



**This is my first *Newsletter* as the Acting Director of ARMRL. Over the Summer I have been able to reorganize the laboratory and our revamped team will, I hope, be more robust and flexible as we look towards the 2012 Olympic Games and to becoming Public Health England in 2013.**

Carbapenem-resistant Enterobacteriaceae continue to dominate our reference services, with at least 20 isolates every week requiring molecular follow-up to confirm or refute presence of a carbapenemase. I write below on plans to introduce arrays for this purpose, and also on the problems of spotting isolates with OXA-48-like enzymes in the absence of molecular results.

Whether there is any need to detect carbapenemases or ESBLs for the purpose of individual patient management is, somewhat counter-intuitively, the subject of debate and controversy; in this

issue David considers EUCAST and CLSI recommendations that detection of these resistance mechanisms should be considered only for epidemiological or infection control purposes. Rob outlines changes to our Gram-negative reference antibiotic panel and plans to charge for more services from April 2012. While we try to keep charging to a minimum, we will introduce fees when fully-susceptible isolates are referred (there can be no justification for sending these to a reference laboratory for resistance), or when customised testing is requested; isolates confirmed to have resistance(s) of public health significance will continue to be tested free of charge. Mechanisms of resistance in enterococci have not changed substantially for several years, but as outlined below we have begun to receive a few isolates with elevated MICs of daptomycin or tigecycline.

Lastly, all at ARMRL would like to wish you a Happy New Year!

**Neil Woodford**

## Fixed menu or à la carte?

Accurate susceptibility testing data are crucial for treatment, for evaluating resistance mechanisms, and for the surveillance and control of emerging resistance. ARMRL's remit is primarily to investigate resistance of public health importance, and our standard phenotypic method is to determine MICs by agar dilution then to interpret these against BSAC and EUCAST guidelines, inferring resistance mechanisms by interpretive reading. We provide MICs of a wide selection of relevant antibiotics for resistant isolates of any species within our remit. These are our fixed antibiotic menus, allowing us to detect and characterise resistant phenotypes and to provide susceptibility data for therapeutic guidance.

Interpretive reading of the antibiograms is only possible by judiciously selecting the antibiotics tested. Our fixed menus therefore include some antibiotics that are most suited to detect resistance mechanisms of public health importance. For this purpose we test multiple  $\beta$ -lactam/  $\beta$ -lactamase inhibitor combinations, and also test carbenicillin as a marker of efflux in *Pseudomonas aeruginosa*. These provide clues to help

us unravel the multiple mechanisms that exist in many referred isolates, although it remains notoriously hard to differentiate carbapenem resistance contingent upon ESBL/AmpC activity in conjunction with porin loss from true carbapenemase activity by MICs alone. We regularly rethink the panels to reflect emerging resistance problems. Indeed, as this *Newsletter* goes out, we are introducing temocillin as a standard agent for Enterobacteriaceae; temocillin MICs may help identify OXA-48-like carbapenemases, as Neil writes below, and will expand therapeutic guidance.

Such investigations of unusual resistance are and will remain free-of-charge to NHS laboratories. Nevertheless, some customers request tests that fall outside of our *modus operandi* and we can no longer bear the cost of these. From April 1st 2012, we will introduce charges for:

- isolates for which customers require à la carte testing of specified antibiotics not in our standard panels, unless the request is supported by pan-resistance to agents in our panels.
- isolates that we find fully susceptible to fixed menu agents; we get several every week and, even if sent

accidentally, they do not warrant reference investigation. Isolates sent as polymyxin-resistant, but which prove susceptible will not be charged, because the resistance is often unstable and may be lost in transit.

- isolates referred only for confirmation of an intrinsic resistance e.g. *P. aeruginosa* or *Acinetobacter* sent for confirmation of ertapenem resistance (again, at least one is sent most weeks)
- 'difficult-to-test' bacteria including non-TB mycobacteria, actinomycetes etc, which may challenge testing in the referring laboratory and/or treatment of infected individuals, but rarely cause outbreaks. We view testing of such isolates as referred rather than reference work.

