Impact of Antimicrobial Resistance on Human Health

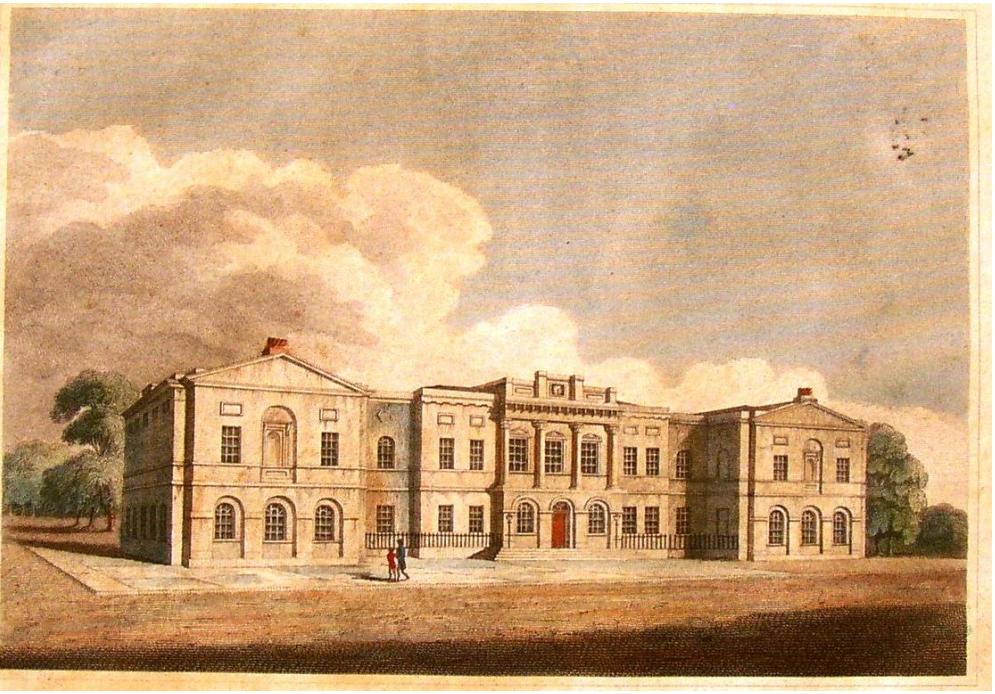
Robert Cunney

HSE HCAI/AMR Programme

and Temple Street Children's University Hospital

Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

Sir Patrick Dun's Hospital



Sir Patrick Dun's Hospital.
REGISTER OF INTERN PATIENTS.

No.	Patient's Name	Age	Religion	Residence	Recommended by
38	Mary Andrews	29	R.C.	Newtown Park Blackrock	
39	A. K. Askins	19	P.	6 Ormond Rd	
40	Wm McClure	31	R.C	10 East Rd	
41	Kate Lynch	8	R.C	12 Hanover St	
42	Margt Martin	32	R.C.	Tallanstown Co Louth	
43	Mary Granger	4	R.C.	17 Thorncastle St	
44	Geo Huggins	5	R.C	15 Lone Place	
	Mary Brown	22	R.C	2 Grattan Court	
	Sarah Bloom	20	Hebrew	38 Lombard St	
	Wm Darcy	17	R.C.	25 Queens Terrace	
	Lilly Graham	17	P	12 Baggot St	
	Teresa Jackson	21	R.C.	5 Alexcorn Rd	[illegible]
	Geo Ellis	4	R.C.	11 Upp Erill St	
	Thos Wildridge	38	R.C.	8 Townsend St	
	Edric Moulang	11	P	Boys' Home	
	Mary Clery	20	R.C.	3 Lone St	
	Charles Morris	30	P	16 Warrington Place	[illegible]
	K Moore	4	P	4 Stephens Place	
	Michl Cullen	62	R.C.	4 Upp Mayor St	Pickford
	Bridget McKeown	12	R.C.	20 Aungier St	
	Michl Giles	48	R.C.	6 Clarence St	
	Kate Fitzpatrick	50	P.	Clonsilla Co Dublin	
	[illegible] Reardon	39	R.C.	29 Mountpleasant Terrace	[illegible]
	Mary Brodrick	17	R.C.	48 Haddington Rd	
	[illegible] Carberry	30	R.C.	26 Sandwith Place	
	[illegible]	22	R.C.	43 Shelbourne Rd Pembroke	

Admitted by	Date of Admission		Date of Discharge		Diagnosis
Dr Mavan	Nov	13	Dec	4	Endometritis
Dr Finny	Nov	13	Nov	20	Tonsillitis
Dr Taylor	Nov	13	Nov	16	Fractured spine
Dr Finny	Nov	14	Nov	21	Measles
Dr Ball	Nov	14	Nov	18	Tumour of thumb
Dr Finny	Nov	14	Dec	11	Diphtheria
Dr Finny	Nov	14	Nov	22	Mumps
Dr Taylor	Nov	14	Dec	10	Mastitis
Dr Finny	Nov	14	Nov	30	Favus
Dr Taylor	Nov	14	Nov	23	Wound of hand
Dr Finny	Nov	15	Nov	30	Chlorosis
Dr Mavan	Nov	16	Dec	6	Vaginitis
Dr Taylor	Nov	16	Nov	19	Contused side
Dr Taylor	Nov	16	Nov	23	Contused leg
Dr Finny	Nov	17	Nov	26	Epilepsy
Dr Finny	Nov	17	Dec	10	Gastric Ulcer
Dr Finny	Nov	17	Nov	27	Gout
Dr Finny	Nov	17	Nov	22	Pneumonia
Dr Bennett	Nov	18	Nov	24	Contused legs
Dr Taylor	Nov	19	Jan	4	Tubercular abscess
Dr Finny	Nov	19	Dec	4	Syphilis
Dr Ball	Nov	19	Dec	8	Epithelioma of arm
Dr Bennett	Nov	19	Dec	11	Rheumatism
Dr Finny	Nov	19	Nov	24	Rheumatism
Dr Taylor	Nov	19	Jan 1	1	Bubo & Cellulitis
Dr Finny	Nov	19	Dec	19	Pneumonia

Date of Admission		Date of Discharge		Diagnosis
Nov	13	Dec	4	Endometritis
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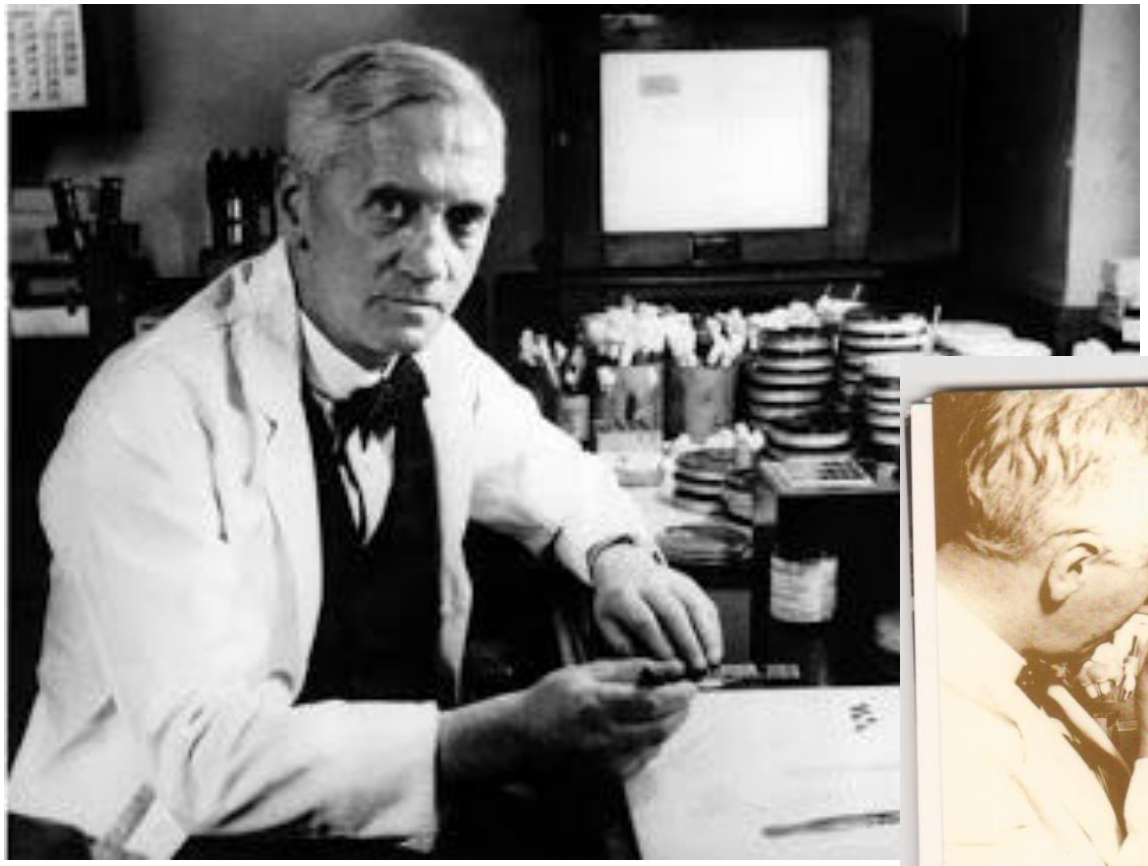
	19	Dec	4	Syphilis
	19	Dec	8	Epithelioma of arm
	19	Dec	11	Rheumatism
	19	Nov	24	Rheumatism
	19	Jan 1	1	Bubo & Cellulitis
	19	Dec	19	Pneumonia

