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Optimal use of antibiotic resistance surveillance systems

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ABSTRACT

Increasing concern about the emergence of resistance in clinically important pathogens has led to the establishment of a number of surveillance programmes to monitor the true extent of resistance at the local, regional and national levels. Although some programmes have been operating for several years, their true usefulness is only now being realised. This review describes some of the major surveillance initiatives and the way in which the data have been used in a number of different settings. In the hospital, surveillance data have been used to monitor local antibiograms and determine infection control strategies and antibiotic usage policies. In the community, surveillance data have been used to monitor public health threats, such as infectious disease outbreaks involving resistant pathogens and the effects of bioterrorism countermeasures, by following the effects of prophylactic use of different antibiotics on resistance. Initially, the pharmaceutical industry sponsored surveillance programmes to monitor the susceptibility of clinical isolates to marketed products. However, in the era of burgeoning resistance, many developers of antimicrobial agents find surveillance data useful for defining new drug discovery and development strategies, in that they assist with the identification of new medical needs, allow modelling of future resistance trends, and identify high-profile isolates for screening the activity of new agents. Many companies now conduct pre-launch surveillance of new products to benchmark activity so that changes in resistance can be monitored following clinical use. Surveillance data also represent an integral component of regulatory submissions for new agents and, together with clinical trial data, are used to determine breakpoints. It is clear that antibiotic resistance surveillance systems will continue to provide valuable data to health care providers, university researchers, pharmaceutical companies, and government and regulatory agencies.

Keywords Antibiotic resistance, resistance, review, surveillance

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INTRODUCTION

Antibiotic resistance is often described as a unidirectional, progressive process associated with antibiotic use. Typically, antibiotic resistance arises and increases in incremental steps that are the result of genetic mutation, the acquisition, incorporation and expression of exogenous genetic material introduced into a naive genome, or clonal dissemination. A desire to monitor, model and predict antibiotic resistance has resulted in the development and use of surveillance systems at the local level (primarily hospital-based systems), as well as regionally, nationally and internationally. Antibiotic resistance presents an ongoing challenge in the effective treatment of patients with infections.

Antibiotic resistance surveillance systems have several important goals. These include: identifying, understanding and predicting trends in resistance; detecting the emergence of new resistance mechanisms; developing, implementing and monitoring the impact of new empirical antibiotic prescribing, infection control and public health guidelines; identifying outbreaks of resistant organisms; assisting in the detection of a bioterrorist event; identifying the need for new antibiotics (targeted and broad-spectrum agents) and potential cellular targets for new agents; identifying the need for new diagnostic tests; educating health care providers, patients and the general public; and providing data for new drug

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applications (NDAs) and other submissions to federal licensing agencies (Table 1) [1,2].

Pathogens that have acquired resistance to antibiotics prescribed currently, or that demonstrate intrinsic antibiotic resistance to those agents, or that possess enhanced virulence characteristics continue to emerge. Antibiotic resistance surveillance systems can provide insights into the areas where resistance is most prevalent, where the prevalence of resistance is increasing the fastest, and species which pose the most significant public health threats [2–5]. Given the potential for variability in resistance, and the mobility of resistant organisms and resistance determinants (e.g., plasmids, transposons), the need for and benefits of local and geographically broader surveillance can be understood readily. Access to timely and accurate antibiotic resistance data may also help to prevent inappropriate reactions to anecdotal reports of resistance, which can unfairly bias the perceived efficacy of an agent, complicate antibiotic strategies, and confuse laboratory testing efforts. In this review, a brief description of the types of antibiotic resistance surveillance systems available currently will be followed by an account of the optimal uses of surveillance systems by health care providers, university researchers, pharmaceutical and biotechnology companies, and government and regulatory agencies.