We recognise that our fixed menus, tailored to cover the majority of our referrals, may not meet your exact requirements on every occasion, and so we offer you the option of paying for customized testing. Remember, though, that if we confirm a genuinely exceptional resistance, the work is always free

**ROBERT HILL**

## ...But is an MIC all you need?

Recent [advice](#) from EUCAST asserts that the practice of reporting ESBL producers as resistant to all cephalosporins is unnecessary and that, with low breakpoints ( $S < 1$ ,  $R > 2$  for cefotaxime and ceftriaxone;  $S < 1$ ,  $R > 4$  for ceftazidime) cephalosporins can be reported 'as found'. CLSI has given similar advice, with more liberal breakpoints for ceftazidime and cefepime. Various pharmacodynamic and animal data are presented to support this view, along with some clinical cases.

Such advice seems, to me, to be misguided on three counts. First, whilst there are cases where cephalosporins have been effective against infection due to low-MIC ESBL producers, there are others where, even with MICs of 0.5 to 4 mg/L, they have failed. Since CTX-Ms are now the prevalent ESBLs, the testing ground looks likely to be the activity of ceftazidime, to which these ESBLs may confer low-level resistance. And, here the two clinical studies give conflicting results, one with 7/7 cures and one with 4/7 failures, 3 of whom died. Second, routine susceptibility categorisation is less precise than the MIC determinations used in animal models of infection by ESBL producers and in post-hoc outcome analyses, meaning that ESBL producers with MICs of 1-4 mg/L oscillate between  $S$  /  $I$  and  $R$  according to who tests them and how. In these circumstances, seeking ESBLs directly is an invaluable fail-safe in guiding patient treatment. Third, although EUCAST continues to advocate ESBL detection for epidemiological purposes, the likely consequence of not seeking them for treatment purposes is that some labs will not seek them at all, leading to loss of valuable epidemiological information.

In short, we should continue to seek ESBLs directly and, where they are found, to apply the utmost caution in using any cephalosporin.

**DAVID LIVERMORE**

## Temocillin vs. KPC producers

Few  $\beta$ -lactams escape carbapenemases. Aztreonam is stable to IMP, VIM and NDM metallo-enzymes, but is inactivated by the ESBLs and AmpC enzymes that very often accompany them. Oxyimino-cephalosporins are stable, or nearly so, to OXA-48 but, once again, are compromised by the ESBLs that often accompany this carbapenemase. In short, any activity by aztreonam against individual MBL producers, and any by oxyimino-cephalosporins against those with OXA-48 is really a matter of luck.

The case of temocillin and KPC is far more interesting. As we found in one small, [published study](#) and have now confirmed in a larger investigation, tabulated below, the MICs of temocillin for isolates of *Klebsiella*, *E. coli* and *Enterobacter* with KPC carbapenemases are mostly 16-32 mg/L, above the EUCAST systemic breakpoint of  $S < 8$  mg/L,  $R > 8$  mg/L, but below the BSAC urinary breakpoint of  $S < 32$  mg/L,  $R > 32$  mg/L. These MICs are only one or two doubling dilutions above the modal values for Enterobacteriaceae lacking KPC (or other)  $\beta$ -lactamases. Moreover, introduction of a plasmid encoding KPC-3 enzyme only raised the MIC of temocillin for an *E. coli* recipient by one doubling dilution, from 8 to 16 mg/L.

Species	MIC (Mg/L)				
	8	16	32	64	128
<i>Klebsiella</i> spp.	-	31	27	15	2
<i>E. coli</i>	1	8	6	-	-
<i>Enterobacter</i> spp.	1	-	2	1	-

But, beyond these MICs, and the near stability of temocillin to KPC enzymes, there are only unknowns. We are unaware of any patients with infections, urinary or otherwise, due to strains with KPC carbapenemases having been treated with temocillin, or of relevant animal studies. What is certain, given the growing prevalence of KPC carbapenemases, proliferating worldwide, is that answers to these questions are urgently needed.

Last, it should be added that temocillin is not stable to metallo-carbapenemases or to OXA-48 and, as Neil writes below, the consistent resistance of strains with the latter enzyme may aid their recognition.

**DAVID LIVERMORE**

## ARMRL's international activities

Over the years, ARMRL has hosted many international colleagues on research visits, and has enjoyed co-authoring the numerous publications that have arisen. In 2010 I registered ARMRL as an [ESCMID Collaborative Centre](#). This scheme funds non-UK ESCMID members to visit us to discuss our work, share experiences and, ideally, to establish longer-term collaborative projects and friendships. To date we have hosted three ESCMID Observers for periods of 1-3 weeks, Valia Dimou (Greece), Ilker Balkan (Turkey) and Rosane Coutinho (Brazil). More recently, I registered as a host with the [ASM International Fellowship Program](#), which funds visitors for up to 6 weeks. These international visits have been a great success for all concerned; Valia returned for another two-month period over the summer to study OXA-48 carbapenemases, so we must be doing something right!

