

Technology Appraisal of New Antibiotics- UK perspective from NICE

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Topic Selection (Technology Appraisals & Medtech Innovation
Briefings)

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The background: why NICE was set up

- Established in 1999
- Aim: to reduce variation in the availability and quality of treatments and care (the so called 'postcode lottery')
- To resolve uncertainty about which medicines and treatments work best and which represent best value for money for the NHS



Media Stories

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Home sweet home
Gary Young on snapshots of migration

Superhero overload!
Joe Queenan

Fashion's most influential woman
Isabel Marant by Jess Cartner-Morley



Flushed out Turkish police try to force protesters from Taksim Square



A protester is knocked off his feet by water cannon in Taksim Square, Istanbul, yesterday as police try to disperse the demonstrators. Photo by: Reuters/Corbis

Girl fled to France with teacher after police check

Peter Walker

A schoolgirl has told a court how she ran away to France with her teacher after a police check on her school bag revealed a hidden stash of drugs.

The girl, now 16, was caught by police in France after she had been seen in a car with her teacher. She was charged with possession of drugs.

When police searched the teacher's car, they found a large quantity of drugs. The teacher was charged with possession of drugs.

The girl was charged with possession of drugs. She was released on bail.

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UK raises alarm on superbugs

Calls for clampdown on overuse of antibiotics to limit lethal infections

See sample
Piers Hurrey
Doris Langford

Antibiotics will save the UK at least a billion pounds a year, but the overuse of the drugs is a growing concern. A new report from the World Health Organization (WHO) warns that the overuse of antibiotics is a global challenge that is up there with climate change, nuclear disarmament and the environment.

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Bugs re

'will

BUGS that are resistant to antibiotics are expected to kill more people than cancer within decades, George Osborne said last night.

Without new drugs, common infections will be responsible for ten million deaths a year around the world by 2050, he claimed - more than the eight million a year who die from cancer now.

As well as disastrous consequences for health, the Chancellor warned that a lack of effective antibiotics may have an 'enormous economic cost' over the same period - slashing global economic output by 3.5 per cent - or £70trillion.

He highlighted the potentially catastrophic toll as he called for a

Antibiotics

cancer'

adding: ...ion, anti- ...ll become ...mankind

problem, ...hing, both ...nd money ...the world ...to agree a

need the ...id industry ...r in radical

ssioned the ...l to review ...ommenda- ...month. ...ctors were ...g struck off

if they handed out too many antibiotics. Prescription rates are spiralling, and GPs face being referred to regulators if they continue to dole out antibiotics like sweets.

Doctors have been found prescribing them for coughs, colds and hayfever. In some GP practices, up to 97 per cent of patients who ask for antibiotics get them.

