



## Keynote Lecture 3.1

### Roles of a national antibiotic reference laboratory

#### David Livermore

Antibiotic Resistance Monitoring & Reference Laboratory  
Health Protection Agency Centre for Infections  
61 Colindale Avenue, London NW9 5EQ

The roles of a national reference laboratory vary with the context in which it operates. How prevalent is resistance? Is it a major concern? How is healthcare arranged: is the state a near-monopoly provider, as in the UK, or does the laboratory serve independent providers? Is the laboratory the sole centre of expertise, or does it function alongside professional societies and interested academics? Is it expected to provide a free service, or to charge? Several models exist, ranging from a statist institution able to compel submissions, to a largely commercial operation, providing demand-led services for the further investigation of 'difficult' isolates.

Despite this variable geometry, some roles are surely core: (i), investigation of isolates with exceptional resistances, (ii) support of resistance surveillance; (iii), development of methods and setting standards for resistance detection, and (iv) provision of advice. It is hard to see how these could be fulfilled without some level of state support funding.

#### Investigation of unusual resistance

This is the laboratory's primary role, examining referred isolates and seeking to answer: (i) is the isolate as resistant as the sending laboratory claims, (ii) what antibiotics might still be useful, (iii) what is the mechanism of the resistance, (iv) what, if any, are the public health implications and how might these be mitigated?

This begs the question of 'What is unusual resistance?' The Table lists resistances that should be exceptional anywhere, deserving investigation. In addition, reference laboratories often seek isolates with internationally problematic resistance that are still rare locally. Thus laboratories in the Netherlands and Scandinavia study local isolates of methicillin-resistant *S. aureus*, fearing that these may be harbingers of wider emergence. By contrast, the UK laboratory, (<http://www.hpa.org.uk/cfi/armrl>), facing a situation where MRSA account for 15% of all in-patient isolates, offers a charged service to confirm *mecA* in isolates giving borderline results in conventional tests.

The laboratory should also concentrate on resistances undergoing rapid change. Priorities here vary over time. In the past 15 years the UK laboratory has successively emphasised MRSA, penicillin-resistant pneumococci, VRE, *Escherichia coli* with extended-spectrum  $\beta$ -lactamases, ciprofloxacin-resistant gonococci, carbapenem-resistant *Acinetobacter* spp., and, latterly, ertapenem-resistant *Klebsiella pneumoniae* and *Enterobacter cloacae*, as these have successively risen to prevalence. Aside from the standard questions, detailed above, the laboratory seeks also to determine whether the accumulation reflects repeated evolution, plasmid transfer, or clonal spread. In this phase the laboratory seeks all isolates with the resistance in question.

Gradually, once-rare resistances become common. If the laboratory provides a free service, it then faces a problem as hospitals, which formed the habit of referring such strains when they were rare, continue to do so. Effort is then placed on demand management and on enabling diagnostic laboratories to investigate these resistance types themselves (see below). Some argue that the laboratory should charge for confirmation of resistance that are already widespread, but this is slippery ground since genuinely unusual isolates continue to occur among expanding groups – e.g. community-acquired MRSA among the generality of nosocomial MRSA, or ESBL producers with some anomaly of resistance. The reference laboratory should encourage submission of these. Moreover, resistance types that have become nationally common may still be locally rare, and it seems appropriate for the reference laboratory to help confirm such strains until they become more familiar.

An increasing group of submissions, as routine microbiology becomes more mechanised, are those giving anomalous reactions on automated susceptibility testing systems – e.g. where ESBL production has been inferred by the machine but cannot be confirmed in conventional tests. Often these prove to have acquired AmpC enzymes. This, again, seems to me to be a justifiable role, with any consistent problems taken up with the manufacturer.

