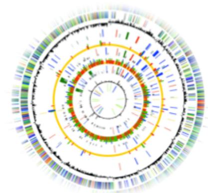
Denver Russell Memorial Teleclass Lecture



Antimicrobial resistance-
a global *One Health* challenge

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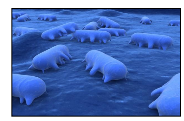
Cardiff University, Wales



www.webbertraining.com February 18, 2020

Lecture overview -

- review of the discovery of antibiotics/antimicrobial compounds
- in brief, discuss the use of antimicrobial agents in a *One Health* context
- evaluate how resistance to antibiotics/antimicrobial compounds emerges and becomes disseminated
- examples of transmission of AMR genotypes
  - multi-drug resistant (MDR) *Salmonella* Indiana in poultry
  - detection of *mcr-1* and its variants
  - identification of *tet*(X4)-encoding resistance to tigecycline in *E. coli* cultured from food-producing animals
- analyse the metagenomics of antimicrobial resistance (AMR)

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Discovery of antibiotics/antimicrobial compounds -

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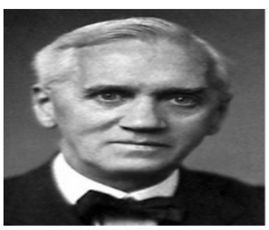

Sir Alexander Fleming
Prize share: 1/3

Ernst Boris Chain
Prize share: 1/3

Sir Howard Walter Florey
Prize share: 1/3

- **Antibiotics have revolutionized modern medicine** and enables physicians to undertake new treatments, such as surgery; organ transplantation; cancer chemotherapy among others
- these drugs are **among the most commonly prescribed medicines**, with some 70 billion clinical doses administered in 2010
- **antibiotics are naturally occurring molecules and can be purified from many soil bacteria, with many of these compounds being detected in pristine environments, that pre-date human use**
- **it is not surprising to note that defense or resistance to these molecules is also detectable**
- DNA sequencing of ancient permafrost sediment samples, detected genes that conferred resistance to several antimicrobial classes

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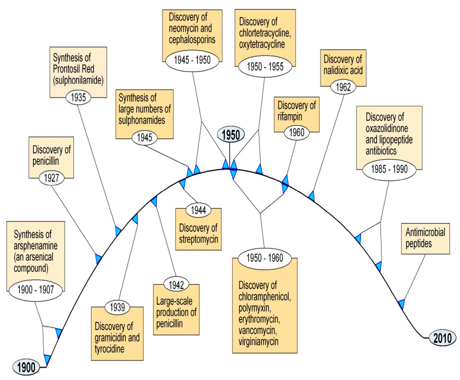
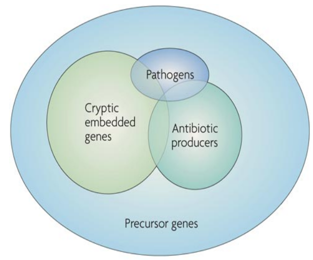
Antibiotics
– history of discovery & the Resistome



Antibiotics are defined as *naturally-derived, low molecular weight microbial metabolites* that can *kill/inhibit susceptible bacteria*



***The same antibiotics* are used to treat animals, humans & plants**

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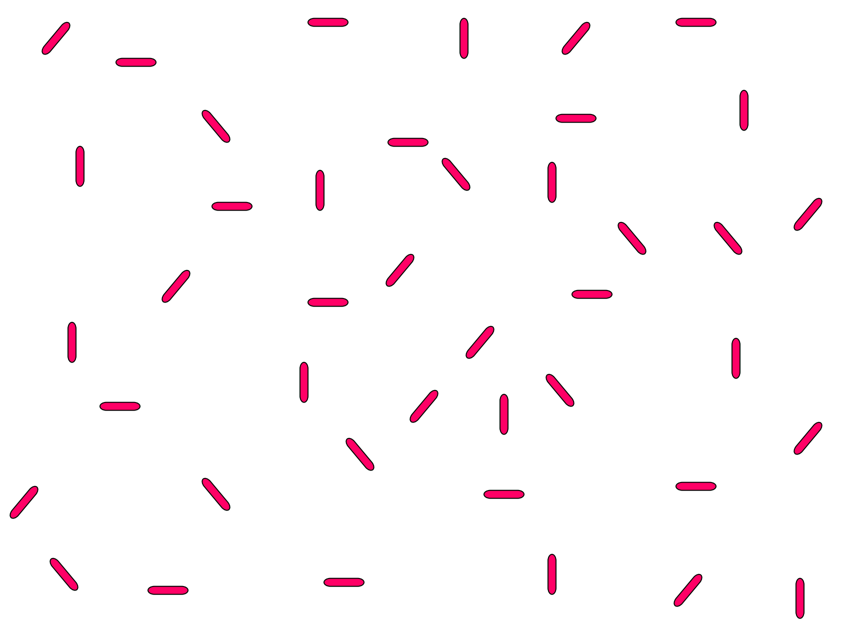

