ABSTRACT
Healthcare-associated infections (HCAIs) are an important and costly complication of healthcare throughout both primary and secondary sectors. In the European Union alone, the financial burden associated with HCAIs is up to €10b annually. HCAIs add unacceptable costs to healthcare economies – a 2- to 3-fold overall increase in the cost of the affected patient’s care in terms of extended hospital stay and associated costs. Increasing resistance following the use, mis-use, and over-use of antibiotics poses a world-wide problem that is compounded by the fact that no new antibiotics are in the pipeline. The recent and expanding appearance of carbapenemase resistance is of particular concern, as some strains of *Klebsiella pneumoniae* that produce carbapenemase are almost pan-resistant, meaning that antimicrobial therapy is virtually impossible. There is, however, good evidence that control measures can be effective. In the UK, the overall numbers of methicillin-resistant *Staphylococcus aureus* (MRSA) and *Clostridium difficile* infections have fallen due to increased compliance with infection prevention/control procedures. In particular, the delivery of care bundles containing evidence-based interventions has proved highly effective in preventing MRSA bacteraemias along with the “clean-your-hands” campaign and other measures such as universal admission screening. Surgical site infection (SSI) is probably the most preventable HCAI, yet due to the inconsistent implementation of level 1A evidence-based interventions, the UK and US have shown disappointing failures to reduce SSI. The reason for this lack of progress in SSI likely reflects poor compliance with guidelines and checklists.

BACKGROUND OF ANTIBIOTIC RESISTANCE AND HEALTHCARE-ASSOCIATED INFECTIONS
After noting in 1928 that *Penicillium notatum* inhibited *Staphylococcus aureus* in a Petri dish, Alexander Fleming and his colleagues went on to successfully treat Police Constable Alexander for staphylococcal bacteraemia, although the patient relapsed and died when the antibiotic ran out. Nevertheless, a new class of antimicrobial drugs had been born, and although we have ever since relied on antibiotics to prevent and control infection, we did not heed Fleming’s prophetic warning that inappropriate use might lead to resistance. We now know that resistance inevitably follows the introduction of new antibiotics within 15-20 years or even as little as 2-3 years\(^1\). Until recently, however, there has always been an alternative antibiotic when resistance was encountered. Now, times have changed; no new class of antibiotic has been introduced for well over a decade, and there are no new antibiotic classes in the pipeline, rather just combinations of existing agents. Although there are many reasons for this lack of progress, it is mostly related to economic factors bound to research and development, regulatory procedures, and financial returns on investment for pharmaceutical companies.

With increasing antibiotic resistance, healthcare-associated infections (HCAIs) have become a more challenging problem. These iatrogenic complications, which are acquired through contact with healthcare services and institutions and are associated with considerable morbidity and mortality, are to a significant extent avoidable. Their costs to healthcare are enormous - up to €10b annually in Europe due to added costs of treatment and extended hospital stays. Additionally, some individuals become reservoirs of resistant organ-
isms (i.e., carriers) for whom suppression is expensive and complex, resulting in national screening programmes or “search and destroy” strategies. Today, the leading HCAIs are hospital-acquired pneumonia (not ventilator-associated); urinary tract infection (UTI), including those associated with catheters; ventilator-associated pneumonia; prosthetic and surgical site infection (SSI) caused by Staphylococci, including methicillin-resistant and -sensitive \textit{Staphylococcus aureus} (MRSA and MSSA, respectively) and multiply resistant coagulase negative staphylococci, which are often associated with joint replacement or intravascular catheters; secondary bacteraemias; and complicated skin and soft tissue infections. \textit{Clostridium difficile} infection (CDI), occurs as a secondary infection due to gut flora disturbances resulting from treatment with other HCAIs.

\section*{Reducing the Rise of Antimicrobial Resistance}

The media has a huge impact on the HCAI political agenda\textsuperscript{b} by driving public awareness and fostering the need for politicians to “do something” about “superbugs”, “killer microbes”, and outbreaks of “flesh-eating viruses”. For instance, the media portrayed England as one of the “dirtiest” countries because of the rise of MRSA bacteraemia between 1991 and 2003. While the actions of politicians may have been driven by media influence, infection prevention and control teams have turned the tide through hand hygiene campaigns, improved clinical practice with respect to invasive devices, undertaking root cause analysis when infections occur, and implementing search and destroy campaigns (historically effective in the Low Countries and Scandinavia). The contribution of individual interventions is difficult to assess, but together with care bundles for central venous and peripheral intravenous catheter use and improvements in antibiotic stewardship, rates of MRSA bacteraemia continue to decline in the UK with impressive zero tolerance in NHS Trusts. It has been claimed by one UK “red top” daily newspaper, however, that MRSA has been minimised through a “plea to medics” to wash their hands.

