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Antimicrobial resistance monitoring: a review of information resources

Kuzmenkov A.Yu., Vinogradova A.G.

Research Institute of Antimicrobial Therapy, Smolensk State Medical University
28, Krupskaya Str., Smolensk, 214019

ABSTRACT

In the last decades, the problem of antibiotic resistance has been occupying one of the key positions in the global public health system, and it requires attention from the medical community. Antimicrobial resistance monitoring systems play an important role in tracking the changes in antimicrobial susceptibility for timely correction of antimicrobial therapy. The pharmaceutical industry applies epidemiological data obtained through such monitoring to the creation of new medicines and modification of the antimicrobial substances developed earlier.

The article describes some of the international and Russian monitoring systems created at different times. It should be noted that during development, regional-level data are used, while a number of projects present information on a global scale. The completed comparative analysis of available systems revealed both positive aspects and parameters in need of renovation. At the same time, the standardization of collecting basic data for monitoring programs requires significant changes. The majority of systems are able to examine only a limited range of microorganisms and antimicrobials. An important point in the functioning of monitoring systems is a search for the optimal way to visualize output data in tables, interactive maps, and graphics. A significant amount of projects demand further work on the result presentation options. Constant monitoring is a significant component in modern concepts of antibiotic resistance control due to the increasing occurrence of resistant organisms.

Key words: analytical systems, antibiotic resistance, antimicrobials, surveillance.

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Мониторинг антибиотикорезистентности: обзор информационных ресурсов

Кузьменков А.Ю., Виноградова А.Г.

Научно-исследовательский институт антимикробной химиотерапии (НИИАХ), Смоленский государственный медицинский университет (СГМУ)
Россия, 214019, г. Смоленск, ул. Крупской, 28

РЕЗЮМЕ

В последние десятилетия проблема антибиотикорезистентности занимает одну из ключевых позиций в системах общественного здравоохранения во всем мире и требует особого внимания со стороны медицинского сообщества. Для отслеживания динамики чувствительности микроорганизмов, с целью

✉ *Vinogradova Alina G.,* e-mail: alina.vinogradova@antibiotic.ru.

своевременной коррекции антимикробной терапии, важную роль играют системы мониторинга антибиотикорезистентности. Полученные в рамках мониторинга эпидемиологические данные также используются в фармацевтической промышленности при создании новых лекарственных препаратов и модификации разработанных ранее антимикробных субстанций. В статье рассматриваются некоторые из зарубежных и российских систем мониторинга, созданные в разное время. Следует отметить, что при разработке используются данные на уровне отдельных регионов, а ряд проектов представляют информацию в глобальном масштабе. Результаты проведенного сравнительного анализа имеющихся систем выявили как положительные стороны, так и параметры, которые требуют модернизации. При этом в наибольших изменениях нуждается процесс стандартизации сбора исходных данных для программ мониторинга. Большинство систем лимитировано по спектру рассматриваемых микроорганизмов и антимикробных препаратов. Важным моментом для функционирования систем мониторинга является поиск оптимального способа визуализации выходных данных при помощи таблиц, интерактивных карт и графиков. Значительное количество проектов требует дальнейшей проработки вариантов представления результатов. Возрастающая частота резистентных микроорганизмов требует постоянного мониторинга, являющегося важной составляющей современных концепций сдерживания антибиотикорезистентности.

Ключевые слова: системы анализа, антибиотикорезистентность, антимикробные препараты, эпидемиологический надзор.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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INTRODUCTION

For the first time, reports on the emergence of antimicrobial resistance appeared in the 1940s. The first cases registered were connected with penicillin resistance. Then, as various antimicrobials were introduced into clinical practice, virtually all known pathogens acquired resistance to one or more drugs [1]. As a consequence, antibiotic resistance monitoring is a key element in the fight against this threat. Its main components include continuous collection, analysis, and interpretation of information related to antibiotic resistance. A monitoring system with the ability to permanently track the dynamics of antibiotic resistance in all clinically significant isolates, studied in healthcare facilities, can be considered impeccable. The data on resistance rates are suitable for research programs on infection control and the rational use of antibiotics. They are also used in the development of practical measures aimed at reducing antibiotic resistance [2].

