


# Hopes, Hypes and Multivallate Defences Against Antimicrobial Resistance


## Professor Neil Woodford, Public Health England

### Denver Russell Memorial Teleclass



Public Health  
England

Denver Russell Memorial Teleclass Lecture




## Hopes, hypes and multivallate defences against antimicrobial resistance

Professor Neil Woodford (@Prof\_Neil)  
Antimicrobial Resistance & Healthcare Associated Infections (AMRHAi) Reference Unit


Hosted by Prof. Jean-Yves Maillard  
Cardiff University, Wales

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## Links between AMR ...and Badbury Rings (Dorset) ?



<http://www.castlesfortsbattles.co.uk>

- a multivallate iron age hillfort
- layers of challenging defence
- ..., but not impregnable !



Badbury Rings aerial by Google  
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# Hopes, Hypes and Multivallate Defences Against Antimicrobial Resistance


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## The UK's long record of high-level leadership







- AMR has a cyclical history
- hard now to be genuinely original
- much done, thought or written before
- recurring losses of momentum, necessitating new waves of activity


3
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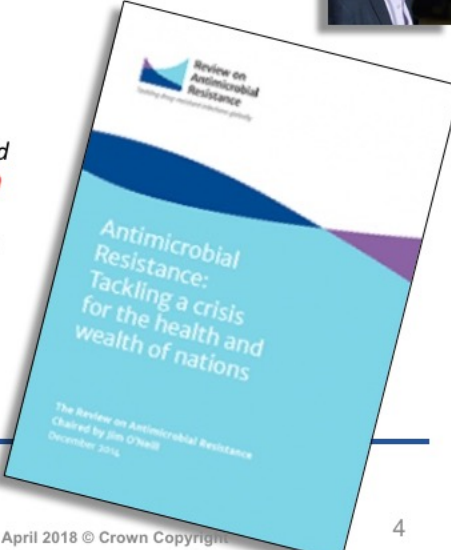
## Jim O'Neill's *Review on AMR*

Commissioned by the UK Prime Minister, July 2014 to revitalize antibiotic discovery – focused on economics.

*"Drug-resistant infections already kill hundreds of thousands a year globally, and by 2050 that figure could be **more than 10 million**. The economic cost will also be significant, with the world economy being hit by **up to \$100 trillion by 2050** if we do not take action."*

[www.amr-review.org](http://www.amr-review.org), 2015







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## Scientists kick back, 2016

*“There is undoubtedly a large clinical and public health burden associated with AMR, but it is challenging to quantify the associated excess morbidity and mortality.”*

*“Current global estimates of the burden of AMR are not very informative; we need detailed, reliable data to be able to improve AMR control measures, preferably based on comprehensive, population-based surveillance data from low-, middle-, and high- income countries.”*

**The art of predicting “broad brush estimates” of people dying from AMR**

November 30, 2016 | mardcarter | Epidemiology

*“The AMR Review even acknowledged “that the reported numbers are “broad brush estimates,” [...] that “more detailed and robust work will no doubt be done by academic researchers,” and that there is a lack of data, urging for improvement of infection surveillance.”*

PLOS MEDICINE

ESSAY

**Will 10 Million People Die a Year due to Antimicrobial Resistance by 2050?**

Mariska E. A. de Kraker<sup>1\*</sup>, Andrew J. Stewardson<sup>2</sup>, Stephan Harbarth<sup>1</sup>

<sup>1</sup> Infection Control Program, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland, <sup>2</sup> Infectious Diseases Department, Austin Health, Heidelberg, Australia

\*mariska.dekraker@hug.ch

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## Global commitment to combat AMR



General Assembly of the United Nations

High-Level Meeting on Antimicrobial Resistance

21 September 2014 @ 10:00 am - 6:00 pm



**HIGH-LEVEL MEETING ON ANTIMICROBIAL RESISTANCE**

21 SEPTEMBER 2014, UN HEADQUARTERS, NEW YORK

AMR Framework for Action Supported by the IACG



**IACG | Interagency Coordination Group on Antimicrobial Resistance**

Working Document | August 2017

- WHA 2014 resolution
- WHO Global AMR Action Plan 2015 – *framework for action*
- Global Health Security Agenda: AMR action package - *mechanism and collaboration to accelerate implementation*
- Many other national action plans
- UNGA, 2016
- UN Inter-Agency Coordination Group, 2017

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### Defining our defences against AMR

- Public awareness
- Sanitation and hygiene
- Antibiotics in agriculture and the environment
- Vaccines and alternatives
- Surveillance
- Rapid diagnostics
- Human capital
- Drugs
- Global Innovation Fund
- International coalition for action

Review on Antimicrobial Resistance  
Tackling drug-resistant infections globally


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## Defence : New Drugs

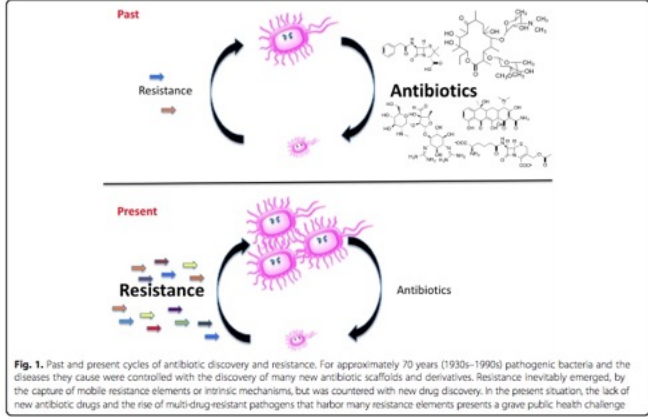
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Spotlight graphic: courtesy Tracey Guise, BSAC

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Countering the problem - then and now



**Fig. 1.** Past and present cycles of antibiotic discovery and resistance. For approximately 70 years (1930s–1990s) pathogenic bacteria and the diseases they cause were controlled with the discovery of many new antibiotic scaffolds and derivatives. Resistance inevitably emerged, by the capture of mobile resistance elements or intrinsic mechanisms, but was countered with new drug discovery. In the present situation, the lack of new antibiotic drugs and the rise of multi-drug-resistant pathogens that harbor many resistance elements presents a grave public health challenge.

