Antimicrobial Resistance Surveillance and New Drug Development

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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...
Public ARS Programs

These agencies require that drug manufacturers provide data of their candidate(s) against a collection of relevant bacteria early in clinical development. Antimicrobial agents and methodology vary among participating centers. Regulatory agencies also require that drug companies perform premarketing surveillance programs 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.

### 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.

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### 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

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**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.
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 (Figure 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, ceftazidine-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).
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 blaKPC 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)90 and MIC90 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], ceftazidime [81], ceftaroline [82], ceftazidime-avibactam [83], ceftobiprole [84], cefotolozane-tazobactam [85], delafloxacin [86], dalbavancin [22], daptomycin [87], isavuconazole [88], linezolid [21], meropenem-vaborbactam [89], micafungin [90], oritavancin [91], plazomicin [92], posaconazole [79], televacine [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
Funding for the manuscript was provided by [27]. 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.

Acknowledgments

We thank all participants of the SENTRY Program for their work in providing isolates.

Financial support. Funding for the manuscript was provided by JMI Laboratories.

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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