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

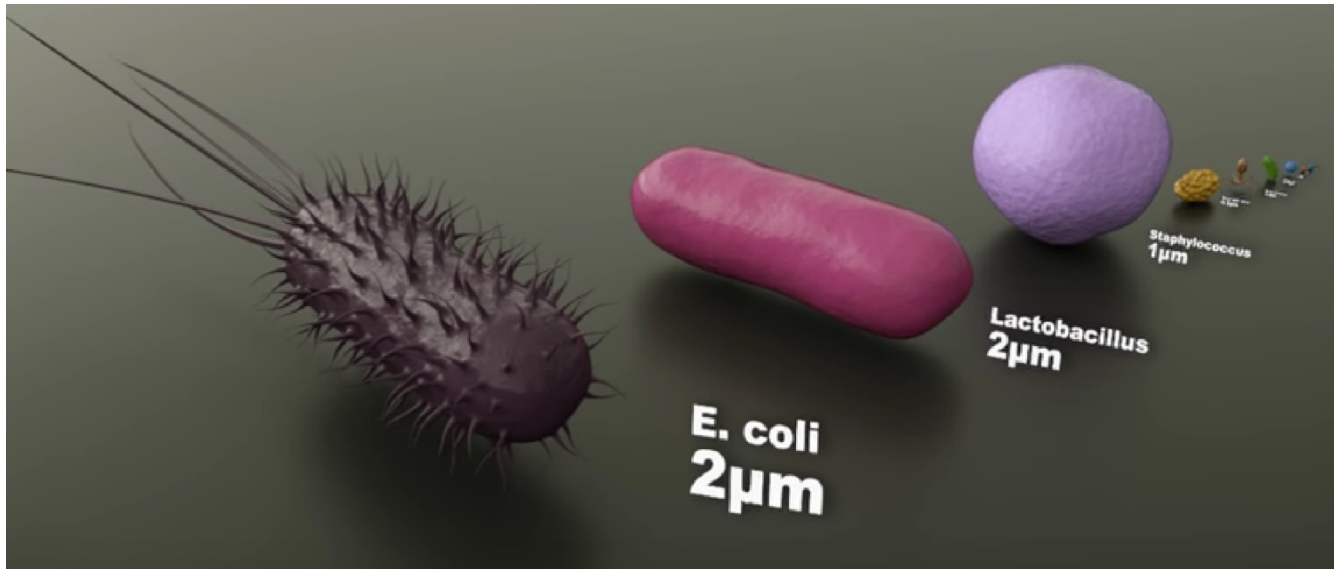
- Discussion paper: Gut microbiome and faecal transplants

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=h0xTKxbIEIU



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

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]

CCHF [Spain]
Chikungunya [Pakistan]
Lassa fever [Togo]
Ntwetwe virus

Ebola [West Africa]
Avian influenza H5N6
Lassa fever [Benin]
Bourbon virus

Guinea worm [Angola]
Lyme disease
Avian influenza H7N4
Monkeypox [Liberia, UK]
Nipah virus

Ngari virus
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 paliacephalus— suspected Nipah virus reservoir

EBLV-2 [Scotland]
SARS-CoV
Avian influenza H7N2

Human retroviruses, HTLV3, HTLV4

West Nile virus [USA]
Itaya virus

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]

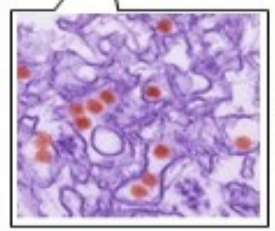
Lassa fever [Ghana]
Plasmodium cynomolgi
Swine influenza H3N2v

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)

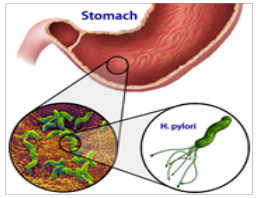
Pandemic H1N1 Flu

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)

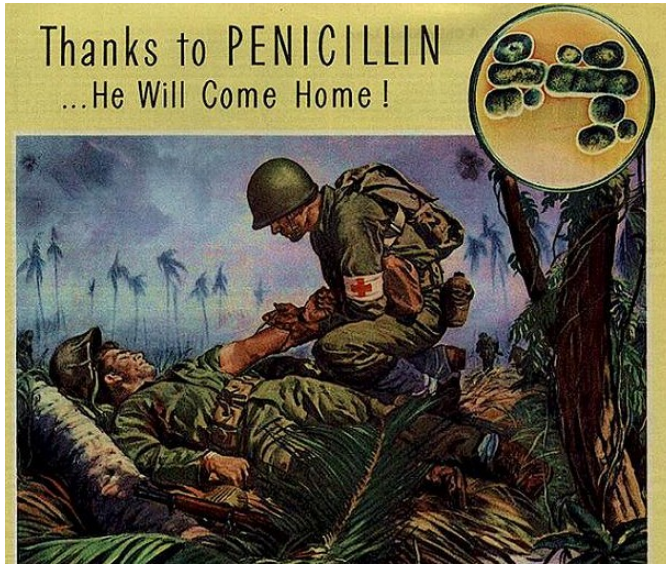
Emerging and re-emerging infectious diseases today

- 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 ?

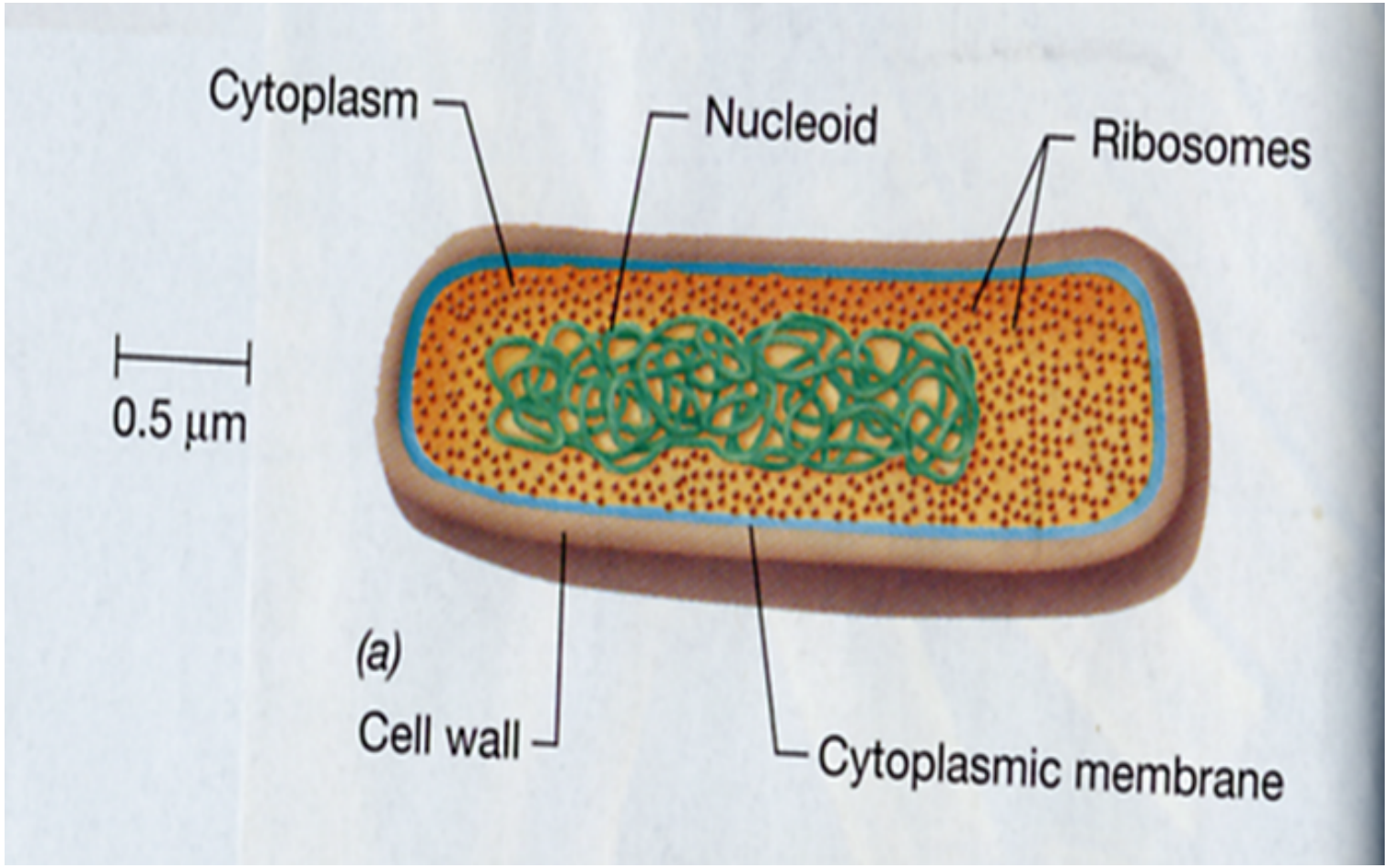
Emerging and re-emerging infectious diseases today

- 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)
  - Hospital-acquired infection
- Diseases thought 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 ?

