Antimicrobial resistance: a bitter pill to swallow

Valerie Bevan reports on behalf of the British Society for Microbial Technology from its recent annual scientific meeting, held at Public Health England Colindale in London.

Over 150 biomedical and medical scientists attended the annual British Society for Microbial Technology (BSMT) symposium in Colindale, which covered the scientific, economic and behavioural challenges posed by the threat of antimicrobial resistance (AMR) in healthcare and public health. The meeting was convened in response to the 2013 annual report by the Chief Medical Officer for England, Professor Dame Sally Davies, which compared the AMR threat to humanity with global warming and terrorism. She has also made the point that development of new antimicrobials has slowed: no new class of antimicrobial agents has been launched since the 1980s.

Professor Eric Bolton, who chaired the day, opened the proceedings with a list of over 140 agents produced since 1935 showing that the rate of production has slowed considerably over the past 15 years. The meeting covered UK and European antibiotic stewardship initiatives and related scientific developments; the veterinary perspective; the views of the pharmaceutical industry; and the current state of knowledge on the AMR threat in respect of specific pathogens and disease groups. The three presentations in the afternoon session centred on resistance in tuberculosis, the threats from pets and the specific issue of testing for carbapenemase-producing Enterobacteriaceae.

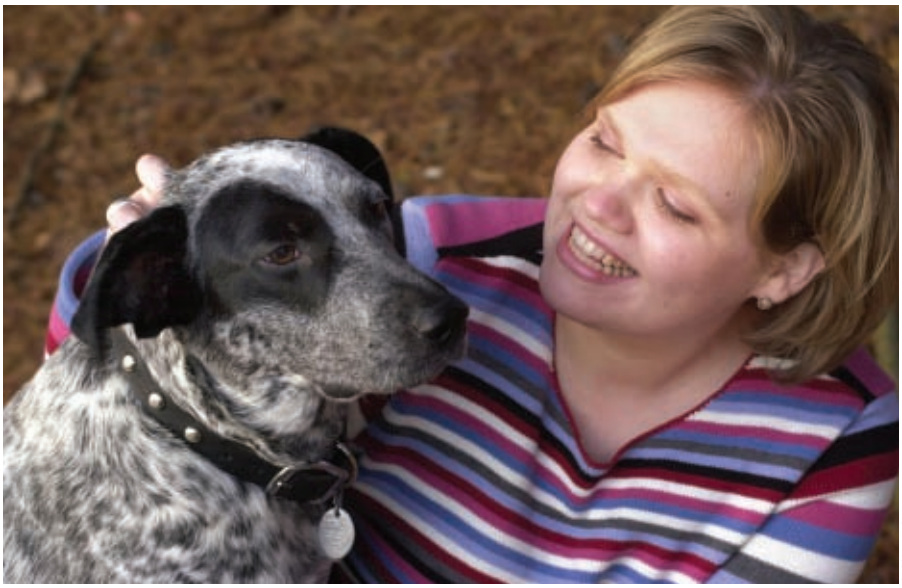
ANTIMICROBIAL RESISTANCE: A DISASTER IN THE MAKING?

In an introductory presentation, the Deputy Chief Medical Officer for England, Professor John Watson, described how the UK's cross-government AMR strategy 2013–2018[1] is being implemented. This is under the supervision of a high-level steering group that will, among other tasks, produce annual progress reports and develop outcome measures for the strategy; it will also encourage global cooperation, foster research and development, and promote high standards of antibiotic stewardship in order to extend the useful life of existing treatments – key aims of the strategy and themes that were elaborated on by other conference speakers.

Implementation faced many challenges, Professor Watson said, including the need for improved surveillance, diagnostics, pharmaceutical product development and antibiotic stewardship. On the subject of surveillance, he noted the establishment of a new English Surveillance Programme for Antimicrobial Usage and Resistance (ESPAUR), one of the aims of which is to improve the collation of data on antibiotic use in primary and secondary care, and investigate possible correlations with AMR trends and infection rates.