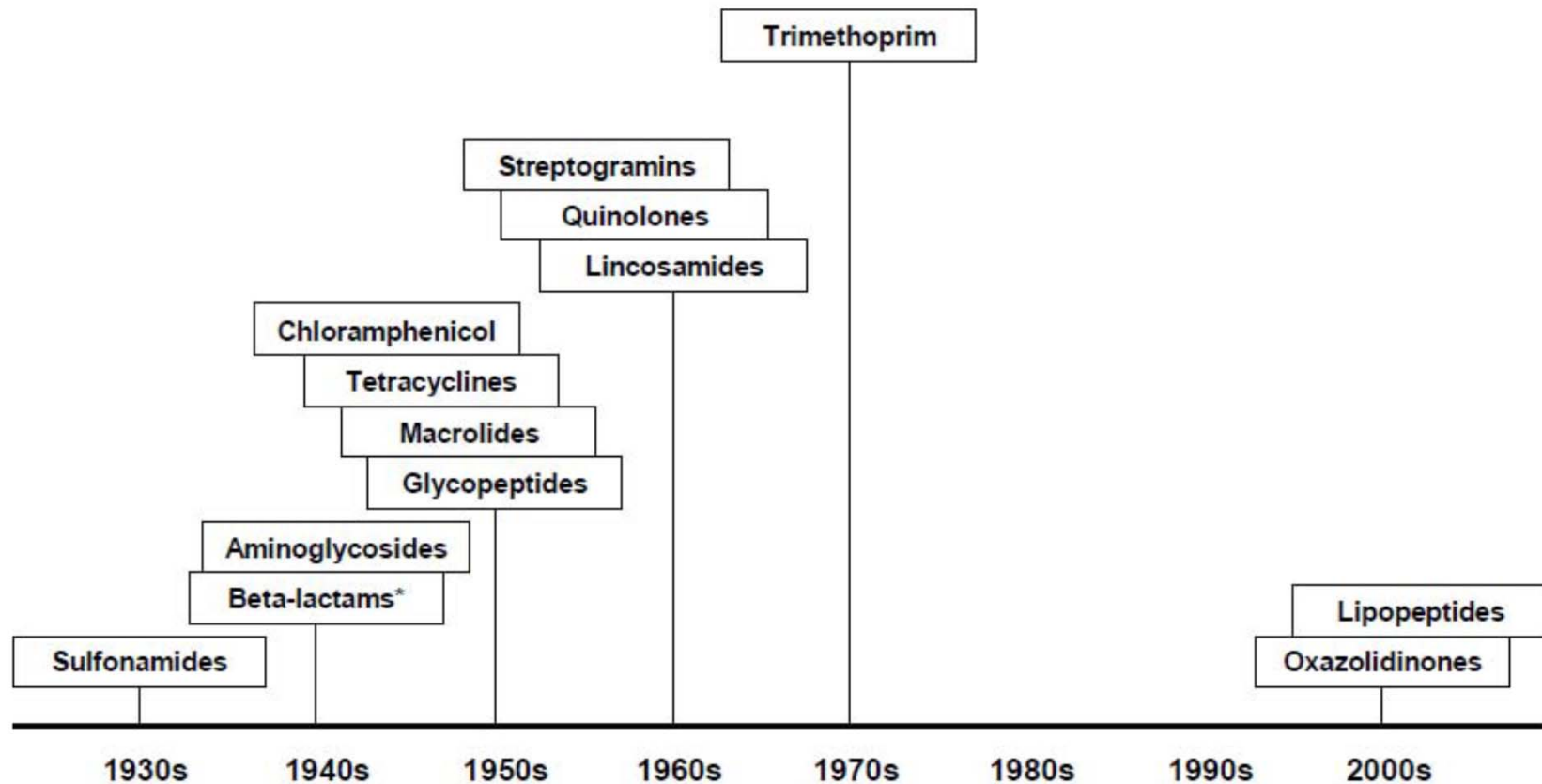
Almost 42million antibiotic prescriptions were issued on the NHS in 2013 - up 14 per cent on 2003.

Professor Colin Garner, of Antibiotic Research UK, said: 'Effective antibiotics underpin all modern medicine. We are in danger of going back to a pre-antibiotic era unless we quickly find significant funds to find new antibiotics, as well as safeguarding our current ones.'

