Antimicrobial Resistance Surveillance and New Drug Development

Helio S. Sader, Paul R. Rhomberg, Andrew S. Fuhrmeister, Rodrigo E. Mendes, Robert K. Flamm, and Ronald N. Jones

JMI Laboratories, North Liberty, Iowa

Surveillance represents an important informational tool for planning actions to monitor emerging antimicrobial resistance. Antimicrobial resistance surveillance (ARS) programs may have many different designs and can be grouped in 2 major categories based on their main objectives: (1) public health ARS programs and (2) industry-sponsored/product-oriented ARS programs. In general, public health ARS programs predominantly focus on health care and infection control, whereas industry ARS programs focus on an investigational or recently approved molecule(s). We reviewed the main characteristics of industry ARS programs and how these programs contribute to new drug development. Industry ARS programs are generally performed to comply with requirements from regulatory agencies responsible for commercial approval of antimicrobial agents, such as the US Food and Drug Administration, European Medicines Agency, and others. In contrast to public health ARS programs, which typically collect health care and diverse clinical data, industry ARS programs frequently collect the pathogens and perform the testing in a central laboratory setting. Global ARS programs with centralized testing play an important role in new antibacterial and antifungal drug development by providing information on the emergence and dissemination of resistant organisms, clones, and resistance determinants. Organisms collected by large ARS programs are extremely valuable to evaluate the potential of new agents and to calibrate susceptibility tests once a drug is approved for clinical use. These programs also can provide early evaluations of spectrum of activity and postmarketing trends required by regulatory agencies, and the programs may help drug companies to select appropriate dosing regimens and the appropriate geographic regions in which to perform clinical trials. Furthermore, these surveillance programs provide useful information on the potency and spectrum of new antimicrobial agents against indications and organisms in which clinicians have little or no experience. In summary, large ARS programs, such as the SENTRY Antimicrobial Surveillance Program, contribute key data for new drug development.

Keywords. antimicrobial agents; antimicrobial resistance; NDA; new drug development.

The worldwide spread of antimicrobial resistance continues to challenge physicians and drug development researchers, and it has been recognized as a global public health threat [1]. Because of the geographical diversity, complexity, and continuously evolving dynamics of resistant organisms and complex resistance mechanisms, structured surveillance is a key tool for planning actions to manage this problem [2]. Antimicrobial resistance surveillance (ARS) programs may have many different objectives, including the following: (1) detecting the emergence of novel resistance phenotypes and mechanisms of resistance; (2) recognizing, understanding, and predicting trends in resistance; (3) monitoring the impact of the introduction/clinical use of new antimicrobial agents; (4) identifying outbreaks of resistant organisms; (5) guiding infection control and public health measures; and (6) providing data for new drug applications (NDAs) or other submissions to regulatory agencies, such as the US Food and Drug Administration (FDA) and European Medicines Agency (EMA).

Based on their main objectives, the ARS programs can be grouped in 2 major categories: public health ARS programs and industry-sponsored ARS programs. Certainly these 2 groups have some overlaps, but public health ARS programs predominantly focus on health care and infection control, whereas the industry ARS programs focus mainly on drug development (Table 1).

Although some public health ARS programs focus on specific organisms or organism groups and may collect selected organisms for further evaluation, most major public health ARS programs collect data directly from health care or public health facilities and combine the data in a large database [3–5]. Public health ARS programs provide very valuable information needed to identify infection-related problems, to measure the impact of prevention efforts, and to decrease the incidence of health care-associated and community-acquired infections. Examples of major public ARS programs are the Centers for

Table 1. Main Characteristics of Industry and Public Antimicrobial Resistance Surveillance (ARS) Programs

Industry ARS Programs	Public ARS Programs
Designed to comply with requirements from regulatory agencies	Focus on health care and infection control
Collect organisms for testing in a central laboratory	Collect data and combine them in a large database
Test all organisms against the same antimicrobials and by the same methodology	Antimicrobial agents and methodology vary among participating centers
Store all organisms for further characterization	Possibly store only selected organisms
Provide valuable information on the emergence, spread, and molecular characterization of resistant organisms	Provide valuable information needed to identify infection-related problems and to measure the impact of prevention efforts and public health policies

Disease Control and Prevention's (CDC) National Healthcare Safety Network [6], the European Antimicrobial Resistance Surveillance Network [7], and the World Health Organization's Global Antimicrobial Resistance Surveillance System [8]. Although public health ARS programs represent very valuable programs, most have some limitations, including the use of different antimicrobial susceptibility testing methods and/or breakpoint interpretative criteria at participating centers, and they may only capture categorical results (susceptible [S]/intermediate [I]/resistant [R]). Furthermore, laboratories may test different agents within a drug class, or they may perform selected testing (cascade testing, which is not testing or reporting the susceptibility results for broad-spectrum or new antimicrobials if the isolate is susceptible to narrow-spectrum and/or old agents) and have a decentralized quality assurance system. All of these factors can introduce bias. We reviewed the main characteristics of industry ARS programs and how they contribute to new drug development.

INDUSTRY ANTIMICROBIAL RESISTANCE SURVEILLANCE PROGRAMS

Antimicrobial resistance surveillance programs sponsored by industry are generally performed to comply with requirements from regulatory agencies responsible for commercial approval of antimicrobial agents, such as the FDA, EMA, and others (Table 1). These agencies require that drug manufacturers evaluate the in vitro activity and spectrum of an antimicrobial agent, including its active components and major metabolites, against a collection of relevant bacteria early in clinical development, usually when submitting an investigational new drug application. Companies should provide data of candidate(s) tested against a series of clinically relevant and contemporary collection of organisms to allow assessment of in vitro activity and potential clinical indication(s). Regulatory agencies also require that drug companies perform premarketing surveillance as part of the NDA package and to benchmark a given agent before clinical use, as well as postmarketing surveillance

to monitor potency, spectrum, and emergence of resistance over time (usually 5 or more years) after clinical approval and introduction into the market (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM182288.pdf) [9]. Thus, industry ARS programs are usually designed to fulfill these regulatory commitments.

In contrast to public health ARS programs, which typically collect health care and clinical data, industry ARS programs frequently collect the organisms and perform the testing in a central laboratory (Table 1). Many important testing aspects are standardized to avoid introducing method and quality assurance bias. For example, only 1 isolate per infection episode is included in the program, and all organisms of the same group are tested against the same antimicrobial agents (no cascade testing). Other characteristics of industry ARS programs include rigid quality control and storage of the organisms for further phenotypic and/or genotypic characterization as needed.

Most industry ARS programs are related to a specific antimicrobial agent or drug company, with very few exceptions, such as the SENTRY Antimicrobial Surveillance Program and the British Society for Antimicrobial Chemotherapy (BSAC) Resistance Surveillance Program. The SENTRY Program (www.jmilabs.com/antimicrobial-surveillance/) collects and processes bacterial and fungal isolates causing a variety of infection types in a large number of medical centers worldwide. The organisms are consecutively collected (prevalence mode) to provide a real scenario of the distribution of species causing infections and a current representation of susceptibility phenotypes. Isolates are centrally processed for viability, purity, and bacterial identification and susceptibility tested by the reference broth microdilution method against numerous antimicrobial agents. Isolates of interest are subjected to further molecular characterization by next-generation sequencing and bioinformatics tools. Some results are made publicly available in an interactive website (https://sentry-mvp.jmilabs.com). The BSAC Program collects isolates from bacteremia and respiratory tract infections from many medical centers in the United Kingdom and Ireland, and results are available at www.bsacsurv.org [10]. Both SENTRY and BSAC programs are sponsored by a consortium of pharmaceutical companies.