TYPES OF ANTIBIOTIC RESISTANCE SURVEILLANCE SYSTEM

Local surveillance systems

All clinical microbiology laboratories that conduct in-vitro susceptibility testing should disseminate surveillance data annually, or more frequently, to all local health care providers and other appropriate groups as required. For health care providers, surveillance data should be collated in the form of tables that may be constructed according to National Committee for Clinical Laboratory Standards (NCCLS) M39-P guidelines [6]. Ideally, local surveillance consists of continuous tracking of antibiotic resistance trends among all clinically relevant isolates tested at an institution, with the results available to health care providers and relevant other groups through the publication of

Table 1. Uses of antibiotic resistance surveillance system data by hospitals, university researchers, pharmaceutical companies and governments

	Users of antibiotic resistance surveillance data				
Uses of antibiotic resistance surveillance system data	**Hospitals**	**Community health care providers**	**University researchers**	**Pharmaceutical companies**	**Governments**
Guide patient therapy	x	x			
Identify trends in antibiotic resistance: assess the magnitude of new resistance threats; follow the dynamics of resistance trends	x	x	x	x	x
Detect new resistance mechanisms			x	x	
Monitor impact of empirical prescribing	x	x			x
Monitor effects of infection control interventions	x				
Identify outbreak of antibiotic-resistant organisms	x				
Detect bioterrorist events	x	x			x
Monitor antibiotic resistance during the product development cycle			x	x	
Identify needs for new antibiotics: monitor the needs for targeted-spectrum antibiotics			x	x	
Identify the need for new diagnostic tests and unmet medical needs			x	x	
Education and continuing education on antibiotic resistance	x	x	x	x	x
Strategic information to support new antibiotic drug target development			x	x	
Identifiy high-profile isolates for antibiotic screens to guide structure–activity-relationship strategies for novel targets			x	x	
Antibiotic resistance modelling			x	x	
Benchmark the activity of new antibiotics; pre- and post regulatory approval				x	x
Regulatory agency submissions such as new drug applications (NDAs) or other regulatory documents				x	x
MIC interpretative criteria submissions (breakpoint determinations) to government or regulatory agencies				x	x

appropriate reports. Antibiotic susceptibilities may vary considerably, depending upon the demographics of the patient population served by a laboratory (e.g., patients from nursing homes, intensive care units, community hospitals, university-affiliated teaching hospitals, HIV or paediatric clinics) and the isolates tested. Resistance data can also be linked to supportive research programmes in infection control and antibiotic usage, and may be beneficial in the development of practical measures designed to reduce the burden of antibiotic resistance [1]. Surveillance should serve as an early-warning system, and its usefulness hinges on the rapid dissemination of information to those concerned so that timely responsive measures can be initiated. Clinical microbiology laboratories must communicate antibiotic resistance surveillance data clearly to health care providers and ensure that it is received and understood. It is imperative that local health care providers are aware of local, regional, national and international surveillance initiatives, as pathogenic organisms can move unhindered between hospitals, countries and continents. Persons involved in political and public health decisions must respond to changes in antibiotic resistance patterns and approach antibiotic resistance as a global problem that requires local enterprise.

Regional, national and international surveillance systems

Regional, national and international surveillance systems use isolates from hospital and reference clinical microbiology laboratories, as well as state public health laboratories, to project wide trends in resistance that may not exist in individual hospitals, but are important for the awareness of health care providers. Regional, national and international antibiotic resistance surveillance systems must be designed thoughtfully, be well-maintained, be longitudinal, and involve a consistent and appropriate collaboration of laboratories over time. There are many examples of regional, national and international surveillance systems in the USA, Europe and elsewhere. This review attempts to summarise the types of data collected and their optimal use. For example, in the USA, the Active Bacterial Core Surveillance/Emerging Infections Program Network, a collaboration between the Centers for Disease Control and Prevention and several state health departments and universities participating in the Emerging Infections Program Network, was designed to estimate the burden of community-acquired invasive bacterial infections that manifest typically as sepsis and meningitis [7]. The Active Bacterial Core system determines the incidence and trends of these diseases in a multistate population, and uses molecular and microbiological methods to characterise *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Neisseria meningitidis* and *Haemophilus influenzae* [7]. Other examples of government-sponsored programmes in the USA include the National Nosocomial Infections Surveillance (NNIS) system, and the Intensive Care Antimicrobial Resistance Epidemiology study, a subset of hospitals participating in the NNIS System. The Intensive Care Antimicrobial Resistance Epidemiology study provides data on the prevalence of antimicrobial resistance and antimicrobial use in USA hospitals. Antibiotic resistance surveillance studies are also sponsored commonly by pharmaceutical companies; such multi-year studies include the Alexander Project [8], MYSTIC [9], SENTRY [10] and TRUST [11,12]. Other international antibiotic resistance surveillance initiatives include the European Antimicrobial Resistance Surveillance System, the Asian Network for Surveillance of Resistant Pathogens, and the International Network for the Study of Emerging Antimicrobial Resistance.