A VETERINARY PERSPECTIVE

Professor Peter Borriello, Chief Executive, Veterinary Medicines Directorate, discussed some of the similarities and differences between human and veterinary medicine. He indicated that misunderstandings about use of antimicrobials in veterinary practice abound, including misleading news items which tend to raise alarm. He highlighted some of the initiatives underway and, quoting the EU Commission's action plan, he commented that resistance is accelerated and spread by a number of factors: inappropriate use of therapeutic antimicrobials, use of antimicrobials for non-therapeutic purposes, pollution of the environment by antimicrobials, and increasing global trade and travel. Three of the Commission's 12 actions are joint human and veterinary activities and five are veterinary specific covering issues such as improved surveillance and the prudent use of antimicrobials in veterinary medicine.



CDC/James Gathany

Antimicrobial use and resistance in dogs and horses in the UK is an important issue, as a quarter of all households keep a dog and 1% have a horse or pony.

CDC/Chris Zahniser

In India, environmental pollution of ciprofloxacin is found to make up almost 1 g/kg of the organic material of the river sediment downstream from pharmaceutical factories.

Many different factors influence prescribing behaviour in veterinary medicine, including experience, access to/cost/speed of sensitivity testing, and recommendations (which may not be adhered to for several reasons including convenience of administration). Revision of the Veterinary Medicinal Products Directive (2001/82/EC) may include increased controls on usage, revision of authorised indications, and collection of prescription level data from veterinary surgeons.

Professor Borriello indicated the various approaches across countries and concluded that improved education and training was needed, along with cheaper and more rapid tests. He stressed the need to prolong the life of the existing antibiotics, to reduce the need for use, to improve AMR surveillance, and to develop new or alternative agents.

GLOBAL PERSPECTIVES ON ANTIMICROBIAL RESISTANCE

Professor Gunnar Kahlmeter, who has chaired the European Committee on Antimicrobial Susceptibility Testing for more than 10 years, and been on advisory committees for national and European AMR surveillance for more than a decade, discussed the many and diverse European and global initiatives in antimicrobial susceptibility testing and AMR surveillance. The now-agreed European breakpoints for testing are being implemented in all European countries and in several countries outside Europe. Also the EUCAST disk-diffusion method is being implemented in an increasing number of countries.

The World Health Organization (WHO) global report on surveillance[2] indicates that very high rates of resistance have been observed in all WHO regions, and many gaps exist in the information on pathogens of major public health importance. Importantly, key tools to tackle AMR, including surveillance systems, do not exist in many countries.

Attempts to reduce resistance face significant barriers. One example is found in India where environmental pollution of ciprofloxacin is found to make up almost 1 g/kg of the organic material of the river sediment downstream from pharmaceutical factories; another example is that reducing the use of antimicrobial agents where resistance has already occurred does not appear to influence resistance.

ANTIMICROBIAL RESISTANCE IN THE FOOD CHAIN

Professor David McDowell gave an holistic view linking food to human health, animals and the environment. He pointed out how resistance may change during the food production process, and described the impact of differences between 'traditional' and 'new' forms of food production. In traditional food processing, methods of treatment are primarily bactericidal, causing considerable collateral damage to other desirable food characteristics. In the 'new' forms of food processing, food quality tends to be preserved, but the sublethal stresses applied are principally bacteriostatic. These differences have implications for the development and dissemination of AMR, as the surviving stressed organisms undergo both phenotypic and genomic changes.

David presented laboratory data showing that pathogens stressed by increased concentrations of sodium choride, or reduction in pH, develop higher levels of AMR, and are stimulated to disseminate such resistance to other food-related species. These observations highlight the need to achieve a better understanding of how sublethal stress stimulates AMR in foods, and to review elements of current and new food processing technologies to develop safer alternative combination treatments.

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PHARMACEUTICAL INDUSTRY PERSPECTIVE

Providing a pharmaceutical industry perspective, Dr Ian Morrissey, who is Director of New Business and Project Development for Europe, Middle East and Asia at IHMA Europe Sàrl, provided a thought-provoking presentation highlighted the 65 years of antibiotic usage where failed stewardship and reduced research in recent years has led to the current antibiotic crisis. He pointed out that the human medical need for antibiotics changes over an individual's lifetime and is subject to external influences such as surgery or old age. Alongside the human requirements for antibiotics are animal and environmental demands.

Ian showed how antibiotics are developed through stages of *in vitro* and *in vivo* testing. Resistance may be detected at any of these development stages which renders a potential antimicrobial useless and, in turn, an expensive error for the pharmaceutical industry. This leads to the paradox for companies where antibiotic resistance creates opportunities for them but also reduces their return on investment. Ultimately, the medical need should balance with the commercial profit generated by companies. Importantly, however, it is commonly accepted that other therapies such as cancer drugs can be expensive, whereas antibiotics are traditionally considered as being cheap.