#### Support of resistance surveillance

Reference submissions do not form a good surveillance sample, since by definition they are biased towards resistance and lack a denominator (1). Moreover, once attention is drawn to a resistance type, referrals increase. To

achieve more representative surveillance the laboratory may establish sentinel surveillance studies, collecting-in consecutive examples of a particular species or resistance type from multiple sites, allowing prevalence to be estimated (2). These surveys are complementary to routine susceptibility data collection by epidemiologists. The sentinel surveys provide microbiological quality and details – with the potential for molecular investigation – whilst the routine data provides mass information, albeit with much greater quality issues (do all the laboratories test the same antibiotics, and do they test them in the same way?) Taken together, the two strategies provide powerful tools to monitor resistance trends.

## Research and Development

The reference laboratory needs to develop methods for its own use, e.g. multiplex PCR to distinguish related modes of resistance. In addition, it should seek to develop or promote methods enabling local laboratories to distinguish rising resistance types. Whether it does this unilaterally or in collaboration with academic societies (as in the UK) depends on local circumstances and on whether international methods, such as those of EUCAST or the CLSI are used. The laboratory must also investigate the genetic and biochemical mechanisms in new resistance type; here, the line separating reference microbiology and research becomes hazy....

The wider role of reference laboratories in research is controversial, with sponsoring governments often arguing that research is the role of other agencies. Few reference microbiologists would agree, not least because it is unlikely that high-calibre staff would be attracted without the opportunity to undertake research! My personal view is that the reference laboratory's role is on the 'cutting edge of applied research' and that this research must be of public health relevance.

## Advice

More than anything, the reference laboratory's role is to provide advice, primarily to referring clinical laboratories, but also to governments, professional societies, and the media. Moreover, there are wider messages that we want to provide to and, for this we publish a twice-yearly newsletter, distributed in the UK and available internationally via <http://www.hpa.org.uk/cfi/armrl/newsletter>.

## Reference List

- (1) Livermore DM, MacGowan AP, Wale MC. Surveillance of antimicrobial resistance. Centralised surveys to validate routine data offer a practical approach. *Brit Med J* 1998; **317**:614-615.
- (2) Potz NA, Hope R, Warner M, Johnson AP, Livermore DM. Prevalence and mechanisms of cephalosporin resistance in Enterobacteriaceae in London and South-East England. *J Antimicrob Chemother* 2006; **58**:320-326.

**Table.** Exceptional resistances, needing confirmation

Organism	Resistances to:
<i>S. aureus</i>	<b>Any of:</b> vancomycin, teicoplanin, linezolid, quinupristin/dalfopristin, daptomycin, tigecycline
Coagulase-negative staphylococci	<b>Any of:</b> vancomycin, linezolid, quinupristin/dalfopristin, daptomycin, tigecycline
JK coryneforms	<b>Any of:</b> vancomycin, teicoplanin, linezolid, quinupristin/dalfopristin, daptomycin, tigecycline
<i>S. pneumoniae</i>	<b>Any of:</b> meropenem, vancomycin, teicoplanin, linezolid, quinupristin/dalfopristin, daptomycin, tigecycline
Group A, B, C, $\beta$ -haemolytic streptococci	<b>Any of:</b> penicillin, vancomycin, teicoplanin, linezolid, quinupristin/dalfopristin, daptomycin, tigecycline
Enterococci	Linezolid, daptomycin, tigecycline <b>Both</b> Ampicillin <b>and</b> quinupristin/dalfopristin Teicoplanin <b>but not</b> vancomycin
Enterobacteriaceae	Meropenem, imipenem (except <i>Proteus</i> spp.), also ertapenem for <i>E. coli</i> only
<i>Acinetobacter</i> spp.	<b>Any of:</b> meropenem, imipenem, colistin
<i>Pseudomonas aeruginosa</i>	Colistin <b>Any third-generation cephalosporin, or carbapenem</b>
<i>H. influenzae</i>	Ciprofloxacin, any third-generation cephalosporin
<i>M. catarrhalis</i>	
<i>N. meningitidis</i> *	<b>Any of:</b> penicillin (high level), ciprofloxacin
<i>N. gonorrhoeae</i>	<b>Any</b> third-generation cephalosporin, azithromycin
<i>Bacteroides</i>	<b>Any of:</b> metronidazole, co-amoxiclav, carbapenems
<i>C. difficile</i>	<b>Any of:</b> metronidazole, vancomycin