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We don't have enough antibiotics in development to tackle the resistance issues we face now


...and the success of those in development is not guaranteed

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## WHO Priority Pathogens list

- antibiotics specifically active against multidrug- and extensively drug-resistant Gram-negative bacteria.
- antibiotics for the paediatric population and for oral formulations for community diseases with a high morbidity burden such as drug-resistant *Neisseria gonorrhoeae*, *Salmonella typhi* and ESBL-producing *Enterobacteriaceae*.
- new classes of antibiotics without cross- and co-resistance to existing classes should be supported.
- must also reduce the burden of infections e.g. increased vaccination coverage, improved sanitation or sustained implementation of infection control measures

[www.who.int/medicines/publications/WHO-PPL-Short\\_Summary\\_25Feb-ET\\_NM\\_WHO.pdf](http://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf)

**Priority 1: CRITICAL\***

*Acinetobacter baumannii*, carbapenem-resistant  
*Pseudomonas aeruginosa*, carbapenem-resistant  
*Enterobacteriaceae*\*, carbapenem-resistant, 3<sup>rd</sup> generation cephalosporin-resistant

**Priority 2: HIGH**


*Enterococcus faecium*, vancomycin-resistant  
*Staphylococcus aureus*, methicillin-resistant, vancomycin intermediate and resistant  
*Helicobacter pylori*, clarithromycin-resistant  
*Campylobacter*, fluoroquinolone-resistant  
*Salmonella* spp., fluoroquinolone-resistant  
*Neisseria gonorrhoeae*, 3<sup>rd</sup> generation cephalosporin-resistant, fluoroquinolone-resistant

**Priority 3: MEDIUM**

*Streptococcus pneumoniae*, penicillin-non-susceptible  
*Haemophilus influenzae*, ampicillin-resistant  
*Shigella* spp., fluoroquinolone-resistant

\* Mycobacteria (including *Mycobacterium tuberculosis*, the cause of human tuberculosis), is subjected to review for inclusion in this prioritization exercise as it is already a globally established priority for which innovative new treatments are urgently needed.  
 \* Enterobacteriaceae include: *Klebsiella pneumoniae*, *Escherichia coli*, *Enterobacter* spp., *Serratia*, *Proteus* spp., and *Providencia* spp., *Morganella* spp.

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## New anti-Gram-negatives

Name	Phase	Company	Class
Ceftolozane+ tazobactam	FDA approved Dec 19, 2014	Merck	Novel cephalosporin + beta-lactamase inhibitor
Ceftazidime+ avibactam	FDA approved Feb 25, 2015	Pfizer / Allergan	Cephalosporin + novel beta-lactamase inhibitor
Meropenem+ vaborbactam	FDA approved Aug 29 2017	The Medicines Company	Meropenem + novel beta-lactamase inhibitor

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[www.pewtrusts.org](http://www.pewtrusts.org)  
[www.drugs.com](http://www.drugs.com)

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### Most CPE are multi-resistant, 2016

Antibiotic	Proportion of susceptibility, % (n=708)								
	metallo-enzyme producers (NDM, VIM, IMP) (n=261)			non-metallo-enzyme producers (KPC, OXA-48-like, KPC + OXA-48-like, GES, IMI, SME, FRI-2) (n=422)			others (MBL + non-metallo-enzyme: NDM + OXA-48-like) (n=25)		
	<i>E. coli</i>	<i>Klebsiella</i> spp.	<i>Enterobacter</i> / <i>Citrobacter</i>	<i>E. coli</i>	<i>Klebsiella</i> spp.	<i>Enterobacter</i> / <i>Citrobacter</i>	<i>E. coli</i>	<i>Klebsiella</i> spp.	<i>Enterobacter</i> / <i>Citrobacter</i>
Imipenem (IPM) (S <=2 mg/L)	5	2	3	83	42	42	0	0	0
Meropenem (S <=2 mg/L)	5	1	3	87	40	49	0	0	0
Ertapenem (S <=0.5 mg/L)	0	0	0	3	1	0	0	0	0
Ampicillin (S <=8 mg/L)	0	0	0	0	0	0	0	0	0
Co-amoxiclav (S <=8 mg/L)	0	0	0	0	0	0	0	0	0
PIP-tazobactam (S <=8 mg/L)	4	0	2	0	0	7	0	0	0
Cefotaxime (S <=1 mg/L)	0	0	0	29	12	11	0	0	0
Ceftazidime (CZT) (S <=1 mg/L)	0	0	0	42	19	22	0	0	0
CAZ-avibactam (S <=8 mg/L)	0	0	0	98	96	96	0	0	0
Ceftolozane-tazobactam (S <=1 mg/L)	0	0	0	52	17	30	0	0	0
Aztreonam (S <=1 mg/L)	20	28	47	49	20	30	0	0	100
Ciprofloxacin (S <=0.25 mg/L)	5	7	15	46	19	34	0	0	0
Gentamicin (S <=2 mg/L)	27	21	20	62	58	61	0	3	100
Tobramycin (S <=2 mg/L)	28	4	5	61	40	56	0	3	100
Amikacin (S <=8 mg/L)	50	49	55	92	68	88	100	3	100
Colistin (S <=2 mg/L)	97	83	97	98	86	93	100	64	100
Tigecycline (S <=1 mg/L)	96	61	88	98	64	84	100	36	100
Total number	78	123	60	133	200	89	2	22	1

Active in vitro against <=10% isolates  
Active in vitro against 50-80% isolates  
Active in vitro against >90% isolates

a = two isolates susceptible to avibactam alone

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### Developmental anti-Gram-negatives, May 2017

Name	Phase	Company	Class
IPM + relebactam	Phase 3	Merck	Carbapenem + novel beta-lactamase inhibitor
Cefiderocol (S649266)	Phase 3	Shionogi	Siderophore cephalosporin
Omadacycline	Phase 3	Paratek	Tetracycline
Eravacycline	Phase 3	Tetraphase	Tetracycline
Plazomicin	Phase 3	Achaogen	Aminoglycoside

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## Assessing the potential of the antibiotic pipeline - I

### Urgent threat pathogens

The Centers for Disease Control and Prevention considers three bacteria to be urgent threats to public health.<sup>4</sup> While a number of promising antibiotics with the potential to treat infections caused by these bacteria are in the pipeline, more drug candidates are needed to meet current and future patient needs.



