Preparing for the black swans of resistance

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Disclosures

Consult / advisory – Achaogen, Adenium, Allecra, AstraZeneca, Basilea, BioVersys, Centauri, McKinsey, Meiji, Merck, Nordic, Roche, Shionogi, TAXIS, Tetraphase, VenatoRx, Wockhardt, Zambon, Zealand

Lectures – Astellas, AstraZeneca, Cardiome, Beckman-Coulter, Cepheid, Nordic, Merck/MSD, Pfizer

Sponsored research – Achaogen, AstraZeneca, Meiji, Melinta, Merck, Roche, Tetraphase, Wockhardt

Shareholdings – Dechra, GSK, Merck, Perkin Elmer, Pfizer amounting to <10% of portfolio value

And occasionally I'm asked to foretell the future

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Brokers & marketing divisions want to project sales, asking

- What % of *Klebsiella* will have carbapenemases in 2020?
- Will KPC go up as ESBLs did after 2003?
- 'Will KPC spread in Germany, France like in Italy?

UK Dept of Health Elicitation, 'roulette method' with 10 chips to spread on a probability scale in response to questions

- 'Do I think pan-resistant gram-negatives will emerge? Persist? Accumulate? By how much? In 5 or 20 years?

The easy response is to extrapolate past trends into the future

Grigore *et al. BMC Med Res Med* 2016;**16:**85; Carter *et al. Antibiotics* 2017, in press

Carbapenemase producing Enterobacteria referred to PHE

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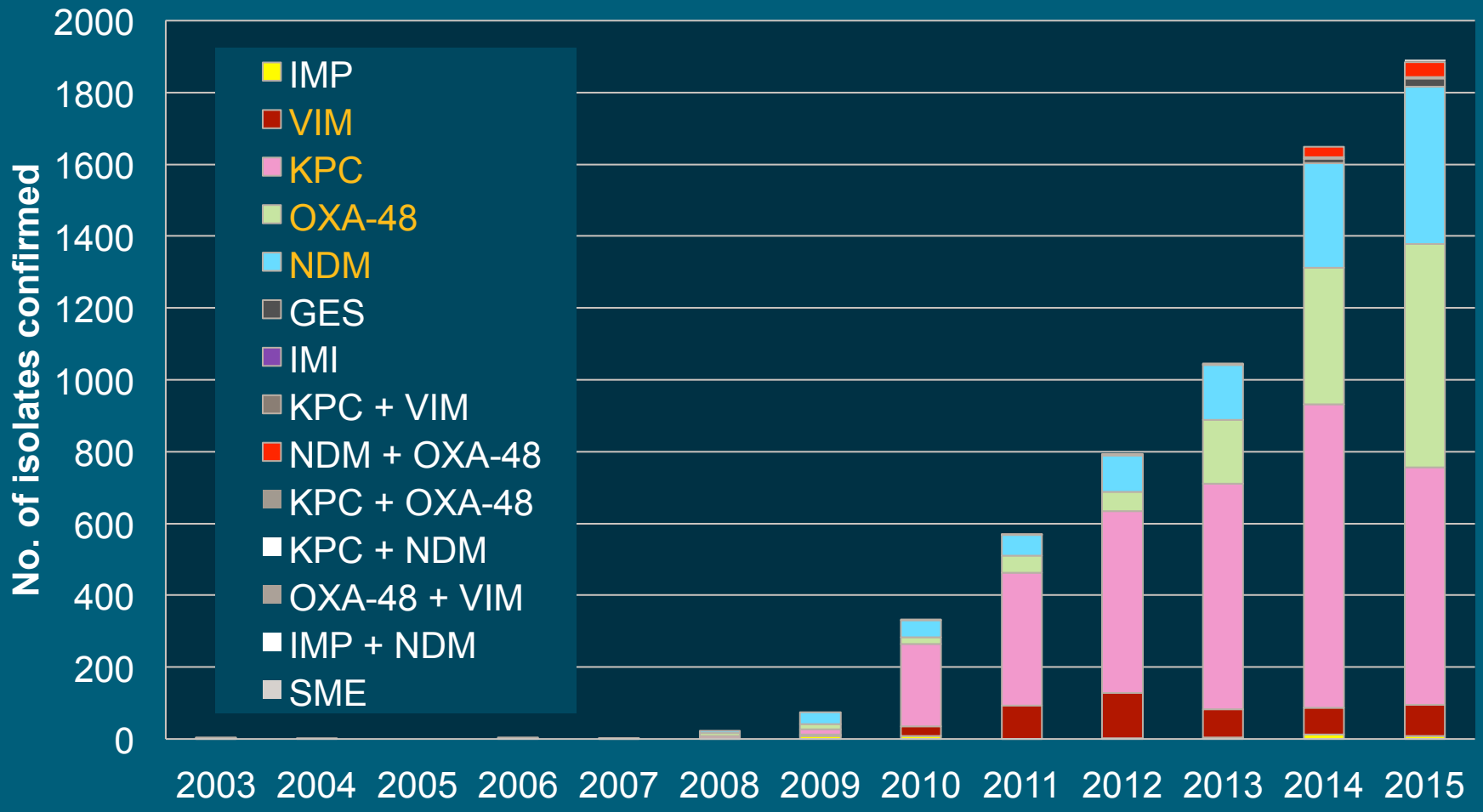

