Preparing for the Black Swans of Resistance

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Running Head: Black Swans of resistance

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Abstract

The need for governments to encourage antibiotic development is widely agreed, with ‘Market Entry Rewards’ being suggested. Unless these are to be spread widely – which is unlikely given the $1 billion sums proposed– we should be wary, for this approach is likely to evolve into one of picking, or commissioning, a few ‘winners’ based on extrapolation of current resistance trends. The hazard to this is that, whilst the evolution of resistance has predictable components, notably mutation, it also has completely unpredictable ones, contingent upon “Black Swan” events. These include the ‘escape’ of ‘new’ resistance genes from environmental bacteria and the recruitment of these genes by promiscuous mobile elements and epidemic strains. Such events can change the resistance landscape rapidly and unexpectedly, as with the rise of *Escherichia coli* ST131 with CTX-M-ESBLs and the emergence of ‘impossible’ vancomycin-resistant enterococci. Given such unpredictability, we simply cannot say with any certainty, for example, which of four current approaches to combatting metallo-β-lactamases (MBLs) offers the best prospect of sustainable, prizeworthy, success. Only time will tell, though it is encouraging is that multiple potential approaches to overcoming these problematic enzymes are being pursued. Rather than seeking to pick winners, governments should aim to reduce development barriers, as with recent relaxation of trial regulations. In particular, once β-lactamase inhibitors have been successfully trialled with one partner, there is scope to facilitate licensing them for partnering with other established β-lactams, thereby insuring against new emerging resistance.

Introduction: growing resistance and declining antibiotic development

Recent years have seen a dramatic proliferation of gram-negative opportunistic pathogens resistant to multiple antibiotics, including carbapenems. In countries where these bacteria are most prevalent, notably India, it is common practice to administer colistin empirically to patients with severe infections.[1] Even in less-affected countries, carbapenems are increasingly being employed for empirical therapy, leaving little left in reserve. In the community, resistance has complicated the treatment of infections as diverse as cystitis,[2] typhoid,[3] gonorrhoea[4] and tuberculosis.[5] Simultaneously, the flow of new antibiotics has faltered for reasons that have been well rehearsed.[6] Two of these are paramount. First, there is the problem of finding drugs that can enter Gram-negative bacteria and evade efflux.[7,8] Secondly, regulatory requirements have grown over time, increasing the cost and complexity of clinical trials.[9,10] This latter change particularly impacts the ultimate revenue return from antibiotics, as they are only given briefly and their use is being increasingly restricted, limiting sales of new agents.[6,11] Not surprisingly, several major pharmaceutical companies have quit the field altogether, while others were lost to mergers and takeovers.

This combination of growing resistance and a dwindling pipeline threatens our future ability to treat infection, giving ample reason to fear for the future viability of intensive care and transplant medicine, and even to manage some long-controlled community infections.

Responding to the challenge

Infection control, which reduces the need to use antibiotics, with their contingent selection pressure, is vital to containing resistance. Stewardship is crucial too, though it is easier to describe bad stewardship than to define optimal usage diversity and treatment duration.[12] Many of us believe that stewardship must advance from its present model, predicated on resistance epidemiology and risk assessment, to individualised treatment informed by rapid diagnostics,[13,14] But the deployment of these diagnostics is slow and the current pace of microbiology remains little changed since the 1950s, typically taking two days to complete: one day to grow the bacteria and another to test resistance, with the patient being treated empirically in the interim. Mass spectroscopy has accelerated identification, but not susceptibility testing.

Against this background, new antibiotics will be needed, and the UK Government's O'Neill Review,[15] the WHO[16] and US Pew Trust[17] all argue that governments and international agencies should seek to encourage and reinvigorate work in the field. Two types of incentive are proposed and, to some degree, deployed: Push and Pull.[18,19] 'Push' provides early finance, typically small-scale, to support discovery and early development. The challenge is in then raising the capital to progress whatever discoveries are made. Pull incentives aim to reward the developers of valuable new agents, and potentially involve much larger sums. Most radically, it is proposed to give prizes. Thus, O'Neill,[15] argues for "market entry rewards" of *c.* $1 billion for the successful production of new antibiotics, to be funded from a percentage of G20 countries' existing healthcare spending". Such a policy, presently under discussion, requires a 'picking of winners' and, as e.g. with military

aircraft, seems liable, if adopted, to evolve into a commissioned development model.