Antibiotics

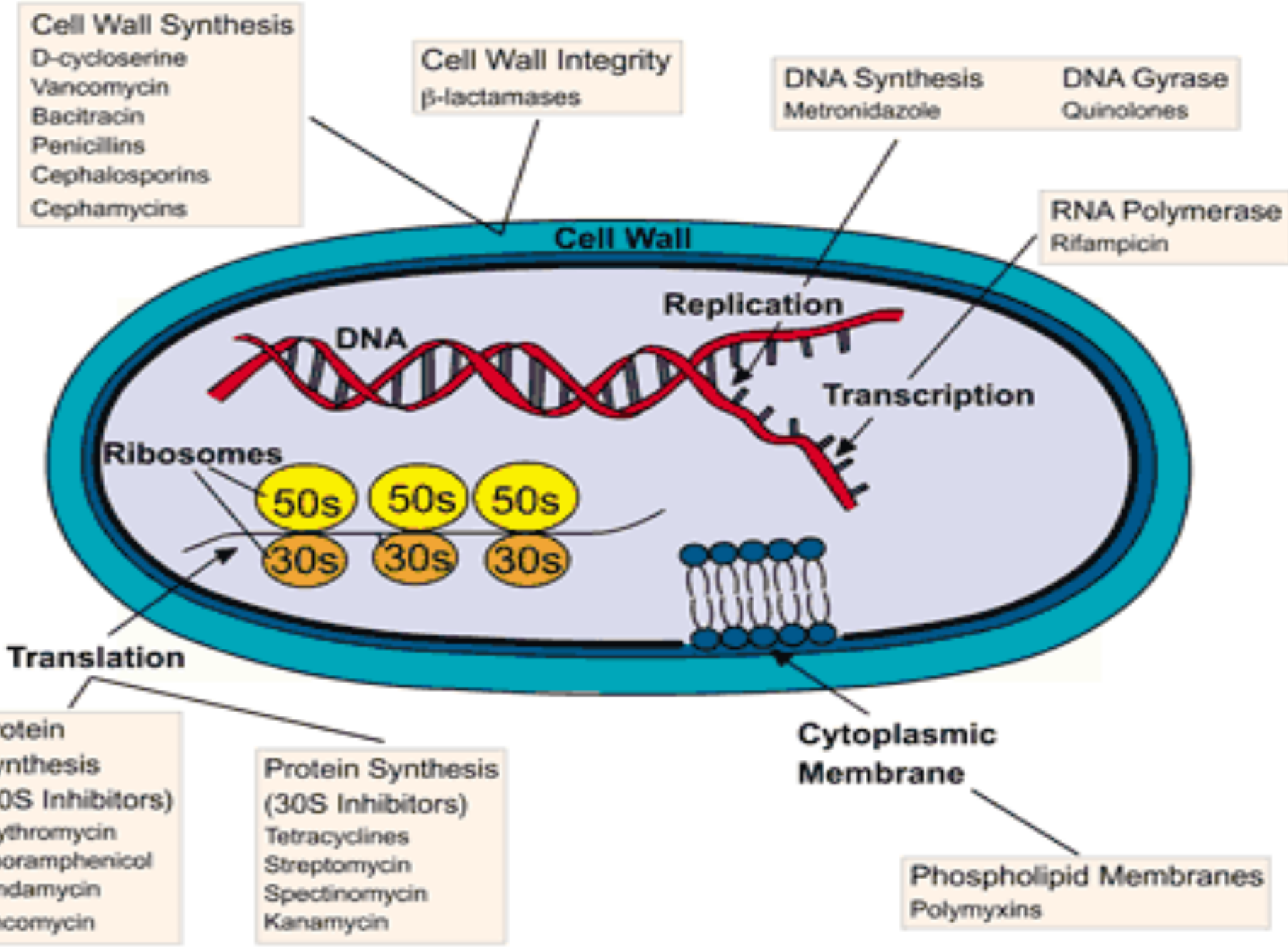


How do antibiotics work?