- 3** antibiotics are in development to treat drug-resistant gonorrhoea infections. An estimated 246,000 drug-resistant cases occur in the United States each year.<sup>5</sup>
- 6** antibiotics are in development to treat patients with *Clostridium difficile* infections, which can sometimes result in life-threatening diarrhea. The CDC estimates that nearly 500,000 Americans acquired *C. difficile* infections in 2011; 15,000 of them died as a result.<sup>6</sup>
- 7** or more antibiotics are in development with the potential to treat infections caused by carbapenem-resistant Enterobacteriaceae (CRE). Infections caused by this resistant pathogen can kill up to 50 percent of patients if the bacteria infect the bloodstream.<sup>7</sup>

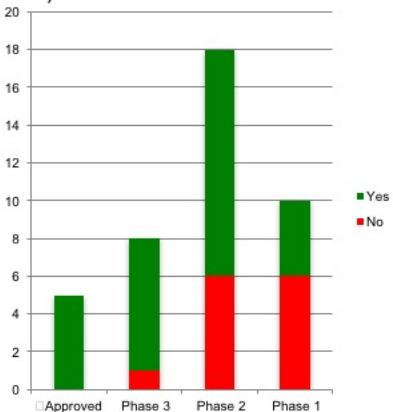
NOTE: This infographic is based on analysis as of March 2017.

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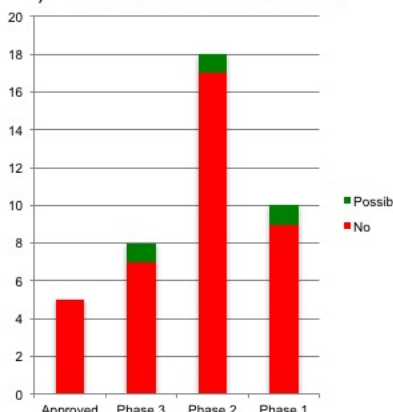
## Assessing the potential of the antibiotic pipeline - II

### a) FDA fast-tracked molecules



Phase	Yes	No
Approved	5	0
Phase 3	7	1
Phase 2	12	6
Phase 1	4	6

### b) \*\*\*Active vs. >90% UK CPE\*\*\*



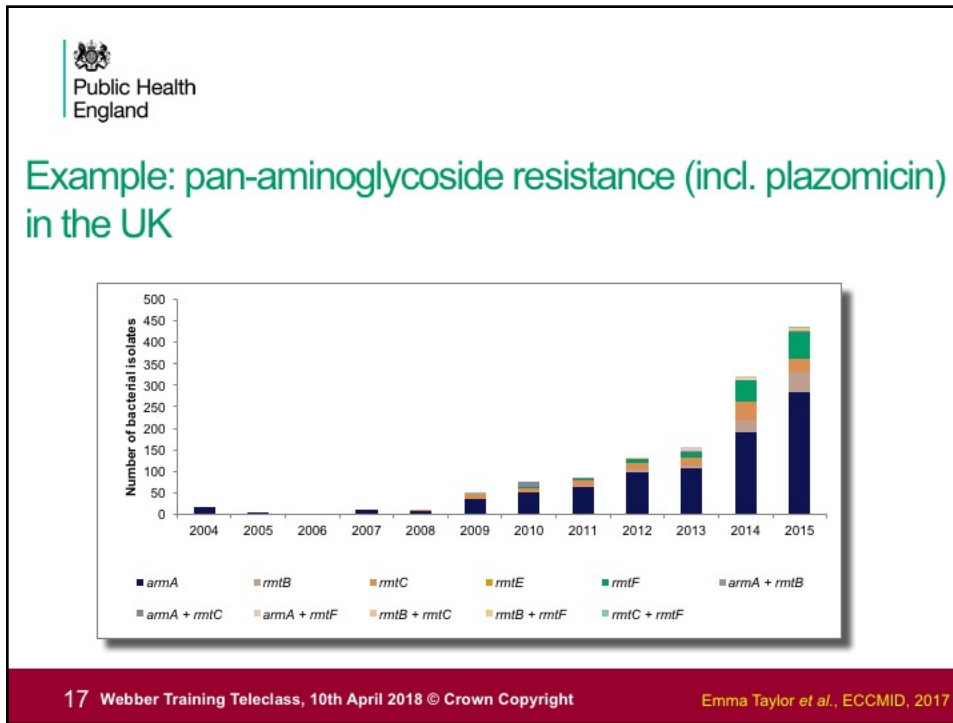
Phase	Possible	No
Approved	0	5
Phase 3	1	7
Phase 2	1	17
Phase 1	1	9

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Association of RMases with carbapenemases

RMase	NDM*	OXA-48-like*	NDM + OXA-48-like	Other	Total
<i>armA</i>	140	22	17	3	182 (46%)
<i>rmtB</i>	43	2	8	2	55 (14%)
<i>rmtC</i>	51	1	11	0	63 (16%)
<i>rmtD</i>	0	0	0	1	1
<i>rmtF</i>	28	47	3	0	78 (20%)
2 RMases	7	7	3	0	17 (4%)
Total (% +ve)	269 (57%)	79 (11%)	42 (82%)	6 (1%)	396 (21%)
RMase -ve	207	642	9	624	1482

c. 98% have NDM and / or OXA-48 like enzymes

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## Assessing the potential of the antibiotic pipeline - III

### A GO / NO GO decision: Delafloxacin Stumbles in Gonorrhea Study

Posted on February 2, 2015 by Harald — No Comments |

The treatment history of *N. gonorrhoeae* makes for fascinating reading. This organism has always been able to keep the upper hand in the war of bug versus drug. Once susceptible to sulfa drugs, to penicillin, tetracyclines and fluoroquinolones, it sequentially become resistant in the matter of a decade to every class of drug. At one time it looked like the organism would become PCN-susceptible again but that hope did not really materialize. Hence, we are all a bit nervous about the time when ceftriaxone loses its efficacy.