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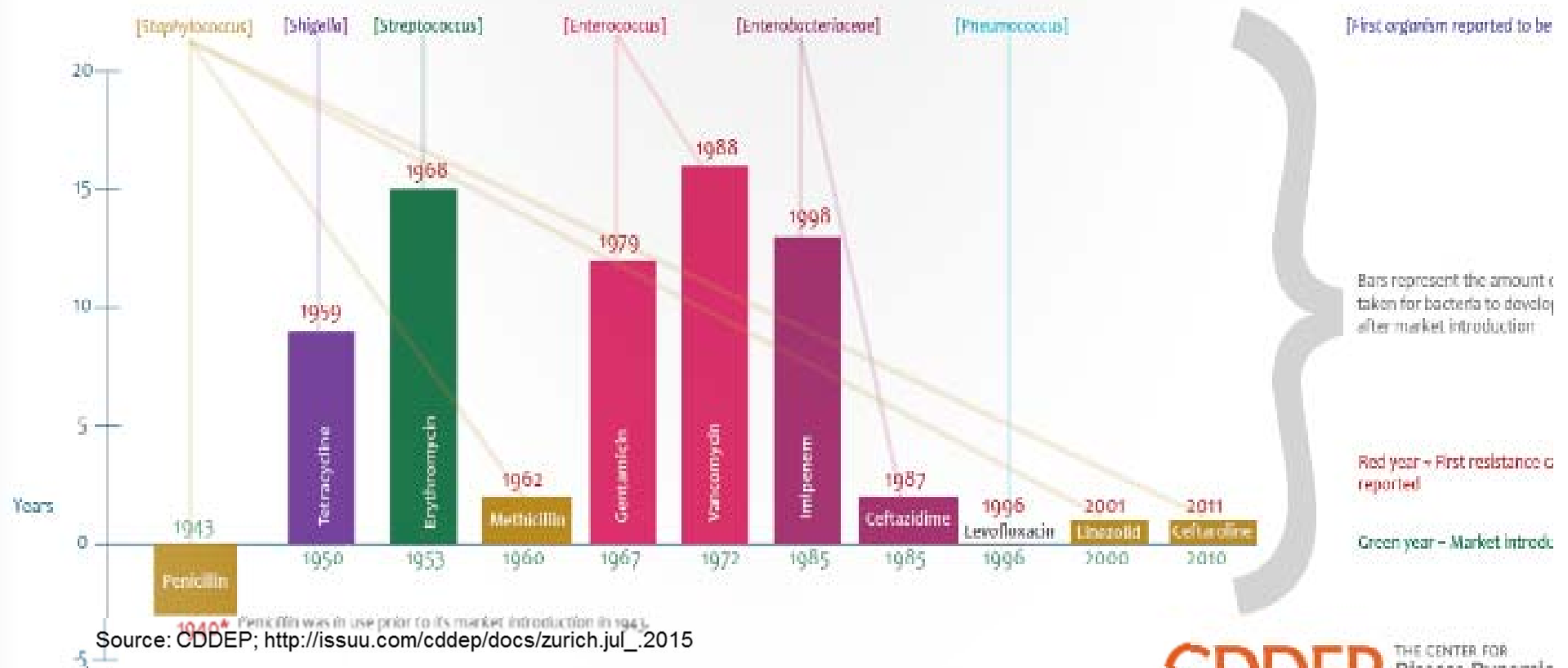
NICE