CONTRIBUTION OF ANTIMICROBIAL RESISTANCE SURVEILLANCE PROGRAMS TO NEW DRUG DEVELOPMENT

Establishing the Need
The need for a new antimicrobial agent is generally driven by the emergence and broad dissemination of a new pathogen and/or resistance mechanism that is not well controlled by clinically available drugs. For example, the emergence and wide dissemination of methicillin-resistant *Staphylococcus aureus* or multidrug-resistant (MDR) Gram-negative bacilli, mainly carbapenem-resistant *Enterobacteriaceae* (CRE), prompted the

development of a series of drugs to address these problems. However, it is difficult to differentiate the emergence of resistance mechanisms responsible for sporadic cases that can generate a large number of scientific publications and reports from those occurrences that disseminate broadly and affect a large number of patients.

Carbapenem-resistant *Enterobacteriaceae* isolates producing acquired carbapenemases were initially identified in the 1980s [11, 12]; however, despite a large number of anecdotal reports in the late 1990s and early 2000s, the frequency of CRE infections remained low in most regions of the world until the widespread dissemination of *Klebsiella pneumoniae* carbapenemase (KPC)-producing strains in the last decade [13]. Data from the SENTRY Program indicates that the overall frequency of CRE in the United States increased from 0.1%–0.3% in 1999–2003 to 0.7% in 2004 and 1.2% in 2005, remained between 1.4% and 2.0% from 2005 through 2015, and then declined in 2016 and 2017 (Figures 1 and 2). In summary, data from the SENTRY Program and other large ARS programs documented the continued increase in the frequency of CRE, initially in the United States and then worldwide in the late 2000s, that stimulated the development of novel drugs to address these difficult-to-treat organisms [14–18].

In contrast to CRE, vancomycin-intermediate *S. aureus* (VISA) and vancomycin-resistant *S. aureus* (VRSA) isolates remain rare. The first VISA clinical isolate was reported from Japan in 1996 [19], and the first VRSA isolate was reported from the United States in 2002 [20]. Many VISA and VRSA cases were reported in the early 2000s, but data from the SENTRY Program and other large ARS programs have documented that vancomycin, and newer antistaphylococcal drugs such as linezolid and daptomycin, remain very active against *S. aureus* worldwide, with >99.9% susceptibility rates [21–24]. Thus, clinical approval of many anti-Gram-positive agents in the last decade, combined with commercial reasons and data from ARS programs, motivated many pharmaceutical companies to prioritize developing antimicrobials to treat MDR Gram-negative organisms over those to treat *S. aureus* and other Gram-positive infections. These priority changes resulted in an important shift, with several anti-Gram-positive agents being approved in the early years of the decade (eg, ceftaroline in 2010 and dalbavancin, oritavancin, and tedizolid in 2014) and anti-Gram-negative agents being approved more recently (eg, ceftolozane-tazobactam in late 2014, ceftazidime-avibactam in 2015, meropenem-vaborbactam in 2017, and plazomicin in 2018).

Other important information that can be provided by ARS programs and contribute to drug development is the frequency of bacterial species causing different infection types; however, a given ARS program needs to be designed to obtain this data (ie, needs to collect organisms or data by prevalence mode or 1 isolate per patient per infection episode, consecutively collected). Increasing prevalence of organisms not covered by currently available antimicrobials may indicate the need for developing new agents. For example, data from the SENTRY Program indicate that the frequency of *Stenotrophomonas maltophilia* isolated from patients hospitalized with pneumonia increased from 3.0% to 4.4% worldwide and from 3.2% to 4.7% in North America when comparing 2005–2006 with 2015–2016 [25]. More recent results indicate that *S. maltophilia* represents the fifth or sixth most common organism isolated from patients with pneumonia in US medical centers [26, 27]. These data certainly support the clinical development of antimicrobial agents for treating infections caused by this generally MDR organism.
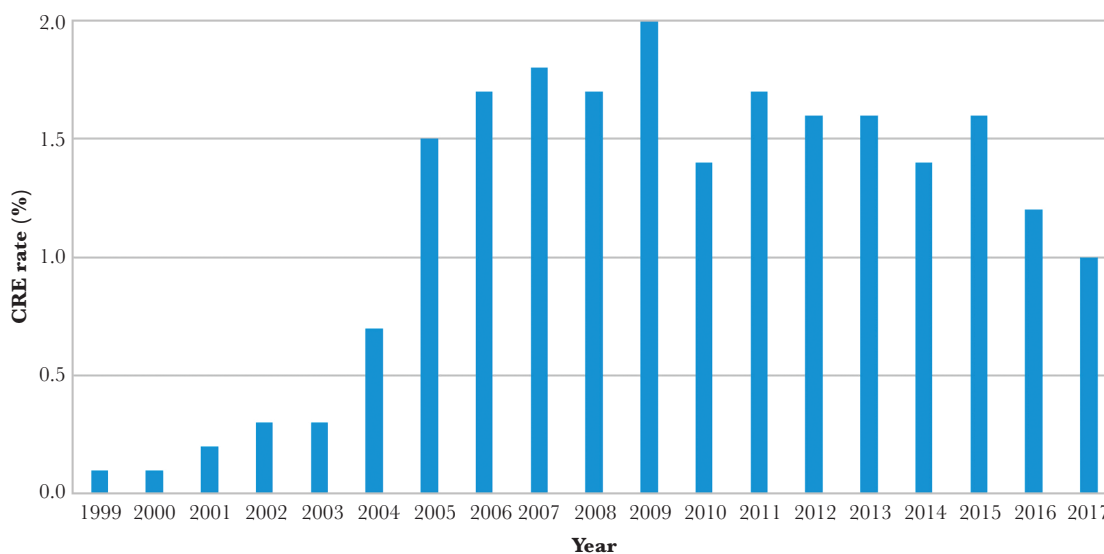
Figure 1. Carbapenem-resistant *Enterobacteriaceae* (CRE) rates in the United States (SENTRY Program, 1999–2017).
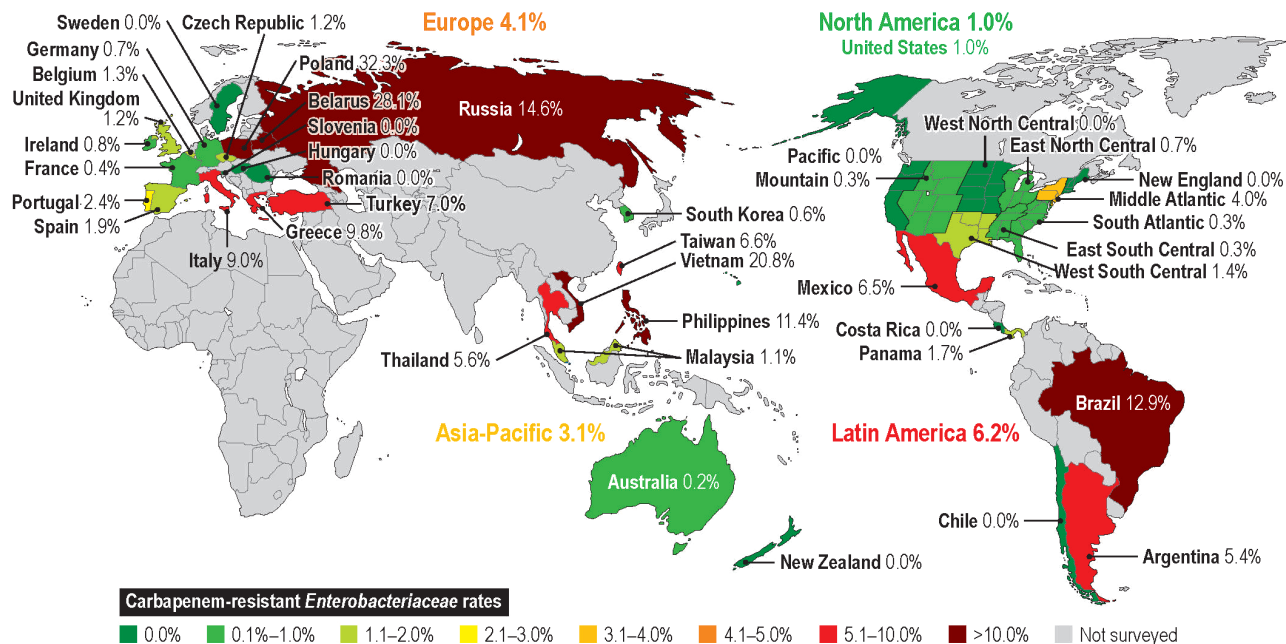
Figure 2. Carbapenem-resistant *Enterobacteriaceae* rates among nations surveyed by the SENTRY Program in 2017.

