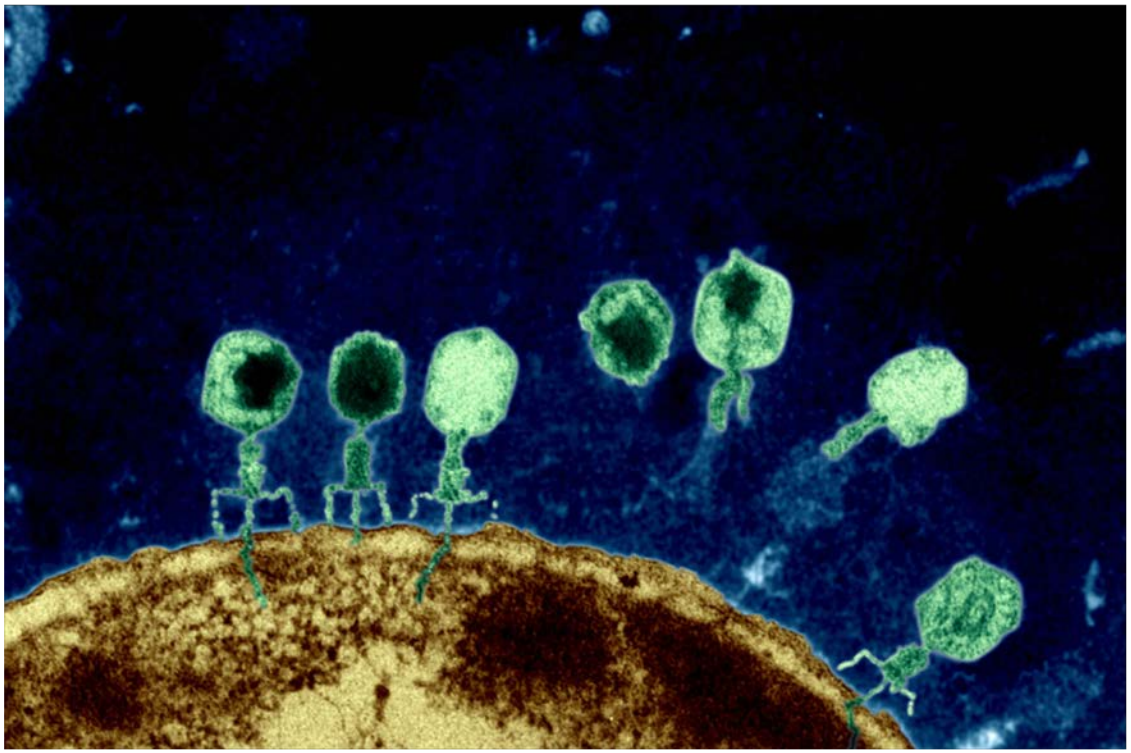
Bacteriophages, how significant will their impact be?



Department of Genetics and Genome Biology
University of Leicester
mrjc1@le.ac.uk

Thanks to Leicester Phage Lab

Janet Nale
Jinyu Shan
Anisha Thanki
Chris Turkington
Nathan Brown
Jeff Chen
III and Microbiology Colleagues
Natalie Allcock

Andy Millard
Ed Galyov

Andrew Kropinski (Guelph)

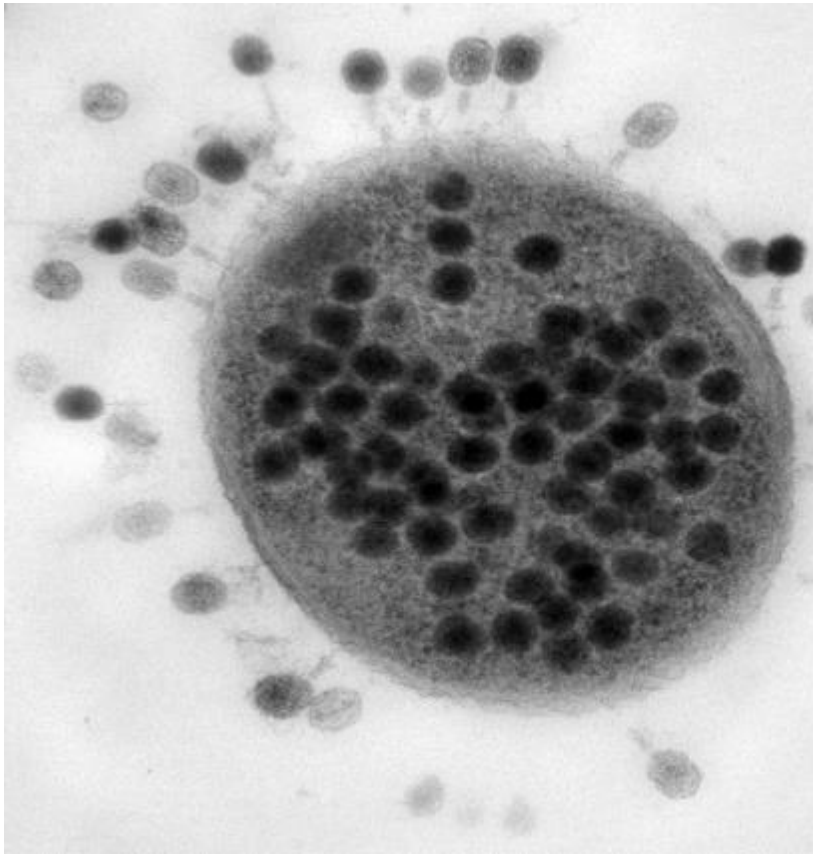
Gill Douce
Janice Spencer
(Glasgow)

Phages for Global Health

ENBIOTIX
AMPLIPHI BIOSCIENCES CORPORATION
BILL & MELINDA GATES foundation
The Leverhulme Trust
Sparks For children's health
MRC Medical Research Council
wellcome trust
THE ROYAL SOCIETY CELEBRATING 350 YEARS
Innovate UK

