An Introduction to Current Topics in Biology

Topic 4: Microbiology & Infectious Disease

Dr Ruth Grady

(sign into BoB for video)

Content

- Microbes and infectious diseases
  - General concepts of infectious disease
  - Emerging and re-emerging infectious diseases
  - Antibiotics & phage therapy

- Antibiotic resistance; sexually transmitted diseases

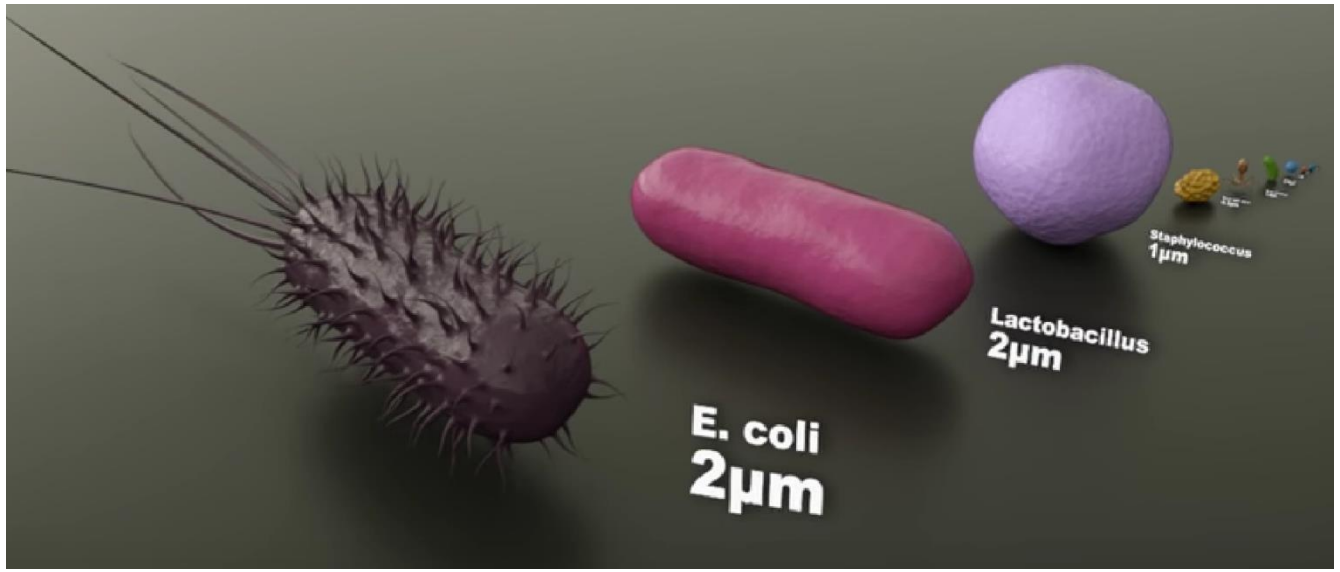
- Discussion paper: Gut microbiome and faecal transplants

Microorganisms

- Viruses (nm or 10^{-9} m range)
  - Genetic elements that replicate *inside* cells
  - ‘sub-cellular parasites’
  - Consist of nucleic acid surrounded by protein
  - Classified by type of nucleic acid/how replicate/ single or double-stranded
- Bacteria (µm or 10^{-6} m range)
  - Single-celled prokaryotic microorganisms
  - No membrane-bound nucleus

What are microbes?

- https://www.youtube.com/watch?v=h0xTKxbIElU



Too slow to play in class but worth a view (2 min 20 s)

What do microbiologists worry about today?

Timeline of new and emerging infections since 1998

Prairie dog— monkeypox reservoir in 2003 outbreak in USA

Camel – MERS reservoir

Aedes albopictus – vector for chikungunya

Emergence of a female Guinea worm from a sufferer's lower leg

Ngari virus

Nipah virus

Rift Valley fever [Saudi Arabia and Yemen]

Monkeypox [USA]

Chaparevirus

Plague [Algeria]

Lujo virus [southern Africa]

Multi-drug resistant *P falciparum* [SE Asia]

MERS-CoV

Mojiang Paramyxovirus

Cholera [Haiti]

Ebola [West Africa]

Avian influenza H5N6

Lassa fever [Benin]

Bourbon virus

CCHF [Spain]

Chikungunya [Pakistan]

Lassa fever [Togo]

Ntwetwe virus

Guinea worm [Angola]

Lyme disease

Avian influenza H7N4

Monkeypox [Liberia, UK]

Nipah virus

1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018

SARS-CoV-2

2019

Pteropus poliocephalus— suspected Nipah virus reservoir

West Nile virus [USA]

Itaya virus

EBLV-2 [Scotland]

SARS-CoV

Avian influenza H7N2

Human retroviruses, HTLV3, HTLV4

Oriental rat flea, *Xenopsylla cheopis*, a known plague vector

Candida auris

Heartland virus

Bas-Congo virus

Lassa fever [Mali]

Pandemic influenza 2009 H1N1 virus

Huaiyangashan virus – SFTS virus

Plague [Libya]

Lassa fever [Ghana]

Plasmodium cynomolgi

Swine influenza H3N2v

Prevost's squirrel – VSB 1 reservoir
Image by: Matthias Buehler

Avian influenza H7N9 virus

Sosuga virus

Avian influenza H10N8 virus

Chikungunya [Caribbean]

Variegated Squirrel Bornavirus 1

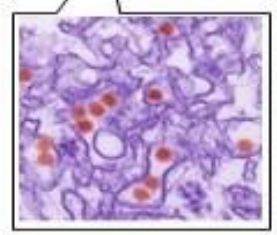
Colpodella sp. Heilongjiang (HLJ)

Monkeypox [Nigeria]

Yellow fever [Brazil]

Rat hepatitisE virus

Zika virus [Americas]



Zika virus

Images taken from the CDC Public Health Image Library: https://phil.cdc.gov

Future?

New infectious diseases since 1980

Bovine Spongiform Encephalopathy

Extensively drug-resistant tuberculosis

E. coli O157:H7
Lyme disease

Hepatitis C

Bird Flu H5N1
(in humans)

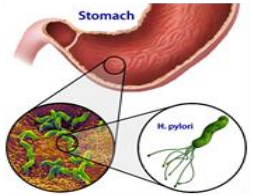
Pandemic H1N1 Flu

SARS-CoV-2:
Covid-19

1980 | 1990 | 2000 | 2010 | 2020?

HIV/AIDS

Helicobacter pylori (Stomach ulcers)



vCJD (variant Creuzfeldt–Jakob disease)

SARS coronavirus

Middle East respiratory syndrome coronavirus (MERS-CoV)

Emerging and re-emerging infectious diseases today

- Old diseases now known to be microbiological
  - *e.g.* stomach ulcers (*Helicobacter pylori*);
- An old infection (re-) emerging because it has become resistant to treatment
  - *e.g.* XDR-TB (extensively drug-resistant TB)
  - Hospital-acquired infection
- Diseases (th)ought to have been eradicated but now re-emerged *e.g.* Syphilis; Chlamydia
- A recognised infection spreading to new populations (*e.g.* Zika /Ebola) or appearing in new areas
- A new infection resulting from changes in existing microorganisms
  - *e.g.* Bird/swine flu; SARS
- Discovering new tricks & roles for bacteria – role of gut bacteria in health and disease ?

Emerging and re-emerging infectious diseases today

- Old diseases now known to be microbiological
  - *e.g.* stomach ulcers (*Helicobacter pylori*); cancer (HPV); Multiple sclerosis (EBV)
- An old infection (re-) emerging because it has become resistant to treatment
  - *e.g.* XDR-TB (extensively drug-resistant TB)
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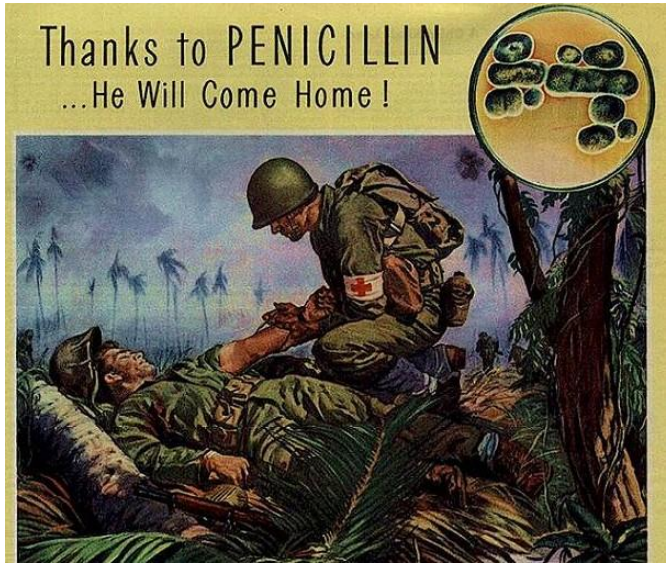
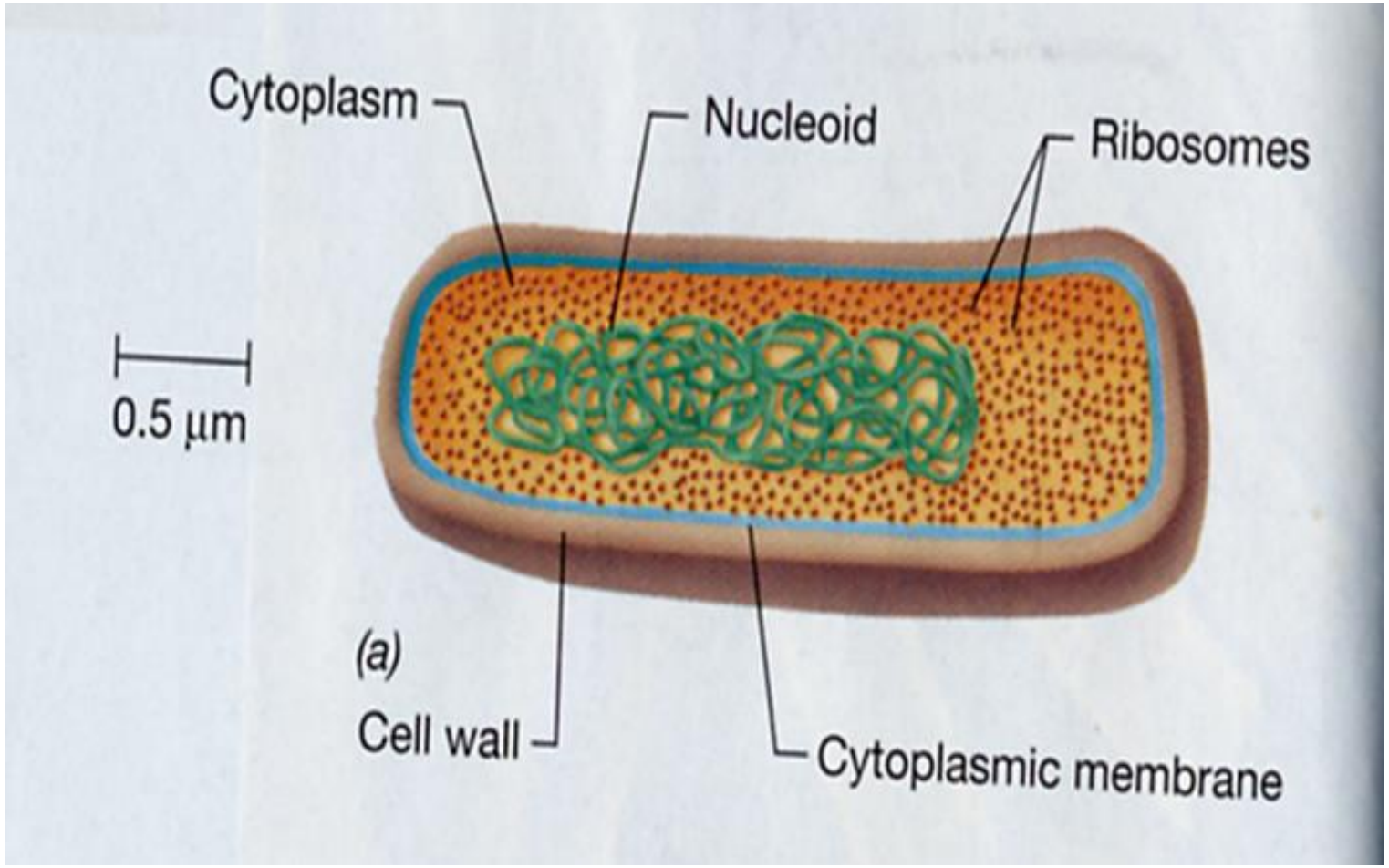
Antibiotics