Predicting the future

Picking winners requires prediction of the future. In science we habitually do this by extrapolating from past trends. When I am phoned by market forecasters, venture capitalists or stockbrokers, seeking my views on the future of resistance, the easiest response is to look at the growing tally of carbapenemase producers and to extend the line. Sometimes their questions are leading: 'Will *Klebsiella* with carbapenemases will spread like ESBL producers?' 'What about *Escherichia coli*?' 'Will carbapenemase-producing *Klebsiella* in the UK, France and Germany will reach the 30% seen in Italy?' 'When?' Here the easy answer is to recall that resistance accumulates more slowly in northern Europe than southern and to adjust time frames accordingly.

Modelling by governments and international agencies[15-17,20] is more sophisticated but still depends on extrapolating from past trends. O'Neill[15] goes so far as to predict resistance rates, along with contingent mortality and costs in 2050, a third of a century ahead, based on analyses by the accountancy and consulting firms, KPMG and RAND. I can now guarantee to see a slide with these projections at every resistance congress I attend.

Is the future predictable?

Is the long-term future so knowable? A simple game is to divide the past 210 years, from 1800, into decades and ask if the landscape of Europe at the end of each period was predictable at its start. For 1800 and 1810, with Napoleon's wars raging, the answer is unequivocally 'No', as also for 1910,

1930, 1940 and 1980. For other decades the answer is a qualified ‘Yes’, giving a predictable: unpredictable ratio of 15:6. These aren’t brilliant odds and, if one plays 33-year periods, and worldwide, they become much worse. Or consider financial markets, whose history is strewn with the ruin of those who assumed trends would persist. Long Term Capital Management is a recent classic:[21] a hedge fund whose principals included two Nobel Laureates. Its rationale was that brief recurrent pricing anomalies between long- and short- maturity bonds could be identified by computer programs and then profitably ‘arbitraged.’ Effectively, the fund bought whichever bond maturity seemed under-priced and simultaneously short-sold whichever seemed over-priced, waited for the anomaly to unwind, then closed both positions and took the profit. Because these anomalies were tiny, investors’ funds had to be ‘geared’ by considerable borrowing. From 1994 to 1998, the approach succeeded, yielding 30-fold greater profits than simply holding US Treasury Bonds long term, but then failed catastrophically, losing $120 billion when the Asian financial crisis struck, changing the pricing of risk.

The point – famously highlighted by Nassim Taleb[22] – is that seemingly stable trends are more vulnerable than we suppose to sudden reversal owing to ‘Black Swan’ events, and, crucially, that history hinges on these Black Swans as much as on the periods of steady progress. ‘Black Swan’, in context, means an unexpected and impactful event. The Roman satirist Juvenal wrote of something being "*rara avis in terris nigroque simillima cygno*" ("A rare bird in these lands and very much like a black swan"), suggesting impossibility. Fourteen hundred years later, in sixteenth century London, ‘Black Swan’ was a byword for the implausible, as with ‘flying pigs’ nowadays. Then the early

European explorers of Australia found that their notion that 'All swans are white' was mistaken… The likelihood of any one Black Swan event is tiny but the number of possible Black Swans events is large. Thus, in any activity involving uncertainty, occasional bird-strikes –some of them heavy– become inevitable. Donald Rumsfeld was derided for talking of 'Unknown Unknowns',[23] but captures the point: long-term planning is most vulnerable to what we do not anticipate.

Black Swan events in the evolution of resistance

Antibiotic usage is undoubtedly the driver of accumulating resistance. But use does not *cause* the initial emergence of resistance. An antibiotic that 'caused' resistance would be a mutagen and would be denied a license. Rather, resistance originates by random processes – mutation and the acquisition of resistance genes mobilised from the chromosomes of other bacteria. We can predict mutation risk to some degree by *in vitro* experiments, and agents that readily select resistant mutants *in vitro* generally do so in patients too, meaning that they are best avoided as monotherapy.[24] Examples include fusidic acid and streptomycin for all species, oxyimino cephalosporins (e.g. cefotaxime, ceftazidime and ceftriaxone) for AmpC-inducible Enterobacteriaceae[25,26] and imipenem for *Pseudomonas aeruginosa*.[27] More generally, it is 'brave' (meaning 'high risk'.) to develop any agent where the mutation frequency against multiple target pathogens exceeds 10^{-8}, even if *in vitro* studies suggest that the mutants are 'unfit'.[28] It is possible, along these lines, to foresee threats to recently-licensed anti-gram-negative agents. Ceftazidime/avibactam is vulnerable to KPC mutants with increased affinity for ceftazidime. Such mutants can easily be obtained *in vitro*[29] and were selected

in 3/31 KPC *K. pneumoniae* patients treated with ceftazidime/avibactam in Pittsburgh.[30] For ceftolozane/tazobactam there are reports of *in vivo* selection of *Pseudomonas aeruginosa* mutants with sequence mutations AmpC also conferring ceftazidime/avibactam resistance.[31,32]