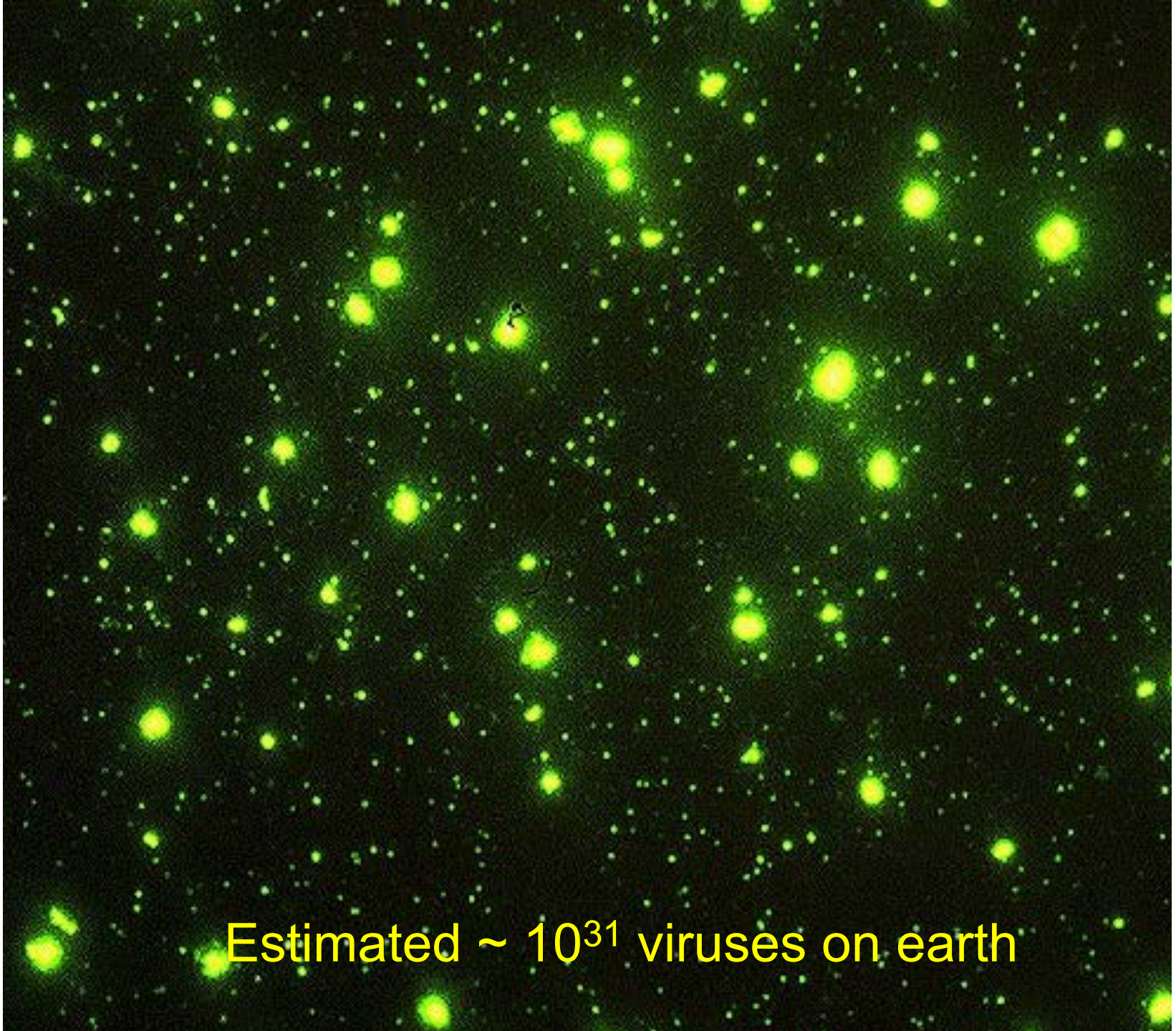
Outline

- What is a phage?
- How phages can help address the AMR challenges?
- To make this happen what do we need to do?



What is a phage and how does it work?

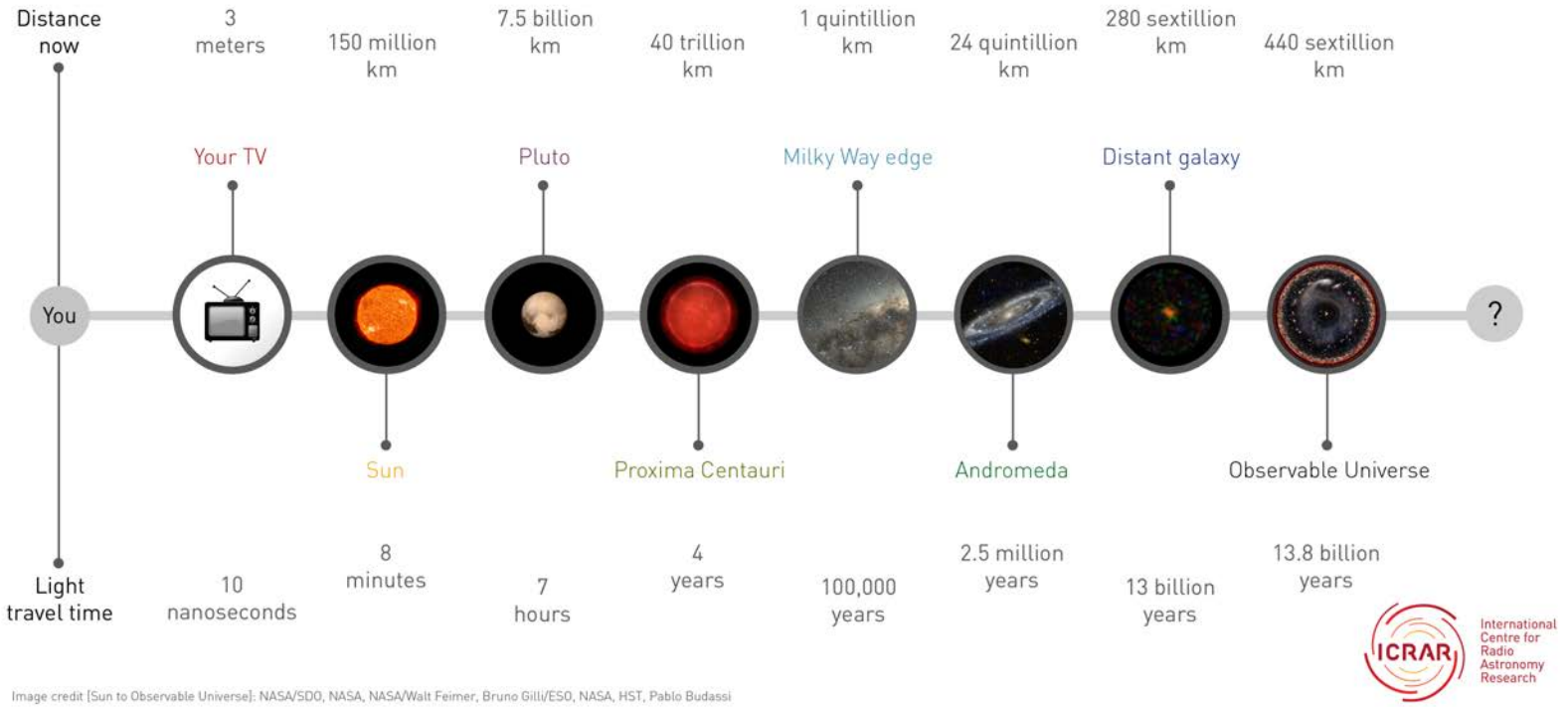
https://vimeo.com/10701736



(Courtesy J.D.Fuhrman)