Antibiotic resistance monitoring programs are able to indicate regions where the problem is widespread, geographical objects with increased rates of resistance, and microbial species that pose a serious threat to public health [3–5]. Moreover, the monitoring system is an early warning tool, and its efficiency depends on the time needed for interested stakeholders to access the information and their ability to take actions. At the same time, access to up-to-date and reliable information on the antibiotic resistance level contributes to the formation of an adequate response to private reports of antibiotic resistance in cases involving an improper assessment of the expected drug efficacy, which may consequently complicate antimicrobial therapy [2, 6].

Several key objectives are pursued in developing an antibiotic resistance monitoring system: to detect, analyze and predict changes in antibiotic resistance indicators and outbreaks of infections caused by microorganisms with modified resistance; to detect new resistance mechanisms; to compare the activity of new antibiotics before and after their introduction into clinical practice. In addition, a key point is the opportunity to educate medical staff, patients, and general public on antibiotic resistance issues.

It should be noted that for about 30 years since the detection of resistant microorganisms, the concept of monitoring antibiotic resistance has not existed in its modern sense. Only individual publications describing cases of antimicrobial ineffectiveness existed.

INTERNATIONAL ANTIBIOTIC RESISTANCE MONITORING PROGRAMS

Indirectly, antibiotic resistance monitoring systems have been in place since 1970, when several US clinics reported cases of hospital-acquired infections [7]. The immediate task was to collect data on nosocomial infections and susceptibility of germs to antimicrobials. This local system subsequently became the basis of the USA National Nosocomial Infection Surveillance System [8, 9].

Modernization of antibiotic resistance monitoring programs unequivocally shows that the quality of the organization has reached a new level. At present, the following levels of current initiatives to monitor antibiotic resistance can be determined: local, regional, national, and international. In addition, the levels can be hierarchical and different sources of funding can be applied to the systems [10, 11]. For instance, in a number of European countries, microbiological laboratories working on antibiotic resistance issues are obliged to provide the results of the observations to concerned organizations and healthcare providers at least once a year [12]. Moreover, local monitoring is realized by hospital laboratories, systematically reporting on the microbial susceptibilities. Europe, the USA and other countries develop regional, national, and international surveillance systems [8, 13, 14].

The group of national initiatives for antibiotic resistance monitoring includes Active Bacterial Core Surveillance (ABC system, USA). It was created as part of an infection research program in collaboration with the Centers for Disease Control and Prevention (CDC, USA) to assess the severity of invasive bacterial infections, which in a significant number of cases are manifested as sepsis and meningitis [4]. This project website published reports on the incidence of infections caused by different groups of *Streptococcus*, *H. influenzae*, MRSA (Methicillin Resistant *Staphylococcus Aureus*), *N. meningitidis* and contains information on some demographic characteristics [15]. The system also comprises a trend estimation of infectious diseases in the territory of several American states employing both molecular and microbiological methods.

Furthermore, the following programs exist: National Nosocomial Infections Surveillance (NNIS system, USA) and Global Emerging Infections Surveillance (GEIS, USA) [16, 17]. It should be noted that the NNIS report combines information from 300 clinics for the period from 1992 to 2004 and contains data on the frequency of nosocomial infections and various demographic indicators [18]. Limited information on antibiotic resistance, which includes only particular pathogens, is one of the main disadvantages.