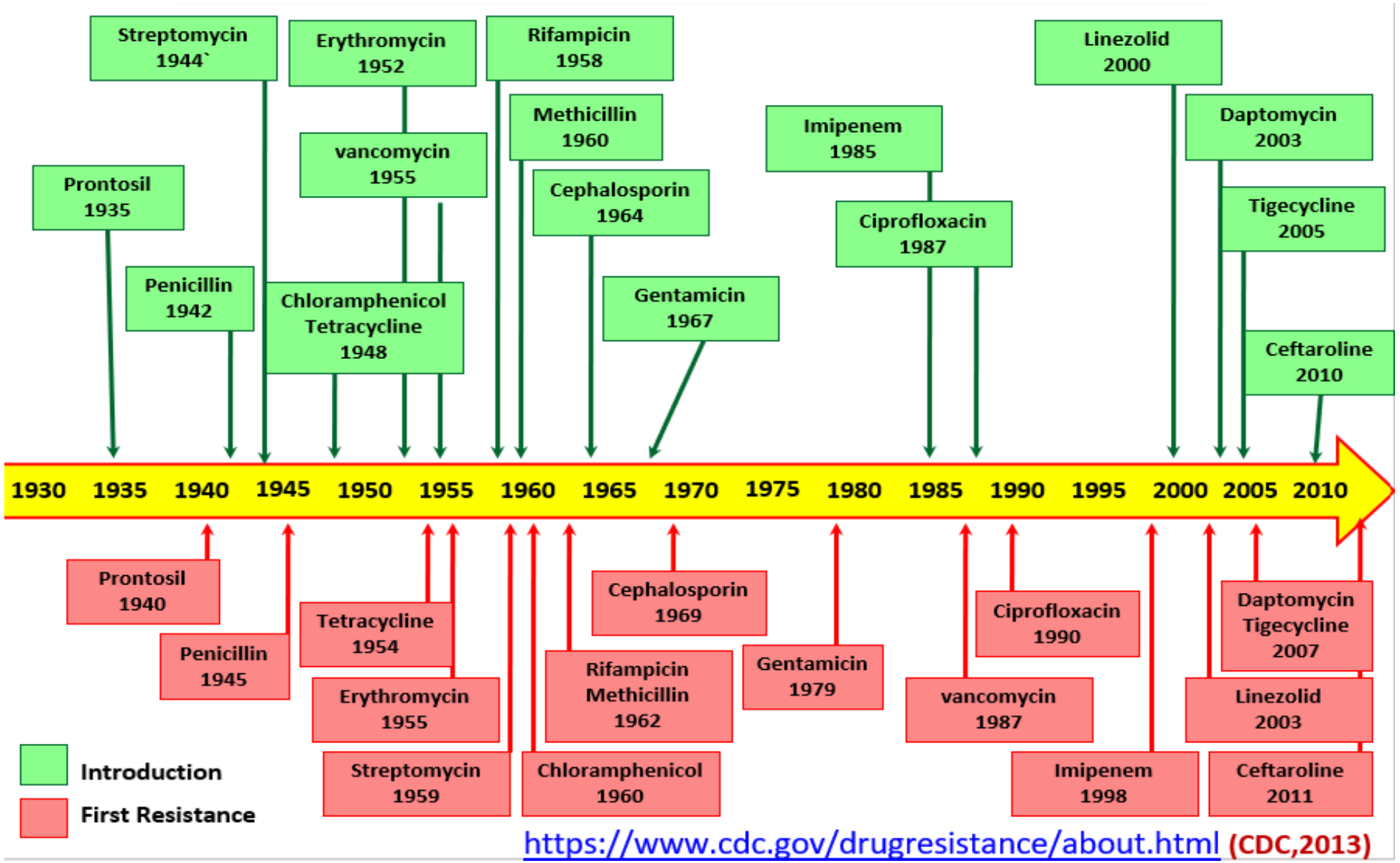


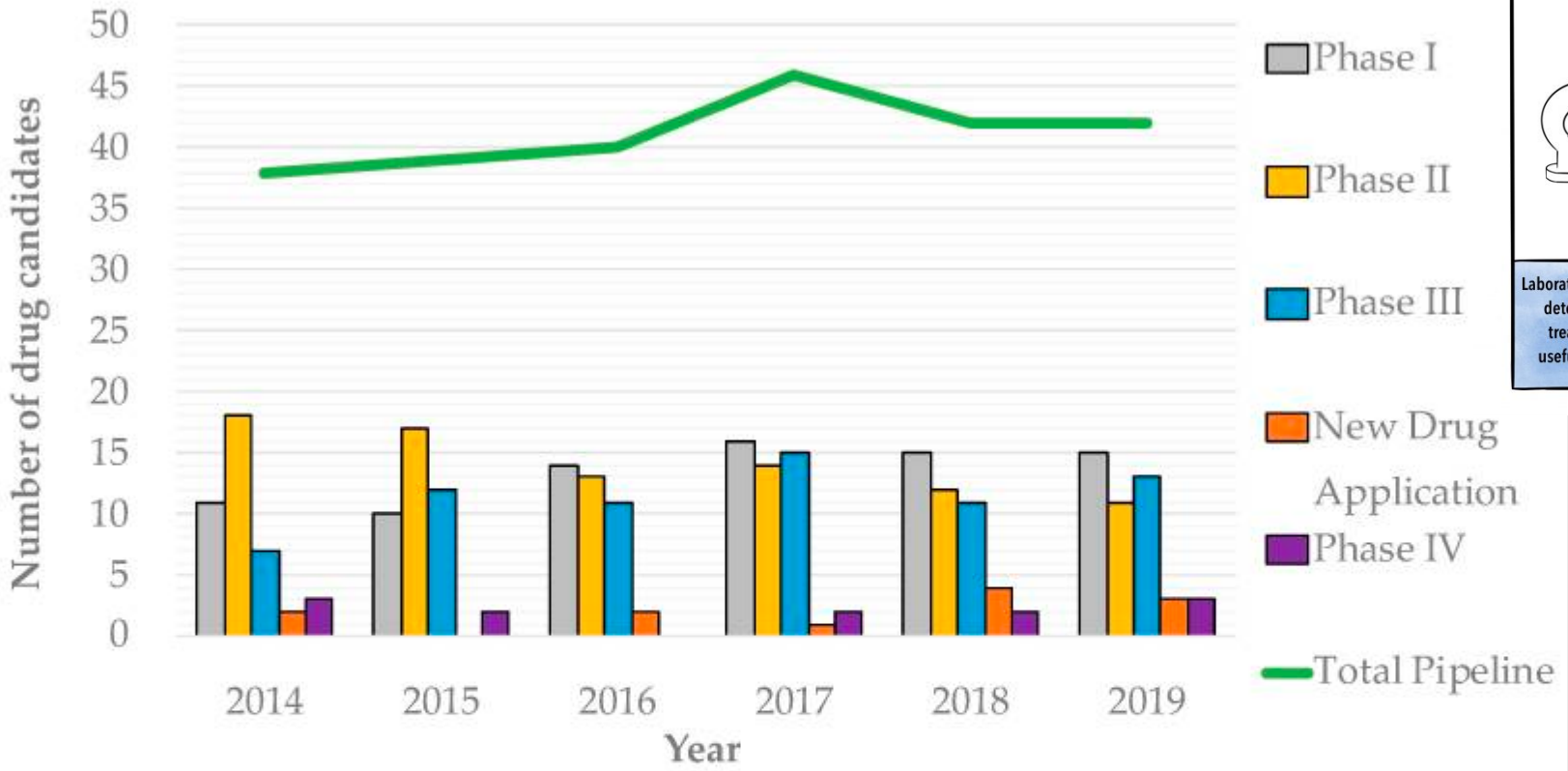
How do Antibiotics work?

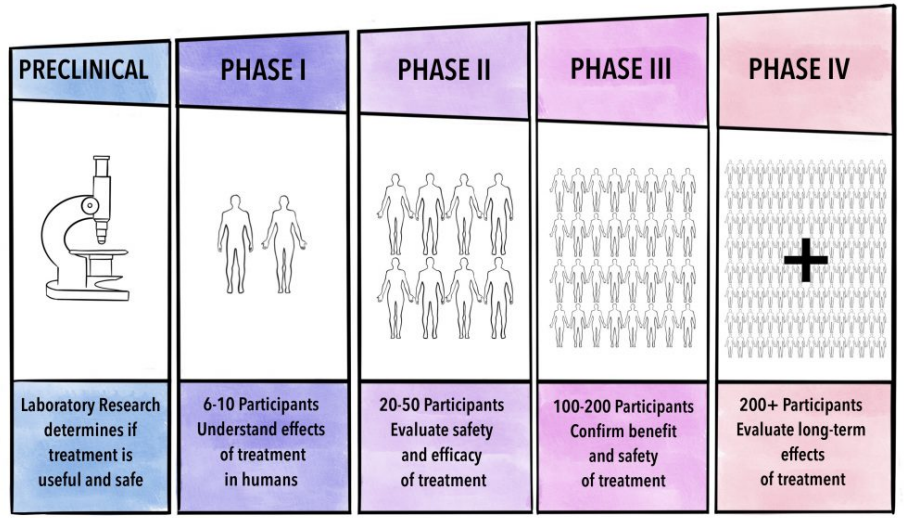
- Inhibit cell wall formation (penicillin)
- Inhibit protein synthesis (tetracycline; erythromycin)
- Several other mechanisms……



Use of antibiotics and resistance





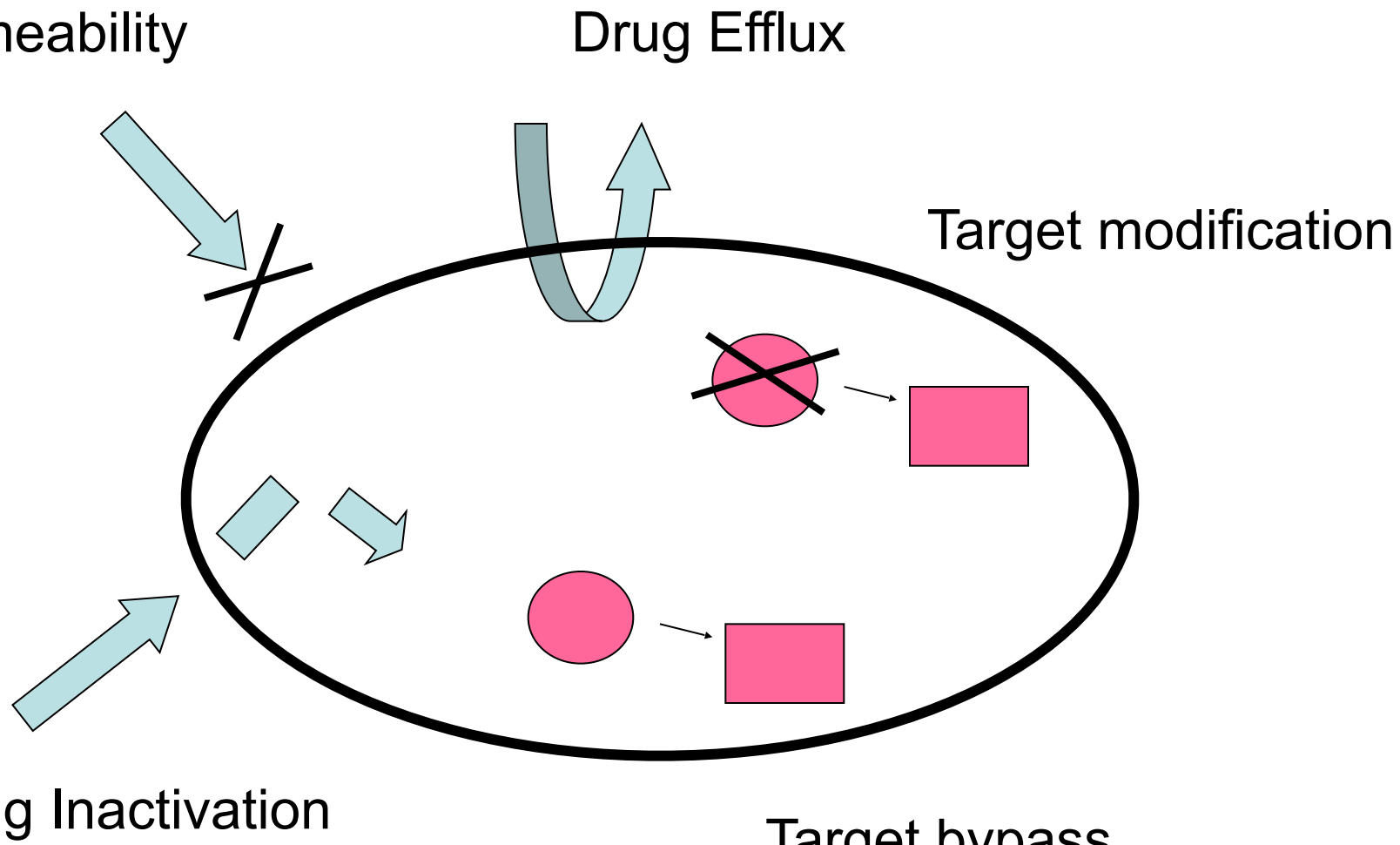


Why is investing in new antibiotics not attractive commercially?

