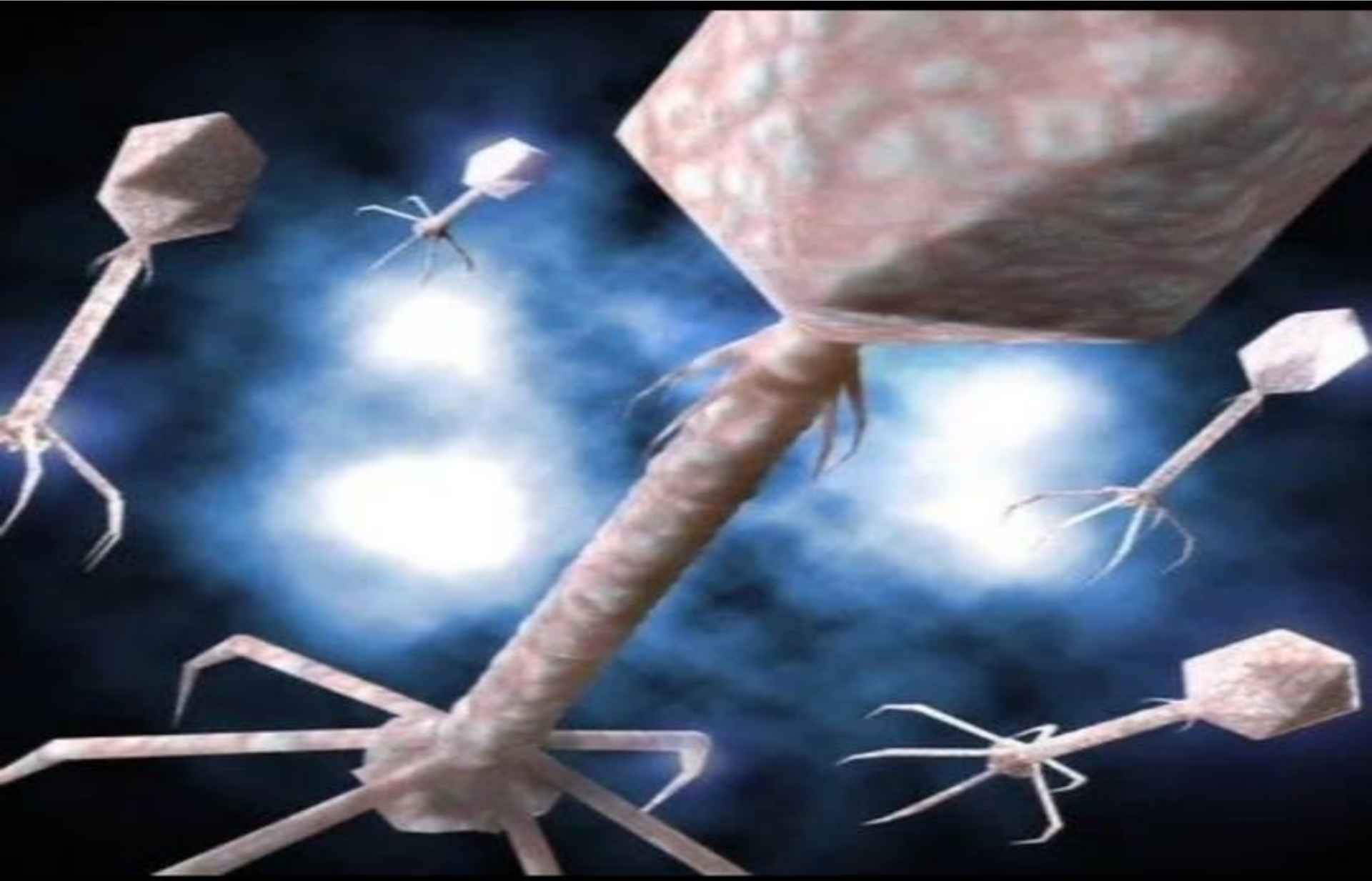


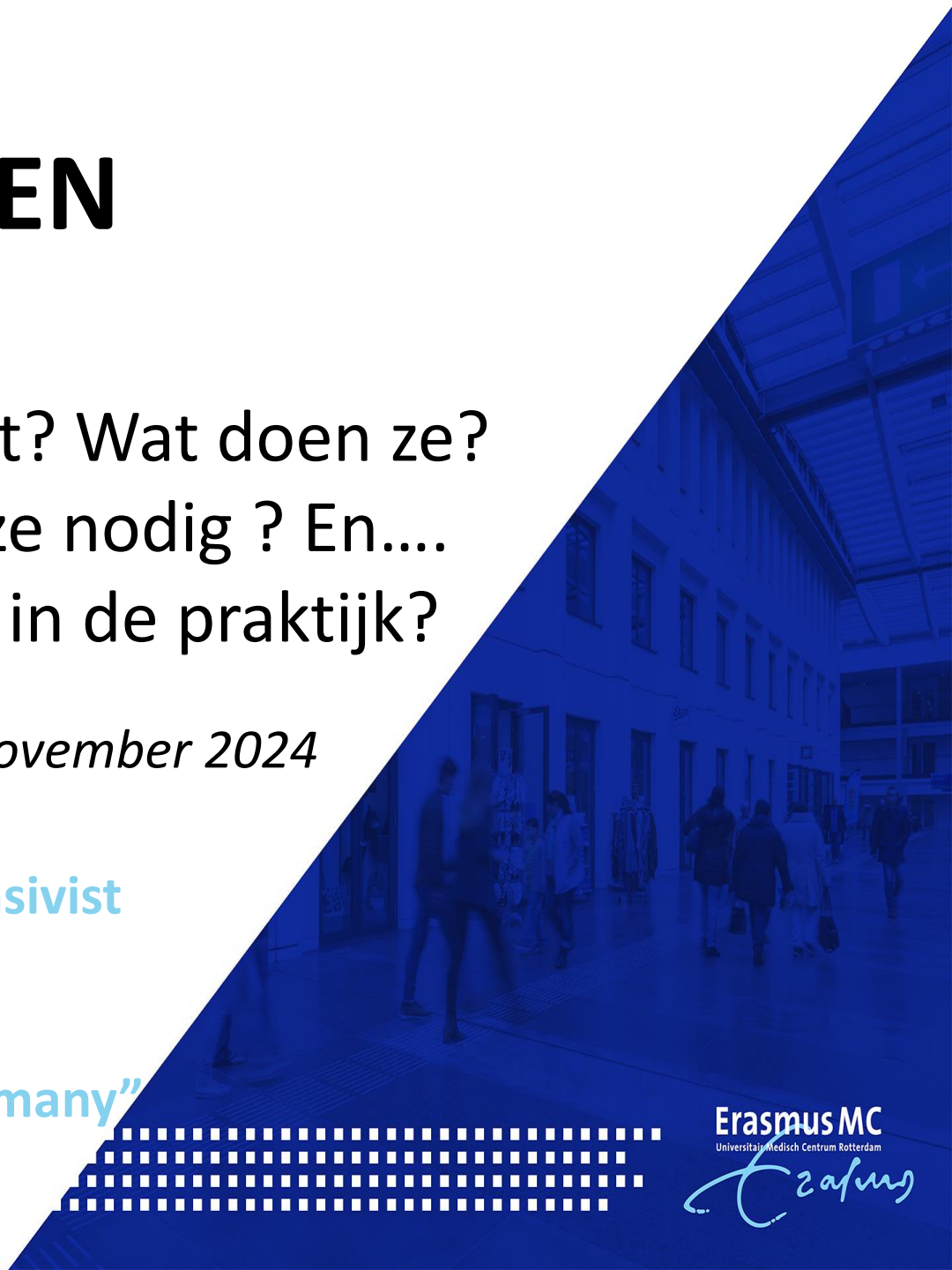
BACTERIOFAGEN

DE NIEUWE ANTIBIOTICA?

Waarom? Wat zijn het? Wat doen ze?
Waarom hebben we ze nodig ? En….
Worden ze toegepast in de praktijk?

Lezing Wessel Knoops 12 November 2024

Dr. Ard Struijs Internist-intensivist
Intensive Care Volwassenen
ErasmusMC Rotterdam
Medical Advisor “Phage Germany”
a.struijs65@gmail.com

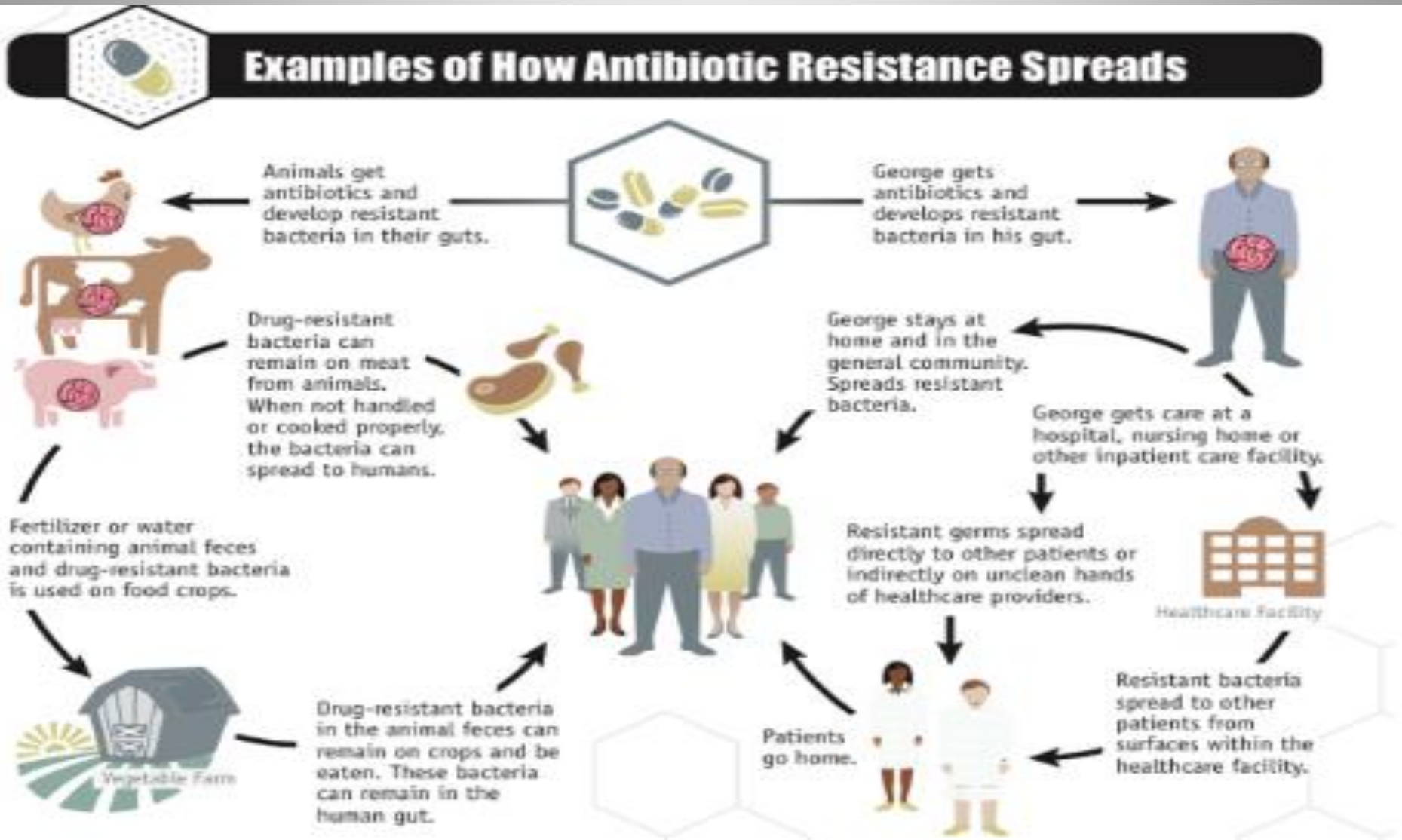


Hoe ontstaat antibioticaresistentie?

