Epidemiology of emerging/re-emerging antimicrobial-resistant bacterial pathogens

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The rapid global expansion of bacteria resistant to antimicrobials is the most important development over the past year in emerging bacterial diseases. The critical events are the emergence of *Staphylococcus aureus* with decreased sensitivity to vancomycin, worldwide resistance to penicillin in *Streptococcus pneumoniae*, and the remorseless progression of multiply-resistant *Mycobacterium tuberculosis*. Most startling was the isolation from a human in Madagascar of a plague bacillus possessing a plasmid readily transferable to *Escherichia coli*, which confers multiple antibiotic resistance. The hospital environment continues to see the transmission of resistant organisms, notably vancomycin-resistant enterococci. Finally, as food markets become more open around the world, food-borne outbreaks of *E. coli* 0157 and cholera demonstrate how difficult it can be to establish effective health and safety barriers.

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Abbreviations

VRSA	vancomycin-resistant *S. aureus*
MRSA	methicillin-resistant *S. aureus*
WHO	World Health Organisation

Introduction

Over the past three or four decades, many people became accustomed to the idea that we had entered an era of decline of infectious diseases, with bacteria conquered by antimicrobials and viruses by vaccines. Recent events have enlightened us somewhat brutally. We are now in retreat against many infectious diseases (malaria, tuberculosis, dengue fever and AIDS), and are returning to the pre-antimicrobial era with several bacteria (*Staphylococcus aureus*, *Streptococcus pneumoniae*, *Salmonella typhi* and *Mycobacterium tuberculosis*). We underestimated the ability of microbes to acquire new genetic information that can re-establish them in hostile environments. Although the outbreaks of new bacterial diseases have not yet overwhelmed us, a rapidly expanding list of antimicrobial-resistant organisms are infecting us in our homes, places of work and, particularly, in our hospitals. The emergence of antimicrobial-resistant organisms in virtually every part of the globe will be the subject of this review.

Antimicrobial-resistant bacterial pathogens

Yersinia pestis

Plague bacillus resistant to multiple antibiotics was isolated from a 16-year-old boy with bubonic plague in the Ambalavao district of Madagascar. Although the boy recovered on treatment with intramuscular streptomycin and oral cotrimoxazole, *Yersinia pestis* isolated at the Institute Pasteur in Madagascar was found to contain a plasmid encoding resistance to the recommended antimicrobials: ampicillin, chloramphenicol, kanamycin, streptomycin, sulfonamide and tetracycline [1••]. Furthermore, the plasmid carrying the genes coding for resistance likely came from a member of the *Enterobacteriaceae* [1••] and it was demonstrated that this plasmid is easily spread among *Y. pestis* and to further *E. coli* strains. This plasmid mobility implies that further resistant strains can be expected to evolve in patients, or in rodent or flea hosts. Plague foci have been expanding in recent years in Asia, Africa, and North and South America, so the implications of resistant *Y. pestis* are considerable. Recommendations for treatment and prophylaxis may require revision. Furthermore, the continued exchange of genetic information between disparate organisms means that any organism may, under the lightest of antimicrobial pressure, easily acquire a resistant plasmid.

Streptococcus

Clinical isolates of *S. pneumoniae* highly resistant to penicillin and the clinical failure of high-dose penicillin are now being reported in all parts of the globe [2–6]. This mean that in many poor countries we lose the mainstay of pneumonia treatment in children. More expensive drugs place treatment out of the reach of the poor which will undoubtedly lead to increased mortality due to this organism. Furthermore, a relationship between prior treatment with penicillin and an increase in the carriage of penicillin-resistant strains of *S. pneumoniae* has been demonstrated [7,8]. *S. pneumoniae* capsular types 23F and 19kF have been isolated in Asia, South America, Europe and North America with elevated minimum inhibitory concentration to penicillin, chloramphenicol, tetracycline, sulfamethoxazole and erythromycin [4,9–11]. Studies in Central and Eastern Europe suggest a patchwork of sensitivity and resistance, consistent with the gradual spread of the resistant organisms to virtually all parts of the globe [12]. Patients infected with HIV are also more likely to carry pneumococci and have pneumonia caused by *S. pneumoniae*, especially antimicrobial resistant strains [13,14]. Resistant organisms are spreading to areas as remote as New Guinea and Iceland, and physicians can no longer follow global recommendations for the treatment

of *S. pneumoniae*. The implication is that the individual physician now has to be aware of the local situation in his choice of antimicrobials and, in many places, such information may not be readily available. The result may be the use (often inappropriate) of an increased range of antimicrobials, which in turn will accelerate resistance to a wider array of drugs.