PHE data on file

Deaths due to antimicrobial resistance by 2050

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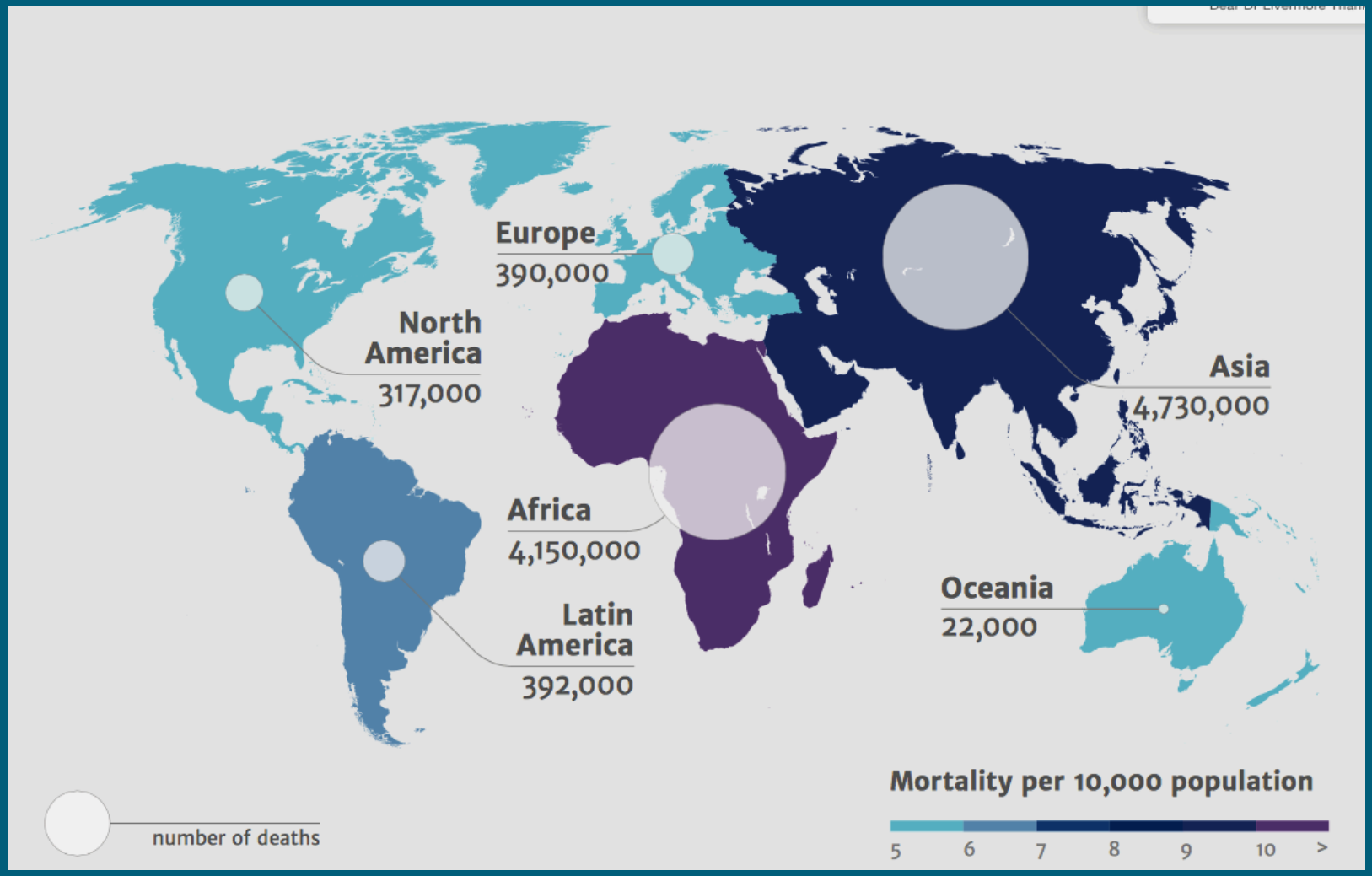