Through these formal schemes and *ad hoc* approaches, we have filled our vacancies for international visitors throughout 2012 and are already taking bookings for 2013. We look forward to welcoming all who are scheduled to arrive in 2012, beginning with Tomislav Kostyanov (Bulgaria) and Adela Alvarez-Buylla (Spain) in January/February.

Anyone seeking an international placement in ARMRL should send their CV and preferred dates for a visit to [armrl@hpa.org.uk](mailto:armrl@hpa.org.uk) in the first instance. We can't make promises, but we'll do our best to accommodate you.

**NEIL WOODFORD**

## Micro-arrays for carbapenemases

Most Enterobacteriaceae confirmed by ARMRL to be resistant to at least one carbapenem are then screened by PCR for carbapenemase genes. This is laborious work for Daniele since it involves multiple assays. We recently published a [successful trial of a commercial array](#), which can detect genes encoding major carbapenemases (also CTX-M-, TEM- and SHV-type ESBLs). We will begin more extensive use of this [Check-Points CT-102](#) array in 2012, initially alongside our in-house PCR assays to build our validation file. We hope to be using the arrays as our first-line method for confirming carbapenemases by April.

**NEIL WOODFORD**

# Inferring OXA-48 carbapenemases

As frequently highlighted in this *Newsletter*, the UK's 'big 5' carbapenemases are the NDM, VIM and IMP families of metallo-enzymes and the KPC and OXA-48- non-metallo-enzymes. These same five groups top the global charts too. Some countries have one dominant type (e.g. KPC in the USA and Greece, NDM in India and Pakistan, OXA-48 in Turkey and North Africa), but the UK 'enjoys' them all, which keep us on our toes. There have been outbreaks of hospital infection caused by OXA-48 producers (most commonly *K. pneumoniae*) in several European countries, including the UK. Very recently, OXA-48 carbapenemase producers have been isolated from several Libyan trauma victims being treated in the UK.

The gene that encodes OXA-48 enzyme escaped from the chromosomes of *Shewanella* spp. and moved to plasmids and, thereby, into Enterobacteriaceae (though not yet to *Pseudomonas* or *Acinetobacter*). By itself OXA-48 enzyme confers resistance or reduced susceptibility to carbapenems and penicillin-inhibitor combinations, but producers remain susceptible to oxymino-cephalosporins unless they have co-resident mechanisms such as ESBLs or AmpC. This causes problems for detection by some automated systems, which tend not to 'believe' 'carbapenem-R, cephalosporin-S' phenotypes. Even when producers have co-resident mechanisms and broader  $\beta$ -lactam resistance, inferences of carbapenemase production have poor specificity, whether made by computer algorithms or human 'experts' because the MIC distributions of carbapenems for producers are very similar to those of ESBL/AmpC producers with reduced carbapenem susceptibility or resistance owing to porin loss.

High-level resistance to both piperacillin-tazobactam and temocillin may be useful indicators of OXA-48 production in enterobacteria that have resistance or reduced susceptibility to carbapenems, but lack the imipenem-EDTA synergy that would indicate the likely presence of a metallo-carbapenemase. Addition of temocillin to our Gram-negative panel will allow us to evaluate this in the coming months. Molecular assays remain the 'gold standard' for defining carbapenemases.

**NEIL WOODFORD**

# Staffing

We bid adieu in September to David Livermore as Director of ARMRL, though he continues as HPA Lead for Resistance, and to be in ARMRL for a day or two most weeks. Russell Hope also left us to join the HCAI-AMR department in HPA's Health Protection Services, with responsibility for the various mandatory surveillance programmes that are run for the Department of Health. These departures gave scope for some reorganization within ARMRL... I have pleasure in welcoming Katie Hopkins, who joins us from the HPA's Laboratory of Gastrointestinal Pathogens (LGP). As an HPC-registered Clinical Scientist, Katie will help Robert and myself with clinical reporting and, together with Daniele Meunier, will continue our drive to validate and introduce new techniques and technologies. Katie's arrival will also facilitate closer interaction with colleagues in LGP, as we look to rethink *Salmonella* susceptibility testing. Congratulations to Shazad Mushtaq, promoted to become our Surveys and Contracts Manager, and to Hiran Dhanji who joins him to work on our commercial activities. A warm welcome back to Tabassum ('Tabs') Noorie, who returns to RMMU to work with Daniele delivering molecular services.