There is a small ray of hope, that being conjugated pneumococcal vaccine which appears to reduce carriage and thus spread pneumococci [15] (and to which HIV-infected individuals respond [16]). Fortunately, many of the antimicrobial-resistant strains of pneumococci isolated have belonged to one of the 23 capsular types contained in the vaccine currently being tested [11,15,17,18]. Thus, pneumococcal vaccine may well become an important tool in the prevention pneumococcal disease, which may force the pace for broader use of the vaccine and hopefully its further development and, ultimately, a combination of the rational use of antimicrobials with a vaccine would appear to be the best hope. There are at present no data concerning the increase in morbidity and mortality in previous years that may have resulted from the emergence of antimicrobial-resistant *S. pneumoniae*.

Staphylococcus

An isolate of *S. aureus* resistant to vancomycin (VRSA) was reported in 1997 from a patient in Japan [19]. Although methicillin-resistant *S. aureus* (MRSA) have been around for more than a decade, their frequency is increasing worldwide; vancomycin resistance is new. Control of the spread of MRSA has been through the classical methods of barrier nursing techniques, cohorting and vigorous attention to the sterility of invasive procedures, with the recent addition of molecular epidemiology techniques [19]. MRSA has hitherto been treatable with vancomycin. This last line of treatment has generally been used judiciously in hospitals and its limited distribution and control of use in well-managed settings were thought to be sufficient to ensure its continued efficacy. Now we are seeing antimicrobials sold in quantity throughout the world and used and prescribed by a range of individuals with highly variable training. In some parts of the world, antimicrobials, even vancomycin, can be bought over the counter, and in such settings few, if any, hospitals have antimicrobial-use policies or even microbiology laboratories capable of generating accurate sensitivities. Nevertheless, in such places, invasive procedures and immunosuppressive regimes are increasingly used. Coupled with the ease with which *S. aureus* acquires new genetic elements, this situation is a recipe for untreatable infections.

The report from Japan, and the subsequent identification of an isolate with similar resistance patterns to vancomycin in the United States demonstrates the possibility of multiple foci of VRSA [20•]. Resistant organisms must have been silently, or at least imperceptibly, emerging in multiple areas, possibly circulating in populations on opposite sides of the globe. It seems reasonable to expect the spread to continue. As with MRSA, hospitals will be able to partially control the situation with traditional methods, but in developing countries this is likely to be much more difficult.

Vancomycin-resistant *E. faecium* are increasingly reported to be associated with nosocomial transmission and infection [20•,21]. Vancomycin is used as a growth promoter in pig and poultry farms and the excretion of resistant strains by animals contaminates food supplies. The frequency of transmission of such strains to humans remains to be demonstrated, but the risk is evident. Two recent reviews discuss in detail the complex and important issue of vancomycin resistance in *S. aureus* and *E. faecium* [22,23]. It is encouraging to see reports that reflect the use of the newer technique of molecular marking in the epidemiological control of hospital infections such as MRSA or antimicrobial-resistant *E. faecium*, and their application to the understanding of transmission.

Neisseria gonorrhoea

Gonococci with reduced sensitivity to fluoroquinolones are now emerging widely from the Far East and South-East Asia, (21% sensitivity in Thailand, full resistance elsewhere) [24••,25•]. This resistance is predominantly chromosomally mediated, particularly with ciprofloxicin. In Thailand, virtually all strains were also penicillin- and tetracycline-resistant, about half of which was plasmid mediated. All of the strains remained sensitive to spectinomycin [25•]. As with *S. pneumoniae*, treatment will vary locally depending on patterns of resistance, information that may not be readily available to the prescribing physician.

Mycobacterium tuberculosis

The march of antimicrobial resistance in *Mycobacterium tuberculosis* continues unabated [26••,27•,28•]. Tuberculosis has receded where HIV infection is now greatly improved with therapy, and where stringent isolation and control of *Mycobacterium tuberculosis* patients was practicable [29•]. On the other hand in many places with high rates of infection no such reduction has been seen. The recent review of the problem of antimicrobial resistance by the World Health Organisation (WHO) shows that it is now widespread, and is not only associated with HIV. To further compound matters, a multidrug-resistant outbreak of nosocomially spread *M. bovis* has been described [30]. The lack of facilities in many parts of the world for culture and antimicrobial sensitivity of *Mycobacterium tuberculosis*, has masked the growing problems of resistance. The lack of accurate information compounds the difficulty in providing adequate treatment. Many of the drugs now required are too expensive and people will continue to receive ineffective drugs, increasing the development of resistant strains, prolonging the initiation of treatment and providing further opportunity for spread. Progress has

been made in defining resistance genes, but this is not yet translated into simple procedures for guiding antimicrobial therapy. The major problem in most parts of the world is that diagnosis is inaccurate and delayed, so treatment is too late to prevent spread. The misuse of antimicrobials is now so widespread that resistant MTB are seen in the most remote and unexpected areas. Although the Bacille Calmette-Guerin (BCG) vaccine prevents severe disease in young children, it has little overall effect in preventing the spread in older populations, and offers no solution to the current problem.