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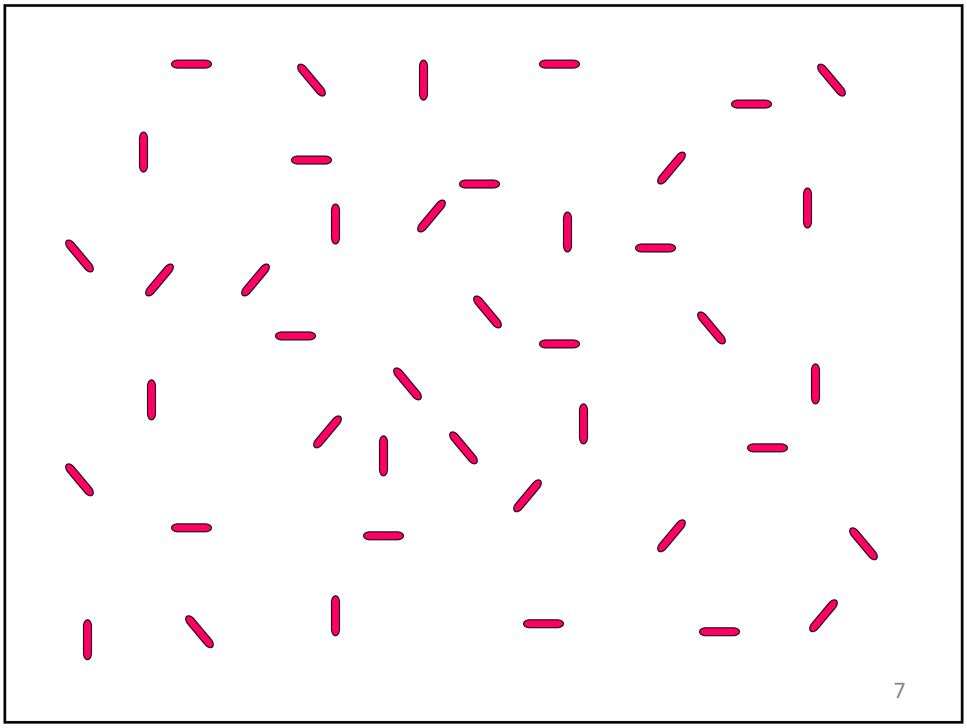
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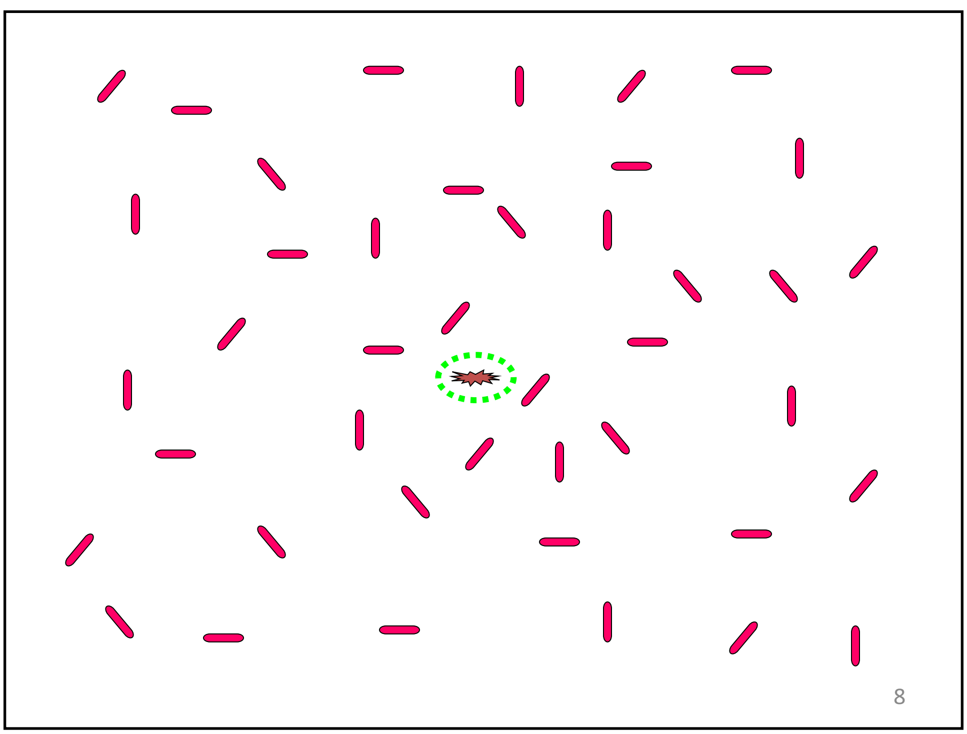
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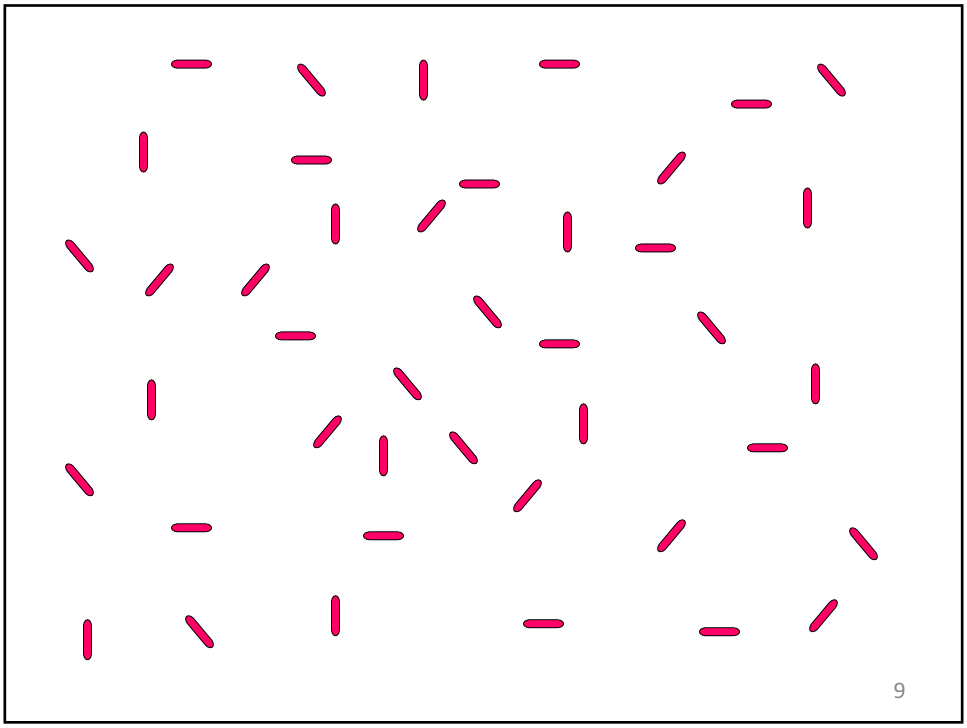
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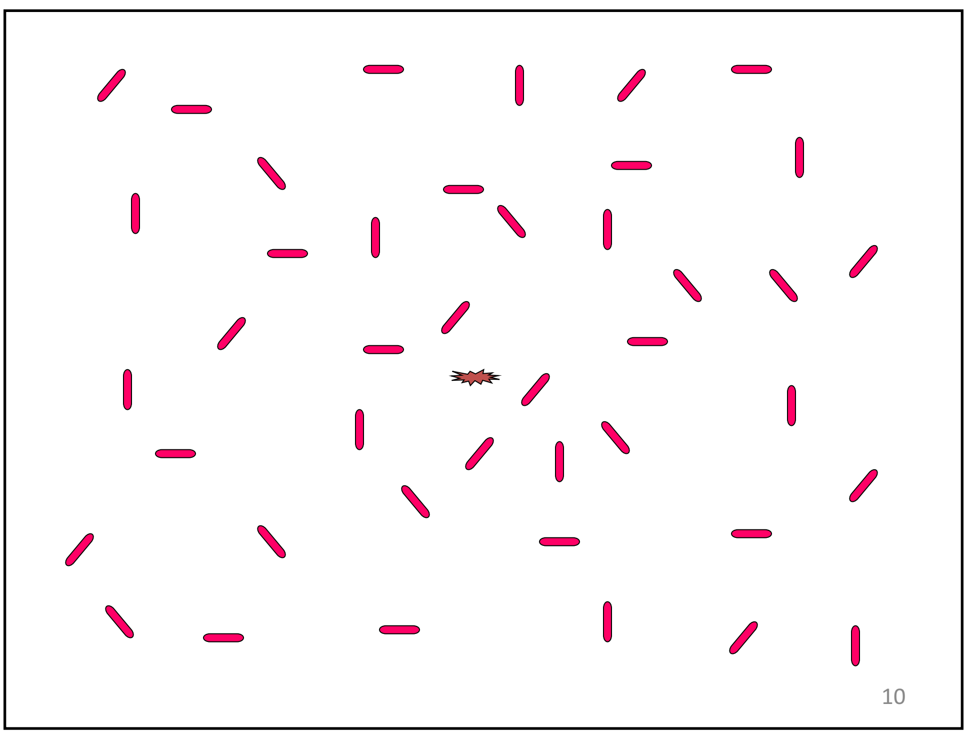
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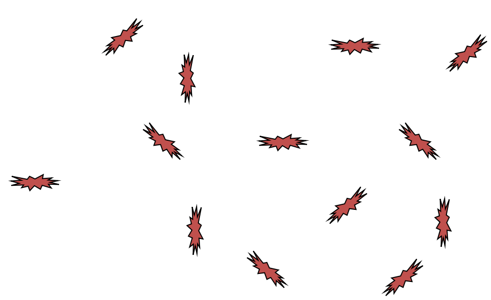

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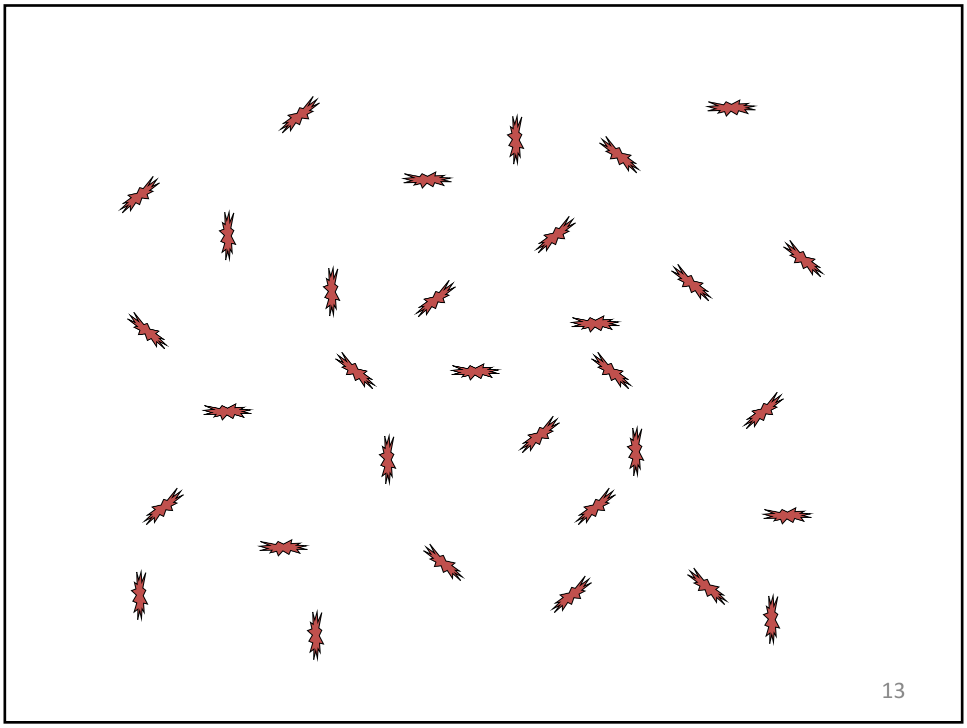
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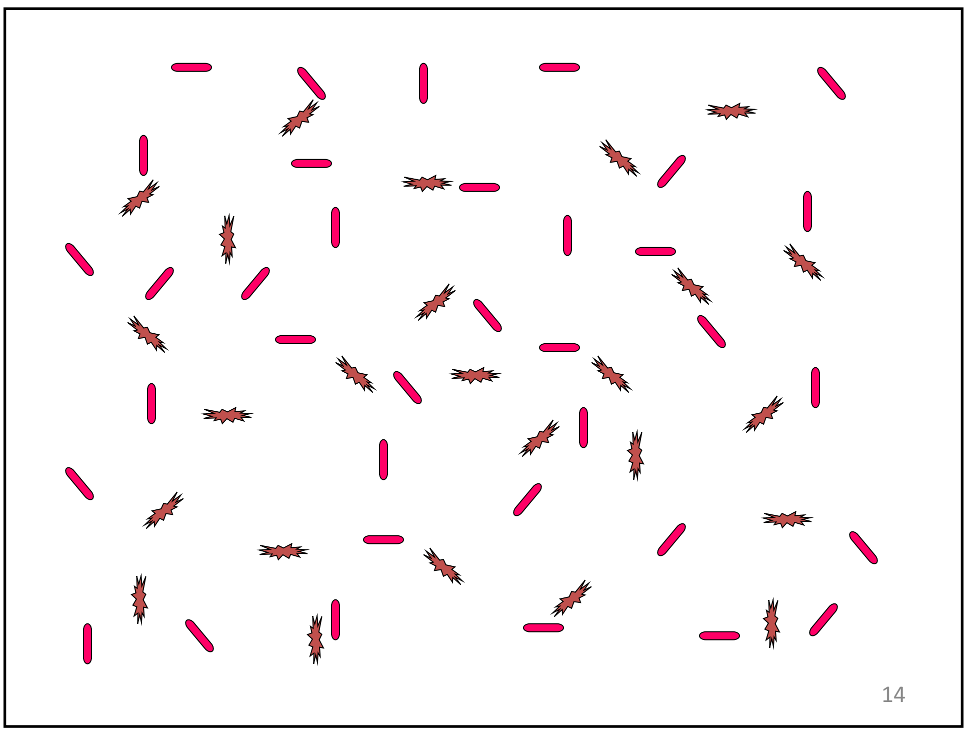
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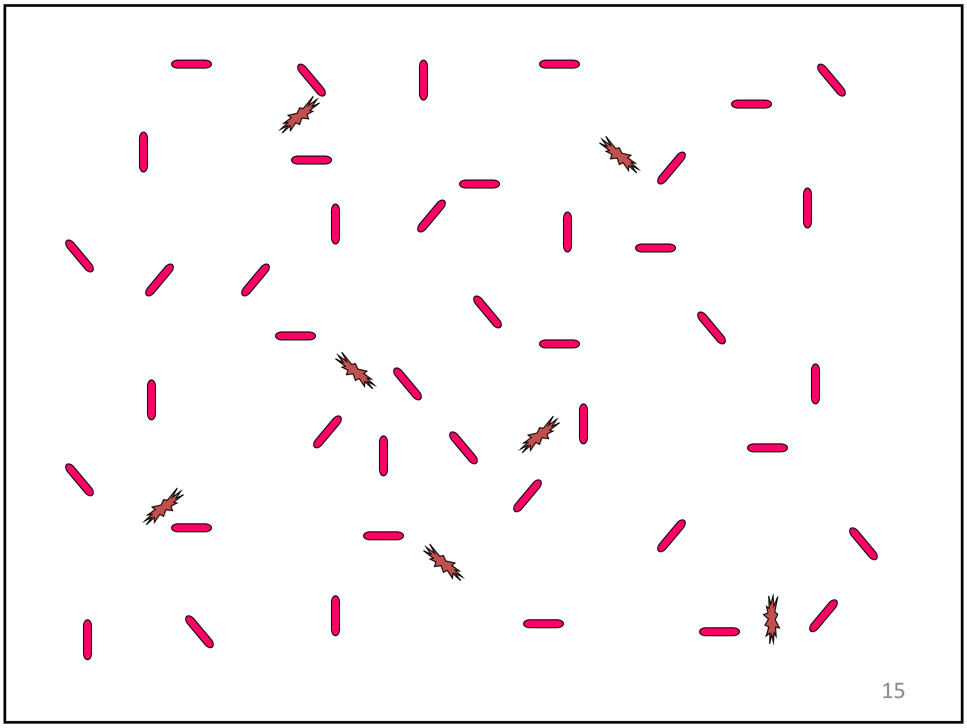
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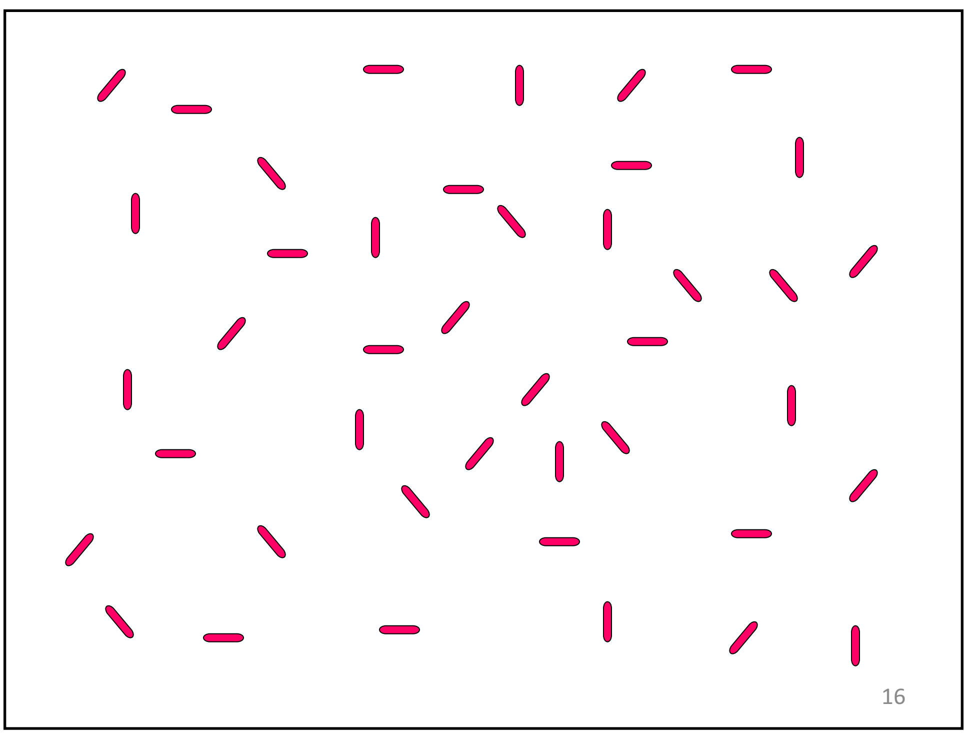
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Emerging bacterial resistance –the challenge