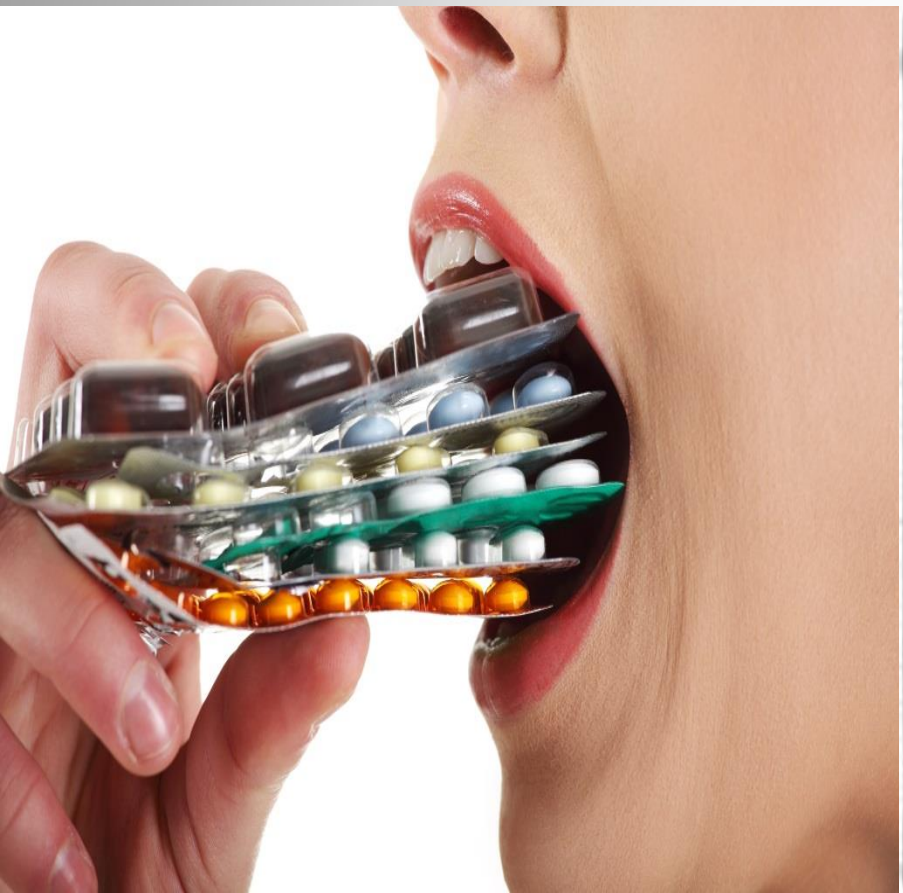
© Illustratie: CDC

Hoe verspreidt antibioticaresistentie zich?

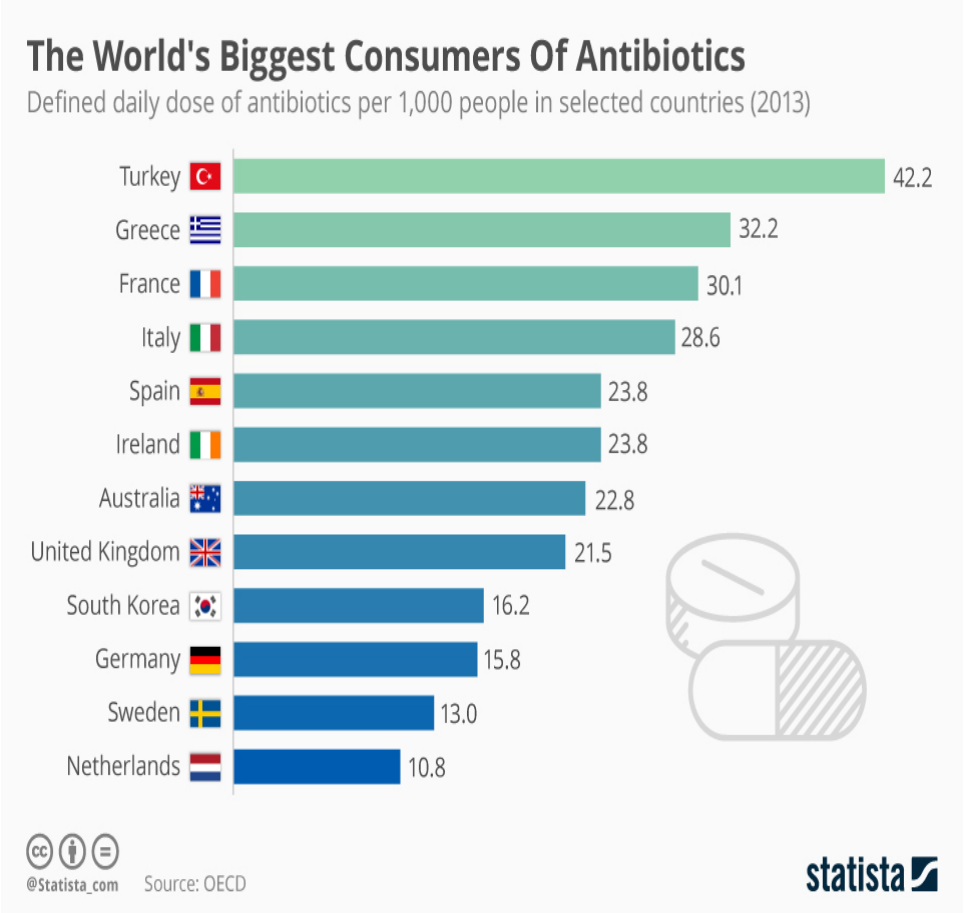
© Illustratie: CDC



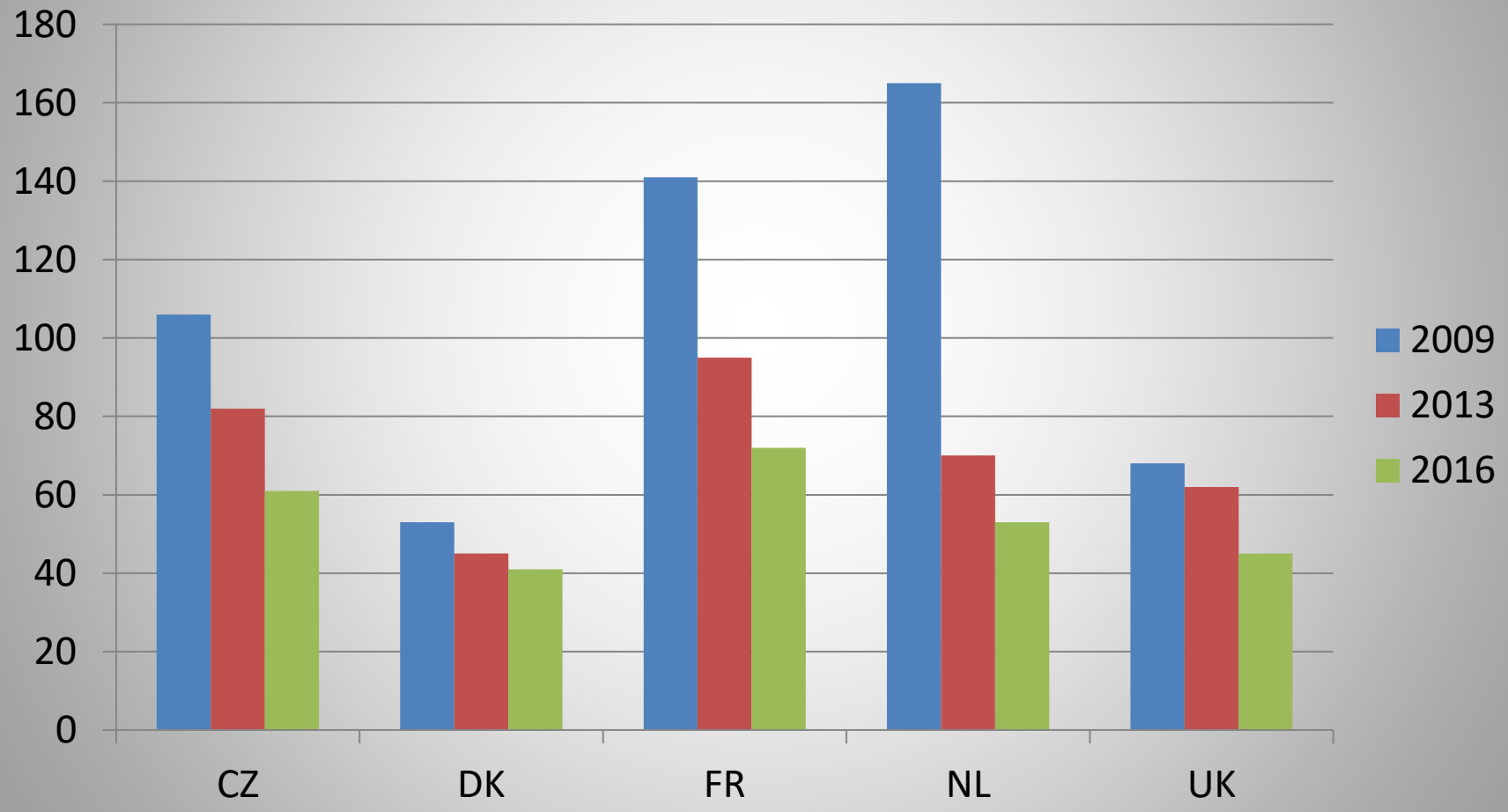
Te hoog antibioticagebruik door mens en vee