Concern about slowing pipeline



NICE

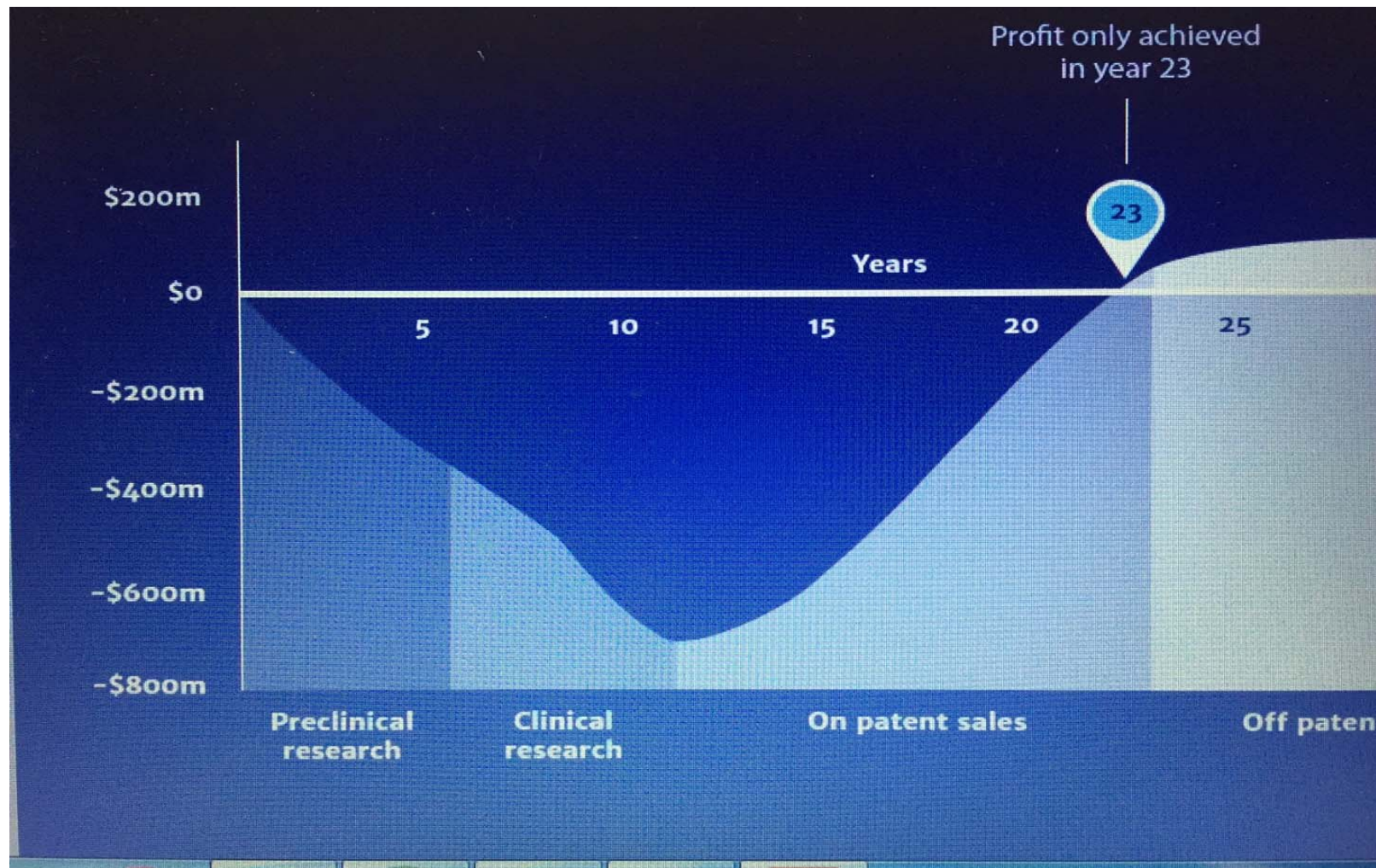
Once an antibiotic is introduced, resistance is not far behind...



Data source: Antibiotic Resistance Threats in the United States, 2013.
US Centers for Disease Control and Prevention (CDC)