Escherichia coli → Susceptible → Treatable

Penicillin G *1st generation*

Escherichia coli PenR → Resistant → Treatable

Cefoxitin *2nd generation*

Escherichia coli PenR; FoxR → Resistant → Treatable

Cefotaxime *3rd generation*

Escherichia coli PenR; FoxR CtxR → Resistant → Treatable

Colistin

Escherichia coli PenR; FoxR; CtxR; ColR → Resistant → Untreatable

The *final bacterium* is *untreatable* using our existing arsenal of drugs

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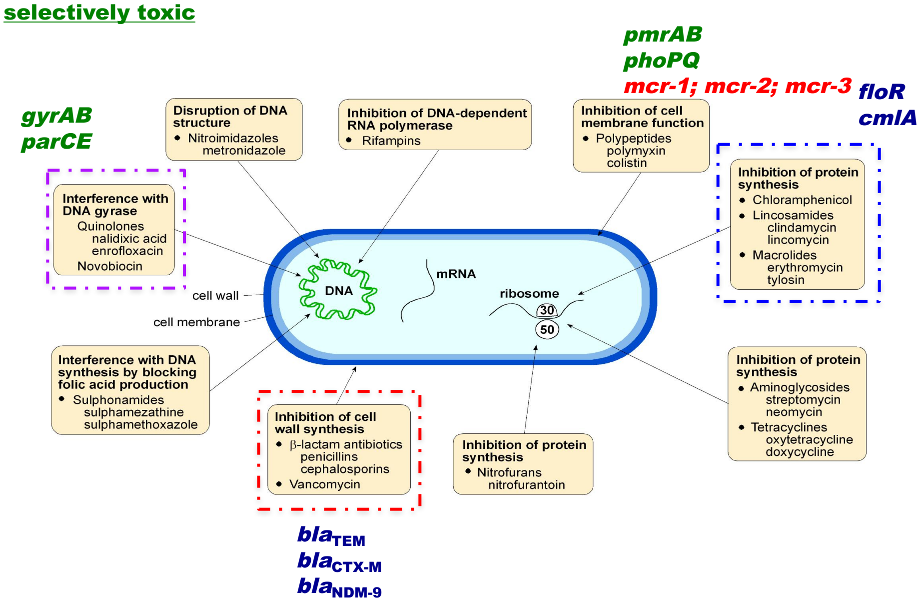
Antibiotics target unique structures in a susceptible bacterial cell and they are **selectively toxic**



Resistance may emerge due to structural changes in these targets in the bacterial cell after application of the drug

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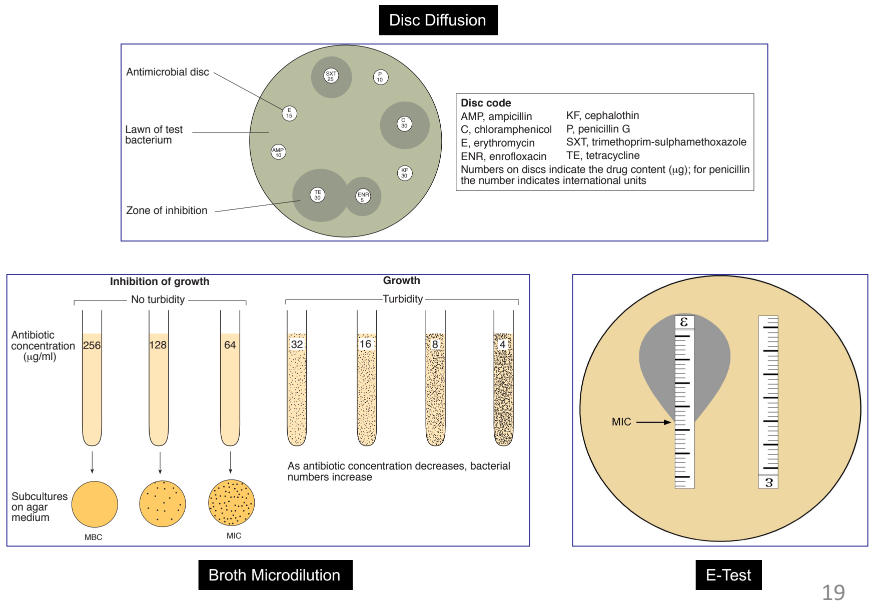
Antimicrobial susceptibility testing (AST methods) -



Global epidemiology of antibiotic resistance & use -

- decreasing efficacy of antibiotics used to treat infections has quickened in recent years with the **emergence of carbapenem-resistant Enterobacteriaceae**
- in high-income countries, high rates of antibiotic use has been documented in hospitals, the community and in agriculture
- **increased/continued selection pressure has sustained the persistence of resistant bacterial strains**
- **in developing countries, antibiotic resistance is also increasing**
- resistance emerges following mutations of genes on the chromosome and/or following the acquisition of a mobile genetic element
- these events gave rise to resistant strains including **MRSA; *E. coli* ST131; *Klebsiella pneumoniae* ST258 & *Salmonella* Typhimurium DT104**