https://amr-review.org/

Black Swans

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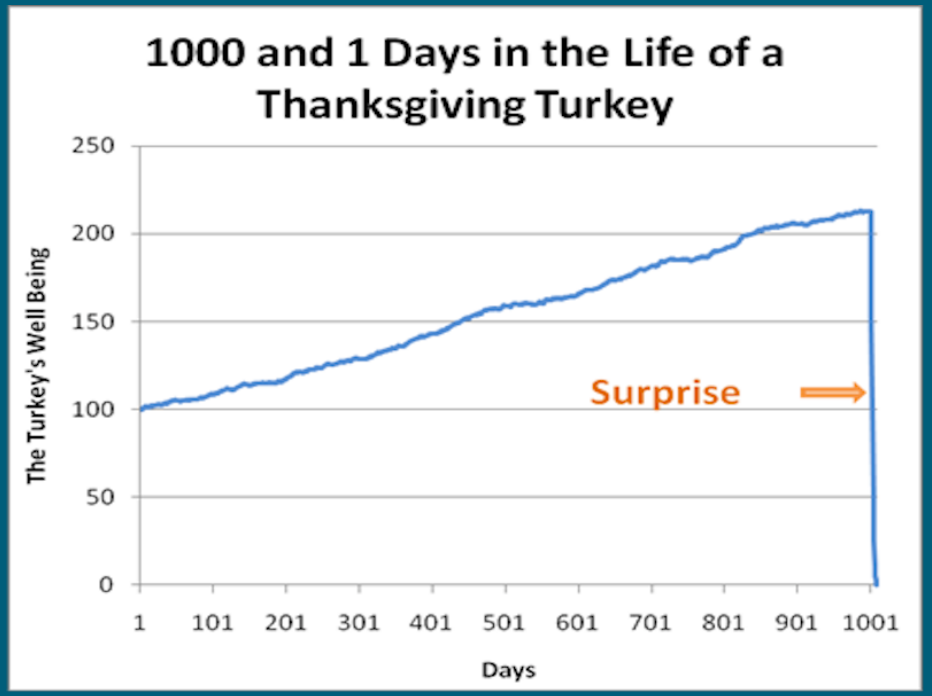
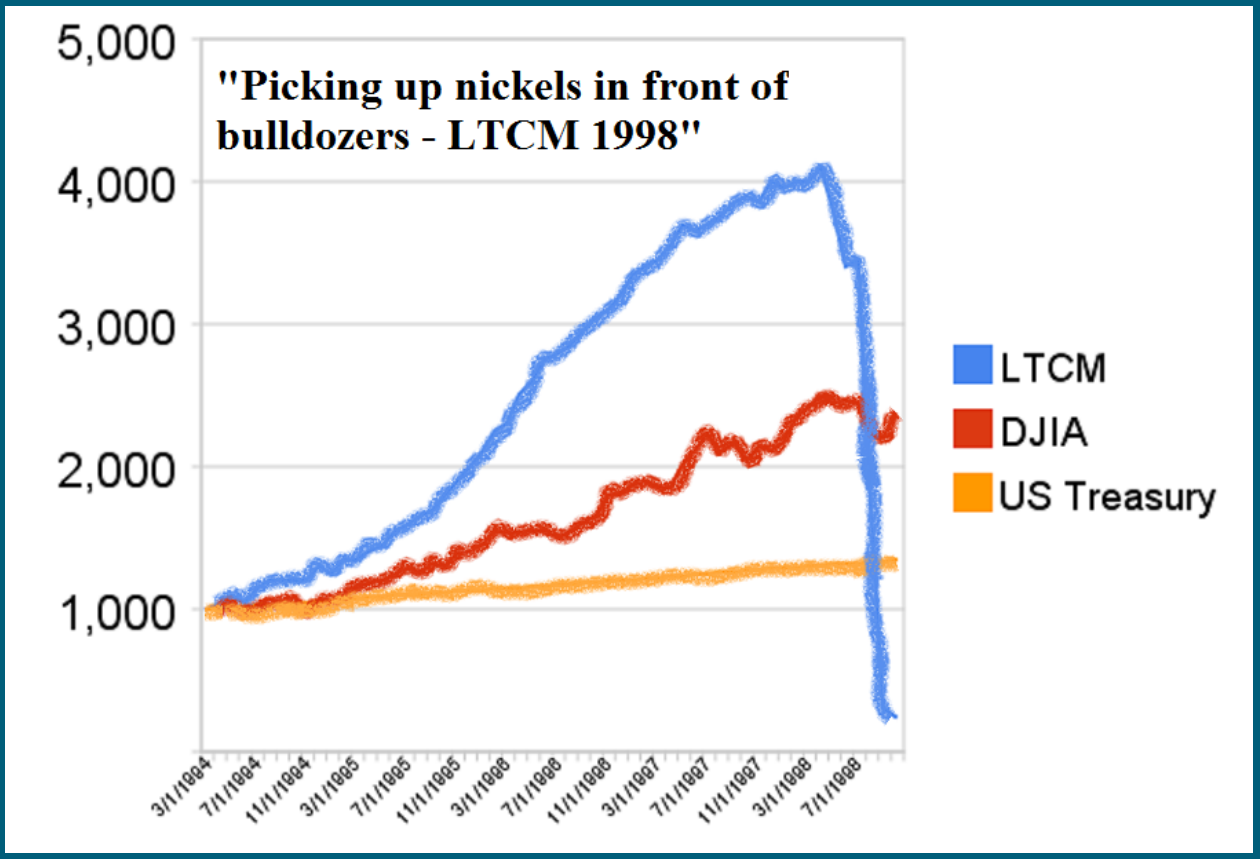


Long-Term Capital Management



2 Nobel laureates in economics on the board

Exploited pricing anomalies between long- & short-dated bonds

Anomalies are tiny, so need to borrow heavily & invest huge sums

Caught out when Asian financial crisis of 1998 fundamentally changed the relative pricing of long and short dated securities

Jesse Livermore, Bethlehem Steel, & the Lusitania Break, 1915

- 'War Speciality Stock'; steel & shipbuilding
- 7 Apr – Breaks $87 –previous high - nears $100 'trigger' point
- 8 Apr – Buys 500 at $98 to $99; price runs to $117
  - 13 Apr –$145, 'Had my stake'
  - Not going to make fortune on 500 shares'
  - Uses shares as collateral to buy more

- 7 May – Steel at $159… Germany U-boat torpedoes *Lusitania*
- 8 May - $130….. 'got me in the solar plexus'

LeFevre / Livermore, Reminiscences of a Stock Operator, 1923
Livermore, How to Trade Stocks, Duell, Sloan Pearce, 1940
Preston , Wilful Murder, Sinking of the Lusitania, Random House 2011

How bacterial evolution proceeds

- Periods of accumulation; **reflects use/infection control**
- Mutant selection; **predictable, reflects usage**
  - AmpC mutants in cephalosporin R_x of *Enterobacter* infection
  - Imipenem R_x of *P. aeruginosa* infection
- Escape of new genes to mobile DNA; **unpredictable**
  - Black swan events
  - Occasional massive shifts– if the 'new' mobile gene spread or associates with 'fit' clone(s)

Gene escapes that changed the rules

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Before		Reached	Source
1961	*mecA*	*S. aureus*	Rare *Staph* spp.
1965	bla_{TEM}	Enterobacteriaceae / other G-ves	???
	erm	Staph and Strep	*Streptomyces*
Various	*aac, aph, ant, ArmA*	All	*Streptomyces*
1986	VanA/VanB	Enterococci (Staph)	
1987	bla_{CTX-M}	Enterobacteriaceae	*Kluyvera*
1997	bla_{KPC}	Enterobacteriaceae / other G-ves	???
1990s	bla_{OXA-23}	*A. baumannii*	*A. radioresistens*
1999	bla_{OXA-48}	Enterobacteriaceae / other G-ves	*Shewenella*
2006	bla_{NDM}	Enterobacteriaceae / other G-ves	???
2011	*mcr1*	Enterobacteriaceae	*Moraxella*?