Antibiotica gebruik

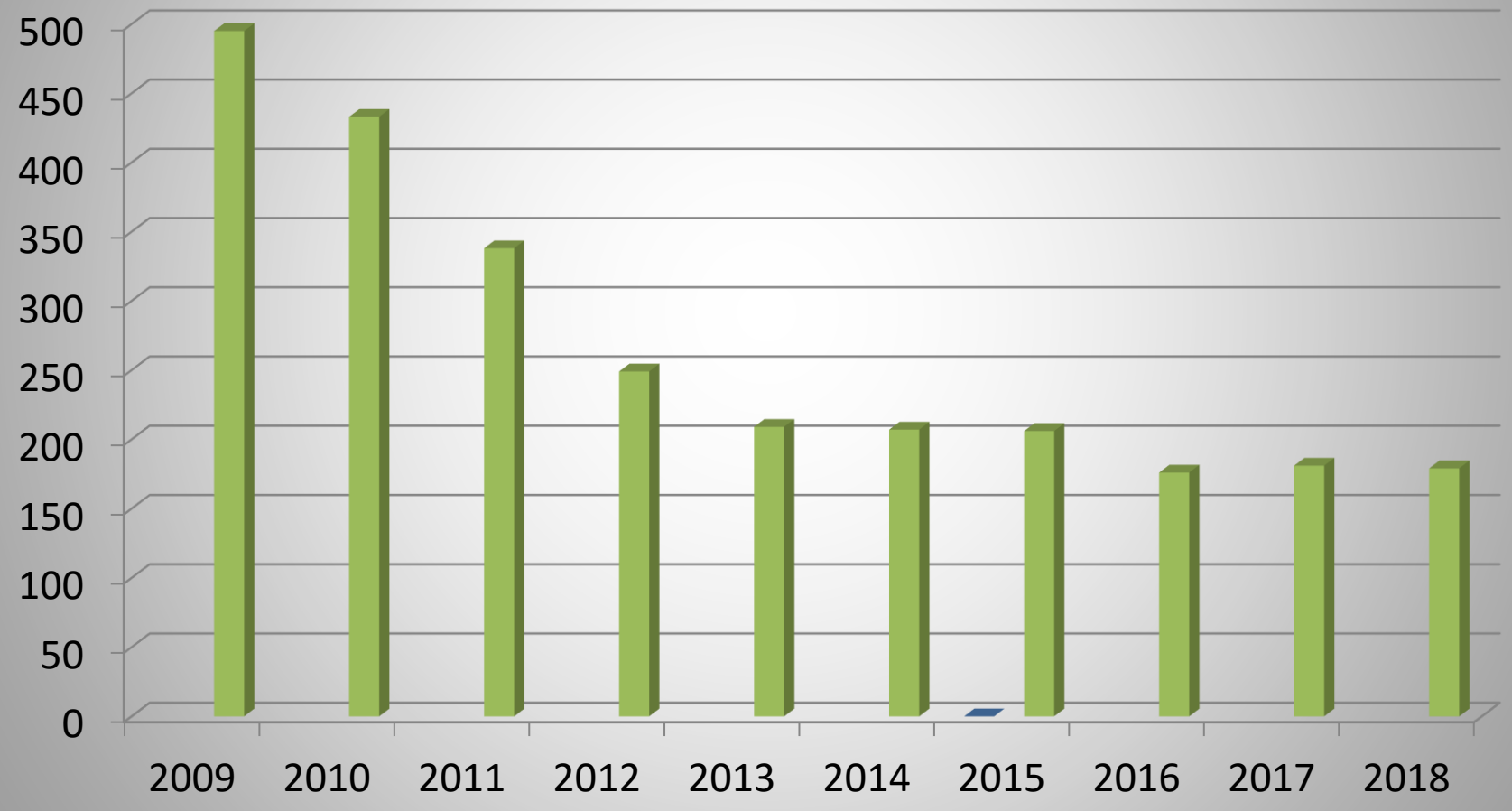


ESVAC verkoopdata veterinaire antibiotica in mg/pcu



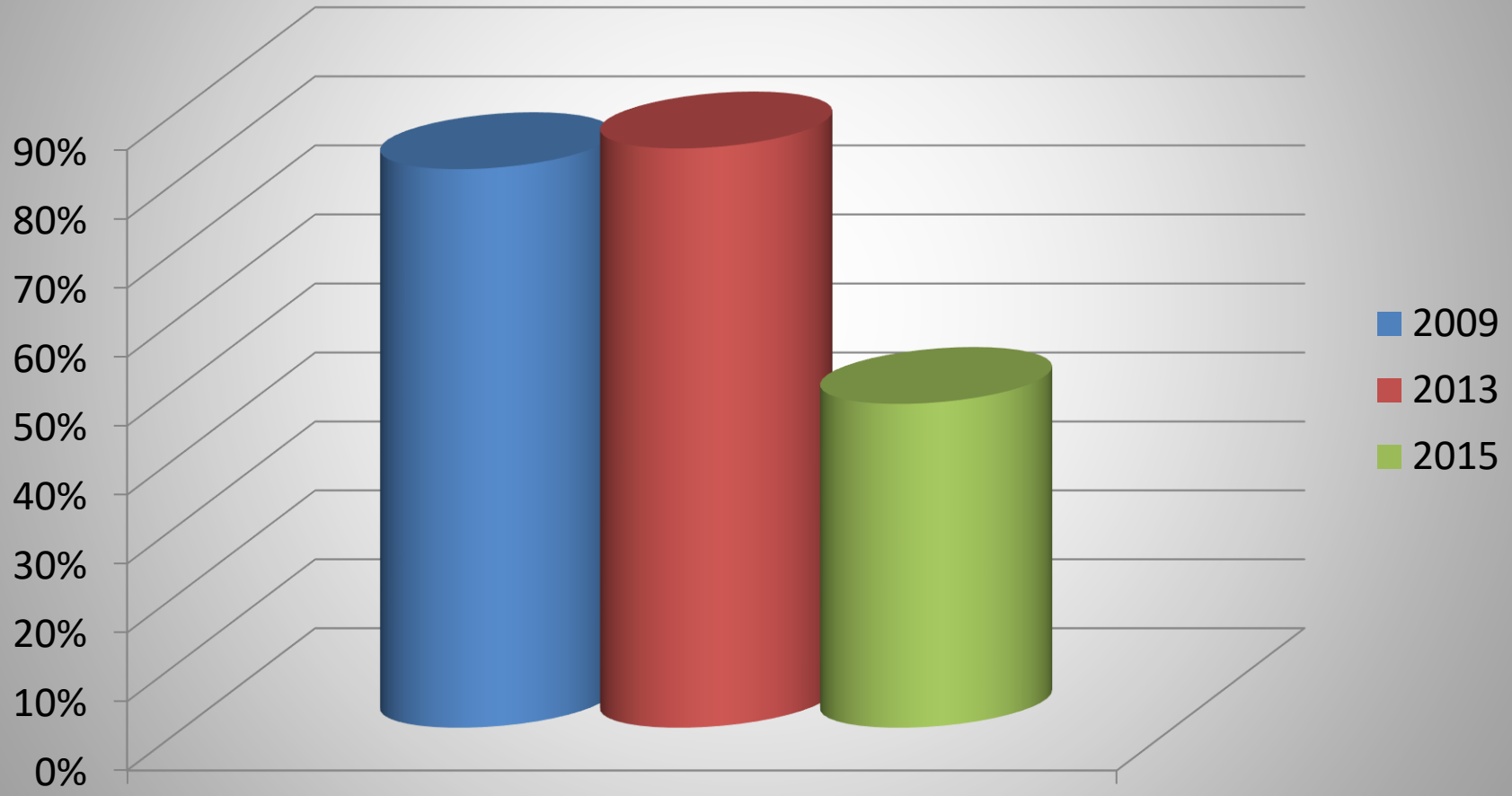
Stevige daling antibioticagebruik in Nederlandse veeteelt stokt

Fidin data 2014



Kippenvlees met ESBL-positieve bacteriën

Data: Jan Kluytmans



Vegetariër worden? Ook geen oplossing.

- Enkele studies uit NL en Fr vonden resistente bacteriën op groenten die rauw gegeten worden
- Sterkste bewijs: De EHEC uitbraak in Duitsland in 2011 (53 doden, 4.000 infecties, 855 zeer ernstige)

NOS

Resistente bacteriën in groenten

maandag 18 apr 2011, 19:46 (Update: 19-04-11, 08:46)

Radijs op het land arneheijenga / Flickr / Creative Commons by-nc-sa

Nederlandse wetenschappers hebben in groenten bacteriën gevonden die resistent zijn voor een groot aantal antibiotica.

De onderzoekers van de VUmc in Amsterdam vonden in zeven van de in totaal 120 onderzochte groentenmonsters een ESBL-houdende resistente bacterie. Dat zijn enzymen die bacteriën aanmaken waardoor ze resistent worden voor veel antibiotica.

De bacteriesoorten komen op grote schaal voor in menselijke en dierlijke darmen en luchtwegen.

Ook biologisch

De monsters waren afkomstig van vijftien verschillende groentensoorten die op of in de grond groeien. In taugé, radijs, lente-ui en pastinaak werd de bacterie aangetroffen.

In totaal waren zeven monsters ESBL-positief. Opmerkelijk genoeg waren vier van de zeven besmette monsters van biologische kweek.

Hoe de groenten besmet raken, is nog niet onderzocht. De meest waarschijnlijke hypothese is dat bemesting met dierlijke mest daarbij een rol speelt. Ook is het mogelijk dat de resistente bacteriën al in de grond zaten.

In het journaal-item zijn ook groenten te zien die niet zijn betrokken bij het onderzoek. Zie de herstelrubriek.

Rivieren over de hele wereld vervuild met antibiotica

MA 27 MEI, 13:07 BUITENLAND

Antibioticaresistentie in rivieren in veeteeltgebied

En in de modder en het slib van die rivieren

- 8 antibiotica getest
- Sommige *E. Coli* en *S.aureus* isolaten waren resistent voor 7 antibiotica
- Veeteelt en lozingen van afvalwater

Enorme vervuiling door lozingen farmaceuten India en China, meer actieve stof in liter water dan in patiënt die behandeld wordt

Asanikunta meer India foto Patrik Skön

Kazipally meer India foto Patrik Skön

Waar komen de eerste resistente bacteriën dan vandaan?