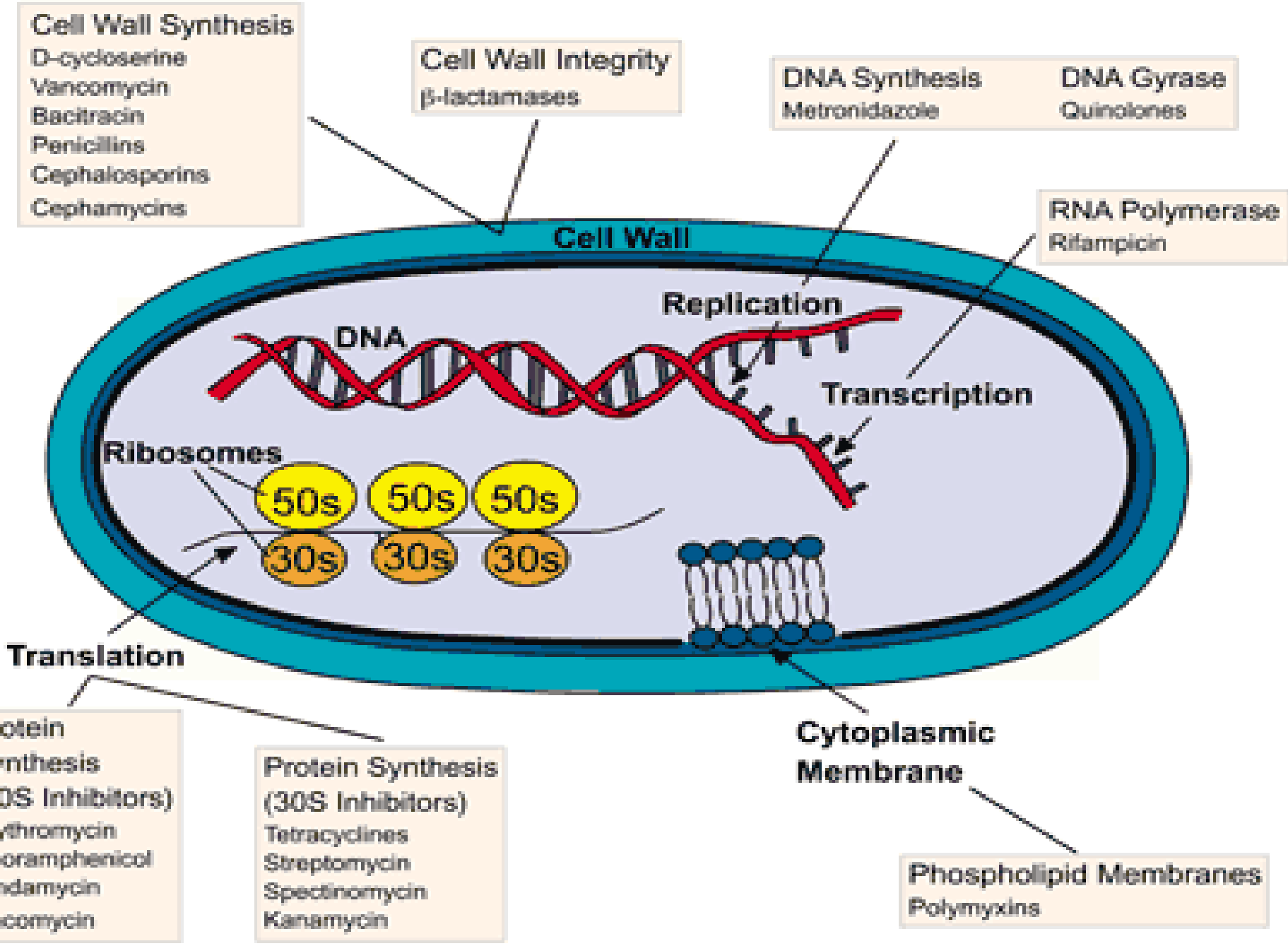


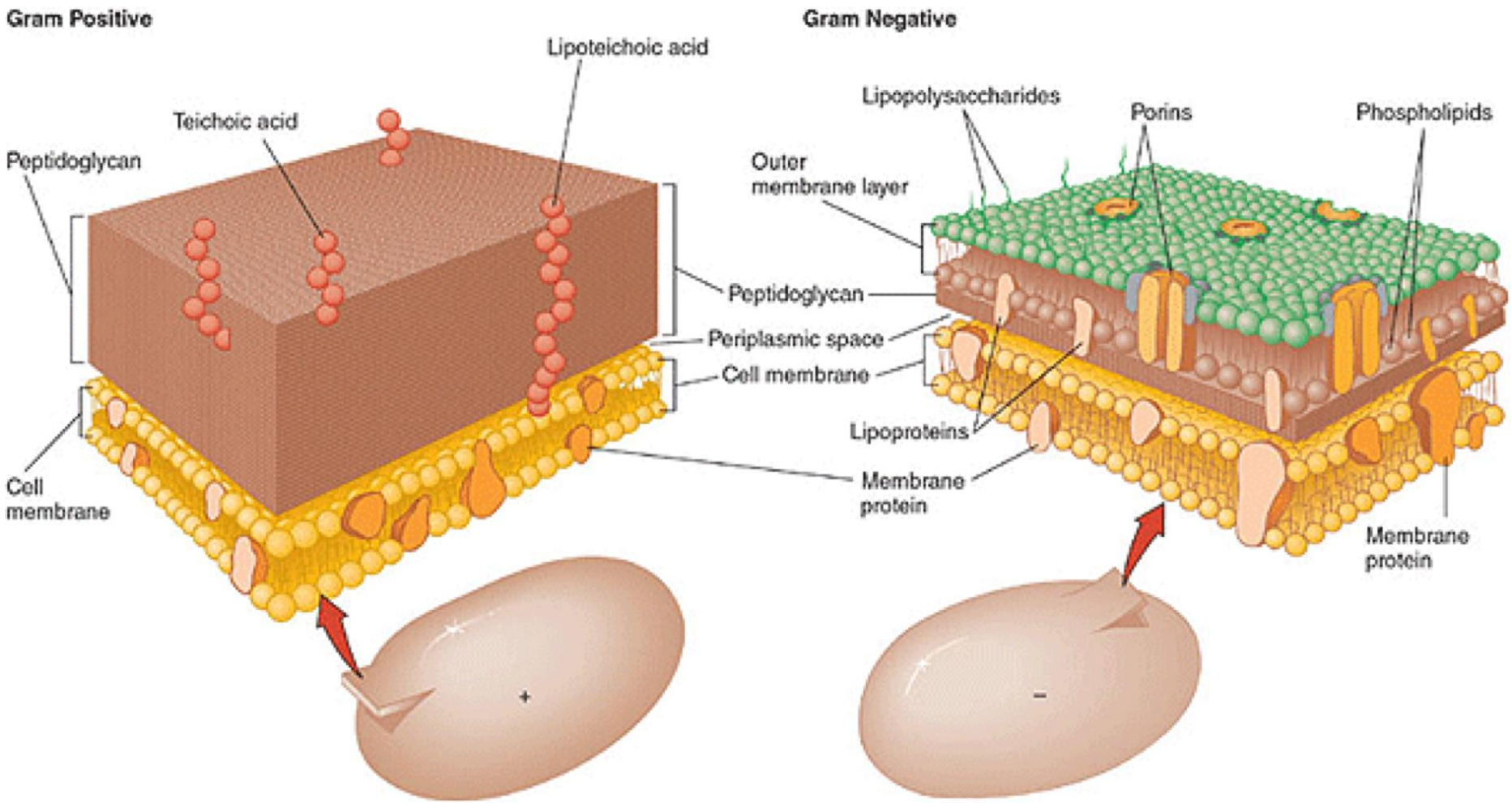
How do antibiotics work?



