THE NEED FOR SPEED

RAPID METHODS IN CLINICAL MICROBIOLOGY

Microbiologist **Mark Wilks** highlights the potential rapid molecular methods presented in the recent conference of the British Society for Microbial Technology.

Diagnostic microbiology is essentially like gardening, with the leisurely timescale that the word conjures up. Unlike diagnostic virology, where culture has been totally abandoned, rapid molecular methods have made relatively little impact in microbiology.

Many outsiders find this absurd and put it down to the inherent conservatism of the profession, but it's not that simple. If it were, then MALDI-TOF could not have achieved total coverage in large- and medium-sized laboratories in just a few years, although very few laboratories had any experience of mass spectrometry (or any idea of what the term meant).

The difference is that generally cultural methods work in microbiology, but not in virology. Most clinically relevant bacteria can be grown in a reasonable period of time, although you may have to look for the right bacteria in the first place to stand a chance of growing them. Set against this, if the sample was taken when the patient was already on antibiotics, the chances of getting a positive result are greatly reduced, where rapid molecular methods have an apparent advantage.

Uptake of technology

The recent Annual Scientific Conference of the British Society for Microbial Technology focused on the perennial topic of rapid methods and their place in diagnostic microbiology.

Vanya Gant, Clinical Director for Infection at University College Hospital London, gave a thoughtful overview of this area and some of the pitfalls that he has encountered.

The case for rapid diagnostics seems obvious in a patient where severe infection is suspected and treatment cannot wait. Here broad-spectrum has to be used until the results of culture and antibiotic susceptibility results are obtained. In theory, in many cases a switch to a narrow-spectrum antibiotic can be applied and the use of a broad-spectrum antibiotic reserved, thus delaying the development of resistance. There should be improved appropriate treatment and hence outcomes for the patient, improved infection control and outbreak monitoring with rapid identification and typing of bacteria and the detection of possible outbreaks. To the clinician responsible for treatment,

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however, much of this seems academic and if the patient is improving on the broad-spectrum antibiotic, why change?

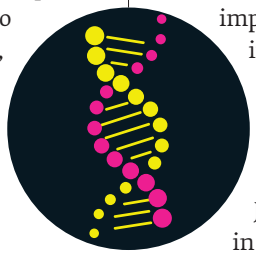
Vanya described his evaluation of a novel micro-array system which gave accurate and rapid speciation of bacteria from positive blood cultures. Although the performance of the system was not in doubt and publication in *The Lancet* provided extensive favourable coverage Vanya asked us if we could guess how many kits were sold. The answer was two.

There are many reasons for this, one of which is that new techniques nearly always cost more than the existing method and can, therefore, have a disastrous effect on the laboratory consumables budget.

Another common problem with molecular methods is distinguishing infection from colonisation – something which is especially true with respiratory and gastrointestinal samples. For example, what is the clinical significance of very low numbers of *Clostridium difficile* or *Clostridium difficile* toxin detected by molecular methods in a patient who is apparently well?

Keep the costs down

Meanwhile, technical developments continue apace – microfluidic chips were described, which may replace quantitative PCR and may turn out to be incredibly cheap. The cost of DNA sequencing is always said to be declining exponentially. In one sense this is true – it is now possible to sequence a human genome in a matter of hours at a cost of about $200. If the human genome is 1000 times bigger than the typical bacterium, such as *Escherichia coli,* it ought to take a couple of minutes and a couple of pence to sequence a bacterium. However, the reality is that it still costs about a hundred pounds to sequence a bacterium and it might take a couple of days or even weeks to batch samples to get the economies of scale and keep the costs down to even that level.



In some cases, manufacturers have become intoxicated with the exuberance of their own technology – DNA sequencers get smaller and smaller to such an extent that some connect to an iPhone and are smaller than the phone itself, but it's hard to see what the value of this could be.

Gemma Clark, a Clinical Scientist from the University of Nottingham, described the introduction of increased efficiency to meet winter demands for rapid detection of respiratory viruses. An in-house system for detecting respiratory viruses by multiplex PCR was replaced by a commercial system provided by AusDiagnostics. The process involved a complete rethink of how the lab was organised, from sample handling and processing, to validation of the new essay to result interpretation.

Turnaround times were maintained or reduced, despite a 30% increase in annual workload, there was improved staff satisfaction and improved EQA performance, which had been a major problem with the existing in-house assay.

Going one step further, Justin O'Grady, Senior Lecturer in Microbiology from the University of East Anglia, gave a talk on rapid meta-genomic diagnosis of hospital-acquired pneumonia. Using the Oxford Nanopore MinION system, he showed it was possible to achieve turnarounds from sample to pathogen genome and antimicrobial resistance results in approximately eight hours.

Whilst it is technically possible to reduce the time to diagnosis by the methods described, it's often harder to show that it actually affects patient management or shows patient benefits. While there are likely to be an increasing number of health economics studies to provide these data, it's a sobering thought that more than 40 years ago Raymond Bartlett, an American microbiologist, showed that unless a report was received on the ward by 11am, when the ward round began, it had no impact on patient management until the next day.

Low tech

In some cases, a low-tech solution may produce impressive results on its own. Consultant Microbiologist at Sherwood Forest NHS Foundation Trust, Mike Weinbren, described a long but successful battle to reduce the time interval between when a blood culture is taken and when the bottle is actually placed on the blood culture analyser. This project did not involve the introduction of complex and expensive new technology but something which was much simpler (at least, in theory) so that the haematology laboratory – which operates for 24 hours a day – could put the blood culture bottles on the analyser immediately on receipt. A comprehensive education programme about the importance of blood cultures and the need for rapid incubation and an extensive audit of the process gave dramatically improved results. BMS

Mark Wilks is Lead Clinical Scientist, Microbiology at Barts Health NHS Trust and a Committee member of the British Society for Microbial Technology.