Limitations often exist in multicentre antibiotic resistance surveillance systems; these include the absence of timeliness in the publication of data in peer-reviewed scientific journals, the lack of denominator data when considering the relevance of the resistance rates generated, and the inclusion of duplicate, inappropriately identified or clonal strains that can skew surveillance data. In addition, many surveillance initiatives are focused narrowly on one or few organisms (e.g., *Salmonella*, *Neisseria*, *Strep. pneumoniae*) and a limited set of test antibiotics, and are not continuous. Decisions are required to determine which organisms and antibiotics are tested. Resistance rates reported in centralised studies may depend on the organisms selected for inclusion and the number of strains tested. In contrast, decentralised studies may be prone to inter-laboratory testing errors. Because the cost of centralised surveillance studies is so high, many such studies

are supported by the pharmaceutical industry as post-marketing surveillance. Such studies are, by necessity, restricted in their focus, with only particular sites of infection or subsets of organisms represented, and a defined range of antibiotics tested, which invariably includes an investigational or proprietary agent marketed recently [13]. Ideally, multicentre surveillance should be representative of all types and sizes of institutions; however, currently it tends to include only larger university-affiliated hospitals, which may over-represent the prevalence of resistance because of the types of patient treated by larger hospitals. Consideration of the patient isolates included in any surveillance study is critical to interpretation of the study, including the way in which the results might help to control resistance and facilitate optimal use of the data by health care providers, university researchers, pharmaceutical companies, and government and regulatory agencies [14].

OPTIMAL USE OF ANTIBIOTIC RESISTANCE SURVEILLANCE SYSTEMS

Hospital and community health care providers

In-vitro activity can be a useful tool, but it does not necessarily correlate with in-vivo results. The safety and efficacy of any agent in treating clinical infections caused by specific bacterial pathogens must be established in well-controlled studies. Regardless of surveillance data or the MIC for an isolate, patient-, antibiotic- and pathogen-specific factors are important in determining the resolution of a patient's infection, and there is significant interaction between factors in each of these three groups. Treatment regimens for patients with suspected or demonstrated infections should be developed following consideration of symptoms, laboratory findings and relevant medical history, and in the context of appropriate local and wider antibiotic resistance trends. Individual in-vitro susceptibility results may or may not correlate with clinical outcome, but need to be considered when treating patients with confirmed or suspected infections. Very low MICs may predict cure, but can never guarantee it [15–17]. Resistance can lead to therapeutic failure, lengthy hospitalisation, morbidity, and even death. The benefits of MIC testing during therapy to follow the possible emergence of resistance in a pathogen, particularly in the case of patients with serious infections or who are immunocompromised, have been demonstrated previously [18,19].

Surveillance for antibiotic susceptibilities provides health care providers with some, but not all, information on two (i.e., pathogen and antibiotic) of the three factors important to patient outcomes. Many concurrent factors can influence the outcome of an infection, only one of which is the in-vitro susceptibility of the pathogen to the antibiotic(s) selected for treatment. Antibiotic prescribing based upon pharmacodynamic principles that predict efficacy, predict bacterial eradication, and prevent the emergence of resistance, are important to the success of therapy [20,21]. The ability to predict resistance in a particular patient will depend upon the level of resistance to an antibiotic found in the likely array of pathogens in a particular hospital or region. Many less serious infections will resolve without antibiotic treatment.

