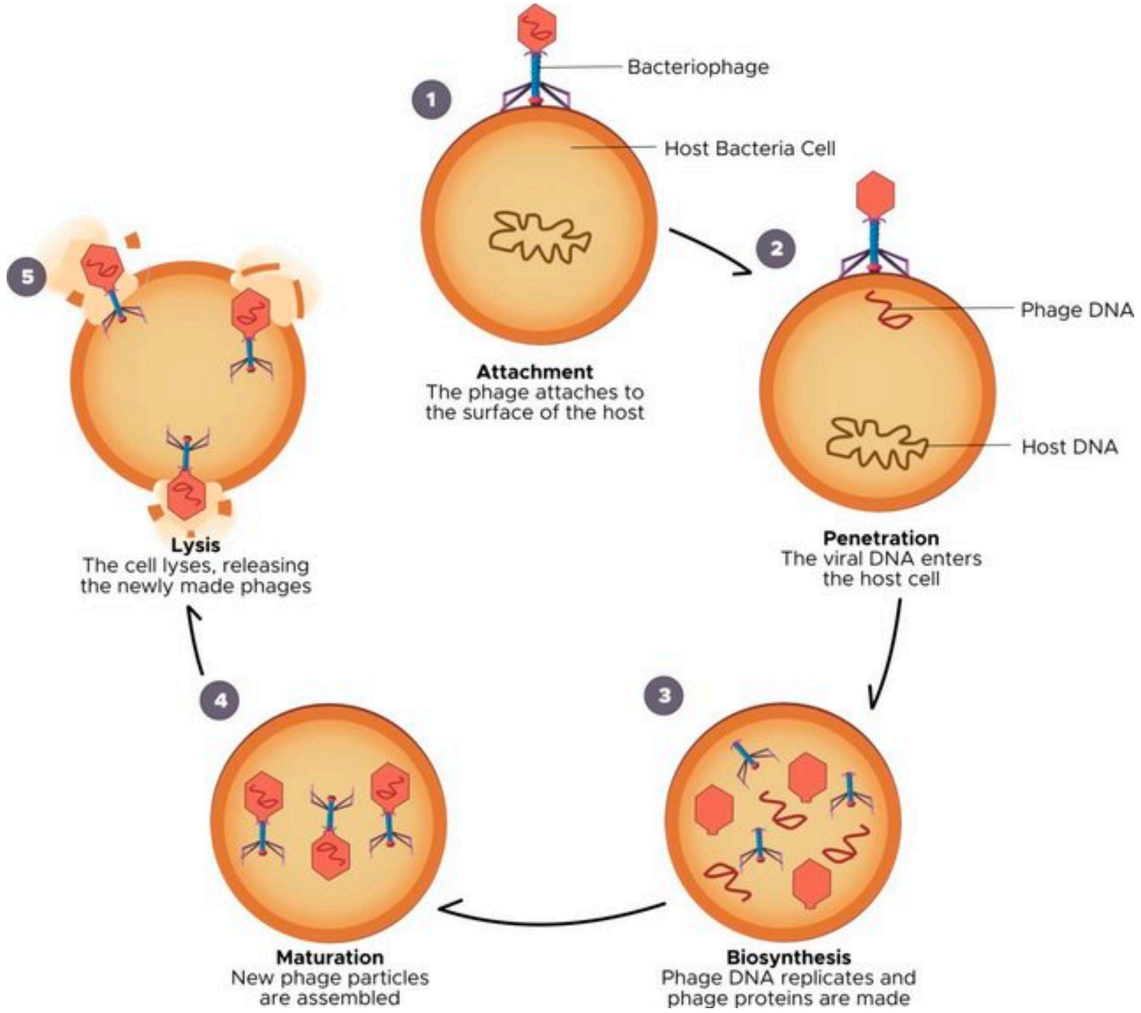
The only ones that need to be scared: Bacteria

How do they infect bacteria?



Attachment
The phage attaches to the surface of the host

How do they infect bacteria?



Source: Adesanya et al. AIMS Microbiology 2020

Phage specificity

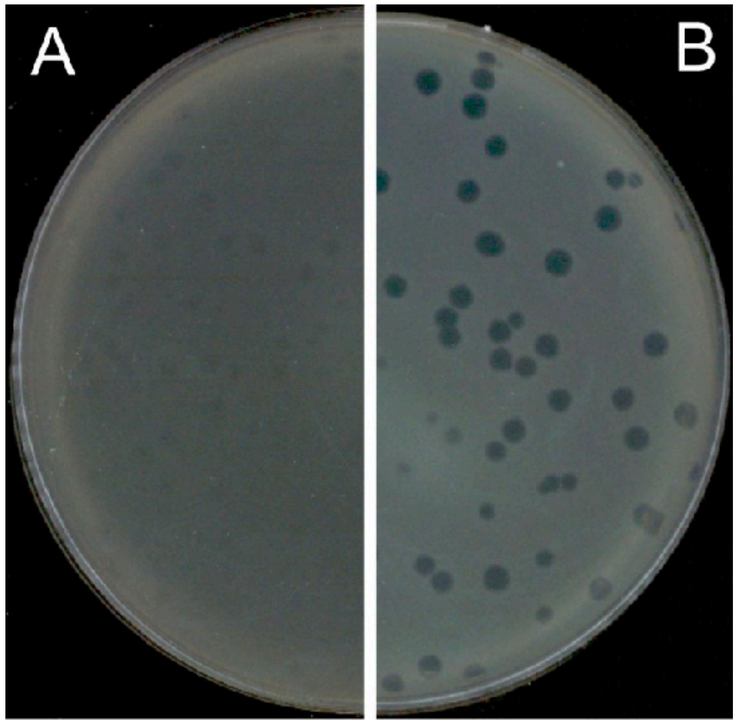
Phage	Classification	Genome length (kb)	Phage particle dimensions	Phage isolation source (Reference)	Bacterial host/s
ϕBrb01	Siphoviridae	33.91 ± 2.41	Head 55–60 nm, tail 105 × 9 nm	Municipal sewage (Klieve et al., 1991)	*Bacteroides* sp. AR20***, *Bacteroides* (*Prevotella*) *ruminicola* ss *brevis* AR22, AR23
ϕBrb02	Siphoviridae	33.02 ± 1.16	Head 55–60 nm, tail 105 × 9 nm	Municipal sewage (Klieve et al., 1991)	*Bacteroides* sp. AR20***, *Bacteroides* (*Prevotella*) *ruminicola* ss *brevis* AR7, AR22, AR23
ϕRa02	Podoviridae	12.8	Head 25 nm, tail 18 nm*	Bovine fecal waste material (Klieve et al., 2004)	*Ruminococcus albus* AR67
ϕRa04	Podoviridae	14.0	Head 25 nm, tail 18 nm*	Bovine faecal waste material (Klieve et al., 2004)	*Ruminococcus albus* AR67
ϕSb01	Siphoviridae	30.9 kb ± 4.4	Head 60 nm, tail 110 × 7 nm	Bovine rumen fluid (Klieve and Bauchop, 1991)	*Streptococcus bovis/equinus* 2B, *S. equinus* Sb04, Sb17

Source: Gilbert et al. Front. Microbiol. 2017

Plaque assay

Healthy bacteria = Phage not infecting

Dying bacteria = Phage infecting



Source: Santos et al. BMC Microbiology 2009

Why should you care about phages?

The short answer: We screwed up!