Challenge of Antibiotic Reimbursement



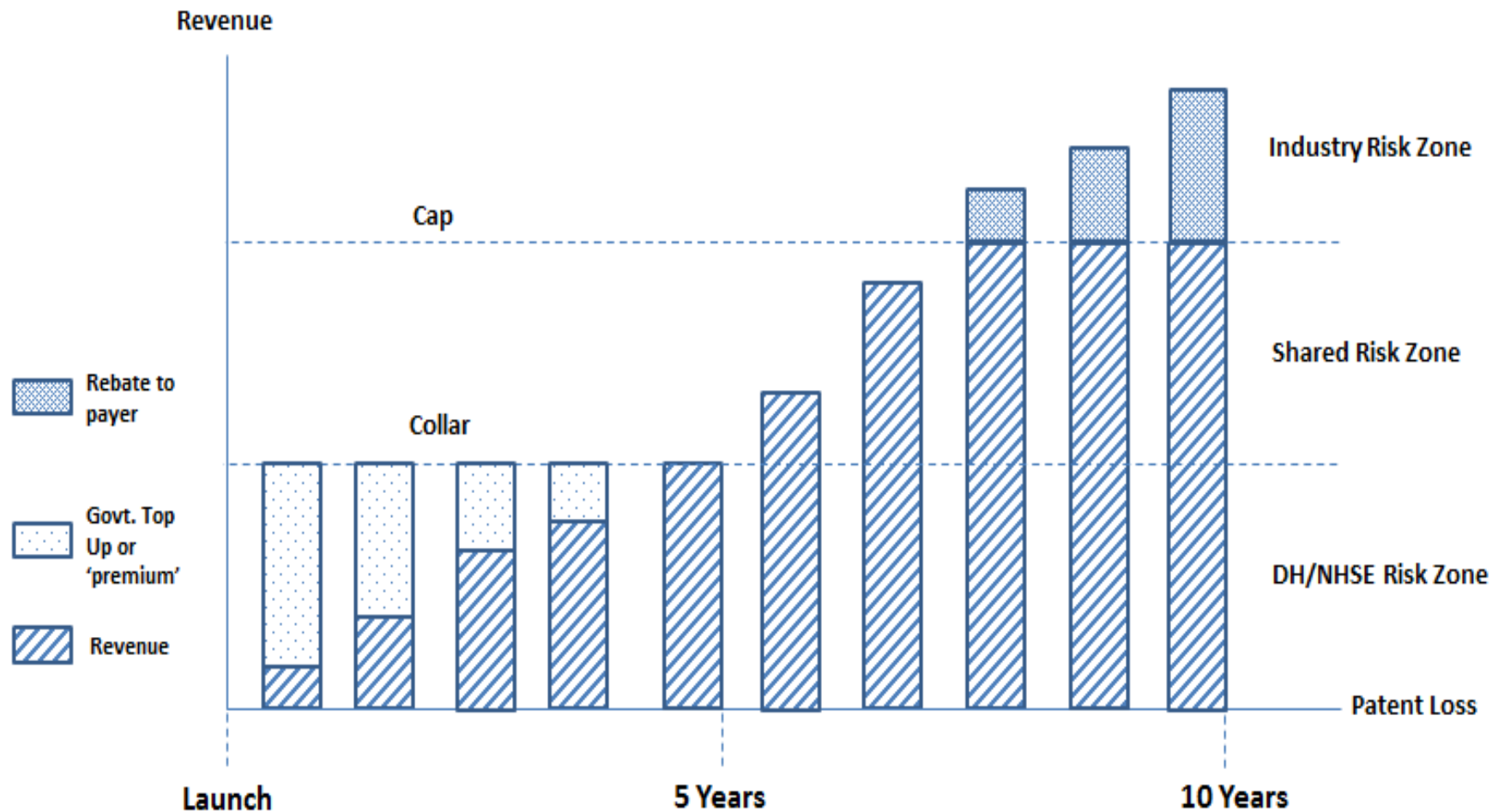
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O'Neill Report 2016

UK & International Efforts

- O'Neill review of AMR UK (May 2016)
- **Common themes**
 - Grant fund R&D
 - 'Pull' incentives that **delink** payment from prescribing volume i.e.
 - encourage **stewardship**
 - Co-ordinate globally on surveillance & development
- WHO Essential Medicines List 2017
- EU IMI-DRIVE AB & New Drugs for bad bugs
- CDDEP, CARB-X, GARDP

Delinkage; example of 'cap & collar' approach



NICE

NICE & Antibiotics & Health Technology Assessment

- NICE asked by Department of Health to explore whether current Health Technology Assessment methodology can be applied to antibiotics
- & feed into a potential UK delinked reimbursement system for new antimicrobials

What did NICE do next?