Providing Information on the Frequency of Clinically Relevant Resistance Mechanisms

Information on the mechanisms of resistance responsible for significant changes in the antimicrobial susceptibility patterns of clinical isolates are crucial for planning drug development strategies. The best example is the "recent" development of a series of novel β-lactamase inhibitors after the increased prevalence of carbapenemase-producing, mainly KPC-producing, *Enterobacteriaceae.*

The SENTRY Program has incorporated the molecular characterization of selected organism subsets since the early years of the program [28–33]. In addition to identifying and describing novel resistance genes [33–36], the SENTRY Program has monitored the occurrence of many resistance genes over time [37–47].

The *cfr* gene, which mediates resistance to oxazolidinones, including linezolid and tedizolid, was first reported in a human staphylococcal isolate in the United States by the SENTRY Program in 2007 [48]. The emergence of this gene raised concerns about the future clinical utility of oxazolidinones against staphylococci and other Gram-positive pathogens. Thus, the SENTRY Program continued to monitor the occurrence of *cfr* and *optrA* that mediate oxazolidinone resistance in Gram-positive organisms surveyed, documenting that the prevalence of these genes remained very low worldwide, with the occurrence of only sporadic cases and locally/regionally contained outbreaks [47, 49].

The first KPC-producing CRE in the United States was isolated in North Carolina in the late 1990s as part of the CDC's Project Intensive Care Antimicrobial Resistance Epidemiology,

another example of the importance of ARS programs [50]. This initial case was followed by a report of 19 cases of KPC-2-producing strains from 7 hospitals in the New York area [51]. Although there were many reports of KPC-producing strains in the early 2000s, data from the SENTRY Program indicated that the occurrence of KPC cases showed a substantial increase only in 2004–2005 and remained centered in New York and surrounding areas for many years [44, 46]. Furthermore, contemporary SENTRY Program data has demonstrated that, although bla_{KPC} represents 95% of the carbapenemase genes among CRE from US medical centers, its occurrence declined in 2016–2017 [52].

In summary, the emergence of novel mechanisms of resistance is usually followed by a large number of publications about the topic, and β-lactamases represent good examples. β-lactamases that hydrolyze carbapenems efficiently, such as the serine carbapenemase SME and the metallo-β-lactamase (MBL) IMP, were initially detected in *Enterobacteriaceae* in the 1980s [53, 54]. Since then, a number of new class A variants (eg, KPC and GES enzymes), class B MBLs (eg, IMP, VIM, SPM, and NDM), and class D carbapenemases (eg, OXA-23, OXA-24, and OXA-48) have been extensively reported. However, based on data from large ARS programs, the occurrence of most of these carbapenemases, with exception of KPC, remain low and/or restricted to specific geographic locations [55–57].

Source of Organisms for Early Drug Discovery

Surveillance programs that collect microorganisms, such as the SENTRY Program, as opposed to those that capture only data, provide a source of valuable microorganisms that can be

selected for use in drug discovery efforts. A large collection of global isolates provides greater opportunity to find less common or emerging isolates/phenotypes. From these surveillance data sets, specialized isolate sets with known susceptibility phenotypes and genotypes can be created to screen antimicrobial libraries. Compounds demonstrating potential activity are used to provide scaffolds for further exploration through chemical modifications against the selected pathogens. This primary screening effort can consist of testing against only a few bacterial isolates. Larger groups of bacterial isolates chosen to include a variety of important phenotypes and genotypes consisting of a few dozen to hundreds of organisms are generally tested as a secondary screen. If this testing proves favorable, then tertiary screening of isolates representative of the larger population of organisms (including susceptible and various resistance types) can be performed. Tertiary screening can be done on minimal organism groups (20–50 organisms per organism species or resistant subset), allowing for the generation of minimum inhibitory concentration $(MIC)_{50}$ and MIC_{90} values for bacteria groups and their resistant subsets. Compounds that demonstrate a promising activity profile during tertiary testing are candidates for testing against a broader contemporary surveillance set of organisms where minimally 100 organisms per genus/species and preferably 250 or more are tested [9].

Early Data on Spectrum of Activity

Regulatory agencies require that drug companies evaluate the activity of an antimicrobial agent against a relevant collection of bacteria in early clinical development. The choice of pathogens studied and the sample size of such isolate collections required to support an NDA are guided by the target product profile and intended indications for the antibacterial agent [9]. Results of early studies on the in vitro spectrum provide a benchmark to monitor future changes in the susceptibility of clinically important organisms to the novel agent after its approval and clinical application.

The development requirement for the early assessment activity of an antibacterial agent is described in the guidance for microbiology data for systemic antibacterial agents provided by the FDA [9]. This guidance describes the requirement for a sufficient number of clinically relevant bacteria to assess the potential clinical efficacy of the agent for the intended indication. The guidance also provides suggestions for the number of genera and species that should be tested. Sample sizes of ≥100 isolates are suggested for most organism groups. For *Enterobacteriaceae*, ≥300 isolates are suggested. However, the adequate number of organisms varies according to drug class, clinical indications, and spectrum of the antimicrobial agent.