No such simple predictor can be applied to gene escapes, for we have no way of knowing what gene will escape, when it will do so, nor which organisms it will reach. Such escapes are Black Swan events, and Table 1 lists important past examples and sources.[33-35] Note that we remain ignorant of the origins of many now widely dispersed and impactful genes, including *bla*$_{TEM}$. Our ignorance also extends to predicting how extensively an escaped gene will spread. *bla*$_{TEM-1}$ has been vastly more successful than *bla*$_{TEM-2}$, though both have been in circulation for similarly long periods[36] and may be post-escape mutants of one another. It is likely that *bla*$_{TEM-1}$'s success is because it is carried by *Tn*3, which spreads efficiently among plasmids.[37,38] If so, its recruitment by this transposon was another Black Swan event, not (yet) replicated by *bla*$_{TEM-2}$.

Then there is the issue of which bacterial strains acquire escaped genes and whether these have epidemic potential. It is useful here to consider the trajectory of oxyimino cephalosporin resistance in *Escherichia coli*, illustrated in Figure 1.[39] During the 1990s this rate remained trivial, at 1-2% in the UK, despite selective oxyimino-cephalosporins being heavily used.[40] At the start of the 1990s *c.* 50% of *E. coli* isolates carried *bla*$_{TEM-1}$,[41] so it would have been reasonable to expect a steady cephalosporin-driven accumulation of isolates with *bla*$_{TEM-ESBL}$ variants in the gut flora. Yet, this did not occur and the cephalosporin resistance rate for *E. coli* was no higher in 2000 than in 1990.

This rate only rose after 2002, with the conjunction of two Black Swan events: first the escape of *bla*$_{CTX-M}$ genes from the chromosomes of *Kluyvera* spp. to (principally) IncFII plasmids[42] and, secondly, the acquisition of these plasmids by fluoroquinolone-resistant variants of *E. coli* ST131, a lineage with epidemic potential.[43] ST131 isolates with CTX-M ESBLs now account for the majority of ESBL *E. coli* infections.[43,44] Nothing before 2000 predicted the changes seen after 2002 and no one, looking the 2002-6 trajectory alone, would suppose it was preceded by a long period when another type of ESBL failed to accumulate.

There is a further trap. We look back on the past, knowing what did happen and seek to rationalise it, creating a prism where the events that occurred begin to look inevitable. The trigger for the First World War was Gabriel Principe's slaying of the Austrian Crown Prince and his wife on June 28th 1914, initiating a cascade of events leading to the start of a general war in early August.[45] It is easy to follow the grim logic of the chain reaction and to forget that the trigger was a Black Swan event. Principe could only shoot the Prince because the latter's motorcade took a wrong turning and, realising the mistake, stopped next to him, giving a bad shot an easy target. Had this not happened, the powder trail would have remained unlit, though it might have been ignited by another event, or maybe not.

Similarly with resistance. We know what genes have escaped and proliferated; considerable molecular research is undertaken to explain *how* they escaped and proliferated. But we do not know what other genes might have escaped but have not yet done so, nor if, and when, they will do so in the future. Consequently, it is naïve to model the future trajectory of

carbapenem resistance on present trends for OXA-48, KPC, VIM, IMP and NDM when, next year, the *blaB* carbapenemase gene of *Chryseobacterium meningosepticum* (say) may escape, perhaps achieving the same differential in success that $bla_{\text{CTX-M}}$ achieved relative to $bla_{\text{TEM-ESBL}}$. The fact that there are more genes that could escape is well illustrated by the work of D'Costa *et al*., who found soil streptomycetes – a common source of escaped genes (Table 1) – that could hydrolyse daptomycin or glycosylate telithromycin, compromising activity.[46,47]