An important consideration for users of any antibiotic resistance surveillance system is the fact that sampling bias may be associated with some samples submitted to clinical laboratories for diagnostic purposes. Collection of specimens is affected not only by disease, but also by other factors, such as patient age. For example, recent decreases in physician requests for routine urine cultures for patients with acute cystitis may alter the spectrum of isolates included in surveillance data. As the treatment of acute cystitis in otherwise healthy adult females is now largely empirical, isolates tested in laboratory-based studies may be predominantly from patients who have failed previous antibiotic therapy, or from patients with other underlying risk factors. Therefore, surveillance data for urinary tract isolates has the potential to over-represent resistance and may not be applicable directly to the treatment of otherwise healthy adult females with uncomplicated urinary tract infections [22]. At the other extreme, it is safe to assume that all blood isolates and isolates from other sterile sites are tested for antibiotic susceptibility by clinical microbiology laboratories. The fact that many hospital antibiograms do not differentiate bacterial isolates by specimen source may also be an important consideration for health care providers. Another important consideration is that *c.* 75% of all antibiotic use in humans is known to be commu-

nity-based, but surveillance studies obtain their test isolates primarily from hospital laboratories. Therefore, are surveillance data relevant for community-based physicians? Admittedly, many hospital laboratories accept some specimens from community-based patients, but the relative numbers of specimens will depend directly on local practices and infrastructure, as well as specimen source, all of which will have an impact on the pathogens cultured, identified and tested for antibiotic susceptibility. Moreover, most patients who receive antibiotics do not have specimens submitted for culture, and the susceptibility of their isolates remains unknown [1].

University researchers, and pharmaceutical and biotechnology companies

Identification of new medical needs for the discovery and development of novel antibiotics

Antibiotic surveillance networks can be designed to capture information that will aid researchers examining the multifactorial nature of antibiotic resistance, as well as determining the clinical significance of resistance phenotypes. A better understanding of established resistance phenotypes, as well as their niches and evolving resistance profiles, will contribute significantly to the development of derivatives and novel antibiotics with both directed and extended spectra, as well as diagnostic tests.

Antibiotic resistance is a dynamic phenomenon that is a major driving force behind antibiotic drug discovery and development on the part of industry, and is influenced by a variety of different factors imposed by human, bacterial, viral, fungal and parasitic pathogens. Some of the common factors that may influence antibiotic resistance include changes in medical practice, advances in medicine, health care financing and health care policies. In the case of human pathogens, the commonest factors influencing antibiotic resistance include the genetics, physiology and ecology of the pathogen. Antibiotic resistance surveillance systems are important tools for determining the different resistance categories that are encountered in clinical practice, which in turn provides valuable information for new antibiotic development strategies. Antibiotic resistance may be either *de novo* when it develops in organisms in which resistance to a drug has not been encountered previously (e.g., vancomycin-resistant staphylococci), or epidemic when it results from the amplification and spread of a phenotype encountered previously. Both types of resistance must be considered and evaluated when predicting the need for the antibiotics of the future. Surveillance systems have shown that the emergence and development of resistance is unequal for different organisms and does not correlate easily with drug usage. For example, *Strep. pneumoniae and Staphylococcus aureus* show high rates of resistance to penicillin and oxacillin, respectively, in the USA. In contrast, *Strep. pyogenes* has remained completely susceptible to penicillin, despite widespread use of this agent to treat patients with streptococcal pharyngitis. Therefore, constant monitoring of antibiotic resistance trends will continue to be a major driving force behind pharmaceutical strategies to identify the types of novel antibiotic that will be needed in the future.

Monitoring antibiotic resistance during the antibiotic product development cycle

Many strategies for the discovery of new antibacterial agents are influenced by microbial factors driving the need to discover novel agents that are active against organisms resistant to currently available agents [23–25]. Since it can take 12 years from the discovery of an antibiotic candidate in the research laboratory to its final approval by the regulatory authorities and launch on to the market [26], the discovery scientist would benefit from a crystal ball to be able to predict effectively new medical needs and resistance mechanisms that are likely to prevail when the antibiotic is launched. Therefore, it is important to monitor the dynamics of resistance throughout the antibiotic development cycle, since the environment in which a new product is released may be different from the resistance environment that was present when the new chemical entity was discovered. Antimicrobial surveillance studies conducted at regular intervals will provide useful data on resistance trends over time to ensure that the product still has a viable commercial potential in terms of meeting medical needs. Even negative surveillance data will provide valuable information for a pharmaceutical developer, and will assist in decisions to terminate potential products that show no competitive advantage over agents marketed currently, or that are no longer effective

against target pathogens because of burgeoning resistance.