In the past you could easily die from…

Source: https://www.hsph.harvard.edu/ecpe/

… breathing in a bug

Source: https://medicalgearoutfitters.com/blogs/firstaid/

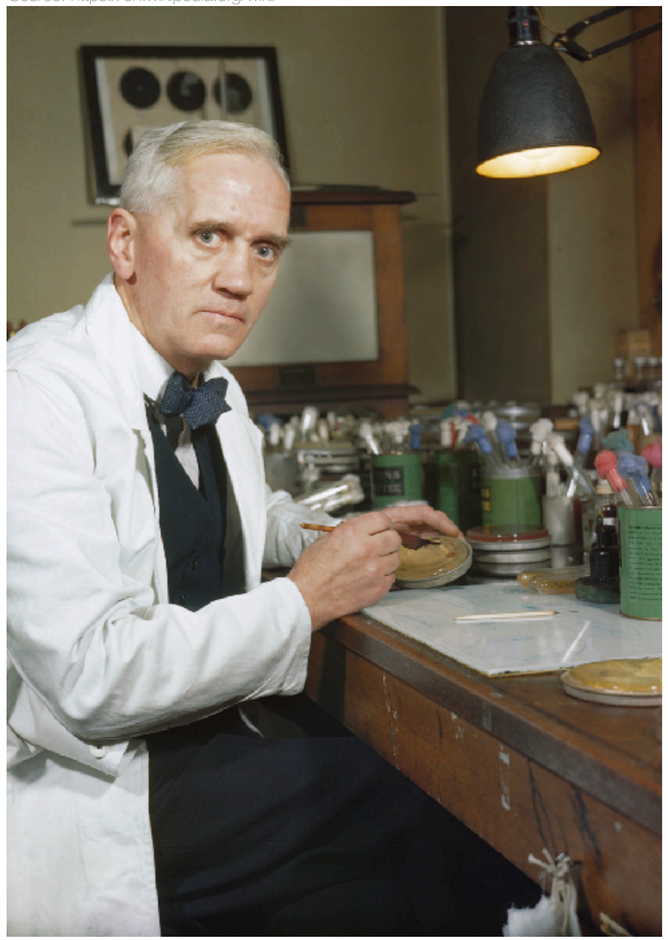
… cutting your finger

Source: https://www.eatsmartproducts.com/blogs/blog/

… eating leftovers

Until this guy came along

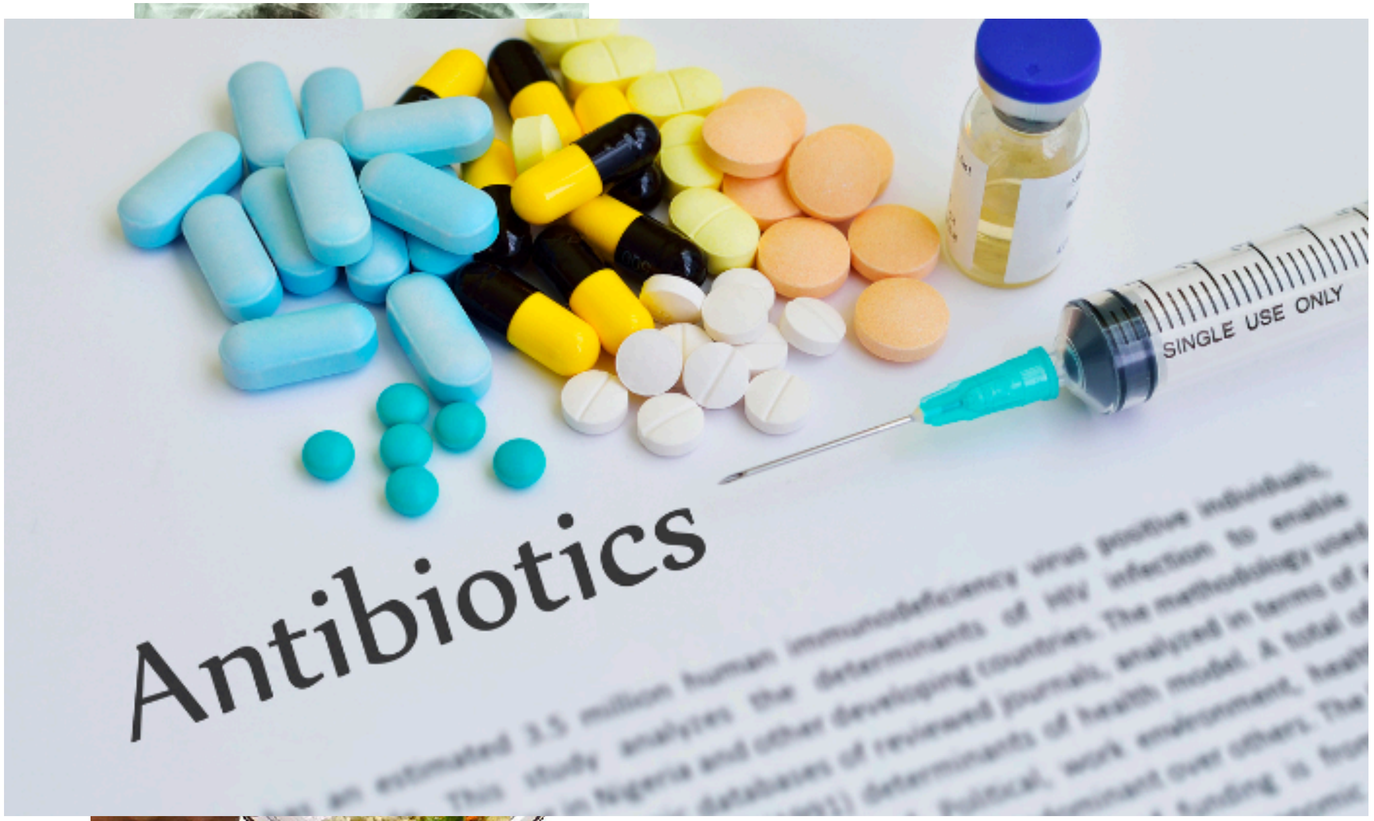
Source: https://en.wikipedia.org/wiki/



Alexander Fleming

We found antibiotics!

Source: https://www.hsph.harvard.edu/ecpe/



Source: https://www.urgentcaremds.com/

… eating leftovers

Until this guy came along

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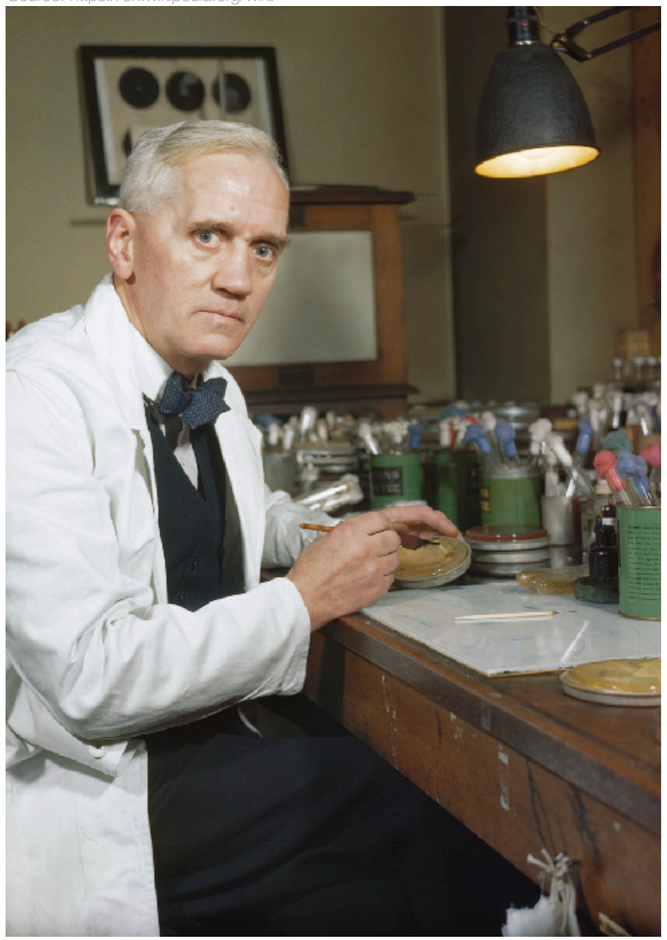
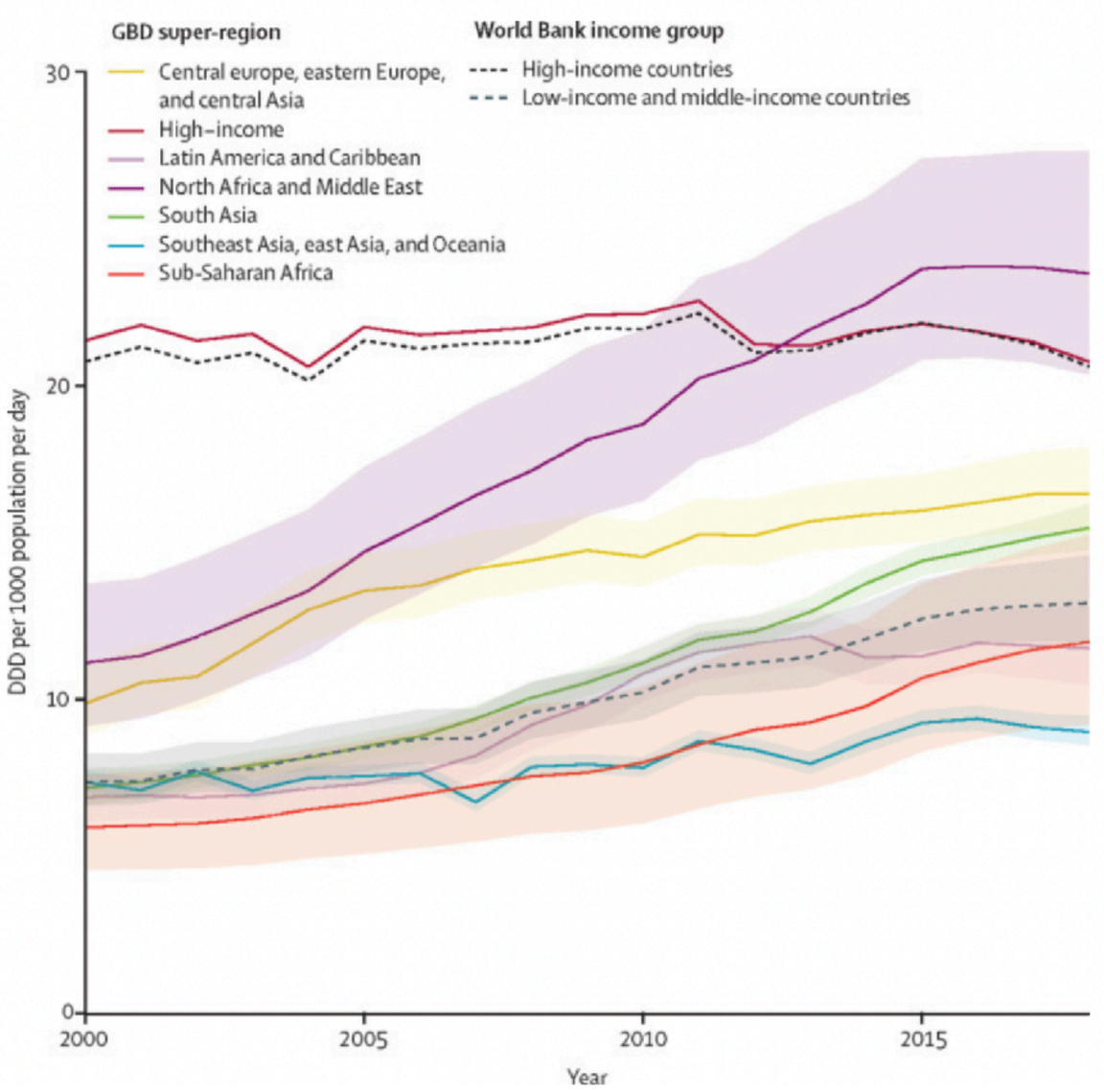