What is more, we trap ourselves into thinking that the types of resistance that will escape in the future will resemble those that spread previously, when this need not be so. For 30 years we thought of aminoglycoside resistance as being due to aminoglycoside-modifying enzymes, and pharmaceutical companies remodelled aminoglycosides to evade acetylation, phosphorylation or nucleotidylation.[48] But then we discovered other escaped genes – *armA* and *rmt*– could methylate the ribosomal RNA to block the binding of all systemic three-ring aminoglycosides.[49]

Perhaps the most unexpected Black Swan event was the escape of the *VanHAXY* operon to *Tn*1546, putatively from *Paenibacillus* spp.[50,51] This provided a complete system to replace normal peptidoglycan precursors, conferring vancomycin resistance in the enterococci that acquired the transposon. This should be a salutary lesson, illustrating that what is possible in resistance extends beyond what seems reasonably predictable. In the early years of my career I taught – as did many others – that 'Vancomycin resistance is impossible because it binds to a fundamental cell wall substrate, conserved across bacteria….' Quite wrong, as it turned out.

Future Black Swan events may take a similarly unexpected form. Instead of a new MBL escaping from *C. meningosepticum* (say), envisage instead a plasmid-borne β-lactam-resistant PBP3 spreading among Gram-negative bacteria. This would be akin to *mecA*-mediated resistance in MRSA.[52] Crucially, it would reduce susceptibility to almost all anti-Gram-negative β-lactams and inhibitor combinations; all that would wholly escape would be the few analogues that primarily target other PBPs – ampicillin, cephaloridine, imipenem and mecillinam.[53,54]

Put simply, the future of resistance, over the coming third of a century, is as unknowable to us as were the coming 33 years – up to the end of the Second World War – were to those late Edwardians who, looking back over a century of steady progress, confidently boarded *Titanic* in April 1912. As Lawrence Beesley, who survived that sinking, wrote:

"It seems to me that the disaster about to occur was the event that not only made the world rub its eyes and awake but woke it with a start, keeping it moving at a rapidly accelerating pace …." [55]

What can be done to prepare?

The fact that future Black Swan events are unknowable is not a counsel of despair. It does not mean that no preparations can be made. But it is a counsel of humility and does have a bearing on which preparations are appropriate. Crucially, it argues that we should admit ignorance and spread risk, rather than concentrate effort and rewards on a few anticipated 'winners'.

Suppose a system of G20 (or whatever) prizes had been in place in the 1980s during the last flurry of anti-Gram-negative development? Which β-lactam should have been rewarded? Cefotaxime, as first up, with 10-100-fold

lower MICs for Enterobacteriaceae than earlier cephalosporins? Ceftazidime, for including *Pseudomonas aeruginosa* in its spectrum of activity? Imipenem, for its ability to bypass cephalosporin-hydrolysing AmpC and ESBL enzymes? Aztreonam, for evading MBLs? Hindsight suggests answers that were not evident at the time. ESBLs – now seen as the main Achilles Heel of the cephalosporins – only became a significant issue late in the 1980s,[56] around 4 years after imipenem was launched and 7-8 years after cefotaxime. The first acquired MBL was not described until 1991,[57] and none was a major problem until NDM-1 from 2007/8.[58] An aztreonam-inhibitor combination (to protect against co-produced ESBLs) was only proposed in 2011.[59] What is important, surely, is not whether imipenem and aztreonam were prizeworthy in the 1980s. Rather, it is that they were ready and waiting when they were needed. Just as were vancomycin and colistin, many years after they were first launched…

Which brings us back to the present. Table 2 lists developmental β-lactams active against MBL producers.[60-67] These fall into four broad groups: (i) MBL-stable monobactams protected against co-produced ESBLs and AmpC β-lactamases with inhibitors (ii) MBL-labile β-lactams combined with triple-action diazabicyclooctanes; (iii) β-lactams combined with MBL-inhibiting boronates and (iv) MBL-stable β-lactams. All have *in vitro* activity against most MBL producers, but each carries limitations and/or uncertainties. Which should be rewarded? One? All? The first to market? The truth is that we do not know which approach is best even in the short term, let alone which will best avoid falling victim to future Black Swan events. Rather than trying to pick a winner among these approaches, we should be heartened that a diversity of options

290 are progressing, and should encourage this, for it increases our odds of
291 keeping ahead.