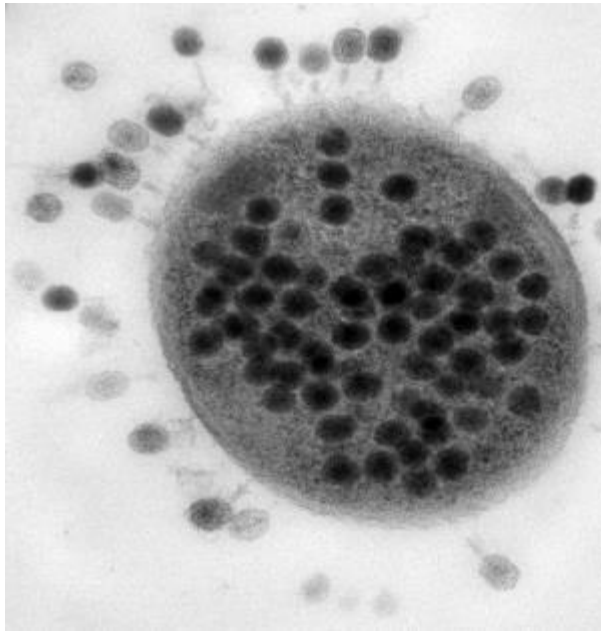
Diversity and abundance being revealed by the ‘sequencing revolution’….

- Bacterial sequencing
  - shown how common phages are in bacterial genomes
- Metagenomic sequencing -
  - Getting a better handle on phage numbers/diversity



Natural roles of phages

- Phage are ancient and ubiquitous
  - 10^{31}
  - we are constantly surrounded with them
  - they play key roles in maintaining microbial balance



Population dynamics

Release carbon and nutrients

Evolution via horizontal gene transfer

Can be exploited to target
and kill problematic bacteria

World Health Organization

Health topics | Countries | News | Emergencies | About us

Home / News / Detail / Stop using antibiotics in healthy animals to prevent the spread of antibiotic resistance

Stop using antibiotics in healthy animals to prevent the spread of antibiotic resistance

العربية | 中文 | Français | Русский | Español

7 November 2017 | News Release | Geneva

WHO is recommending that farmers and the food industry stop using antibiotics routinely to promote growth and prevent disease in healthy animals.

The new WHO recommendations aim to help preserve the effectiveness of antibiotics that are important for human medicine by reducing their unnecessary use in animals. In some countries, approximately 80% of total consumption of medically important antibiotics is in the animal sector, largely for growth promotion in healthy animals.

- WHO guidelines on use of medically important antimicrobials in food-producing animals

Over-use and misuse of antibiotics in animals and humans is contributing to the rising threat of antibiotic

Media Contacts

Related

THE TIMES

Max 25C min 5C

Wednesday July 2 2014 | thetimes.co.uk | No 71238

Only 60p to members

Butter! Meat! Eggs! Cheese!

Why we can all eat fat again Times2

the game

World Cup special

Pullout insie

Superbugs threaten return to dark ages

Worldwide

Britain to lead fight against antib

Chris Smyth Health Correspondent

Britain will lead a global fightback against antibiotic-resistant superbugs to prevent the world from being "cast back into the dark ages of medicine", David Cameron is to announce today.

at an alm
antibiotics
back into t
treatable i
once again
"That s
happened

Newsweek

U.S. WORLD BUSINESS TECH & SCIENCE CULTURE SPORTS CAREER

Empowering Business

Microsoft Cloud

What is the career path of a successful CEO?

TECH & SCIENCE

Beyond Antibiotics

BY ROGER HIGHFIELD / MAY 27, 2014 4:58 AM PDT

There is much we can learn from phages, even though they are nothing more than a scrap of genetic code in a protein overcoat

Roger Highfield

NEWS IN FOCUS

CLIMATE CHANGE Grasslands experiments aim to fix holes in vegetation knowledge p.16

REGENERATIVE MEDICINE Salvaged stem-cell trial offers fresh hope for spinal injuries p.18

POLICY Constitutional changes free up German science funding p.19

ENERGY Race to build an artificial leaf in the lab heats up p.22

Bacteriophages could be a resource for fighting drug-resistant bacterial infections.

MICROBIOLOGY

Phage therapy gets revitalized

The rise of antibiotic resistance rekindles interest in a century-old virus treatment.

BY SARA REARDON

For decades, patients behind the Iron Curtain were denied access to some of

them to treat patients for nearly a century.

Now, faced with the looming spectre of antibiotic resistance, Western researchers and governments are giving phages a serious look.

Phagoburn: the first large, multi-centre clinical trial of phage therapy for human infections, funded by the European Commission.

Ryland Young, a virologist at Texas A&M University in College Station, attributes the previous lack of Western interest to clinicians' preference for treating unknown infections with broad-spectrum antibiotics that kill many types of bacterium. Phages, by contrast, kill just one species or strain. But researchers now realize that they need more precise ways to target pathogenic bacteria, says microbiologist Michael Schmidt of the Medical University of South Carolina in Charleston. Along with the rising tide of strains resistant to last-resort antibiotics, there is growing appreciation that wiping out the human body's beneficial microbes along with disease-causing ones can create a niche in which antibiotic-resistant bacteria can thrive. "Antibiotics are a big hammer," Schmidt says. "You want a guided missile."

Finding a phage for a bacterial target is relatively easy, Young says. Nature provides an almost inexhaustible supply: no two identical phages have ever been found. As a bacterium becomes resistant to one phage — by shedding the receptor on the cell surface that the virus uses to enter — the Eliava Institute researchers simply add more phages to the viral cocktails that patients receive. Kutateladze says that they update their products every eight months or so, and do not always know the exact combination of phages that make up the cocktail.

Resch, who is one of the leaders of the Phagoburn study, says that regulatory agencies would need to figure out how to oversee such a rapidly evolving product before the therapy could progress beyond clinical trials. He hopes that phage therapy will be treated in a similar way to the seasonal influenza vaccine, for instance, which is updated every year as new flu strains emerge.