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



- 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

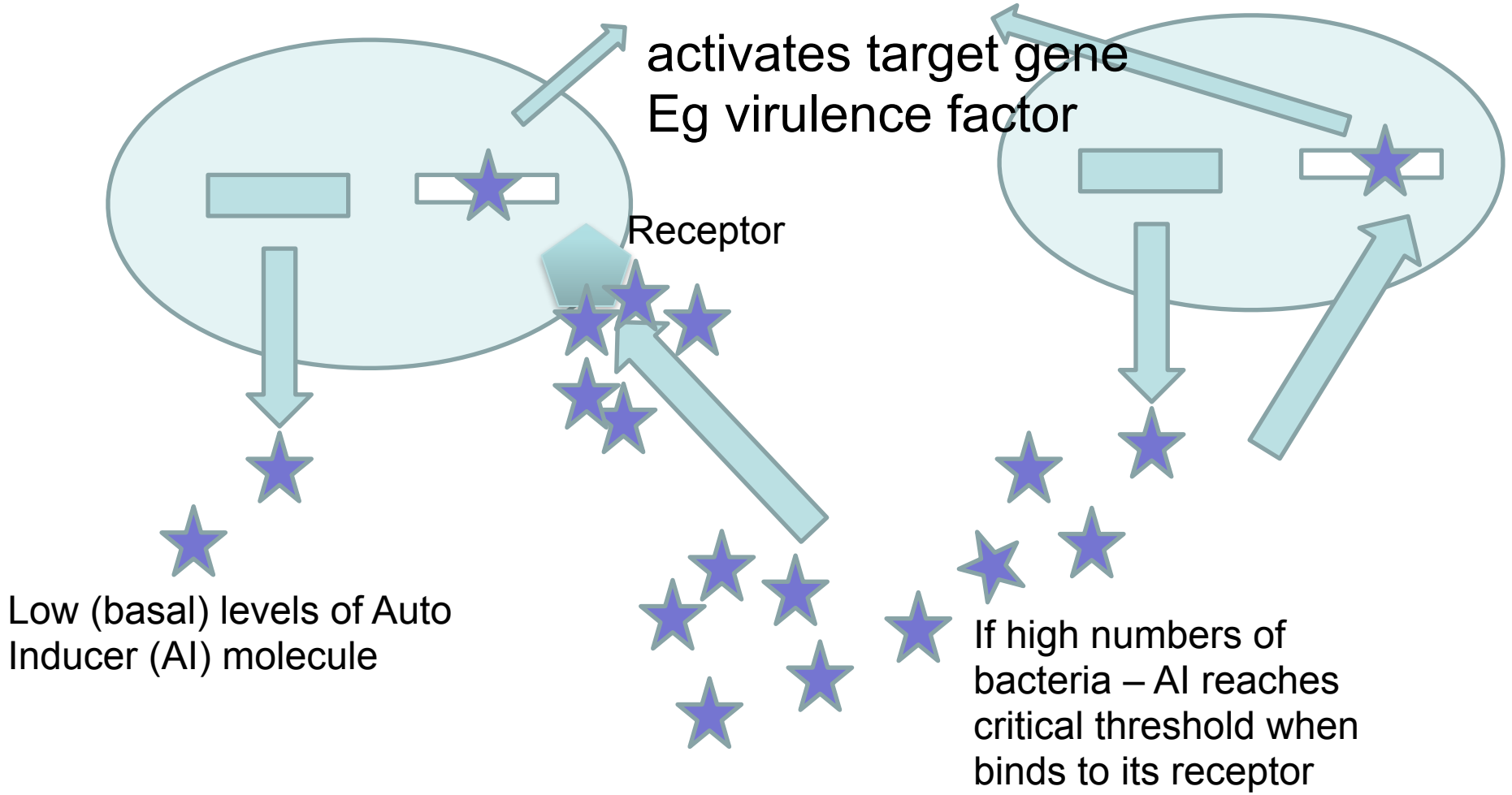
https://learningonscreen.ac.uk/ondemand/index.php/clip/231194

(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)

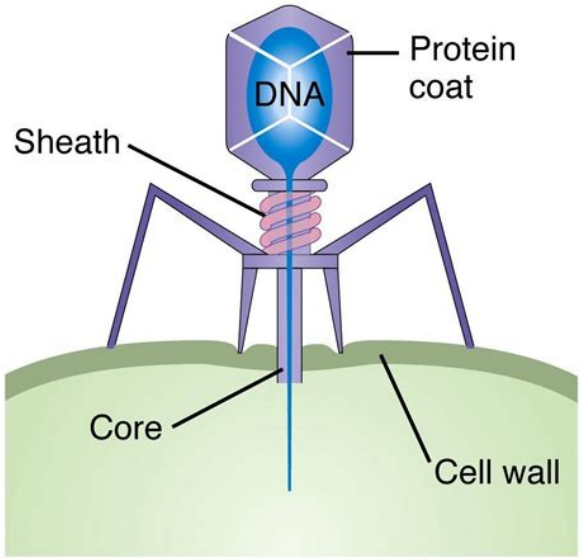
- Hanssen, N.M., de Vos, W.M. and Nieuwdorp, M., 2021. Fecal microbiota transplantation in human metabolic diseases: from a murky past to a bright future?. Cell Metabolism, 33(6), pp.1098-1110.

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

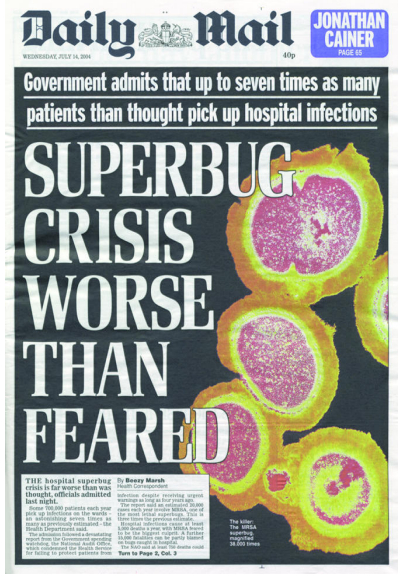
- Low dosing levels/ biofilm disruption
  - Multiply in hosts; then cleared naturally
  - Few side effects?
- Can avoid killing normal microflora
- Use of cocktails – less resistance?

- 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!