292 ## Encouraging diversity in development

293 How best to encourage this diversity in drug development? The answer must
294 lie in reducing cost and barriers to entry, for surely the G20 cannot commit to
295 offering $1 billion to every hopeful molecule that successfully passes clinical
296 trials? (Which is exactly the reason why the rewards model would likely evolve
297 into one of commissioned development of expected 'winners').

298 There are some encouraging developments. Historically, antibiotics required
299 two Phase III trials per indication, showing non-inferiority to a 'standard-of-
300 care' comparator.[68] Such trials model empirical usage and are
301 unrepresentative when, in most of the developed world, stewardship
302 reasonably demands that new agents are reserved for microbiologically-
303 directed treatment of infections caused by multiresistant pathogens. Anyone
304 doubting the wastage of this traditional antibiotic-development pathway should
305 consider ceftazidime/avibactam. Some 81-86% of the patients included in the
306 two pivotal Phase III studies so far published had ceftazidime-susceptible
307 pathogens.[69,70] For these individuals, whose recruitment cost its sponsor
308 roughly $100,000 per patient, the trials assessed only the safety of avibactam,
309 not its efficacy against relevant β-lactamases (though this was convincingly
310 demonstrated elsewhere[71]). The deficiencies of this expensive and wasteful
311 approach are now being rectified to a degree: meropenem-vaborbactam was
312 licensed by the FDA on the basis of one sizeable Phase III complicated
313 urinary tract infection trial together with a resistant pathogens trial,
314 representing multiple infection types. This approach should deliver relevant

information less expensively, thereby lowering barriers to entry. However, more radical approaches are needed, at least for β-lactamase inhibitors, which represent one of the main areas of current development. Early combinations – amoxicillin/clavulanate, ampicillin/sulbactam and piperacillin/tazobactam – were developed by 'penicillin companies' (Beecham and Lederle) to extend the utility their products.[72] Meanwhile, other companies developed 'β-lactamase-stable' cephalosporins. Both approaches achieved early success, which was eroded over time because (i) the penicillins, being highly labile, were hard to protect against strains with large amounts of enzyme, (ii) AmpC enzymes evaded these early inhibitors and (iii) ESBL-mediated resistance undermined 'β–lactamase-stable' cephalosporins. One answer – to combine an inhibitor of Class A enzymes with the most-AmpC-stable cephalosporin (cefepime) – was obvious[72], but was impossible in practice because different companies, not interested in collaborating, held the relevant patents. Cefepime/tazobactam combinations came to be marketed in India, where trial requirements are less stringent and patent law weak, but, contained only small amounts of tazobactam (typically 125 mg per 1g of cefepime) and are probably suboptimal.. Only now, facilitated by the US GAIN (Generating Antibiotic Initiatives Now) Act is high dose (2+2g q8h) cefepime/tazobactam under development, two decades after it was first suggested.[73,74]

In the case of avibactam – the broadest spectrum inhibitor now available – the decision to partner with ceftazidime was predicated on seeking an antipseudomonal cephalosporin and on the only viable alternative, cefepime, being established in fewer markets and, at the time of the decision, subject to

claims – later refuted – of poor efficacy and excess mortality[75,76] Aztreonam/avibactam entered development later, predicated on also covering MBL producers (Table 2).[59]

Now, with mutational resistance to ceftazidime/avibactam emerging among isolates with KPC carbapenemase[29,30] and aztreonam/avibactam lagging 3 years behind, it is appropriate to reflect these decisions. The mutational ceftazidime/avibactam resistance entails the KPC enzyme becoming a 'better' ceftazidimase[77] and has less effect on other cephalosporin/avibactam combinations. Might cefepime/avibactam therefore have been a better idea than ceftazidime/avibactam? Or would it just have selected different mutants? Since the mutations conferring ceftazidime/avibactam resistance reduce meropenem resistance (see above), a potential answer is to co-administer meropenem with ceftazidime/avibactam to block this line of evolution.[29,78] Meanwhile, with metallo-carbapenemase producers increasing and aztreonam/avibactam being unavailable, some doctors are adopting a 'home brew' approach to treat infections due to MBL producers, co-administering ceftazidime/avibactam with aztreonam - with anecdotal reports of success.[79,80]. Both these strategies – adding meropenem to ceftazidime/azibactam for infections due to strains with KPC enzymes and adding aztreonam to ceftazidime/avibactam for those due to MBL producers are cumbersome ways to partnering avibactam with alternative b-lactams to ceftazidime, which becomes superfluous in the regimen.