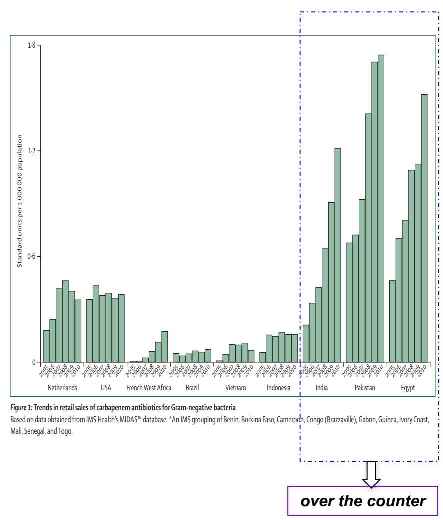
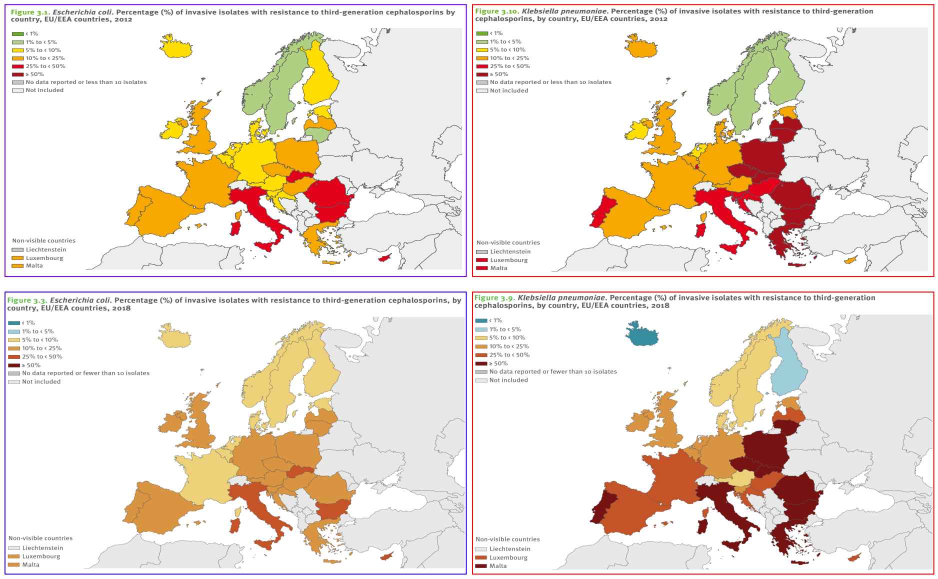


Figure 1: Trends in retail sales of carbapenem antibiotics for Gram-negative bacteria
Based on data obtained from IMS Health's MIDAS™ database. *An IMS grouping of Benin, Burkina Faso, Cameroon, Congo (Brazzaville), Gabon, Guinea, Ivory Coast, Mali, Senegal, and Togo.

[Laxminarayan *et al.*, *The Lancet* (2013) **13:** 1057-1098]



a north-south gradient of resistance, consistent with availability of drugs

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Antibiotic therapy can be likened to a four-edged sword -

- ***Personal benefit*** **through individual treatment**
- ***Community benefit*** **by controlling the spread of disease**
- ***Emergence of resistant bacteria*****, following selection during treatment and its impact on the community health**
- **Costs associated with the animals/individuals health *via* collateral damage of the drug on bacteria that normally live on or in healthy animals/individuals- The Microbiome**

The Microbiome-

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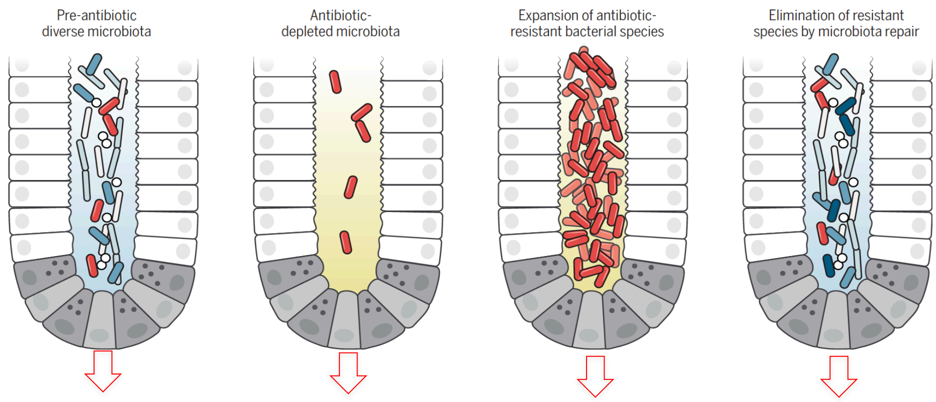
Impact of antibiotic therapy on the microbiome -



- the **microbiota** includes all kinds of bacteria
- an intact microbiota can function to provide **colonisation resistance**

- loss of obligate anaerobes from lower GIT
- expansion of γ-proteobacteria and enterococci
- **enviroment becomes oxygenated**

- amplification of resistant bacterial populations
- **increased opportunity for gene mobility**

- re-establishing the microbiome may restore ***colonisation resistance***
- **reduce the risk of resistance being disseminated**

[Pamer, *Science* (2016) **352:** 535-538 doi: 10.1126/science.aad9382]

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Antimicrobial agents in a *One Health* context -

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Sales of antibacterial agents in 10 European states in 2007-

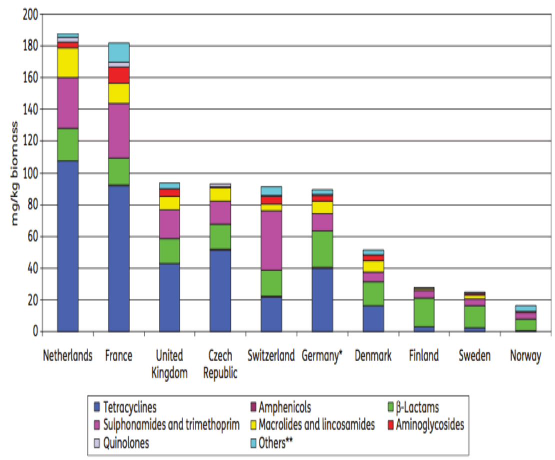

Figure 1. Amounts, in mg, of veterinary antibacterial agents sold in 2007 per kg biomass of pig meat, poultry meat and cattle meat produced plus estimated live weight of dairy cattle. *2005 data. **The substances included vary from country to country.

[Grave *et al., J. Antimicrob. Chemother.* (2010) **65:** 2037-2040]

- data on annual sales of veterinary antibacterial compounds for therapeutic use are published annually by 10 European states
- **what treatments these drugs were used for is unclear**
- amounts of veterinary antibacterial compound used relative to food-producing animal biomass varied from 18-188 mg/kg
- across the 10 states studied, **48% of sales were accounted for by tetracyclines**; 17% STX and 16% β-lactams
- **usage patterns varied between countries** (tetracyclines more frequently used in NL; CZ & F)
- **cephalosporin sales accounted for between 1 and 7%, depending on the country**

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Antibacterial compound usage in animals -

Therapy

- Animal medicine
  - equine animals
  - companion animals

  ⇨ Drugs administered on an individual basis
- Food-producing animals ⇨ Drugs administered on an herd/flock basis –mass medication

Prophylaxis

⇩ Drugs are administered to herds of animals to *prevent the emergence of disease*

Metaphylaxis

⇩ Medicines administered to animals housed together to treat sick animals and to control the spread of disease to those animals *not showing clinical signs*

Growth promotion ⇨ To increase the growth rates of food-producing animals

- *fed as a supplement in the animals feed*
- *at sub-therapeutic levels without veterinary prescription*
- *fed for long periods of time*

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Antibiotics as used in food-producing animals -

Antibiotic/ Antimicrobial compound
- therapeutic
- production

Selective pressure → **Emergence of resistant bacteria**

residue / **Metabolic**

Evolutionary → **AMR bacteria (zoonoses)**

Is there a link between humans and animals?

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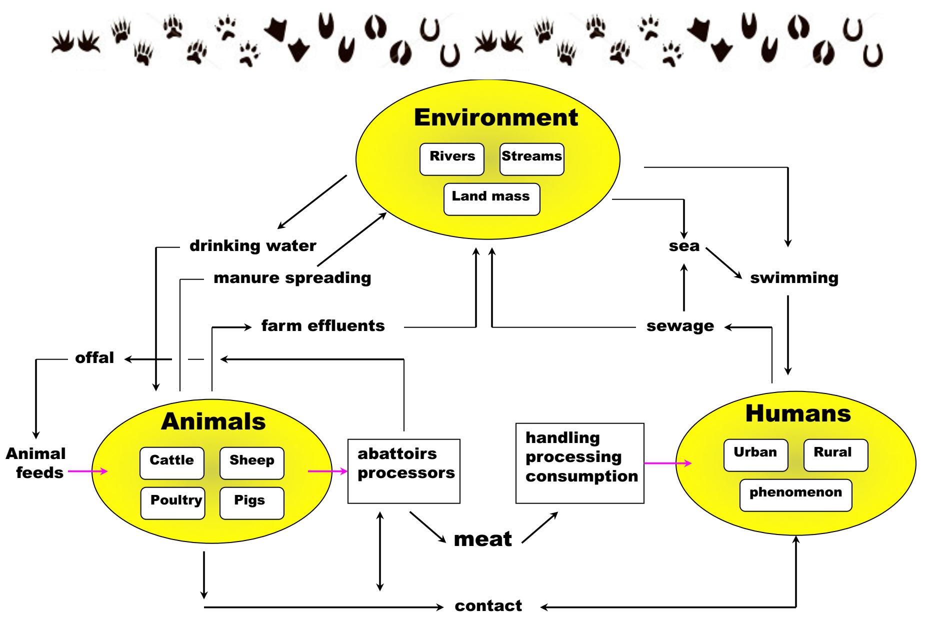