Unfortunately, infection prevention and control issues are not at the top of busy clinicians’ agendas. Despite that mandatory infection control lectures are considered therapeutic for sleep-deprived staff members, infection/prevention team-led training, surveillance, and feedback on local infection data have significantly reduced rates of MRSA and CDI. Interestingly, this does not seem to have been the case with \textit{Escherichia coli} bacteraemia, the majority of which occur in community settings. Root cause analysis of increasing rates of infection in community settings suggests a relationship among use of urinary catheters, UTI, and the lack of effective antibiotics available to general practitioners. The evidence base for long-term urinary catheter use and related complications is poor, but we know that catheterisation is not an intervention without complication. Urinary catheters are foreign bodies, and colonisation with \textit{Proteus mirabilis} and \textit{Providencia rettgeri} can cause biofilm formation, encrustation, and blockage\textsuperscript{a}.

\section*{A Further Look at Extended Spectrum \(\beta\)-Lactamases}

\(\beta\)-lactamases are enzymes that destroy the \(\beta\)-lactam ring of penicillins and cephalosporins. Common coliforms producing these enzymes are becoming resistant to most \(\beta\)-lactam antibiotics, and simple \textit{E. coli} UTIs may be impossible to treat in primary care due to a lack of effective oral therapies. Controlling the spread of resistance in community settings is a huge challenge\textsuperscript{a}, as plasmid-mediated resistance facilitates spread and makes resistance difficult for microbiology laboratories to detect\textsuperscript{a}. This in turn leads to challenges in antibiotic formulary construction and a lack of information for clinical decision-making. Again, the media has drawn attention to extended spectrum \(\beta\)-lactamase-related deaths and has demanded tougher action, despite these deaths not being related to spread in hospitals. Carbapenem antibiotics are the current last resort in this battlefield, but already there are increasing numbers of carbapenemase-producing \textit{Enterobacteriaceae}, such as New Delhi metallo-\(\beta\)-lactamase producers and carbapenemase-resistant \textit{Klebsiella pneumonia}, which have implications for global travel, health-care tourism, overseas military action, and inter-hospital transfers.

\section*{Concerted Action is Needed}

Resistance to antibiotics is an issue for all, not just clinicians and specialists but also health-care and procurement managers, politicians, and, of course, patients and carers. It is time to move on from MRSA and CDI, which are coming closer to being under control. Multi-drug resistant Gram negatives, such as carbapenemase-resistant \textit{Klebsiella}, should in principle present no differences in terms of control. Reduction of HCAIs can be achieved through the use of care bundles (provided that compliance is measured and reported) together with strict hand hygiene and environmental cleaning. Care bundles addressing intravascular care have proved effective in preventing MRSA bacteraemia, but similar success has not been found in reducing SSIs on either side of the Atlantic, despite that such bundles may contain several elements with a level I evidence base. The problem is related to poor compliance. We all need to understand that the real problem posed by antibiotic resistance is not just the over-use or
mis-use of antibiotics; it is any antibiotic use that risks the development of resistance. We need to preserve the gift of antibiotics.

A world without antibiotics is almost unimaginable in the modern era. Formerly fatal infections such as meningitis, bacteraemia, and pneumonia would become killers again; postoperative SSIs would increase to 30% or more after “at risk” contaminated/dirty surgery due to the lack of effective agents for prophylaxis; transplantation of tissue and organs might need to cease; cancer chemotherapy with the attendant risk of infection would be too risky; joint replacement and implants, such as vascular grafts, would become very high risk procedures; and post-partum and neonatal infections would return. Although there are options for action that involve the development of new antibiotics and vaccines, the motivation for such actions remains poor. Certainly we can sustain the effectiveness of existing antibiotics with close antibiotic stewardship. Perhaps better communication and precision concerning the choice and duration of antibiotic use could occur between microbiological laboratories and clinicians at the front line.

The burden of infection can be reduced by monitoring and enforcing hygiene and other public health measures, the adoption of novel immunisation strategies (which have been so effective for polio and smallpox), and continuous improvement in the design of healthcare environments.

Antibiotics will always have a role in treating cellulitis and lymphangitis before they progress to systemic inflammatory response syndrome, sepsis, or multiple organ dysfunction syndrome. In situations in which host defences are poor, such as immunosuppression or diabetes, and in which the bioburden in chronic wounds is out of control and leads to critical colonisation and local spreading infection, there will always be a need to consider antibiotic therapy, although early intervention with topical antiseptics should also be considered. HCAIs are not an inevitable part of the provision of healthcare. Effective infection control measures help us protect patients from themselves and each other when in their most vulnerable states. Staff delivering healthcare should continually reflect on their practice. We owe this level of care to the memory of Alexander Fleming and his legacy.

References