Might not it be better for regulators to require full trials of treatment with a combination of a new inhibitor with one β–lactam with then, if these are successful, to grant restricted licenses for combinations of that inhibitor with

365 other licensed β–lactams, based on pharmacodynamic modelling and small
366 trials demonstrating efficacy against pathogens with relevant resistances?
367 This would increase flexibility to contend both with current problems and
368 future Black Swan events. If, for example, the postulated plasmid-borne β-
369 lactam-resistant PBP3 were to spread, imipenem-inhibitor combinations would
370 become more attractive compared with combinations involving PBP3-
371 targetted (i.e. most) β-lactams.
372 In order to prepare for a future certain to contain new Black Swan events, we
373 also should reflect on vancomycin and colistin. Both were launched in the late
374 1950s on trials that would be considered wholly unacceptable today.
375 Vancomycin was licensed for staphylococcal endocarditis on the strength of a
376 single study involving six patients, complemented by several cases of
377 compassionate use, together with contention that, with penicillin lost to
378 resistance, no other agent was effective. Both vancomycin and colistin were
379 swiftly overtaken by other new agents perceived as less toxic or more
380 efficacious - methicillin in vancomycin's case and aminoglycosides and β-
381 lactams in colistin's. For 20 years vancomycin use was minimal.[81] Then, with
382 the rise of MRSA in the 1980s, it found its niche, becoming the mainstay of
383 treatment. Colistin's time came later, early in the twenty-first century with the
384 rise in infections due to carbapenemase-producing Gram-negatives.[82] It is
385 hard to see how either drug would nowadays have been kept on the market
386 through their long fallow years but it is fortunate that they were. I do not know
387 the best answer here. Longer patents would increase the chance of ultimate
388 return on an agent that gained little immediate traction. However, this would
389 be of little value to a single-product biotech company and, unless restricted to

the immediate product, such patents might stifle development of better analogues. What is certain is that a strategy of 'picking winners' would not work either– any international body that gave $1 billion prizes to agents that had failed to find a role for 20 years, and which were perceived to be toxic, would swiftly be lambasted for wasting taxpayers' money.

Finally, there is the issue of the issue of non-antibiotic game changers. Just once in my career a bacterial pathogen posing concerns about resistance– type b *Haemophilus influenzae* [83]– had been essentially eliminated, in this case by a vaccine. Yet vaccines against tuberculosis, cystitis (and the ascending *E. coli* infections it sometimes precipitates), MRSA and gonorrhoea all remain tantalising possibilities, involving organisms where resistance presents real and present concerns.[84,85] Other non-antibiotic approaches (see e.g. Czaplewski *et al.* for a summary)[86] may succeed too, though almost all must be seen as being high risk. One could not call the success of one of these approaches a Black Swan event, for it would not arise quite unexpectedly, but it would have considerable scope to greatly alter projected numbers of infections and deaths due to antibiotic-resistant bacteria.

Conclusions.

Even with improvements in infection control, stewardship and diagnostics, resistance will present new challenges. Some, like the emergence of mutations conferring resistance to ceftazidime/avibactam and ceftolozane/tazobactam are predictable. Others, involving the escape of 'new' resistance genes, and the spread of these to epidemic strains are Black Swan events. We know that they will occur; but their future shape, nature and impact is unpredictable.

Claims of resistance impact by 2050 should be taken with a very large pinch of salt but, more than this, we should be wary of believing that we can predict what the future resistance landscape will look like, let alone use this for future 'market entry rewards'. Instead, the best 'anti-fragile' strategy to prepare for an uncertain future lies in diversity, in the hopes that at least one approach will prove effective not only against problem resistances now proliferating but also help safeguard against the next Black Swan event. Rather than having the G20, WHO or whoever, try to pick winners and claim the 'market is broken'; international efforts should concentrate on repairing the market, reducing developmental costs and barriers to entry, thereby pulling in new players and diverse innovation – regardless of whether this involve conventional small molecules or non-conventional approaches.

Steps such as the US GAIN Act are to be lauded, as it has encouraged development of cefepime/tazobactam and the US reappraisal of i.v. fosfomycin, as is the simplification of trial requirements illustrated by the development of meropenem-vaborbactam. Yet, more needs to be done, especially increasing the scope for new combinations of already-licensed β–lactams and β–lactamase inhibitors and to ensure that agents that find little immediate role become, and remain, available.