Well done to Hiran Dhanji and Mike Hornsey, both awarded their PhDs by the Open University over the summer. Mike, who now works with David Wareham at Queen Mary University of London, will long remember his viva, which was held during the week of riots and was terminated by order of the Metropolitan Police as the Colindale site was closed early! 'Farewell' to Tom Gaulton who finished practical work for his proteomics-based PhD Studentship in July, though he continues to work at Colindale whilst writing his thesis. Welcome to Holly Ciesielczuk who joined the team in October. Her PhD project will compare *E. coli* from bacteraemia and urinary tracts, and is supervised by myself, Russ and David Wareham.

Finally, good-bye to Parmina Khan (University of Hertfordshire) who left us in September after a year as an undergraduate BMS trainee, and welcome to Jo Payne (University of Kent), who has joined us in the same capacity.

**NEIL WOODFORD**

# Enterococci non-susceptible to daptomycin or tigecycline

The resistance mechanisms of enterococci were a focus of my research for at least 15 years after I joined the then PHLS in 1988. Since the early 2000s relatively little has happened in the genus, except occasional linezolid resistance, and the 'van alphabet' (mechanisms of glycopeptide resistance) gradually extending to at least *vanM*.

Now, though, genuinely novel resistance issues have arisen in the genus. This summer saw publication of two papers (Arias et al.; Palmer et al.) that defined mechanisms of resistance to daptomycin; both implicated genes involved in phospholipid metabolism.

There are no EUCAST/BSAC breakpoints or epidemiological cut-off (ECOFF) values for enterococci vs. daptomycin,

and its precise mode of bactericidal action remains elusive, but these human shortcomings don't stop enterococci (or staphylococci for that matter) from becoming more resistant than normal.

ARMRL MIC data for c. 1600 enterococci indicate that MICs >2 mg/L are unusual for *E. faecalis*, whereas MICs >4 mg/L are unusual for *E. faecium*; these criteria are used in-house to determine whether referred isolates merit further work. We have received a few *E. faecium* with daptomycin MICs 8-64 mg/L, in some cases matched with susceptible isolates of the same strain from the same patient. Christian Lavallée (Canada) began working on these in the final days of his training Fellowship with us.

During 2010 and 2011, we also received our first isolates of *E. faecium* with 'resistance' to tigecycline (MICs 8 mg/L, compared with normal values of  $\leq 0.25$  mg/L), though again there are no specific breakpoints, and here too we are fortunate to have matched susceptible isolates. Initial studies by Mike Hornsey and David Wareham have implicated up-regulated efflux, which is the principal mechanism underlying tigecycline resistance in several Gram-negative genera (albeit mediated by different types of pump), but there are hints of inter-strain differences among the enterococci.

The resistance mechanisms of these highly unusual isolates will be studied further in 2012.

**NEIL WOODFORD**

# ARMRL Services

## MIC determinations (Antibiotic Resistance & Evaluations Unit)

We determine and interpret antibiograms of referred isolates for four main reasons:

1. Investigation of exceptional resistance ([www.hpa.org.uk/cfi/armrl](http://www.hpa.org.uk/cfi/armrl)).
  2. Evaluation of resistance mechanisms.
  3. Therapeutic guidance, particularly in multi-resistant infections.
  4. When the sending lab gets different results by different methods.
- Our standard method is BSAC agar dilution, with weekly runs for Gram-negative and -positive organisms. Exceptionally Etests are used, e.g. for urgent requests (please phone first). Investigation of unusual resistance is not charged for NHS labs.
  - We do not undertake disc testing, but do offer interpretations over the telephone, based on your results.
  - The only species we do not accept are Category 3 organisms, *Mycobacterium tuberculosis*, *Neisseria* spp., most anaerobes and fungi, which should be sent to the appropriate HPA laboratories (see [www.hpa.org.uk](http://www.hpa.org.uk)).

- We do accept non-TB mycobacteria, *Nocardia*, *Actinomyces*, etc., providing therapeutic guidance, but will charge.
- Endocarditis isolates can be referred to ARMRL for sensitivity testing and therapeutic guidance, irrespective of resistance, with MICs reported by phone. This is a charged service, but charges are waived where the isolate is confirmed by us to have exceptional resistances.