Transmission routes to humans associated with resistant (zoonotic) bacteria
- One Health paradigm

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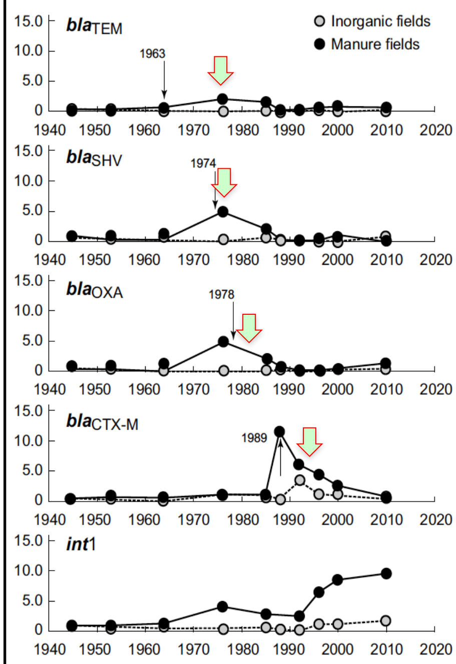
Appearance of penicillin resistance genes in agriculture soils & clinical isolates-



[Graham *et al.*, *Scientific Reports* (2016) **6:** 22550 doi: 10.1038/srep21550]

- ***using archived soil samples, since 1923, b-lactam-encoding resistance genes (bla) along with class 1 integrons were quantified by qPCR***
- soils from manure (M) and inorganic fields (IF) were included for study
- **the total number of *bla*-encoding resistance genes detected in M soils were higher, compared to IF soils, post-1940**
- ***bla*$_{TEM}$ and *bla*$_{SHV}$ genotypes dominated between 1963-1974**
- ***bla*$_{OXA}$ and *bla*$_{CTX-M}$ came later after 1978**
- these dates paralleled the identification of clinical isolates, suggesting that the discovery of antibiotic resistance genes in manure are historically connected
- **class 1 integron levels continued to rise**

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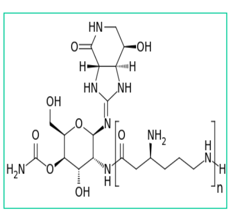
Illustrative examples of AMR transmission from animals to humans -

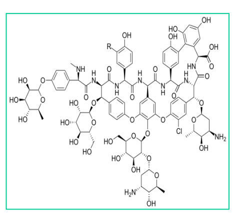
Aminoglycosides



Nourseothricin (NTC)

sat; stat; nat

Glycopeptides

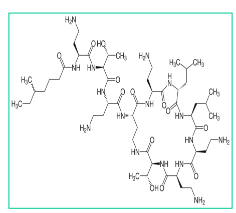


Avoparcin

vanA

Vancomycin-resistant enterococci (VRE)

Polymyxins



Polymyxin E (colistin)

mcr-1; mcr-2; mcr 3-9

Colistin-resistant Enterobacteriaceae

Antimicrobial-based *growth promoters* contribute to resistance dissemination

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World Health Organisation (WHO) –important drug classes preserved for human health -

- **Critically important antibiotics (CIA)-**
  include the following- gentamycin; streptomycin; apramycin; neomycin; kanamycin; ampicillin; amoxicillin/clavulanic acid; carbapenems; 3rd/4th generation cephalosporins; monobactams; penicillin G; nalidixic acid; fluoroquinolones (FQ); macrolides; linezolid; **tigecycline**; **colistin**

- **Highly important antibiotics-**
  include the following- phenicols; 1st/2nd generation cephalosporins; cloxacillin; lincosamides; (virginiamycin); sulphonamides; chlorotetracycline; oxytetracycline

- All other antimicrobial compounds are classified as important-

- **the high priority classes-**
  include the following- 3rd/4th generation cephalosporins; FQ; macrolides & glycopeptides

carbapenems; oxazolidinones & glycylcyclines are *not licensed* for veterinary use

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Antimicrobial resistance is spreading worldwide -

- ***almost all disease-causing bacteria resistant***

- b-Lactamase-mediated resistance gave rise to > 1,000 enzymes now known to inactivate b-lactam drugs, since before 1990 & some examples include-

- **New Delhi metallo-b-lactamase-1 (NDM-1) discovered in 2008 and has now spread worldwide *[environmental origin]***

- **carbapenem-resistant *Klebsiella pneumoniae* (KPC) are commonly encountered in *clinical settings***

- **extended spectrum b-lactamase (ESBL)-encoding genes are rapidly spreading through Enterobacteriaceae from *foods of animal origin and clinical settings***

- these trends are globally consistent

Risk factors associated with the *dissemination* of antibiotic resistance

⇩

- **bacterial interspecies gene transmission**
- **poor sanitation**
- **hygiene in hospitals & the community**
- **agriculture/veterinary use**
- **global trade (in food)**
- **foreign travel**

the general public do not appear to understand the challenge facing society

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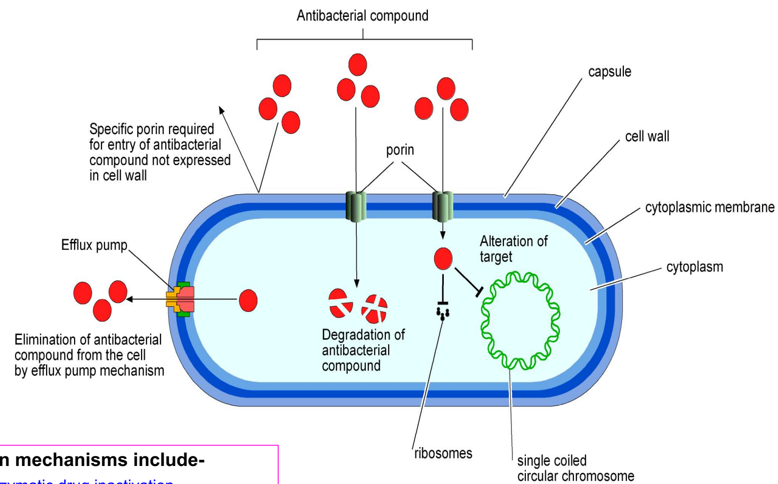
Resistance mechanisms elaborated by bacteria -



Main mechanisms include-

- enzymatic drug inactivation
- drug modification or replacement of the drug target
- **active efflux**
- reduced drug uptake

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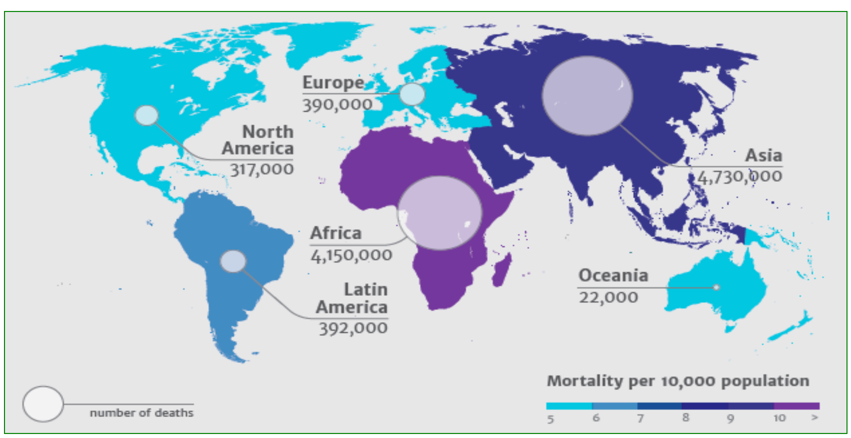
Deaths attributable to AMR every year by 2050



[Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations. The Review on Antimicrobial Resistance. Chaired by Jim O' Neill. December 2014].

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How resistance to antibiotics/antimicrobial compounds becomes disseminated -

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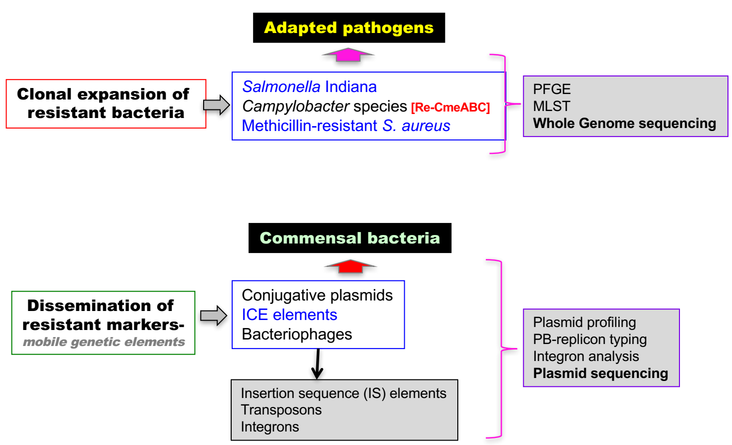
Emergence and expansion of adapted bacterial zoonoses -