The fact that the European Union (EU) is contributing €3.8 million (US$5.2 million) to the Phagoburn study shows that it is willing to consider the approach, Resch says. Beginning

Alternatives to conventional antibiotics

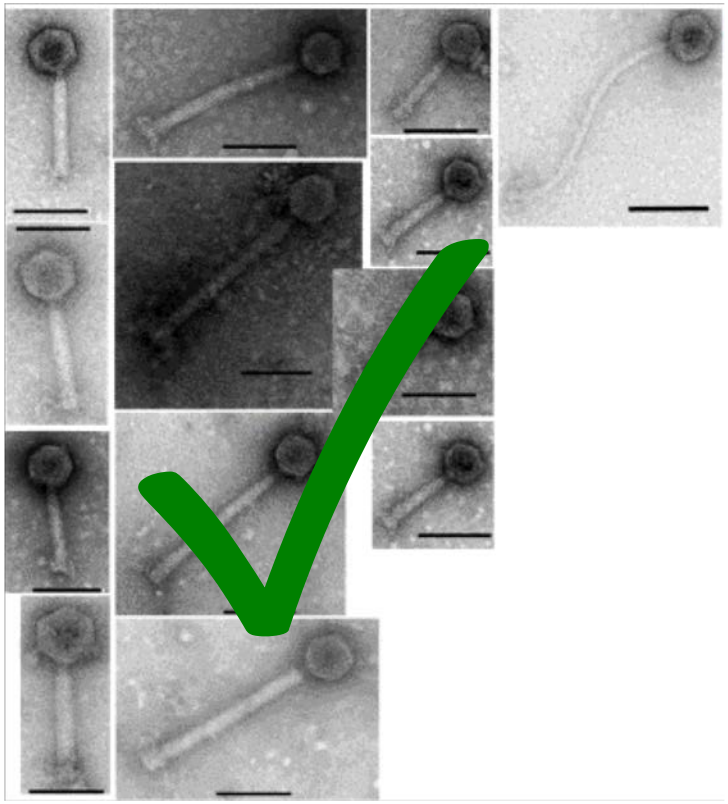
- Antibodies
- Probiotics
- Lysins
- Wild Bacteriophages
- Engineered phages
- Immune stimulation
- Vaccines
- Antimicrobial peptides
- Host/innate defense peptides
- Antibiofilm peptides

Alternative Approach	Comment	Likely spectrum of activity and initial use	Recommendation over the next 5 years	Refs
Tier 1 (Primarily translational - funding to clinical evaluation)				
Antibodies	Antibodies that bind to and inactivate a pathogen, its virulence factors, or its toxin(s) were widely considered one of the alternative approaches most likely to have clinical impact. Antibodies were considered a relatively low risk area with strong underpinning science, safe history of use and a high degree of technical feasibility.	Prevent G+ and G- infection, possibly also adjunct use	Basic R&D and Translational	2–6
Probiotics	Probiotics are defined as "live microorganisms which when administered in adequate amounts confer a health benefit on the host organism". It is considered likely that defined mixtures of bacteria or the use of non-toxigenic spores of *C. difficile* will provide therapeutic and prophylactic therapies that will improve on current clinical practice in the treatment of CDAD/AAD	Prevent or treat CDAD/AAD	Translational	7–12
Lysins	Phage lysins are enzymes used by bacteriophage to destroy the cell wall of a target bacterium and are potential replacements for antibiotics because of their direct antibacterial action and also as adjuncts because they may act to reduce bacterial burden and/or weaken biofilms which may aid traditional antibiotic activity	Treat G+ infection	Basic R&D and Translational	13–20
Wild-type Bacteriophages	Wild-type bacteriophage which infect and kill bacteria have potential to replace antibiotics at least for some indications	Treat G+ and G- infection	Basic R&D and Translational	21–25
Engineered Bacteriophages	The ability to screen wild type phage for optimal starting points and to subsequently genetically engineer and/or to perform iterative selections to artificially evolve innovative new phage for therapeutic use is compelling	Treat G+ and G- infection	Basic R&D and Translational	26–29
Immune Stimulation	Successful antimicrobial therapy depends on a supportive immune response. Immune stimulation has been proposed as a potential adjunct approach in conjunction with antibiotic therapy. Re-purposing of phenyl butyrate and vitamin D to enhance expression of natural antimicrobial peptides appears feasible. Bacterial extracts are registered and used clinically in some regions. If successful, additional clinical trials to confirm their efficacy could encourage wider use	Prevent or provide adjunct therapy for G+ and G- infection	Basic R&D and Translational	30–36
Vaccines	With potential to substantially reduce the incidence of infection and therefore the need to use antibiotics, vaccines are arguably the most powerful alternative to antibiotics.	Prevention, G+ more than G- infection	Basic R&D, esp. on new adjuvants	37–51
Tier 2 (strong support for judicious funding while monitoring for breakthrough insights)				
Antimicrobial Peptides (AMPs)	The advantages of AMPs are broad spectrum activity including most major Gram-negative and Gram-positive pathogens; their bactericidal and rapid action; low target-based resistance and their lack of immunogenicity. The wealth of activity and literature has not led to therapeutic breakthrough for systemic treatments. Several projects are now in development.	Treat or Adjunct for G+ and G- infection	Translational	52–60
Host/Innate	Host defense peptides and innate defense regulators are small natural	Adjunct for	Basic R&D	61

Czaplewski, Bax, Clokie, et al. (2016). Alternatives to antibiotics-a pipeline portfolio review. Lancet Infectious Diseases

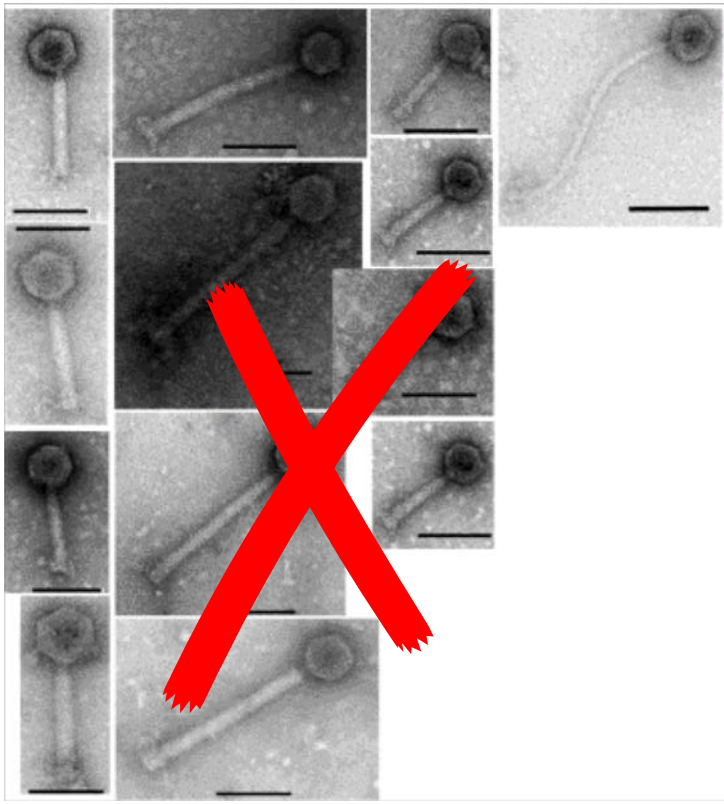
Why phages/phage products over the other alternatives?

- Specific
  - Limited problems associated with killing useful bacteria
- Useful for
  - antibiotic resistant bacteria
  - Preserve last line antibiotics
  - Eg cephalosporin resistance
  - Biofilms
  - difficult to access areas
- Our bodies are used to phages
- Nature has done the work



Why NOT phages/phage products over the other alternatives?