Permafrost, 30.000 jaar oude grondmonsters

Lechuguilla-grot 200 km lang, 500 m diep, >4 miljoen jr afgesloten

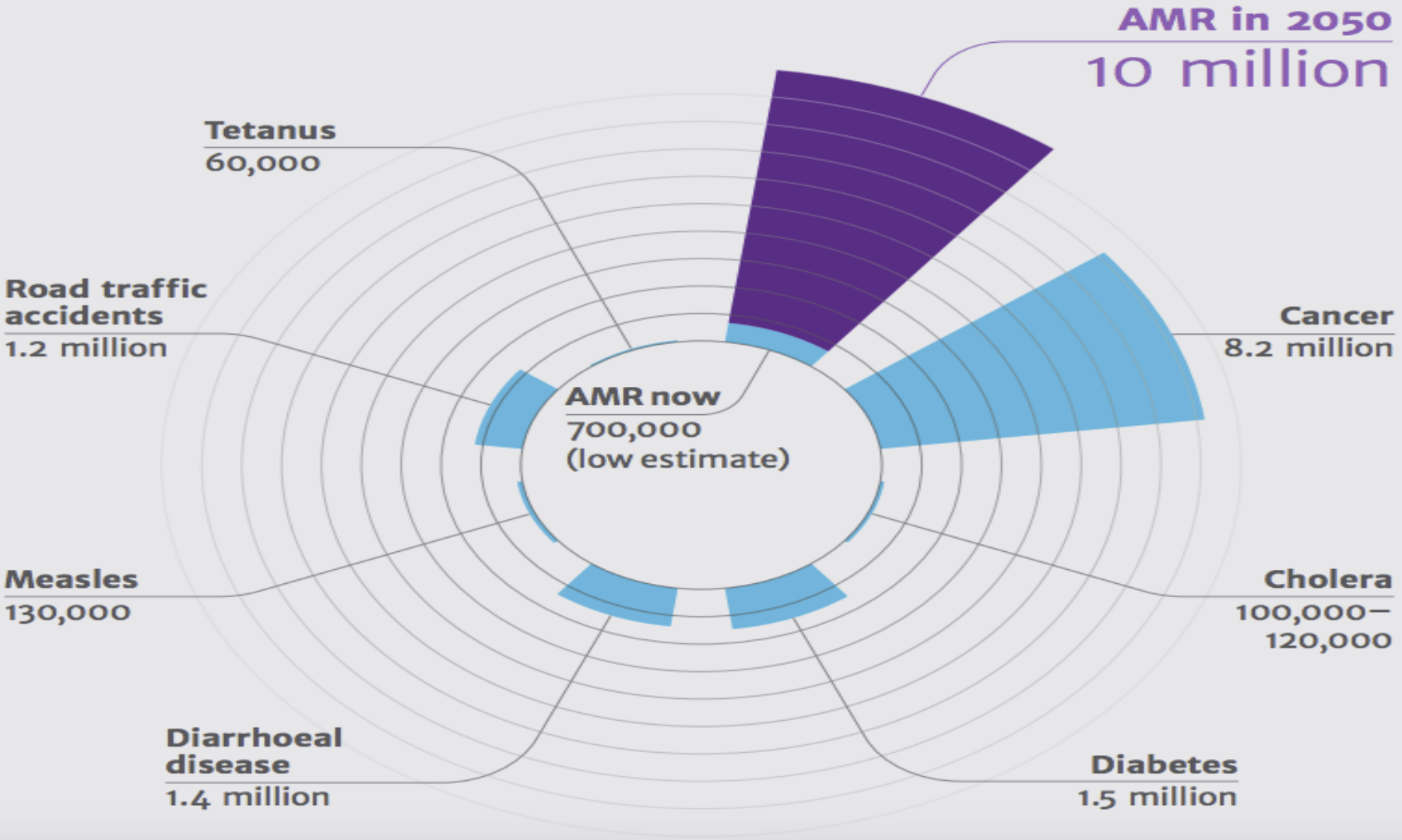
When the Drugs Don't Work

Antibiotic Resistance as a Global Development Problem

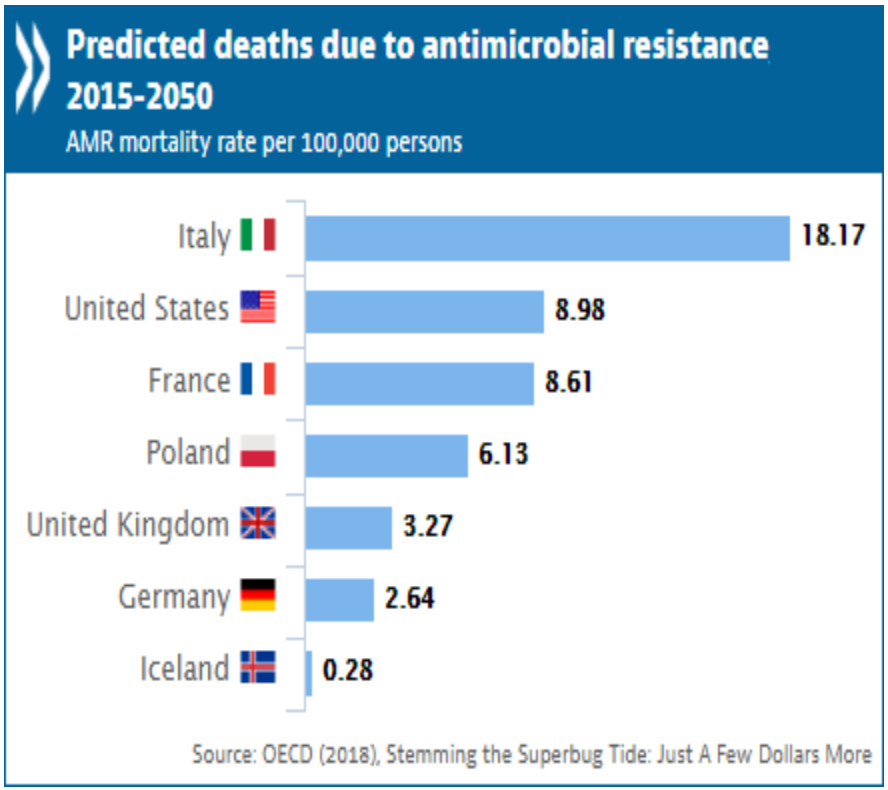
Dag Hammarskjöld Foundation

ReAct

Deaths attributable to AMR every year compared to other major causes of death



Doden per land door AMR



Bacteriofagen

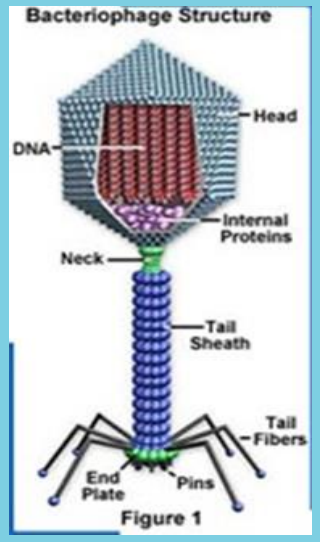
Bacteriofagen

- The most abundant and ubiquitous organism on Earth

  10^4 - 10^8 / ml particles in aquatic systems

  10^9 / g particles in soil

  > 6300 different bacteriophages discovered and described



Small viruses able at killing bacteria while they do not affect other cell lines

Unveiling the role and life strategies of viruses from the surface to the dark ocean

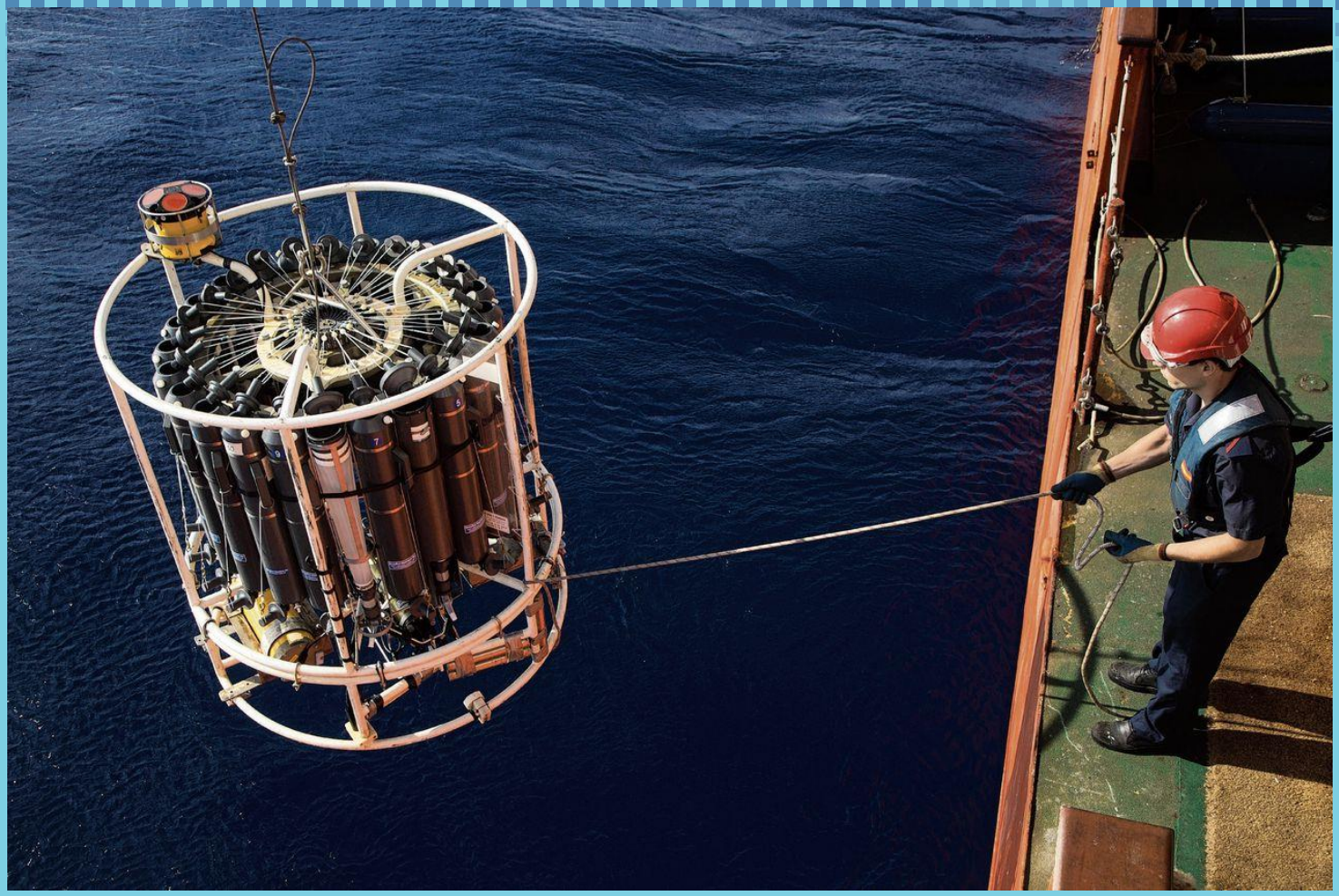
by Elena Lara, Dolors Vaqué, Elisabet Laia Sà, Julia A. Boras, Ana Gomes, Encarna Borrull, Cristina Díez-Vives, Eva Teira, Massimo C. Pernice, Francisca C. Garcia, Irene Forn, Yaiza M. Castillo, Aida Peiró, Guillem Salazar, Xosé Anxelu G. Morán, Ramon Massana, Teresa S. Catalá, Gian Marco Luna, Susana Agustí, Marta Estrada, Josep M. Gasol, and Carlos M. Duarte

Science
Volume 3(9):e1602565
September 6, 2017

Published by AAAS

Malaspina Expedition

Malaspina Expedition



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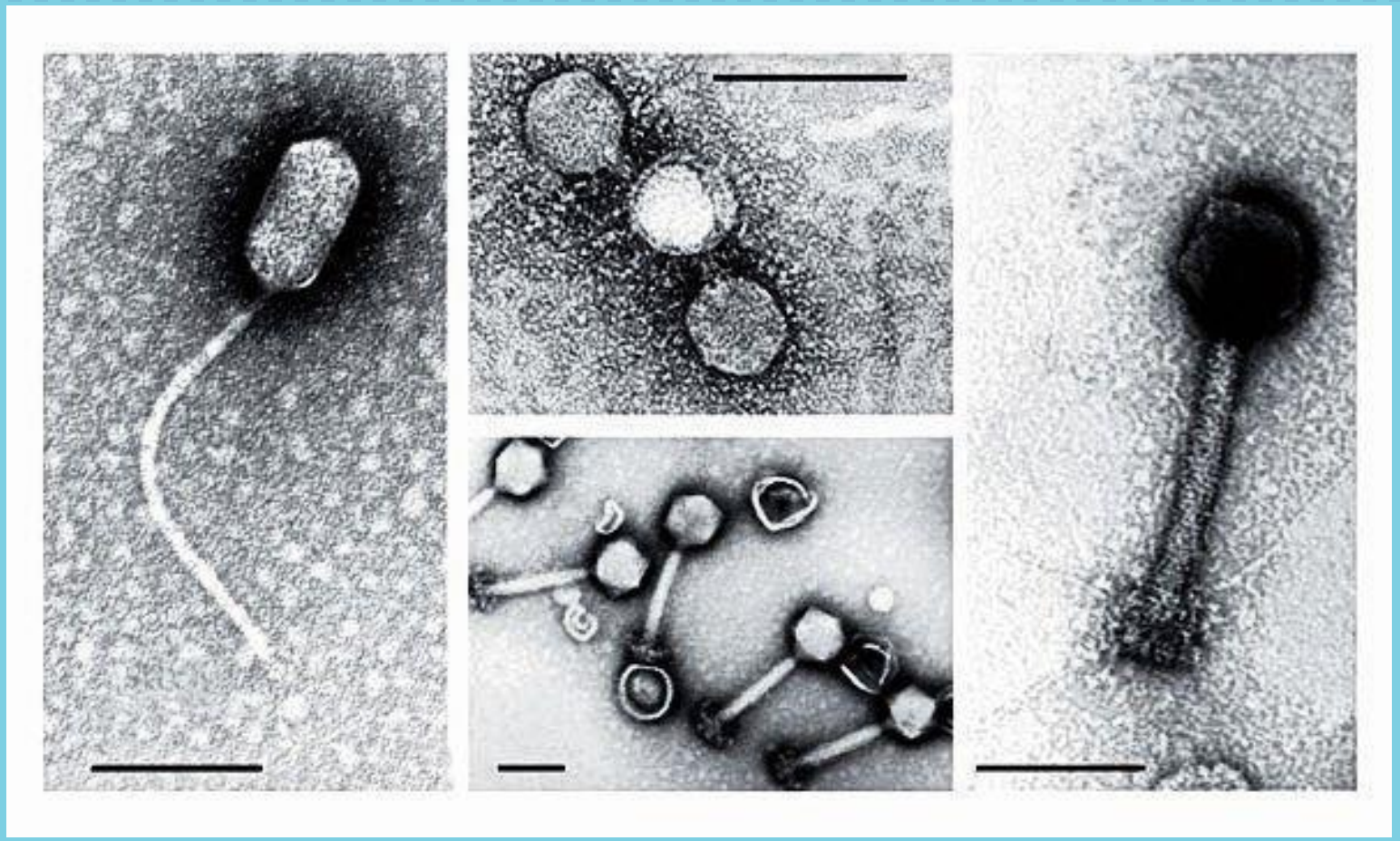

