

The Importance of Antimicrobial Resistance Monitoring Worldwide and the Origins of SENTRY Antimicrobial Surveillance Program

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The origins of how and why the SENTRY Antimicrobial Surveillance Program was created are briefly described, with additional details on how the isolates are collected and tested as well as the important uses of the data in monitoring antimicrobial resistance and drug development.

Keywords. antimicrobial agents; antimicrobial resistance; SENTRY; surveillance.

Antimicrobial resistance (AMR) is an ongoing problem with multidrug-resistant strains of bacteria and fungi impacting medical progress in many regions of the world. Collecting AMR surveillance data is an essential approach to (1) define the scope of the resistance problem, (2) develop interventions that improve the appropriate application of antimicrobial agents, and (3) decrease resistance selection pressure [1, 2]. Other important efforts are underway to understand the mechanisms of resistance whereby microorganisms avoid the effects of antimicrobials and to use that information to discover/develop new compounds, or modify older agents, that retain potent activity against key target pathogens [3]. Trends in AMR have been described in numerous single-center and population-based surveys conducted throughout the world. However, the dynamic nature of AMR trends in the United States and elsewhere suggests that this issue still merits considerable monitoring and more comprehensive, well organized surveillance programs.

One important aspect of any antimicrobial surveillance program is longitudinality. By conducting surveillance of specific pathogens over time, one can assess the emergence of specific strains or species and discover changes in the antimicrobial susceptibility profile of the organisms. Furthermore, when longitudinal surveillance encompasses a broad geographic distribution, one may eventually develop a useful understanding of regional, national, or even global trends of species distributions and AMR [1].

The SENTRY Antimicrobial Surveillance Program (SENTRY Program) was designed to track AMR trends and the spectrum of microbial pathogens across various infection types on a global scale. The SENTRY Program has unique features that distinguish it from other excellent contemporary surveillance designs. Whereas most surveillance initiatives are based in a single nation, may track only nosocomial infections, and/or rely primarily on categorical susceptibility testing result inputs from participating centers (diverse susceptibility testing methods), the SENTRY Program monitors both nosocomial and community-onset infections on a global scale and uses validated reference identification and susceptibility testing methods via a central monitoring laboratory model.

The SENTRY Program, which is being recognized for its 20 years (1997–2016) of existence through this publication, originated from the recommendations of the American Society for Microbiology (ASM) Task Force on Antimicrobial Resistance that convened in 1994 [1, 4]. That task force was assembled to discuss the concern of rising AMR rates and the lack of available antimicrobial agents to treat emerging health threats. Three major components were outlined during that meeting: (1) education, (2) basic research and development, and (3) surveillance. The surveillance component highlighted a number of variables that notably included such an endeavor and would likely require a consortium funding approach that would involve government, professional societies, independent foundations, and pharmaceutical industry contributions. Unfortunately, it was soon recognized that no mechanism existed to bring these stakeholders together in a complementary manner to launch a jointly funded national surveillance system.

Shortly after the task force meeting, Professor Ronald Jones, MD (University of Iowa College of Medicine) was approached by Bristol-Myers Squibb to implement a surveillance program in which its portfolio of antimicrobial agents and other marketed

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therapeutic drugs would be monitored against a large and diverse collection of clinical isolates across years. This initial concept morphed into the SENTRY Program, which was launched in 1997 [5].

The SENTRY Program utilized many of the components desired by the ASM task force [4], including a focus on monitoring the most prevalent bacterial and fungal pathogens in contemporary human infectious diseases through various objectives (defined in the next paragraph), a wide net cast globally to recruit and collect organisms from a large number of sentinel medical centers (hence, the name SENTRY) that represented a broad geographic human population, and a central laboratory processing approach to apply standardized reference antimicrobial susceptibility testing methods. The study was jointly coordinated through the University of Iowa (Iowa City, IA), University of Utrecht (Utrecht, Netherlands), and the Women's and Children's Hospital (Adelaide, Australia), and regional testing was performed at those 3 reference laboratories. Scientific oversight was initially provided through Professor Jones and a consortium of key opinion leaders.