Food-borne pathogens

On the bright side, the potential threat from the 0139 strain of *Vibrio cholerae* identified in Asia in 1993 and thought to be the likely source of the eighth pandemic, has mysteriously sunk from view. It appeared to be in the process of replacing the 01 strain in the early outbreaks in Bangladesh, India and Pakistan but then subsided to the point of almost disappearing. Nevertheless, food- and water-borne epidemics remain at the forefront of epidemic (and endemic) bacterial diseases, and are the overall cause of more morbidity than any other bacterial group. *E. coli* 0157 continues to crop up in large and small epidemics, resulting in enormous costs in terms of food recalls and other measures [31]. Because this disease is particularly prominent in the developed world, we hear and read more about it than the traditional gastric infections such as salmonella, shigella and campylobacter, which continue unabated and with an increasing emergence of resistant strains. A new player in the large water- and food-borne epidemic scene is the protozoan *Cryptosporidium parum* causing cryptosporidiosis, which has been reviewed recently [32]. This has caused large outbreaks because of water contamination and imported raw foods. It is a substantial cause of persistent diarrhoea in young children, with subsequent substantial weight loss [33,34]. This raises the problems presented by the development of increased raw food trade internationally. If those countries importing food can work constructively with those exporting it, this will result in improved quality of food for all. Compounding the problems are the difficulties created by false positive tests due to poor laboratory training resulting in 'pseudo-epidemics' in places where no diagnostic facilities had previously existed.

Lest most of us in the western world, and particularly those reading this review, forget, much of the world is struggling with highly antimicrobial-resistant shigella [35–37] and salmonella infections [38,39]. In parts of Asia, ~30–40% of the isolations from blood cultures at hospitals are *S. typhi*, and in some places over half are resistant to four or more groups of antimicrobials. This is an issue that can no longer escape attention as we open more food markets and travel more extensively as populations grow. We run the risk of increasing the spread of antimicrobial-resistant infections to many areas of the world where they are not currently found. Although newer approaches to vaccines, particularly highly effective mucosal vaccines, offer a great deal of hope, classical means of controlling the quality of food and water are ever more important, and ultimately protect more people.

Conclusions

I cannot but help observe that we are swimming against a biological tide of overwhelming proportions, which is compounded by the lack of information from precisely those parts of the world where infectious diseases are highly endemic and populations are expanding rapidly. At the same time, antimicrobials are being used in large quantities with no accurate diagnostic facilities or reporting systems. Local physicians throughout the world have little information on which to base their choice of antimicrobials and little incentive to limit use to conserve efficacy. Without simple and rapid diagnostic tests for common respiratory and gastrointestinal illnesses in the physician's office or clinic, antimicrobials will continue to be misused, and the selection pressure for resistance will increase. Presently, we also need more information on the relationship between the carriage of organisms and the potential for disease. Should a program of surveillance for carriage of potentially dangerous organisms (e.g. highly resistant staphylococci) be applied to certain at-risk populations (e.g. hospital patients)? What is the relationship between carriage and transmission or subsequent disease, and can we effectively alter carriage to reduce risks? It is encouraging that some of the vaccines now in use, or planned for widespread use, will reduce the carriage of the offending organism (e.g. *Haemophilus influenzae* and *S. pneumoniae*). This is particular needed, in the poorest parts of the world. This is an issue that must take on something more than market forces; if it does not we will all in some way be affected by the consequences of our inaction.

Clearly the rapid rise and spread of antimicrobial-resistant organisms places a heavy burden on the daily decision of physicians trying to treat patients with these infections. The system of scientific publication, laudable as it is for the documentation of scientific advances, is woefully inadequate as a timely disseminator of information on antimicrobial resistance. It seems to me that the efforts being made by WHO and many other organizations to create an electronic network for the rapid transmission of information about antimicrobial resistance must be accelerated. The model of ProMed (e-mail: promed@usa.healthnet.org) for general information on infectious diseases is an excellent one to emulate, but for antimicrobial sensitivity it would need careful formatting and careful technical editing to ensure that antimicrobial testing and reporting are standardized and thus comparable. We need to use all the modern tools of diagnosis and communication at our disposal to wage an effective war against microbes, which have had millions of years to hone their biological escape mechanisms.

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