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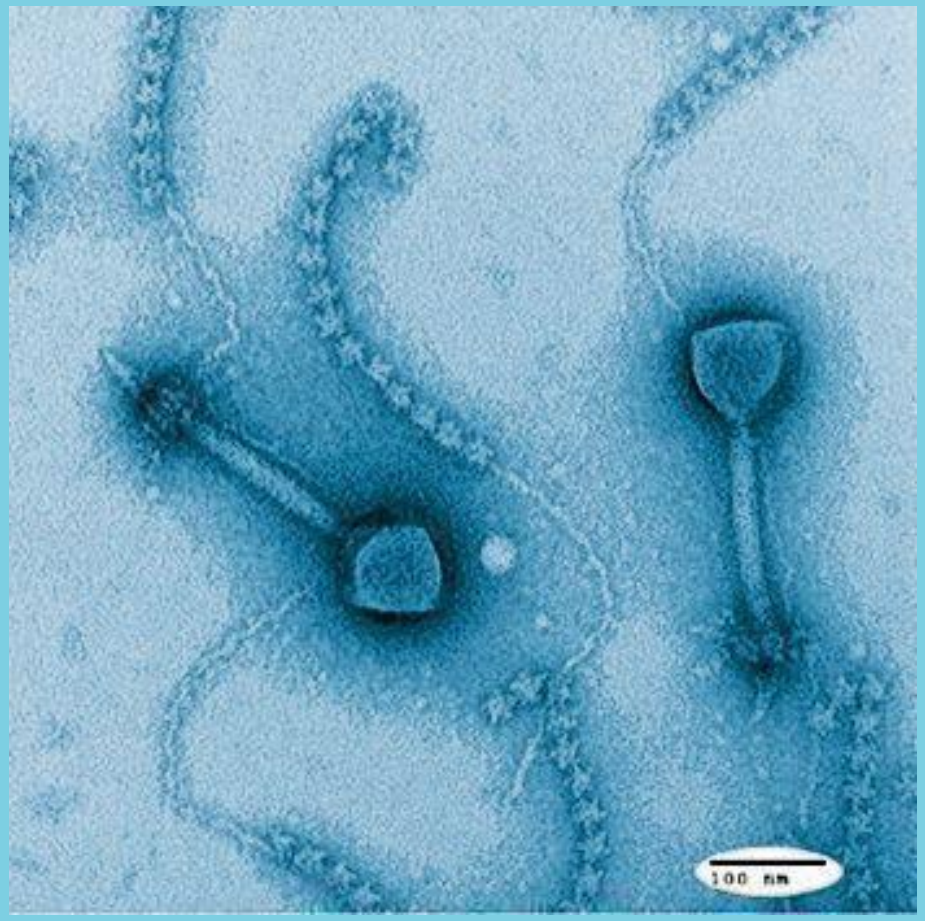
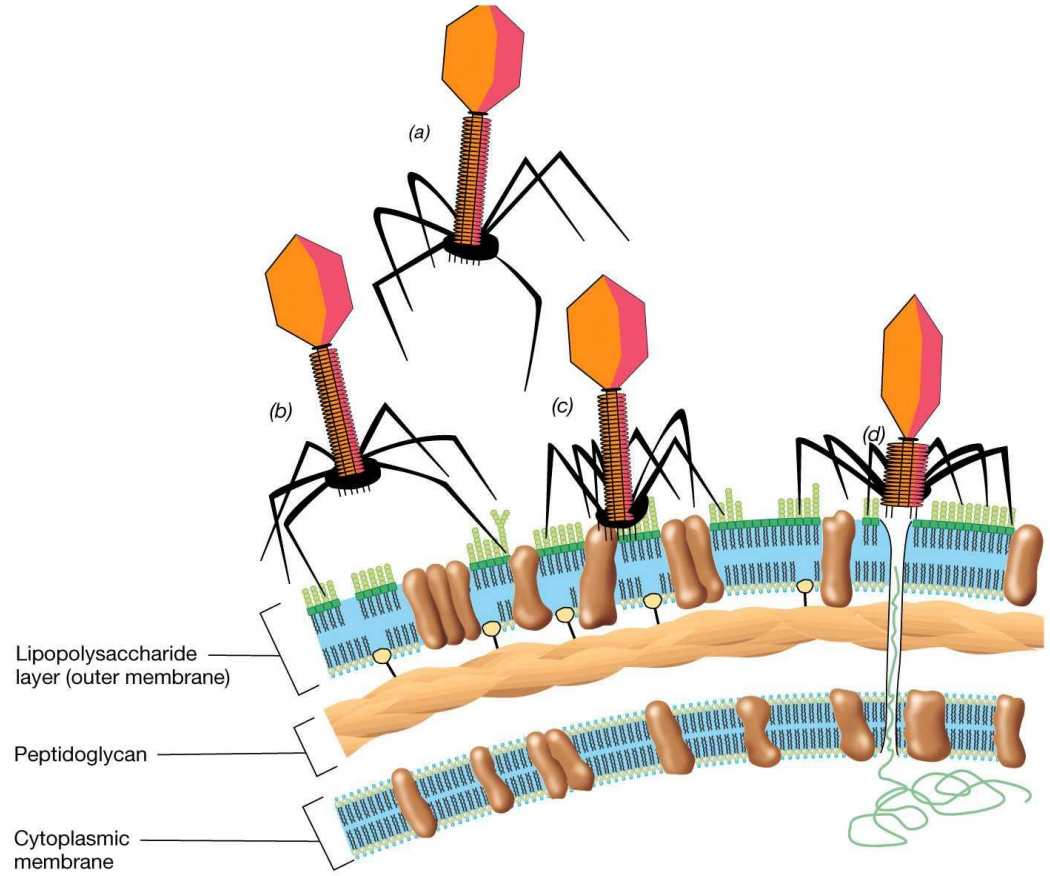


Malaspina Expedition

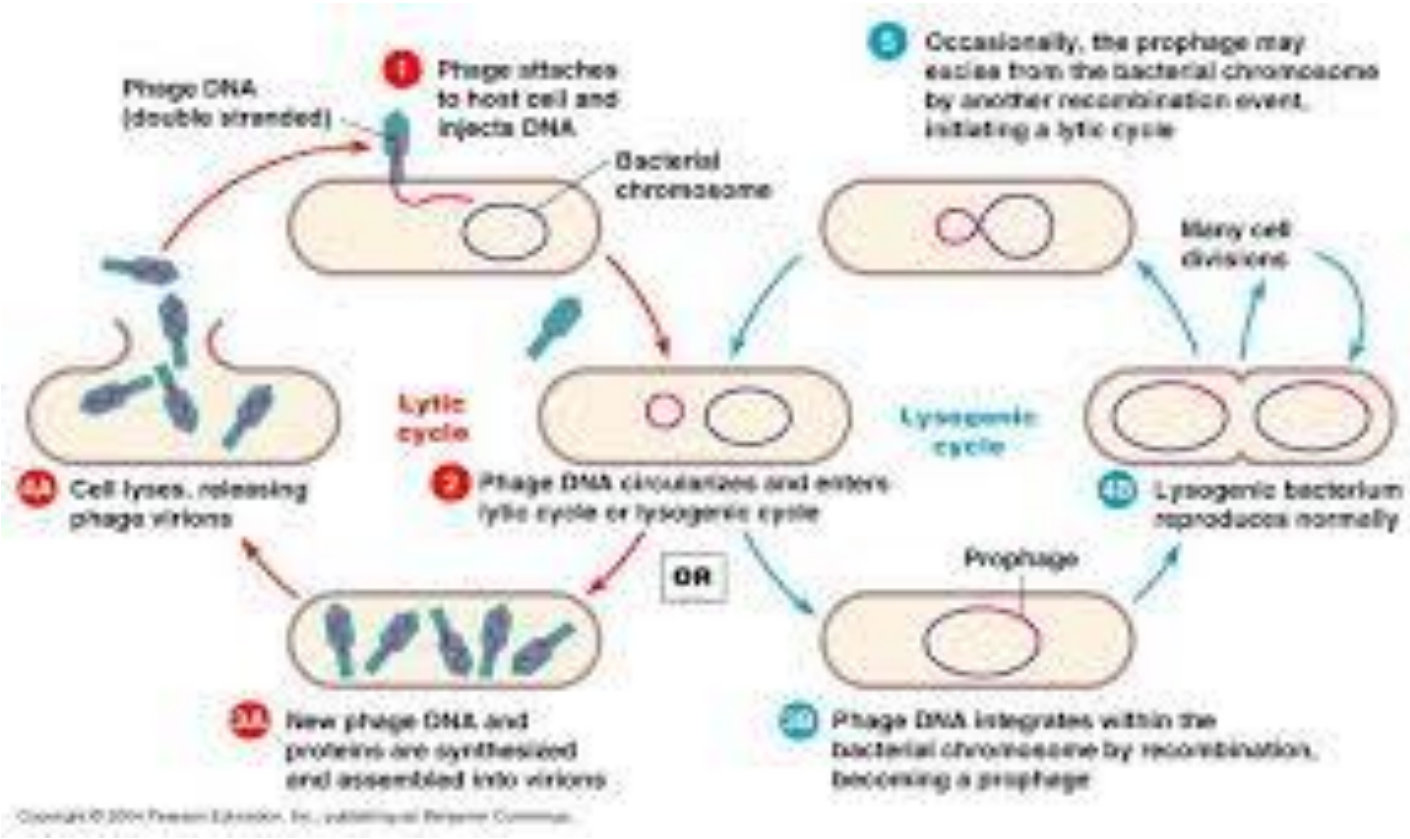
- **Oorlog in de diepzee: de bacteriën tegen de virussen**
- De diepzee blijkt te krioelen van de bacteriën en vooral virussen. Een kwart van de bacteriën sterft er door een virusaanval.
- Hester van Santen
- 7 september 2017

Aanhechting en injectie van het faaggenoom in de bactericel



Celwand van Gram-negatieve bacterie (bvb. *Pseudomonas aeruginosa)*


shutterstock.com • 1126283543



Some human phage therapy studies performed in the former Soviet Union

*Parenthetically are healthy volunteers

Year	Authors	Target organisms	Disease	n*	Details
1974	Sakandeldze et al.	Proteus Staphylococcus Streptococcus		236	Subcutaneous or through surgical drainage Success = elimination of infections in 92%
1976	Pipiia et al.		Abscessing pneumonia		Parenteral, Multiple treatment approaches including use of phages
1978	Zhukov-Verezhnikov et al.	E. coli, Proteus Staphylococcus Streptococcus	S.I.	60	Improved efficacy using phages selected against bacterial strains isolated from individual patients versus commercial phage preparations
1978	Litvinova et al.	E. coli Proteus	Antibiotic-associated dysbacteriosis	500	Premature/low-birth-rate infants; phages used in combination with bifidobacteria
1980	Ioseliani et al.	E. coli, Proteus Staphylococcus Streptococ	Lung and pleural infections	45	Successful phage use in combination with antibiotics

*Parenthetically are healthy volunteers

Year	Authors	Target organisms	Disease	n*	Details
1984	Anpilov and Prokudin	Shigella	Dysentery (prophylaxis)		Double-blinded; ca. 10-fold lower incidence of dysentery in phage-treated group
1989	Kochetkova et al.	Pseudomonas Staphylococcus	Post-surgical wounds	65	Cancer patients; treatment was successful in 82% in comparison to 62% of antibiotic only treatment
1991	Sakandelidze et al.	Enterococcus E. coli, P. aeruginosa Proteus Staphylococcus Streptococcus	Infectious allergoses	936	Phages only, n = 360, 86% success; antibiotics only, n = 404, 48% success; antibiotics plus phages, n = 576, 83% success
1992	Bogovazova et al.	K. ozaenae K. pneumoniae K. rhinoscleromatis		109	Adapted phages used; treatment reportedly effective;
1993	Miliutina and Vorotyntseva	Salmonella Shigella	Salmonellosis		Phages versus combined phages and antibiotics was examined with combination effective but not antibiotics alone
1995	Perepanova et al.	E. coli, Proteus Staphylococcus	Acute and chronic urogenital inflammat	46	92% for marked clinical improvement; 84% for bacteriological clearance

What is the problem with Phage Therapy

- RCT's are lacking or non-conclusive
- -E coli trail Nestle
- -Phagoburn Trail
- Its impossible to registrate Phages as medicine due to missing formats
- Its impossible to perform studies cause Medical Ethical comittees have no safety data to base their decisions on
- No money for trails
- Compassionate use in the Netherlands impossible because than it has to be on the market within a year
- Only procedure left is unautherised medication but that requires lot of paperwork

How do we solved this

- Mobilise public opinion and desperate patients searching for Phage Therapy by TV talkshows and internet
- Using route of non-registrated medication by ministry of Health an Health Inspection
- Patients ordered themselves from Eastern Europe or go there for therapy
- Set up Biobank and Registry on efficacy, efficiency, adverse events and safety, fysiological principles of Phage Therapy.
- Include patients that cannot be treated by regular medicine
- Doctors and patients who are willing to search for the borders, pioneers
- In the Erasmus Medical Centre we formed a multi-disciplinary team of pioneers who set their target to make Phage Therapy available for everybody.