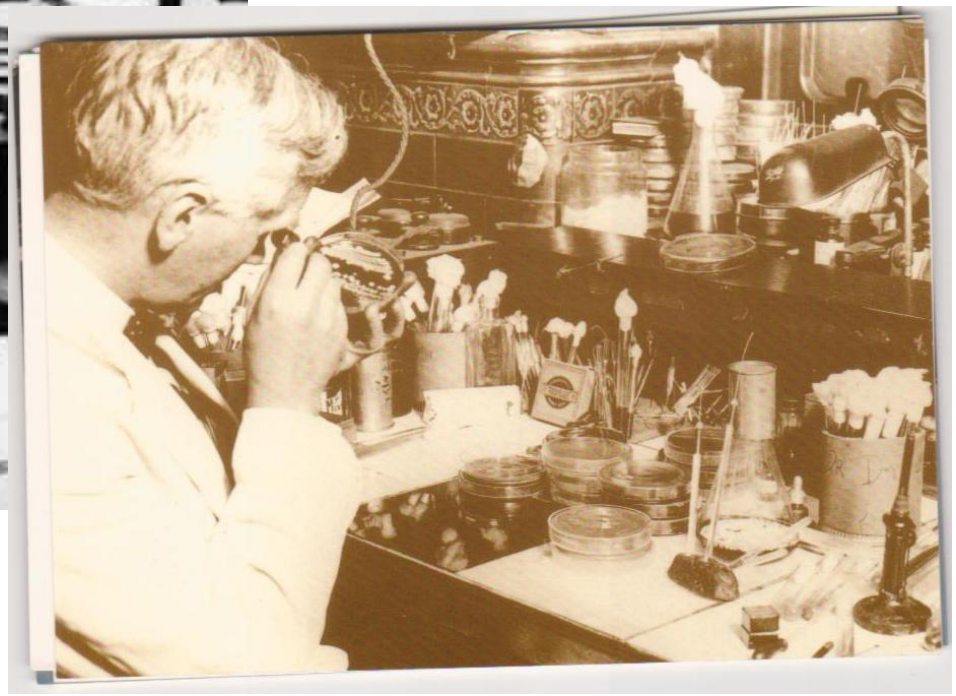
Jan.	14	Jan.	24	Enteric	Died.
Jan.	14	Jan.	31	Inguinal hernia	cured
Jan.	14	Feb.	5	Rheumatism	cured
Jan.	14	Jan.	28	Pneumonia	
Jan.	14	March.	4	Pleurisy	cured E.W. Taylor Jan 1901
Jan.	15	Feb	28	Carcinoma of Tongue	Died
Jan.	16	Jan	22	Tubercular Abscess	
Jan.	16	April	20	Transverse myelitis	improved
Jan.	16	Jan.	26	Painful tumour of arm	excised.
Jan.	17	Feb.	8	Fracture of Clavicle & rib	cured
Jan.	17	Feb	12	Dermoid cyst in neck	excised
Jan.	17	Jan	18	"Fever"	Died
Jan.	17	Feb.	11	Tubercular ulcer	excised
Jan.	17	Jan.	21	Bronchitis	
Jan.	18	Jan.	18	Crushed hand	3 fingers amputated
Jan.	18	Feb	6	Septic endocarditis	Died.
Jan.	18	Feb	8	Ulcer in knee, Sebaceous cyst	cured
Jan.	18	Feb	2	Sebaceous Cyst of Scalp	Excised
Jan	19	Feb.	2	Chronic Nephritis,	Died
Jan.	20	Jan.	23	Carbolic acid poisoning	
Jan.	21	Feb.	26	Abscess in neck	Drained
Jan.	21	Feb	4	Urethral Stricture, piles	Stricture dilated Piles excised
Jan.	21	Feb	7	Anaemia	cured
Jan.	21	Feb	3	Abscess in tonsil	cured
Jan.	21	Jan.	21	Ganglion of wrist	Incised
Jan.	22	Feb.	26	Cystitis	Cystotomy

E.W. Taylor
Jan 22/1901

March	21	March	29	Pneumonia	cured
March	22	April	24	Disseminated Sclerosis	unchanged
March	22	April	4	Synovitis of Knee	cured
March	23	April	7	Hemiplegia, Latent [illegible]	improved
March	23	May	8	Pleural Effusion	cured
March	23				
March	25	April	7	Septic finger	amputated
March	25	April	11	Bronchitis	cured
March	25	April	24	Enteric ?	cured
March	25	April	8	Pneumonia	cured
March	25	Feb	3	Morbus Coxae	Cured
March	26	April	1	Phthisis	Died
March	26	April	13	~~Enlarged glands~~ [illegible] E.W.T. 24 March 1901	Cured
March	26	April	2	Meningitis	Died
March	26	April	1	Burns	cured
March	26	April	3	Rotheln	cured
March	27	June	29	Dysmenorrhoea [illegible]	cured
March	27	March	31	Influenza	cured
March	27	April	2	Gonorrhoea	cured
March	27	May	15	Fracture of Tibia & Fibula	cured
March	27	April	1	Bronchitis	cured
March	28	April	20	Septic corn	cured
March	28	March	31	Pneumonia	Died
March	28	March	29	Cerebro spinal Meningitis	Died
March	29				
March	29	April	11	Hallux Valgum	cured

Alexander Fleming





ON THE ANTIBACTERIAL ACTION OF CULTURES OF A PENICILLIUM, WITH SPECIAL REFERENCE TO THEIR USE IN THE ISOLATION OF *B. INFLUENZÆ.*

ALEXANDER FLEMING, F.R.C.S.

From the Laboratories of the Inoculation Department, St. Mary's Hospital, London.

Received for publication May 10th, 1929.

WHILE working with staphylococcus variants a number of culture-plates were set aside on the laboratory bench and examined from time to time. In the examinations these plates were necessarily exposed to the air and they became contaminated with various micro-organisms. It was noticed that around a large colony of a contaminating mould the staphylococcus colonies became transparent and were obviously undergoing lysis (see Fig. 1).

Subcultures of this mould were made and experiments conducted with a view to ascertaining something of the properties of the bacteriolytic substance which had evidently been formed in the mould culture and which had diffused into the surrounding medium. It was found that broth in which the mould had been grown at room temperature for one or two weeks had acquired marked inhibitory, bactericidal and bacteriolytic properties to many of the more common pathogenic bacteria.

British Journal of Experimental Pathology, 1929

Howard Florey and Ernst Chain

PENICILLIN AS A CHEMOTHERAPEUTIC AGENT

BY

E. CHAIN, PH.D. CAMB.
H. W. FLOREY, M.B. ADELAIDE,
A. D. GARDNER, D.M. OXFD, F.R.C.S.
N. G. HEATLEY, PH.D. CAMB.
M. A. JENNINGS, B.M. OXFD,
J. ORR-EWING, B.M. OXFD,
A. G. SANDERS, M.B. LOND.