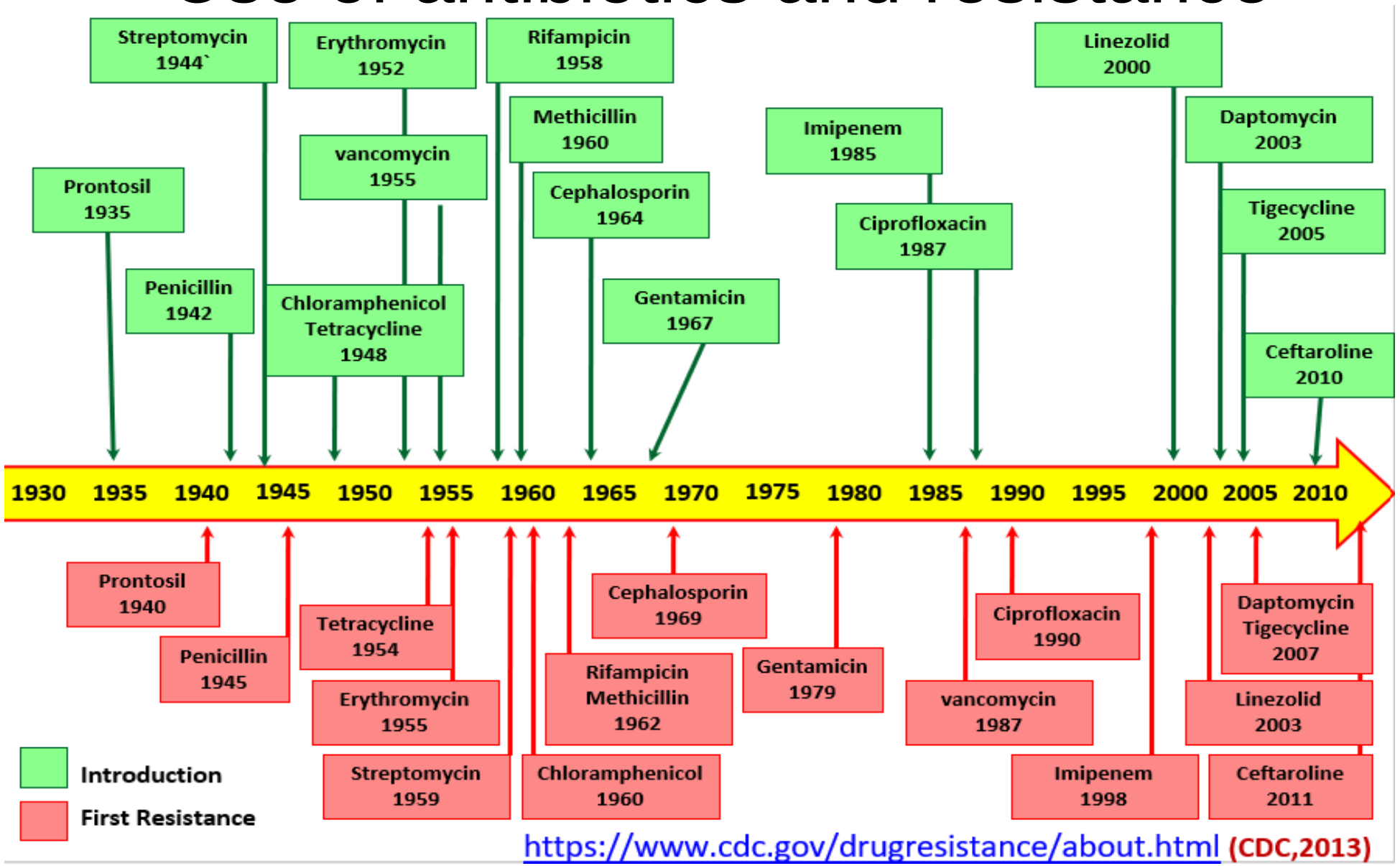
How do Antibiotics work?

- Inhibit cell wall formation (penicillin)
- Inhibit protein synthesis (tetracycline; erythromycin)
- Several other mechanisms… …

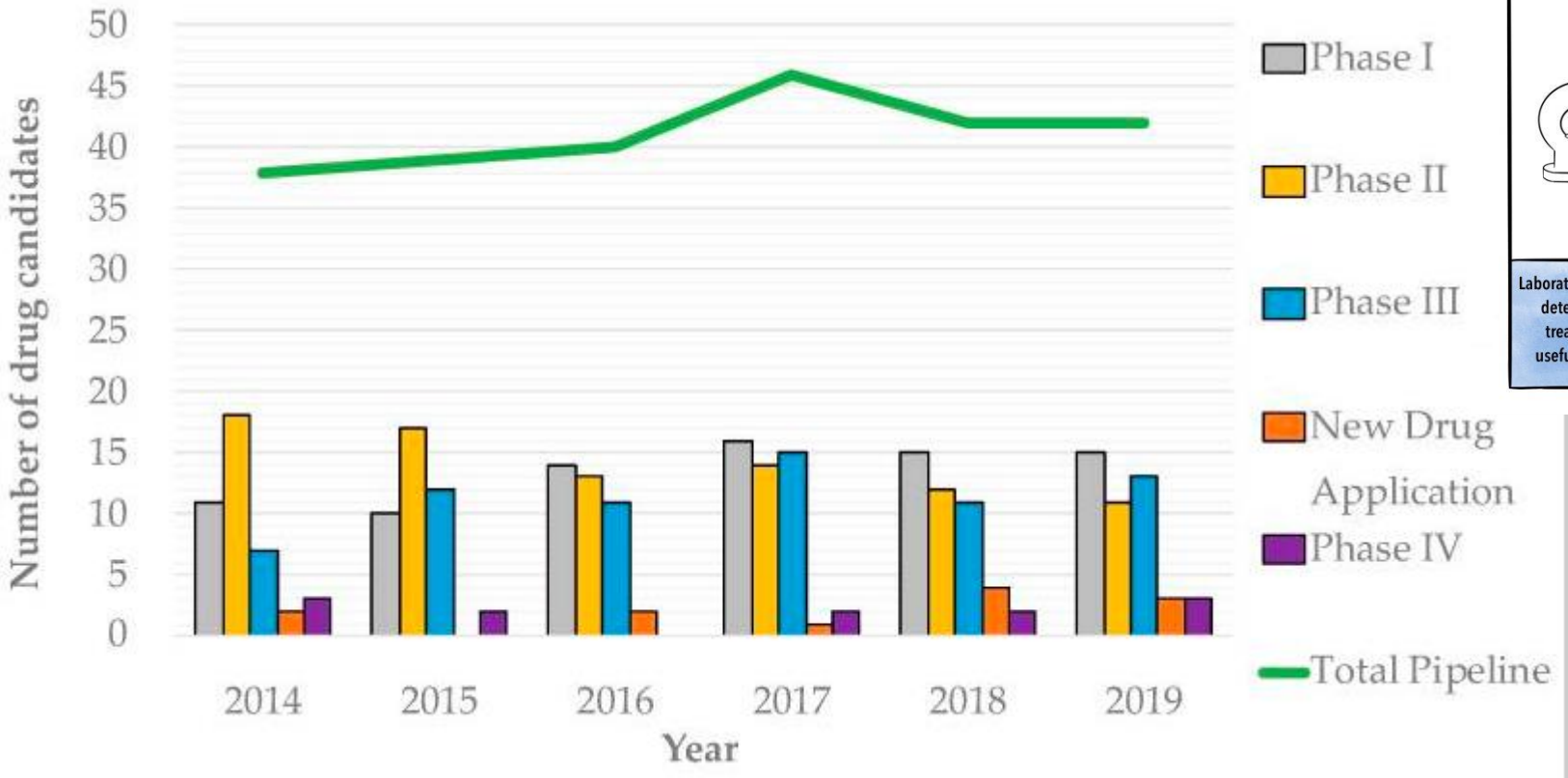


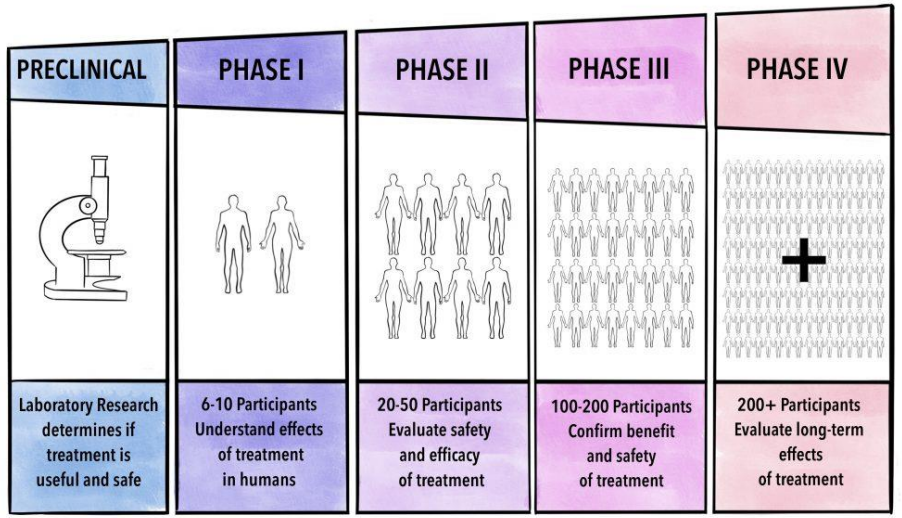


Use of antibiotics and resistance



https://www.cdc.gov/drugresistance/about.html (CDC,2013)





Why is investing in new antibiotics not attractive commercially?

Evolution of the total antibiotic pipeline and the antibiotic pipeline by stage of development, which includes: Clinical Trials ranging from Phase I, to evaluate safety; Phase II, to access effectiveness and safety; Phase III, to gather statistically significant data on safety, effectiveness and benefits-versus-risk; submission of a New Drug Application, for marketing approval; and lastly, Phase IV for post-marketing surveillance.