In the early 2000s, several systems were combined into a single National Healthcare Safety Network (NHSN, USA). The final data of this program for 2006–2008 provide information about infections caused by different medical interventions and the use of diagnostic and therapeutic devices [19]. NHSN established an online monitoring system for antibiotic resistance in catheter-associated urinary tract infections, central line-associated bloodstream infections, and surgical site infections, in order to provide timely and complete data [20]. The structural elements of the application are an introduction page containing information on data collection methods; summary indicators of antibiotic resistance; and a map and an interactive table on selected microorganisms. Moreover, a graphic display of susceptibility indicators according to the patient's age, type of surgical interventions and health facilities is available to the user in the additional section. There are some drawbacks of the system, the main ones being a limited spectrum of antimicrobials and microorganisms and a lack of choice in localization of infections and hospital units. The database adopted as the basis for NHSH is not updated regularly; the latest available information dates back to 2015.

Public Health England (PHE) provides direct financial support in the development of several antibiotic resistance monitoring projects – Second generation surveillance system (SGSS) and the British Society for Antimicrobial Chemotherapy (BSAC). The characteristic feature of SGSS is presentation of summary information in the form of a report on the frequency characteristics of selected microorganisms and their susceptibility to antibiotics. The disadvantage of this system is the absence of possibility to access the website as an unregistered user. Moreover, the system contains only generalized data and non-interactive visualization [10]. BSAC involves participation of several countries: England, Wales, Scotland, Northern Ireland, and the Republic of Ireland [6]. The system forms publications and provides information with selection filters via the website; the output data cover the strain distribution of all susceptibility categories and minimum inhibitory concentration (MIC) distribution, as well as genetic markers of antibiotic resistance. Weak points include the lack of graphical and cartographic representation of data and the inability to consider data at primary aggregation levels.

The Centers for Disease Control and Prevention (CDC, USA) conducted a study on antibiotic resistance in 10 countries within reinforcement of resources for surveillance, response and emerging infectious disease control. The implementation of activities depended on the country. A research project in Egypt included a university and several public hospitals to monitor nosocomial infections and antibiotic resistance. The demographic analysis was the basis for systematic surveillance in Thailand and several African countries, such as Kenya [21].

International projects on antibiotic resistance monitoring include the European Antimicrobial Resistance Surveillance Network (EARS-Net) [13], the Latin American Surveillance Network of Antimicrobial Resistance (ReLAVRA – acronym in Spanish) [22], the Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR) [23], the Asian Network for Surveillance of Resistant Pathogens (ANSORP) [24], the Antibiotic Resistance Surveillance and Control in the Mediterranean Region (ARMed) [25,26], the Gonococcal Antimicrobial Surveillance Programme (GASP) [27], international research "Bacterial Infections and Antibiotic Resistant Diseases among Young Children in Low-Income Countries" (BIRDY) [28, 29], CDDEP(the Center for Disease Dynamics, Economics & Policy)-ResistanceMap [30], and the Global Antimicrobial Resistance Surveillance System (GLASS) [31].

EARS-Net was organized with financial support from the European Centre for Disease Control (ECDC) in 1999. EARS-Net 2018 report contained data on antimicrobial resistance of *E. coli, K. pneumoniae, P. aeruginosa, S. pneumoniae, Acinetobacter* spp., *S. aureus, E. faecalis, E. faecium* with selected antimicrobials being tested; and blood and cerebrospinal fluid were clinical materials [13, 32]. The data from the previous year are the base for an annual report. In addition, the trend in the dynamics of antimicrobial resistance for the last three years is shown in the form of tables and maps with gradient colors. The monitoring results are presented as an interactive system, not only in PDF. The main negative characteristics of the system are the limited spectrum of microorganisms and antibiotics and delayed access to results.

The Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR) includes European countries that are not part of EARS-Net and several Central Asia countries. The organization is financially supported by the WHO Regional Office for Europe (the World Health Organization Regional Office for Europe); the Dutch National Institute for Public Health and the Environment, the Ministry of Health, Welfare and Sport (the Netherlands); and the European Society of Clinical Microbiology and Infectious Diseases. At this time, 19 countries are members of CAESAR. The first CAESAR report was published in 2014 and included data from 9 member countries that submitted results of antimicrobial susceptibility testing (AST) for 8 species (*E. coli, P. aeruginosa, K. pneumoniae, Acinetobacter* spp., *S. pneumoniae, S. aureus, E. faecalis* and *E. faecium*), with blood and cerebrospinal fluid as clinical materials. The report structure consists of introductory information about the project, participating countries, and the specific data collection. The outcome of AST is presented in the form of tables for each country [23]. The system is insufficient in the selection of comparative indicators. There are no options to choose the localization of infections and hospital units, and data presentation abilities are limited. In addition, the final data contain a certain number of microorganisms with only delayed access to the monitoring results.