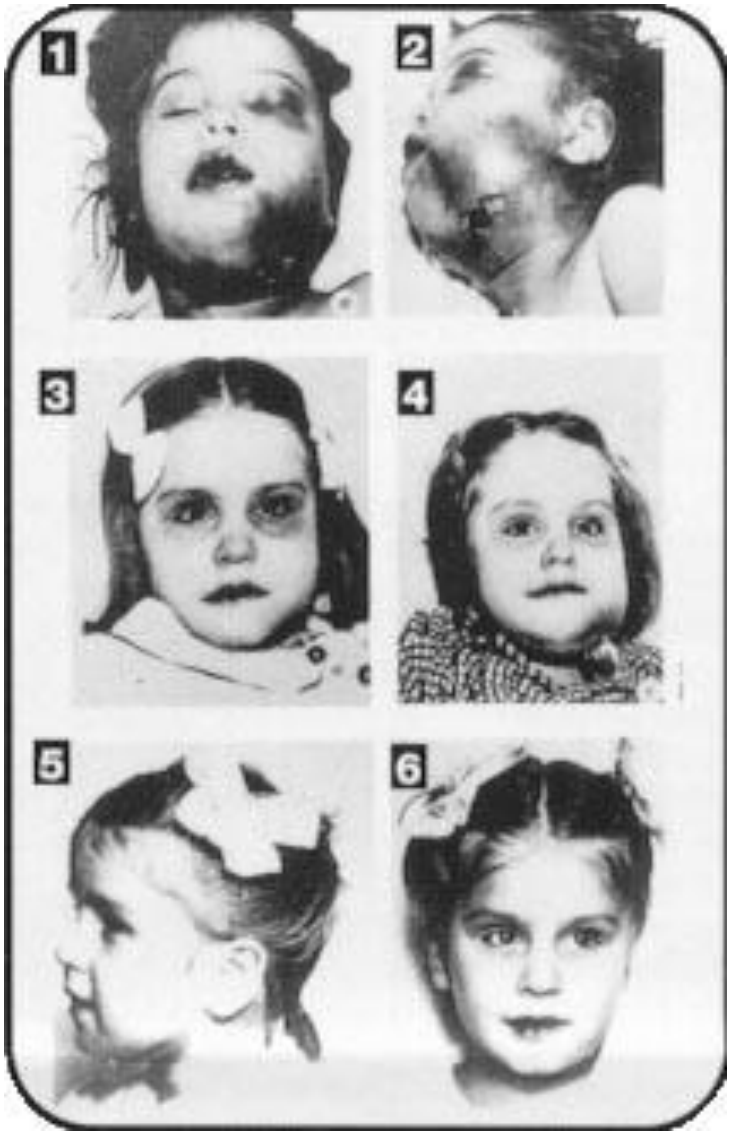
(*From the Sir William Dunn School of Pathology, Oxford*)

IN recent years interest in chemotherapeutic effects has been almost exclusively focused on the sulphonamides and their derivatives. There are, however, other possibilities, notably those connected with naturally occurring substances. It has been known for a long time that a number of bacteria and moulds inhibit the growth of pathogenic micro-organisms. Little, however, has been done to purify or to determine the properties of any of these substances. The antibacterial substances produced by *Pseudomonas pyocyanea* have been investigated in some detail, but without the isolation of any purified product of therapeutic value.

Recently, Dubos and collaborators (1939, 1940) have published interesting studies on the acquired bacterial antagonism of a soil bacterium which have led to the isolation from its culture medium of bactericidal substances active against a number of gram-positive micro-organisms.[1] Pneumococcal infections in mice were successfully treated with one of these substances, which, however, proved to be highly toxic to mice (Hotchkiss and Dubos 1940) and dogs (McLeod et al. 1940).

Following the work on lysozyme in this laboratory it occurred to two of us (E. C. and H. W. F.) that it would be profitable to conduct a systematic investigation of the chemical and biological properties of the antibacterial

1. See *Lancet*, 1940, 1, 1172.



Deaths due to infection among US soldiers in four wars

Admission rate and death rate expressed as number per annum per 1,000 average strength]

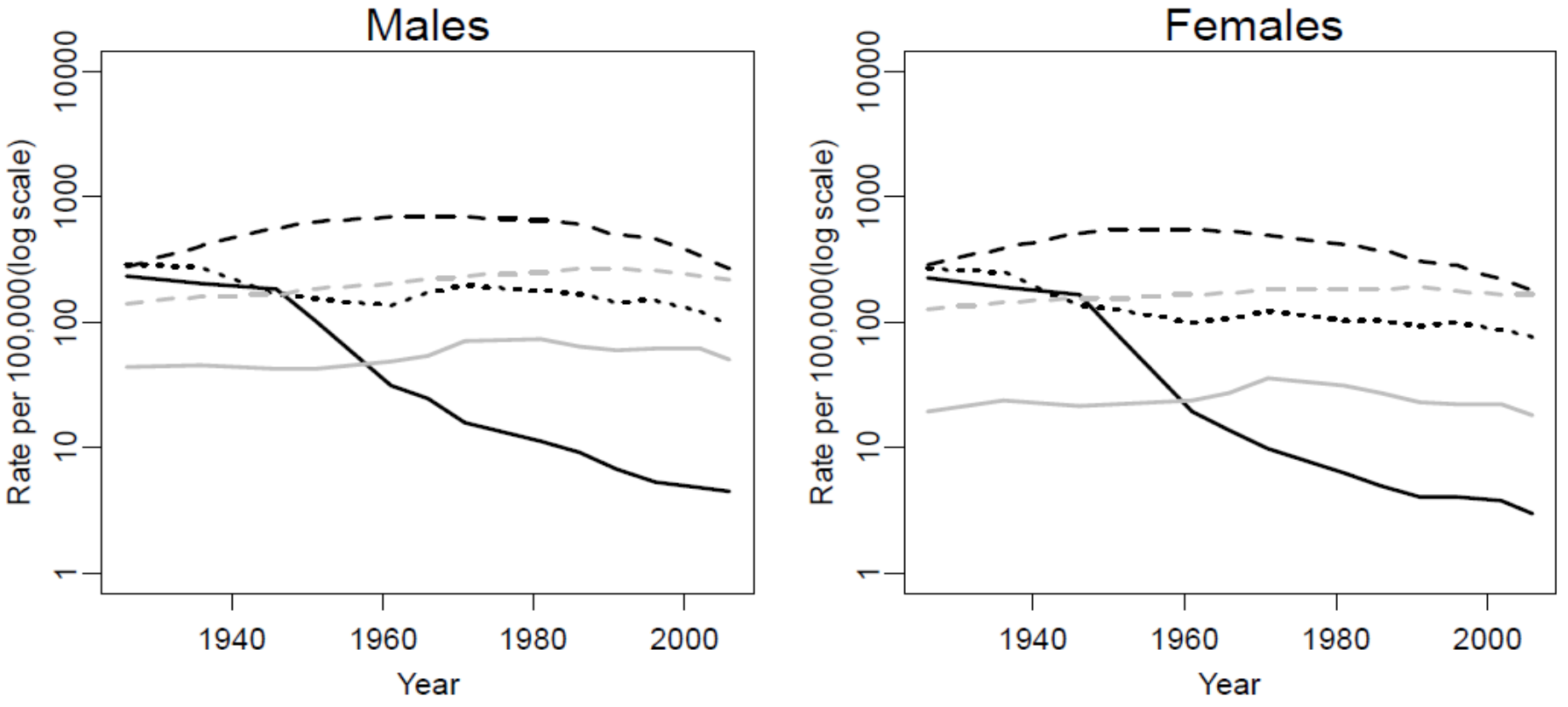
War	Admission rate	Death rate
Civil War (white Union troops) (1861–65)	[1] 1, 030. 34	[1] 34. 77
Spanish-American War (1898)	[1] 986. 89	[1] 20. 81
World War I (1 Apr. 1917–31 Dec. 1919)	[2] 427. 03	[2] 10. 43
World War II (1942–45)	112. 46	. 15

[1] Includes all types of pneumonia.
[2] Excludes rheumatic fever.

Source: (1) The Medical and Surgical History of the War of the Rebellion. Medical History. Washington: Government Printing Office, 1870, vol. I, pt. I, pp. 636–641. (2) Annual Report of The Surgeon General, 1900, p. 402. (3) The Medical Department of the United States Army in the World War. Statistics. Washington: Government Printing Office, 1925, vol. XV, pt. 2, pp. 86–108, 134–148. (4) World War II data from preliminary tabulations of individual medical records.