- Engaged with Dept Health & Pharma
ind Not just about HTA al
- del • NICE antibiotics stewardship guideline
- rein • Common infection guidelines (first guideline
- Hol one on sinusitis)
- Lite • Antimicrobial prescribing advice
- Wh (APA) HTA?
- TA methodology research (DH & NICE sponsored)
- Developing criteria to select antibiotics suitable for HTA

Antimicrobial pipeline: UK perspective September 2016

- 28 new antibiotic indications (Phase II/III)
- 15 some activity Vs MRSA or VRE
- 6 active against one or more carbapenemase (CPE) organisms
- 4 active Vs *Clostridium difficile*
- Majority were not new classes & even novel class agents not necessarily game changing

Leonard CT, Ward D, Longson C. Antimicrobial resistance: a light at the end of the tunnel? **Lancet** 2017;389:803

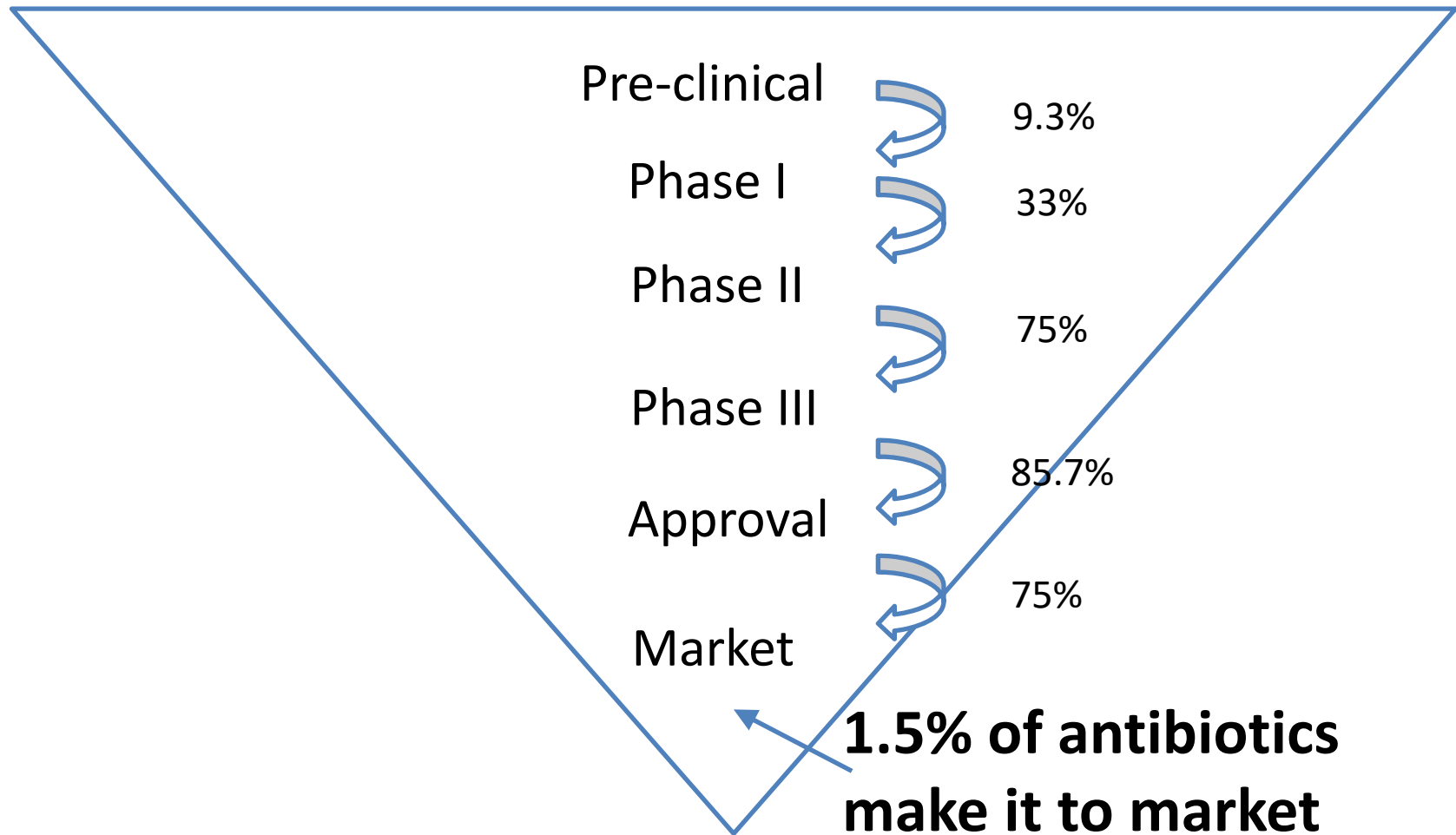
Antimicrobial pipeline: Pew Trust

March 2017

- 41 antibiotics in Phase I-III in 2017
- as opposed to 836 pharmaceuticals for cancer
- Due to documented drop-out rates once drugs enter clinical testing, perhaps 1 in 5 will make it to market.

<http://www.pewtrusts.org/en/research-and-analysis/collections/2016/12/tracking-the-pipeline-of-antibiotics-in-development>

Antibiotics in development drop out rate higher if include preclinical products



NICE TA276 Colistimethate sodium & tobramycin dry powders for inhalation for treating pseudomonas lung infection in Cystic Fibrosis published March 2013

- Tobramycin DPI in CF with P aeruginosa lung infection allowed if 1) Colistin is contraindicated, not tolerated or not been effective; & 2) Tobramycin DPI provided at agreed discount
- Colistimethate DPI allowed if 1) would benefit from continued Colistin but don't tolerate it in nebulised form & Colistimethate provided at agreed discount

Current HTA literature (1)

- Verhoef et al. Cost-effectiveness & pricing of antibacterial drugs. Chem Biol Drug Des 2015;85:4-13.
- Looked at 38 studies on cost-effectiveness of antibiotics.
- Most showed that new antibacterial was cost-effective Vs existing agents

Current HTA literature (2)