RESISTANCE IN TUBERCULOSIS

Dr Ian Laurenson, Director of the Scottish Mycobacteria Reference Laboratory, provided a brief history of the diagnosis and treatment of tuberculosis (TB), pointing out the traditional lengthy culture, sensitivity and treatment periods. One-third of the global population is infected, with about 1.3 million deaths each year (about 4000/day) and 8.7 million new cases diagnosed. Some 21 years ago WHO declared TB was a global health emergency and anticipates it will take a further 21 years to be controlled.

Ian showed the rates of change of case reports in the UK and globally indicated increased incidence of multiresistant (MDR) strains, which emerged in the early 1980s, and extensively resistant (XDR) strains. which emerged in the first decade of the 21st century. The WHO reports acknowledge the improvements in diagnosis and treatment but emphasise that major efforts are needed to improve success rates. The costs of MDR TB are very high in financial and public health

terms: the costs in the USA range from $17,000 for non-MDR TB to $134,000 for MDR TB and $430,000 for XDR TB. New drugs and reapplication of old drugs are in preclinical development but remain costly.

Resistance testing remains a challenge requiring expert input. Accuracy and reproducibility are issues, particularly with pyrazinimide where the critical concentration defining resistance is often very close to the minimum inhibitory concentration (MIC) required to achieve antimycobacterial activity, increasing the probability of misclassification of susceptibility/resistance (S/R). The WHO initiatives have attempted to standardise methods for testing for resistance and recent developments in technology, including molecular methods, are anticipated but will be even more costly.

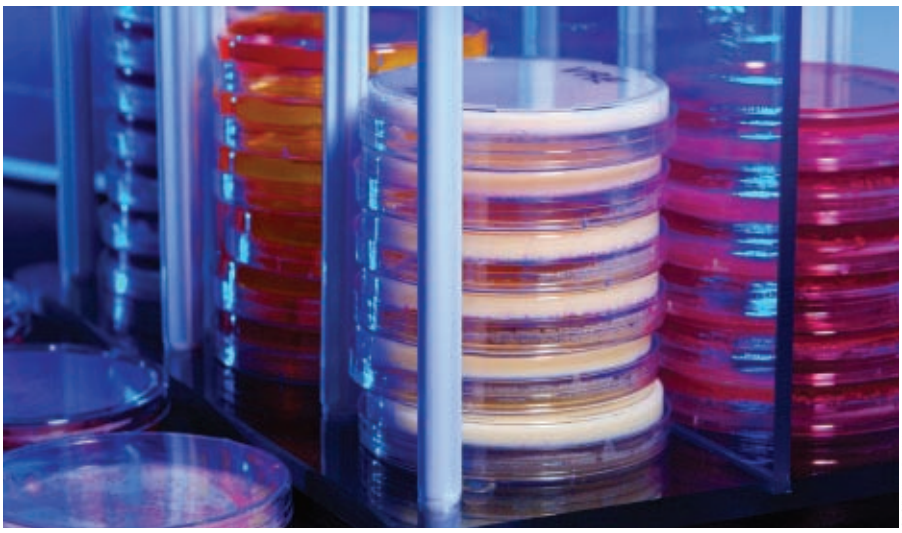
Using a case study, Ian illustrated some of the dilemmas of treating MDR TB and described some of the changes to the complex WHO guidelines for treatment. Summing up, he said that TB diagnostics using rapid diagnostic tools are always improving but diagnosis, treatment and infection control are difficult and costly to manage, especially in the context of human immunodeficiency virus (HIV) infection, poverty, overcrowding, social and political upheaval.

ESBL-PRODUCING *ESCHERICHIA COLI*

A fascinating presentation from Dr Nicola Williams focused on antimicrobial use and resistance in dogs and horses in the UK, where a quarter of all households keep a dog and 1% keep a horse or pony. Some of Nicola's slides illustrated the close proximity that some people live with their pets, so it is not surprising that organisms, including resistant organisms, are shared. Hunt kennel dogs are often fed on fallen livestock and it is apparently fashionable to feed raw meat to household dogs: both practices increase AMR prevalence.