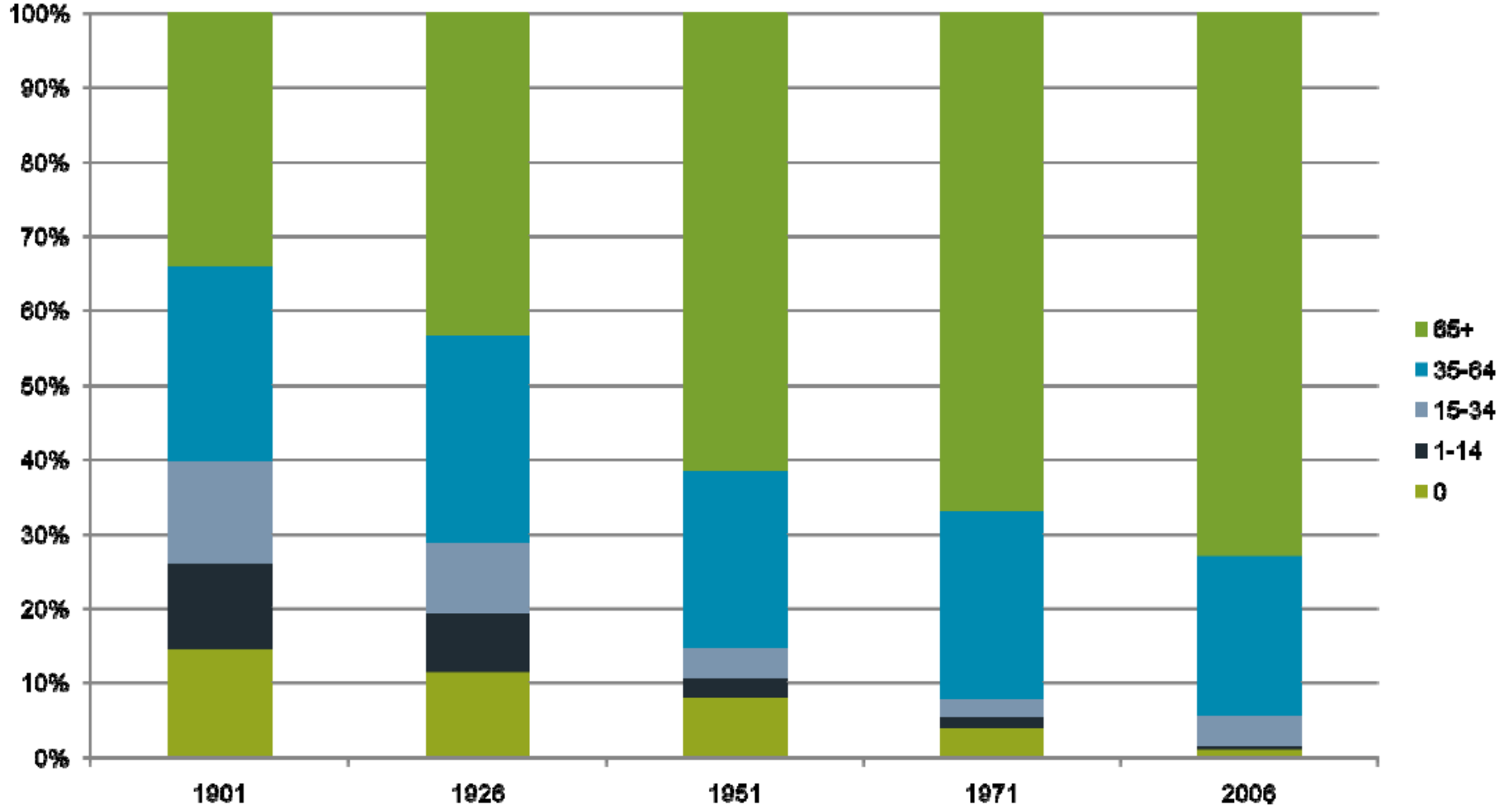
Source: US Army Medical Department, Office of Medical History

Causes of death in Ireland, 1926 - 2006



Data source: Society of Actuaries in Ireland 2011

Deaths by age group in Irish males



Data source: Society of Actuaries in Ireland 2011

LETTERS TO THE EDITORS

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IN THE PRESENT CIRCUMSTANCES, PROOFS OF "LETTERS" WILL NOT BE SUBMITTED TO CORRESPONDENTS OUTSIDE GREAT BRITAIN.

An Enzyme from Bacteria able to Destroy Penicillin

FLEMING[1] noted that the growth of *B. coli* and a number of other bacteria belonging to the coli-typhoid group was not inhibited by penicillin. This observation has been confirmed. Further work has been done to find the cause of the resistance of these organisms to the action of penicillin.

An extract of *B. coli* was made by crushing a suspension of the organisms in the bacterial crushing mill of Booth and Green[2]. This extract was found to contain a substance destroying the growth-inhibiting property of penicillin. The destruction took place on incubating the penicillin preparation with the bacterial extract at 37°, or at room temperature for a longer time. The following is a typical experiment showing the penicillin-destroying effect of *B. coli* extracts. A solution of 1 mgm. penicillin in 0·8 c.c. of water was incubated with 0·2 c.c. of centrifuged and dialysed bacterial extract at 37° for 3 hours, in the presence of ether, and a control solution of penicillin of equal concentration was incubated without enzyme for the same time. (The penicillin used was extracted from cultures of *Penicillium notatum* by a method to be described in detail later. It possessed a degree of purity similar to that of the samples used in the chemotherapeutic experiments recorded in a preliminary report[3].) The growth-inhibiting activity of the solutions was then tested quantitatively on agar plates against *Staphylococcus aureus*. The penicillin solution incubated with the enzyme had entirely lost

B. coli, it was not necessary to crush the organism in the bacterial mill in order to obtain the enzyme from it; the latter appeared in the culture fluid. The enzyme was also found in *M. lysodeikticus*, an organism sensitive to the action of penicillin, though less so than *Staphylococcus aureus*. Thus, the presence or absence of the enzyme in a bacterium may not be the sole factor determining its insensitivity or sensitivity to penicillin.

The tissue extracts and tissue autolysates that have been tested were found to be without action on the growth-inhibiting power of penicillin. Prof. A. D. Gardner has found staphylococcal pus to be devoid of inhibiting action, but has demonstrated a slight inhibition by the pus from a case of *B. coli* cystitis. The bacteriostatic action of the sulphonamide drugs is known to be inhibited in the presence of tissue constituents and pus.[4] That the anti-bacterial activity of penicillin is not affected under these conditions gives this substance a definite advantage over the sulphonamide drugs from the chemotherapeutic point of view. The fact that a number of bacteria contain an enzyme acting on penicillin points to the possibility that this substance may have a function in their metabolism.

E. P. ABRAHAM.
E. CHAIN.

Sir William Dunn School of Pathology,
Oxford.
Dec. 5.

[1] Fleming, A., *Brit. J. Exp. Path.*, **10**, 226 (1929).
[2] Booth, V. H., and Green, D. E., *Biochem. J.*, **32**, 855 (1938).

The Economist | World politics | Business & finance

Antibiotic resistance

The drugs don't work

Running out of ammunition in the war on germs

NewScientist Health

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Don't let up in war against antibiotic resistance

theguardian

Antibiotic resistance: why we must win the war against superbugs

Antibiotic-resistant bacteria kill far more people each year globally than terrorism. Why are we losing the battle against them, asks one doctor