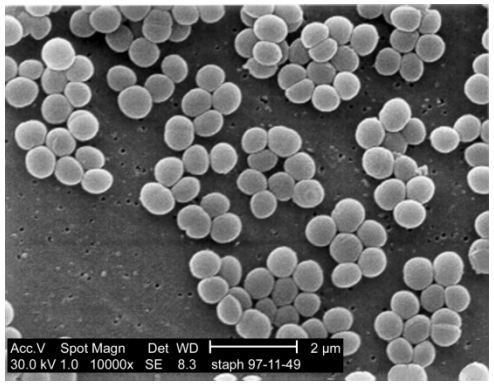
An old infection (re-) emerging because it has become resistant to treatment

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’)

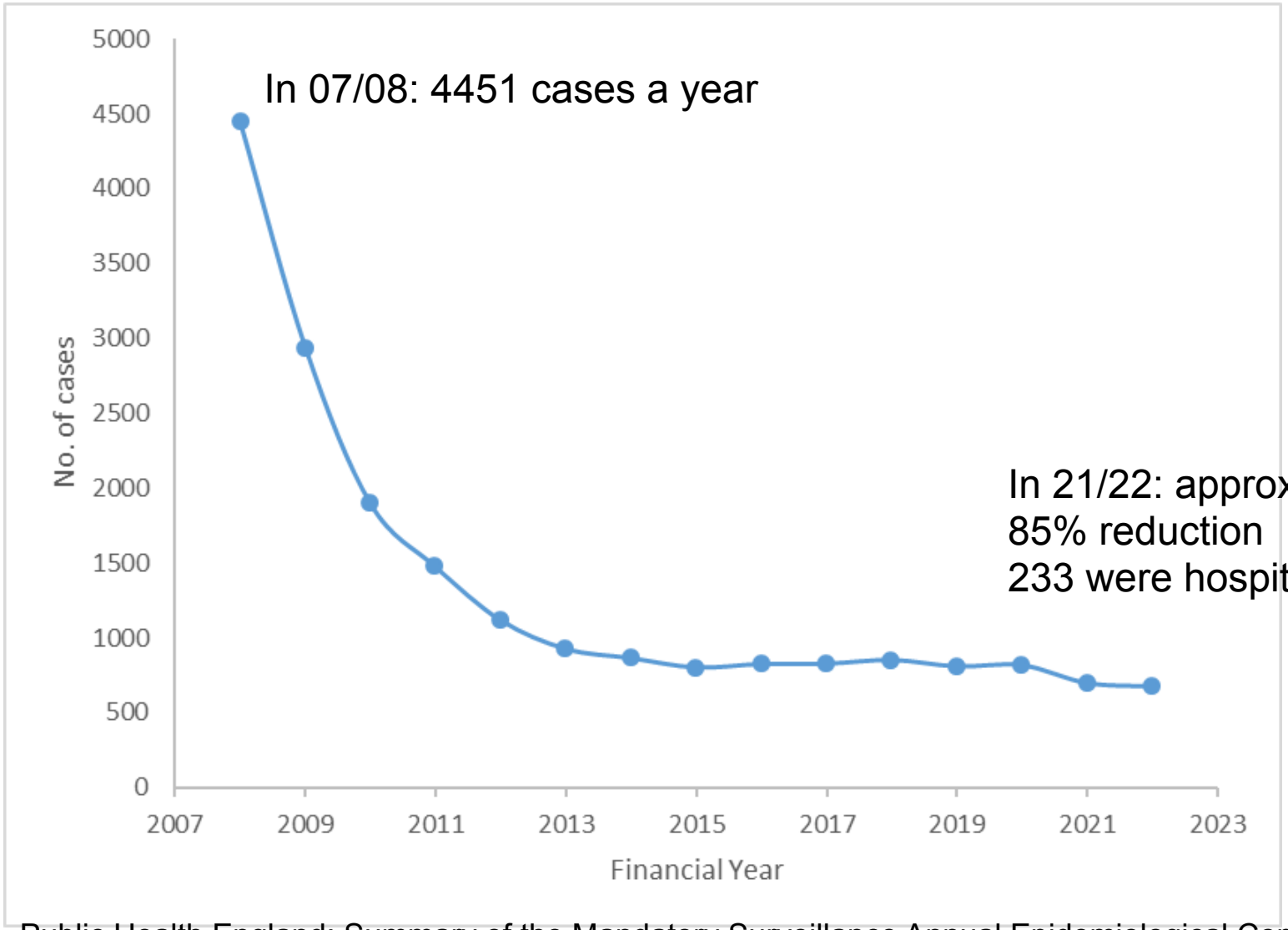


MRSA

- *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

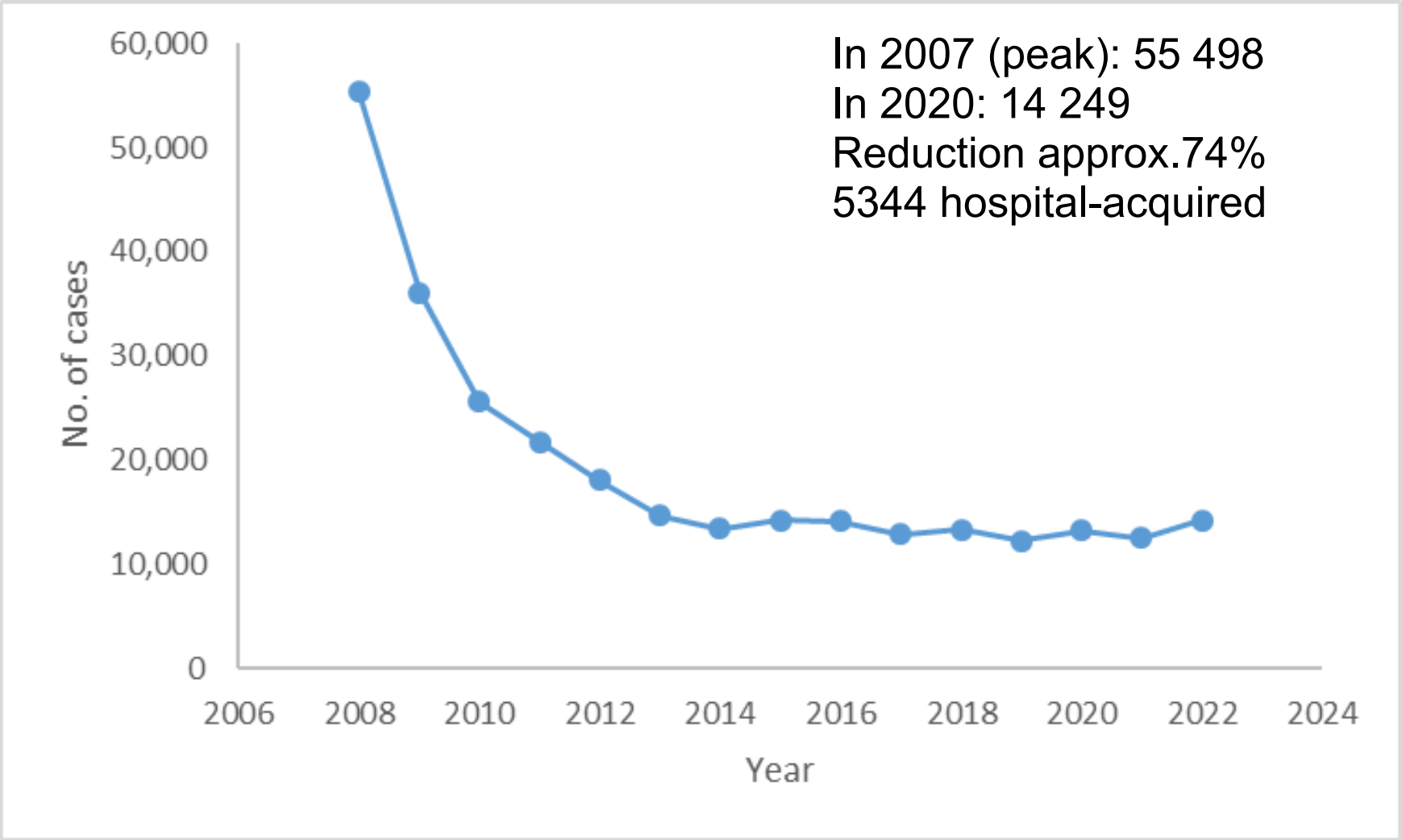
Other important nosocomial bacteria

- *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.