Increasingly, it has become apparent that the effectiveness of some antimicrobial agents currently available is being eroded by the emergence of resistance in key pathogens [27,28]. A wide range of mechanisms have evolved in bacterial pathogens to enable them to resist the activity of many different classes of antibiotics. For example, bacteria can acquire the means to inactivate an antibiotic, modify the antibiotic target, or export the antibiotic actively from the cell. In the case of certain organism and drug combinations, antimicrobial surveillance studies are providing a gloomy picture as it becomes apparent that many pathogens are not only showing resistance to single agents, but in certain cases may be multidrug resistant, commonly defined as resistance to three or more different classes of antibiotic [29,30].

The emergence of resistance to a number of antibiotics, such as β-lactams, macrolides, quinolones and vancomycin, is becoming a major worldwide health care problem. Many different antibiotic surveillance initiatives have highlighted problems associated with emerging resistance in Gram-positive pathogens. One of the most significant challenges has been presented by methicillin-resistant *S. aureus*, the resistance levels of which have reached 60% in Japan [31] and 40% in the USA [32]. The alarming increase in the prevalence of methicillin-resistant *S. aureus* was first highlighted by the NNIS system, which reported rates of 20–40% in the early 1990s. For enterococci, the NNIS system was effective in highlighting emerging resistance to vancomycin, which increased from 0.3% in 1989 to 7.9% in 1993. It is clear that the various antibiotic resistance surveillance systems have been useful to the pharmaceutical industry in identifying resistant Gram-positive pathogens as a key area of medical need in the mid-to-late 1990s. The industry has risen to the challenge with the recent launch of products such as quinupristin–dalfoprostin (Synercid) and linezolid (Zyvox), which are effective against resistant Gram-positive pathogens, including multi-drug-resistant strains [33–35]. There are several other promising candidates, such as daptomycin, oritavancin and dalbavancin, which are currently in Phase III clinical trials and which appear to be effective against infections caused by resistant Gram-positive pathogens.

Although many antibiotic products are available on the market today, most are effective against only a small number of targets that are associated with one or more components of the bacterial cell wall, or events involved in macromolecular (DNA, RNA or protein) biosynthesis. The last two decades have seen the development of many structurally related chemical classes ('me too' products) with increased potency or pharmacokinetic advantages over marketed products (e.g., newer-generation β-lactams, macrolides and fluoroquinolones). As a consequence, the microbial population has been subjected to many closely related chemical analogues, which contribute to the emergence of resistance to many compounds belonging to the same chemical class. Surveillance systems have been useful in monitoring the activity of structurally related antibiotics that are directed against these well-known targets, and the resulting data have been instrumental in guiding studies to identify new and improved products. For example, the new ketolide telithromycin was designed to counter infections caused by macrolide- and penicillin-resistant *Strep. pneumoniae.*

Identification of high-profile clinical isolates to support the discovery and development of novel antibiotics that evade pre-existing resistance mechanisms

The results from antibiotic resistance surveillance studies have helped to convince industry to discover and develop pharmacophores that are directed against novel targets which are essential for microbial growth and which show no cross-resistance to antibiotics currently marketed [36]. The advent of bacterial genomics has resulted in a paradigm shift for the antibacterial drug discovery scientist in terms of configuring new assays to screen for hits that are amenable to optimisation by the medicinal chemist [37–41]. Antibiotic resistance surveillance systems play a major role in supporting the discovery scientist by providing information on the latest clinically relevant phenotypes that will need, ultimately, to be covered by the products that are discovered and developed. Major advantages of large surveillance studies include the identification of rare or high-profile isolates that will serve as useful tools for antibiotic screening or profiling of lead molecules. Valuable isolates for the evaluation of new lead molecules will include multi-drug-resistant isolates, as well as clinical isolates that show reduced