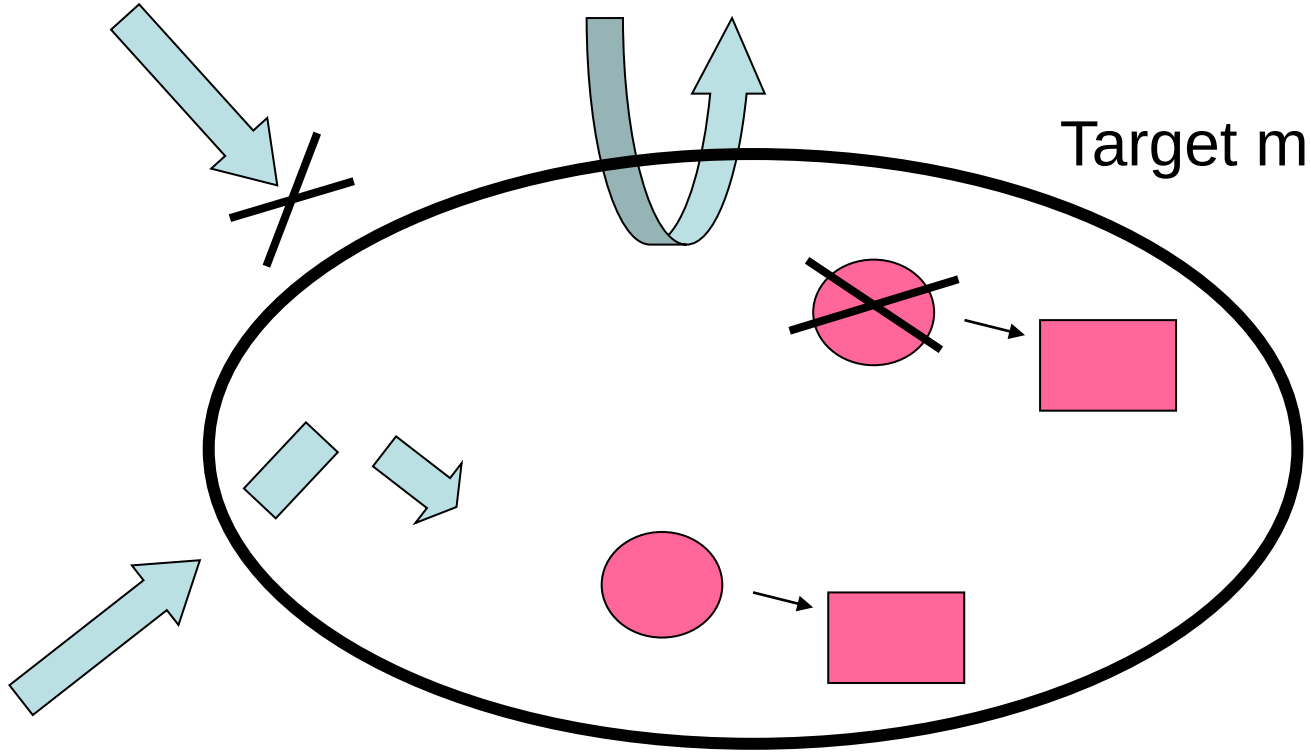
Ribeiro da Cunha B, Fonseca LP, Calado CRC. Antibiotic Discovery: Where Have We Come from, Where Do We Go? Antibiotics (Basel) 2019; 8(2):45.

Mechanisms of antibiotic resistance

Drug Impermeability (innate)

Drug Efflux

Target modification



Drug Inactivation

Target bypass

- One type of antibiotic can be overcome by different mechanisms
- Different classes of antibiotics can have the same mechanisms of resistance
- Need to find new targets?

Why does antibiotic resistance arise?

- Bacteria acquire genes from other bacteria (horizontal transfer of plasmid DNA)
- Bacteria grow quickly and mutations can arise v. quickly
  - Eg. Bacteria can repurpose structures to remove antibiotics

- Overuse of antibiotics
  - ‘over the counter’
- Animal husbandry
- Stopping antibiotics too soon
  - Not finishing a dose

New approaches?

Historical:

- Natural compounds
- Semi-synthetic / synthetic

Genetic era:

- Genome analysis – find homologues / likely candidate genes

Post-genome era:

- Screening libraries of older compounds
- Systems biology

Other alternatives

- Targeting signalling messengers (‘quorum sensing’) between bacteria
- Phage therapy

Quorum Sensing

Bacteria communicate with each other to alter behaviour

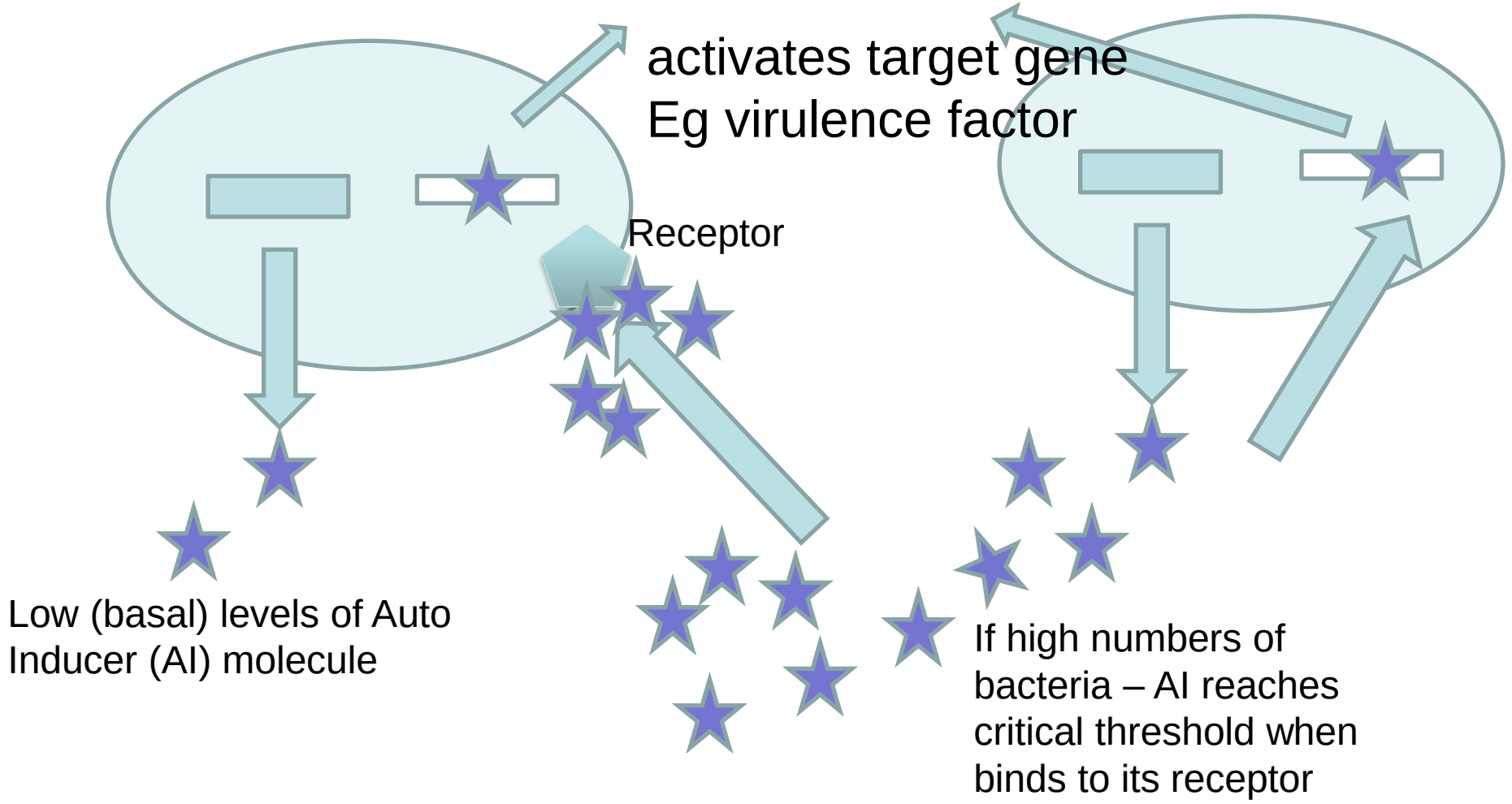
https://learningonscreen.ac.uk/ondemand/index.php/clip/231194

(transcript on notes under slide)

‘Cross-talk’ (communication) between bacteria and with host?

Allows ‘cross-talk’ (communication) between species and with host

- Via small signalling molecules
- ‘autoinducers’
  - Small proteins (oligopeptides) or RNA molecules
- Bind to receptors on /in bacterial cells which alters gene expression
  - Eg bacteria produce toxins or switch off flagella (movement) or bioluminescence



New mechanism to control bacterial growth

- Quorum quenching:
- Interfering with QS signals; bacteria can survive, but not thrive?
- Reduction in antibiotic resistance?

Resources

- UK Health Security Agency. UK website. Available from: Health protection: Infectious diseases - detailed information - GOV.UK (www.gov.uk)
  - Information regarding microbial pathogens, surveillance and characterisation of important pathogens. Produces weekly and monthly bulletins outlining current outbreaks
- Centers for Disease Control and Prevention (USA): http://www.cdc.gov
  - American version of above (note – the clinical guidance may not be the same as in UK but the information is !)

Microbiology Society : Homepage | Microbiology Society

- A good website for topical microbiological stories (press releases and policy consultation responses)

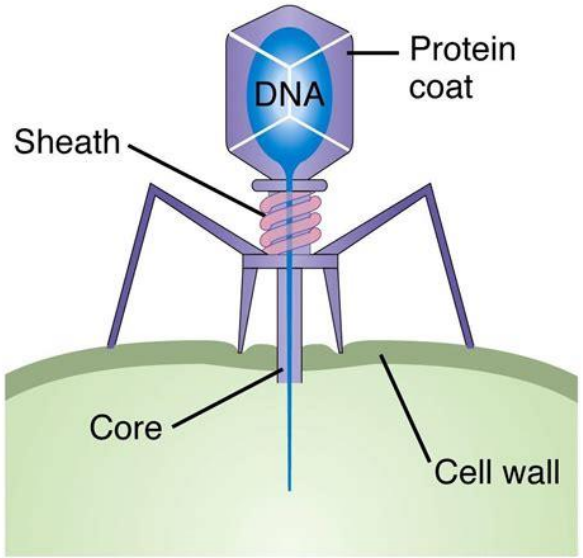
- Hanssen, N.M., de Vos, W.M. and Nieuwdorp, M., 2021. Fecal microbiota transplantation in human metabolic diseases: from a murky past to a bright future?. Cell Metabolism, 33(6), pp.1098-1110.

Topic 4: Microbiology and Infectious Disease

Lecture 2: Phage therapy; antibiotic resistance and sexually-transmitted diseases

Bacteriophage therapy?

- Viruses that infect bacteria: lytic/lysogeny (dormancy)
- Estimated 10^{31} in total on earth!
- Discovered 1915 & 1917 independently
- Highly specific to a strain of bacteria species
  - Killed bacteria; used in 1930s
  - Properties were often ‘oversold’
  - Lack of efficacy
  - Superseded by antibiotics
- In ‘West’: ‘phages studied for Mol. Biol. Research
- In Soviet bloc – cocktails of phage preparations
- Antibiotic resistance – make phages look v attractive!