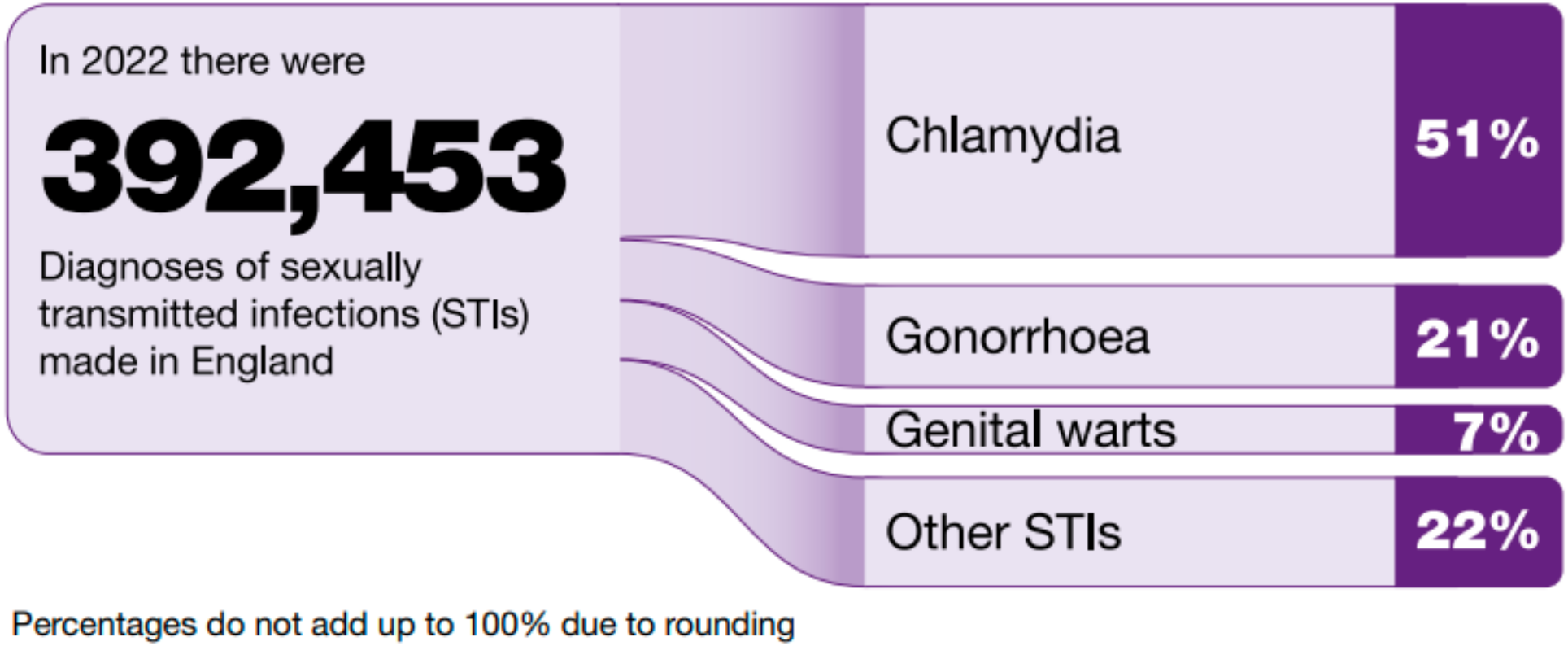
Transfer of microbes from a ‘healthy’ donor to a patient

- 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

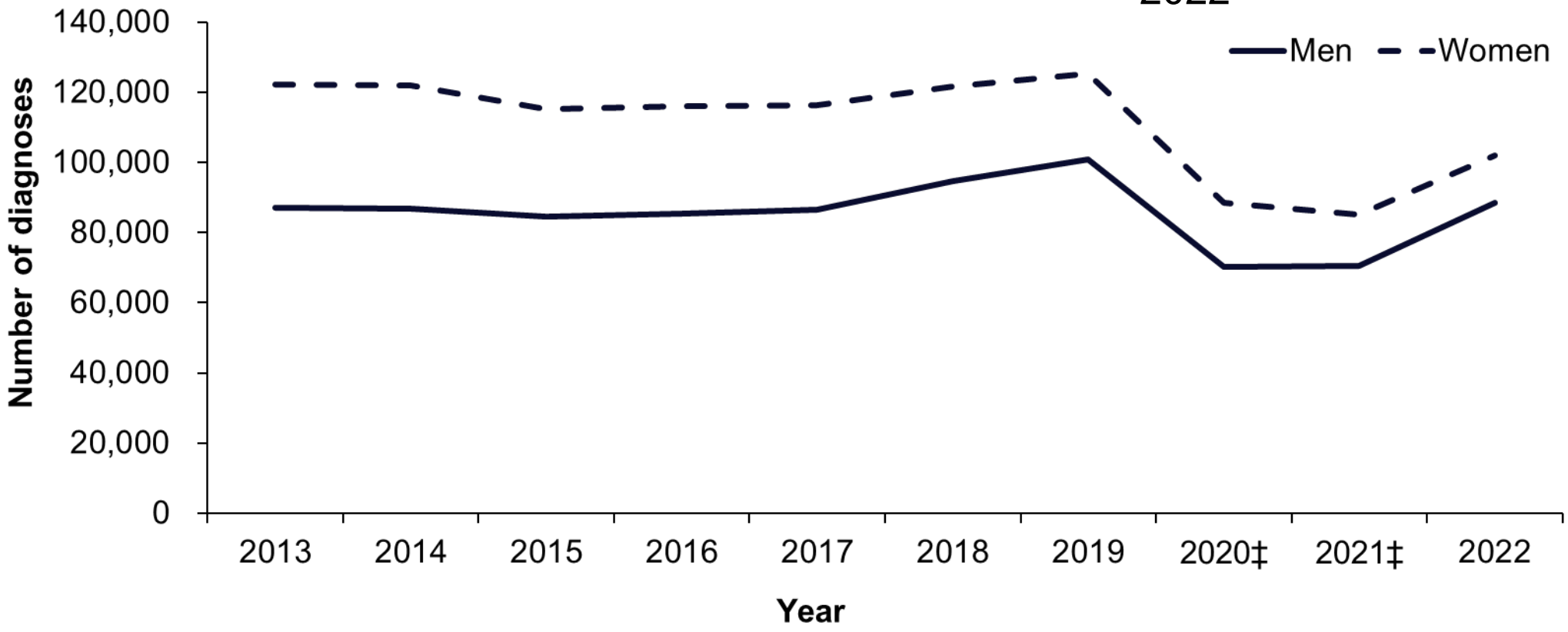
Sexually-transmitted Infections

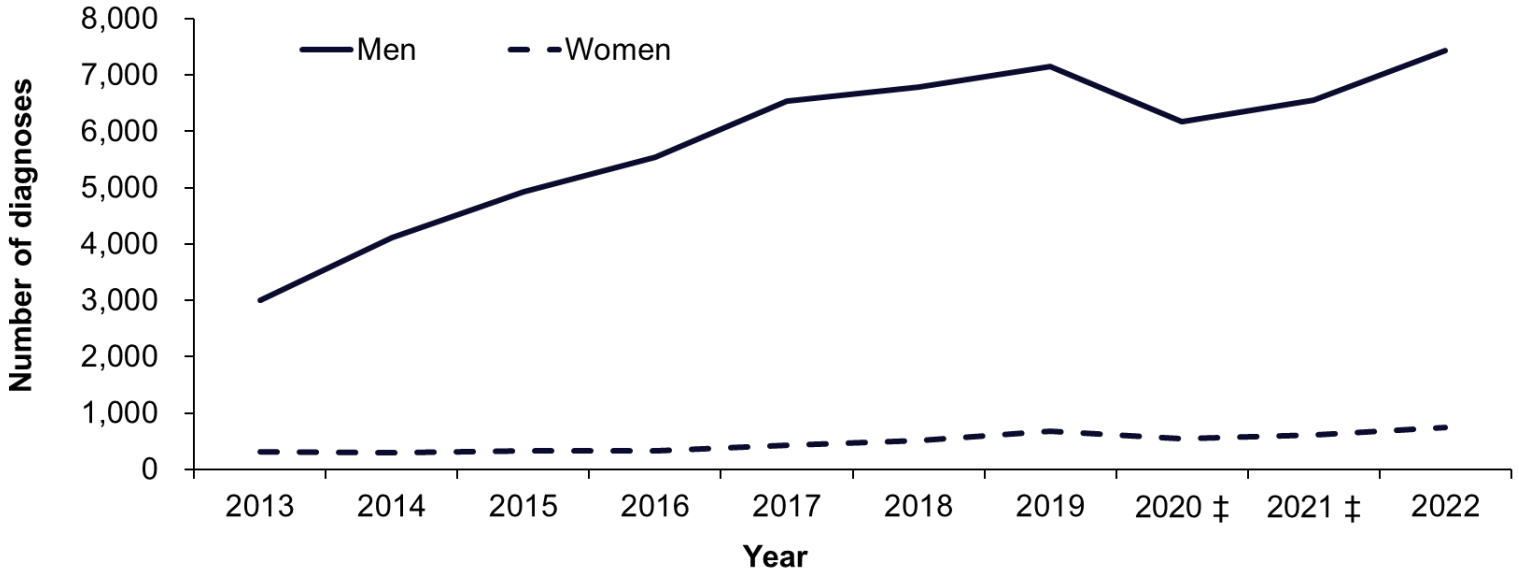
- Chlamydia/ gonorrhoea (‘the clap’)/ syphilis/ HIV/ herpes/