Although the organism collection for early evaluation of spectrum does not need to be large, it should be temporally relevant (less than 3 years old), broadly distributed geographically, and representative of the susceptibility patterns for currently used antibacterial agents for the organisms found in the target product profile. If development in the United States is a goal, then the sample collection should include a majority of isolates from the United States (at least 75% of the sample). For European development, the sample collection should contain isolates from a variety of countries and regions with a representative sample from within the European Union. Furthermore, it is crucial to evaluate subsets of clinical organisms expressing resistance to other drugs of the same class and to evaluate organisms expressing resistance mechanisms that are clinically relevant for the geographic regions to which the drug will be submitted for approval. Only large global ARS programs with centralized testing can provide these types of organism collections for drug development [58–61].

Large ARS programs also play an important role in the development of drugs with narrow or limited spectrums by providing a large collection of target organisms that would be very difficult to obtain in a single investigation. For example, murepavadin is a novel peptide compound that is being developed for treating *Pseudomonas aeruginosa* infections [62]. By using the SENTRY Program organism collection (JMI Laboratories), we were able to evaluate the in vitro activity of this compound against 785 extensively drug-resistant (XDR) *P. aeruginosa* contemporary clinical isolates collected from >100 medical centers over 2 years [63]. Because only approximately 10% of *P. aeruginosa* isolates display an XDR phenotype, it would be necessary to test 10 times more isolates via routine testing to obtain results on the same number of XDR isolates.

Dose Selection and Recommendations for In Vitro Susceptibility Testing Criteria

Antimicrobial susceptibility surveillance data provide key information to interpret the results of pharmacokinetic/pharmacodynamics (PK-PD) target attainment studies and are used to support dose selection decisions for phase 3 clinical trials and recommendations for in vitro susceptibility testing criteria for antibacterial agents during drug development [64, 65].

Results of PK-PD target attainment analyses based on nonclinical PK-PD target and population PK models developed using phase 1 data represent an important model for supporting dose selection early in the development program. It has been demonstrated that the magnitude of PK-PD targets associated with different levels of reduction in bacterial infection burden, as generated using data from in vivo studies, is similar to the magnitude of PK-PD indices associated with successful responses among infected patients enrolled in clinical trials [66]. The concordance between nonclinical and clinical PK-PD targets for efficacy across numerous classes of agents provides the basis for applying PK-PD principles to reduce risk in drug development [2, 67, 68].

The approach to assess PK-PD target attainment in the context of in vitro surveillance data as a means of supporting dose

selection for the development of antibacterial agents or reassessing dosing regimens of marketed agents has become increasingly common in the last 15 years [65]. Such an approach is also used to establish and reassess interpretive criteria for in vitro susceptibility testing for antibacterial agents [69–72].

When establishing interpretive criteria, there are frequently limited numbers of bacteria from the pivotal clinical trials that exhibit MIC or disk zone diameter values near the potential susceptibility breakpoints, especially because the reason to select/advance a new agent would likely be its lack of significant levels of current bacterial resistance. These limited numbers of organisms become an even greater issue with the recent efforts by the FDA to streamline clinical trial size, such as in the Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD pathway) [73]. Isolates from surveillance data provide a reservoir of organisms through which such non-"wild-type" isolates can be found. These isolates are valuable in determining the PK-PD targets and in establishing and refining interpretive criteria and the corresponding diagnostic test systems (MIC and disk testing) throughout the useable life of an anti-infective agent [74].

Large ARS programs are also an important source of challenge organisms for the development and calibration of commercial susceptibility testing methods, such as automated systems and stable gradient strip tests. When an antimicrobial agent is clinically approved, isolates expressing resistance or even decreased susceptibility may be difficult to obtain. These types of isolates are critical for the calibration of a commercial susceptibility test, and sometimes they can only be obtained from large ARS program collections.

Selecting the Most Appropriate Geographic Regions to Perform Clinical Trials

In the current environment of drug development, a greater interest is in drugs with narrow or limited spectrums [63]. Given the pathogen-specific nature of these drugs, they are unlikely to generate cross-resistance to other compounds or negatively impact the patient's native bacterial flora, which are unintended sequelae of treatment with broad-spectrum agents. However, these compounds are planned for a limited population, and there are several challenges associated with conducting clinical trials to evaluate antimicrobial agents intended for use in a limited population of patients [75, 76]. Thus, the 21st Century Cures Act established the LPAD pathway, and the FDA offers incentives, via the LPAD pathway, for developing antibacterial and antifungal drugs to treat serious or life-threatening infections in patients with unmet needs [73] (available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM610498.pdf).

Even with FDA incentives, challenges remain. Two recent examples are the plazomicin and meropenem-vaborbactam clinical trials for the treatment of CRE infections in which both studies ended early due to difficult enrollments (both ended up with approximately 70 patients total for both treatment arms) [75, 76]. Because there are such a limited number of patients, clinical trials should be performed in geographic regions where the frequency of the target organisms is higher, and the large global ARS programs may provide this type of information to drug sponsors and regulators. Thus, if the drug is intended for treating CRE infections, it would be important to select regions with elevated CRE rates, such as some eastern European and Latin American countries. Figure 2 displays the CRE rates for the countries that participated in the 2017 SENTRY Program, data that can be very useful for recruiting medical centers to perform clinical trials on antimicrobials intended to treat CRE infections.

Furthermore, in these scenarios, there may not be sufficient clinical data to fully determine how effective the narrow-spectrum agent will be in patients infected with difficult-to-treat organisms. There would be reasons to provide data on characterized isolates that likely can only come from surveillance collections; thus, leveraging surveillance programs for these infrequent types of isolates are likely to be an important component of the NDA package [63, 77, 78].

Postmarketing Surveillance

Regulatory agencies require that the drug company perform postmarketing surveillance with the purpose of following the potency and spectrum of a new antimicrobial agent for several years (usually 5) after it is approved and introduced into the market [9]. This requirement typically involves testing key target organisms from a geographically distributed network of hospitals for centralized laboratory reference testing.

The SENTRY Program served as a platform for postmarketing surveillance programs of many antimicrobial agents, including anidulafungin [79, 80], caspofungin [79, 80], cefepime [81], ceftaroline [82], ceftazidime-avibactam [83], ceftobiprole [84], ceftolozane-tazobactam [85], delafloxacin [86], dalbavancin [22], daptomycin [87], isavuconazole [88], linezolid [21], meropenem-vaborbactam [89], micafungin [90], oritavancin [91], plazomicin [92], posaconazole [79], tedizolid [93], telavancin [94], tigecycline [77], and voriconazole [95].

For example, the Linezolid Experience and Accurate Determination of Resistance (LEADER) and the Zyvox Annual Appraisal of Potency and Spectrum (ZAAPS) programs monitored the in vitro activity of linezolid and key comparator agents in the United States (LEADER) and worldwide (excluding United States; Zyvox Antimicrobial Potency Study and ZAAPS) from 1999–2000 when it was approved until 2016 [49, 96]. The LEADER and ZAAPS programs involved approximately 200 medical centers worldwide. The results of these 2 programs produced a large number of scientific publications and showed that the compound remained very active against target

Gram-positive organisms after >15 years of extensive clinical use [21]. These surveillance programs also identified the emergence of many mechanisms of oxazolidinone resistance over the monitored years, but the frequency of those resistant genotypes remained low, stable, and geographically restricted [47].