Partridge *FEMS Micro Revs*; 2011;**35:**820; Canton *CMI* 2009; **15:**20; Xavier *et al., EuroSurv* 2016;21; 7 July

Black swans that've bitten me

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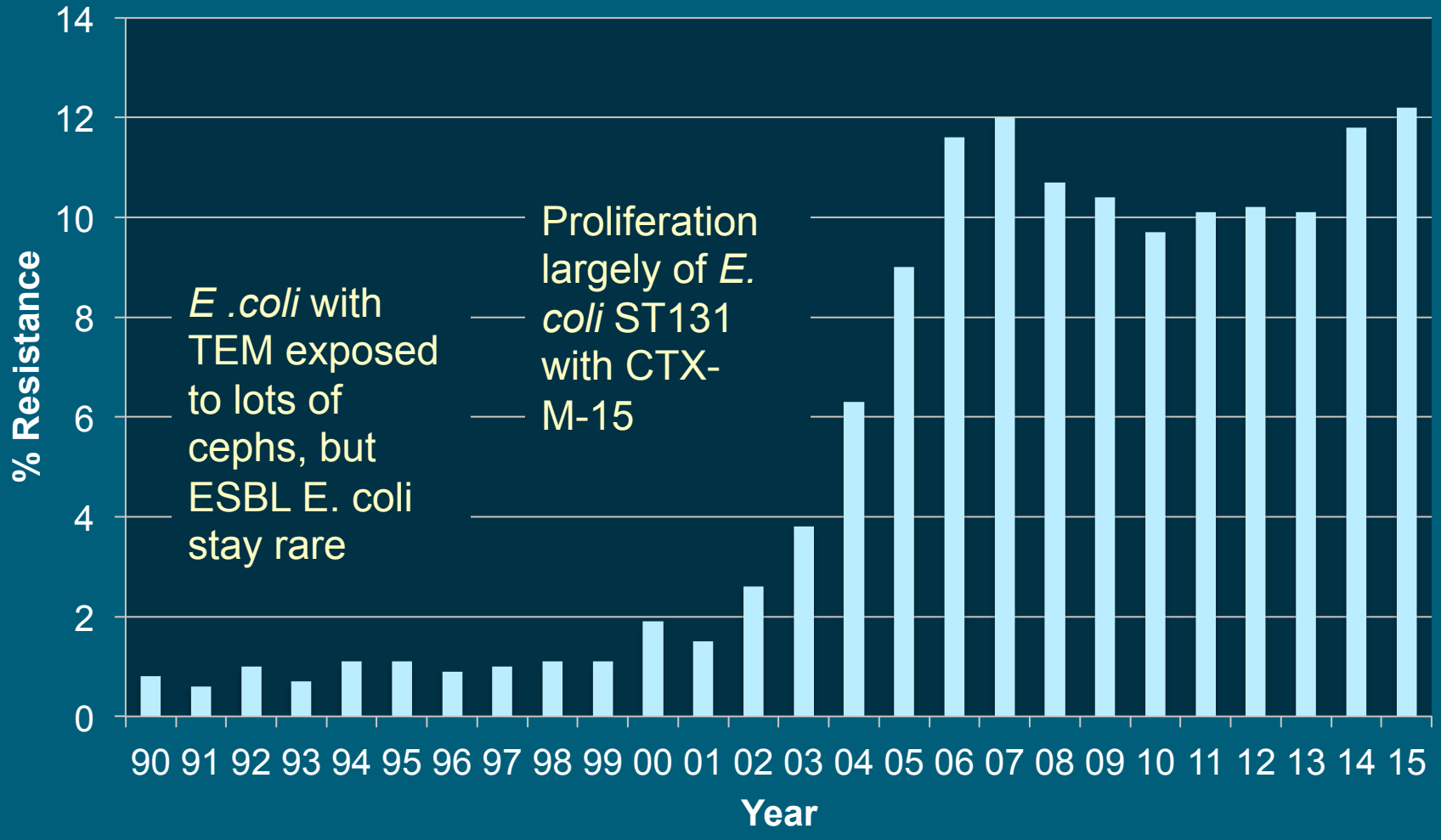
Early years teaching …
'Vancomycin attacks a substrate, not an enzyme,' so you won't get resistance

2 Post doc years, studying impermeability in *P. aeruginosa*, which turned out to be efflux

3-gen ceph resistance in bloodstream *E. coli*, PHE



Updated from Livermore *IJAA* 2012;**39**:283

We rationalise what did happen; but history could have unfolded differently

We know what resistance genes have escaped

- We don't know all those that haven't but could have done
  - Nor if they'll escape in future…

We know what DID happen, 1914-18 War

- Franz Ferdinand shot in Sarajevo; route through town had been changed after first assassination attempt, driver not told
  - Suppose driver had followed the correct route; what then?
- Churchill, Hitler fought on Western Front and survived
  - Suppose either hadn't; what then?