Issues with ‘phage therapy

- Phages are immunogenic
  - Cleared from blood; localised use only?
- FDA licensing granted in 2006 for food processing
  - Against food-poisoning bacteria (Listeria)
  - Disinfectant spray on animal feed
    - ‘GRAS’ licensing
- Human use?
  - 2007: Small-scale studies against ear infections
  - Fully sequenced phages: leg ulcers
  - *E. coli* diarrhoeal disease (Bangladesh)
  - 2012: burns victims (military)
  - ‘Compassionate use’: allowed when antibiotics have failed

Pros and Cons

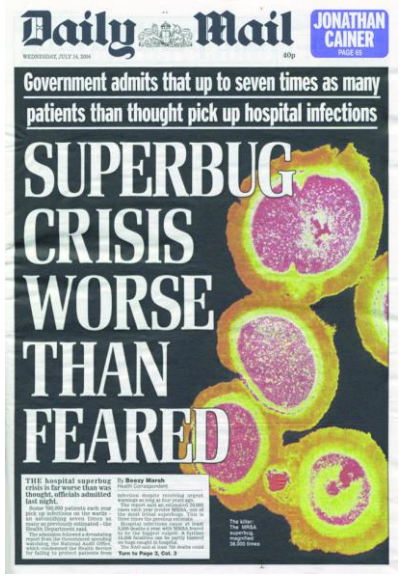
- Low dosing levels/ biofilm disruption
  - Multiply in hosts; then cleared naturally
  - Few side effects?
- Can avoid killing normal microflora
- Use of cocktails – less resistance?

- Know little about their biology
- Latency? Need to select phages carefully
- Worry regarding release of toxins
- Strain variation among clinical isolates
- Resistance?
- IP/patent issues – follow the money!

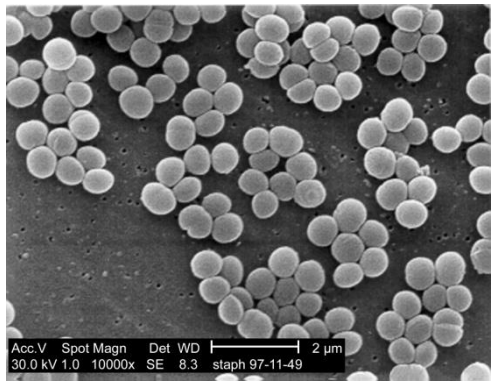
An old infection (re-) emerging because it has become resistant to treatment

Healthcare-associated (nosocomial) infections

- Hospital-acquired/ healthcare-associated/ nosocomial, HAIs
- Not all HCAI are preventable
  - micro-organisms carried by the patient
  - Immuno-compromised patients



- Problem bacteria:
  - Met(h)icillin-resistant *Staphylococcus aureus* (MRSA a.k.a. ‘Superbug’)

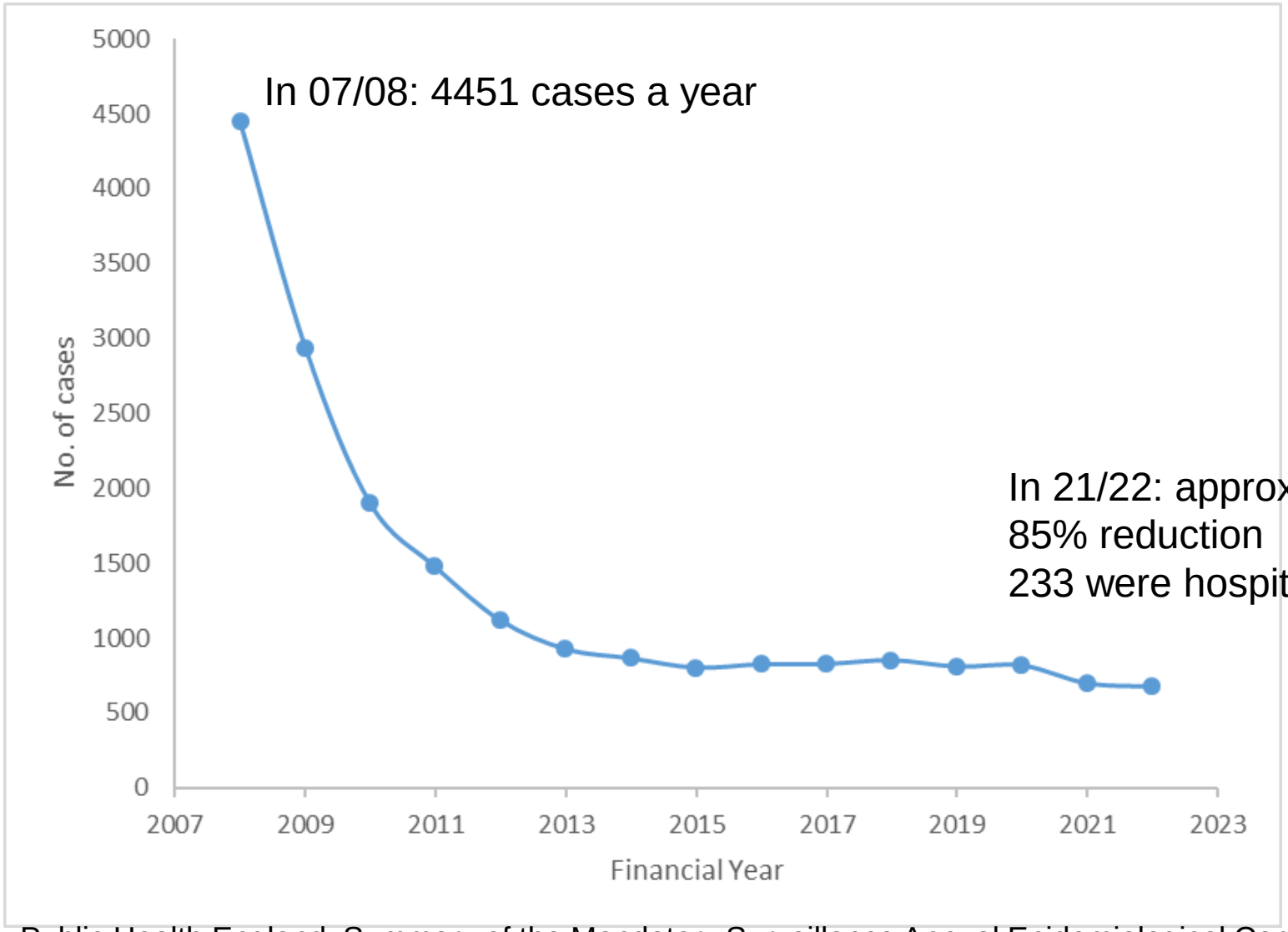


MRSA

- *Staphylococcus aureus*
  - skin & throat commensal
  - boils & carbuncles
- Methicillin-resistant *Staphylococcus aureus*
- 1961 first report of MRSA
- Became a major nosocomial problem
  - community issue too?

- At its peak: approx. 7000 new cases of MRSA blood infections per year; now approx. 700 (incl. HAI and community)

Numbers of MRSA bacteraemia (Year 2007/08 to FY 2021/22)



In 21/22: approx. 673 cases a year
85% reduction
233 were hospital-acquired

Public Health England: Summary of the Mandatory Surveillance Annual Epidemiological Commentary, 2020/21

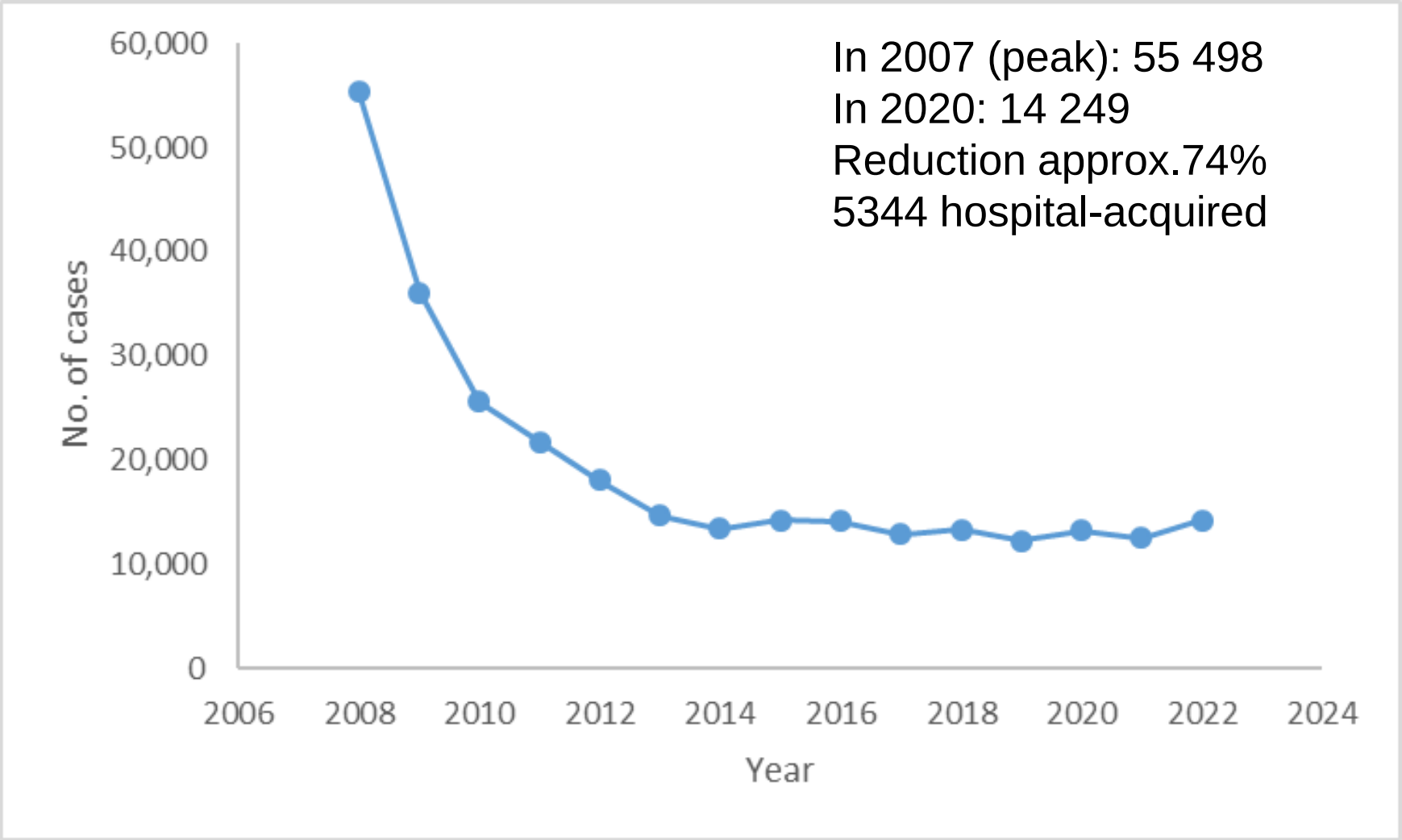
Other important nosocomial bacteria

- *Pseudomonas aeruginosa*
  - Lung infections (esp. in cystic fibrosis)
  - Naturally resistant to many antibiotics
  - Grows as a biofilm