Alexander Fleming

But we overdid it…

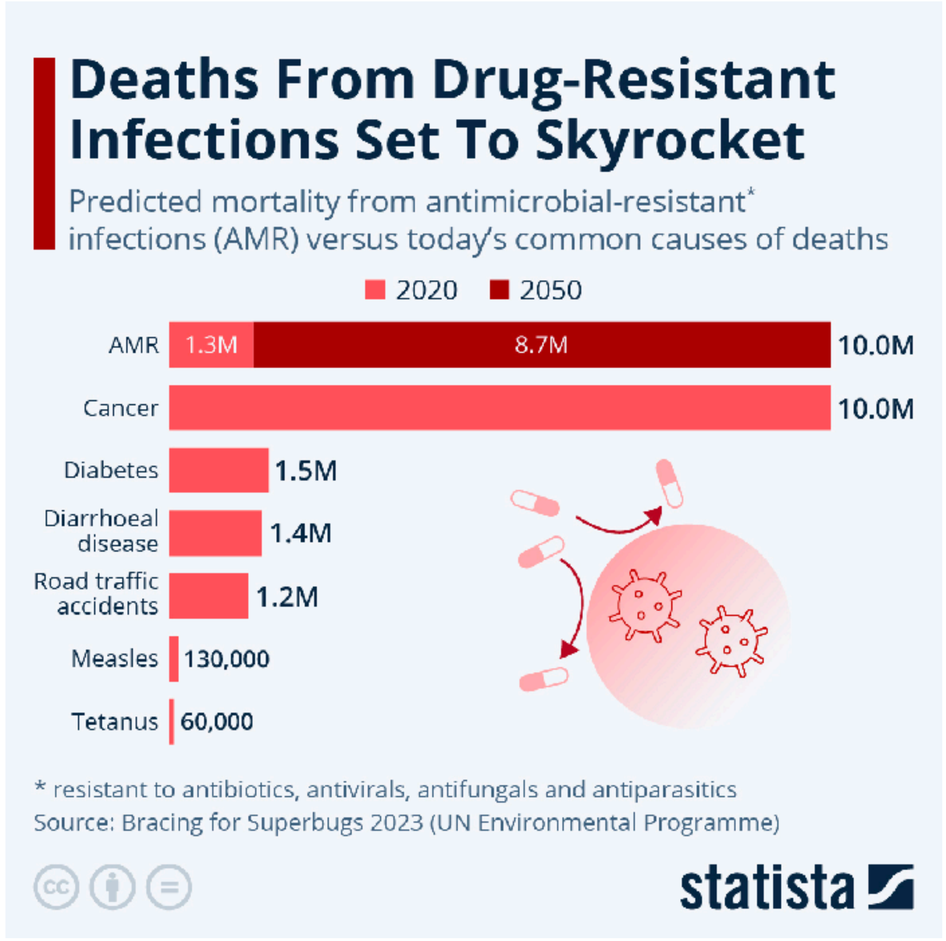
Source: https://www.healthywomen.org/content/blog-entry/



Source: https://www.thelancet.com/journals/lanplh/article/PIIS2542-5196%2821%2900280-1/fulltext

We created Methicillin-resistant Staphylococcus aureus (MSAR) and other “superbugs”

Definition: Superbugs are strains of bacteria that are resistant to most of the antibiotics and other medications commonly used to treat the infections they cause. A few examples of superbugs include resistant bacteria that can cause pneumonia, urinary tract infections and skin infections.



UF study: Silent MRSA carriers have twice the mortality rate of adults without the bacteria

March 29, 2021 · By Jill Pease · Media Contact · Share

NBC NEWS U.S. AIRSTRIKES POLITICS U.S. NEWS WORLD BUSINESS HEALTH NBC NEWS TIPLINE VID

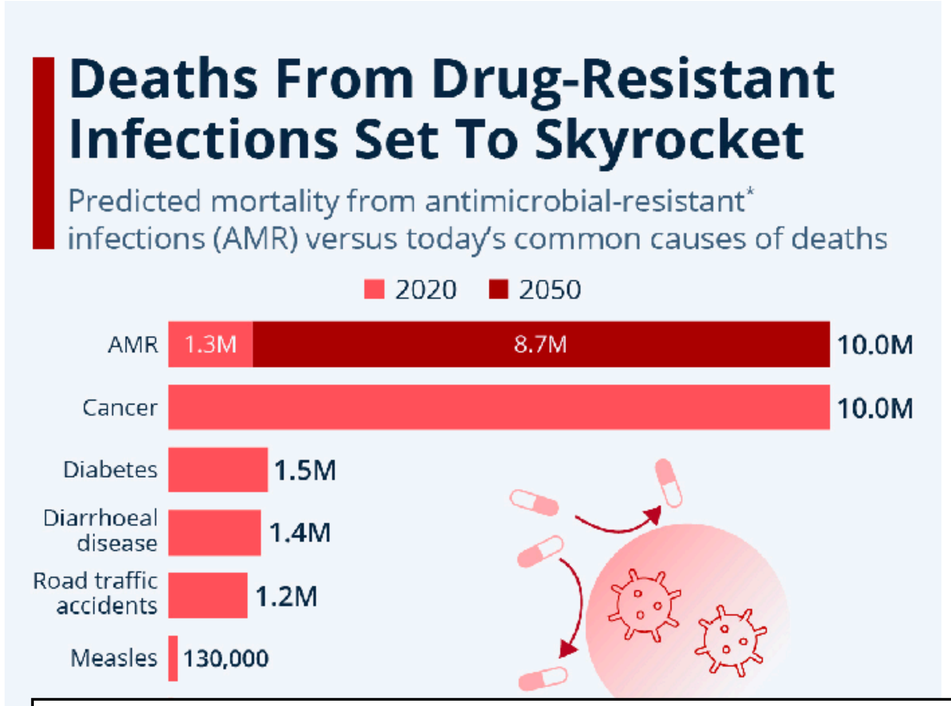
Deadly superbug MRSA can linger on surfaces in the home for months

But good hygiene can help prevent the bacteria from spreading.

Infectious Disease Experts Update Rules on 'Superbug' Spread in Hospitals

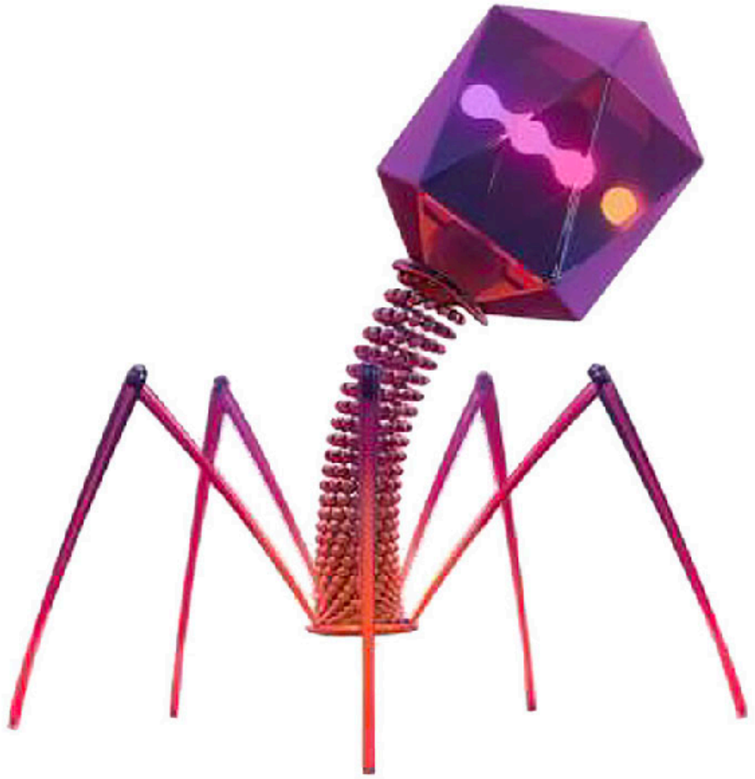
By HealthDay | June 27, 2023, at 1:38 p.m.

We created Methicillin-resistant Staphylococcus aureus (MSAR) and “superbugs”



The days of dying from cutting your finger could come back!