One important distinction of the SENTRY Program was applying prevalence-based collection objectives in the surveillance model whereby consecutive isolates per infection type were collected overall and/or on a month-to-month basis to diversify the submitted isolates and reduce seasonality or other epidemiological concerns related to specific pathogens [5–7]. At the onset of the program, 6 core collection objectives addressed the most common types of infection: bloodstream infections, community-acquired respiratory tract infections (fastidious pathogens only), pneumonias in hospitalized patients, skin and soft tissue or wound infections, urinary tract infections, and invasive fungal infections. Although the total contribution of clinical isolates per objective has varied over the years, these major collection objectives remain intact today. Other collection objectives have been introduced throughout the life of the SENTRY Program, and some of these represented a one-time objective for scientific pursuits (eg, gastroenteritis pathogens) or were introduced into the surveillance life cycle due to the emerging needs of drug development and indications being sought for regional regulatory submission (eg, intra-abdominal infections).

After 1999, the scientific advisors recommended disseminating summary data that had been generated from the SENTRY Program. A supplement was published by *Clinical Infectious Diseases* that presented 3 years of results from testing key bacterial pathogens [8]. The wide dissemination of data is also a hallmark of the SENTRY Program, with more than 400 published articles in peer-reviewed microbiology and infectious disease journals and countless posters presented at international scientific conferences. In addition to reporting on the changing patterns of resistance over time, a number of noteworthy scientific discoveries or revelations have stemmed from the SENTRY Program. These have included the following: (1) the discoveries of various metallo enzymes

and other β -lactamases, including *bla*_{IMP-13} (GenBank no. NG_049176), *bla*_{IMP-16} (GenBank no. NG_049179.1), *bla*_{IMP-33} (GenBank no. JN848782.2), *bla*_{SPM-1} (GenBank no. AJ492820.1), *bla*_{GIM-1} (GenBank no. NG_049143.1), *bla*_{VIM-18} (GenBank no. AM778091.1), *bla*_{VIM-23} (GenBank no. GQ242167.1), *bla*_{VIM-35} (GenBank no. JX982634.1), and *bla*_{VIM-37} (GenBank no. JX982636.1); (2) the documented occurrence of *mcr-1* genes in US surveillance isolates found before the initial reported cases; and (3) the changing serotypes of *Streptococcus pneumoniae* associated with the introduction of various pneumococcal vaccines [9–13].

Another important aspect of SENTRY Program surveillance is the breadth of antimicrobial agents included in the program each surveillance year. The genesis of our program support was provided by a single pharmaceutical sponsor, and investigational agents were initially limited to that sponsor's product, in addition to other relevant and clinically available agents used for contemporary infectious disease practice. Eventually, the SENTRY Program moved to the consortium-funded design approach in which numerous sponsors funded the program through contractual support. This model allowed numerous investigational drugs and combination agents to be included in the surveillance and each isolate tested to have 20–30 drugs included in the antibiogram profile. Contributing SENTRY Program medical centers can access their antibiogram data (for approved drugs) for submitted isolates, providing an opportunity to gain immediate access to newly approved drug susceptibility information that may not be accessible by other means due to limited diagnostics. It has become clear that automated susceptibility testing system approvals for new drugs can significantly lag behind US Food and Drug Administration release [14].

Other notable SENTRY Program features include the central reference laboratory design, where reference testing reagents and standard operating protocols and methods are used in the yearlong testing schedules that include rigid quality assurance. In addition, where possible, the same sites have been recruited and included each year to preserve the longitudinality of surveillance data.

Expanded technology has also played an important role in the SENTRY Program. Several advancements have improved the quality and speed of the testing services and analyses performed. Initial organism identification methods and processes relied on traditional microbiologic methods and training, along with biochemicals and other automated commercial testing systems (Vitek, and Vitek 2; bioMérieux). Eventually, matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) became the preferred technology for identification due to its rapid, accurate results and low cost per test. However, there are still many organisms for which traditional manual methods and/or biochemical and other reagents are used to differentiate species or provide backup for MALDI-TOF MS in cases in which the confidence

score does not meet the threshold for certain identification confirmatory assignment. Sequencing methods are also applied for identification purposes, as needed.