- *Clostridioides* (C*lostridium) difficile*
  - Diarrhoeal infection predominantly in ill patients
  - Spores not killed by alcohol hand gel
  - Some antibiotic-resistance now seen

- Carbapenemase-Producing Enterobacteriaceae (CPE)
  - Commensal on skin and in the gut (approx. 25 % of healthy people)
  - Cause urine infections, wound infections, pneumonia and septicaemia
  - Resistant to many antibiotics

Reports of *C. difficile* infection



Experimental treatment: faecal microbiota transplants

Hanssen, N.M., de Vos, W.M. and Nieuwdorp, M., 2021. Fecal microbiota transplantation in human metabolic diseases: from a murky past to a bright future? Cell Metabolism, 33(6), pp.1098-1110.

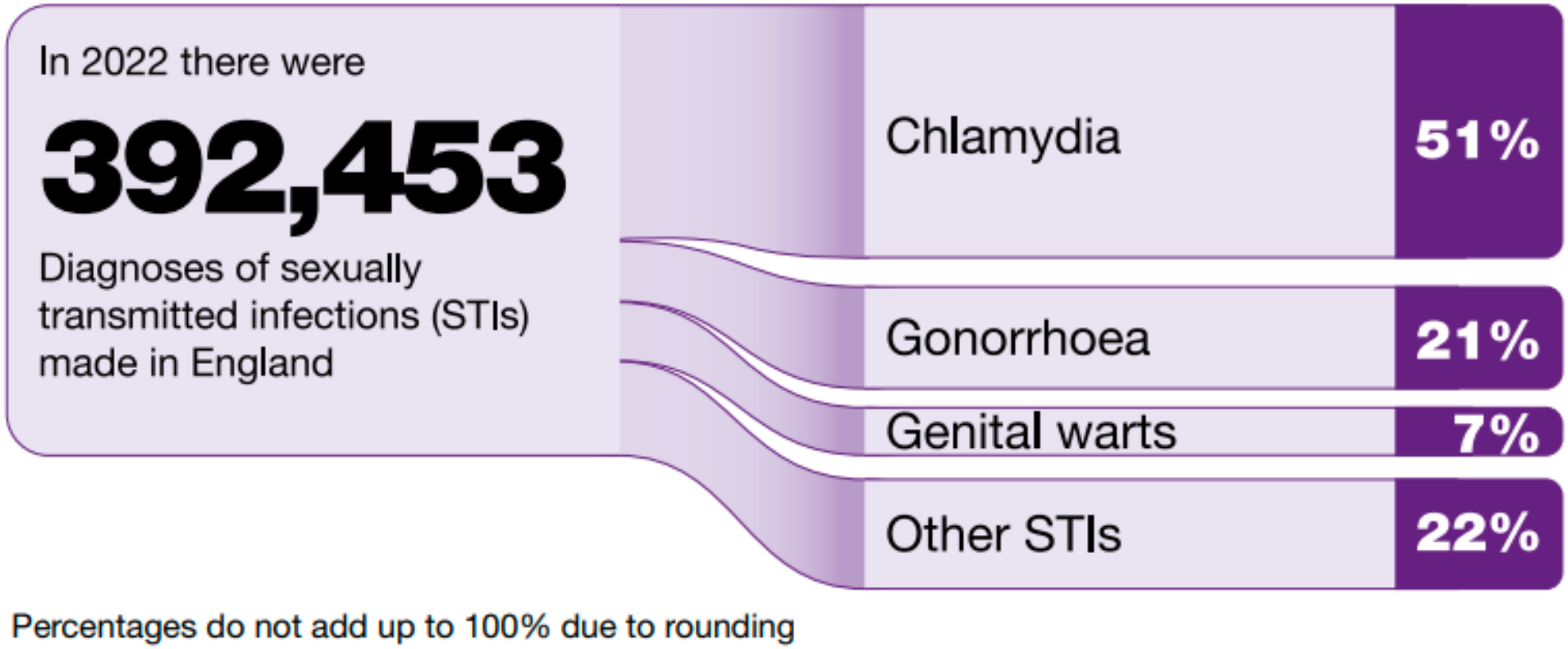
Transfer of microbes from a ‘healthy’ donor to a patient

- High success rate (85% cure) for chronic C. diff infections following faecal microbiota transplant (FMT) from healthy to ill patients
- Not defined as to what a healthy microbiome is
  - Maybe more than one? Maybe not the actual bacteria but their metabolites?
- Risks of transplanting
  - Transmit depression/ anxiety/ obesity?
- Ethical implications
  - Changes may affect the local community? (as microflora can pass on – informed consent?)
  - Can they be passed to offspring?

Diseases thought to have been eradicated but now re-emerged

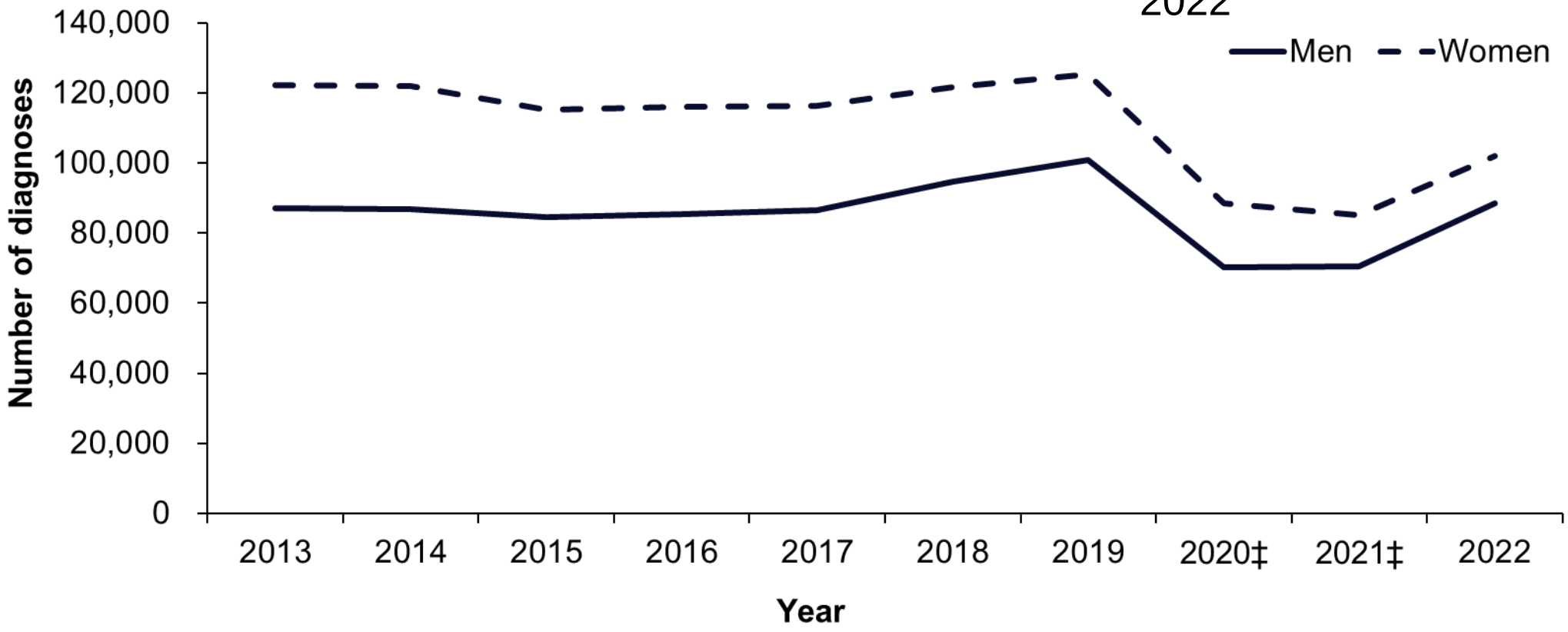
Sexually-transmitted Infections

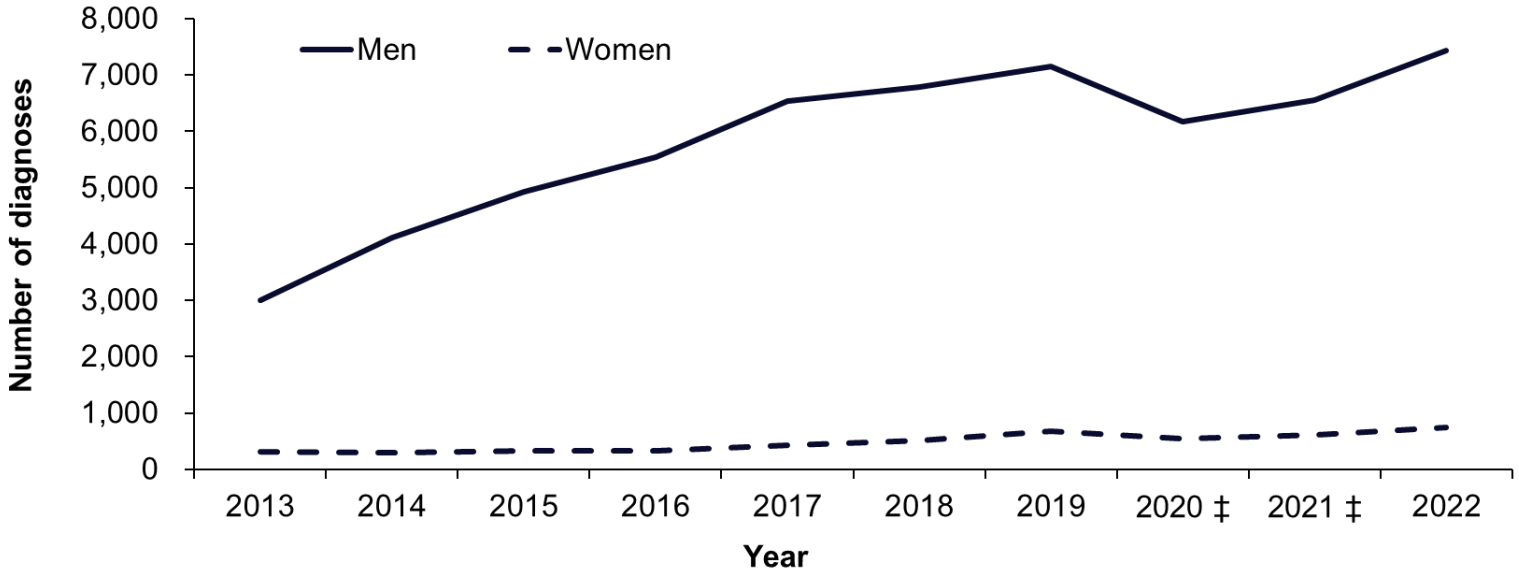
- Chlamydia/ gonorrhoea (‘the clap’)/ syphilis/ HIV/ herpes/