Now we hear that delafloxacin, a promising new fluoroquinolone, did not make the grade: According to a recent press release, Melinta (formerly Rib-X) had to stop the Phase 3 gonorrhea study for reasons of "insufficient efficacy".[1]

### Cempra's solithromycin fails to match standard of care in GC study, development in NASH suspended; shares ease 10% premarket

Feb. 28, 2017 7:17 AM ET | By Douglas W. House, SA News Editor

- Cempra (NASDAQ:CEMP) is down 10% premarket on light volume in response to its announcement that a Phase 3 clinical trial, SOLITAIRE-U, assessing lead product candidate solithromycin compared to standard of care (intramuscular ceftriaxone plus oral azithromycin) for the treatment of uncomplicated genitourinary gonorrhea (GC) with or without concomitant chlamydia infection failed to demonstrate the non-inferiority of solithromycin. The success rates for standard of care were 84.5% in microbiological intent-to-treat population and 100% in microbiologically evaluable population compared to 80.5% and 91.3%, respectively, for solithromycin.

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[www.seekingalpha.com](http://www.seekingalpha.com)

  
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## Too much publicity may be a bad thing

thebmjopinion Latest Authors Topics

### Anthony McDonnell and Neil Woodford: Hype can undermine hope for new antibiotics

January 22, 2018

Every time a newly discovered molecule or preclinical drug makes the headlines as a "cure for drug resistant infections," we risk people thinking that the problem has been solved

Winning the "battle" against drug resistant infections will require new antibiotics, as well as public and professional behavioural change, better diagnostics, hygiene practices, and vaccines—all to either reduce unnecessary antibiotic use or to limit the spread of infections. No single new antibiotic is going to completely solve the problem of resistant infections, nor are most of the antibiotics in the early stages of development likely to make it to market.

Yet researchers often tout early stage successes in antibiotic development to the media as being potential game changers in preventing resistant infections. These statements are often misguided. Furthermore, they may undermine wider policy efforts to improve the research and development system for antibiotics because they create the impression that our current research system is adequate.

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Resistance to new agents: never say 'never' !



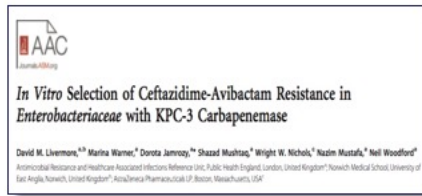
"Now, here, you see, it takes all the running you can do, to keep in the same place."

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Bacteria can be made resistant...

• In the lab:



• An ICAAC 'top 10 beta-lactamase' paper

- In-vitro selection of CAZ-AVI mutants of *E. cloacae* and *K. pneumoniae*, all with the KPC-3 enzyme.
- CAZ-AVI mutants at up to 16 x MIC, with frequencies of ca.  $10^{-9}$
- CAZ MICs rose; MICs of carbapenems, other cephalosporins and PTZ reduced
- The most frequent change was Asp179Tyr, increasing CAZ specificity
- Clinical relevance uncertain

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Livermore et al. 2015; 59:5324-30

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...or can become resistant in the clinic

Antimicrobial Agents and Chemotherapy

**Emergence of Ceftazidime-Avibactam Resistance Due to Plasmid-Borne *bla*<sub>KPC-3</sub> Mutations during Treatment of Carbapenem-*pneumoniae* Infection**

Open Forum Infectious Diseases  
ID CASE

Ryan K. Shields,<sup>1,2</sup> Liang Chen,<sup>1</sup> Avin Snyder,<sup>1</sup> Ruchi Pandey,<sup>1</sup> Cornelius J. Clancy<sup>1,2,4</sup>

**Emergence of Ceftazidime-Avibactam Resistance and Restoration of Carbapenem Susceptibility in *Klebsiella pneumoniae* Carbapenemase-Producing *K pneumoniae*: A Case Report and Review of Literature**

Ryan K. Shields,<sup>1,2</sup> M. Hong Nguyen,<sup>1,2</sup> Ethan G. Press,<sup>1</sup> Liang Chen,<sup>1</sup> Barry R. Krovacek,<sup>1,2</sup> and Cornelius J. Clancy<sup>1,2,4</sup>

<sup>1</sup>Department of Medicine, University of Pittsburgh, Pennsylvania; <sup>2</sup>DR Pathogen Laboratory, University of Pittsburgh Medical Center, Pennsylvania; <sup>3</sup>Public Health Research Institute, Tuberculosis Center, New Jersey Medical School, Rutgers University, Newark, New Jersey; <sup>4</sup>Pittsburgh Healthcare System, Pennsylvania

- Clinical failure of CAZ-AVI in 10/37 CPE patients
- CAZ-AVI-R *K. pneumoniae* from three patients after CAZ-AVI for 10-19 d.
- D179Y/T243M, D179Y or V240G mutations in *bla*<sub>KPC-3</sub>, which were not present in baseline isolates
- MEM-S phenotype restored in *K. pneumoniae* from two patients; clinical successful R<sub>x</sub> in one case
- clinical impact of CAZ-AVI-R may be ameliorated if carbapenem-S is restored

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 Shields et al. CID 2016; 63:1615-8  
 Shields et al. AAC 2017; 61. pii: e02097-16

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New drugs, but the companies still pass the baton

**Pfizer to Acquire Small Molecule Anti-Infective Business from AstraZeneca**

**Pfizer to Acquire Small Molecule Anti-Infective Business from AstraZeneca**

STRONG FIT WITH PFIZER'S EXISTING ANTI-INFECTIVE PORTFOLIO  
 PFIZER'S FOCUS ON THE INFECTIOUS DISEASE AND EXPERTISE IN THIS CATEGORY WILL HELP ENABLE BROADER ACCESS TO ANTI-INFECTIVE PORTFOLIO  
 EXPECTED TO ENHANCE RELIABLE REVENUE GROWTH POTENTIAL FOR PFIZER'S ESSENTIAL HEALTH BUSINESS