Another example of a comprehensive postmarketing surveillance program that uses the SENTRY Program platform is the INFORM Program in the United States [27, 83]. The program has monitored the in vitro activity of ceftazidime-avibactam and the frequency of clinically relevant β-lactamases and other β-lactam resistance mechanisms in >70 US medical centers since 2011, years before the compound was approved by the FDA in 2015. Moreover, screening β-lactamase genes on *Enterobacteriaceae* isolates with an extended-spectrum β-lactamase phenotype began in 2012, initially by multiplex polymerase chain reaction and then by whole-genome sequencing. The implementation of molecular testing allows for monitoring the occurrence of clinically important β-lactamases and other resistance mechanisms that may affect the activity of ceftazidime-avibactam and other β-lactams tested as comparator agents [44, 97]. It is also important to note that postmarketing surveillance provides useful information on the potency and spectrum of new antimicrobial agents for which clinicians have little or no experience.

CONCLUSIONS

Global ARS programs that use centralized testing, such as the SENTRY Program, play an important role in new antibacterial and antifungal drug development. The main characteristics of the most valuable programs include (1) consecutive collection of isolates to establish current and real-world distribution of species and susceptibility phenotypes, (2) coverage of a wide geographic area, (3) susceptibility tests using reference methods, (4) centralized testing and quality assurance, (5) molecular characterization of important organisms, and (6) storing organisms for further studies. Results from these programs provide insights on the emergence, spread, and molecular characterization of resistant organisms. They provide information on the important resistance mechanisms for new drugs to target and provide organisms that can be used to evaluate the potential of new agents. Furthermore, these global ARS programs help drug development clinical scientists identify the geography and patient types to focus clinical trials and to monitor the impact of newly introduced agents to the market.

References

1. Boucher HW, Talbot GH, Benjamin DK Jr, et al. 10 x '20 Progress–development of new drugs active against Gram-negative bacilli: an update from the Infectious Diseases Society of America. Clin Infect Dis **2013**; 56:1685–94.
2. Núñez-Núñez M, Navarro MD, Palomo V, et al. The methodology of surveillance for antimicrobial resistance and healthcare-associated infections in Europe (SUSPIRE): a systematic review of publicly available information. Clin Microbiol Infect **2018**; 24:105–9.
3. Langley G, Schaffner W, Farley MM, et al. Twenty years of active bacterial core surveillance. Emerg Infect Dis **2015**; 21:1520–8.
4. Centers for Disease Control and Prevention (CDC). Fatal and nonfatal injuries involving fishing vessel winches--Southern shrimp fleet, United States, 2000–2011. MMWR Morb Mortal Wkly Rep **2013**; 62:157–60.
5. Weston EJ, Wi T, Papp J. Surveillance for antimicrobial drug-resistant *Neisseria gonorrhoeae* through the enhanced gonococcal antimicrobial surveillance program. Emerg Infect Dis **2017**; 23:S47–52.
6. Weiner LM, Webb AK, Limbago B, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2011-2014. Infect Control Hosp Epidemiol **2016**; 37:1288–301.
7. Alvarez-Uria G, Midde M. Trends and factors associated with antimicrobial resistance of *Acinetobacter* spp. invasive isolates in Europe: a country-level analysis. J Glob Antimicrob Resist **2018**; 14:29–32.
8. Sirijatuphat R, Sripanidkulchai K, Boonyasiri A, et al. Implementation of global antimicrobial resistance surveillance system (GLASS) in patients with bacteremia. Plos One **2018**; 13:e0190132.
9. Food and Drug Administration. Microbiology Data for Systemic Antibacterial Drugs-Development, Analysis, and Presentation Guidance for Industry. Silver Spring, MD: U.S. Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER); **2018**.
10. White AR, Surveillance BWPOR. The British Society for Antimicrobial Chemotherapy Resistance Surveillance Project: a successful collaborative model. J Antimicrob Chemother **2008**; 62(Suppl 2):ii3–14.
11. Yang YJ, Wu PJ, Livermore DM. Biochemical characterization of a beta-lactamase that hydrolyzes penems and carbapenems from two *Serratia marcescens* isolates. Antimicrob Agents Chemother **1990**; 34:755–8.
12. Potter RF, D'Souza AW, Dantas G. The rapid spread of carbapenem-resistant *Enterobacteriaceae*. Drug Resist Updat **2016**; 29:30–46.
13. van Duin D, Doi Y. The global epidemiology of carbapenemase-producing *Enterobacteriaceae*. Virulence **2017**; 8:460–9.
14. Bush K. A resurgence of β-lactamase inhibitor combinations effective against multidrug-resistant Gram-negative pathogens. Int J Antimicrob Agents **2015**; 46:483–93.
15. Gupta N, Limbago BM, Patel JB, Kallen AJ. Carbapenem-resistant *Enterobacteriaceae*: epidemiology and prevention. Clin Infect Dis **2011**; 53:60–7.
16. Jacob JT, Klein E, Laxminarayan R, et al. Vital signs: carbapenem-resistant *Enterobacteriaceae*. MMWR Morb Mortal Wkly Rep **2013**; 62:165–70.
17. Nordmann P, Naas T, Poirel L. Global spread of carbapenemase-producing *Enterobacteriaceae*. Emerg Infect Dis **2011**; 17:1791–8.
18. Tzouvelekis LS, Markogiannakis A, Psichogiou M, et al. Carbapenemases in *Klebsiella pneumoniae* and other *Enterobacteriaceae*: an evolving crisis of global dimensions. Clin Microbiol Rev **2012**; 25:682–707.
19. Hiramatsu K, Hanaki H, Ino T, et al. Methicillin-resistant *Staphylococcus aureus* clinical strain with reduced vancomycin susceptibility. J Antimicrob Chemother **1997**; 40:135–6.
20. Centers for Disease Control and Prevention (CDC). *Staphylococcus aureus* resistant to vancomycin--United States, 2002. MMWR Morb Mortal Wkly Rep **2002**; 51:565–7.
21. Mendes RE, Deshpande L, Streit JM, et al. ZAAPS programme results for 2016: an activity and spectrum analysis of linezolid using clinical isolates from medical centres in 42 countries. J Antimicrob Chemother **2018**; 73(7):1880–1887.
22. Pfaller MA, Mendes RE, Duncan LR, et al. Activity of dalbavancin and comparator agents against Gram-positive cocci from clinical infections in the USA and Europe 2015-16. J Antimicrob Chemother **2018**; 73:2748–56.
23. Sader HS, Fey PD, Limaye AP, et al. Evaluation of vancomycin and daptomycin potency trends (MIC creep) against methicillin-resistant *Staphylococcus aureus* isolates collected in nine U.S. medical centers from 2002 to 2006. Antimicrob Agents Chemother **2009**; 53:4127–32.
24. Sader HS, Farrell DJ, Flamm RK, Jones RN. Analysis of 5-year trends in daptomycin activity tested against *Staphylococcus aureus* and enterococci from European and US hospitals (2009–2013). J Glob Antimicrob Resist **2015**; 3:161–5.
25. Sader HS, Castanheira M, Flamm RK, et al. Geographic and temporal variation on the frequency of occurrence and antimicrobial susceptibility of bacteria isolated from patients hospitalised with bacterial pneumonia: results from 20 years of the

SENTRY Program (1997–2016). In: European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) 2018. Madrid, Spain. 21–24 April 2018. (No. P0929).