Work in Liverpool has found that consumption of commercial dry food or cooked homemade diets is protective against AMR and MDR faecal *Escherichia coli*. Another Liverpool study found that 26% of dogs and 17% of horses received antimicrobials, and less than 4% of practices had a written policy on antimicrobial use. In a further Liverpool study, in mainland GB nearly 80% of community horses had at least one antimicrobial-resistant *E. coli*; the figures for MDR were 35%, and 9% for extended-spectrum β-lactamase (ESBL)-mediated *E. coli*; the figures for ESBL-mediated *E. coli* were higher in recently hospitalised horses. In dogs, 45% had a history of at least one antimicrobial-resistant *E. coli* in faeces; the figures for MDR and ESBL-mediated *E. coli* were 18% and 4%, respectively.

Dr Williams concluded by saying that recently hospitalised horses and dogs have a significantly higher prevalence of ESBL-producing *E. coli* than those in the community, and that the high prevalence of ESBL and AmpC-producing *E. coli* in some small animal hospitals is worrying; antimicrobial prescribing practices need to be strengthened; and it is likely that there is a higher level of risk for transmission of ESBL-producing *E. coli* to individuals who live or work closely with animals, including dog owners, kennel workers, horse owners, yard workers (livery, racing and riding), horse riders, veterinary surgeons and veterinary staff.



CDC/Melissa Dankel

Selective and chromogenic agars have a role to play in isolating the 'Big 5' carbapenemases, but not all are suitable and two agars may be needed to maximise sensitivity.

DETECTING CARBAPENEMASE-PRODUCING ENTEROBACTERIACEAE

In the final presentation of the day, Professor Neil Woodford looked specifically at detecting carbapenemase-producing Enterobacteriaceae, and explored why there is not a single 'best' method for these important organisms. There is international consensus that carbapenem resistance is a critical AMR threat, with resistance already present and increasing in a number of organisms. He commented that the profusion of abbreviations (eg CRE, CPE, CRO, CPO) is confusing, and described the 'Big 5' carbapenemase families (ie KPC, VIM, NDM, OXA-48 and IMP).

Detecting resistance in the clinical laboratory is essential for identifying infected/colonised patients to enable appropriate patient management, rapid implementation of infection control procedures, and to prevent onward transmission. However, there are difficulties with detecting carbapenemase producers in diagnostic laboratories because their susceptibilities often overlap with those of strains that have other, non-transferable mechanisms of carbapenem resistance. Neil indicated that selective and chromogenic agars have a role to play, but not all are suitable for all 'Big 5' carbapenemases, and two agars may be needed to maximise sensitivity.

Neil stressed, however, that detecting resistance in the clinical laboratory is too slow if using traditional sensitivity testing methods and followed up with supplemental tests (eg rapid phenotypic or molecular diagnostics) is essential. The likelihood of an adverse outcome increases with each hour that a seriously ill patient continues to receive ineffective therapy, but he illustrated the difficulties in giving appropriate empirical therapy for infections caused by multiresistant carbapenemase producers.

Neil reviewed the range of rapid commercial molecular systems available, noting that capability to detect the 'Big 5' families varies among the different kits; none, of course, would be able to find novel carbapenemases. Some tests are suitable for use on isolated bacteria while others are also suitable for use directly on clinical specimens. Thus there is not a single best method, but there is a standard approach outlined in the UK Standards for Microbiology Investigations: Laboratory Detection and Reporting of Bacteria with Carbapenem-Hydrolysing Beta-Lactamases (Carbapenemases),[3] and a revision of this document is due this year. ■

REFERENCES

1 Department of Health. *UK Five-Year Antimicrobial Resistance Strategy 2013 to 2018*. See also, *HPR* **7** (37). London: DH, 2013.

2 World Health Organization. *First WHO Global Antimicrobial Resistance Surveillance Report, HPR* ***8*** *(20)*. Geneva: WHO.

3 Public Health England. UK SMIs (www.hpa.org.uk/smi).

Dr Valerie Bevan CSci FIBMS is chair of the British Society for Microbial Technology and an IBMS Council member.

The presentations given at the BSMT meeting are available on the society's website (www.bsmt.org.uk).

The BSMT will celebrate its 30th anniversary at its annual meeting next year on Friday 15 May. Please contact Valerie with suggestions for topics.