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

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

Carbapenemase producing Enterobacteria referred to PHE

PHE data on file
Deaths due to antimicrobial resistance by 2050

- North America: 317,000
- Europe: 390,000
- Africa: 4,150,000
- Latin America: 392,000
- Asia: 4,730,000
- Oceania: 22,000

https://amr-review.org/
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

<table>
<thead>
<tr>
<th>Before</th>
<th>Reached</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>1961</td>
<td><em>mecA</em></td>
<td>Rare <em>Staph</em> spp.</td>
</tr>
<tr>
<td>1965</td>
<td><em>bla</em>&lt;sub&gt;TEM&lt;/sub&gt;</td>
<td>??</td>
</tr>
<tr>
<td></td>
<td><em>erm</em></td>
<td>Staph and Strep</td>
</tr>
<tr>
<td>Various</td>
<td><em>aac, aph, ant, ArmA</em></td>
<td>All</td>
</tr>
<tr>
<td>1986</td>
<td>VanA/VanB</td>
<td>Enterococci (Staph)</td>
</tr>
<tr>
<td>1987</td>
<td><em>bla</em>&lt;sub&gt;CTX-M&lt;/sub&gt;</td>
<td><em>Kluyvera</em></td>
</tr>
<tr>
<td>1997</td>
<td><em>bla</em>&lt;sub&gt;KPC&lt;/sub&gt;</td>
<td>??</td>
</tr>
<tr>
<td>1990s</td>
<td><em>bla</em>&lt;sub&gt;OXA-23&lt;/sub&gt;</td>
<td><em>A. baumannii</em></td>
</tr>
<tr>
<td>1999</td>
<td><em>bla</em>&lt;sub&gt;OXA-48&lt;/sub&gt;</td>
<td><em>Shewenella</em></td>
</tr>
<tr>
<td>2006</td>
<td><em>bla</em>&lt;sub&gt;NDM&lt;/sub&gt;</td>
<td>??</td>
</tr>
<tr>
<td>2011</td>
<td><em>mcr1</em></td>
<td><em>Moraxella</em>?</td>
</tr>
</tbody>
</table>

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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

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

- *E. coli* with TEM exposed to lots of ceph, but ESBL *E. coli* stay rare
- Proliferation largely of *E. coli* ST131 with CTX-M-15

Updated from Livermore *IJA* 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

- 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

<table>
<thead>
<tr>
<th>Single &amp; multi-step mutants (X+Y)</th>
<th>CAZ-AVI 4 mg/L</th>
<th>Ceftaroline –AVI 4 mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Parent</td>
<td>Mutants</td>
</tr>
<tr>
<td><strong>Klebsiella</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCTC13438 (29+2)</td>
<td>1</td>
<td>4-128</td>
</tr>
<tr>
<td>H…643 (24+6)</td>
<td>1</td>
<td>8-128</td>
</tr>
<tr>
<td><strong>Enterobacter</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H…226 (28+5)</td>
<td>0.5</td>
<td>4-128</td>
</tr>
<tr>
<td>H…216 (7+0)</td>
<td>0.25</td>
<td>8-64</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th></th>
<th>PA105A</th>
<th>PA147A</th>
<th>109-E9</th>
<th>110-G8</th>
<th>101-E5</th>
<th>103-H8</th>
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</thead>
<tbody>
<tr>
<td>Ceftolozane-tazo</td>
<td>1</td>
<td>&gt;64</td>
<td>2</td>
<td>32</td>
<td>2</td>
<td>&gt;32</td>
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<tr>
<td>Ceftazidime</td>
<td>4</td>
<td>&gt;32</td>
<td>32</td>
<td>64</td>
<td>16</td>
<td>64</td>
</tr>
<tr>
<td>C’tz-avibactam</td>
<td>4</td>
<td>&gt;32</td>
<td>4</td>
<td>32</td>
<td>4</td>
<td>&gt;32</td>
</tr>
<tr>
<td>Piperacillin/tazo</td>
<td>16</td>
<td>64</td>
<td>64</td>
<td>16</td>
<td>64</td>
<td>32</td>
</tr>
<tr>
<td>Meropenem</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>4</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Imipenem</td>
<td>&gt;32</td>
<td>1</td>
<td>16</td>
<td>2</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>2</td>
<td>8</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>≥8</td>
<td>≥8</td>
<td>≥32</td>
<td>≥32</td>
<td>≥32</td>
<td>≥32</td>
</tr>
<tr>
<td>Colistin</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Rx for</td>
<td>Wound, 6 weeks</td>
<td>RTI, 2 weeks</td>
<td>RTI, 10 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change</td>
<td>Gly183Asp</td>
<td>Deletion 229-247</td>
<td>Glu247Lys</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MacVane et al. AAC 2017;61:e01183; Fraile-Ribot et al., JAC 2017 epub
## Screening 480 soil streptomycetes

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Resistant (n)</th>
<th>Tested for inactivation (n)</th>
<th>Able to inactivate (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalexin</td>
<td>442</td>
<td>16</td>
<td>3</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>52</td>
<td>52</td>
<td>0</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>107</td>
<td>46</td>
<td>0</td>
</tr>
<tr>
<td><strong>Daptomycin</strong></td>
<td><strong>480</strong></td>
<td><strong>80</strong></td>
<td><strong>64</strong></td>
</tr>
<tr>
<td>Erythromycin</td>
<td>128</td>
<td>128</td>
<td>9</td>
</tr>
<tr>
<td>Novobiocin</td>
<td>12</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>49</td>
<td>49</td>
<td>20</td>
</tr>
<tr>
<td>Synercid</td>
<td>294</td>
<td>71</td>
<td>14</td>
</tr>
<tr>
<td><strong>Telithromycin</strong></td>
<td><strong>83</strong></td>
<td><strong>83</strong></td>
<td><strong>4</strong></td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>478</td>
<td>80</td>
<td>0</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>5</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

D’Costa et al., Science 2006; 131:374
Glycosylation of telithromycin by a soil streptomycete

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

<table>
<thead>
<tr>
<th></th>
<th>MIC (mg/L) or behaviour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefotaxime</td>
<td>2</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>32</td>
</tr>
<tr>
<td>Cefepime</td>
<td>64</td>
</tr>
<tr>
<td>Pip-tazo</td>
<td>&gt;64</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>&gt;16</td>
</tr>
<tr>
<td>Imipenem/meropenem</td>
<td>16</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>4</td>
</tr>
<tr>
<td>Ceph-clav synergy</td>
<td>No</td>
</tr>
<tr>
<td>Ceph-cloxacillin synergy</td>
<td>No</td>
</tr>
<tr>
<td>Carbapenem-EDTA synergy</td>
<td>No</td>
</tr>
<tr>
<td>Hodge bioassay with cephs or carbapenems</td>
<td>No activity seen</td>
</tr>
</tbody>
</table>

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?

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*?
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?

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

- 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 $\beta$-lactamase inhibitors?

- 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 $\beta$-lactamases
  - In 1980s, sulbactam licensed alone in Germany & France
Ceftazidime/avibactam in two Phase III trials

<table>
<thead>
<tr>
<th>Ceftazidime/avibactam arm</th>
<th>cIAI</th>
<th>cUTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftazidime-S</td>
<td>289</td>
<td>311</td>
</tr>
<tr>
<td>Ceftazidime-R</td>
<td>47</td>
<td>75</td>
</tr>
</tbody>
</table>

& trial patients cost $100,000 each...

Mazuki et al., CID 2016; 62: 1380
Wagenlehner at al., CID 2016; 63: 754
Vancomycin & colistin

- 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

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
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.