- Oppong et al. **Cost effectiveness of amoxicillin for lower respiratory tract infection**
Economic evaluations of antibiotics which look only at immediate costs of care, & not the wider implications & cost of resistance will underestimate the true cost
2060
ICER = £11949 when MDR costs & healthcare costs included
resistance excluded
If broader societal costs included ICER = £589,856

Current HTA Literature (3)

- Canadian Agency for Drugs & Technologies in Health. Daptomycin for vancomycin-resistant enterococcal infection: A review of the clinical effectiveness, cost-effectiveness and guidelines. 14th January 2016.
- Unable to assess the cost-effectiveness & commented on the non-inferiority trials as being an issue

Current HTA Literature (4)

- Meropol SB. **Valuing reduced antibiotic use for pediatric acute otitis media.** Pediatrics 2008 Apr; 121(4):669-73.
- Am Acad Pediatrics 2004- urges parents to weigh benefits of reduced antibiotic usage Vs risk of extra cost & extra sick days
- able to ascribe a value to benefits of not prescribing antibiotics i.e. stewardship

Antibiotics: what is different? High level thoughts

- Modest pipeline & relative lack of new classes of agent in development & urgent need (e.g. Carbapenemase)
- Need to look beyond the basic costs of care when doing cost-effectiveness analysis
- Role of diagnostics undervalued in HTA & real world

Diagnostics in appropriate antibiotic prescribing- NICE products

- MIB78 Quikread Go for CRP testing in primary care; MIB81 Alere Afinion CRP for C-reactive protein testing in primary care
- DG18 Procalcitonin testing for diagnosing & monitoring sepsis.
- MIB114 Febri-Dx for C-reactive protein & Myxovirus protein A testing in primary care (July 2017)

Antibiotic HTA-what is different? (1)

serving a delinked scheme

- Non-inferiority trials
- Using PK/PD data & sensitivity & resistance spectrum as part of value assessment
- Multiple bacterial targets & clinical scenarios (with different value assessments & unlikely to be different delinked payments for different indications)
- New drugs used in combination with existing drugs

Antibiotic HTA-what is different? (2)