What can we expect next

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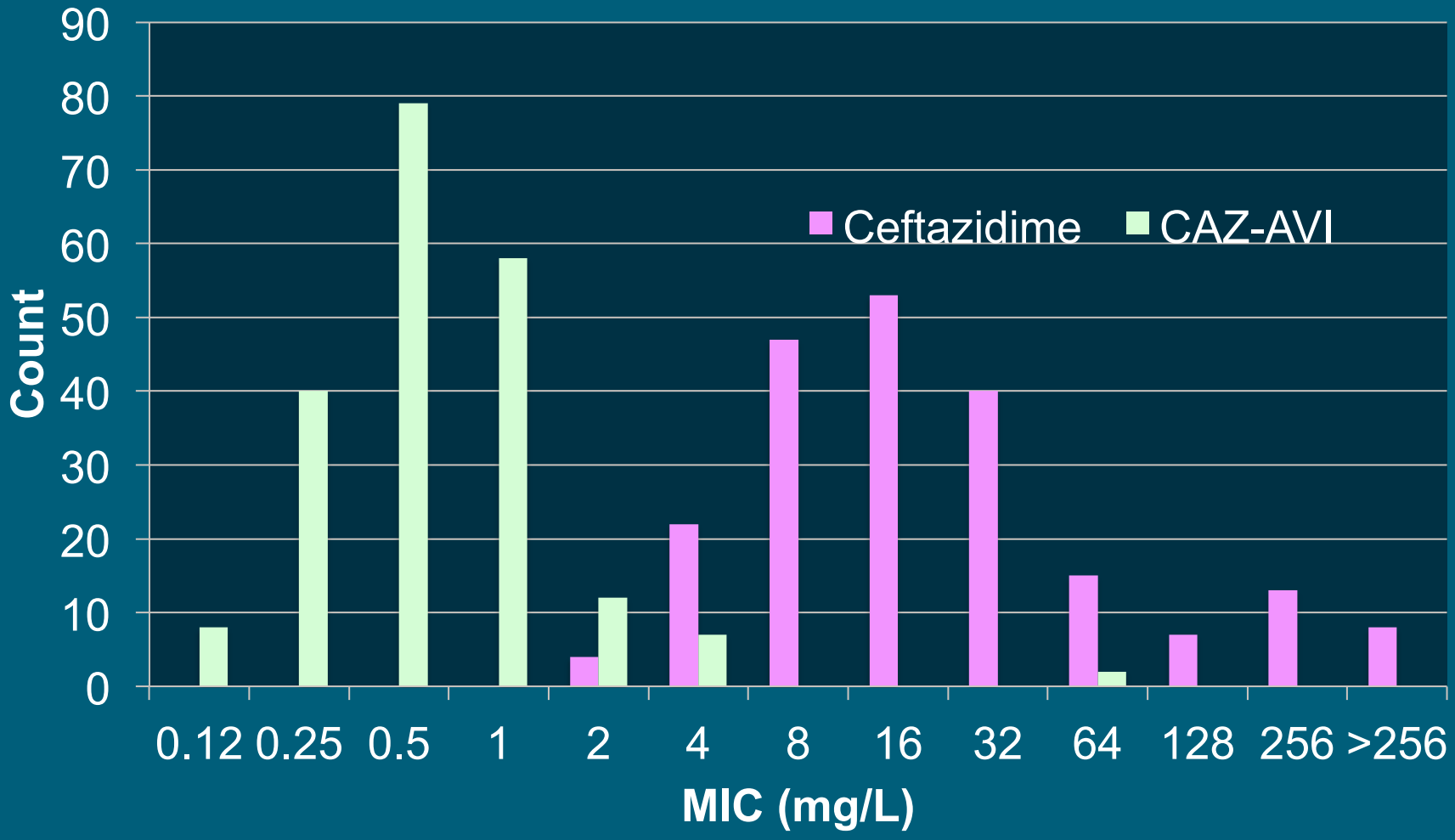
- Some existing resistance up-trends will continue
  - Especially if antibiotic use is heavy & infection control poor
- Stewardship and infection control will have successes
  - But infection control difficult if resistance has spread to community
  - Success of stewardship IN REDUCING RESISTANCE unpredictable
- Resistance mutations to new β-lactamase inhibitor combos

And new black swans will take flight

Ceftazidime-avibactam, 207 referred KPC Enterobacteriaceae, Year from July 2015



138 *Klebsiella*, 33 *E. coli*; 30 *Enterobacter/Citrobacter*; 6 others

MICs (mg/L) CAZ-AVI- *bla*$_{KPC}$ mutants: avibactam combinations

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Single & multi-step mutants (X+Y)	CAZ-AVI 4 mg/L		Ceftaroline –AVI 4 mg/L	
	Parent	Mutants	Parent	Mutants
Klebsiella				
NCTC13438 (29+2)	1	4-128	0.5	0.5-8
H…643 (24+6)	1	8-128	1	0.5-4
Enterobacter				
H…226 (28+5)	0.5	4-128	0.5	1-8
H…216 (7+0)	0.25	8-64	0.5	0.5-2

13/14 mutants sequenced had changes to *bla*$_{KPC}$, mostly around Ω loop

Livermore *et al*. AAC 2015;**59**:5324

Ceftazidime-avibactam vs. Carbapenem-R Enterobacteriaceae

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University of Pittsburgh, consecutive CAZ-AVI patients

- 37 carbapenem-R; 31 with KPC; 31 *Klebsiella*
- Various infections: 12 pneumonias, 10 bacteraemias
- Clinical cure = 67%
- 90-day survival = 62%
- Microbiological failure = 10 (27%)
- **3 KPC cases with resistance selected (MICs 64-128 mg/L)**