Principal points

- Make it possible to do Phage Therapy in Netherlands
- Select Non conventional treatable patients offer them Phage Therapy with explanation of status, offer them adequate medical control and follow-up, Create database to answer questions on, physiology of PT, safety efficacy adverse events, mode of action and administration routes.
- Best situation, better care naar best care
- Bettere Health with lower costs, One Health principe
- PT safely available for everybody for reasonable price

What have we solved

- We asked the minister of health to define preconditions for PT.
- We need GMP produced Phages.
- Choose way of administration, we choose intravenously instead of orally.
- Choose between Magistrale bereiding (Belgium way) of specialized (Pharmaceutical) componay
- Choose between monophage, cocktail, personalised or Russian cocktails Polyphage.
- Choose monitorring, resistance and efficency PT
- Choose between combination of PT with or without antibiotics.

Hoe lossen we dit op

Proc. Natl. Acad. Sci. USA
Vol. 93, pp. 3188–3192, April 1996
Microbiology

Long-circulating bacteriophage as antibacterial agents

(phage/bacteria/reticuloendothelial system/toxins/antibiotic resistance)

CARL R. MERRIL*, BISWAJIT BISWAS*†, RICHARD CARLTON†, NICOLE C. JENSEN*†, G. JOSEPH CREED*, STEVE ZULLO*, AND SANKAR ADHYA‡

What did we decide

- We choosed personalized, intraveunous administraton of personalised monophage cocktail, cause:
  - We want to be sure that we give the right Phages to our patients
  - We want to be sure and control that the Phage reach the infection in the highest concentration and the lowest half time
  - We monitoren the bacteriae and the Phage on developping resistance and eventually change the Phages

  Consequeces

  Choose of producent Phages is limited and Belgium way “Magistral Bereiding” is impossible

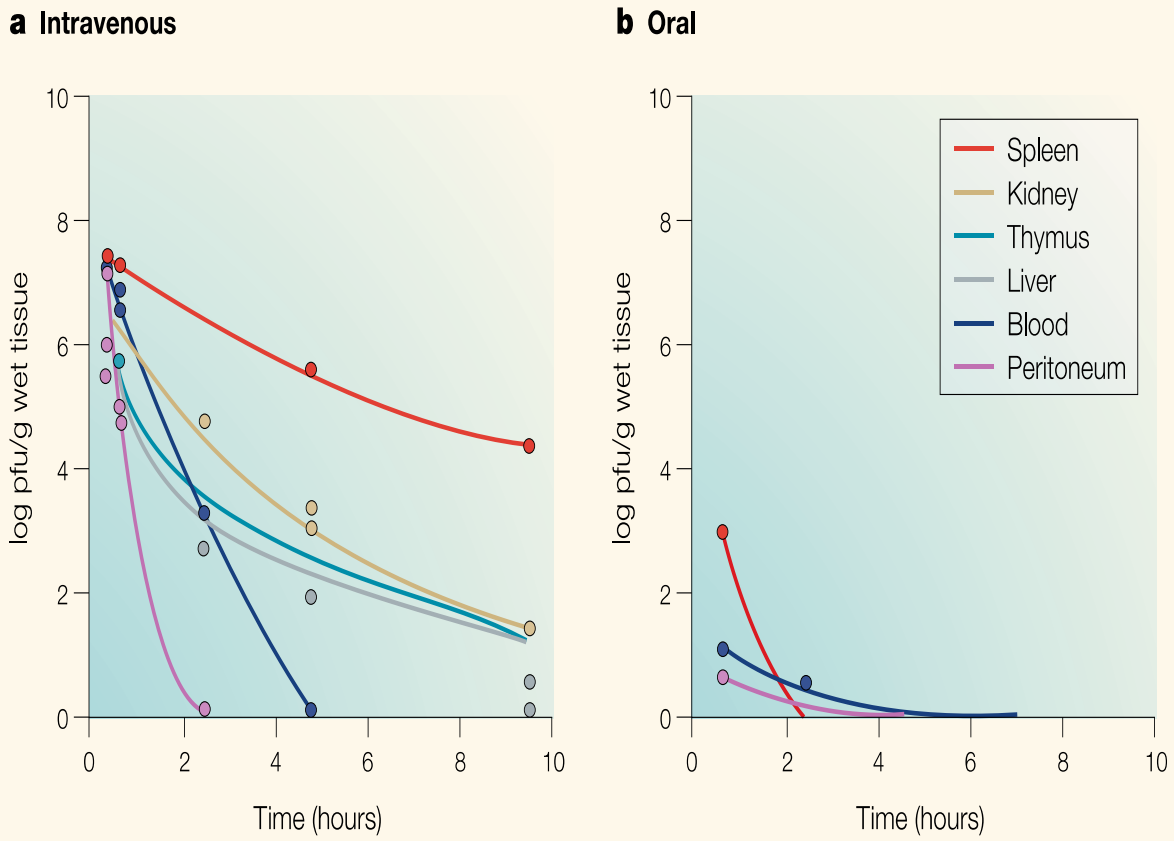


Figure 2 | **Systemic distribution of phage following intravenous and oral administration of phage.** These experiments demonstrate that oral administration is not an effective method for the delivery of phage to systemic sites as the blood and tissues levels were seven to eight orders of magnitude lower with oral administration than those achieved by systemic administration of phage. pfu, plaque-forming units.

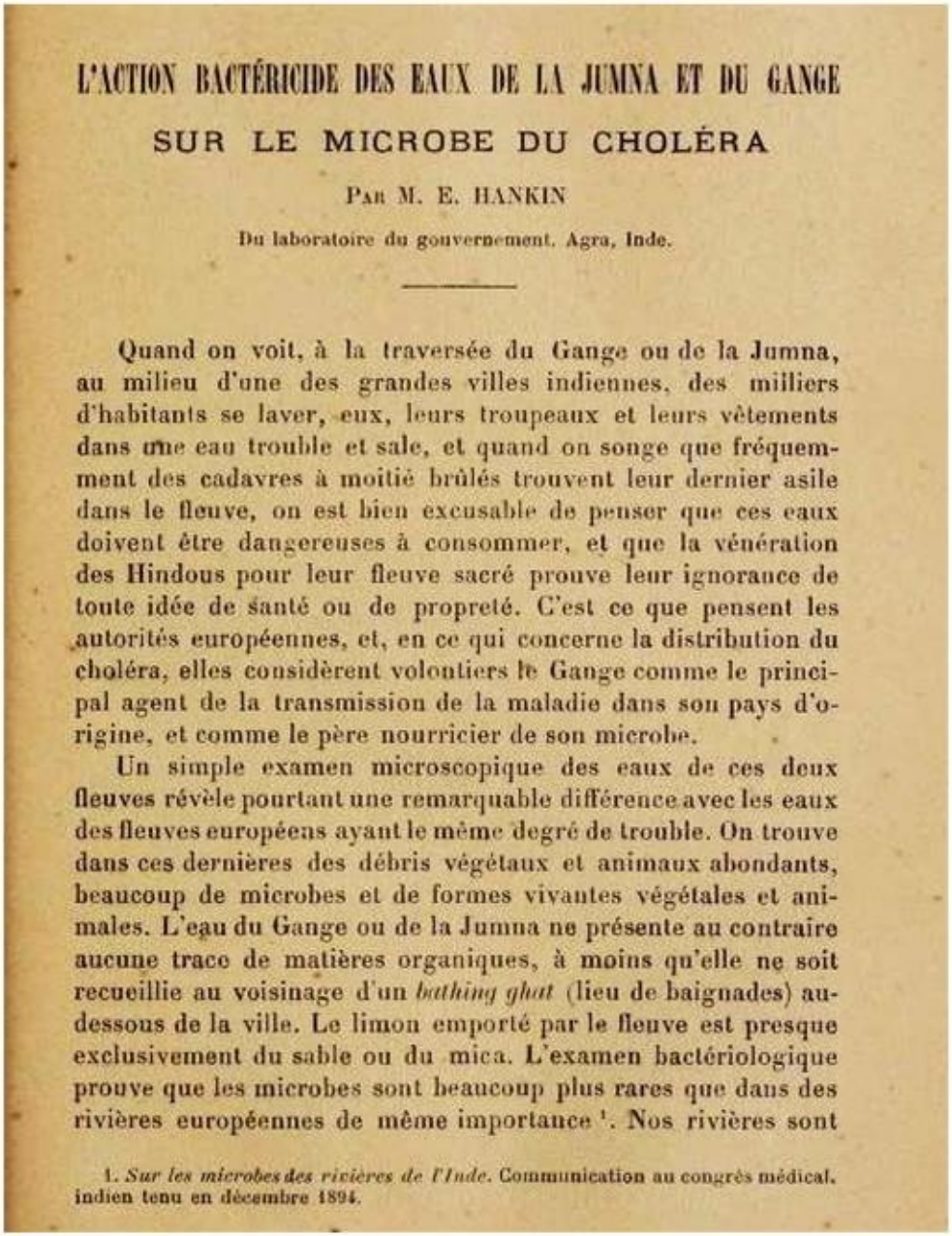
Geier, M. R., Trigg, M. E. & Merril, C. R. The fate of bacteriophage λ in non-immune germ-free mice. *Nature* **246**, 221–223 (1973).

Future

- Simplify procedures in Europe
  - EMA rules and conditions
  - Define research perspectives and collaborate European Wide
- Production of bacteriofages in Europe
- Proper registration of PT as medicine
- Develop optimal way of administration and formulation
- Generate efficacy, safety Data
- Apply in One Health setting
- Cost-effective
- Infected prosthesis or artificial organs
- Combination therapies

TAKE HOME

- The phage can be administered as an alternative or in addition to traditional antibacterial treatment, not only as ”last chance” therapy
- They are effective, safe and in most cases free from adverse effects
- Sensitivity test is needed for optimal treatment results
- Phage cocktails can be used quickly without culture results, adopted phage are a possible option in chronic and resisted cases
- More evidence-based clinical research is needed…



L'ACTION BACTÉRICIDE DES EAUX DE LA JUMNA ET DU GANGE

SUR LE MICROBE DU CHOLÉRA

PAR M. E. HANKIN

Du laboratoire du gouvernement. Agra, Inde.

Quand on voit, à la traversée du Gange ou de la Jumna, au milieu d'une des grandes villes indiennes, des milliers d'habitants se laver, eux, leurs troupeaux et leurs vêtements dans une eau trouble et sale, et quand on songe que fréquemment des cadavres à moitié brûlés trouvent leur dernier asile dans le fleuve, on est bien excusable de penser que ces eaux doivent être dangereuses à consommer, et que la vénération des Hindous pour leur fleuve sacré prouve leur ignorance de toute idée de santé ou de propreté. C'est ce que pensent les autorités européennes, et, en ce qui concerne la distribution du choléra, elles considèrent volontiers le Gange comme le principal agent de la transmission de la maladie dans son pays d'origine, et comme le père nourricier de son microbe.