Wednesday, August 24, 2016 - 2:05pm EDT

Pfizer Inc. (NYSE:PFZ) today announced that it has entered into an agreement with AstraZeneca to acquire the development and commercialization rights to its late-stage small molecule anti-infective business, primarily outside the United States. The agreement includes the commercialization and development rights to the newly approved E1 and Zovista™ (zinc-finger nucleoside) anti-infective candidates, the marketed agents Hesper™ (hesperadin) and Zintun™ (zinc-finger nucleoside), and the clinical development assets adoxolan-oxadiazole (ADOX) and CXL. Zovista specifically addresses multi-drug resistant Gram-negative infections, including carbapenem resistance, one of the most significant unmet medical needs in bacterial infections treated with hospital and ambulatory care.

**The Medicines Company brings out the ax, looking to jettison hundreds of jobs in top-to-bottom restructuring**

By JOHN CARROLL | Oct 23, 2017 07:47 AM EDT

The Medicines Company CEO Clive Meanwell is circling all the wagons around its late-stage PCSK9 development plans for inclisiran.

The Alysium partner said today that once the biotech completes an effort to sell off its infectious disease group, the company — which had 410 staffers in February — will chop its remaining work force down to a more affordable group of less than 60 staffers.


Clive Meanwell, The Medicines Company


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## Securing new drugs

- **More predictable market to make antibiotics R&D commercially sustainable**
  - lump-sum payments for ‘successful’ drugs
  - ‘de-link’ profitability from sales
- **jump-start a new innovation cycle in antibiotics**
  - Global AMR Innovation Fund
  - boost early-stage R&D into drugs and diagnostics
- **reduce barriers to drug development**
  - lower costs
  - improve the efficiency of research
  - lower global regulatory barriers






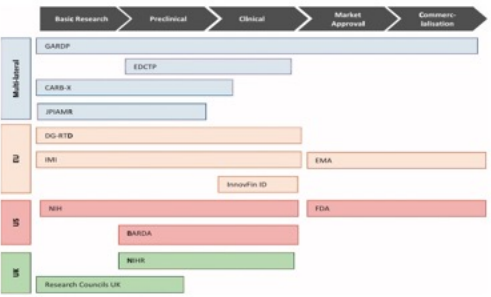
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 Tackling drug-resistant infections globally

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## Need a more balanced reimbursement ‘ecology’



**Table 2 Active initiatives based on their underlying incentives**


	Only push incentives	Only outcome-based pull incentives	Only regulatory incentives	A hybrid of push-pull incentives
Multi-lateral	4	0	0	1
EU level	3	0	1	0
USA	1	0	1	1
UK	2	0	0	0
Total	10	0	2	2
Percent of total	71.4%	0.0%	14.3%	14.3%

- *overly committed to early-stage push funding*
- *limited late-stage push funding for clinical development*
- *almost no pull incentives to facilitate transition [...] to commercialisation*


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### New drug development vs. focus on antibiotic stewardship

- Not mutually exclusive
- In the future, new antibiotics must be viewed differently
  - not regarded as 'cure more' replacements by prescribers
  - not regarded as market blockbusters by manufacturers
- Changes in behaviour and expectation are essential
- **\*\*\*This must be underpinned by better and faster diagnostics\*\*\***
  - old drugs should be used for 'susceptible infections'
  - new drugs must be held in reserve for 'resistant infections'

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## Defence : New Diagnostics

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Spotlight graphic: courtesy Tracey Guise, BSAC

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## Why new AMR diagnostics ?

- Prescribers must know earlier and more often that the infecting bacteria are susceptible to the drug they intend to use
  - Reduce empirical, broad-spectrum prescribing
- We need instruments and tests that can be deployed widely throughout the developed and developing world
- These new generations of diagnostics for AMR will facilitate
  - improved antibiotic stewardship
  - improved individual patient management
  - reduced onwards transmission of resistant bacteria

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## A recent UK analysis

“...many technologies are stuck at the laboratory phase or, having developed technical accuracy, have not progressed to clinical trials that provide cost-effectiveness and ultimately influence practice.”

Products are too often “pushed” by industry, not “pulled” by clinicians



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<http://www.cebm.net/>

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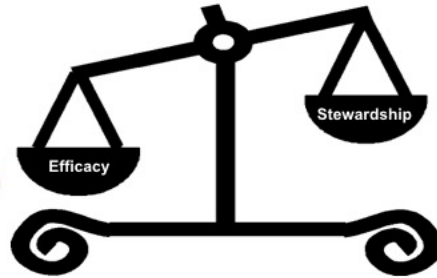
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Public Health  
 England

Gonorrhoea: a paradigm for better AMR diagnostics

- International approach to treatment
- Recommendation changes when resistance rate exceeds 5%
- Many patients are over-treated to prevent under-treating a few
- Gonococci in UK (2016):
  - >85% are PEN-susceptible
  - >65% are CIP-susceptible
- Neither drug is used
- Can't detect AMR at presentation



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*N. gonorrhoeae*



- World's first dual R<sub>x</sub> failure:
  - Single case, no onwards transmission
  - MICs, CTR 0.25 mg/L; AZI 1 mg/L (both R by EUCAST)
- Outbreak of HL-AZI-R gonorrhoea
  - MICs, >256 mg/L (not a formal criterion)


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Fifer et al. NEJM 2016; 374: 2504-6