Initial epidemiological and molecular screening for genetic relatedness and resistance mechanisms were performed using riboprinting and traditional polymerase chain reaction methods. Eventually, the progression of resistance among Gram-negative species isolates led to the growth in deoxyribonucleic acid microarray techniques and methods for the rapid detection of β -lactamase enzymes and other important resistance mechanisms. Gene sequencing was always viewed as an important and vital tool in describing the genome of unique and resistant pathogens, but at the outset of the SENTRY Program and only until recently, a large-scale investigation using sequencing methods was not a scalable option due to the costs and relevant timing. Within the last few years, advances in next-generation sequencing (NGS) equipment, both in terms of acquisition and testing costs, and small equipment footprint designs have made it routinely possible to apply NGS methods for our molecular investigations [15, 16].

Finally, advances in computers, software design, and capabilities including available laboratory information management systems (LIMS) and web-enabled program features and accessibility have greatly improved the operational and data analysis aspects of the SENTRY Program surveillance. Initial program oversight and data review were predominantly performed manually and individual isolate reviews were completed by laboratory scientists. Internally and externally developed LIMS programs have allowed for better management of the operational process. Computer-based algorithms led to a rapid and more efficient review of data, resulting in high-quality assurance of testing results and recognition of outliers (nonwild-type strains or potential test errors) in drug-pathogen results. Laboratory information management systems also created greater efficiencies that allowed for higher volumes of tests to be performed, including the expansion of antimicrobial agents tested per pathogen processed.

CONCLUSIONS

Approximately 1 million isolates have been collected and tested as part of the SENTRY Program, producing more than 30 million minimum inhibitory concentration data points over this 20-year period. SENTRY Program data, including the related demographic information associated with each clinical isolate, has been used in many new drug regulatory applications and has been used to collect data to comply with postdrug-approval AMR monitoring requirements. Furthermore, data from the SENTRY Program has been utilized for scientific dissemination at various international and regional conferences as abstracts/posters and for submissions to peer-reviewed infectious disease and microbiology focused journals, averaging more than 20 manuscripts per

year. The SENTRY Program has supported new drug development efforts by providing data that indicates key resistance trends to pharmaceutical sponsors as they seek direction for their chemistry discovery efforts to develop candidate agents.

Although the SENTRY Program has many strengths, we wish to point out limitations of the data collected, tested, and reported. With the focus on utilizing a prevalence-based approach, many organisms for which there is an unmet medical therapeutic need may not be collected in sufficient numbers due to their low incidence or because they may not be cultured and isolated due to the application of rapid tests in routine clinical laboratory diagnosis. Thus, pathogens such as *Clostridium difficile* (a Centers for Disease Control and Prevention [CDC] priority pathogen), other anaerobes, or sexually transmitted disease pathogens are not well represented in the SENTRY Program. Although there is a broad geographic representation of medical centers (especially in the United States) that participate in our program, the initial ASM task force model advocating 1 site for each 1 million persons was not financially viable or practical from a study management perspective. Some countries may only have a few sites providing organisms for that nation, which is problematic and could introduce bias. Furthermore, some countries or regions, such as Africa, may not be represented at all, mainly due to limited commercial development opportunities and/or the compromised ability to establish collection systems in those geographic areas.

Finally, we wish to recognize the great efforts of other surveillance systems that monitor AMR worldwide. These systems are national government initiatives, such as the following: the CDC ABC Surveillance Program; global (the Global Antimicrobial Resistance Surveillance System by the World Health Organization); local hospital or regional programs (the European Antimicrobial Resistance Surveillance Network [17]) to collect and monitor epidemiology data from laboratory information systems; or other commercial programs [18, 19]. These systems will provide important complementary phenotypic (categorical) rates and changes in those rates over time; however, as noted previously, the government and local/regional programs will likely not have susceptibility testing data for newly approved antimicrobial agents produced by reference quantitative methods.

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