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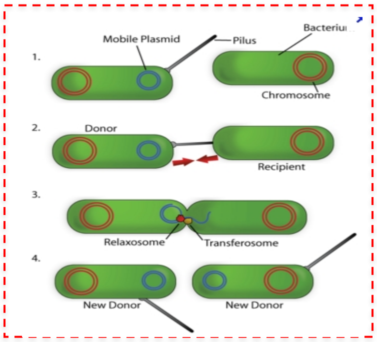
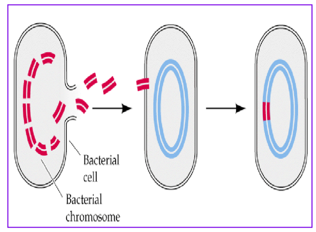
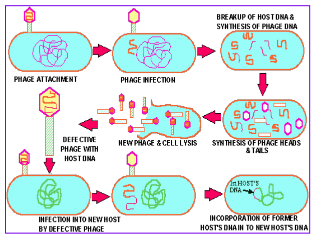
Transfer of resistance markers between bacteria -



Conjugation



Transformation



Transduction

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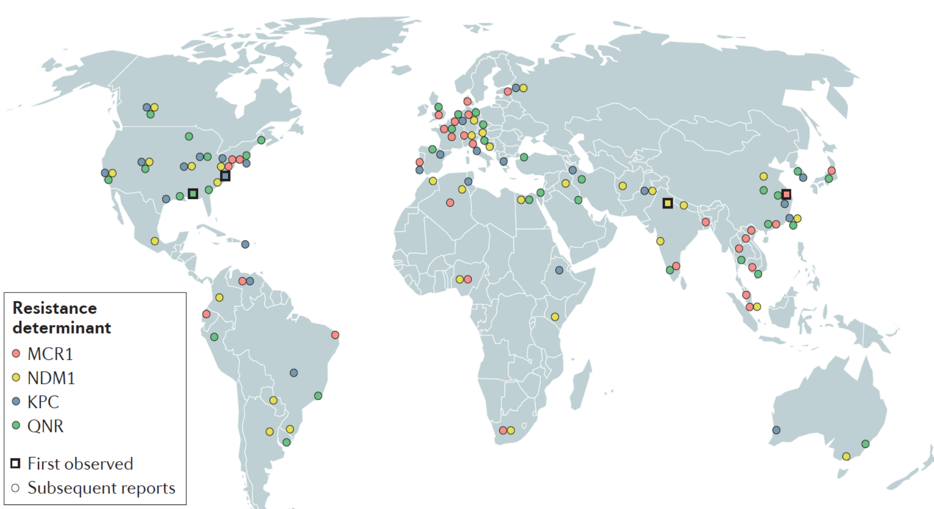
Global dissemination of *acquired* resistance determinants -



- **in the antibiotics *arms race*, humanity is rarely ahead**
- **relatively myopic focus on resistance among human pathogens**

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Examples of AMR genotypes-

***Salmonella* recovered from whole chicken carcasses at retail outlets -**

Experimental strategy-

- conventional microbiological methods &
- AST testing

Salmonella epidemiology in China -

- *Salmonella*-contaminated chicken products are an important vehicle for much of the food-borne infection cases reported in China
- Some 40% of the 2,203 food-borne disease outbreaks reported between 2006-2010 in China were attributed to microorganisms
- **Of these 70-80% had a defined aetiology linked to *Salmonella***
- ***Salmonella* infections have become a major public health issue**
- Most cases of salmonellosis are self-limiting and do not require chemotherapeutic intervention
- **Emergence of a *Salmonella* Indiana co-resistant to ceftriaxone and ciprofloxacin are now being regularly reported**

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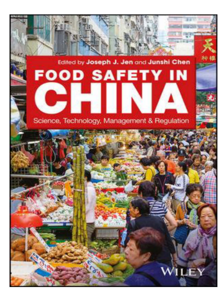
Summary of the study -

- Aim of the study was to describe the serovar diversity and antimicrobial resistance phenotypes identified in NTS isolates from retail chicken carcasses across 6 provinces in China
- **Samples tested numbering 1,438 whole chickens tested, provided 2,210 *Salmonella* isolates for study**
- Serotyping was performed by conventional- and molecular-based methods and susceptibilities tested against a panel of 11 compounds representing nine classes of antimicrobial drug



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AST analysis of *Salmonella* serovars -

Number of Class of Antibiotic Resistance	No. of strains of dominant serovars (Percentage)											
	Total (n = 2210)	Enteritidis (n = 673)	Indiana (n = 365)	Infantis (n = 211)	Typhimurium (n = 163)	Agona (n = 162)	Derby (n = 81)	Rissen (n = 68)	Dabou (n = 58)	Thompson (n = 50)	Hadar (n = 46)	Other Serovars (n = 333)
0	438 (19.8%)	68 (10.1%)	6 (1.6%)	16 (7.6%)	24 (14.7%)	135 (83.3%)	7 (8.6%)	12 (17.6%)	4 (6.9%)	19 (38.0%)	0 (0.0%)	147 (44.1%)
1	645 (29.2%)	271 (40.3%)	12 (3.3%)	141 (66.8%)	34 (20.9%)	9 (5.6%)	15 (18.5%)	32 (47.1%)	43 (74.1%)	11 (22.0%)	0 (0.0%)	77 (23.1%)
2	160 (7.2%)	20 (3.0%)	19 (5.2%)	15 (7.1%)	9 (5.5%)	0 (0%)	10 (12.3%)	3 (4.4%)	11 (19.0%)	0 (0.0%)	42 (91.3%)	31 (9.3%)
3	175 (7.9%)	128 (19.0%)	18 (4.9%)	1 (0.5%)	10 (6.1%)	0 (0%)	4 (4.9%)	2 (2.9%)	0 (0.0)	0 (0.0%)	2 (4.3%)	10 (3.0%)
4	198 (9.0%)	148 (22.0%)	15 (4.1%)	0 (0%)	16 (9.8%)	1 (0.6%)	9 (11.1%)	2 (2.9%)	0 (0.0)	0 (0.0%)	2 (4.3%)	5 (1.5%)
5	101 (4.6%)	14 (2.1%)	25 (6.9%)	1 (0.5%)	19 (11.7%)	6 (3.7%)	9 (11.1%)	7 (10.3%)	0 (0.0)	1 (2.0%)	0 (0.0%)	19 (5.7%)
6	209 (9.4%)	21 (3.1%)	62 (17.0%)	37 (17.5%)	27 (16.6%)	11 (6.8%)	3 (3.7%)	9 (13.2%)	0 (0.0)	6 (12.0%)	0 (0.0%)	33 (9.9%)
7	184 (8.3%)	3 (0.5%)	109 (29.9%)	0 (0%)	24 (14.7%)	0 (0%)	24 (29.6%)	1 (1.5%)	0 (0.0)	13 (26.0%)	0 (0.0%)	10 (3.0%)
8	100 (4.5%)	0 (0%)	99 (27.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0.0%)	0 (0.0%)	0 (0.0)	0 (0.0%)	0 (0.0%)	1 (0.3%)
≥3 (MDR)	967 (43.8%)	314 (46.7%)	328 (89.9%)	39 (18.5%)	96 (58.9%)	18 (11.1%)	49 (60.5%)	21 (30.9%)	0 (0.0)	20 (40.0%)	4 (8.7%)	78 (23.4%)
≥5	594 (26.9%)	38 (5.7%)	295 (80.8%)	38 (18.0%)	70 (42.9%)	17 (10.5%)	36 (44.4%)	17 (25.0%)	0 (0.0)	20 (40.0%)	0 (0.0%)	63 (18.9%)

AST summary –

- some 438 isolates tested were found to be susceptible;
- 1,772 were resistant to at least one antimicrobial compound;
- resistance to nalidixic acid was common (70% of the collection) followed by resistance to ampicillin (43%), tetracycline (42%);
- ***none of the isolates were resistant to carbapenems;***
- ***55% of the collection were defined as having a MDR phenotype (3 or more classes)***

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[Hu, *et al.*, (2017) *Food Control* **81:** 46-54]

Antimicrobial resistance profile	Number of Isolates	Number of ESBLs positive isolates
CHL-CIP-NAL-AMP-CAZ-CTX-SXT	1	1
CHL-CIP-NAL-AMP-SAM-CAZ-CTX-SXT	1	0
CHL-CIP-NAL-AMP-SAM-TET-CTX-SXT	13	13
CIP-NAL-AMP-SAM-CTX	1	1
CIP-NAL-AMP-TET-CTX	1	1
GEN-CHL-CIP-NAL-AMP-CTX-SXT	2	2
GEN-CHL-CIP-NAL-AMP-SAM-CAZ-CTX-SXT	15	14
GEN-CHL-CIP-NAL-AMP-SAM-CTX	4	4
GEN-CHL-CIP-NAL-AMP-SAM-CTX-SXT	19	18
GEN-CHL-CIP-NAL-AMP-SAM-TET-CAZ-CTX	11	11
GEN-CHL-CIP-NAL-AMP-SAM-TET-CAZ-CTX-SXT	32	32
GEN-CHL-CIP-NAL-AMP-SAM-TET-CTX	9	9
GEN-CHL-CIP-NAL-AMP-SAM-TET-CTX-SXT	66	65
GEN-CHL-CIP-NAL-AMP-TET-CTX	1	1
GEN-CHL-CIP-NAL-AMP-TET-CTX-SXT	1	1
GEN-CIP-NAL-AMP-CTX-SXT	1	1
GEN-CIP-NAL-AMP-SAM-CTX-SXT	1	1
GEN-CIP-NAL-AMP-SAM-TET-CTX	1	1
GEN-CIP-NAL-AMP-SAM-TET-CTX-SXT	3	3
Total	183	179

Salmonella Indiana ESBL & FQ resistant profiles-

- *Salmonella* Indiana were the most resistant of the serovars detected with 98% being resistant to all compounds tested ***with the exception of carbapenems***
- ***Salmonella* Indiana was also found to be resistant to (fluoro)quinolones**
- 183 *S.* Indiana isolates were co-resistant to ciprofloxacin and cefotaxime of which 179 were ESBL-positive
- **more than half of the isolates represented by this serovar were found to be resistant to nine or more antimicrobial compounds**