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

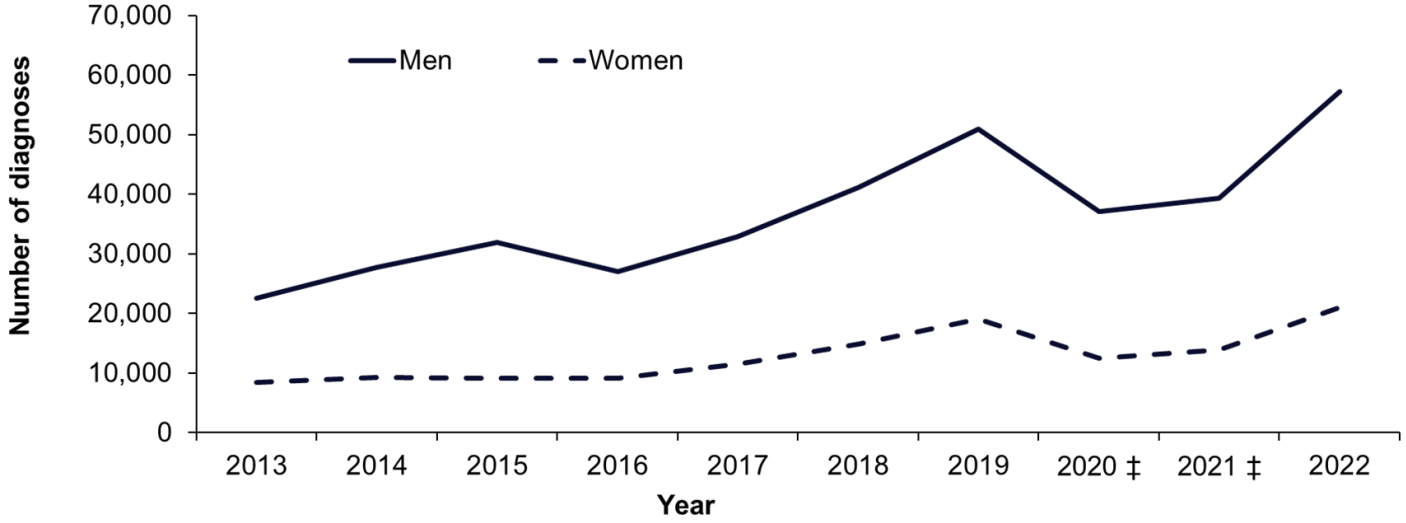
NB
Chlamydia – most commonly diagnosed sexually-transmitted infection approx. 200 000 cases in 2022





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)

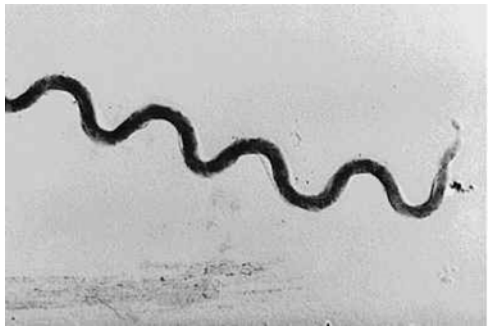
N. gonorrhoeae resistance

- 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….

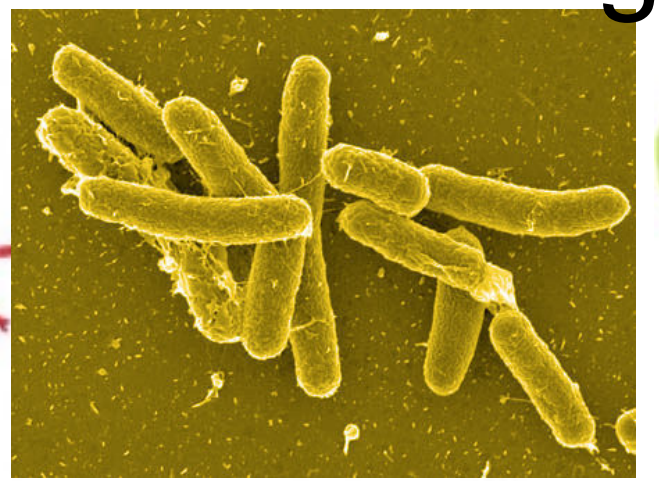
- 2015-2021: 9 cases detected in UK (all associated with international travel from Asia-Pacific area)
- First 6 months of 2022: 10 cases ..

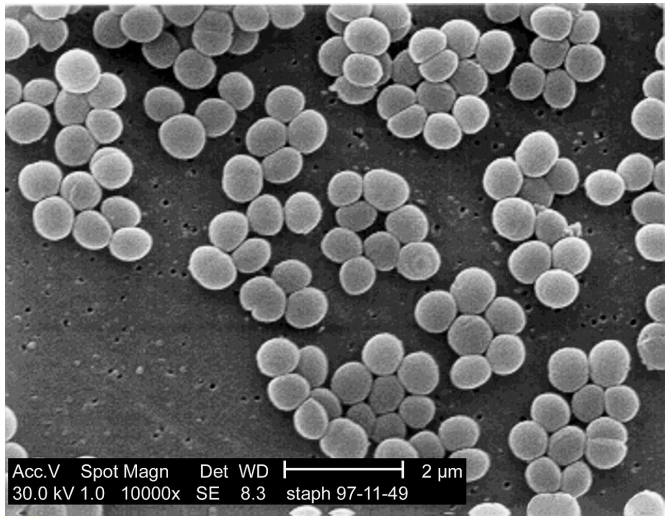
Syphilis

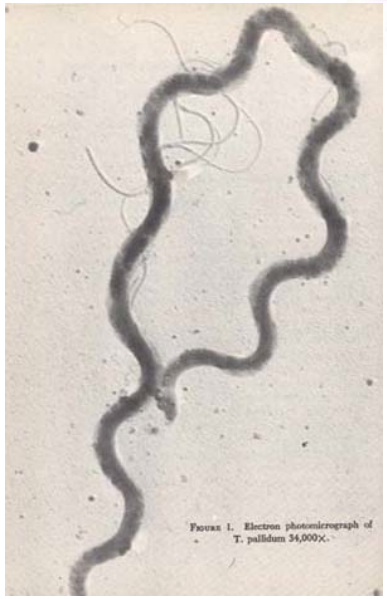


- Bacteria: *Treponema pallidum*
- Unusual shape and cell wall: ‘spirochaetal’
- Hard to grow in the lab. (intracellular growth & anaerobic) and no animal model
  - Limited knowledge about mechanisms of pathogenicity
- Three (four) stages in infection process (distinct presentations)
    - Primary/ secondary/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