Infectious Disease

Global War Urged on Antibiotic Resistance

The Telegraph

Australian researchers strengthen last line of defence in superbug war

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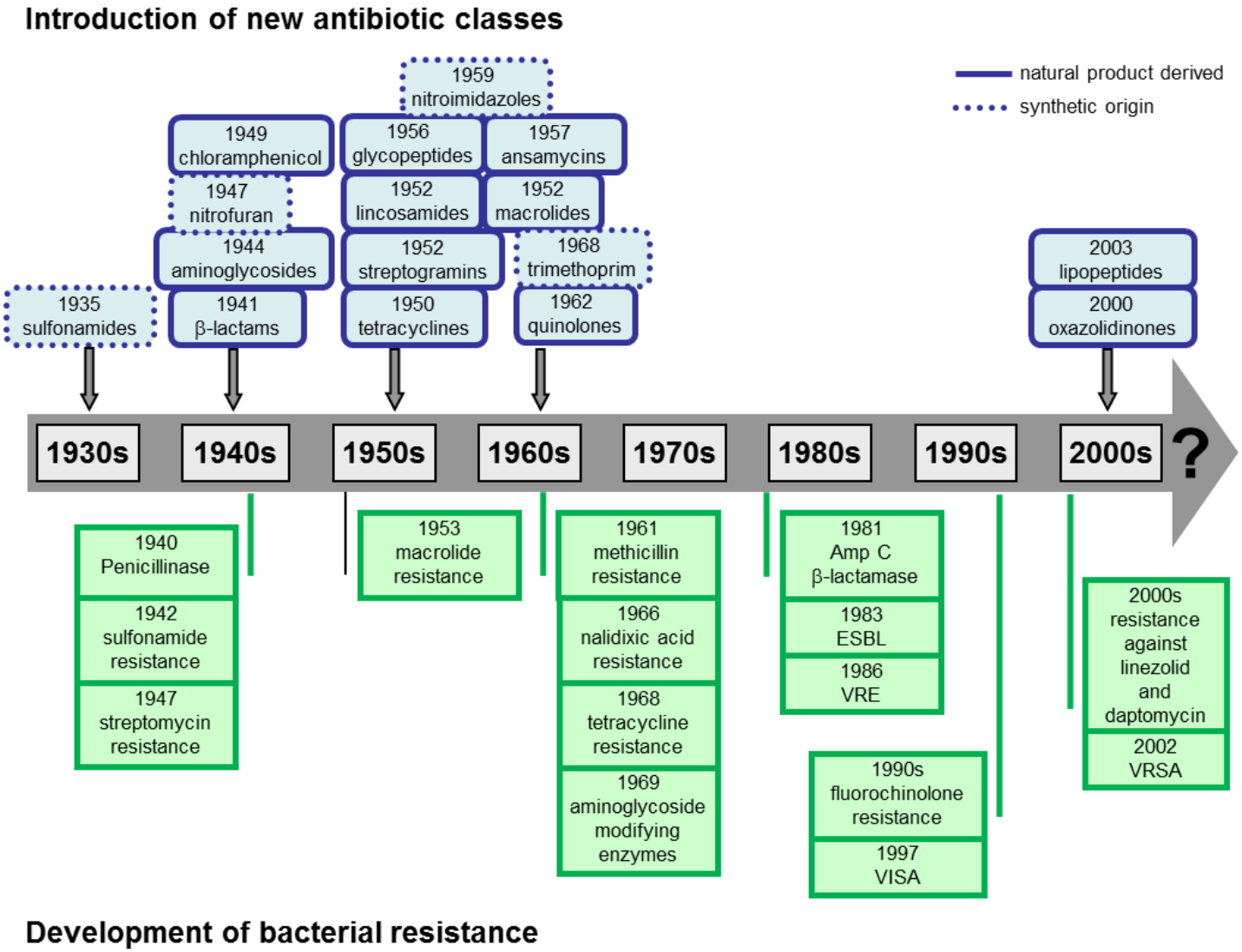
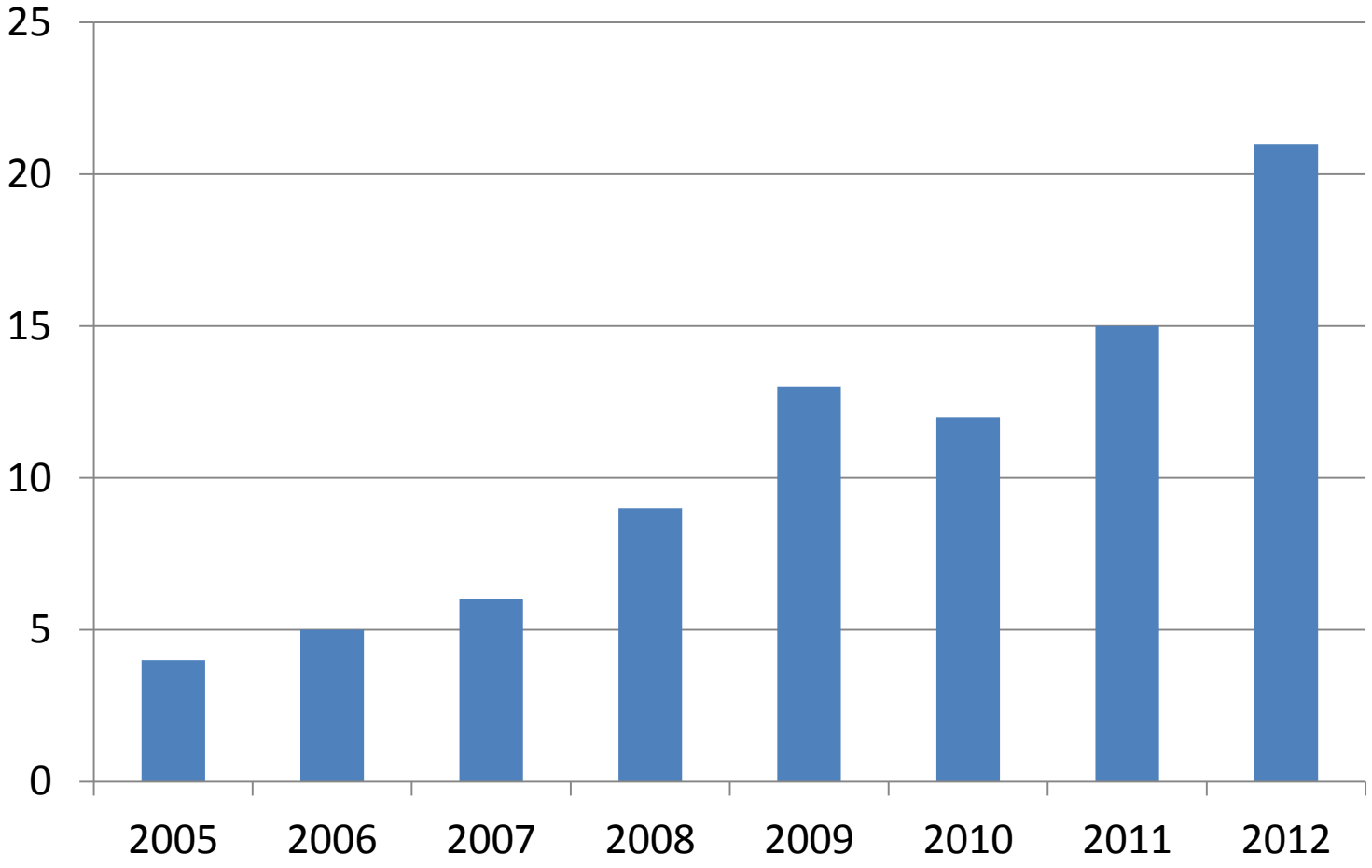
Why antibiotics are losing the war against bacteria

As bacteria become ever more resistant to drugs, world health experts fear a future without antibiotics

Development of antibiotics, and antibiotic resistance



Countries reporting carbapenem-resistant *Klebsiella* bloodstream infections in Europe



Data source: EARS-Net (report generated from data submitted to TESSy, The European Surveillance System on 2014-05-02)

Carbapenem-resistant *Klebsiella* (CRE) in Italy

late 2008

The first reported cases of KPC-Kp (ST258)

Giani *et al* – JCM 2009
Rossolini GM – unpublished

early 2011

ST258, ST512 (CC258)

Fontana *et al* – BMC Res Notes 2010
Marchese *et al* – J Chemother 2010
Ambretti *et al* – New Microb 2010
Gaibani *et al* – Eurosurv 2011
Mezzatesta *et al* – CMI 2011
Agodi *et al* – JCM 2011
Richter *et al* – JCM 2011
Di Carlo *et al* – BMC Gastroenterol 2011
Rossolini GM – unpublished

late 2012

ST512
ST258

ST101
ST15
ST147-like

AMCLI – CoSA CRE network
Frasson *et al* – JCM 2012
ARISS-CoSA study – unpublished

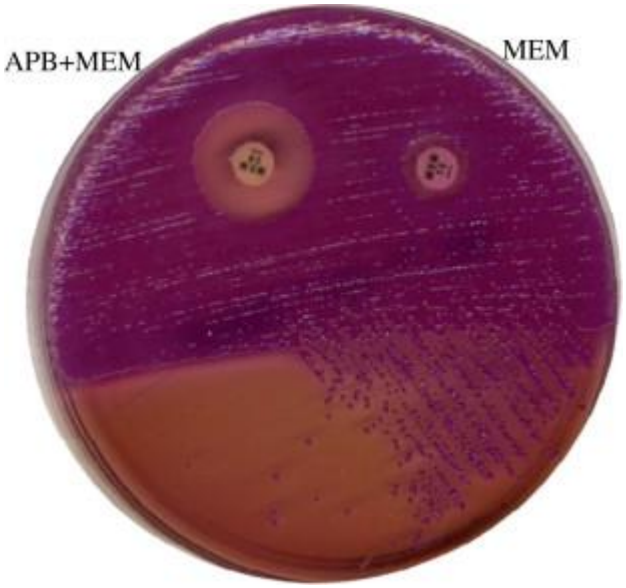
Data source: GM Rossolini, ARHAI Network Meeting, Berlin, Dec 2012

Mortality associated with CRE bloodstream infections

Author	Country	Pts	Mortality
Borer, ICHE 2009	Israel	32	crude: 72% attributable: 50%
Nguyen, DMID 2010	USA	48	30-day: 42%
Mouloudi, ICHE 2010	Greece	19	In-hospital: MBL, 56%; KPC, 79%
Ben-David, CMI 2011	Israel	42	In-hospital: 69% Infect.-related: 48%
Zarkotou, CMI 2011	Greece	53	Overall: 53%
Qureshi, AAC 2012	USA	41	28-day crude: 39%
Tumbarello, CID 2012	Italy	125	Overall: 42%

Why are the resistant Gram negatives on the rise?