UK Health Security Agency: Sexually transmitted infections in England, 2022

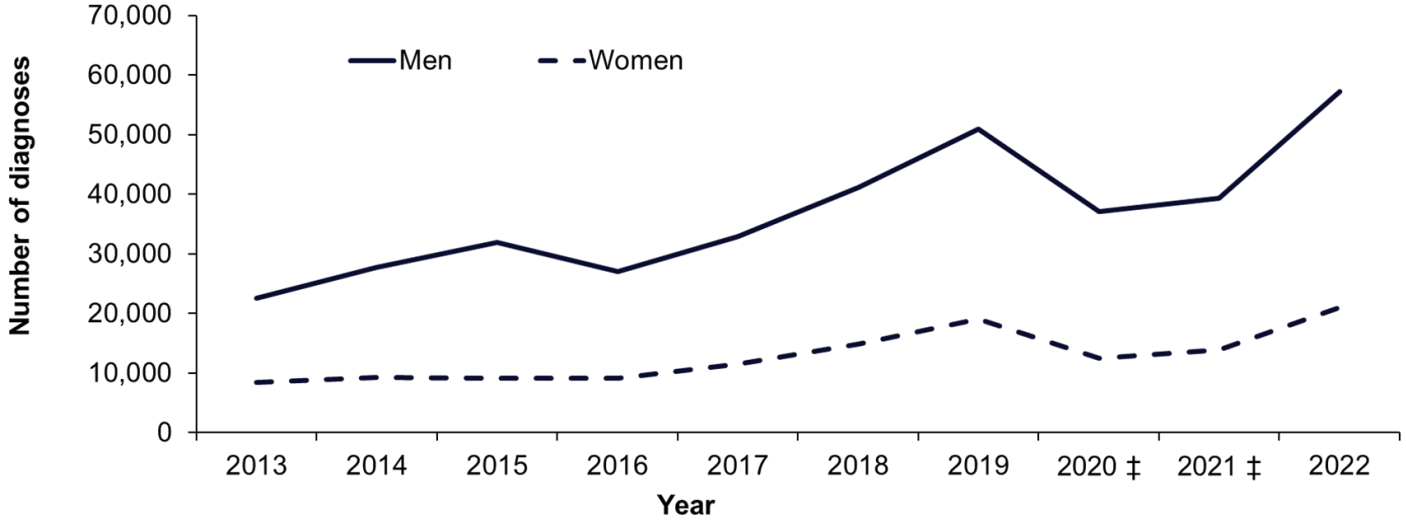
NB
Chlamydia – most commonly diagnosed sexually-transmitted infection approx. 200 000 cases in 2022





New diagnoses of syphilis (primary, secondary and early latent) 2013 – 2022, England.

In 2022, 8195 new diagnoses for all in England: highest since 1948
(743 in women)



New diagnoses of gonorrhoea 2013 – 2022, England.

NB
Chlamydia – most commonly diagnosed sexually-transmitted infection > 200 000 cases in 2021

UK Health Security Agency: Sexually transmitted infections in England, 2022

Chlamydia vs Gonorrhoea

Chlamydia trachomatis

- Gram negative cocco/bacilli (2 morphologies)
- Hard to see in light microscope (very small!)
- Obligate intracellular bacteria
- Survives inside epithelial cells

Neisseria gonnorhoeae

- Gram negative cocci
- Adhere (via pili and capsules) to epithelial cells of the urethra/cervix; multiply;
- Some cell invasion

Chlamydia/ Gonorrhoea symptoms

Symptoms due to:

- Cell destruction/loss of function - discharge
- Host inflammatory response
- Often asymptomatic (Chl: 50% of men and 70-80% of women)

Chlamydia:

- Pain on urination, unusual discharge from the penis, vagina or rectum or, in women, bleeding between periods or after sex

Gonorrhoea:

- As above; usually thicker, copious yellow-green discharge

- Pelvic inflammatory disease or infertility or arthritis (mother)
- Untreated can lead to miscarriage, premature birth
- Eye infections (new-born)

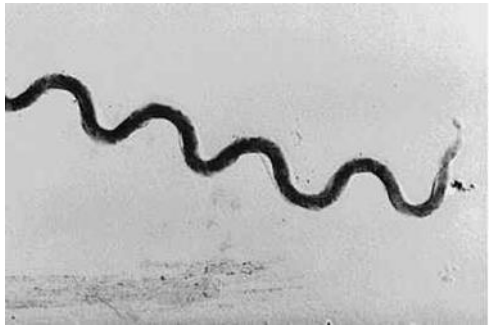
N. gonorrhoeae resistance

- In 2018 a heterosexual man in England was confirmed as having resistant N.g. (1st global report; acquired in Asia); 2 cases in Australia
  - Azithromycin (protein synthesis inhibitor)
  - Ceftriaxone (cell-wall inhibitor)
- Only susceptible to spectinomycin (protein synthesis inhibitor)

On the increase….

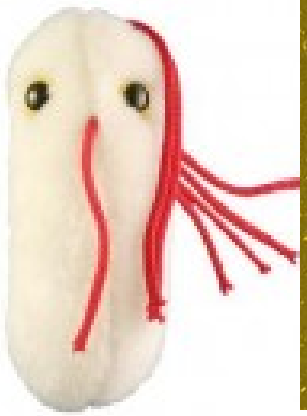
- 2015-2021: 9 cases detected in UK (all associated with international travel from Asia-Pacific area)
- First 6 months of 2022: 10 cases ..

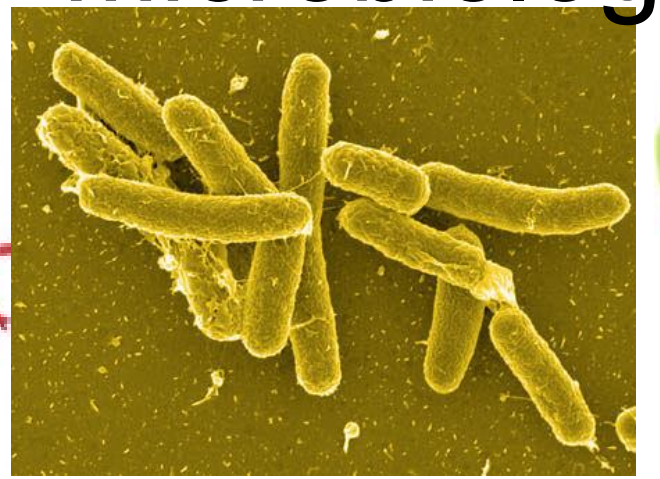
Syphilis

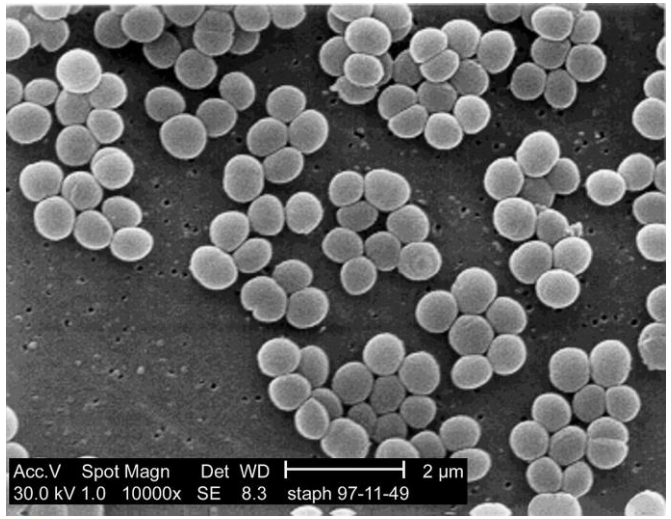


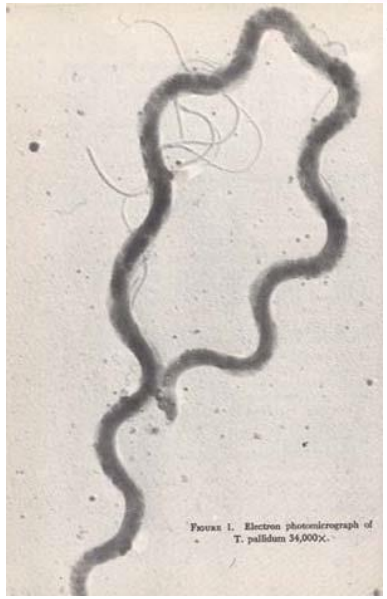
- Bacteria: *Treponema pallidum*
- Unusual shape and cell wall: ‘spirochaetal’
- Hard to grow in the lab. (intracellular growth & anaerobic) and no animal model
  - Limited knowledge about mechanisms of pathogenicity
- Three (four) stages in infection process (distinct presentations)
    - Primary/ secondary/ (latent)/ tertiary