- Specificity also a disadvantage
- Can be difficult to identify, isolate and propagate
- Biological agent so, stability, resistance, physiology of bacteria
- Can be neutralized by antibodies
- Little data on dynamics, efficacy, dosage, formulation, delivery
- Regulatory arena is difficult



History of therapeutic phage use

- Discovered in 1915 (Twort) and 1917 (d'Herelle)
- First used by 1919 in Paris (*Shigella*)
- 1st publication 1921: staphylococcal skin disease

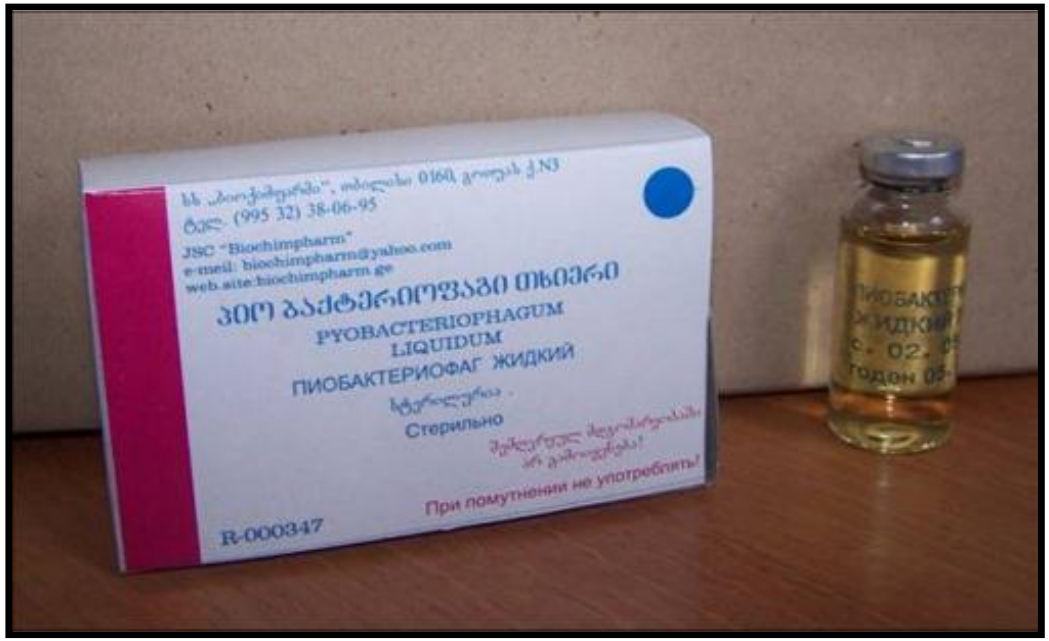
- Made phage preparations at Pasteur until 1978
- George Eliava director of the Institute of Infectious diseases, Georgia trained at Pasteur (1918-1921)

- Established Eliava Institute in Tbilisi, Georgia
- In the 1980s 1200 researchers made 2 tons of phage per year! (mainly diarrhoea and gangrene)
- Phages routinely used in clinical practice

How are phages currently used?

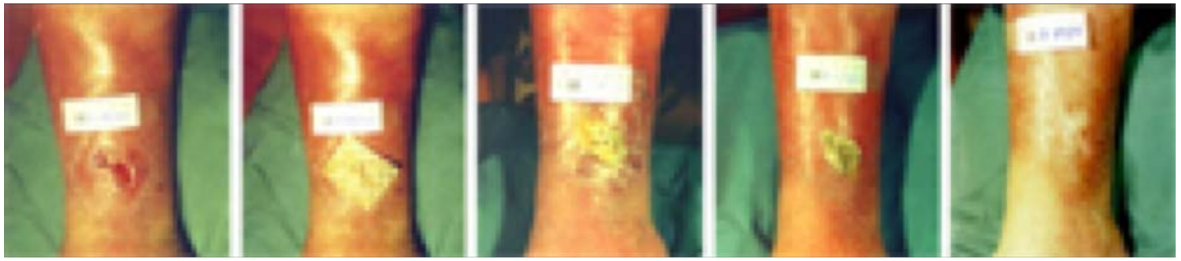
DIRECTLY

- Orally
  - Liquid/tablets
- Topically
  - Creams/Dressings
- Aerosols
- Intrapleural injections
- With surgery



INDIRECTLY

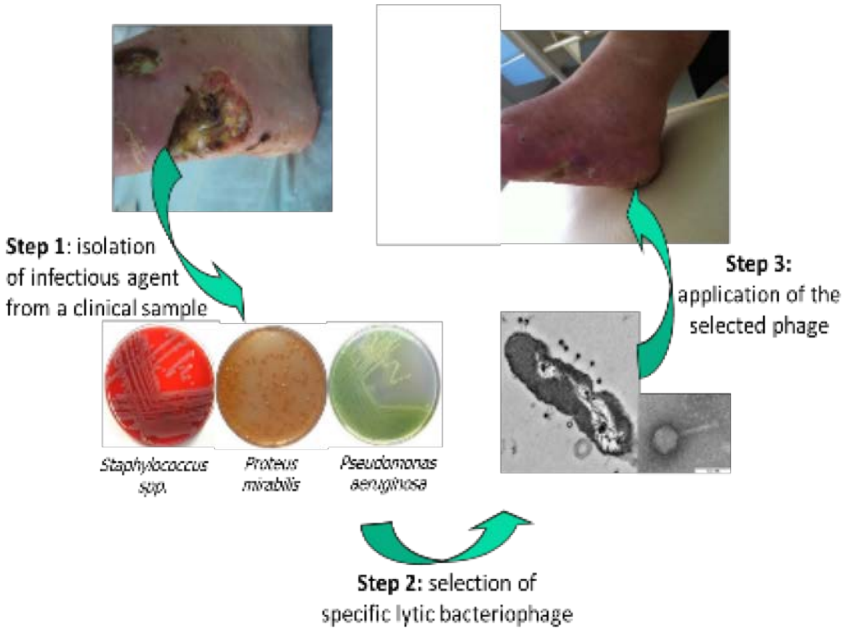
- As a prophylactic
- Phage products
  - lysins



Bacteriophages in PhagoBioDerm™ *Intl. J. Dermatology*, 2002

Case Study: personalised ulcers with mixed infection

- Vlasov et al., 34 patients
  - 16 mixed infections; *S. aureus*, *P. aeruginosa*, *Proteus mirabilis*, *E. coli*
  - 16 single infections
  - 1 fungal and one couldn't identify
- 23 patients treated for 5-7 days
- 8 *Staph*, 3 *P. aeruginosa*, 2 *E. coli* – all complete recovery
- 10 mixed – 5 complete recovery, 4 significant improvement
- Complex mixed patients recovered if 'correct' phages were used