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Salmonella harbouring _mcr-1_ gene
isolated from food in China between 2011-2016-

Experimental strategy-
- conventional microbiological methods;
- AST testing;
- WGS (SMRT® platform) &
- bioinformatic analyses

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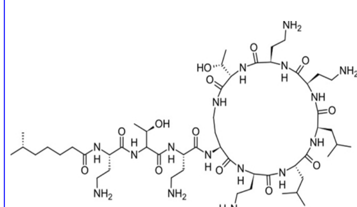
Colistin an old drug that has become important (again) -

- ***colistin is a cationic peptide that belongs to the family of polymyxins***
- ***discovered in 1947 and has a complex biochemical structure***
- **fell into disuse, by 1980's due to nephrotoxicity**
- **these resistance mechanisms are thought to be mediated by genes located on the bacterial chromosome NOT TRANSFERRABLE TO OTHER BACTERIA**
- **in 2015, a transferrable mechanism denoted as *mcr-1* was described, located on a plasmid that moved at high frequency**
- ***mcr-2* has just been in june, 2016, in Belgium and associated with bacterial isolates cultured form bovine and porcine animals**



Polymyxin E (Colistin)-

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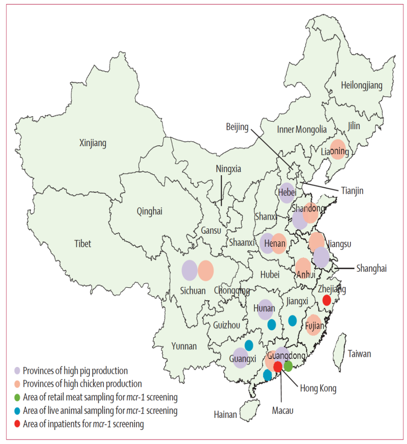
[Liu *et al.*, (2015) *Lancet Infect. Dis.***16:** 161-168. doi 10.1061/S1473-3099(15)00424-7]

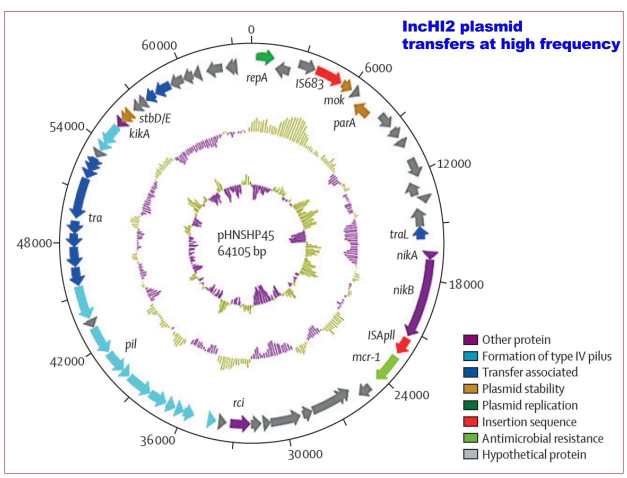
- **China is the worlds biggest poultry and pig producer** [in 2014, 17.5- and 56.7-million tonnes respectively]
- ***China was one of the largest users of colistin for agricultural production*** [global market value in veterinary drugs increased from $ 8.7 billion in 1992 to $ 20.1 billion in 2010 *and this is expected to grow to $ 43 billion by 2018*].
- **Global demand for colistin in agriculture is expected to reach 16,500 tonnes by 2021**



Geographical locations in China positive for colistin-resistant *E. coli*-

47

Transferrable *colistin* resistance –the *mcr-1* gene



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[Liu *et al.*, (2015) *Lancet Infect. Dis.***16:** 161-168. doi 10.1061/S1473-3099(15)00424-7]

Seven colistin isolates of 2,588 *Salmonella* species cultured from foods in China–

Bacterial isolate	CFSA664	CFSA122	CFSA12	CFSA244	CFSA1096	CFSA231	CFSA629
Serotype	Indiana	Typhimurium	Typhimurium	Typhimurium	London	Derby	Typhimurium
MLST type	17	34	34	34	155	40	34
Year.month	2011.6	2013.5	2014.5	2014.4	2015.10	2016.10	2016.7
Region	Jiangsu	Guangxi	Guangxi	Jiangxi	Hubei	Hubei	Guangdong
Food origin	Retail chicken	Dumpling (Retail)	Retail Pork	Retail Pork	Retail Pork	Dumpling (Restaurant)	Egg
Resistant antimicrobial classes	8	7	4	4	10	7	6
ESBLs	+	-	-	-	+	-	+
Number of plasmid	3	2	1	2	1	1	1
Replicon type and size of plasmids harbouring mcr-1	IncI2 (61 kbp)	IncHI2A/HI2 (182 kbp)	IncHI2A/HI2 (148 kbp)	IncI2 (60 kbp)	IncHI2A/HI2 (297 kbp)	IncX4 (33 kbp)	IncHI2A/HI2 (211 kbp)
Antimicrobial resistance genes on plasmids harbouring *mcr-1*	*mcr-1*	*mcr-1*, *aph(4)-Ia*, *aac(3)-IVa*, *aph(3')-Ia*, *aadA1*, *aadA2*, bla_{OXA-1}, *aac(6')-Ib-cr*, *floR*, *catB4*, *cmlA1*, *arr-3*, *sul2*, *sul1*, *sul3*	*aadA2*, *aadA1*, *cmlA1*, *sul3*, *dfrA12*, *Δmcr-1*	*mcr-1*	*mcr-1*, *aph(3')-Ia*, *aadA22*, *aph(6)-Id*, *aac(3)-IId*, bla_{TEM-1B}, $bla_{CTX-M-55}$, *qnrS1*, *lnu(F)*, *mph(A)*, *floR*, *arr-2*, *sul3*, *tet(A)*, *dfrA14*	*mcr-1*	*mcr-1*, *aac(3)-Iva*, *aph(4)-Ia*, $bla_{CTX-M-14}$, *fosA3*

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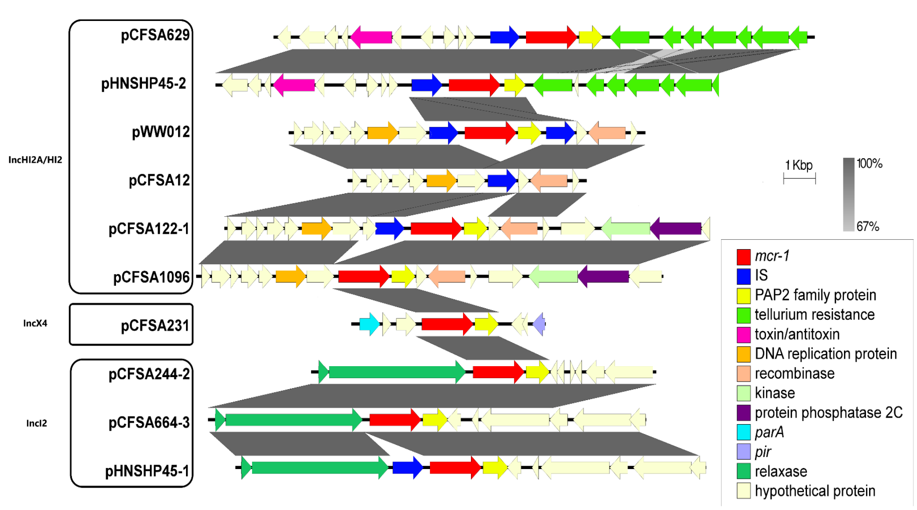
mcr-1 containing genetic environments -



plasmids pHNSHP45 and pHNSHP45-2 (Accession number: KP347127 and KU341381) belonged to *Escherichia coli* strain SHP45, which is the first isolate reported harbouring *mcr-1* gene.

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Selection of plasmids co-expressing resistance to tigecycline and florphenicol -

Experimental strategy-

- conventional microbiological methods;
- AST testing;
- WGS (SMRT® platform) &
- bioinformatic analyses

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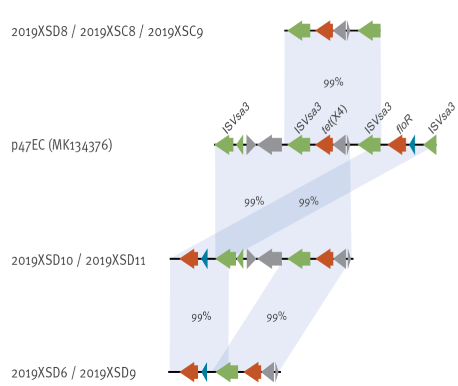
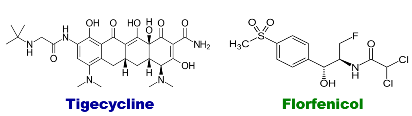
- ***Escherichia coli*** **were cultured from food-producing animals**
- ***bacteria were isolated following selection on tigecycline & seven expressed a MIC (8-32 mg/L) above the breakpoint***
- **the *tet*(X4) gene was identified and contained within a gene cassette** which may support its dissemination by horizontal means on an **IncFII *plasmid***
- **WGS analysis of these isolates identified ST101 & ST48**
- **the *floR*-encoding gene was flanked by IS*6100*, suggesting that tigecycline and florphenicol resistance are being co-selected**





[Li *et al., Euro. Surveill.* (2019) **24:** pii-19003]
[He *et al., Nat. Microbiol.* (2019) 10.1038/s41564-019-0445-2]