Microbiologists and their toys …

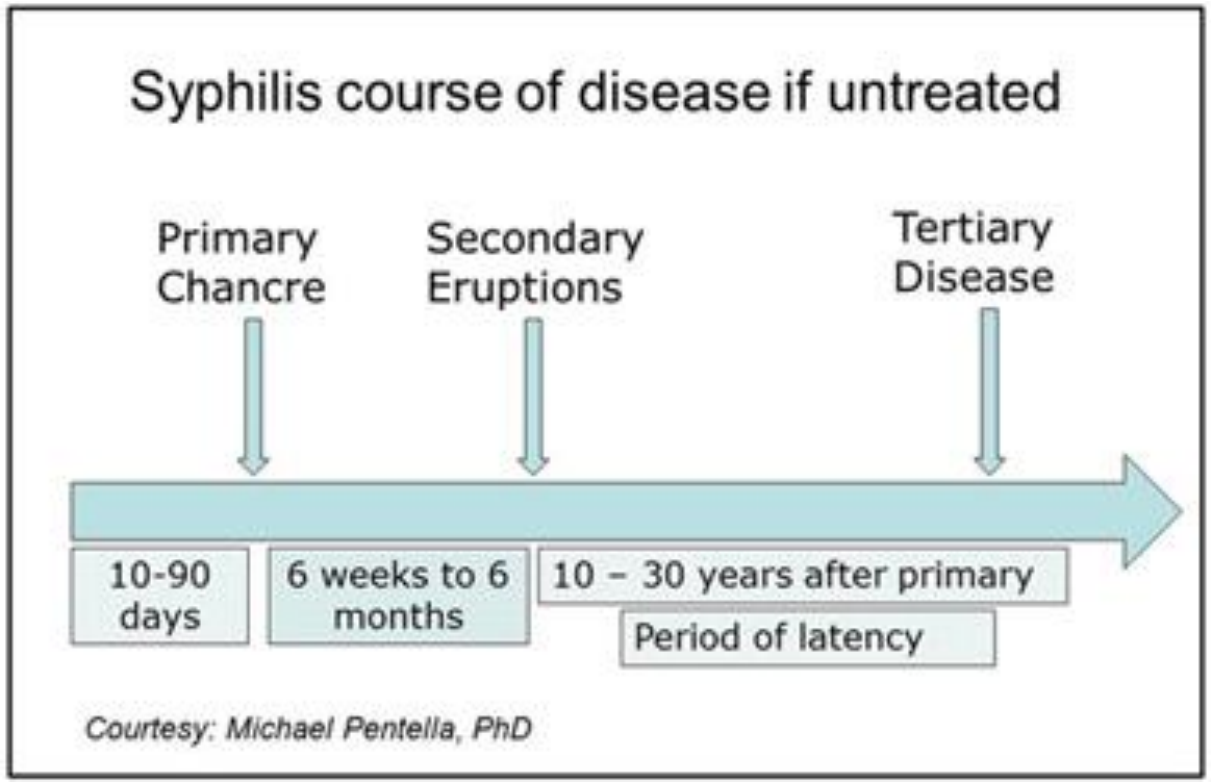








https://www.giantmicrobes.com/uk/

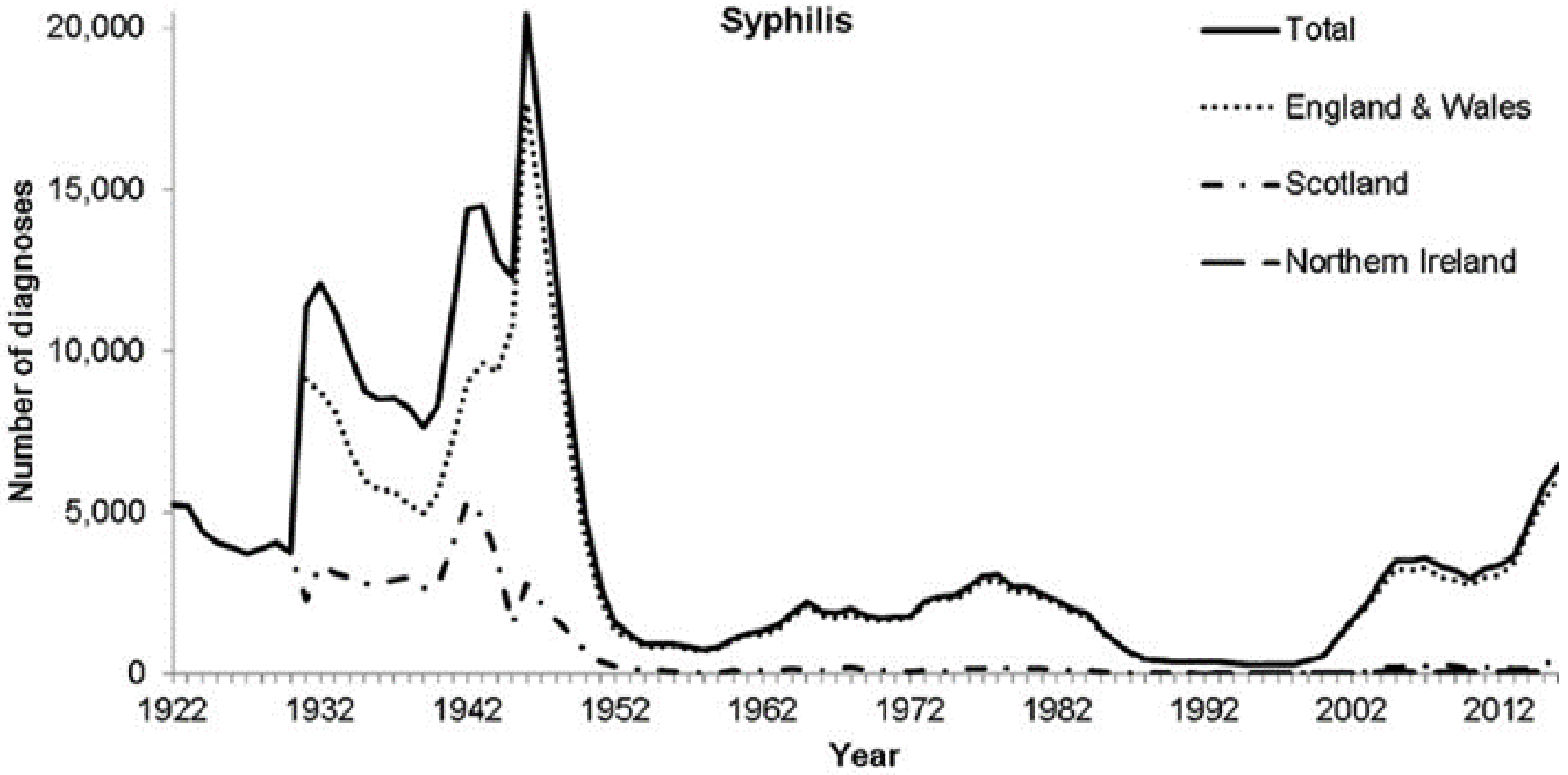


Primary chancre (painless!)

Secondary hypersensitive rash

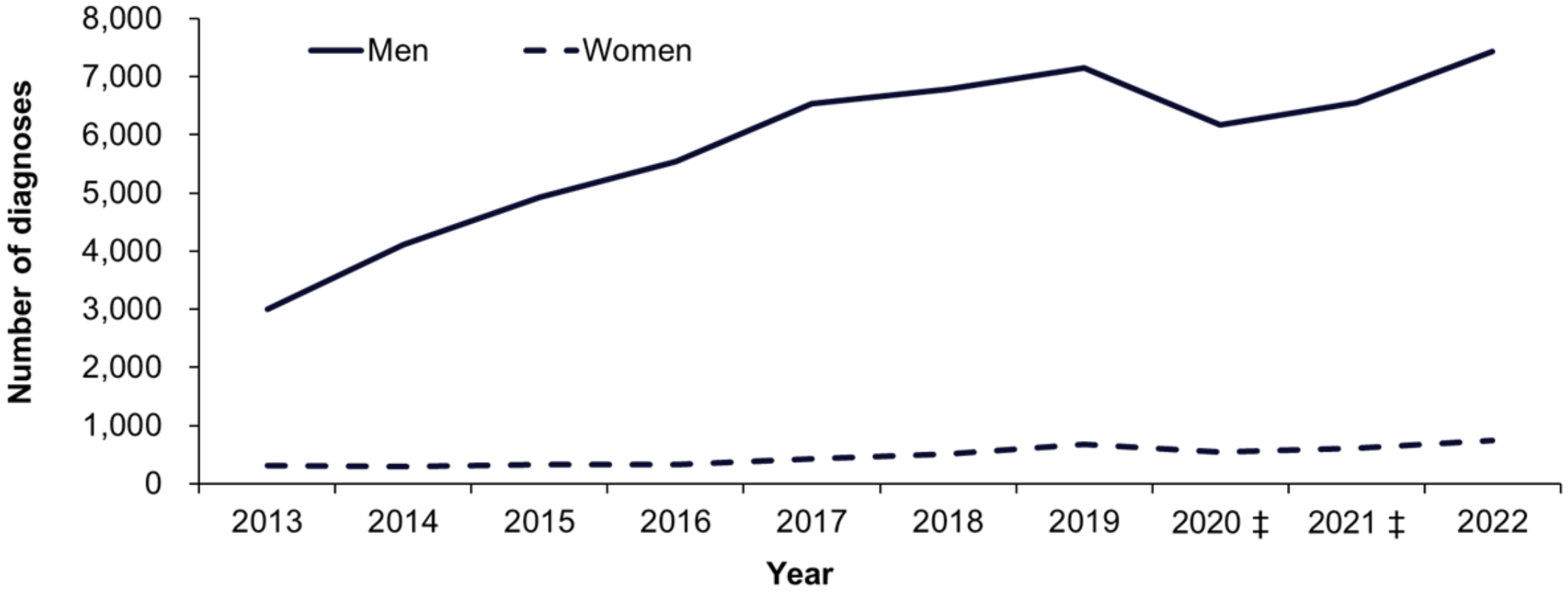
Tertiary syphilis: in approx. 15 % of people, develops years later after an untreated primary infection: neurological/systemic complications

Number of syphilis (primary, secondary and early latent) diagnoses by sex in UK; 1922–2012



UK Health Security Agency

UK Health Security Agency: Number of syphilis (primary, secondary and early latent) diagnoses by sex: England, 2012–2022



UK Health Security Agency: Sexually transmitted infections in England, 2022

Next session: Discussion

Hanssen, N.M., de Vos, W.M. and Nieuwdorp, M., 2021. Fecal microbiota transplantation in human metabolic diseases: from a murky past to a bright future?. Cell Metabolism, 33(6), pp.1098-1110.

Please read before you come to the session, and be prepared to share:
a) 3 things that you didn’t know before reading this paper
b) the 3 things that interested you the most in the paper
c) 3 things you didn't understand fully