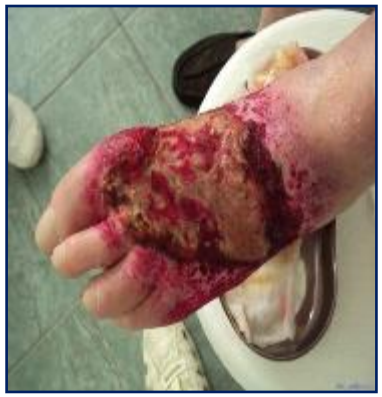


Vlasov et al, Novosibirsk, Russia (Moscow phage conference 2016)

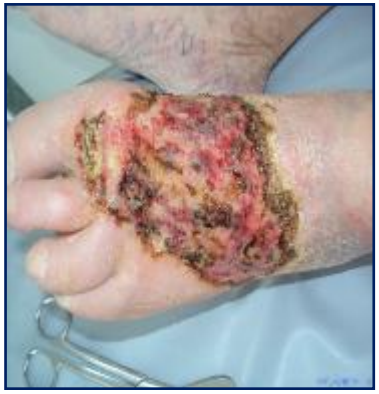
[1]Institute of chemical biology and fundamental medicine, Siberian branch of Russian academy of science, Novosibirsk, Russia; [2]Railway

Clinical Hospital, Novosibirsk, Russia

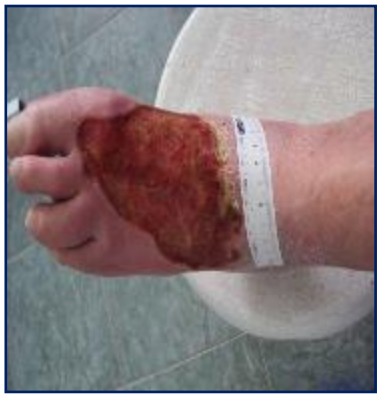
Clinical case of eradication of MRSA infection with the help of phage therapy. Patient Sh., 60 years old, history of diabetes with multiple ulcers



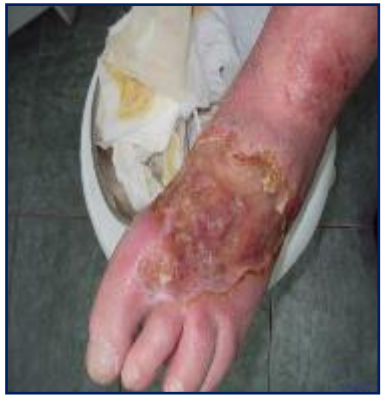
Dec.04



Dec. 14



Dec.25. The end of treatment



Jan.01.Control sampling No MRSA agent.

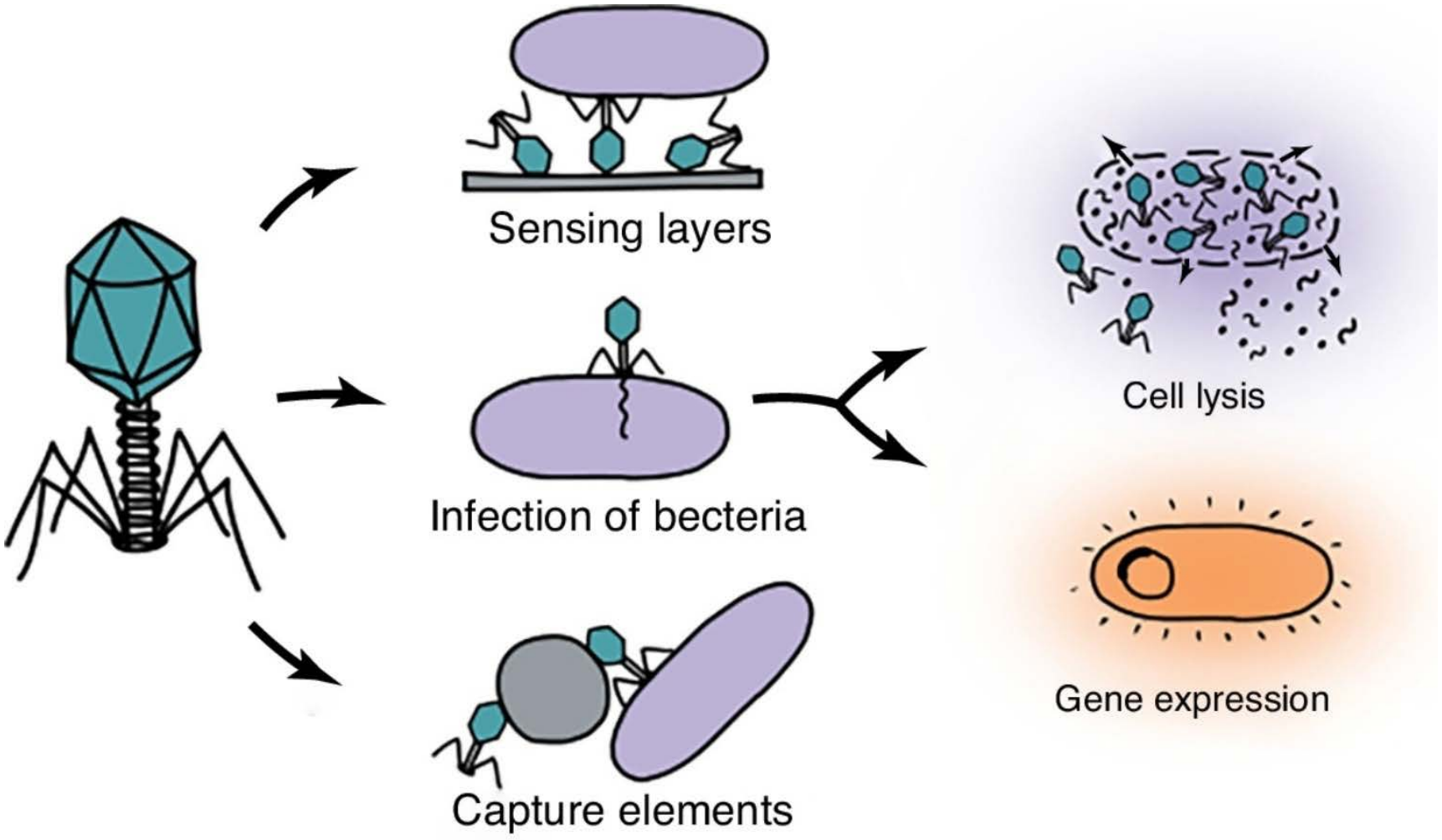
Phage compound pharmacy or off the shelf?

- Compound pharmacy
  - Phages are highly specific so reduce chance of wrong antimicrobial
  - Fresh preparations so know phages active
  - Can specifically target the one pathogen of interest
- Off the Shelf
  - Cheaper
  - Can be standardized, quality checked, regulated
  - Easier to fit into standard practice

Where is phage therapy today?