- Very efficient colonisers
  - Gut
  - Pharynx
  - Urinary tract
- Very high organism load
  - Facilitates spread
  - Environmental dissemination
- Colonisation cannot be eradicated
- ++SELECTION OUT BY ANTIBIOTIC USE



Impact of antimicrobial resistance in hospitals

- 1900 patients, 93 hospitals
  - Bloodstream infections, ventilator-associated pneumonia
- Adjusted for severity of illness, etc.
- Mortality vs. infection with sensitive organism

	OR
– MRSA	1.9
– Ceftazidime-resistant *Pseudomonas sp.*	3.1
– Quinolone-resistant *Enterobacter sp.*	2.3

Suetens, SHEA 1999 Annual Meeting

Financial Cost of Resistance

- Need to use more expensive agents
  - Often multiple agents
  - Often more toxic agents
- Double rate of hospitalisation*
  - Increased length of stay
- Outbreak control
- Diagnostic costs
- Loss of productivity
- Cost of death?
  - US$1-3 million per premature death

Holmberg et al 1987, *Rev Infect Dis* 9: 1065-78

Financial Cost of Resistance

- Antibiotics=scarce resource
  - Consumption (current use) decreases effectiveness (future value)
- Net economic impact of resistance
  - Attributable cost of treating resistant infections minus cost of preventing resistant infections

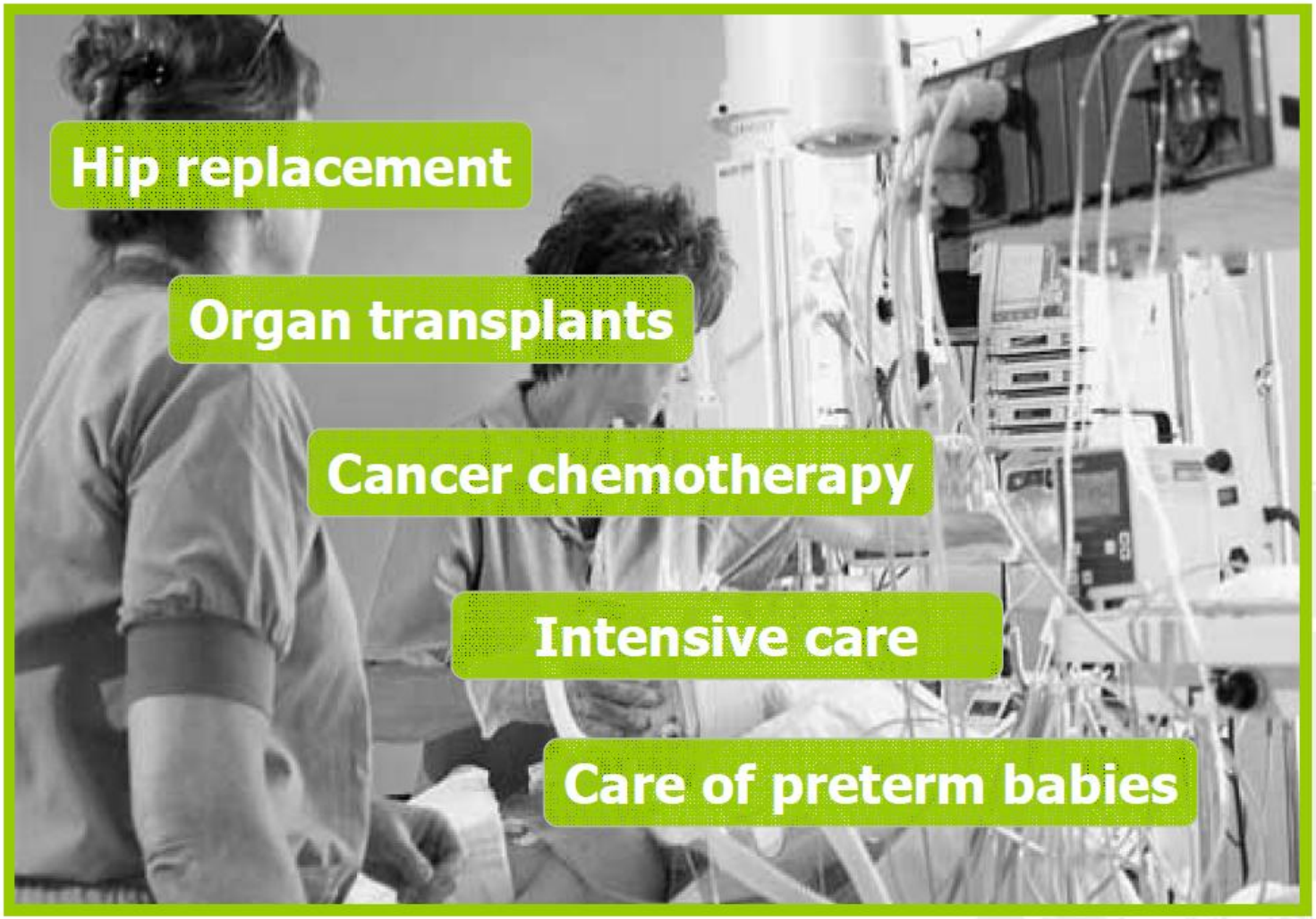
McGowan 2001, *Emerg Infect Dis* 7: 286-92

Unrecognised Cost of Resistance

- Antibiotic use in one patient imposes costs on other patients
- Local persistence of resistant organisms
  - Cost of over-use this year=sum of all future costs of dealing with resistant organisms
- Excess cost of US$5-50 per individual dose
  - Underestimate?
- US$150 million-$30 billion annually

Phelps 1989, *Med Care* 27: 194-203

Aspects of modern medicine not possible without antibiotics



Projected AMR-related global mortality in 2050

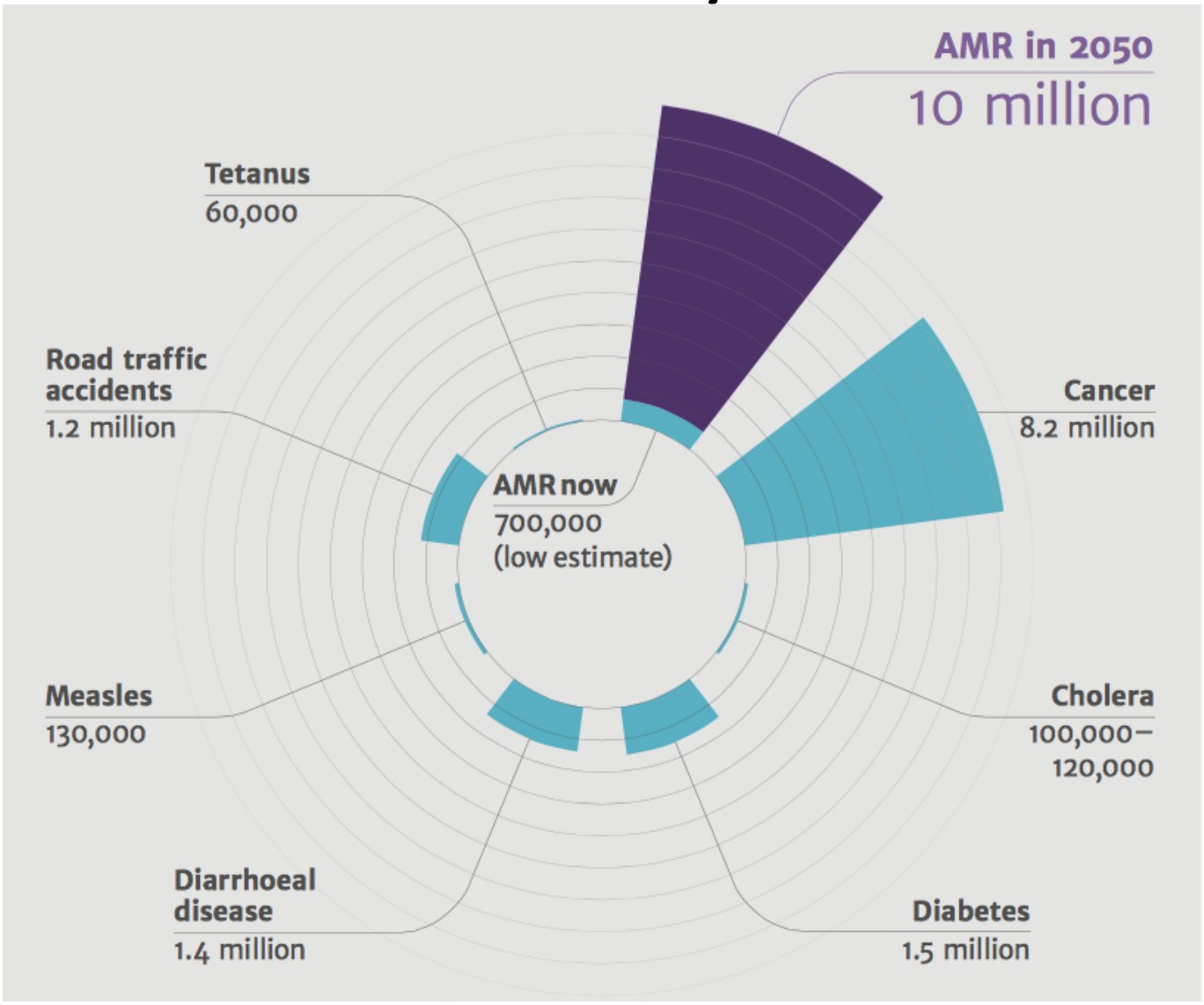


Image source: Review on Antimicrobial Resistance, HM Government UK, December 2014

