Saturday 5 August 2006

BMJ

Surveillance and management of all types of *Staphylococcus aureus* bacteraemia

MRSA policies divert attention from MSSA and may risk lives

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In the United Kingdom reporting of bacteraemia due to methicillin resistant *Staphylococcus aureus* (MRSA) infections is mandatory, and reduction in bacteraemia rates is a performance target for NHS trusts. Rates of *S aureus* bacteraemia remain high around the world, so we need forms of surveillance that will allow better understanding of its causes.

In this week's *BMJ* Wyllie and colleagues describe the use of linked data in Oxfordshire hospitals to investigate secular trends in bacteraemia caused by *S aureus*.[1] Using anonymised data on hospital admissions of patients and linking them to information on isolates of *S aureus*, Wyllie and colleagues found that about a third of patients with *S aureus* bacteraemia died within 30 days. The risk of death was similar for methicillin sensitive and methicillin resistant *S aureus* infections.

Between 1997 and 2003, rates of MRSA in these Oxfordshire hospitals increased while rates for methicillin sensitive *S aureus* (MSSA) strains remained constant. In other words, methicillin resistant strains did not displace methicillin susceptible strains: indeed they added considerably to the burden of disease. This paper serves as a reminder that health services must concentrate efforts on preventing all kinds of *S aureus* bacteraemia, to appreciate the importance of both methicillin resistant and methicillin sensitive strains, and to look critically at the successes and failures of control measures. Furthermore, these findings will reflect the experience of many readers and pose important questions.

Is the increase in rates of bacteraemia related to novel strains of bacteria, to changes in the population of patients, to changes in healthcare practices, or to a combination of factors? And how do these trends relate to the work of infection control teams? Many infection control teams share a common experience: they recognise cases of MRSA; initiate general "search and destroy" procedures such as screening and isolation of patients; then after a period of apparent success they abandon these measures as rates of colonisation increase and services are reconfigured to concentrate on high risk patients.

A mathematical model published two years ago describes how such loss of infection control can occur by stealth: measures for screening and isolation may seem effective for years but, as increasing numbers of colonised patients are discharged and readmitted, infection rates reach a threshold where suddenly resources become overwhelmed.[2] Loss of control at one hospital has knock-on effects at units that share the same pool of colonised patients. Such is the experience in the UK.

Around a third of humans are colonised with *S aureus*. Conservative estimates of the number of MRSA carriers worldwide range from 2 million to 53 million, and this pool is growing.[3] The Netherlands is one of the few countries where this rising tide has been held back. A model developed using Dutch data suggests that one factor necessary for control is attempted eradication of carriage on discharge from hospital.[4] Optimistically, this Dutch model suggests that, even when MRSA becomes endemic, it may be possible to reverse the situation by a coordinated reinstatement of search and destroy measures (including eradication on discharge). To do this properly would require a huge investment in facilities, however, and might take a decade or so to bear fruit.

For practical purposes we may be already past the point of no return. Given that the patients studied by Wyllie and colleagues were general medical and surgical patients and were not selected from high risk groups, it may be more pragmatic to concentrate on measures that prevent all forms of *S aureus* bacteraemia (such as better management of vascular devices) and to optimise treatment of bacteraemia.[5,6]

For example, some doubt remains about the optimal duration of antibiotic treatment for *S aureus* bacteraemia and carefully planned multicentre prospective comparative trials in selected patient groups are needed to evaluate antibiotics, including several recently licensed agents, for the treatment of MRSA bacteraemia. For the longer term we need an objective, evidence based debate about the desirability and feasibility of controlling transmission and colonisation.

Eradication of MRSA alone will not solve the problem of invasive *S aureus* infection, not least because strains of *S aureus* that are sensitive to methicillin still account for many infections. *S aureus* is a genetically diverse species,[7] and the acronym MRSA includes a bundle of successful clones which have acquired the mec gene that confers resistance.[8] Sometimes one cannot see the species for the gene. Measures that focus on detecting carriage draw attention away from the real problem of invasive disease and shake the foundation of reasoned intellectual debate on staphylococcal infection.

As Wyllie and colleagues suggest, collecting patient centred data over long periods at representative

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centres would allow more detailed surveillance and could inform prospective intervention studies on the prevention and treatment of bacteraemia.[1] Along with greater understanding of the evolutionary biology of these strains of bacteria,[7 8] better management of community acquired MRSA, and more rational use of antibiotics (antibiotic stewardship), such surveillance could greatly improve the management of invasive staphylococcal infection and save lives.

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Competing interests: None declared.

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Further lessons from the TGN1412 tragedy

New guidelines call for a change in the culture of research

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As eight young men assembled at a London hospital on 13 March this year, they had no idea that within an hour their lives would be changed irrevocably and they would have contributed to a fundamental rethinking of the development and testing of new drugs. The first trial of TeGenero's TGN1412 (a T cell agonist) in humans took place at Parexel's clinical pharmacology research unit at Northwick Park Hospital, London. The events that followed fuelled speculation not only into the conduct of the trial and the nature of the drug, but also into aspects of research as diverse as comparative molecular biology, bioethics, and health economics.[1]

The Medicines and Healthcare Products Regulatory Agency initiated an investigation, but the *BMJ* and other journals called for a more far reaching inquiry independent of the regulatory agency that had approved the trial. On 5 April the agency released its interim report,[2] and the government announced that an independent Expert Scientific Group, chaired by Professor Gordon Duff, would be appointed "to learn from the Parexel clinical trials incident." On 25 July this group released their interim report and recommendations.[3]

Inevitably, the report has pleased some people and disappointed others.[4 5] Although it shows common sense, thoughtful reflection, and even vision, it fails to answer all the questions asked by the *BMJ*. Part of the problem is that the expert group was given a narrow remit, which focused on the biology and mechanics of high risk "first in man trials." In contrast, the *BMJ* had asked that the events of 13 March be interpreted in the context of the broader social and economic forces that shape research, because things happen for reasons related to the systems that create these factors.[6]

Critics of the trial highlighted many factors that should have indicated the potential for disaster. However, people who are disappointed with the report must understand that the expert group wisely avoided the appearances of a "judicial style inquiry." The group refrained from criticising the parties involved, but reading between the lines shows that many things could have been done better and that these factors were compounded. Another difficult task the group faced was creating a balance between improving safety without being accused of "stifling innovation." Many pieces of the puzzle are still missing (including the clinical data that were withheld from the report, pending publication), and in the end more questions are asked than answered.

The recommendations fall into several broad categories: preclinical development that is both directed and consultative; evidence based transition to testing in humans; more open regulatory and ethical review, including independent scientific expertise; and most importantly, the need for more transparency.[7 8] Although the report is carefully couched in the language of the terms of reference, the reader will realise that the findings have profound implications for all aspects of human research and drug development. There is a Buddhist story about seeking truth, in which disciples enter a darkened temple and on emerging compare their experiences of encountering an elephant. Although each witness to the inquiry described a part of the elephant, it is not clear that the expert group actually realised that there was an elephant in the temple.[9] Specifically, they did not engage the many voices that have pointed to a collapse of integrity in research and the crisis in evidence based medicine that has been built on a corrupt database.[10 11]

It would be easy just to concentrate on the technicalities. For instance, one thing that is clear is "that the preclinical development studies ... did not predict a safe dose in humans." The group's recommendations on dosing are sensible and prudent—for instance, shifting the threshold from one at which adverse effects are observed to one at which biological effects are observed. The deeper issue is why are we asking these questions now? Should they not have been self evident? Another recurrent theme of the report is the

BMJ 2006;333:270–1