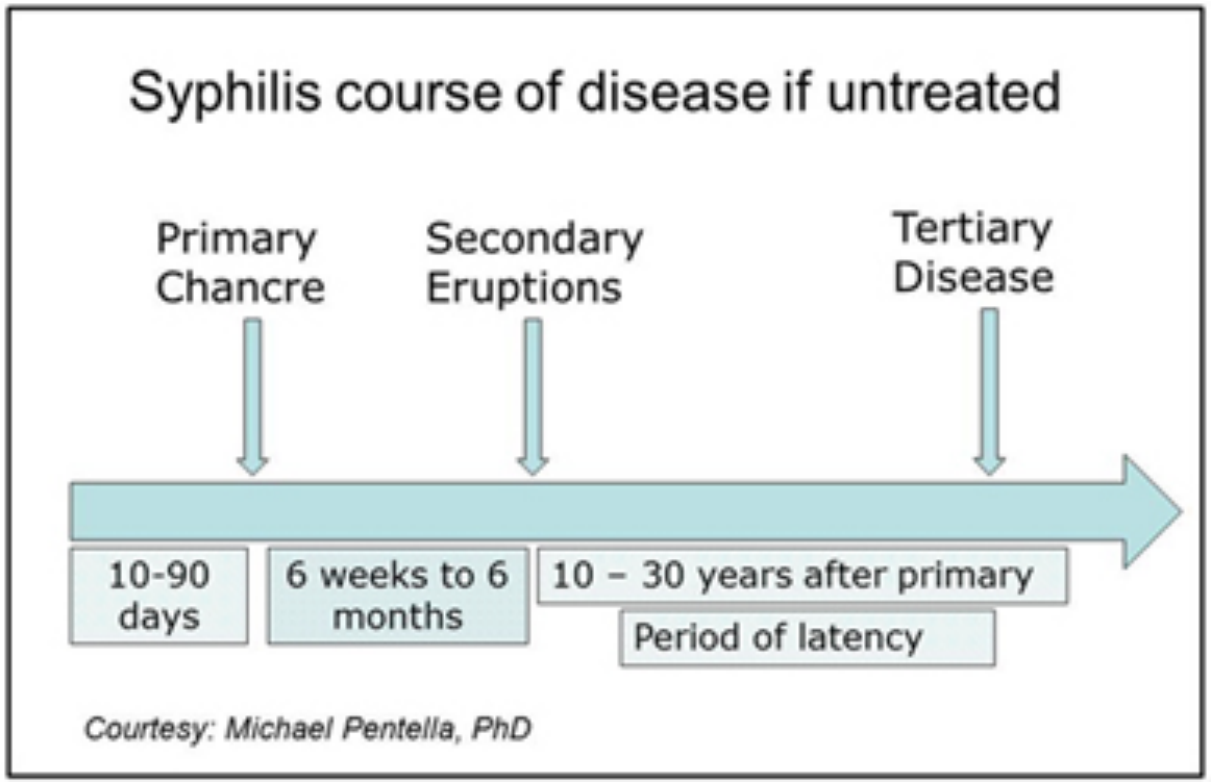
Microbiologists and their toys …







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

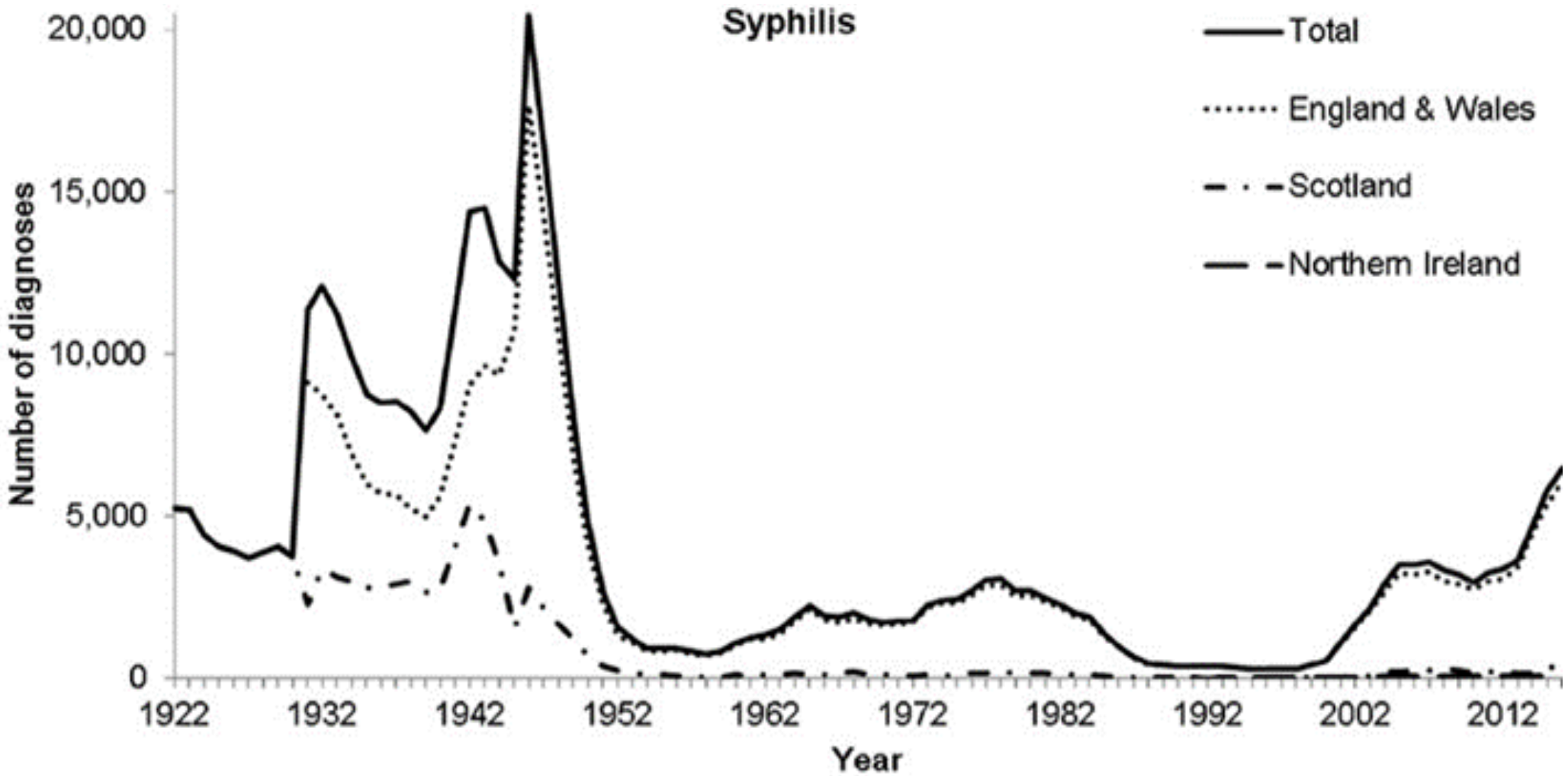


Primary chancre (painless!)

Secondary hypersensitive rash

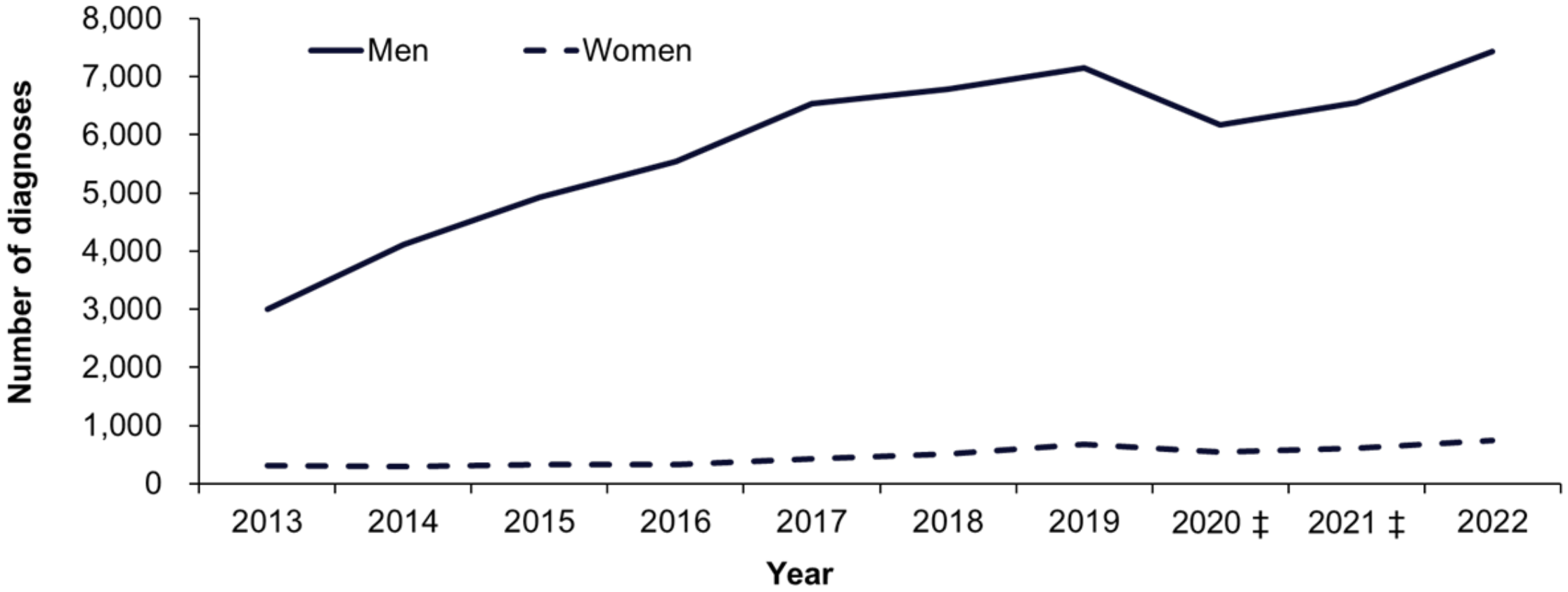
Tertiary syphilis: in approx. 15 % of people, develops years later after an untreated primary infection: neurological/systemic complications

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