We need new medication to treat superbugs



Source: https://www.poultryworld.net/health-nutrition/

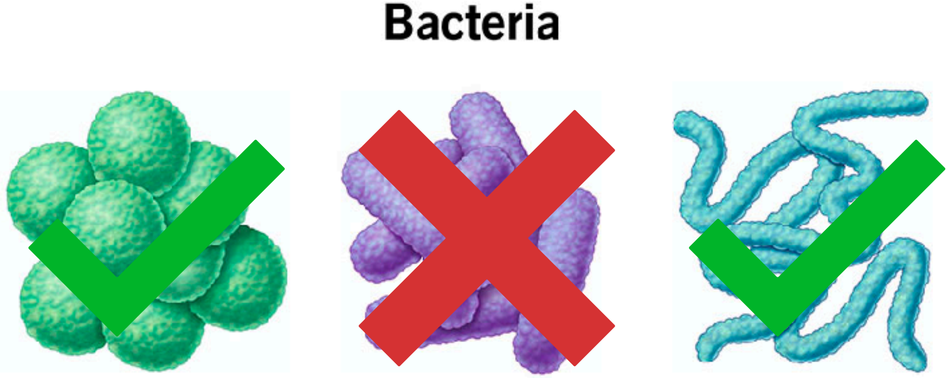
Phages could save us

The concept of phage therapy

Source: https://www.taconic.com/resources/phage-therapy-antibiotic-resistance

Phages could

- Efficiently kill bacteria
- Do not target any human cells
- Target specific bacteria (unlike antibiotics)
- Lessen antibiotic resistance risk
- Enable personalized treatment



Source: https://my.clevelandclinic.org/health/articles/24494-bacteria

Source: https://en.wikipedia.org/wiki/

Felix D'Herelle

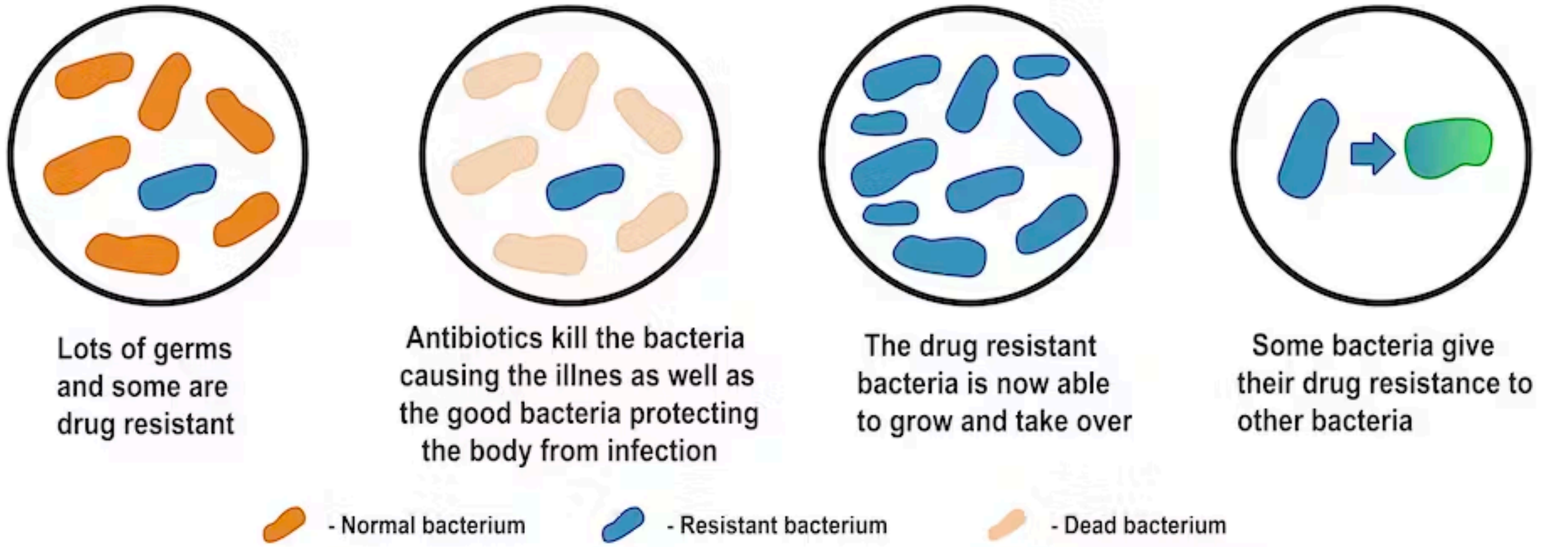
A personal story on phage therapy

Source: https://asm.org/articles/2022/august/phage-therapy-past,-present-and-future

Tom Patterson and Steffanie Strathdee

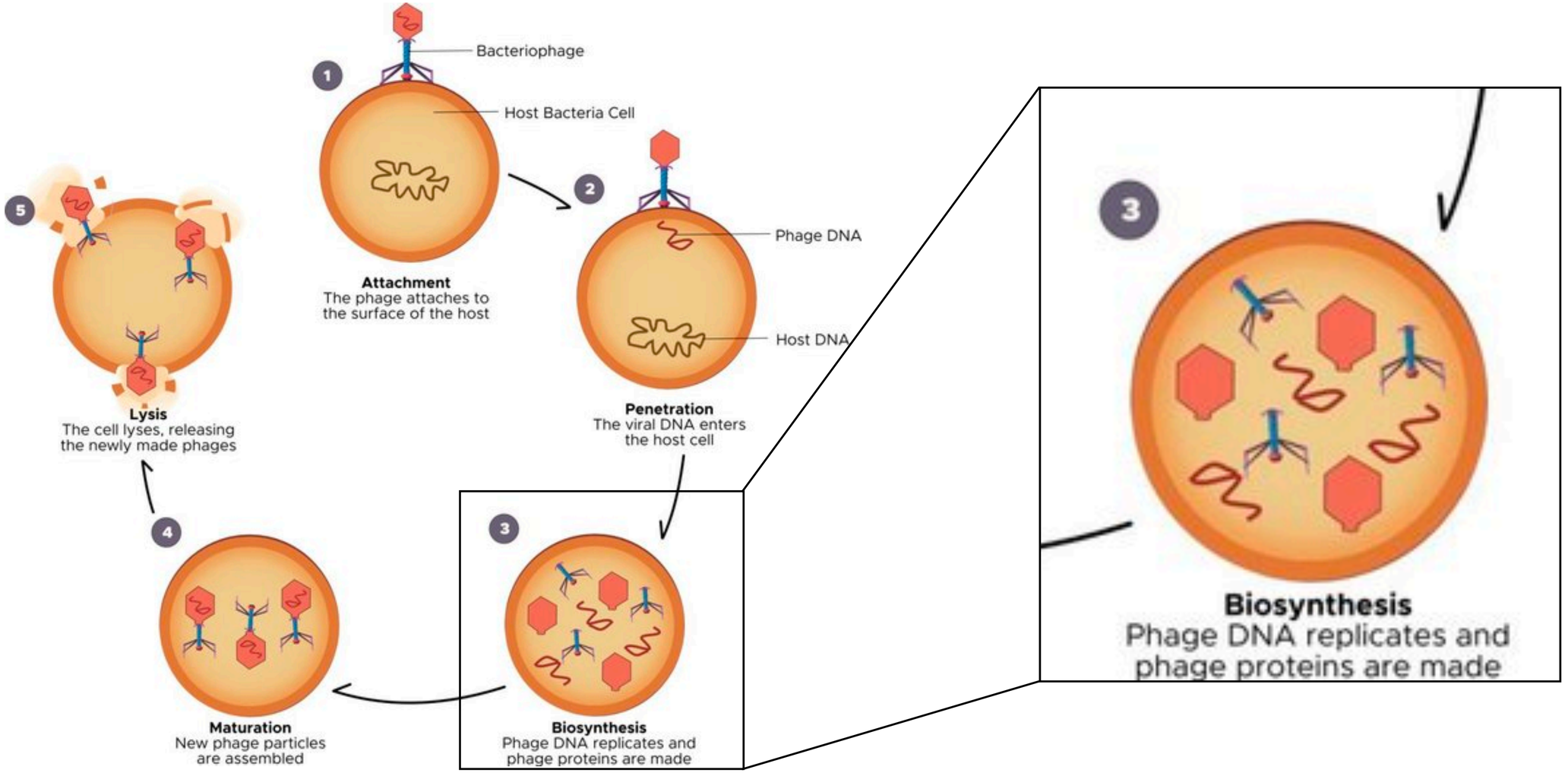
Why don’t we just continue using phage therapy?