26. Sader HS, Flamm RK, Castanheira M. Comparison of ceftazidime-avibactam and ceftolozane-tazobactam *in vitro* activities when tested against Gram-negative bacteria isolated from patients hospitalized with pneumonia in US medical centers (2017). In: IDWeek 2018. San Francisco, CA. 3–7 October 2018. (No. 2427).

27. Sader HS, Castanheira M, Mendes RE, Flamm RK. Frequency and antimicrobial susceptibility of Gram-negative bacteria isolated from patients with pneumonia hospitalized in ICUs of US medical centres (2015-17). J Antimicrob Chemother **2018**; 73:3053–9.

28. Biedenbach DJ, Jones RN. Fluoroquinolone-resistant *Haemophilus influenzae*: frequency of occurrence and analysis of confirmed strains in the SENTRY Antimicrobial Surveillance Program (North and Latin America). Diagn Microbiol Infect Dis **2000**; 36:255–9.

29. Diekema DJ, Pfaller MA, Turnidge J, et al. Genetic relatedness of multidrug-resistant, methicillin (oxacillin)-resistant *Staphylococcus aureus* bloodstream isolates from SENTRY antimicrobial resistance surveillance centers worldwide, 1998. Microb Drug Resist **2000**; 6:213–21.

30. Gales AC, Jones RN, Gordon KA, et al. Activity and spectrum of 22 antimicrobial agents tested against urinary tract infection pathogens in hospitalized patients in Latin America: report from the second year of the SENTRY antimicrobial surveillance program (1998). J Antimicrob Chemother **2000**; 45:295–303.

31. Gales AC, Jones RN, Turnidge J, et al. Characterization of *Pseudomonas aeruginosa* isolates: occurrence rates, antimicrobial susceptibility patterns, and molecular typing in the global SENTRY Antimicrobial Surveillance Program, 1997–1999. Clin Infect Dis **2001**; 32(Suppl 2):S146–55.

32. Pfaller MA, Acar J, Jones RN, et al. Integration of molecular characterization of microorganisms in a global antimicrobial resistance surveillance program. Clin Infect Dis **2001**; 32(Suppl 2):S156–67.

33. Toleman MA, Simm AM, Murphy TA, et al. Molecular characterization of SPM-1, a novel metallo-beta-lactamase isolated in Latin America: report from the SENTRY antimicrobial surveillance programme. J Antimicrob Chemother **2002**; 50:673–9.

34. Toleman MA, Biedenbach D, Bennett D, et al. Genetic characterization of a novel metallo-beta-lactamase gene, *bla*IMP-13, harboured by a novel Tn5051-type transposon disseminating carbapenemase genes in Europe: report from the SENTRY worldwide antimicrobial surveillance programme. J Antimicrob Chemother **2003**; 52:583–90.

35. Castanheira M, Toleman MA, Jones RN, et al. Molecular characterization of a beta-lactamase gene, *bla*GIM$_{-1}$, encoding a new subclass of metallo-beta-lactamase. Antimicrob Agents Chemother **2004**; 48:4654–61.

36. Mendes RE, Castanheira M, Garcia P, et al. First isolation of *bla*(VIM-2) in Latin America: report from the SENTRY Antimicrobial Surveillance Program. Antimicrob Agents Chemother **2004**; 48:1433–4.

37. Jones RN, Deshpande LM, Bell JM, et al. Evaluation of the contemporary occurrence rates of metallo-beta-lactamases in multidrug-resistant Gram-negative bacilli in Japan: report from the SENTRY Antimicrobial Surveillance Program (1998-2002). Diagn Microbiol Infect Dis **2004**; 49:289–94.

38. Toleman MA, Biedenbach D, Bennett DM, et al. Italian metallo-beta-lactamases: a national problem? Report from the SENTRY Antimicrobial Surveillance Programme. J Antimicrob Chemother **2005**; 55:61–70.

39. Sader HS, Castanheira M, Mendes RE, et al. Dissemination and diversity of metallo-beta-lactamases in Latin America: report from the SENTRY Antimicrobial Surveillance Program. Int J Antimicrob Agents **2005**; 25:57–61.

40. Fritsche TR, Sader HS, Toleman MA, et al. Emerging metallo-beta-lactamase-mediated resistances: a summary report from the worldwide SENTRY antimicrobial surveillance program. Clin Infect Dis **2005**; 41(Suppl 4):S276–8.

41. Biedenbach DJ, Toleman MA, Walsh TR, Jones RN. Characterization of fluoroquinolone-resistant beta-hemolytic *Streptococcus* spp. isolated in North America and Europe including the first report of fluoroquinolone-resistant *Streptococcus dysgalactiae* subspecies equisimilis: report from the SENTRY Antimicrobial Surveillance Program (1997-2004). Diagn Microbiol Infect Dis **2006**; 55:119–27.

42. Castanheira M, Deshpande LM, Mathai D, et al. Early dissemination of NDM-1 and OXA-181-producing *Enterobacteriaceae* in Indian hospitals: report from the SENTRY Antimicrobial Surveillance Program, 2006-2007. Antimicrob Agents Chemother **2011**; 55:1274–8.

43. Castanheira M, Farrell SE, Deshpande LM, et al. Prevalence of β-lactamase-encoding genes among *Enterobacteriaceae* bacteremia isolates collected in 26 U.S. hospitals: report from the SENTRY Antimicrobial Surveillance Program (2010). Antimicrob Agents Chemother **2013**; 57:3012–20.

44. Castanheira M, Mendes RE, Jones RN, Sader HS. Changes in the frequencies of β-lactamase genes among *Enterobacteriaceae* isolates in U.S. Hospitals, 2012 to 2014: activity of ceftazidime-avibactam tested against β-lactamase-producing isolates. Antimicrob Agents Chemother **2016**; 60:4770–7.

45. Castanheira M, Griffin MA, Deshpande LM, et al. Detection of mcr-1 among *Escherichia coli* clinical isolates collected worldwide as part of the SENTRY Antimicrobial Surveillance Program in 2014 and 2015. Antimicrob Agents Chemother **2016**; 60:5623–4.

46. Kaiser RM, Castanheira M, Jones RN, et al. Trends in *Klebsiella pneumoniae* carbapenemase-positive *K. pneumoniae* in US hospitals: report from the 2007-2009 SENTRY Antimicrobial Surveillance Program. Diagn Microbiol Infect Dis **2013**; 76:356–60.