Carmeli *et al., LID* 2016;**16:**661; Shields *et al. CID* 2016 epub

AmpC changes selected in ceftolozane/tazo R_x

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	PA105A	PA147A	109-E9	110-G8	101-E5	103-H8
Ceftolozane-tazo	1	≥64	2	32	2	≥32
Ceftazidime	4	≥32	32	64	16	64
C'taz-avibactam	4	≥32	4	32	4	≥32
Piperacillin/tazo	16	64	64	16	64	32
Meropenem	8	8	8	4	8	16
Imipenem	≥32	1	16	2	16	4
Gentamicin	2	8	-	-	-	-
Ciprofloxacin	≥8	≥8	≥32	≥32	≥32	≥32
Colistin	1	1	-	-	-	-
Rx for	Wound, 6 weeks		RTI, 2 weeks		RTI, 10 days	
Change	Gly183Asp		Deletion 229-247		Glu247Lys	

MacVane *et al. AAC* 2017;**61:**e01183; Fraile-Ribot *et al., JAC* 2017 epub

Screening 480 soil *streptomycetes*

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	Resistant (n)	Tested for inactivation (n)	Able to inactivate (n)
Cephalexin	442	16	3
Ciprofloxacin	52	52	0
Clindamycin	107	46	0
Daptomycin	**480**	**80**	**64**
Erythromycin	128	128	9
Novobiocin	12	12	0
Rifampicin	49	49	20
Synercid	294	71	14
Telithromycin	**83**	**83**	**4**
Trimethoprim	478	80	0
Vancomycin	5	5	0

D'Costa *et al., Science* 2006; **131:**374

Glycosylation of telithromycin by a soil streptomycete

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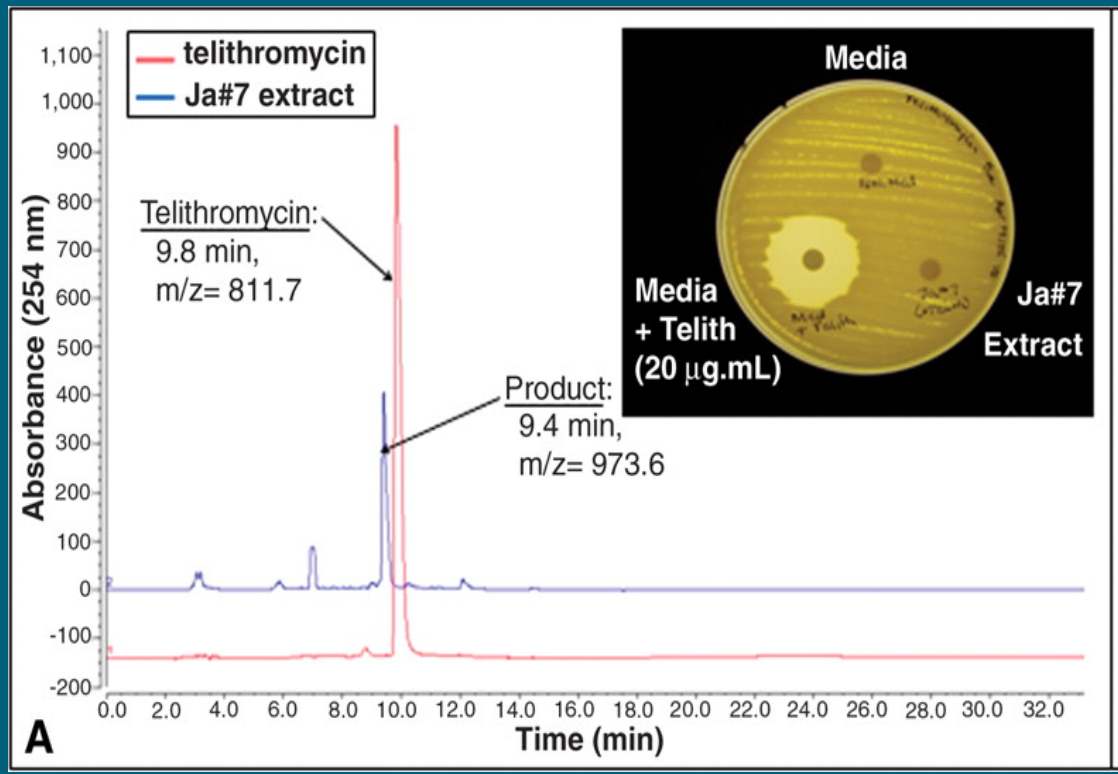

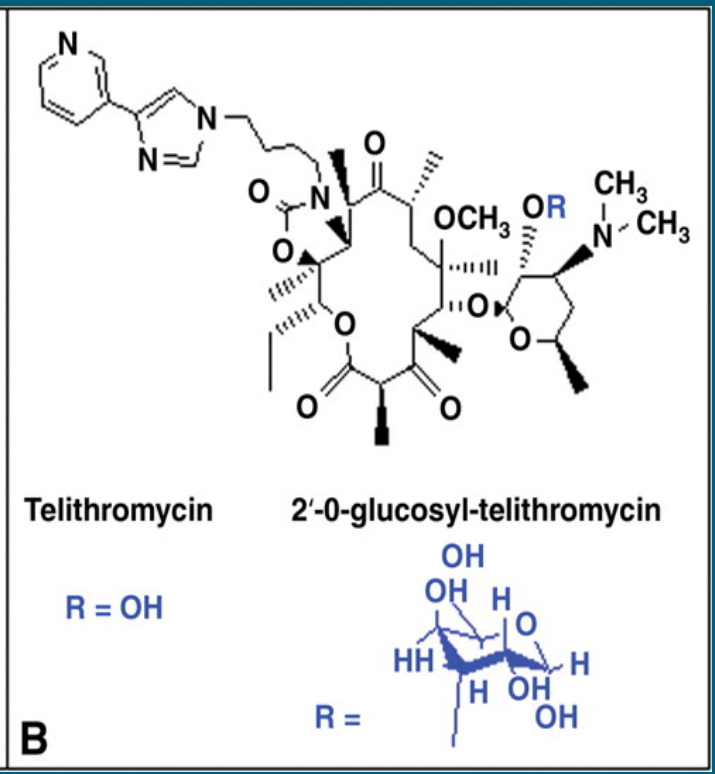

V M D'Costa *et al. Science* 2006;**311:**374

A critical' escape would be a carbapenemase that became 'comfortable' in a fit *E. coli* strain

