The need for new antibiotics

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After a half-century of virtually complete control over microbial disease in the developed countries, the 1990s have brought a worldwide resurgence of bacterial and viral diseases. An important factor in this phenomenon is the acquisition of antibiotic-resistance genes by virtually all major bacterial pathogens. Disturbances of ecosystems, the tremendous increase in the size of populations at high risk because of immunocompromise, the increased frequency of invasive medical interventions, and the prolonged survival of many patients with chronic debilitating disease have amplified the problem to one of global dimensions. Recently, bacterial strains resistant to all available antibacterial agents were identified among clinical isolates of some bacterial species. The dissemination of such multidrug-resistant bacteria has become more rapid during the past decade, thanks to the tremendously increased mobility of human populations.

Nosocomial-acquired pathogens

During the past decades, gram-positive bacteria have gradually emerged as the most frequent cause of nosocomial disease. These pathogens are especially difficult to treat because of their high frequency of drug-resistance strains. Methicillin-resistant strains now make up 60 to 90 percent of all isolates of coagulase-negative staphylococci, the most frequent cause of infections related to intravascular catheters and prosthetic devices. In many European countries the proportion of MRSA among nosocomial staphylococcal isolates increased from <8% in the ‘80s to above 50% in the last five years. *S. aureus* is the most frequent cause of skin and wound infections and bacteremia and the second most frequent cause of lower respiratory infections in nosocomial disease. Strains of MRSA,

formerly confined to large teaching hospitals, had spread in the last years into small hospital units and into nursing homes. The majority of MRSA isolates are also resistant to other antibiotics, necessitating the use of the glycopeptide antibiotic vancomycin and, recently, linezolid. Against those antibiotics also resistance is recently observed. Vancomycin-resistant *Enterococcus faecium* (first reported from the United Kingdom and France in 1987) have been detected in many European hospitals and these strains are also frequently resistant to beta-lactam antibiotics, aminoglycosides, fluoroquinolones, tetracycline, chloramphenicol and teicoplanin.

Untreatable *Ps. aeruginosa, Stenotrophomonas maltophila* or *P. cepacia* have become an increasing problem in patients with cystic fibrosis but also in ICU patients on long time ventilation. *Acinetobacter*, a common free-living microorganism and inhabitant of the human skin that is resistant to all available antibacterial agents has caused fatal disease in patients in intensive care units. Novel, plasmid-borne, extended-spectrum beta-lactamases capable of inactivating antibiotics (such as ceftazidime or imipenem) specifically developed against beta-lactamase-producing gram-negative bacteria have been detected in nosocomial isolates of *Klebsiella* and *Ps. aeruginosa*.

Community-acquired pathogens

Although resistance has been recognised as a substantial problem for a number of community-acquired pathogens, including *Neisseria gonorrhoeae, Salmonella* and *Shigella*, even more ominous is the emergence of multiple-antibiotic resistance among such important community-acquired pathogens as *Mycobacterium tuberculosis* and *Streptococcus pneumoniae*.

Although infections due to the usual strains of tuberculosis have high rates of cure, multidrug-resistance strains have emerged in several countries, with case fatality rates of 40 to 60 percent in patients with normal immunity and over 80 percent in immunocompromised patients.

Resistance to penicillin (intermediate), tetracycline, erythromycin, single or in combination, appeared in *S. pneumoniae* in the 1960s, and resistance to chloramphenicol and co-trimoxazole in the 1970s. Of special concern was the first description of multiresistant strains (including penicillin high-level resistant microorganisms), which were initially reported in the

1970s in South Africa. During the 1980s and the 1990s, *S. pneumoniae* has become resistant to cephalosporins and quinolones, and there has been a spread of penicillin-resistant and multiresistant pneumococci worldwide. Penicillin-resistant *S. pneumoniae* isolates seem to be prone to acquire resistance not only to other beta-lactams but also to non beta-lactam antibiotics, including erythromycin and other macrolides, tetracycline, chloramphenicol and co-trimoxazole.

Clonal spread is an important mechanism for dissemination of resistant *S. pneumoniae* among day-care centres, hospitals and geographical regions. The most remarkable example of these multidrug-resistant pneumococcal clones is the serotype 23F clone, which was initially identified in Spain in the early 1980 and is now found in the most regions of the world.

Currently, the prevalence and patterns of antibiotic resistance in *S. pneumoniae* vary widely from one country to another. Generally, pneumococcal penicillin resistance occurs at a relatively low frequency in Northern Europe. A prevalence of penicillin nonsusceptible *S. pneumoniae* of <15% has been reported by Felmingham et al. (2002) in the Netherland (3.9%), the UK (14.3%) and Sweden (9.4%). In contrast, penicillin resistance is dominant in France and Spain, where its prevalence exceeds 50%. Importantly, high-level resistance predominates in these countries. However, in Northern Ireland and Ireland, penicillin nonsusceptibility has reached 25%.

During the 1990s across Europe there was a steady increase also in macrolide resistance in both penicillin-susceptible and -resistant *S. pneumoniae* isolates. Both the Alexander Project and the PROTEKT study reported overall prevalence of erythromycin resistance of 25% in 1999-2000. Macrolide resistance is most common in France, Spain and Italy, where the respective prevalences are 58.2%, 28.6-35% and 25.5-42.9%.

Regarding the clinical impact of infections by resistant pneumococci, there have been an extremely limited number of controlled studies documenting clinical failures as a result of the rapidly emerging drug-resistance. Compelling evidence that drug-resistant pneumococci affect clinical outcomes in patients with meningitis and otitis exist. However, the clinical relevance of resistance in the therapy of nonmeningeal pneumonia infections remains controversial. Most evidence indicates that the treatment with beta-lactam antimicrobials is effective against pneumococcal pneumonia caused by strains with penicillin MIC<2 mg/L. The same may not be true for isolates with higher MICs.

In the early 1970s, resistance of *H. influenzae* to ampicillin began to emerge and has increased steadily thereafter. Production of beta-lactamase (TEM-1 and ROB-1 types) is the primary mechanism of resistance to ampicillin and other beta-lactam antibacterial by this species. International and national studies showed that the prevalence of beta-lactamase-positive *H. influenzae* varies considerably with geographic region. In Europe synthesis of beta-lactamase occurs with higher rates in France (22-31%), Ireland (17-26%), Belgium (16-18%), UK (15-18%) and Romania (16%), and lower rates in Czech Republic, Poland, Slovak Republic and Germany.

In summary, the emergence and spread of resistant bacterial pathogens is an environmental problem analogous to other problems in the human environment that threaten health at the beginning of 21st century. There is a need for both more prudent use of antibacterial agents but also an urgent need for new antibacterial active drugs.

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