Un simple examen microscopique des eaux de ces deux fleuves révèle pourtant une remarquable différence avec les eaux des fleuves européens ayant le même degré de trouble. On trouve dans ces dernières des débris végétaux et animaux abondants, beaucoup de microbes et de formes vivantes végétales et animales. L'eau du Gange ou de la Jumna ne présente au contraire aucune trace de matières organiques, à moins qu'elle ne soit recueillie au voisinage d'un *bathing ghat* (lieu de baignades) au-dessous de la ville. Le limon emporté par le fleuve est presque exclusivement du sable ou du mica. L'examen bactériologique prouve que les microbes sont beaucoup plus rares que dans des rivières européennes de même importance [1]. Nos rivières sont

1. *Sur les microbes des rivières de l'Inde.* Communication au congrès médical. indien tenu en décembre 1894.

Hankin published his observations in 1896 in the annals of the Institut Pasteur - that was the first evidence of the presence of bacteriophages in water and their antibacterial activities.

It was a viral-like agent with antibacterial properties. It was temperature sensitive and capable of passing through a porcelain filter, and it could reduce titres of the bacterium *Vibrio cholerae* in laboratory cultures.

"L'action bactericide des eaux de la Jumna et du Gange sur le vibrion du cholera„ *Annales de l'Institut Pasteur* (in French) 1896; 10: 511-523.

Godfathers of the bacteriofage therapy

Frederick Twort
1915
Canada

Félix d'Hérelle
1917
Frankrijk

George Eliava
1933
→ Tbilisi, Georgië

In 1915 The Lancet published an article written by Frederick Twort about "the transmissible bacterial lyses". It was the first publication on bacteriophages.

stomach is explored manually up to the cardiac orifice, feeling for the induration around the perforated ulcer. Failing to find an ulcer on the anterior surface the stomach is pulled out with the transverse colon, and its posterior surface explored through an incision in the mesocolon.

A perforation is seldom of more than a quarter of an inch in diameter, though occasionally twice as large as this, and can be firmly occluded by the passage of one or two sutures. These sutures should secure a good wide grip through the whole thickness of the organ, since a small grip will easily tear out of the soft œdematous wall. The occluded ulcer should be invaginated where possible by a series of interrupted sutures taking up the serous and muscular coats. Invagination of the ulcer may, however, prove impossible if the ulcer and area of surrounding induration are very large, or in some instances where the ulcer is at the attachment of the duodenum to the posterior wall. In such cases the occluded ulcer is covered with a graft of detached omentum, or drainage is made down to the ulcer with a gauze pack (Corner [1]) in case the preliminary sutures cut out.

One must next consider whether a gastro-jejunostomy should be done. In most cases where the patient is not likely to die shortly we finish with a gastro-jejunostomy, especially where the ulcer is in the vicinity of the pylorus, since if this be done the patient can be fed after operation much more effectively, and there can be little doubt that many of these patients are suffering from malnutrition, the results of previous dyspepsia, which prevents healing taking place readily. This addition does not add greatly to the duration of the operation (the whole procedure from start to finish averages, we find, about 35 minutes) and improves the prospects of ultimate success. In the less usual cases where the ulcer is on the body of the stomach gastro-enterostomy is not so urgently needed, but nevertheless is advisable.

The Uses of Jejunostomy.

Where the patient's condition is extremely grave and every moment spent on the operation is of importance, we advise simply occluding the ulcer with one or two sutures, placing a gauze drain down to the site of perforation, and performing a jejunostomy for the purpose of feeding the patient early. Jejunostomy is performed on the invagination (Kader) principle, takes less than five minutes to perform, and has the advantage that fluid nourishment can be introduced to the most absorbent surface of the intestinal canal, in a situation where vomiting is impossible, and which, unlike the rectum, is unable to reject the proffered refreshment. The actual results of cases treated by this method were less good than were those of cases treated otherwise simply owing to the very grave condition of the patients; 1 recovered and 3 died. One of the latter, which had been perforated three days, lived four days after operation. Another lived

[1] THE LANCET, Jan. 10th, 1914, p. 101.

Suture and jejunostomy	1	...	2	.....	0	... 1

My best thanks are due to my house surgeons for their notes on the above cases, and especially to Mr. W. S. Perrin, surgical registrar to the London Hospital, for his care in collecting and collating the histories.

Wimpole-street, W.

AN INVESTIGATION ON THE NATURE OF ULTRA-MICROSCOPIC VIRUSES.[1]

BY F. W. TWORT, L.R.C.P. LOND., M.R.C.S.

(*From the Laboratories of the Brown Institution, London.*)

DURING the past three years a considerable number of experiments have been carried out at the Brown Institution on filter-passing viruses. Many of these, previous to the outbreak of the war, were performed by Dr. C. O. Twort, and, unfortunately, circumstances during the present year have made it difficult to continue the work.

In the first instance attempts were made to demonstrate the presence of non-pathogenic filter-passing viruses. As is well known, in the case of ordinary bacteria for every pathogenic micro-organism discovered many non-pathogenic varieties of the same type have been found in nature, and it seems highly probable that the same rule will be found to hold good in the case of ultra-microscopic viruses. It is difficult, however, to obtain proof of their existence, as pathogenicity is the only evidence we have at the present time of the presence of an ultra-microscopic virus. On the other hand, it seems probable that if non-pathogenic varieties exist in nature these should be more easily cultivated than the pathogenic varieties; accordingly, attempts to cultivate these from such materials as soil, dung, grass, hay, straw, and water from ponds were made on specially prepared media. Several hundred media were tested. It is impossible to describe all these in detail, but generally agar, egg, or serum was used as a basis, and to these varying quantities of certain chemicals or extracts of fungi, seeds, &c., were added. The material to be tested for viruses was covered with water and incubated at 37° C. or over for varying periods of time, then passed through a Berkefeld filter, and the filtrate inoculated on the different media. In these experiments a few ordinary bacteria, especially sporing types, were often found to pass through the filter; but in no case was it possible to obtain a growth of a true filter-passing virus.

Attempts were also made to infect such animals as rabbits and guinea-pigs by inoculating two doses of the filtered material, or by rubbing this into the shaved skin. In other cases inoculations were made directly from one animal to another in the

[1] This investigation was made on behalf of the Local Government Board.

Lancet, Jan. 10th, 1914, p. 101

Felix d'Herelle

- ✓ In 1917 Félix d'Herelle isolated first bacteriophages from the stools of patients recovering from dysentery*.
- ✓ He supposed that bacteriophages were agents that cause natural recoveries*.
- ✓ He showed that bacteriophages could be used to treat bacterial infections in humans*.
- ✓ Bacteriophages have been used in medicine since 1919, ten years before the discovery of the penicillin - the first antibiotic*.

Felix d'Herelle at a bacteriophage research center.

.Thacker PD. (2003) *Set a microbe to kill a microbe: drug resistance renews interest in phage therapy*. JAMA;290(24):3183-5.

*http://www.pasteur.fr/en/brief-history-bacteriophages

- ✓ In 1917 d'Herelle and co-workers isolated phages with lytic activity against pathogenic bacteria:

  Escherichia coli, Neisseria meningitis, Pasteurella multocida, Pseudomonas aeruginosa, Salmonella typhi, Shigella dysenteriae, *Streptococcus* species, *Vibrio cholerae*, *Yersinia pestis*.

- ✓ He developed the idea of "phage therapy" as prophylactic and/or therapeutic use of selected bacteriophages in the destruction of pathogenic bacterial cells while remaining completely innocuous to host cells (d`Herelle, 1923).

- ✓ For this idea he deserved the Noble Prize, to which he was nominated eight times (every year since 1925), although he was never awarded one.

MICROBIOLOGIE. — *Sur un microbe invisible antagoniste des bacilles dysentériques.* Note (*) de M. F. D'HERELLE, présentée par M. Roux.

Des selles de divers sujets convalescents de dysenterie bacillaire, et dans un cas de l'urine, j'ai isolé un microbe invisible doué de propriétés anta-

(1) Voir ZWAARDEMAKER et ses collaborateurs, *Koninklijke Academie van Wetenschappen*, 28 avril, 27 mai, 30 septembre, 10 novembre 1916.
(2) R. SIEBECK, *Pflüger's Archiv*, t. 168, 1912, p. 443.
(*) Séance du 3 septembre 1917.

C. R., 1917, 2e Semestre. (T. 165, N° 11.) 50

374 ACADÉMIE DES SCIENCES.

gonistes vis-à-vis du bacille de Shiga. Sa recherche est particulièrement aisée dans les cas d'entérite banale consécutive à une dysenterie; chez les convalescents ne présentant pas cette complication la disparition du microbe anti suit de très près celle du bacille pathogène. Malgré de nombreux examens, je n'ai jamais trouvé de microbes antagonistes, ni dans les selles de dysentériques à la période d'état, ni dans les selles de sujets normaux.

L'isolement du microbe anti-Shiga est simple : on ensemence un tube de bouillon avec quatre à cinq gouttes de selles, on place à l'étuve à 37° pendant 18 heures puis on filtre à la bougie Chamberland L_2. Une petite quantité d'un filtrat actif ajoutée, soit à une culture en bouillon de bacilles de Shiga, soit à une émulsion de ces bacilles dans du bouillon ou même dans de l'eau physiologique, provoque l'arrêt de la culture, la mort des bacilles puis leur lyse qui est complète après un laps de temps variant de quelques heures à quelques jours suivant l'abondance plus ou moins grande de la culture et la quantité de filtrat ajoutée.

Le microbe invisible cultive dans la culture lysée de Shiga car une trace de ce liquide, reportée dans une nouvelle culture de Shiga, reproduit le même phénomène avec la même intensité : j'ai effectué jusqu'à ce jour, avec la première souche isolée, plus de 50 récensemencements successifs. L'expérience suivante donne d'ailleurs la preuve visible que l'action antagoniste est produite par un germe vivant : si l'on ajoute à une culture de Shiga une dilution d'une culture précédente lysée, de façon que la culture de Shiga n'en contienne qu'un millionième environ, et si, immédiatement après, on étale sur gélose inclinée une gouttelette de cette culture on obtient, après incubation, une couche de bacilles dysentériques présentant un certain nombre de cercles d'environ 1^{mm} de diamètre, où la culture est nulle; ces points ne peuvent représenter que des colonies du microbe antagoniste : une substance chimique ne pourrait se concentrer sur des points définis. En opérant sur des quantités mesurées, j'ai pu voir qu'une culture lysée de Shiga contient de cinq à six milliards de germes filtrants par centimètre cube. Un trois-milliardième de centimètre cube d'une culture précédente en Shiga, c'est-à-dire un seul germe, introduite dans un tube de bouillon, empêche la culture du Shiga même ensemencé largement; la même quantité ajoutée à 10^{cm^3} d'une culture de Shiga la stérilise et la lyse en cinq ou six jours.