… like CTX-M-15 ESBL in ST131

But suppose instead we get a plasmid-borne β-lactam-resistant PBP3

UK ref lab sees 1-3 *Klebsiella* per week like this

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	MIC (mg/L) or behaviour
Cefotaxime	2
Ceftazidime	32
Cefepime	64
Pip-tazo	>64
Ertapenem	>16
Imipenem/meropenem	16
Aztreonam	4
Ceph-clav synergy	No
Ceph-cloxacillin synergy	No
Carbapenem-EDTA synergy	No
Hodge bioassay with cephs or carbapenems	No activity seen

Genomic sequencing only found SHV-1 & porin loss

Convinced ourselves - efflux or permeability

Added ceftazidime-avibactam to panel… 16-fold synergy seen

Livermore *et al. JAC* 2017 epub

O'Neill Commission – key recommendations on resistance

- Public education
- More use of diagnostics
- Less use of antibiotics in agriculture
- 'Market entry rewards' for new antibiotics:
  - …..we need e.g. G20 to get together and reward developers of new antibiotics after approval for use……
  - …. c. $1 bn each given to the developers of successful new drugs, if not 'over-marketed' and yet available to patients who need them
- ……. Picking winners……

Paraphrased from https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf

Which ‘winner’ would you pick?

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In the 1980s would you have rewarded:

- Cefotaxime – 100-fold lower MICs than earlier cephs
- Ceftriaxone – like cefotaxime but more convenient
- Ceftazidime – added *P. aeruginosa* to ceph. spectrum
- Cefsulodin – narrow spectrum antipseudomonal
- Imipenem – AmpC/ESBL stable
- Aztreonam – MBL stable… unimportant then!

Best answers only clear in retrospect

……. & may change with time…

Which answer to the 'MBL threat' would you reward?

- MBL-stable monobactam + BLI
  - Aztreonam-avibactam
- MBL-labile β-lactam + triple action diazabicyclooctane
  - Cefepime-zidebactam; meropenem(?)-nacubactam
- MBL-labile β-lactam + boronate
  - Cefepime-VNRX-5133
- Broadly-β-lactamase (inc. MBL)- stable β-lactams
  - Cefiderocol, monobactam LYS228

And maybe MBLs don't cause resistance so effectively *in vivo?*

Chibabhai *et al., Infection* 2018; **46 :**1

In a world of change

- Spread risk
- Favour diversity
- Don’t think you’re clever enough to pick winners
  - Time and experience will choose them

Picking avibactam's partner: ceftazidime or cefepime?

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Ceftazidime favoured because:

- Licensed, familiar, used in more countries
- Lower MICs for *P. aeruginosa*
- Published concerns of cefepime efficacy
  - Later deemed misplaced

Yahav *et al., LID* 2007; **7:** 338
Kim *et al. CID* 2010; **51:**381

Was ceftazidime the right partner choice?

- Cefepime-AVI MICs 4-fold lower than CAZ-AVI
- KPC enzyme mutate to become better ceftazidimases
  - Confer CAZ-AVI resistance
  - Cefepime MICs tend to fall, not to rise
- AmpC can mutate in the lab, conferring CAZ-AVI-resistance
  - Cefepime is more stable to AmpC

Legace-Wiens *et al. AAC* 2010; **55:** 2434; Livermore *et al.* AAC 2015; **59:** 5324;
Livermore *et al., JAC* 2018, in press; MacVane *et al. AAC* 2017;**61:**e01183; Fraile-Ribot *et al., JAC* 2017 epub

'Was ceftazidime the right partner' = WRONG QUESTION

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- We are learning the threats to CAZ / AVI
  - We don't know cefepime/AVI's vulnerabilities…..
- The rise of MBLs prompted devt of aztreonam / AVI
  - But aztreonam/AVI is 3-4 years behind CAZ/AVI
  - Meantimes docs co-administering aztreonam plus CAZ/AVI

Wenzler *et al., DMID* 2017; **88:** 352
Jayol *et al., JAC* 2017 epub
Shaw *et al. JAC* 2017 epub

A better model for β-lactamase inhibitors?

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- Once we know an inhibitor works *in vivo* and is safe from one large trial with one partner….
- **Then**
  - Small trials with multiple partners targeted on infections due to bacteria with relevant β-lactamases
  - In 1980s, sulbactam licensed alone in Germany & France

Ceftazidime/avibactam in two Phase III trials

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Ceftazidime/ avibactam arm	cIAI	cUTI
Ceftazidime-S	289	311
Ceftazidime-R	47	75

& trial patients cost $100,000 each….