Bacteria can get resistant



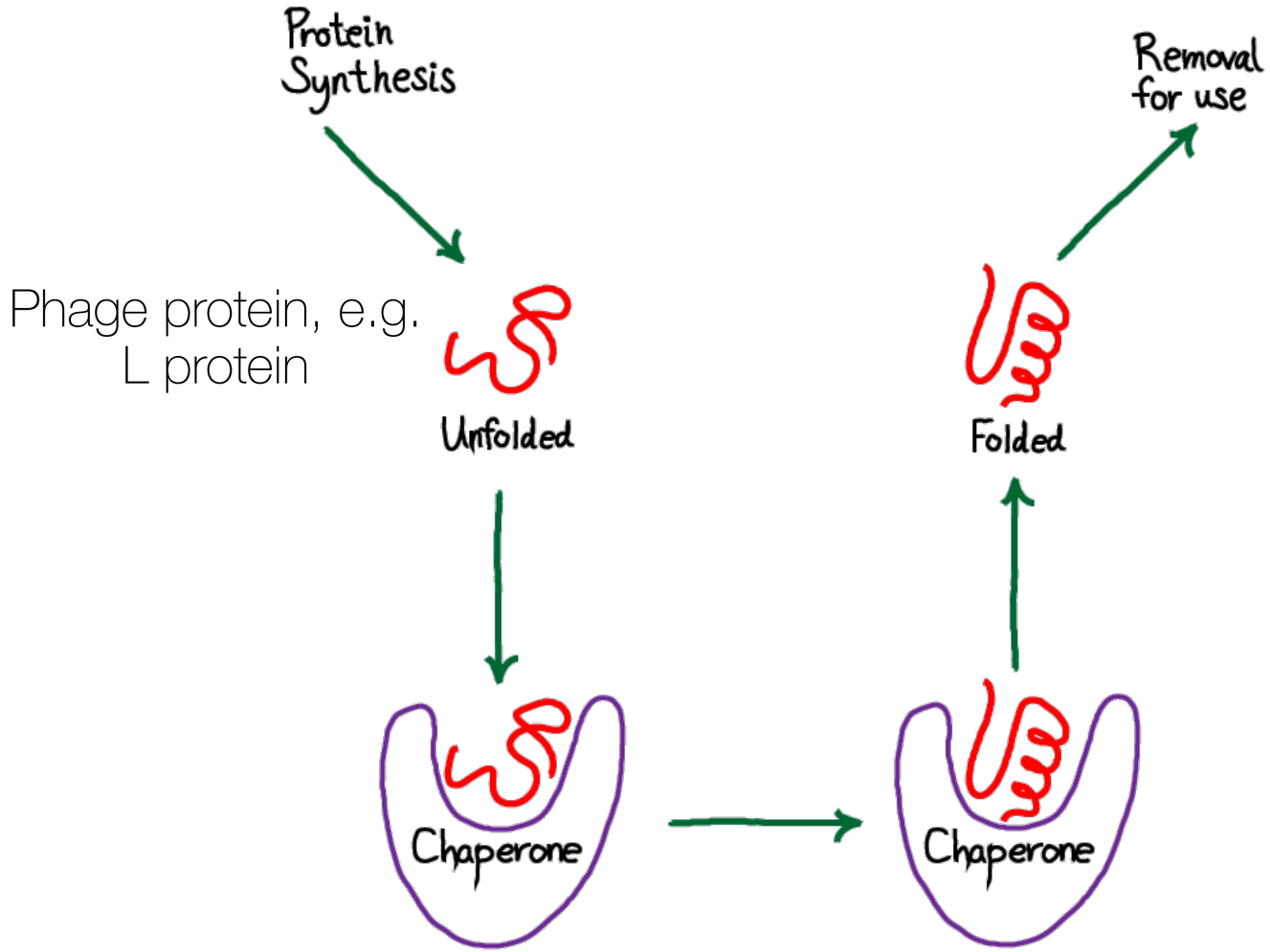
Source: https://theconversation.com/how-to-train-the-bodys-own-cells-to-combat-antibiotic-resistance-106052

How do bacteria get resistant?



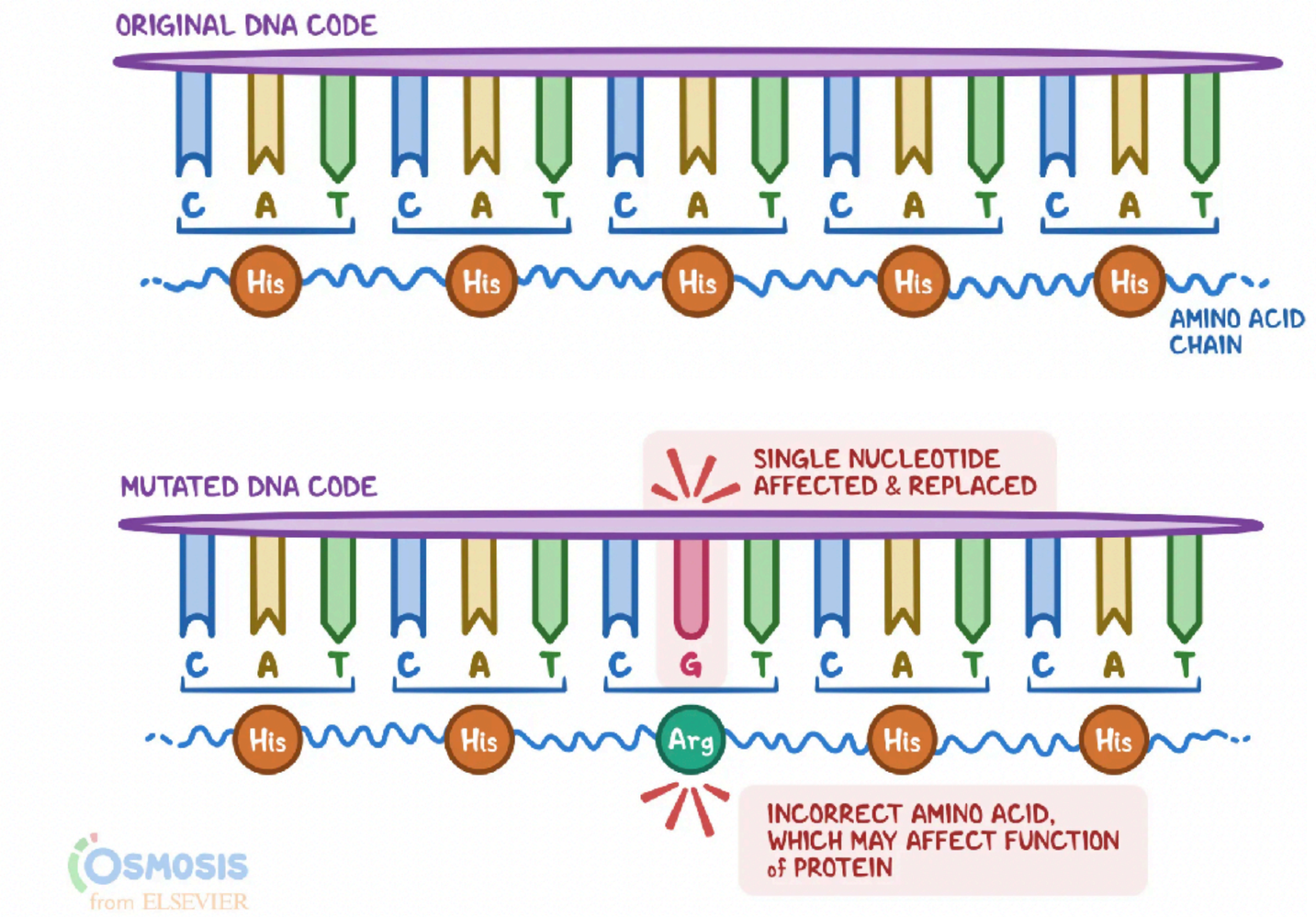
Source: Adesanya et al. AIMS Microbiology 2020

An example for phage dependency on bacterial proteins



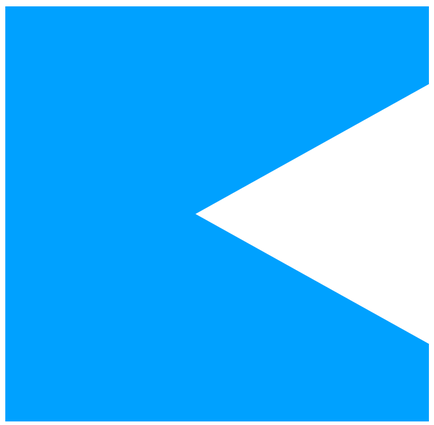
Source: https://physicallensonthecell.org/molecular-machinery/chaperone-aided-protein-folding

How do bacteria get resistant?



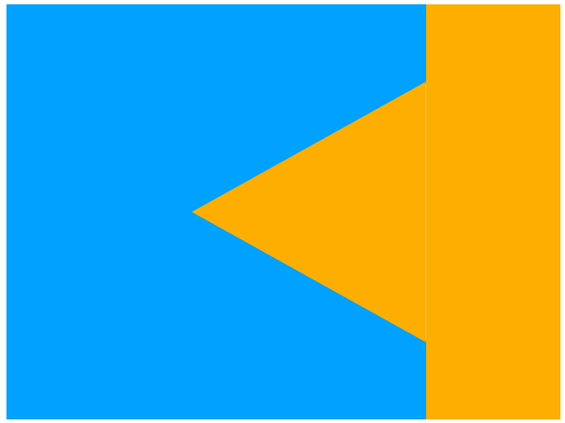
Source: https://www.osmosis.org/answers/missense-mutation

How do bacteria get resistant?