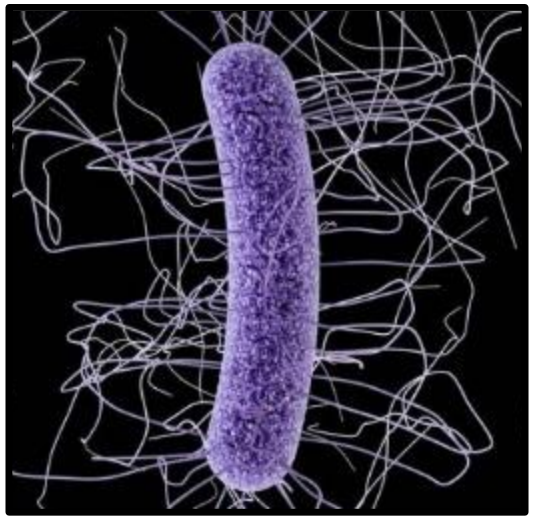
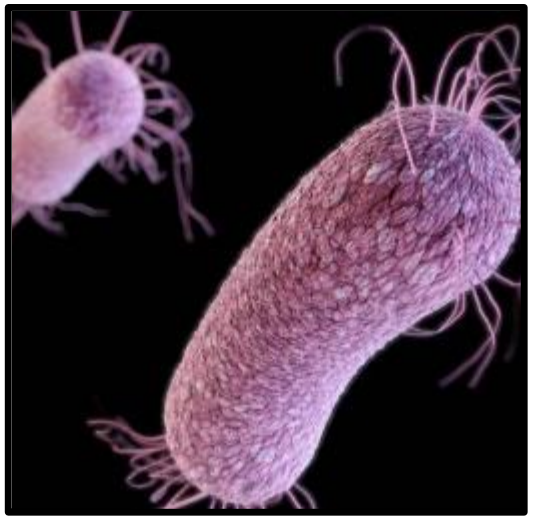
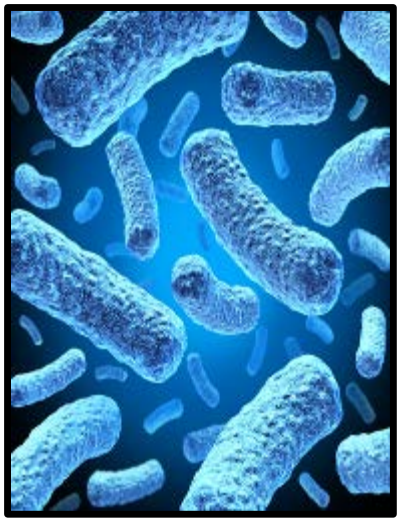
- Used in Georgia, Russia and Poland
- Lots of fundamental research
- Cross UK research council calls for antimicrobial resistance research
- USA, EU, China have invested
- Increasing interest from UK
- ‘Big Pharma’ and many smaller companies interested
- ‘GRAS’ status, *Listeria* phages, in food
- Increased interest in animals/aquaculture and crops