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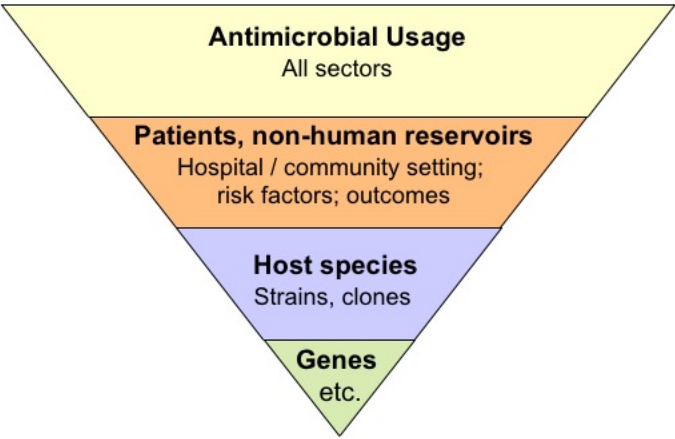
## Defence : Better Surveillance

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Spotlight graphic: courtesy Tracey Guise, BSAC

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### The complexities of AMR



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## Monitoring antibiotic usage in England (ESPAUR)



- Established by PHE in 2013 in response to the strategy
- Focuses on bringing together NHS, PHE, Private sector across all prescribers and clinicians to improve
  - Surveillance data on antibiotic resistance and prescribing
  - Antimicrobial stewardship activities
  - Education and training for healthcare professionals
  - Education and awareness to public

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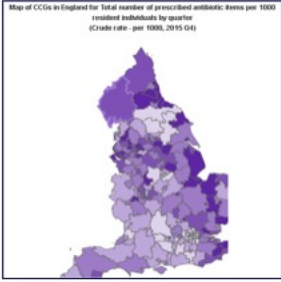


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Indicator	Period	Aintree University Hospitals		England		
		Count	Value	Value	Lowest	Highest
All C. difficile rates by reporting acute Trust and financial year	2014/15	134	57.6	41.0	0.0	114.4
Trust-appointed C. difficile rates by reporting acute Trust and financial year	2014/15	64	27.5	15.1	0.0	62.2

## Open access to surveillance data

- Fingertips: <http://fingertips.phe.org.uk/>
- AMR local indicators hosted on PHE fingertips site contain a selection of data across 5 domains:
  - Antimicrobial Resistance
  - Antibiotic Prescribing
  - Healthcare Associated Infection
  - Infection Prevention and Control
  - Antimicrobial Stewardship
- Indicators are intended as information for action and may enable healthcare organisations to **benchmark** the data for their organisation

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Simple messages ...for targeting action

WHO IS PRESCRIBING?

11%	Hospital inpatients
7%	Hospital outpatients
5%	Dental practices
3%	Other community settings
<b>74%</b>	<b>General practice</b>

1 in 3 patients in hospitals in England are on an antibiotic at any one time

1 in 3 individuals in England takes at least one course of antibiotics each year

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...and more questions to challenge us

Age and sex standardised rates of E. coli bacteraemia. England, 2016/16

Rate per 100,000 population

- Regional variations in E. coli BSI rates
- Why ?
- Socio-economic deprivation scores and other indices ?
- Intervention measures

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Courtesy: Alan Johnson & Susan Hopkins, PHE

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We need to build global capacity

Available National Data\* on Resistance for Nine Selected Bacteria/Antibacterial Drug Combinations, 2013

GLOBAL ACTION PLAN ON ANTIMICROBIAL RESISTANCE

Global Antimicrobial Resistance Surveillance System Manual for Early Implementation

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AMR surveillance in Africa

- no recent (>2013) AMR data published for >40% of countries on the continent and only a few of those were surveillance data.
- high level of resistance to commonly prescribed antibiotics in all regions:
  - trimethoprim (MR: 33.9%–100%), ampicillin (MR: 7.9%–100%) and penicillin (MR: 0%–75%)
- the standardization and quality of microbiological data must be improved.
  - unverified reports of highly unusual resistance patterns [...], such as penicillin-resistant *S. pyogenes* and vancomycin-resistant *S. aureus*.

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## Defence : Alert Reporting

*"Everything more resistant than everything else"*


41

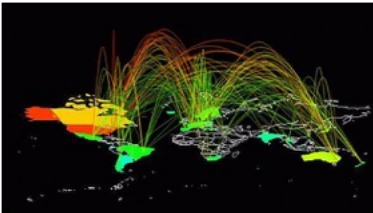
Spotlight graphic: courtesy Tracey Guise, BSAC

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## National & international capacity building

- Without lab testing we're blind to (the extent of) AMR problems
- Improve lab access; aim for a reference lab in every country / region
  - Each serving as the hub of a national network
  - Each acting as a spoke in an international network
  - Performing essential techniques, proficient to international standards
  - Sharing data / experience






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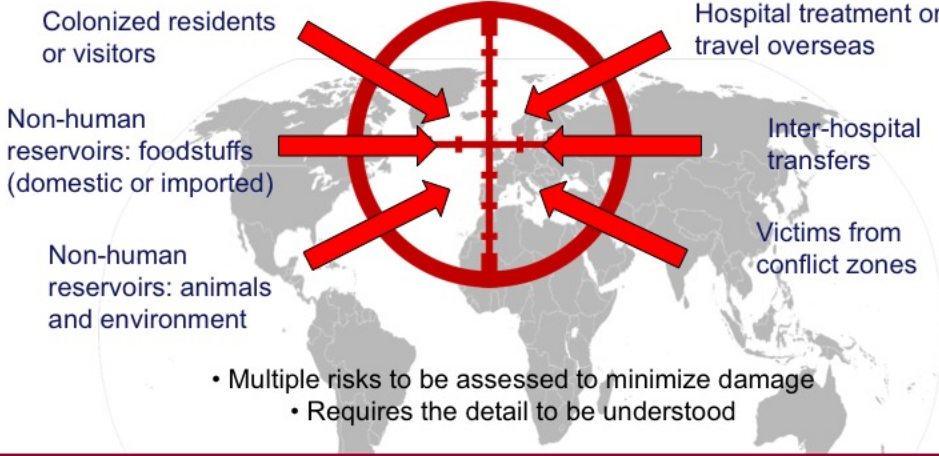
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### International AMR threats to healthcare