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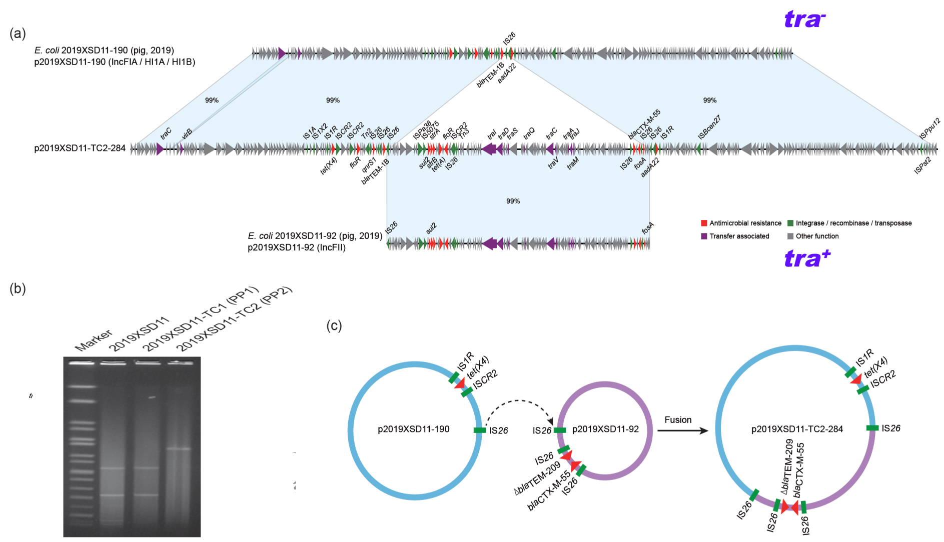

Insertion sequence *26* (IS*26*)-driven plasmid recombination

Metagenomics of antimicrobial resistance -

Metagenomics to characterize microbial ecology -

Metagenomics can be applied to study the <u>bacterial composition</u> of samples recovered directly from <u>any environment</u> -

- **Targeted (PCR-based) metagenomics;** PCR used to detect various bacterial-encoded 16S rDNA genes and this can be applied as a semi-quantitative method

- **Functional metagenomics;** involves the cloning of a DNA fragment into a heterologous genetic background and selecting for a defined phenotype using a selective culture medium, followed by subsequent DNA sequencing to characterise any positive clone

- **Sequence-based metagenomics;** DNA from an environment of interest is purified; fragmented and size-separated then sequenced directly; sequences obtained are compared to entries in the current databases

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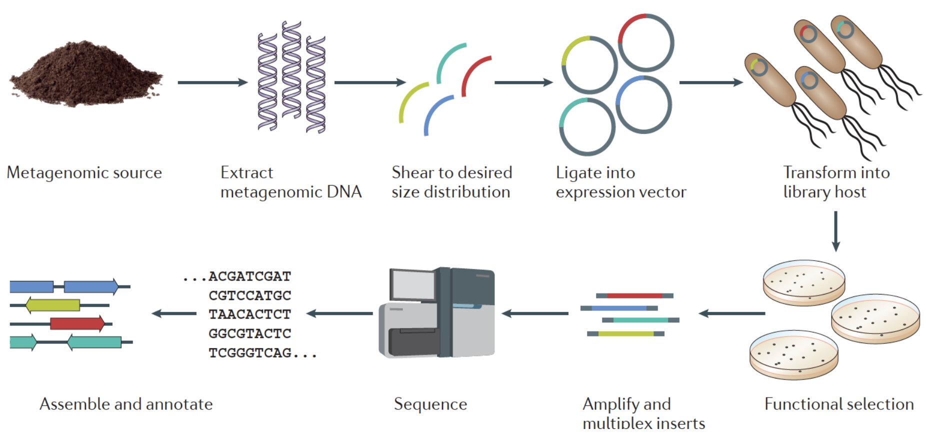
[Penders *et al.*, (2013) *Frontiers in Microbiol*, doi: 10.3389/fmicb.2013.00087]

Steps involved in functional metagenomics -



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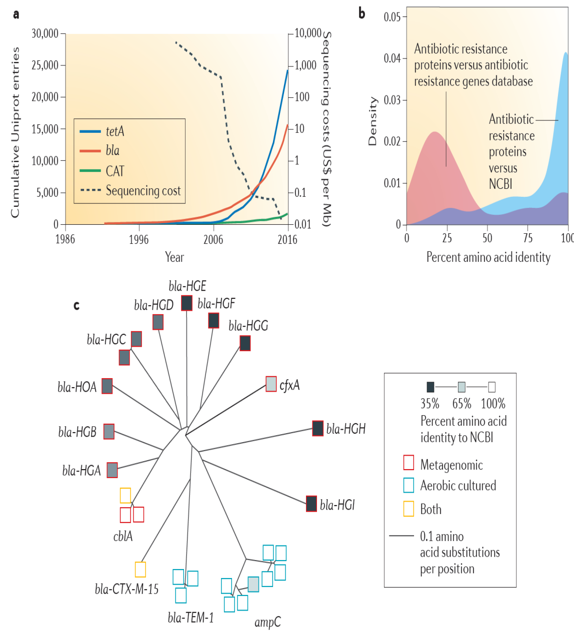
- **development of high-throughput genomic sequencing techniques has enabled the culture-independent study of diverse environments**

- **since 1986, a survey of the UniProt database revealed that there has been an exponential increase in the numbers of hypothetical resistance determinants classified as-**
  - **b-lactamases;**
  - **chloramphenicol acetyltransferases (CAT) or**
  - **tetracycline efflux pumps**

- **functional metagenomics has been invaluable in validating these discoveries and in leading to the discovery of new determinants**



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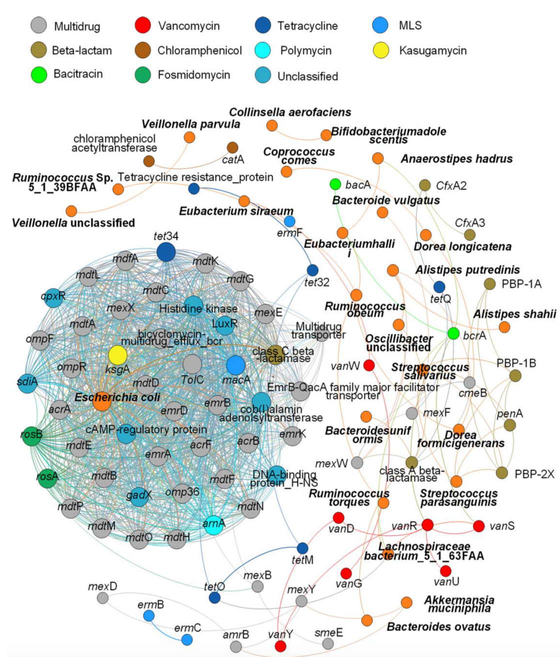
[Crofts *et al.*, *Nat. Microbiol.* (2017) 10.1038/nrmicro.2017.28]

- **bacterial phylogenies identified in the human gut may help to shape the distribution of AMR-encoding genes, as shown in the network figure**

- **Based on this analyses, *E. coli* was a possible host for 45 AMR-encoding genes, 30 of which elaborated a multi-drug resistance phenotype, with the balance being related to b-lactamase-; fosmidomycin-; tetracycline-; MLS-resistance mechanisms and others**

- **similar observations are also being made in soil metagenomes**

- **these observations will guide the development of novel drug discovery strategies in the future, including-**
  - **re-purposing existing drugs in synergistic combinations**
  - **identification of inhibitors of efflux pumps &**
  - **adjuvant therapies**



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[Feng, *et al.*, *Environ. Microbiol.* (2017) 10.1111/1462-2920.14009]

Conclusions -

- AMR is a *One Health* challenge;
- AMR resistance-encoding genes can be disseminated widely by several mechanisms;
- ***matagenomic libraries may be helpful in fueling the discovery of novel antimicrobial compounds***

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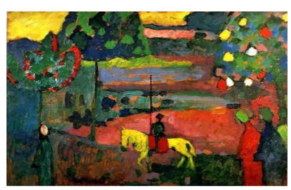

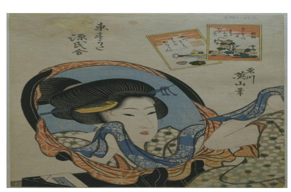

Thank you

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February 19, 2020	*(South Pacific Teleclass)* DEVELOPING AND IMPLEMENTING A PERSONAL PROTECTIVE EQUIPMENT TRAINING PROGRAMME FOR HIGH-CONSEQUENCE INFECTIOUS DISEASE PREPAREDNESS Speaker: **Ruth Barratt**, University of Sydney, Faculty of Medicine
February 27, 2020	ANTIBIOTIC STEWARDSHIP IN NURSING HOMES Speaker: **Prof. Patricia Stone**, Columbia University, School of Nursing
March 3, 2020	*(European Teleclass)* THE EFFICACY OF INFECTION PREVENTION AND CONTROL COMMITTEES IN AFRICAN SETTINGS Speaker: **Eltony Mugomeri** , Africa University, Zimbabwe
March 12, 2020	*(FREE Teleclass)* THE BUZZ AROUND MOSQUITOES AND MOSQUITO-BORNE DISEASES Speaker: **Dr. Marcia Anderson**, Environmental Protection Agency
March 19, 2020	INFECTION PREVENTION AND CONTROL IN HOME CARE AND HOSPICE: COMMON COMPLIANCE ISSUES Speaker: **Mary McGoldrick**, Home Health Systems, Inc.
April 16, 2020	WATERBORNE PATHOGENS: WHY IS THEIR PROFILE CHANGING? Speaker: **Prof. Syed A Sattar**, Centre for Research on Environmental Microbiology, Canada

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