WHO and the Pan American Health Organization collectively founded the Latin American Surveillance Network of Antimicrobial Resistance (ReLAVRA). The network includes 19 countries that share their data on antibiotic resistance annually. Individual publications and the official web portal present the results of the system. Limited possibilities of data visualization and user-configurable filtering and the absence of in-depth data analysis can be considered as disadvantages of the system [22].

Professor Jung-Han (the Samsung medical center, Sungkyunkwan University, Seoul, South Korea) initiated the Asian Network for Surveillance of Resistant Pathogens (ANSORP). The main goal of the project is to implement international prospective studies on antibiotic resistance in the Asian region. The initial project developed by the ANSORP group addressed the pneumococcal resistance monitoring. The resource is updated at certain time intervals and generates reports on the results of prospective studies. In 2018, a working group of researchers began to work on collecting isolates and processing data in pediatric patients [24]. However, since the data presentation is limited to reporting, the expected difficulties in timely data presentation for the user and incomplete coverage of microorganism species arise. The visual component is also one of the underdeveloped aspects of the project.

Over a fouryear period, the Antibiotic Resistance Surveillance and Control in the Mediterranean Region (ARMed) functioned under the sponsorship of the Directorate General for Education and Culture. Cyprus, Egypt, Jordan, Malta (coordinator), Morocco, Tunisia, Algeria, Lebanon, and Turkey participated in the program. Susceptibility rates of *S. aureus, S. pneumoniae, E. coli, E. faecium,* and *E. faecalis* invasive strains and correctness of antibiotics prescription and intake were assessed. Due to the termination of external funding, ARMed has suspended its work [25].

CDDEP ResistanceMap is a website developed with support from the Center for Disease Dynamics, Economics and Policy (Washington, DC; USA) non-governmental organization. The resource presents data on consumption of antibacterial drugs and antibiotic resistance for different regions of the world and individual states [30]. The website provides information on 12 species of microorganisms. Visual presentation of data is possible in several variants: an interactive map, a trend and a bar chart. The system combines the results from several sources, such as the Australian Group on Antimicrobial Resistance (AGAR), the European Antimicrobial Resistance Surveillance Network (EARS-Net), the Canadian Antimicrobial Resistance Alliance (CARA), a private tertiarycare hospital (Kenya), the Public Health Surveillance, Institute of Environmental Science and Research Ltd (ESR, New Zealand), etc. [30]. Despite the big amount of information selected to form the ResistanceMap database, the potential system effectiveness is reduced by the scope of microbial selection, presentation options, and delayed data publication due to the dependence on primary sources.

One of the key positions of the global action plan on antibiotic resistance adopted at the World Health Assembly in 2015 is to strengthen the evidence base in this area [31]. The main ways are to conduct research and monitoring continuously on a global scale. This plan includes the development of the Global Antimicrobial Resistance Surveillance System (GLASS). A road map for five-year work was formulated for this project. During this period, antibiotic resistance is monitored based on clinical and microbiological data on priority bacterial pathogens, with the target of 40% WHO countries participating by the end of the project [33, 34].

Along with national and international general medical organizations, a number of pharmaceutical companies provide material support for the creation and maintenance of antibiotic resistance monitoring systems. Alexander Project, MYSTIC (Meropenem Yearly Susceptibility Test Information Collection), SENTRY, and TRUST are examples of such systems [35–39].