Colonized residents or visitors

Hospital treatment or travel overseas

Non-human reservoirs: foodstuffs (domestic or imported)

Inter-hospital transfers

Non-human reservoirs: animals and environment

Victims from conflict zones


- Multiple risks to be assessed to minimize damage
- Requires the detail to be understood

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### MDR & PDR Gram-negatives

*E. coli*      *K. pneumoniae*      *P. aeruginosa*



Morbidity and Mortality Weekly Report

**Notes from the Field**

**Pan-Resistant New Delhi Metallo-Beta-Lactamase-Producing *Klebsiella pneumoniae* — Washoe County, Nevada, 2016**

Lei Chen, PhD<sup>1</sup>; Randall Todd, DPH<sup>1</sup>; Julia Kishibandi, PhD<sup>2,3</sup>; Marissa Walters, PhD<sup>4</sup>; Alexander Kallen, MD<sup>5</sup>

On August 25, 2016, the Washoe County Health District in Reno, Nevada, was notified of a patient at an acute care hospital with carbapenem-resistant Enterobacteriaceae (CRE) that was resistant to all available antimicrobial drugs. The specific CRE, ...

A point prevalence survey was conducted in the patient unit as the patient was admitted. No additional N ...

This report highlights the first, although surveillance for CRE are resistant to a ...

- MDR increasingly seen in BSI across Europe
- PDR also a reality, but low numbers in most countries
- MBL + ESBL (all beta-lactams) + 16S RMTase (aminoglycosides)
- + resistance to colistin + upregulated efflux

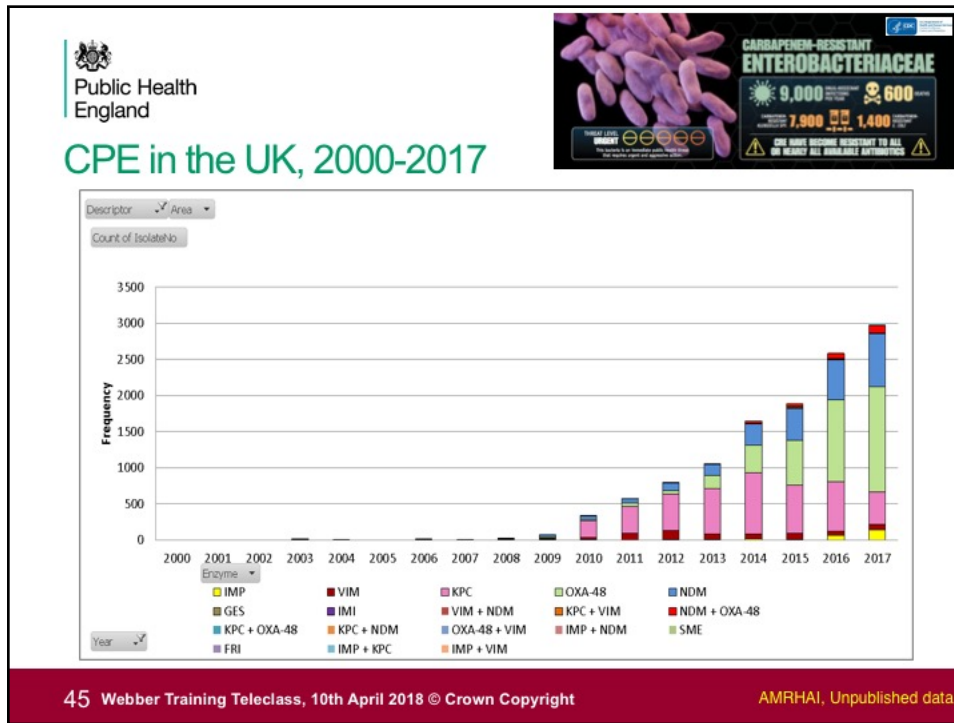
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### Fighting 'AMR' outbreaks is hugely expensive

**Superbug outbreak costs an NHS hospital one million pounds, says new study**

By Kate Whelan

06 November 2016

**Manchester trust struggling to contain hospital bug**

Full screen

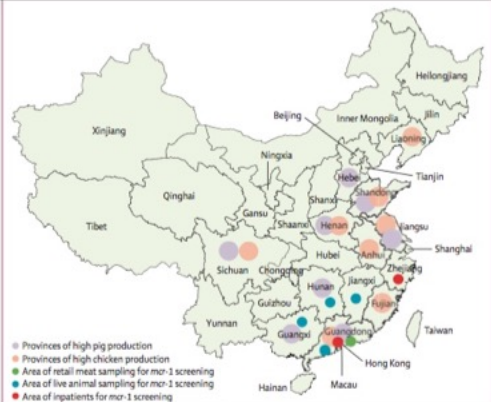
Efforts to contain the spread of highly resistant bacteria have cost a Manchester hospital trust more than £5m in eight months.

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### Discovery of plasmidic colistin resistance; *mcr-1*





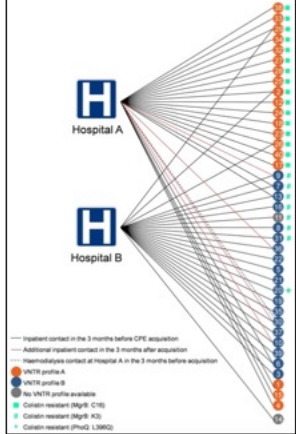
	Year	Positive isolates (%)/number of isolates
<b>Escherichia coli</b>		
Pigs at slaughter	All	166 (20.6%)/804
Pigs at slaughter	2012	31 (14.4%)/216
Pigs at slaughter	2013	68 (25.4%)/268
Pigs at slaughter	2014	67 (20.9%)/320
Retail meat	All	78 (14.9%)/523
Chicken	2011	10 (4.9%)/206
Pork	2011	3 (6.3%)/48
Chicken	2013	4 (25.0%)/16
Pork	2013	11 (22.9%)/48
Chicken	2014	21 (28.0%)/75
Pork	2014	29 (22.3%)/130
Inpatient	2014	13 (1.4%)/902
<b>Klebsiella pneumoniae</b>		
Inpatient	2014	3 (0.7%)/420