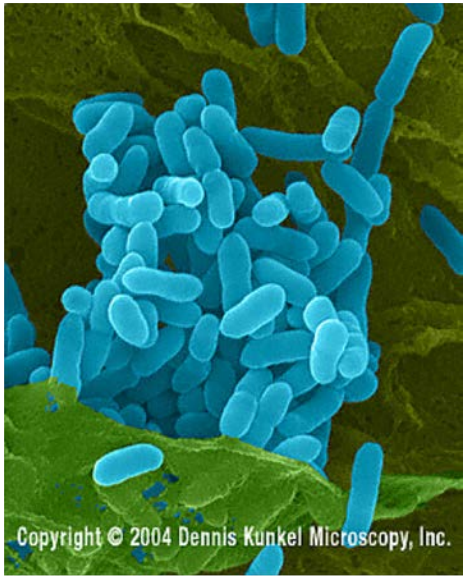
Phage based diagnostics



Richter *et al*, Drug Design Today, 2018

Bacteria/phage systems optimised in my lab…

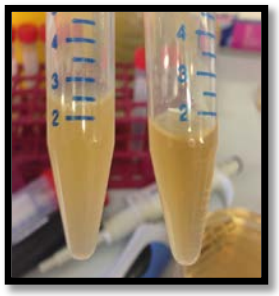



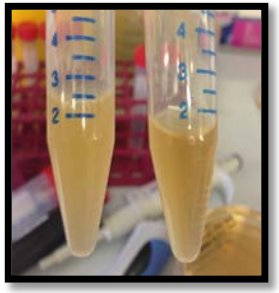
Images from CDC

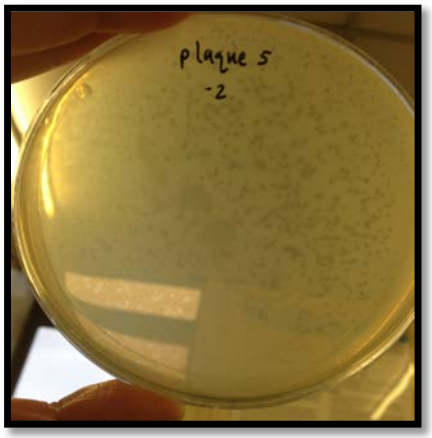
Phage sampling

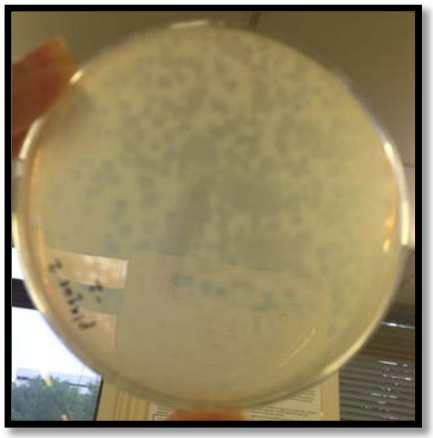
Phage isolation

+



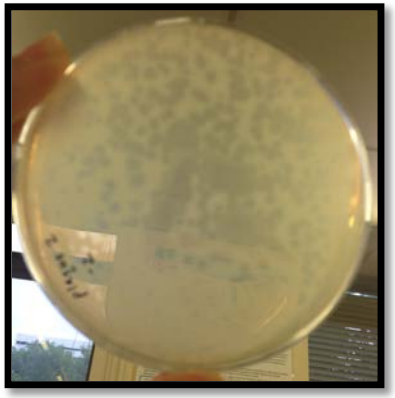




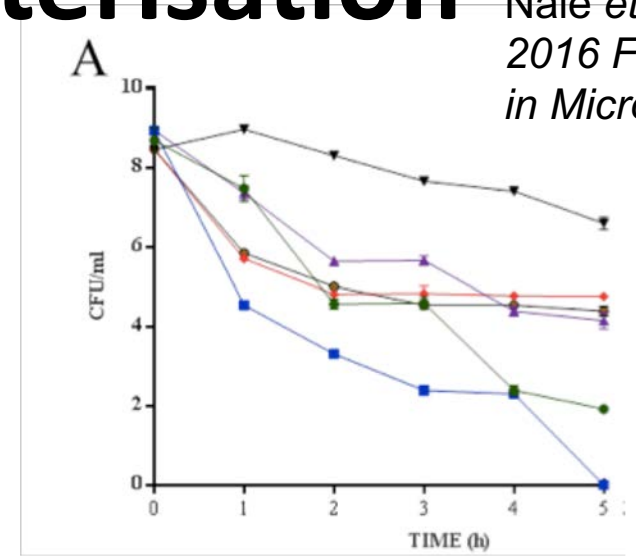


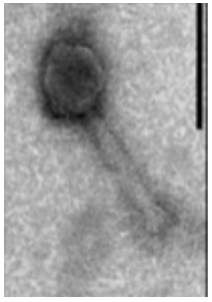
Phage characterisation

Nale *et al.*, 2016
Antimicrob. Agents Chemother

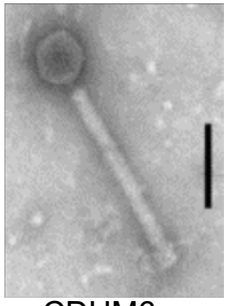


Nale *et al.*, *2016 Frontiers in Microbiology*

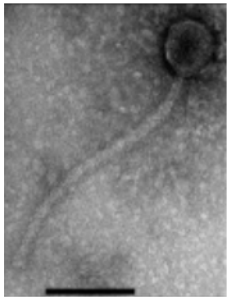




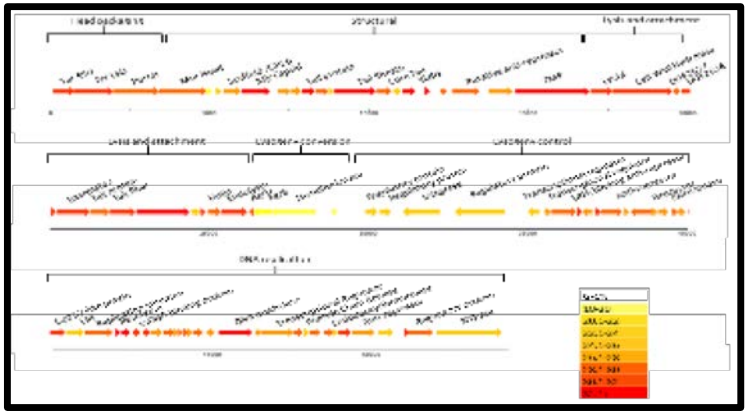
CDHM3
T~120/20
C~60

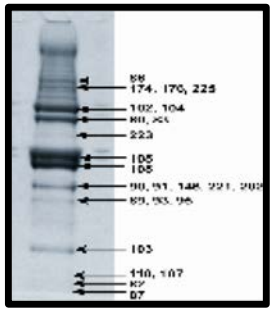


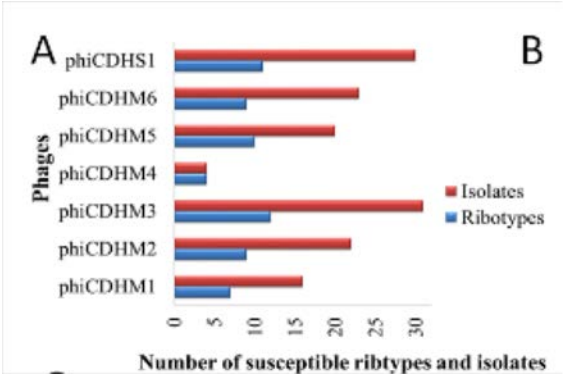
CDHM6
T~230/20
C~50

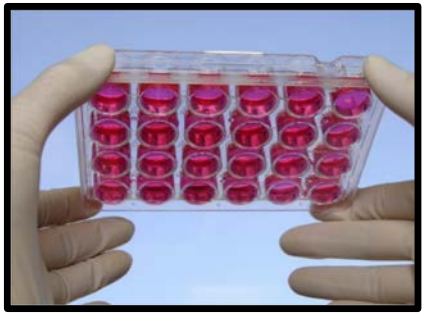


CDHS1
T~270/20
C~50

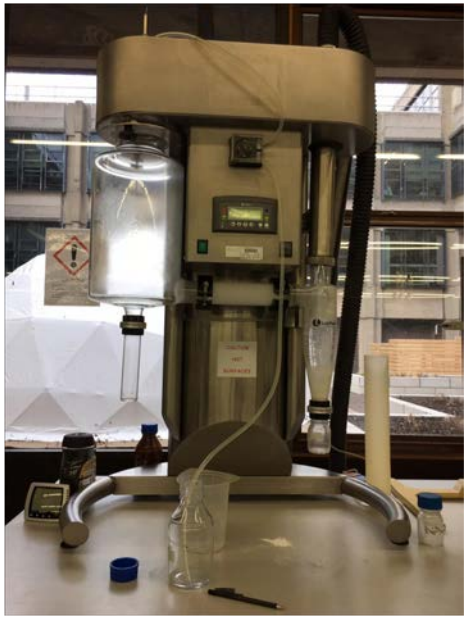








Phage formulation and pig trial



How important could bacteriophages be in the UK?

Map clinical need better to phage research community

What circumstances, infections do health care practitioners treating patients need most?

What do phage biologists do and can provide?

Map these two communities better together

Form consortia of interested parties

- Obtain clinical trial data
- Use phages for compassionate use

Global Impact of Phages

Partnerships and collaborations need to be established

- Shift from single lab projects to bigger teams
- Funding for phage research to tackle AMR, Cross-research council and need input from end-user
- Ismail Serageldin, founding director of Alexandra Bibliotheca (BA), the new Library of Alexandria
  - Need structures/collaborations, not just money
  - Human resources, need infrastructure
  - Institutions need to work together
  - Public/private relationships work

Phage therapy centers worldwide

- USA
  - Yale
  - Texas
  - SDSU
- Tbilisi
- Poland
- Netherlands
- Zurich/Tblisi

Ben Chan
Paul Turner
Jonathan Koff, MD
Yale University

Examples of broader networks happy to expand and help develop new ones

- *Clostridium difficile* phages
  - Large collection of *C. difficile* strains
  - Found phages that target all UK strains
  - Difficult phages but nearly finished pre-clinical work
- Urinary Tract Infections
  - Working with ACF, Melissa Haines and Dr Marie Noelle Vieu, public health consultant
  - Isolated phages that target ESBL *E. coli* and *Klebsiella*
  - Identified highly efficient mixtures

Conclusions

- Phages natural enemies of bacteria
- Exciting time to be studying them
- Don’t work in same way as ‘standard’ antimicrobials
- Change our understanding of disease – modify ecology