Projected AMR-related global mortality in 2050

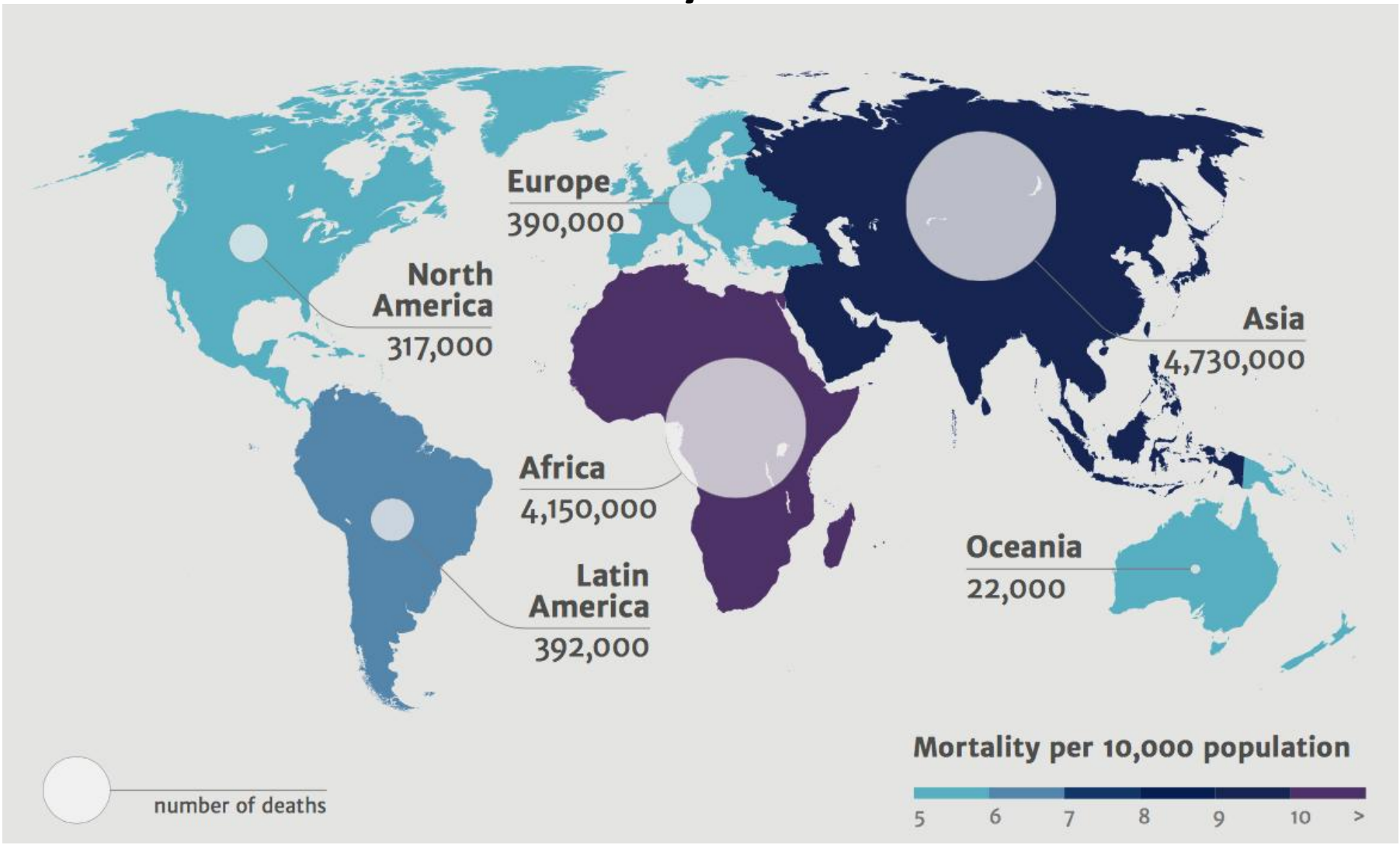
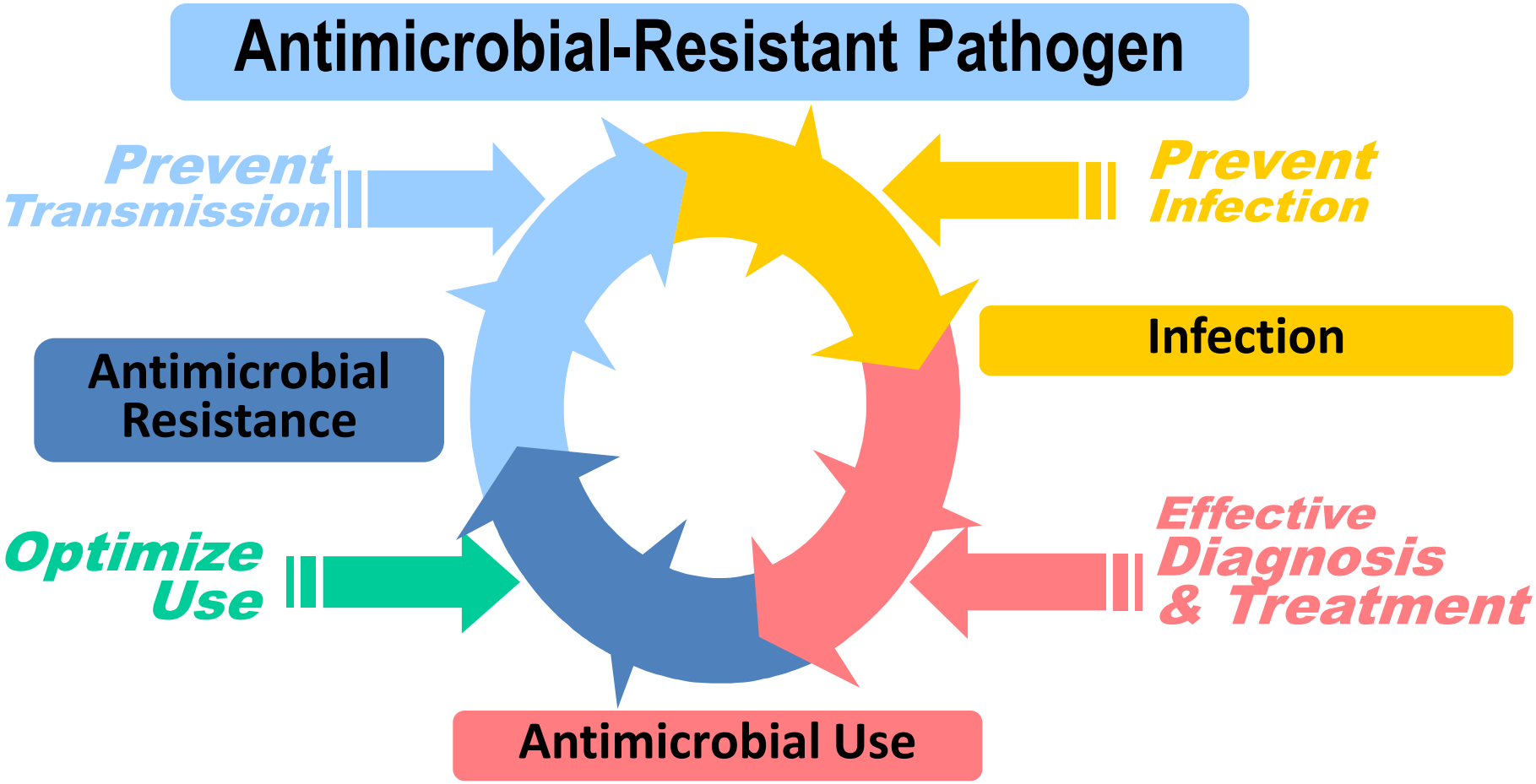


Image source: Review on Antimicrobial Resistance, HM Government UK, December 2014

Could we return to pre-antibiotic era?

- Well……..yes and no……
- Impact of AMR offset by health measures
  - Clean water
  - Vaccination
  - Safe food
  - Infection prevention and control
- But will not eliminate impact

What can we do?



Source: CDC

New vaccines?

- Group A Streptococcus
  - 26-valent vaccine, C5a peptidase, fibronectin binding proteins etc.
- Group B Streptococcus
  - Phase II trials of capsular conjugate vaccine
- *Staphylococcus aureus*
  - Type 5 and 8 CP with *P aeruginosa* exotoxin carrier
  - Iron-regulated surface determinant B (IsdB) vaccine
- Cross-protective Salmonella vaccines
- Universal influenza vaccine
- Th17-mediated protection against Gram-negative bacilli (including MDR strains)?