Table 2: Prevalence of colistin resistance gene *mcr-1* by origin

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 Liu et al. *Lancet Infect Dis.* 2015 Nov 18. pii: S1473-3099(15)00424-7

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### If focus is on *mcr* we may lose sight of other colistin resistance


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 Otter et al. *Sci Rep* 2017; 7(1):12711

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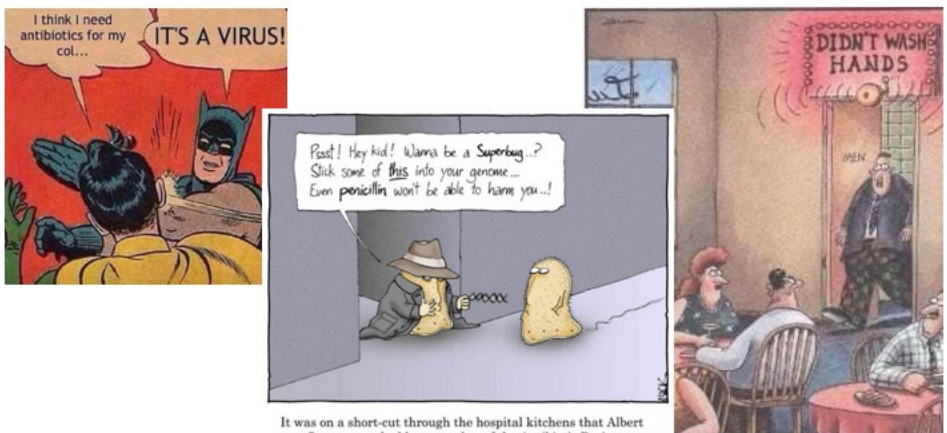
## Defence : Professional and Public Engagement

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Spotlight graphic: courtesy Tracey Guise, BSAC

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### Communicating 'AMR' with graphics is not new



I think I need antibiotics for my col... IT'S A VIRUS!

Pass! Hey kid! Wanna be a Superbug...? Slick some of this into your genome... Even penicillin won't be able to harm you...!

DIDN'T WASH HANDS

It was on a short-cut through the hospital kitchens that Albert was first approached by a member of the Antibiotic Resistance.

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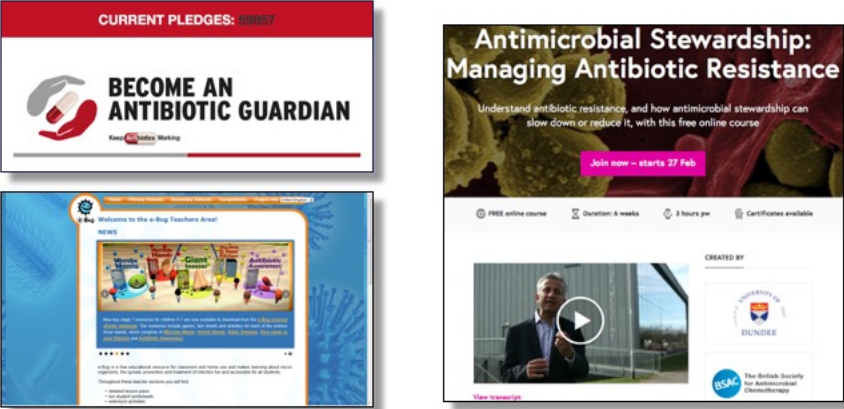
..., but is now mainstream and international



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Groundbreaking UK engagement initiatives



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# Hopes, Hypes and Multivallate Defences Against Antimicrobial Resistance

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## AMR is a societal issue: many stakeholders

- Prescribers – primary and secondary / tertiary care
- Prescribers – veterinarians
- Other healthcare professionals
- Social scientists
- Agriculturalists
- Public Health – local, regional, national
- Patients / public
- Academia + educators
- Industry (pharma and diagnostics)
- Politicians
- Funding agencies
- International agencies and organisations

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## Summary

The fight against AMR needs action on multiple fronts:

- Advocacy at highest level, and engagement downwards
- Better education (prescriber, user and wider public)
- Reducing infections and onwards transmission
- Better diagnostics and wider adoption of them
- Laboratory capacity building
- Better surveillance data to inform (local, national and global) action
- Reducing inappropriate prescribing (multi-sectoral)
- Reducing duration of broad-spectrum antibiotic treatment
- Assessment of any unintended consequences

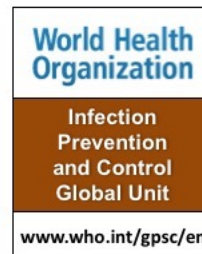
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April 18, 2018	<p><a href="#">GENETIC SIMILARITIES BETWEEN ORGANISMS ISOLATED FROM THE ICU</a>            Speaker: <b>Prof. Slade Jenson</b>, Western Sydney University, Australia</p>
April 19, 2018	<p><a href="#">TOPICAL ANTIBIOTICS TO PREVENT POST-OPERATIVE SURGICAL INFECTION ... IS THE PARADIGM CHANGING?</a>            Speaker: <b>Dr. Hilary Humphreys</b>, The Royal College of Surgeons in Ireland</p> <p><i>(FREE ... WHO Teleclass - Europe)</i></p>
May 3, 2018	<p><a href="#">SPECIAL LECTURE FOR 5 MAY</a>            Speaker: <b>Prof. Didier Pittet</b>, University of Geneva Hospitals</p> <p><i>(FREE CBIC Teleclass)</i></p>
May 10, 2018	<p><a href="#">HOW THE CERTIFICATION BOARD OF INFECTION CONTROL (CBIC) WORKS FOR YOU</a>            Speaker: <b>To be announced</b></p>
May 17, 2018	<p><a href="#">THE SILENT TSUNAMI OF AZOLE-RESISTANCE IN THE OPPORTUNISTIC FUNGUS ASPERGILLUS FUMIGATUS</a>            Speaker: <b>Prof. Paul E. Verweij</b>, Radboud University Center of Expertise in</p>

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