47. Deshpande LM, Castanheira M, Flamm RK, Mendes RE. Evolving oxazolidinone resistance mechanisms in a worldwide collection of enterococcal clinical isolates: results from the SENTRY Antimicrobial Surveillance Program. J Antimicrob Chemother **2018**; 73:2314–22.

48. Mendes RE, Deshpande LM, Castanheira M, et al. First report of cfr-mediated resistance to linezolid in human staphylococcal clinical isolates recovered in the United States. Antimicrob Agents Chemother **2008**; 52:2244–6.

49. Pfaller MA, Mendes RE, Streit JM, et al. Five-year summary of in vitro activity and resistance mechanisms of linezolid against clinically important Gram-positive cocci in the United States rom the LEADER surveillance program (2011 to 2015). Antimicrob Agents Chemother **2017**; 61:e00609.

50. Fridkin SK, Steward CD, Edwards JR, et al. Surveillance of antimicrobial use and antimicrobial resistance in United States hospitals: project ICARE phase 2. Project intensive care antimicrobial resistance epidemiology (ICARE) hospitals. Clin Infect Dis **1999**; 29:245–52.

51. Bradford PA, Bratu S, Urban C, et al. Emergence of carbapenem-resistant *Klebsiella* species possessing the class A carbapenem-hydrolyzing KPC-2 and inhibitor-resistant TEM-30 beta-lactamases in New York City. Clin Infect Dis **2004**; 39:55–60.

52. Sader HS, Flamm RK, Doyle TB, et al. The role of whole genome sequencing on post-marketing surveillance programs: results of the INFORM surveillance program for ceftazidime-avibactam in the United States. In: ESCMID/ASM Conference on Drug Development to Meet the Challenge of Antimicrobial Resistance. Lisbon, Portugal. 4–7 September 2018. (No. 107).

53. Naas T, Vandel L, Sougakoff W, et al. Cloning and sequence analysis of the gene for a carbapenem-hydrolyzing class A beta-lactamase, Sme-1, from *Serratia marcescens* S6. Antimicrob Agents Chemother **1994**; 38:1262–70.

54. Queenan AM, Torres-Viera C, Gold HS, et al. SME-type carbapenem-hydrolyzing class A beta-lactamases from geographically diverse *Serratia marcescens* strains. Antimicrob Agents Chemother **2000**; 44:3035–9.

55. Doi Y, Paterson DL. Carbapenemase-producing *Enterobacteriaceae*. Semin Respir Crit Care Med **2015**; 36:74–84.

56. Centers for Disease Control and Prevention (CDC). Detection of *Enterobacteriaceae* isolates carrying metallo-beta-lactamase - United States, 2010. MMWR Morb Mortal Wkly Rep **2010**; 59:750.

57. Watanabe M, Iyobe S, Inoue M, Mitsuhashi S. Transferable imipenem resistance in *Pseudomonas aeruginosa*. Antimicrob Agents Chemother **1991**; 35:147–51.

58. Castanheira M, Duncan LR, Rhomberg PR, Sader HS. Enhanced activity of cefepime-tazobactam (WCK 4282) against KPC-producing *Enterobacteriaceae* when tested in media supplemented with human serum or sodium chloride. Diagn Microbiol Infect Dis **2017**; 89:305–9.

59. Sader HS, Johnson DM, Jones RN. In vitro activities of the novel cephalosporin LB 11058 against multidrug-resistant *Staphylococci* and *Streptociocci*. Antimicrob Agents Chemother **2004**; 48:53–62.

60. Sader HS, Rhomberg PR, Farrell DJ, Jones RN. Antimicrobial activity of CXA-101, a novel cephalosporin tested in combination with tazobactam against *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and *Bacteroides fragilis* strains having various resistance phenotypes. Antimicrob Agents Chemother **2011**; 55:2390–4.

61. Sader HS, Rhomberg PR, Flamm RK, et al. WCK 5222 (cefepime/zidebactam) antimicrobial activity tested against Gram-negative organisms producing clinically relevant β-lactamases. J Antimicrob Chemother **2017**; 72:1696–703.

62. Martin-Loeches I, Dale GE, Torres A. Murepavadin: a new antibiotic class in the pipeline. Expert Rev Anti Infect Ther **2018**; 16:259–68.

63. Sader HS, Flamm RK, Dale GE, et al. Murepavadin activity tested against contemporary (2016-17) clinical isolates of XDR *Pseudomonas aeruginosa*. J Antimicrob Chemother **2018**; 73:2400–4.

64. DeRyke CA, Lee SY, Kuti JL, Nicolau DP. Optimising dosing strategies of antibacterials utilising pharmacodynamic principles: impact on the development of resistance. Drugs **2006**; 66:1–14.

65. Flamm RK, Sader HS, Castanheira M, Jones RN. The application of *in vitro* surveillance data for antibacterial dose selection. Curr Opin Pharmacol **2017**; 36:130–8.

66. Ambrose PG, Bhavnani SM, Rubino CM, et al. Pharmacokinetics-pharmacodynamics of antimicrobial therapy: it's not just for mice anymore. Clin Infect Dis **2007**; 44:79–86.

67. Ambrose PG, Bhavnani SM, Ellis-Grosse EJ, Drusano GL. Pharmacokinetic-pharmacodynamic considerations in the design of hospital-acquired or ventilator-associated bacterial pneumonia studies: look before you leap! Clin Infect Dis **2010**; 51(Suppl 1):S103–10.

68. ICPD. White paper: de-risking antibiotic drug development with PK-PD. institute for clinical pharmacodynamics; **2017**. Available at: http://icpd.com/downloads/ICPD-White-Paper-De-risking-Drug-Development-with-PK-PD.pdf. Accessed 19 September 2017.

69. DeRyke CA, Kuti JL, Nicolau DP. Reevaluation of current susceptibility breakpoints for Gram-negative rods based on pharmacodynamic assessment. Diagn Microbiol Infect Dis **2007**; 58:337–44.

70. Jones RN, Craig WA, Ambrose PG, et al. Reevaluation of *Enterobacteriaceae* MIC/disk diffusion zone diameter regression scattergrams for 9 beta-lactams: adjustments of breakpoints for strains producing extended spectrum beta-lactamases. Diagn Microbiol Infect Dis **2005**; 52:235–46.

71. Dudley MN, Ambrose PG, Bhavnani SM, et al. Background and rationale for revised clinical and laboratory standards institute interpretive criteria (breakpoints) for *Enterobacteriaceae* and *Pseudomonas aeruginosa*: I. Cephalosporins and aztreonam. Clin Infect Dis **2013**; 56:1301–9.

72. Rennie RP, Jones RN. Effects of breakpoint changes on carbapenem susceptibility rates of *Enterobacteriaceae*: results from the SENTRY Antimicrobial Surveillance Program, United States, 2008 to 2012. Can J Infect Dis Med Microbiol **2014**; 25:285–7.

73. Food and Drug Administration. Limited Population Pathway for Antibacterial and Antifungal Drugs Guidance for Industry. Silver Spring, MD: U.S. Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER); **2018**.

74. CLSI. M23Ed5E. Development of In Vitro Susceptibility Testing Criteria and Quality Control Parameters. 5th ed. Wayne, PA; Clinical and Laboratory Standards Institute; **2018**.