susceptibility to agents launched recently, such as quinupristin–dalfopristin and linezolid. Surveillance isolates with novel resistance phenotypes will be useful in supporting studies to determine the mechanism(s) of resistance, as well as serving as tools for the profiling of new compound leads in structure–activity relationship studies. For example, there has been considerable interest in staphylococcal isolates with reduced susceptibility to glycopeptide agents such as vancomycin. The first vancomycin-intermediate *S. aureus* isolate was identified in Japan in 1997, and this was followed by confirmed reports from the USA and other countries, including the identification of two fully vancomycin-resistant strains in 2002 [42,43]. Ongoing surveillance initiatives such as The Surveillance Network (Focus Technologies, Herndon, VA, USA) play a major role in monitoring such phenotypes and flagging them for confirmation in a reference laboratory. Many surveillance studies that procure isolates for testing at a central laboratory also conduct molecular studies to investigate strains with reduced susceptibility to marketed agents. For example, surveillance isolates with defined mutations in the quinolone-resistance-determining regions of the DNA gyrase and topoisomerase enzymes in *S. aureus and Strep. pneumoniae* were used to profile the activity of novel non-fluorinated quinolones [44,45].

Furthermore, antibiotic resistance surveillance studies will continue to play a major role in supporting discovery scientists in investigation of the issues associated with the pervasiveness and heterogeneity of the genomic targets being studied in large numbers of clinical isolates. It is apparent that many of the current drug discovery initiatives have been based on the assumption that if a novel drug target is present in one isolate, it is going to be present in all isolates of that species. However, as the genomes of more and more organisms become available, it is apparent that genomic diversity among different strains of the same species is more widespread than had been imagined previously [46,47]. For example, the FabI enzyme, which encodes the enoyl ACP (acyl carrier protein) reductase in the fatty acid biosynthetic pathway, has been an attractive target for the discovery and development of novel antibiotics [48]. Although novel compounds with inhibitory action against FabI showed activity against organisms such as *S. aureus*, they demonstrated variable activity against *Strep. pneumoniae*, certain strains of which contained a different enzyme, FabK [48]. Therefore, early evaluation of lead compounds against an extensive and representative selection of appropriate recent clinical isolates should be a necessary prerequisite for clinical development. These results should be instrumental in convincing any pharmaceutical development committee that the antibiotic target is pervasive among the target pathogens, and that any pre-existing resistance mechanisms associated with the antibiotic development candidate are either not significant or non-existent. Therefore, surveillance systems not only provide valuable data on resistance and areas of need, but also provide key isolates with clinically important phenotypes that serve as valuable tools for the discovery, evaluation and optimisation of the novel agents that will be available in the future.

Surveillance data to model future resistance trends

Recent studies have investigated mathematical models to predict the effect on resistance of infection control measures and the impact of calls for change on the use of antibiotics [49,50]. It is likely that data from large surveillance studies conducted over multiple years will be a valuable component in future models to predict resistance trends that are likely to arise in the future, and to confirm or refute those that have been predicted in the past. The results of such models should help to direct pharmaceutical scientists involved in the development of antibiotics to better strategise the types of antimicrobial products that will be required for the market during the next 5–10 years.

Benchmarking the activity of new antibiotics: pre- and post-regulatory approval

Surveillance studies are also important in supporting products that are in Phase III clinical development, and provide a useful component of NDA submissions seeking to convince the regulatory agencies that any pre-existing resistance mechanisms are either non-existent or low in frequency. Many pharmaceutical developers now conduct pre- and post-regulatory approval surveillance studies on their products. Typically, this involves the collection of key target pathogens from a geographically distributed network of hospitals for centralised laboratory testing. The

resulting data are useful to the pharmaceutical sponsor, since they provide a benchmark to monitor any future changes in the susceptibility of clinically important pathogens to their product following its regulatory approval and launch, or to competitor antibiotics following approval and launch. For example, the TRUST surveillance studies have been instrumental in tracking activity of the fluoroquinolone levofloxacin against key bacterial respiratory pathogens on an annual basis since its launch in the USA in 1996 [11,12,50,51]. In particular, TRUST results have been useful in monitoring the activity of levofloxacin against *Strep. pneumoniae*, an organism that is under close scrutiny for the emergence of resistance to fluoroquinolones. The surveillance results have shown that levofloxacin resistance in the USA has remained at <1% after use for 6 years. Surveillance studies are also useful in putting resistance data into perspective by providing opportunities to characterise isolates that have reduced susceptibility or resistance to the test agent.