Bacterial protein

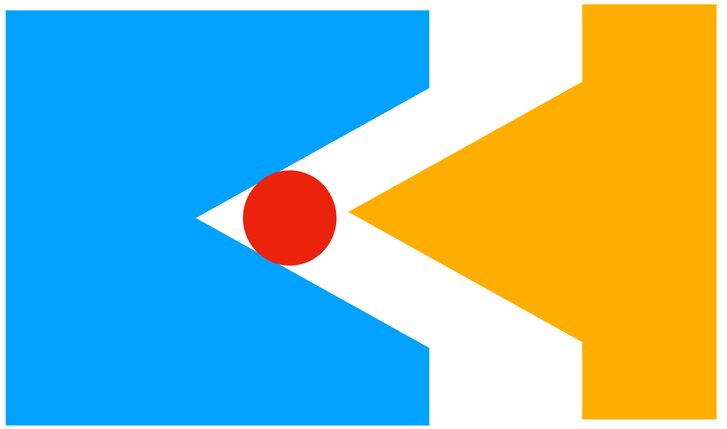
Phage protein



No mutation

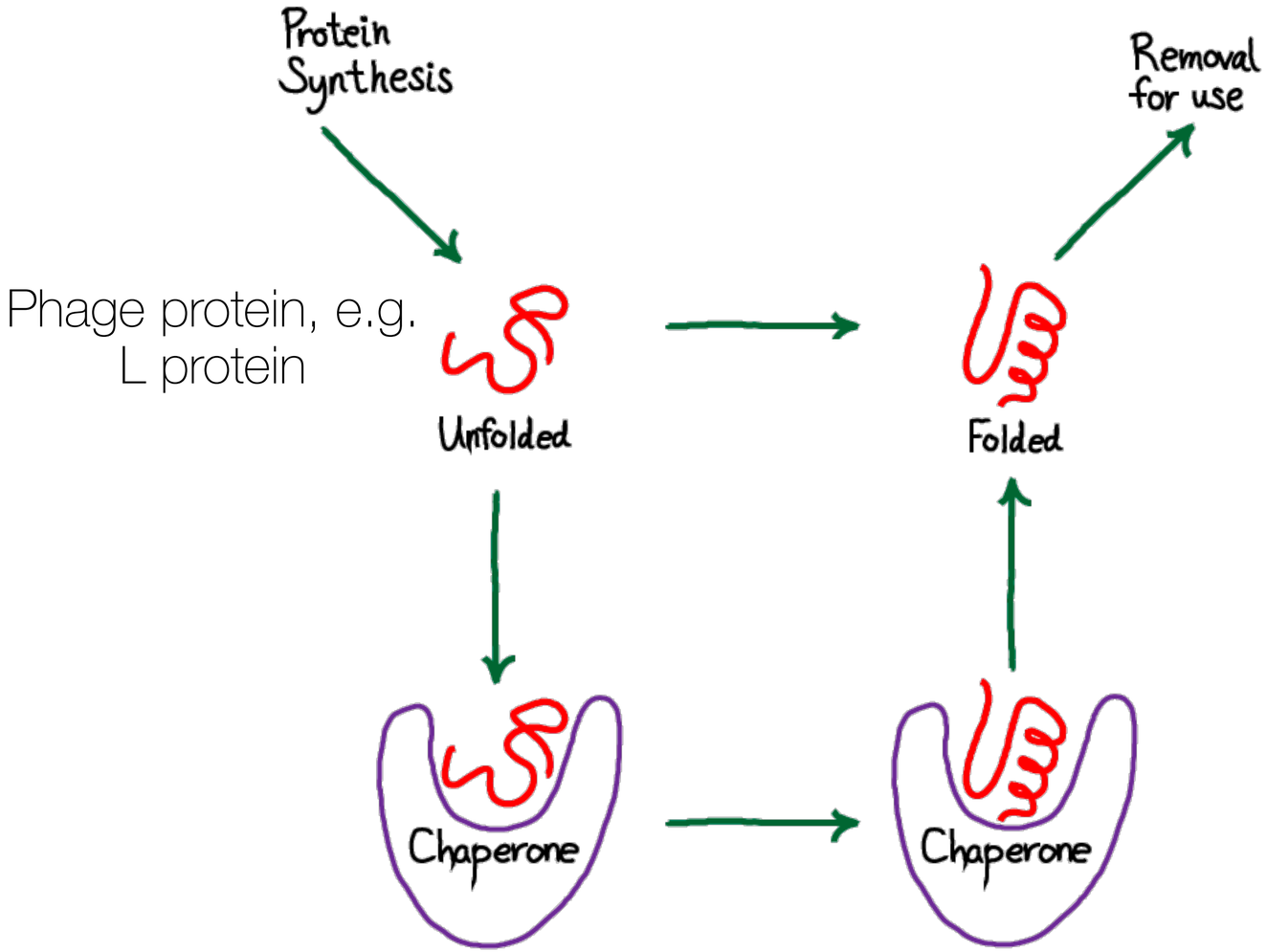
E.g. DnaJ

E.g. L protein



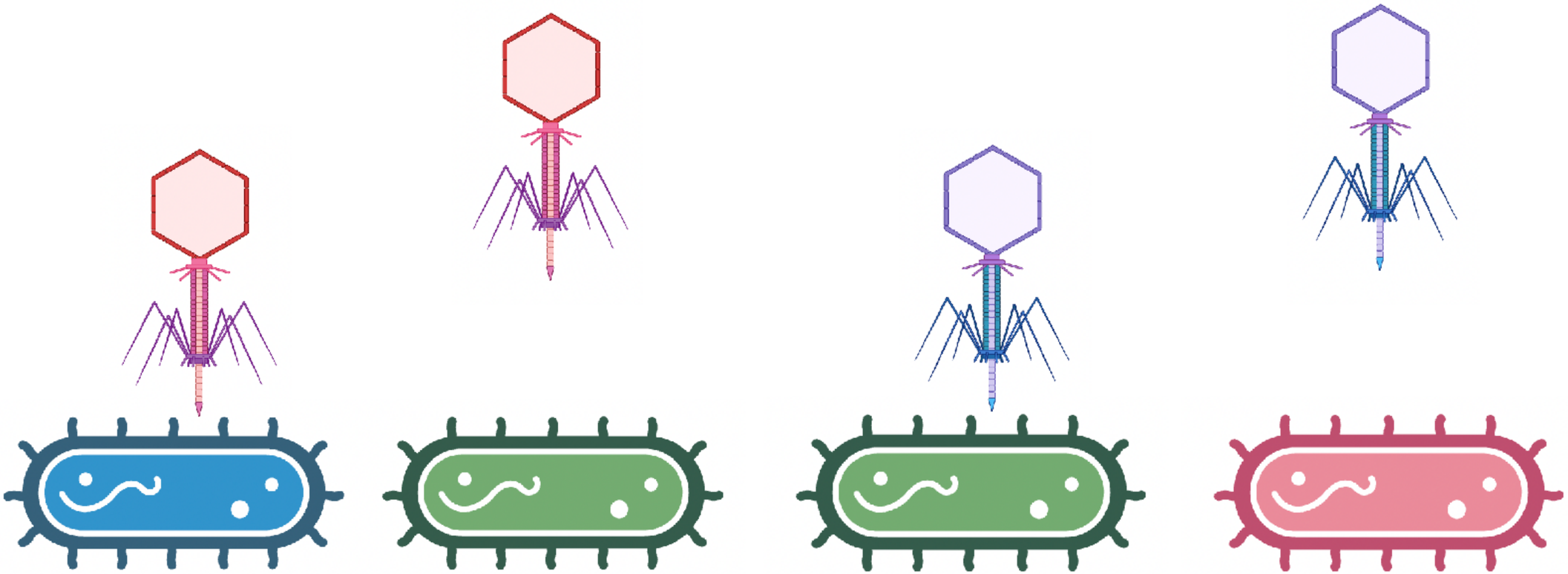
Mutated

But phages are not helpless!



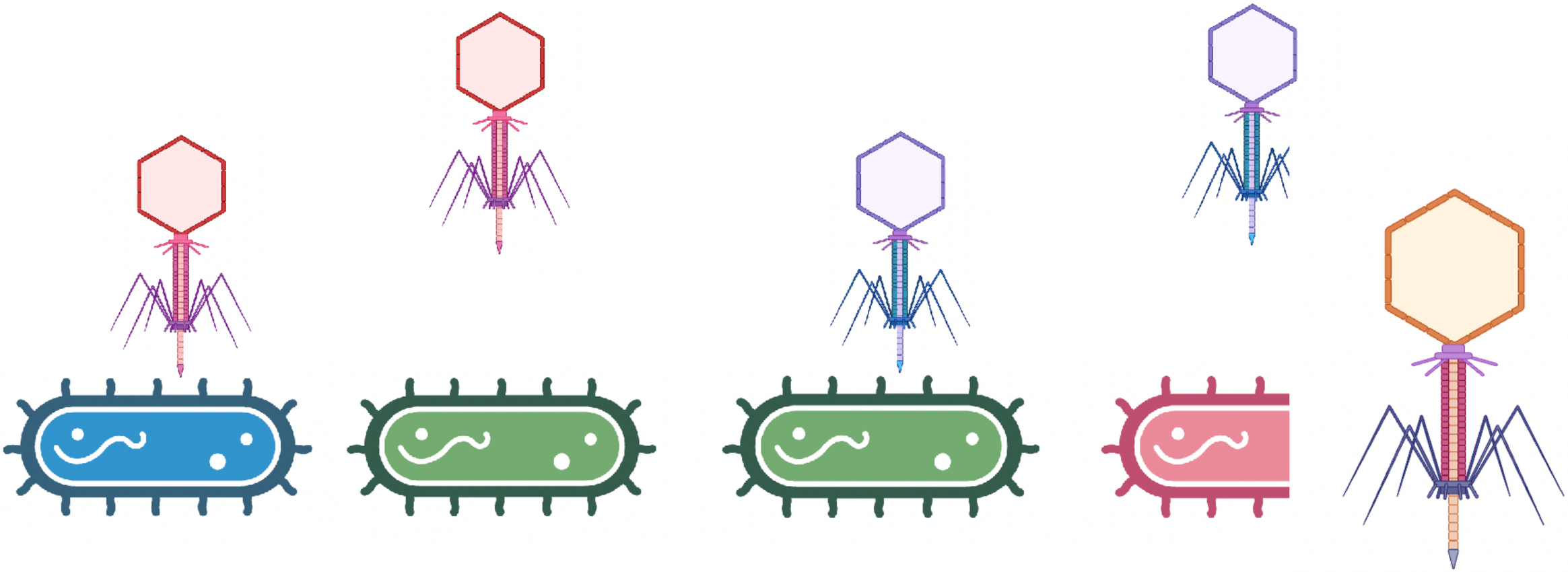
Source: https://physicallensonthecell.org/molecular-machinery/chaperone-aided-protein-folding