75. Alexander EL, Loutit J, Tumbarello M, et al. Carbapenem-resistant *Enterobacteriaceae* infections: results from a retrospective series and implications for the design of prospective clinical trials. Open Forum Infect Dis **2017**; 4:ofx063.

76. Theuretzbacher U, Paul M. Developing a new antibiotic for extensively drug-resistant pathogens: the case of plazomicin. Clin Microbiol Infect **2018**; 24:1231–3.

77. Sader HS, Castanheira M, Flamm RK, et al. Tigecycline activity tested against carbapenem-resistant *Enterobacteriaceae* from 18 European nations: results from the SENTRY surveillance program (2010-2013). Diagn Microbiol Infect Dis **2015**; 83:183–6.

78. Sader HS, Castanheira M, Shortridge D, et al. Antimicrobial activity of ceftazidime-avibactam tested against multidrug-resistant *Enterobacteriaceae* and *Pseudomonas aeruginosa* isolates from U. S. medical centers, 2013 to 2016. Antimicrob Agents Chemother **2017**; 61:e01045.

79. Castanheira M, Deshpande LM, Davis AP, et al. Monitoring antifungal resistance in a global collection of invasive yeasts and moulds: application of CLSI epidemiological cutoff values and whole genome sequencing analysis for detection of azole resistance in *Candida albicans*. Antimicrob Agents Chemother **2017**; 61:e00906.

80. Pfaller MA, Messer SA, Woosley LN, et al. Echinocandin and triazole antifungal susceptibility profiles for clinical opportunistic yeast and mold isolates collected from 2010 to 2011: application of new CLSI clinical breakpoints and epidemiological cutoff values for characterization of geographic and temporal trends of antifungal resistance. J Clin Microbiol **2013**; 51:2571–81.

81. Sader HS, Fritsche TR, Jones RN. Potency and spectrum trends for cefepime tested against 65746 clinical bacterial isolates collected in North American medical centers: results from the SENTRY Antimicrobial Surveillance Program (1998-2003). Diagn Microbiol Infect Dis **2005**; 52:265–73.

82. Sader HS, Mendes RE, Streit JM, Flamm RK. Antimicrobial susceptibility trends among *Staphylococcus aureus* from U. S. hospitals: results from 7 years of the ceftaroline (AWARE) surveillance program (2010–2016). Antimicrob Agents Chemother **2017**; 61:e01043.

83. Sader HS, Castanheira M, Duncan LR, Flamm RK. Antimicrobial susceptibility of *Enterobacteriaceae* and *Pseudomonas aeruginosa* isolates from United States medical centers stratified by infection type: results from the International Network for Optimal Resistance Monitoring (INFORM) Surveillance Program, 2015-2016. Diagn Microbiol Infect Dis **2018**; 92:69–74.

84. Pfaller MA, Flamm RK, Duncan LR, et al. Antimicrobial activity of ceftobiprole and comparator agents when tested against contemporary Gram-positive and -negative organisms collected from Europe (2015). Diagn Microbiol Infect Dis **2018**; 91:77–84.

85. Shortridge D, Pfaller MA, Castanheira M, Flamm RK. Antimicrobial activity of ceftolozane-tazobactam tested against *Enterobacteriaceae* and *Pseudomonas aeruginosa* collected from patients with bloodstream infections isolated in United States hospitals (2013-2015) as part of the Program to Assess Ceftolozane-Tazobactam Susceptibility (PACTS) Surveillance Program. Diagn Microbiol Infect Dis **2018**; 92:158–63.

86. Pfaller MA, Sader HS, Rhomberg PR, Flamm RK. *In vitro* activity of delafloxacin against contemporary bacterial pathogens from the United States and Europe, 2014. Antimicrob Agents Chemother **2017**; 61:e02609.

87. Sader HS, Farrell DJ, Flamm RK, Jones RN. Analysis of 5-year trends in daptomycin activity tested against *Staphylococcus aureus* and enterococci from European and US hospitals (2009-2013). J Glob Antimicrob Resist **2015**; 3:161–5.

88. Pfaller MA, Messer SA, Rhomberg PR, et al. *In vitro* activities of isavuconazole and comparator antifungal agents tested against a global collection of opportunistic yeasts and molds. J Clin Microbiol **2013**; 51:2608–16.

89. Castanheira M, Huband MD, Mendes RE, Flamm RK. Meropenem-vaborbactam tested against contemporary Gram-negative isolates collected worldwide during 2014, including carbapenem-resistant, KPC-producing, multidrug-resistant, and extensively drug-resistant *Enterobacteriaceae*. Antimicrob Agents Chemother **2017**; 61:e00567.

90. Pfaller MA, Rhomberg PR, Messer SA, et al. Isavuconazole, micafungin, and 8 comparator antifungal agents' susceptibility profiles for common and uncommon opportunistic fungi collected in 2013: temporal analysis of antifungal drug resistance using CLSI species-specific clinical breakpoints and proposed epidemiological cutoff values. Diagn Microbiol Infect Dis **2015**; 82:303–13.

91. Pfaller MA, Sader HS, Flamm RK, et al. Oritavancin in vitro activity against gram-positive organisms from European and United States medical centers: results from the SENTRY Antimicrobial Surveillance Program for 2010-2014. Diagn Microbiol Infect Dis **2018**; 91:199–204.

92. Castanheira M, Davis AP, Mendes RE, et al. *In vitro* activity of plazomicin against Gram-negative and Gram-positive isolates collected from U. S. hospitals and comparative activity of aminoglycosides against carbapenem-resistant *Enterobacteriaceae* and isolates carrying carbapenemase genes. Antimicrob Agents Chemother **2018**; 62:e00313.

93. Pfaller MA, Flamm RK, Jones RN, et al. Activities of tedizolid and linezolid determined by the reference broth microdilution method against 3,032 Gram-positive bacterial isolates collected in Asia-Pacific, Eastern Europe, and Latin American countries in 2014. Antimicrob Agents Chemother **2016**; 60:5393–9.

94. Duncan LR, Sader HS, Smart JI, et al. Telavancin activity in vitro tested against a worldwide collection of Gram-positive clinical isolates (2014). J Glob Antimicrob Resist **2017**; 10:271–6.

95. Pfaller MA, Castanheira M, Messer SA, Jones RN. In vitro antifungal susceptibilities of isolates of *Candida* spp. and *Aspergillus* spp. from China to nine systemically active antifungal agents: data from the SENTRY Antifungal Surveillance Program, 2010 through 2012. Mycoses **2015**; 58:209–14.

96. Mutnick AH, Biedenbach DJ, Turnidge JD, Jones RN. Spectrum and potency evaluation of a new oxazolidinone, linezolid: report from the SENTRY Antimicrobial Surveillance Program, 1998-2000. Diagn Microbiol Infect Dis **2002**; 43:65–73.

97. Castanheira M, Mendes RE, Sader HS. Low frequency of ceftazidime-avibactam resistance among *Enterobacteriaceae* isolates carrying *bla*KPC collected in U.S. hospitals from 2012 to 2015. Antimicrob Agents Chemother **2017**; 61:e02369.