Improved diagnostics?

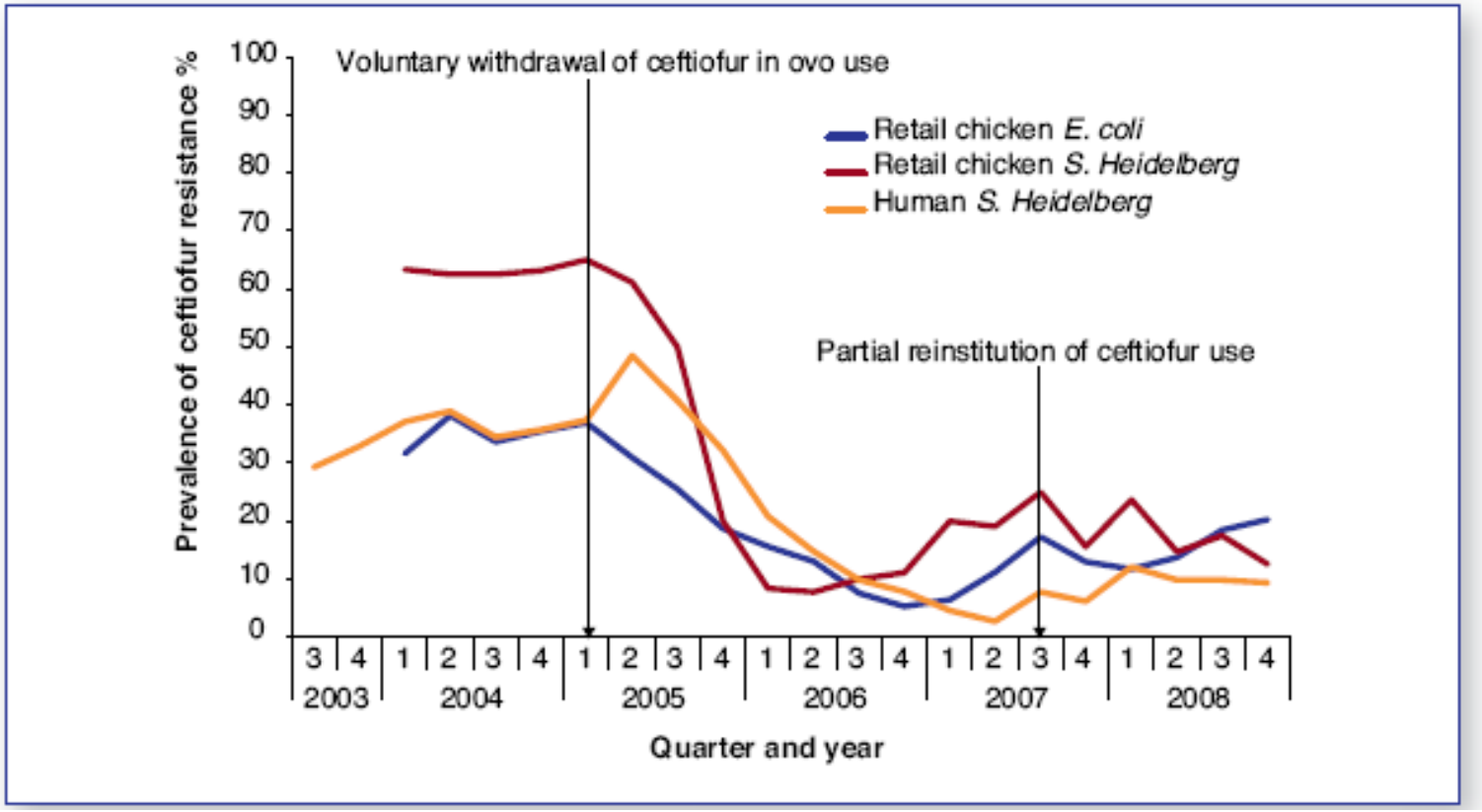
- Mass spectrometry
  - MALDI-TOF
  - PCR-ESI-MS
- Genome sequencing
- DNA arrays
- Inflammatory markers
- Disease-specific cytokine detection
- Near to patient testing

New therapies?

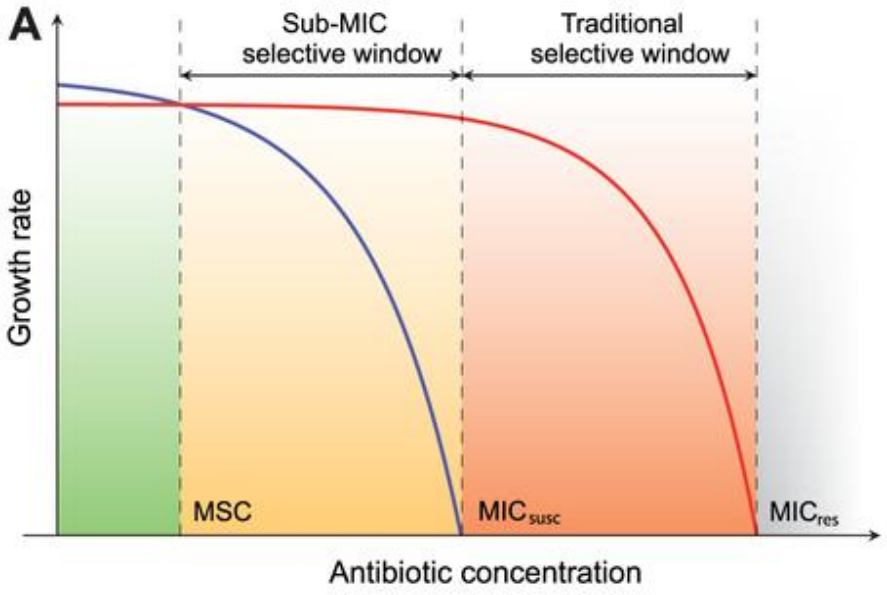
- New antibiotics
- Immune modulation
- Phage therapy
- Antimicrobial peptides
- Biotherapy/probioitcs
- Stimulating host response

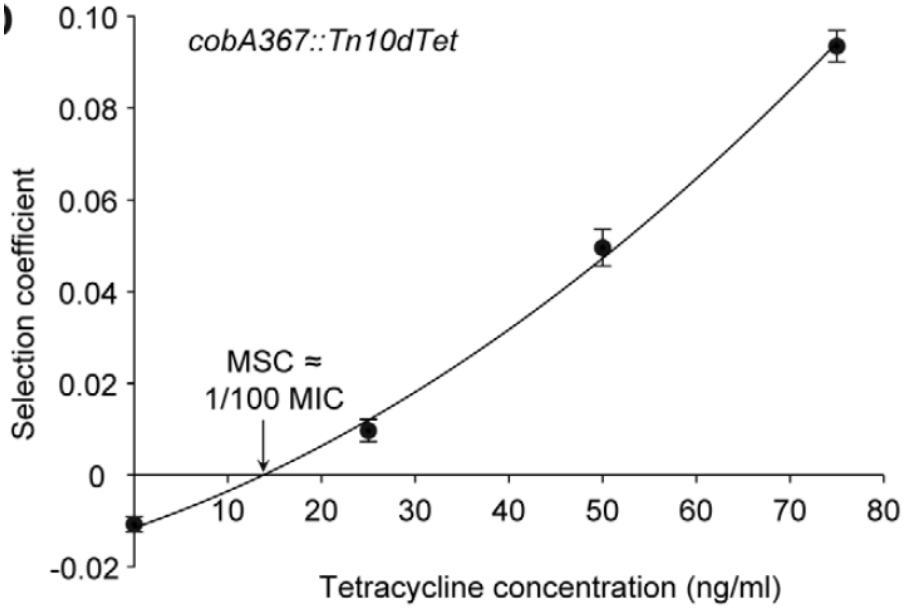
- Antimicrobial stewardship/restriction

Cephalosporin resistance after stopping its use in poultry, Quebec, Canada



Selection of resistant strains by sub-inhibitory concentrations of antibiotics





Gullberg E, Cao S, Berg OG, Ilbäck C, et al. (2011) PLoS Pathog 7(7): e1002158

Strengthen infection control?

- Improved hand hygiene compliance
- Reduce antimicrobial pollution
- Strengthen food chain hygiene
- Expand the role of source isolation in hospitals?
  - But need to counteract negative impact of isolation on patient care
- Environmental hygiene technology in hospitals?

Conclusion

- The “war” against AMR is an un-winnable one
  - At least not with the way we deploy the “weapons” currently at our disposal
- Best we can do is maintain a “truce”
  - Or at least buy time with currently available interventions until new treatments and technologies become available

“The future of humanity and microbes will likely evolve as episodes of our wits versus their genes”

Joshua Lederberg