The SMART (Study for Monitoring Antimicrobial Resistance Trends) is also one of such projects, sponsored by the Merck & Co., Inc. The key objective of this system is to assess *in vitro* susceptibility of Gram-negative microorganisms to 12 antibiotics for intraabdominal and urinary tract infections. This website is designed for professionals working outside the USA [11]. The work results are available as an interactive map, publications and posters starting from 2009. Restricted choice of antibiotics and microorganism species and summary information display without detailed explanation limit the range of SMART applications.

ATLAS, a system supported by Pfizer, is a multi-component resource that includes a database that combines information from three sources: TEST (Tigecycline Evaluation Surveillance Trial), AWARE (Assessing Worldwide Antimicrobial Resistance Evaluation), and INFORM (International Network for Optimal Resistance Monitoring). The system currently obtains data on over 630,000 isolates. The user has a choice of parameters to filter the data by microorganism species, antimicrobials, geographic regions, and years. The output information is available as a heat map, a trend, or a table [40]. Point evaluation of indicators (city category) and multiple comparisons are not available, which emphasizes the need for further development of the project.

DEVELOPMENT AND IMPLEMENTATION OF ANTIBIOTIC RESISTANCE MONITORING SYSTEMS IN THE RUSSIAN FEDERATION

National antimicrobial resistance monitoring projects are regularly organized in the Russian Federation with the direct participation of the Institute of Antimicrobial Chemotherapy (IAC) and the Interregional Association for Clinical Microbiology and Antimicrobial Chemotherapy (IACMAC); they are managed by the Scientific-Methodical Center on Antibiotic Resistance Monitoring (CMAR) [41]. Since the 1990s, there have been various projects, such as RESORT, REVANSH, MARATHON, Pegas, START, NOTA, MARS, STENT, SPARS, Darmis, and NPRS [42]. The results of the projects were presented in electronic reports with tables and graphs. The publication time was delayed for several months, and only statistical data without user-configurable settings were presented.

AMRmap, an online platform for the analysis of antimicrobial resistance data in Russia, has been in function since 2016. Its significant difference is a wide range of tools for visualization, with a choice of a data format: charts, tables or interactive maps. The graphical module varies from bar charts to more rare variants – matrices and graphs. It is necessary to note the implemented system of filters, which allows to receive results on the scale of both federal districts and cities. Methods for assessment of associated resistance and presentation of genetic determinants of antibiotic resistance were designed for AMRmap [43]. The database, which the website is based on, includes the results of multicenter prospective antibiotic resistance studies conducted by IAC and IACMAC covering the period from 1997 to present, with retesting of obtained isolates at IAC central laboratory. Despite continuous updates, the process of input data generating requires further development, with an improvement of data implementation in the platform.

CONCLUSION

Constant high quality work of monitoring systems is an important element in controlling antibiotic resistance. The greatest efficiency in practical application is possible in the conditions of constant database filling, and expansion of criteria forming it. The best option is to conduct monitoring based on multicenter studies with the participation of all healthcare facility types in the project. At the moment, most of the local data come from large hospitals, which reflect the resistance rates due to a larger number of patients. Thus, regular inclusion of new participants in the antibiotic resistance monitoring, with an undiminishing quality and intensity of research protocol processing, will help to assess the situation with antimicrobial resistance more accurately. The data obtained will be used to improve monitoring systems, and the information provided will timely optimize antibacterial therapy on a global and national scale.

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Authors information

Kuzmenkov Alexey Yu., Cand.Sci (Med.), Deputy Director of Institute of Antimicrobial Chemotherapy, Smolensk State Medical University, Smolensk, Russian Federation. ORCID ID: 0000-0001-9562-2096.

Vinogradova Alina G., Research Associate, Institute of Antimicrobial Chemotherapy, Smolensk State Medical University, Smolensk, Russian Federation. ORCID ID: 0000-0002-0951-7810.

(✉) **Vinogradova Alina G.,** e-mail: alina.vinogradova@antibiotic.ru.

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