Les diverses souches du microbe anti que j'ai isolées n'étaient primitivement actives que contre le bacille de Shiga; par culture en symbiose avec les bacilles dysentériques type Hiss ou Flexner j'ai pu, après quelques

Fruciano D.E., Bourne S.(2007) *Can J Infect Dis Med Microbiol*. 18(1): 19-26.

http://www.pasteur.fr/ip/portal/action/WebdriveActionEvent/oid/01s-00002q-016

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ANNUAL GRADUATE FORTNIGHT

BACTERIOPHAGE AS A TREATMENT IN ACUTE MEDICAL AND SURGICAL INFECTIONS*

F. d'HERELLE

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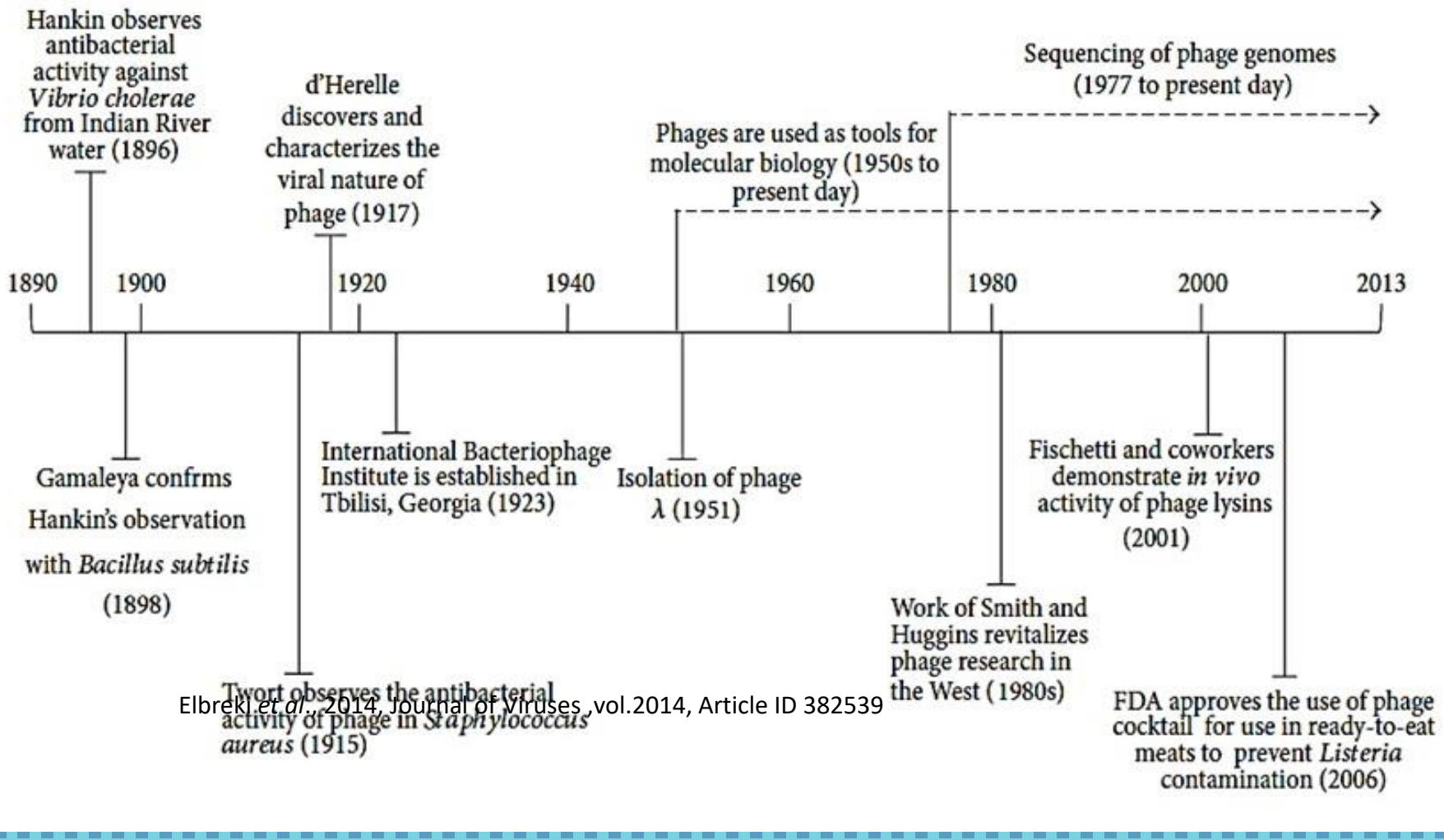
The milestones in phage history



Elbreki *et al.*, 2014, Journal of Viruses ,vol.2014, Article ID 382539

USA

1920 - 30s

Eli Lilly, Abbott Laboratories sterile phage lysates

Discouraging JAMA report (based on > 100 studies of phage therapy), except staph infections and cystitis

Eaton M.D., Bayne-Jones S. Bacteriophage therapy. JAMA 1934,103;1769-76

MacNeal W., Frisbee F. One hundred patients with Staphylococcus septicaemia receiving bacteriophage service. Am. J. Med. Sci. 1936;191:179-195. doi: 10.1097/00000441-193602000-00004

1936 - 40 typhoid patients, Los Angeles area

1950 - 1994 Staph Phage Lysate (SPA) (Delmont Labs) intranasally, topically, orally, sc iv only minor side effects

1987 A veterinary license for SPL, clinical effe4icacy confirmed in dogs by clinical trial

Clinical trial in the Czech Republic (Stafal, 1992-94) registered in the Czech Republic and Slovakia for the topical treatment of Staph. skin infections

Russia 1920s - currently

Vestn Otorinolaringol. 2015;80(1):80-3.

[Prospects for the application of bacteriophages in otorhinolaryngology].

[Article in Russian] Nosulya EV.

Abstract

The objective of the present work was to summarize the available literature data concerning the importance of and prospects for for the application ofbacteriophages for the treatment of the most common diseases of the upper respiratory tract and the ear.

PMID: 26003968 [PubMed - in process]

Romania 1960s (synergism with antibiotics)

Military use

The Finnish Campaign (1939-40)

Afrika Korps 1941-43

Soviet - German war 1941-45

Eliava Institution

Georgia

Eliava Institute In Tbilisi, established in 1930 by Eliava and d'Herelle

(Kutter et al., Curr Pharm Biotechnol 2010,11,69)

1980: 1200 employees, production capacity: 2 tons /week

Tablets, liquid (in the past 80% for the Soviet Army)

Complex cocktails: Pyophage (S,aureus, E.coli, P.aeruginosa, Proteus, Streptococcus)

Intestiphage (23 different enteric bacteria)

Poland

1920s - 2015

1945 - 54 L.Hirszfeld establishment of phage bank, Institute of Immunology and Experimental Therapy, PAS

1954 - 1987 Slopek, > 1000 pts 84-97% success rate reported

2005 - establishment of phage therapy unit (compassionate use based on Declaration of Helsinki and relevant Polish legislation (Constitution of Poland, act on the profession on doctors, ethical code of the Polish Medical Association)

In This Issue of JAMA

Medical News & Perspectives
Phage Therapy's Role in Combating Antibiotic-Resistant Pathogens

Bacteriophagen

The most recent upsurge of interest was triggered by the dramatic story of UCSD psychiatrist Tom Patterson.
In 2015, while on holiday with his wife in Egypt, Patterson became infected with a multiresistant strain of Acinetobacter baumannii. His condition worsened and he was airlifted back to an intensive care unit bed in a hospital attached to his own university. He began to recover but suffered a relapse and fell into a coma.
Patterson's wife, a UCSD infectious disease epidemiologist, had been vaguely aware of phage therapy, and asked Schooley to help. He and his colleagues found three sources of suitable phage and prepared a cocktail, which was administered both intravenously and into Patterson's abdominal cavity. After 4 days, Patterson regained consciousness.
Months later—and 100 lb lighter—he was able to return home.

Erasmus MC
Ervaring


ICU 11
STOP


220

Erasmus MC

Zieke Sven strijdt om te mogen leven

Voor 350.000 euro mag Sven sterven, maar een behandeling voor zijn ziekte van 1900 euro - dat wilde zijn zorgverzekering niet aan mensenlevens

DONEREN

Mijn dood willen we vergeven, maar mijn leven, niet. Het lijkt erop dat ook zijn ene oog is

Een oefening in logaritmisch rekenen:

Tijdstip 0: Eén bacteriecel wordt met één bacteriofaag geïnfecteerd.

Na 20-30 minuten: de bacterie barst en er komen 20-100 nieuwe fagen vrij.

Deze fagen infecteren 20-100 nieuwe bacteriecellen.

Na nog 20-30 minuten: uit elk van deze 20-100 cellen komen telkens 20-100 fagen vrij

Deze fagen …

Even tellen:

Tijdstip 0: 1 faag infecteert 1 bacterie	1 faag	
Na 20 min: 100 fagen	100 fagen	
Na 40 min: 100 x 100 fagen	10 000 fagen	
Na 1 uur: 100 x 100 x 100 fagen	1 000 000 fagen	
Na anderhalf uur: 100 x 100 x 100 x 100 fagen	100 000 000 fagen	
Na 2 uur: 100 x 100 x 100 x 100 x 100 fagen	10 000 000 000	= 10^{10} = 10 miljard

fagen na slechts 2 uur!

Na 2 uur zijn ook reeds 10 miljard bacteriecellen afgedood. En het gaat steeds sneller, tot er een gebrek aan levende bacteriën ontstaat.←→ Antibiotica kunnen alleen maar verminderen: vermenigvuldigen zich niet.

Pros

I. Specificity: phages only minimally impact non-target bacteria or body tissues – safe with no adverse effects
II. Self-regulating mechanism: phage increase their number when in the presence of bacterial targets. The phage converts the cell into a factory for making new phages.
III. Overcome the resistance of the bacteria
IV. Alternative to antibiotics in the situation of arising resistance
V. Less likely to provoke allergy
VI. Phage can be easily combined with other antimicrobial agents

Con

s

I. Phage resistance: Lysogenia in ”moderate” phage – the selection is needed

II. Bacteriophage need to be placed in contact with the infectious site

III. Cold chain for liquid forms

IV. No international clinical recommendations and evidence-based researches

Patients treated with phages

32YR Old CF patient, came in with EMV 11 after use Polish fages, next day completely recovered. High amount of endotoxins. New phages cocktail from USA aimed at three bacteriae from last year sputum. Recovery and increase pulmonary funktion to three years before and low infection parameters

53 Yr old Dutch Turkisch man, car accident in Turkeye with frontal face wound and operations in Turkye. Three month in Netherlands with ventriculitis with acinetobacter baumanii complex. Treated with phages, within three days cultures negative but patient died due to brainstem herniation due to swollen brain.

24 Yr old Camera men CNN car crash Afghanistan, left side crushed, skull bone taken out because of high brain pressure. Multiresistant acineto bacter Baumanii

56 Yr Old patient with LVAD SA driveline infection with abcesses around driveline and LVAD. Inoperable. Phage therapy from Eliava. Now 6 months free.

Voordelen en nadelen van fagen tov antibiotica

1. Smal spectrum van fagen: fagen infecteren slechts enkele soorten of stammen
   Nadeel: je moet eerst weten met welke soort/stam je te maken hebt
   ! Bij chronische infecties geldt dit nadeel veel minder: niet levensbedreigend
   → er is ruim de tijd om de meest actieve faag(combinatie) te selecteren.
   Voordeel: geen effect op commensale bacteriën!

2. Voorkomen van /Ontwikkelen van resistentie tegen fagen
   Nadeel: veel bacteriën zijn van nature resistent tegen de meeste fagen
   Nadeel: resistentie-ontwikkeling van bacteriën tegen fagen is een natuurlijk proces
   Voordeel: je kunt dikwijls nieuwe fagen vinden in de omgeving
   Voordeel: je kan fagen trainen om actiever te worden tegen een bepaalde stam

3. Geen relatie van faagresistentie met antibioticumresistentie
   → fagen kunnen actief zijn tegen multi-antibioticumresistente bacteriën,
   bvb. faag ISP tegen MRSA.
   → fagen kunnen perfect met andere medicatie, incl. antibiotica, gecombineerd worden fagen en antibiotica kunnen elkaars werking versterken

Studies met fagen

- Phase II/III Australian study on endocarditis with SA of PM, MV, AoV

  70% recovery
- CF trail Mayo Clinics and APT trail
- BIOMX trail CF an biofilm
- UTI and PJI trail

Conclusies

- FDA heeft bacteriofagen trails goedgekeurd
- Internationale database gestart (Phagestry)
- EMA moet nog steeds haar goedkeuring geven
- Resultaten in MDR zijn veelbelovend met geringe bijwerkingen
- Resultaten in oplossen biofilm zijn hoopgevend
- Nu reeds indicatie voor niet te behandelen patiënten met goede genezingskans

Toekomst

- Procedure vereenvoudigen
- Productie bacteriofagen naar europa halen
- Registratie mogelijk maken van bacteriofagen als medicament
- Werkingsmechanisme en toedieningsvormen onderzoeken en optimaliseren
- Data genereren
- Toepassen in One Health setting
- Kosten effectief maken
- Geïnfecteerd kunstmateriaal
- Combinatie therapieen

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Vragen??