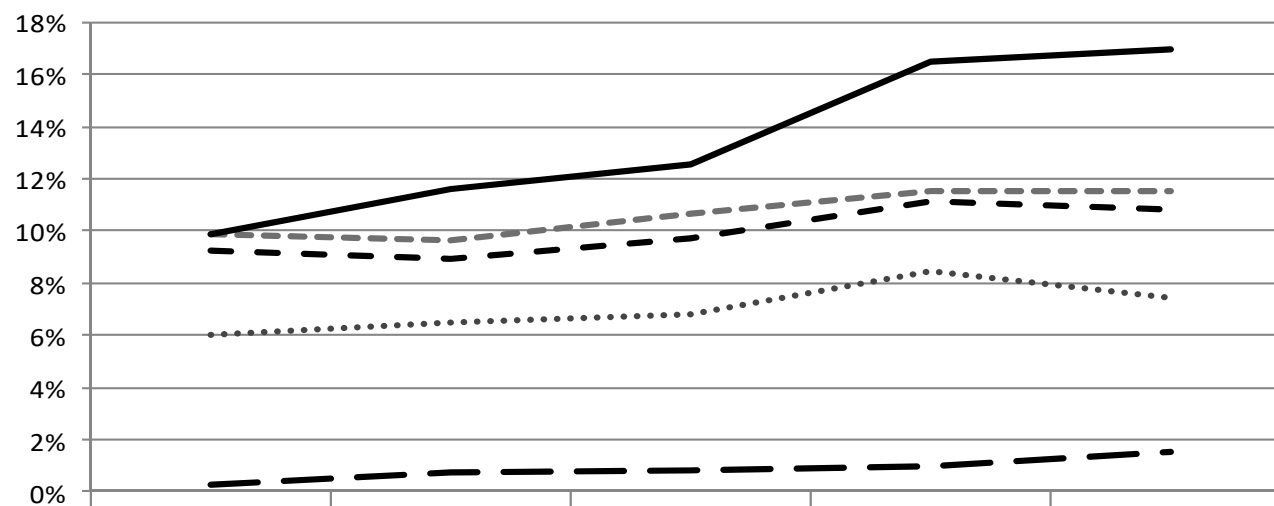
serving a delinked scheme

- Costs of resistance
- Valuing societal benefit
- Forecasting usage
- Forecasting resistance (cf Zavicefta)

Forecasting usage & resistance in UK

Figure 5: *K. pneumoniae* bacteraemia resistance reports (England) ESPAUR Report 2015

Proportion of episodes reported as non-susceptible



— — Ciprofloxacin	9%	9%	10%	11%	11%
- - - 3rd Generation Cephalosporins	10%	10%	11%	12%	12%
..... Gentamicin	6%	7%	7%	8%	7%
———— Piperacillin\Tazobactam	10%	12%	13%	17%	17%
— • Carbapenems	0.3%	0.7%	0.8%	1.0%	1.5%

— — — Carbapenem (inpatients)	100.0%	113.6%	120.4%	130.6%	141.3%
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EEPRU Project- Universities of York & Sheffield-DH & NICE sponsored (ongoing)

- Review HTA literature
- Define the relevant costs, benefits & opportunity costs relevant to assessing value
- Forecasting usage & resistance
- Consider Models of delinked payment
- Stylised cases to test the methodology
- If needed adjust current TA methodology
- Suggestions for further research
- Diagnostics to be considered also

How to prioritise for HTA?

Initial thoughts-not finalised

- Addressing an unmet need e.g. CPE
- WHO priority pathogen list
- Global Union Antimicrobial Resistance GUARD prioritisation criteria
- WHO Essential Medicines list (access, watch, reserve)
- CDC serious or urgent threat list
- Particular need for stewardship (i.e. possible low volume of sales e.g. **Brilacidin** which may be held in reserve for Daptomycin-resistant organisms)

Summary

- Need to incentivise antibiotic development (push & pull)
- Current UK HTA methodology may need adjusting (EEPRU research project reports April 2018)
- Potential for delinked scheme to remove need for volume prescribing
- **Note to Self: Don't forget diagnostics!**