Transparency declaration

Advisory Boards or ad-hoc consultancy for Accelerate, Achaogen, Adenium, Allecra, AstraZeneca, Auspherix, Basilea, BioVersys, Centauri, Discuva, Integra Holdings, Meiji, Melinta, Nordic, Pfizer, Roche, Shionogi, T.A.Z., Tetraphase, The Medicines Company, VenatoRx, Wockhardt, Zambon, Zealand. Paid lectures – Astellas, AstraZeneca, bioMérieux, Beckmann

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709 **Table 1**. ‘Black Swan’ resistance gene escapes to mobile DNA

Genes/ gene families	Reached	Source	Antibiotics affected
mecA	S. aureus	*S. fleurettii*	β-Lactams
erm	Staphylococci and streptococci	*Streptomyces*	Macrolides, lincosamides, streptogramin B
aac, aph, ant, armA	All groups	*Streptomyces*	Aminoglycosides
vanA/vanB	Enterococci (and a few staphylococci)	*Paenibacillus* spp.	Glycopeptides
bla$_{\text{CTX-M}}$	Enterobacteriaceae	*Kluyvera*	β-Lactams, including oxyimino cephalosporins
bla$_{\text{OXA-23}}$	*A. baumannii*	*A. radioresistens*	β-Lactams including carbapenems
bla$_{\text{OXA-48}}$	Enterobacteriaceae and other Gram-negatives	*Shewanella*	β-Lactams including carbapenems

mcr-1	Enterobacteriaceae	*Moraxella*	Polymyxins
qnr	Enterobacteriaceae	*Shewanella*	Fluoroquinolones

710

711 Data are from references 33-35

Table 2. Developmental β-lactams and β-lactamase inhibitor combinations active against MBL producers

Compound	Class and developer	Principe	Apparent weaknesses and risks	Black Swan risks
Aztreonam/avibactam[59]	Monobactam/DBO; (Pfizer)	Aztreonam is stable to MBLs; avibactam protects against co-producer ESBLs and AmpC enzymes	Weak antipseudomonal activity; MICs up to 8 mg/L for some Enterobacteriaceae	Unknown
Cefepime/zidebactam[60]	Cephalosporin/DBO (Wockhardt)	Zidebactam has direct antibacterial activity and, although it does not inhibit MBLs, it achieves synergy with cefepime by an	High frequency of mutational resistance to zidebactam, though this does not compromise the enhancer effect.	Unknown