Co-evolution of phages and bacteria

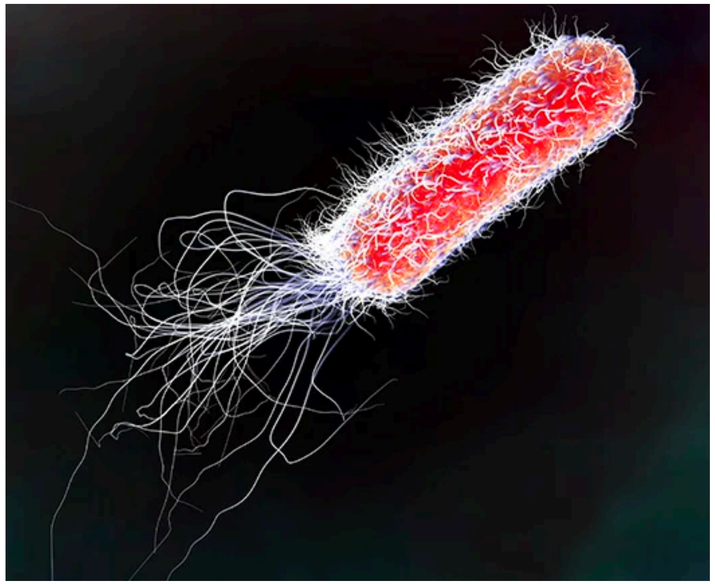


It’s an arms race!

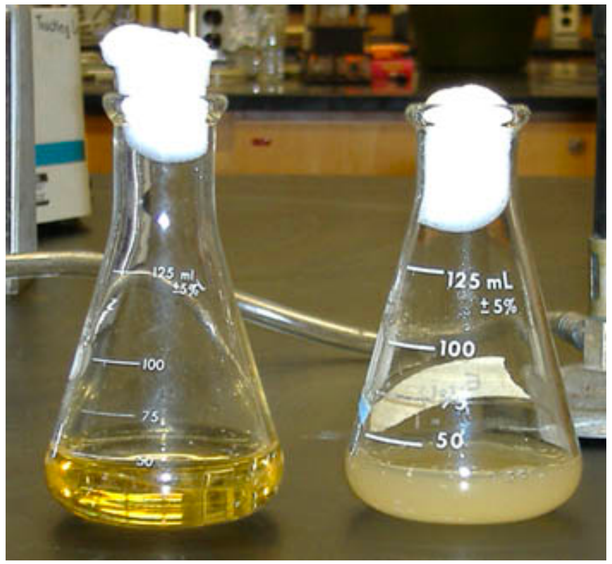
We can engineer phages to overcome resistance



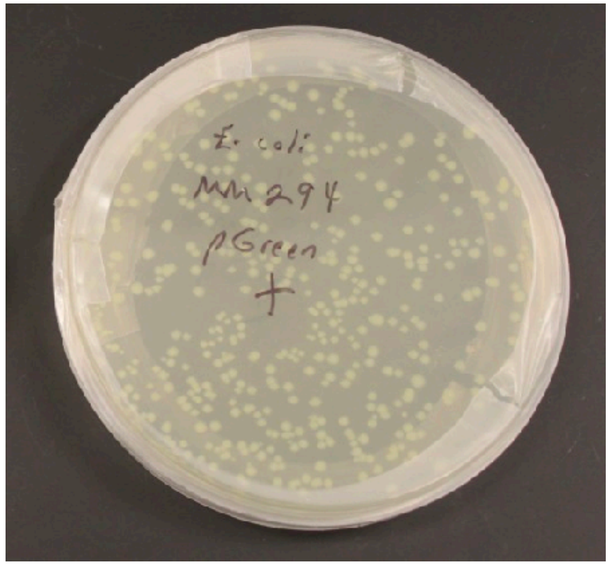
Escherichia coli or E. Coli



Source: https://biolabtests.com/top-facts-ecoli/

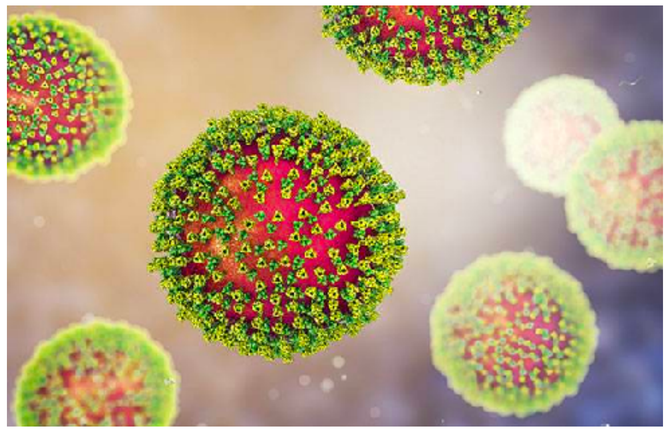


Source: https://app.jove.com/t/2754/

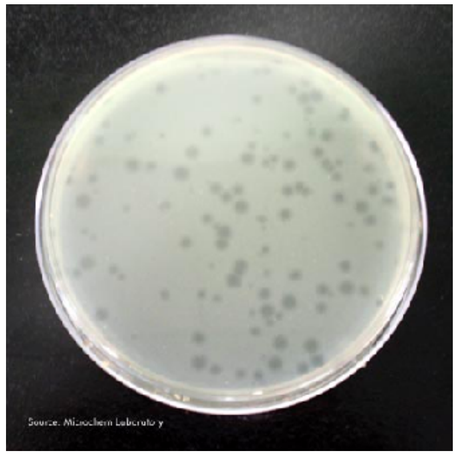


Source: https://hawaiireedlab.com/wpress/?p=49

And it's phage: MS2

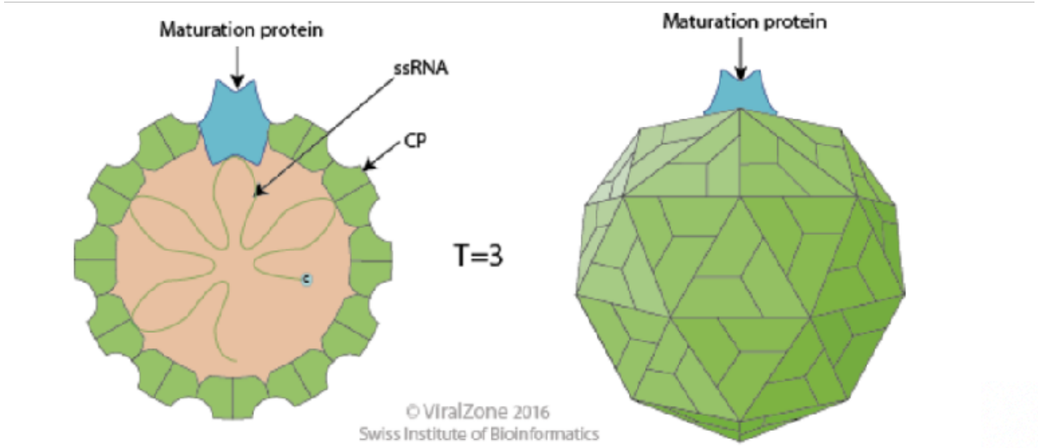


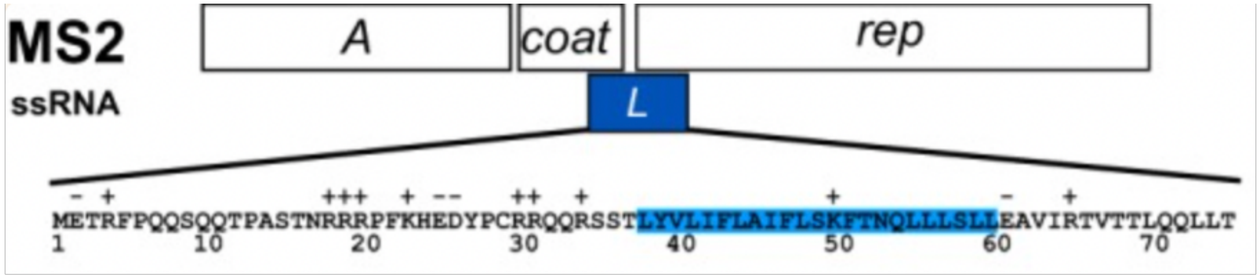
Source: https://www.h-h-c.com/what-is-ms2-bacteriophage-and-its-ultimate-usage/



Source: https://microchemlab.com/information/ms2-bacteriophage-viral-screening-tool/