Molecular analysis of surveillance isolates has provided an opportunity to put resistance data into perspective. Molecular typing by pulsed-field gel electrophoresis of penicillin-resistant pneumococci from Asian children in the Asian Network for Surveillance of Resistant Pathogens study has shown that the high frequency of penicillin and multi-drug resistance was associated with the spread of particular clones in that region [51,52].

Government and regulatory agencies

Regulatory submissions

Many NDAs include surveillance data showing the efficacy of the investigational agent against recent clinical isolates. The data are used to show that such isolates are susceptible to the investigational antibiotic at the time of approval. Furthermore, pharmaceutical sponsors use surveillance isolates to show that the investigational antibiotic is effective against isolates that are resistant to other classes of antimicrobial agents (e.g., isolates of *S. aureus* resistant to linezolid [53,54] and vancomycin [55,56]). Many NDA submissions available publically include susceptibility test results for both clinical trial and surveillance isolates. High-profile isolates with rare phenotypes identified in pre-approval surveillance studies are also extremely important candidates for other studies that, typically, would be included in an NDA submission on a new antibiotic (e.g., time-kill kinetics, synergy, emergence of resistance and post-antibiotic effect studies). Surveillance studies are also important for pharmaceutical sponsors seeking an indication that includes resistant pathogens. Such data, in combination with clinical trial outcome data, would be important in convincing the respective regulatory agency that such an indication is warranted. In such circumstances, the regulatory agency may ask the sponsor to provide ongoing surveillance data to show that the resistance indication continues to be warranted. A discussion paper from the European Agency for the Evaluation of Medicinal Products has noted that some antibiotics are losing their effectiveness rapidly as resistance is spread within and between different bacteria. The paper discussed the need for surveillance systems to gather reliable data on the prevalence of resistance over time in different geographical areas. In the USA, the Food and Drug Administration Task Force on Antimicrobial Resistance provided key recommendations which highlighted the need for better surveillance systems, as well as intensive education for health care professionals and the public regarding optimal usage of antibiotics.

Interpretative criteria (breakpoint determinations)

In the USA, the NCCLS and the Food and Drug Administration are agencies involved in the establishment of breakpoints. The NCCLS guidance document (M23-A2) recommends that data for 100 isolates from each organism group should be presented. The isolates should belong to clinically relevant species and should include susceptible and resistant (if recognised) organisms, including isolates with known resistance mechanisms that are relevant to the agent being investigated. In most cases, isolates identified in surveillance studies will be used in combination with those identified in clinical trials for the assessment of interpretative criteria. Typically, the NCCLS requests disk diffusion and dilution data on at least 500 isolates tested by NCCLS methods. The MIC/zone diameter distributions used for in-vitro test development should be compared with those from a large geographically diverse population of recent clinical isolates.

CONCLUSIONS

Antimicrobial resistance surveillance systems have provided useful data for guiding health care providers, academic researchers, pharmaceutical developers and governmental agencies. Antibiotic resistance is clearly a dynamic phenomenon, and the timely identification and reporting of rare phenotypes is of paramount importance. Surveillance data have been useful in optimising the careful and prudent use of antibiotics marketed currently to ensure continued clinical success. Surveillance and clinical trial data, in concert with pharmacokinetic data, continue to be important in the assignment of interpretative criteria (breakpoints), especially in cases where agents are being indicated for therapy of infections caused by resistant pathogens. Antimicrobial surveillance data will continue to provide valuable strategic information to guide the discovery and development of novel antibiotic products for the future.

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