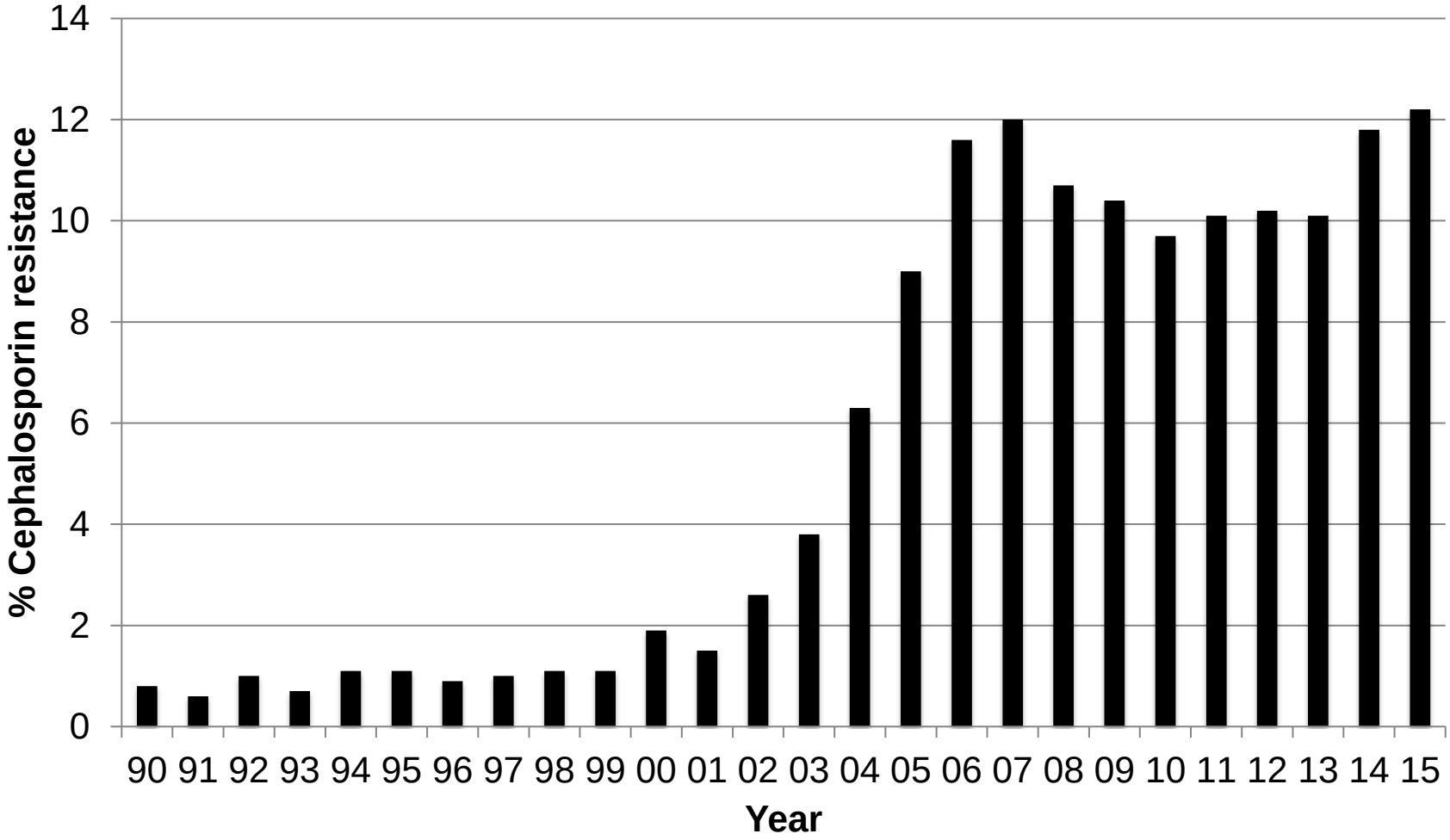
		‘enhancer effect’ reflecting attack on different PBPs.		
Meropenem/nacubactam[61,62,63]	Carbapenem/DBO (Roche)	Nacubactam has direct antibacterial activity and, although it does not inhibit MBLs, it achieves synergy with meropenem by an ‘enhancer effect’ reflecting attack on different PBPs.	As cefepime/zidebactam, but generally slightly less active, particularly against *P. aeruginosa*; enhancer effect weaker than with cefepime.	Unknown
Cefepime-VNRX-5133[64,65]	Cephalosporin/boronate (VenatoRx)	VNRX-5133 is a second generation boronate which, unlike vaborbactam, also inhibits MBLs and OXA-48	Inhibits VIM and NDM enzymes, but not IMP. MICs for some NDM producers remain around 8 mg/L, even with a 1:1 combination.	Unknown

Cefiderocol[66]	Catechol cephalosporin (Shionogi)	As a catechol, cefiderocol is efficiently taken into bacteria via the iron-uptake pathway. It is also near stable to most relevant β-lactamase, including MBLs	MICs for NDM producers, though mostly only 2-4 mg/L, are raised compared to those for bacteria with other MBLs. Long history of development problems with catechol β-lactams raises concern, though cefiderocol seems to evade these. Not clear if bacteria might develop resistance by switching to other iron uptake routes.	Unknown
LYS-228[67]	Monobactam	Monobactams are stable	Early stage; not active	Unknown

	(Novartis)	to MBLs; this has also been engineered to be stable to ESBLs, AmpC enzymes, OXA-48 and KPC types	against *P. aeruginosa*	

Figure 1 legend

Trajectory of oxyimino-cephalosporin (cefotaxime/ceftazidime) resistance in bloodstream *E. coli* in the UK excluding Scotland. From 1990-2000 there was considerable exposure to cephalosporins but little or no accumulation of resistance. The sharp rise from 2002-2006/7 then reflects the emergence (or introduction) of ST131 *E. coli* with CTX-M ESBLs and their proliferation. Updated from ref 39


% Cephalosporin resistance
0
2
4
6
8
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90 91 92 93 94 95 96 97 98 99 00 01 02 03 04 05 06 07 08 09 10 11 12 13 14 15
Year