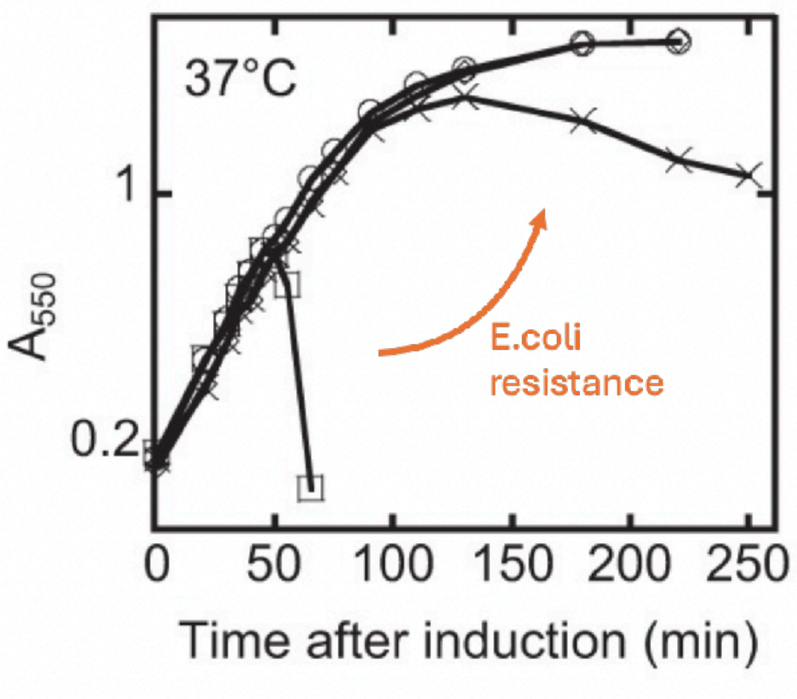
MS2 phages





Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5446614/

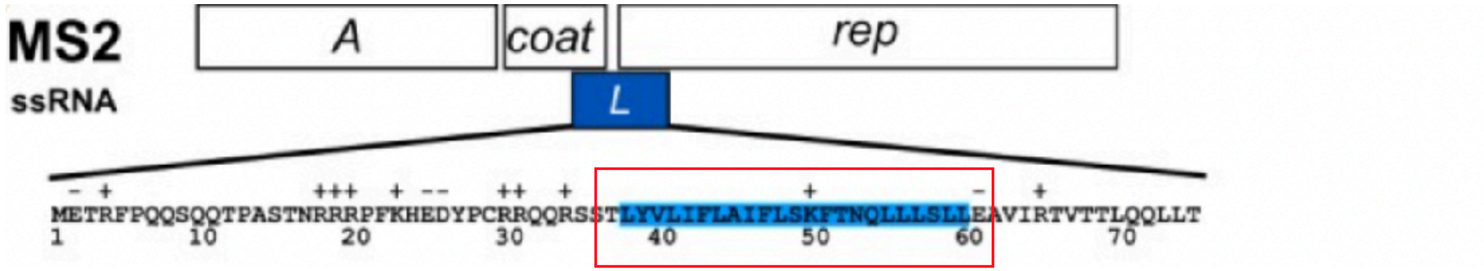
- No tail, no legs
- Genome: single-stranded RNA
- Almost 10x smaller than T4 phage



Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5446614/

○ Non-mutated E.coli only
□MS2 + non mutated E. coli
x MS2 + mutated E. coli

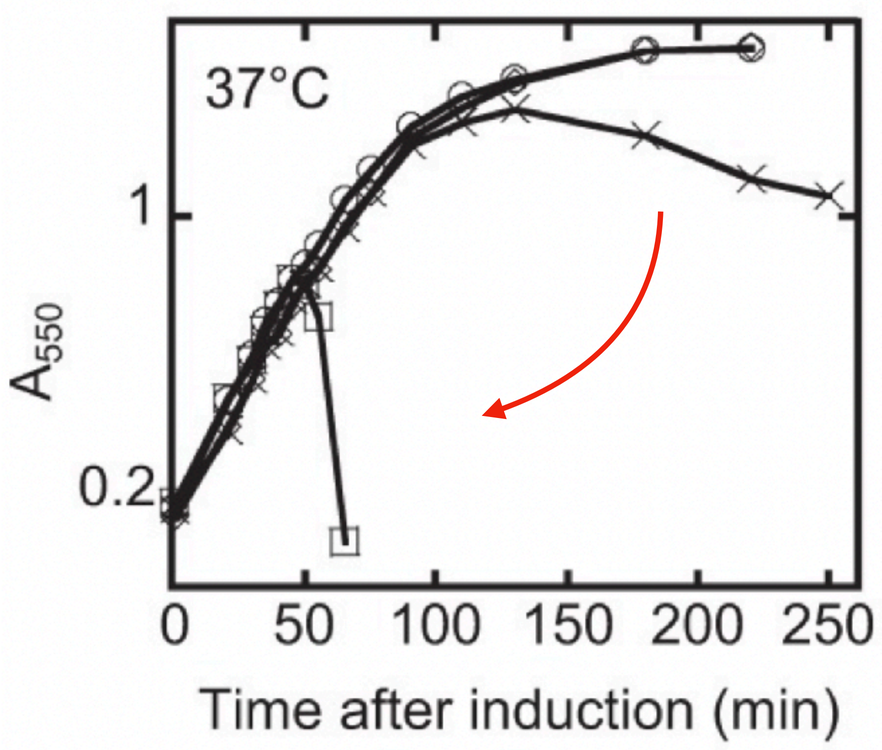
Group project



Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5446614/

What can we do?

- More lysis protein
- Increase lysis protein stability
- Increase toxicity
- Lessen resistance risk



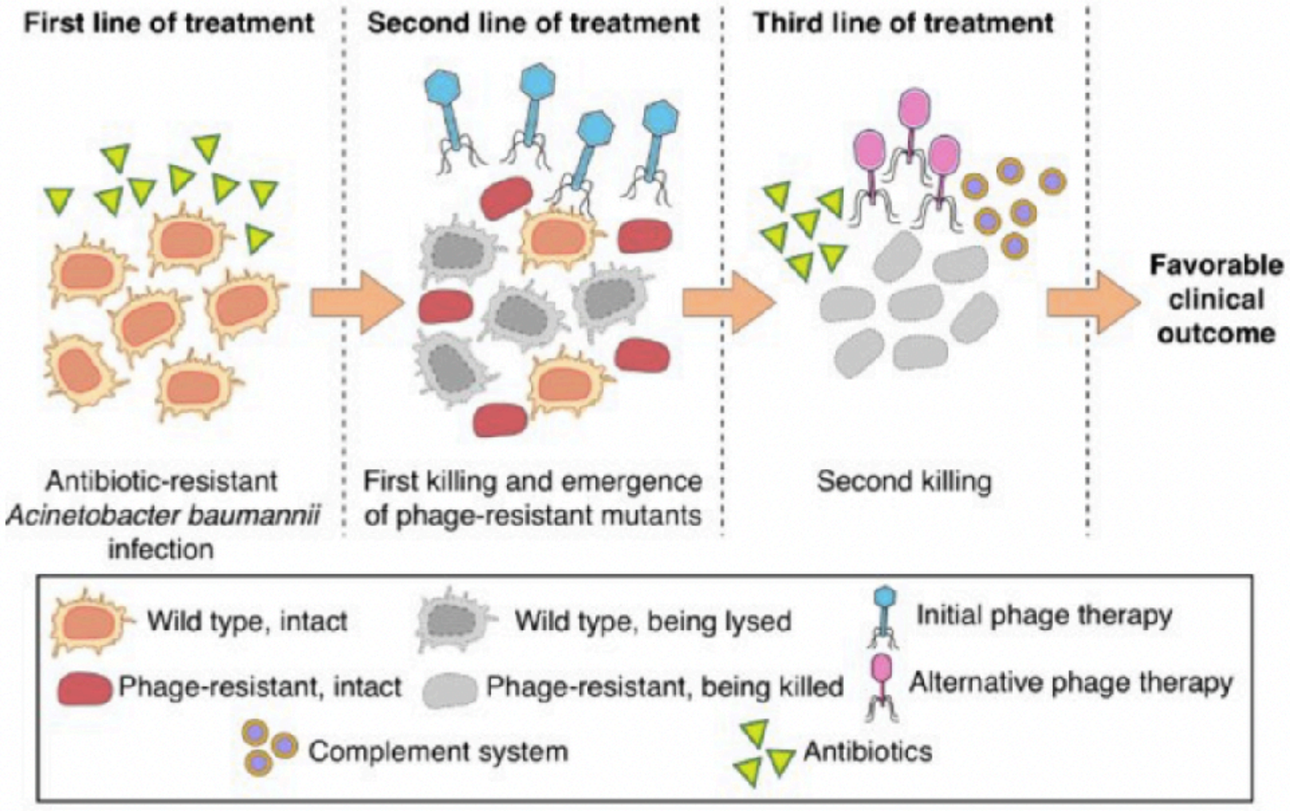
Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5446614/

○ Non mutated E.coli only

□ MS2 + non mutated E. coli

x MS2 + mutated E. coli

Combination of phages with antibiotics



Source: Altamirano, 2020, Preprint (https://www.researchgate.net/publication/339531457_Bacteriophages_targeting_Acinetobacter_baumannii_capsule_induce_antimicrobial_resensitization

Take home messages

- Phages are pretty cool!
- Phages are viruses that infect bacteria
- Bacteria can mutate their DNA to become resistant
- Bacteria can be resistant against antibiotics and against phages, but it’s hard to be resistant against both
- Scientists have tools to modify phages and make them more equipped to battle resistant bacteria