## Molecular Investigation (Resistance Mechanisms Monitoring Unit)

- Genetic tests for resistances are performed (i) to determine whether *S. aureus* with borderline methicillin-resistance have *mecA* (charged); (ii) to test *S. aureus* for *mupA*, determining high-level mupirocin resistance (charged); (iii) to detect carbapenemase genes; (iv) to identify mutations conferring oxazolidinone resistance and (v) to detect genes encoding acquired AmpC enzymes. Except for *mecA* and *mupA* detection, tests are usually done only after

phenotypes have been confirmed.

- ARMRL works with diagnostics companies to evaluate new molecular assays or platforms using characterized isolates with defined resistance mechanisms. Please contact Neil Woodford to discuss.

## New antibiotic evaluations

- ARMRL liaises with pharmaceutical companies on in-vitro evaluation of antibiotics and can undertake multi-centre surveys of the activity of new or established agents. Please contact David Livermore to discuss.

## Sentinel surveillance and multi-centre surveys

- We have a proven track record of running large surveillance/multi-centre surveys of the activity of new or established agents. Please contact Shazad Mushtaq or David Livermore to discuss.

## How to contact us when you need advice...

### Neil Woodford

(Acting Director)

[neil.woodford@hpa.org.uk](mailto:neil.woodford@hpa.org.uk); Tel 020-8327-7255/6511

Mechanisms of resistance; research opportunities; commercial opportunities (molecular test evaluations); visits

### Robert Hill

(Head, Antibiotic Resistance & Evaluations Unit)

[robert.hill@hpa.org.uk](mailto:robert.hill@hpa.org.uk); Tel 020-8327-7237

Clinical reporting of MICs; antibiotic referral service

### Shazad Mushtaq

(Surveys and Contracts Manager)

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Surveys of resistance; contracted antibiotic evaluations

### Rachel Pike (BMS, AREU)

[Rachel.pike@hpa.org.uk](mailto:Rachel.pike@hpa.org.uk); Tel 020-8327-7208

MIC service enquiries

### David Livermore

(HPA Lead for Resistance)

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General enquiries on resistance;  $\beta$ -lactamases; commercial opportunities (antibiotic evaluations); surveys

## A date for your diaries

The 22<sup>nd</sup> European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) will be held in London from 31st March to 3rd April 2012. ARMRL will, as ever, be well-represented. Neil and David are both invited speakers, and ARMRL has submitted several other abstracts, which cover the full breadth of our work. If you're attending, please pop along and say "Hello".

## And finally...

Gerry Wright's group at McMaster University in Canada recently brought the (pre)historic nature of antibiotic resistance into focus. Using carefully controlled molecular approaches, D'Costa et al. detected genes for TEM-type  $\beta$ -lactamases, Tet(M) tetracycline resistance and VanA glycopeptide resistance in 30,000 yr-old permafrost samples from the Canadian Arctic... alongside DNA from mammoths and species of megafauna that are extinct or no longer present in the region. This provides clear evidence that antibiotic resistance *per se* is not a modern problem, although its extent and consequences surely are. Not quite 'Jurassic Park', but extremely exciting work nonetheless. Well done guys!

NEIL WOODFORD

## Publications:

ARMRL and collaborators, July to Dec 2011

1. Beceiro A, Llobet E, Aranda J, Bengoechea JA, Doumith M, Hornsey M, Dhanji H, Chart H, Bou G, Livermore DM, Woodford N. Phosphoethanolamine modification of lipid A in colistin-resistant variants of *Acinetobacter baumannii* mediated by the *pmrAB* two-component regulatory system. *Antimicrob Agents Chemother.* 2011; 55: 3370-9.
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11. Perry JD, Naqvi SH, Mirza IA, Alizai SA, Hussain A, Ghirardi S, Orensa S, Wilkinson K, Woodford N, Zhang J, Livermore DM, Abbasi SA, Raza MW. Prevalence of faecal carriage of Enterobacteriaceae with NDM-1 carbapenemase at military hospitals in Pakistan, and evaluation of two chromogenic media. *J Antimicrob Chemother.* 2011; 66: 2288-94.
12. Stone NR, Woodford N, Livermore DM, Howard J, Pike R, Mushtaq S, Perry C, Hopkins S. Breakthrough bacteraemia due to tigecycline-resistant *Escherichia coli* with New Delhi metallo- $\beta$ -lactamase (NDM)-1 successfully treated with colistin in a patient with calciphylaxis. *J Antimicrob Chemother.* 2011; 66: 2677-8.
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