Mazuki *et al., CID* 2016; **62:** 1380
Wagenlehner *at al., CID* 2016; **63:** 754

Vancomycin & colistin

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- Vancomycin licensed 1955; colistin 1958
- Vancomycin for endocarditis: 6-patient trial
- Swiftly superseded by better / less toxic agents
- Kept available despite minimal market

Kirst *et al. AAC* 1998;**42:**1303

Vancomycin use, US, UK, France, Germany, Italy & Netherlands

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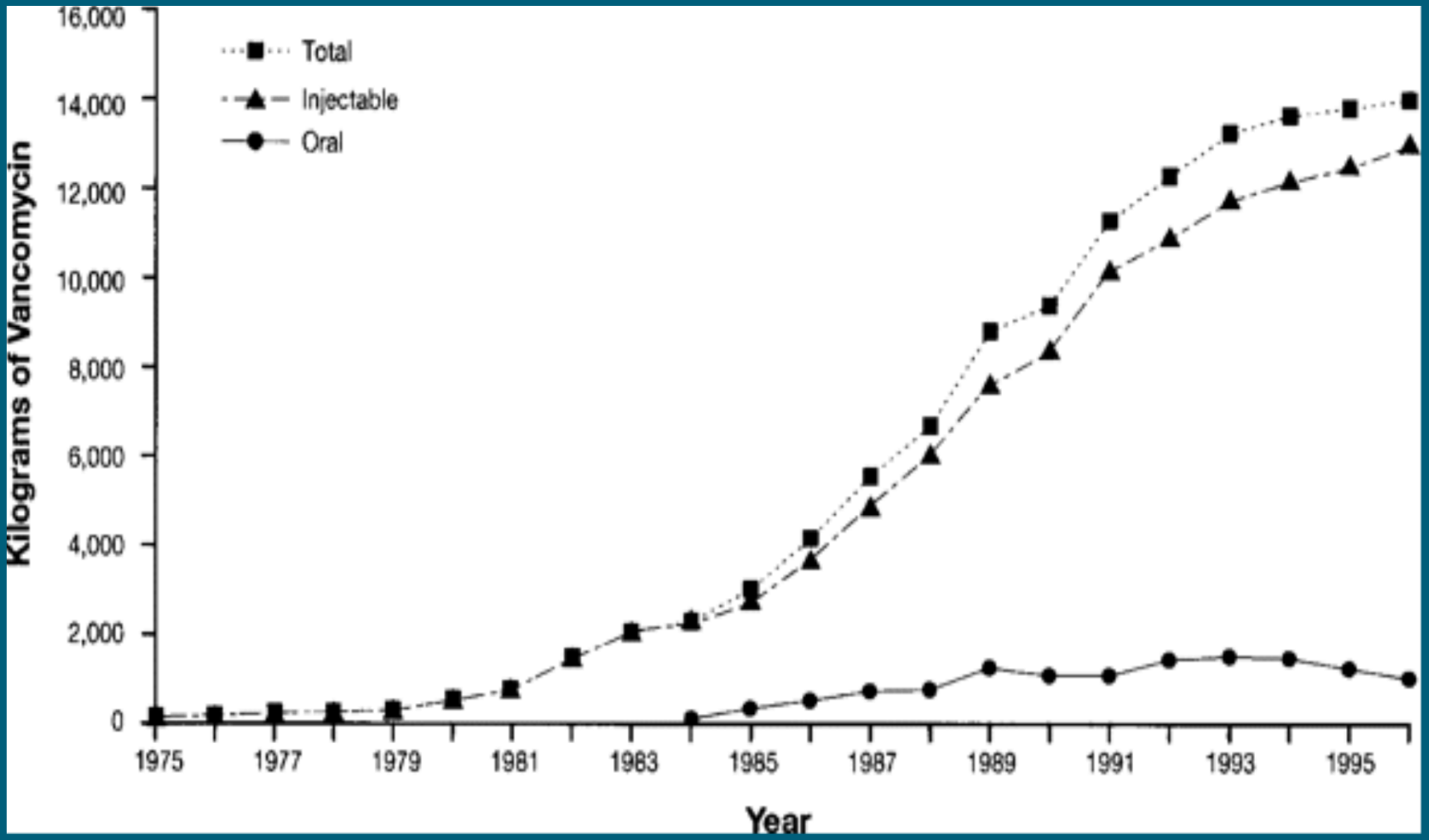

Kirst *et al. AAC* 1998;**42:**1303

Agents that go nowhere for years

- $1 bn Market entry rewards won't go down well
  - ‘Taxpayers funded never-used, toxic antibiotic’*
- ? Restricted license on limited trial data
- ? Longer patent
- ? Pay to keep available

**Daily Mail.* 1 April 2025

Arab proverb: *He who predicts the future lies, even if he tells the truth*

We know only that resistance will throw up new challenges

In a world of uncertainty, future robustness lies in diversity

- Don't think you're clever enough to reliably pick winners
- Encourage innovation with early stage funding, spread widely
- Adapt regulations to encourage multiple antibiotics to market
- Favour small informative clinical trials *vs*. resistant pathogens
- Restrictive licenses with long patents to encourage stewardship

Max Planck Inst for the Study of Societies Discussion Paper 16/6

Uncertainty and the Dangers of Monocultures in Regulation, Analysis, and Practice

Richard Bronk & Wade Jacoby

Uncertainty is endemic to innovative economies and complex societies, but policymakers underestimate how damaging this is for many of their guiding assumptions. In particular, the discourse of best practice, "global solutions for global problems," and regulatory harmonization becomes questionable when there is substantial uncertainty about the future. This uncertainty makes it impossible to know what best practice *will* be and increases the danger that harmonization will result in highly correlated errors and shared analytical blind spots. The transnational harmonization of regulation has well-known advantages, but – especially in technocratic policy areas – also creates vulnerability to unexpected challenges by constraining how we *think* as well as homogenizing how we *act*. Faced with uncertainty, policymakers should be wary of monocultures in regulation, analysis, and practice, and instead focus on *managing* policy diversity to limit its costs.

http://www.mpi-fg-koeln.mpg.de/pu/mpifg_dp/dp16-6.pdf