Surveillance of antibiotic consumption and antimicrobial resistance

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Abstract

Surveillance programs provide invaluable information regarding pathogen incidence and antimicrobial resistance. Health care professionals and policy makers depend on this information for developing responsible and effective treatment strategies that limit the emergence and spread of antimicrobial resistance. Continuous surveillance also reveals trends in pathogen susceptibility to currently and previously prescribed antimicrobial agents.
Routine surveillance of antimicrobial use reveals trends in dosing and allows comparisons of antimicrobial use data with antimicrobial resistance data that can provide important insights into the influence of particular agents. They are also internationally applicable.
Both of these tools provide their maximal benefits when used jointly and in coordination.

Keywords: antibiotic consumption, antimicrobial resistance, surveillance.

Introduction

The discovery of bacteria was a strong stimulus for appropriate preventative and therapeutic regimens. Half a century later, antibiotics were discovered and introduced in medical practice. Antibiotics have changed medicine and have saved many lives, but unfortunately, their use has been accompanied by the rapid appearance of resistant strains. Bacteria responded to antibacterial drugs by manifesting various forms of resistance. As antimicrobial usage increased, so did the level of the resistance and complexity of the resistance mechanisms exhibited by bacterial pathogens (1). Bacterial resistance often results in treatment failure, which can have serious consequences. Resistant bacteria, particularly staphylococci, enterococci, *Klebsiella pneumoniae*, and *Pseudomonas spp* (2-7), are being isolated more frequently in healthcare institutions.

Resistance development and antibiotic use

Antibiotics were developed originally to treat human infectious diseases. However, the broad use (i.e. in veterinary) has exercised a strong selective pressure, and the survival and spread of resistant bacteria are the results. Susceptible bacteria can acquire resistance to an antimicrobial agent via new mutations or through the acquisition of new genetic material from other resistant organisms. Initially, we were unaware of the implications associated with the indiscriminate use of these therapeutic entities and underestimated the genetic flexibility of the microorganisms that were targeted (8). Now, antibiotic resistance is a major public-health problem worldwide, and international efforts are needed to counteract its emergence (9).

Antibiotic consumption is increasingly being recognized as the main cause of this emerging resistance, and differential selection pressure of antibiotics could be responsible for some of these differences (10). Both the amount of antibiotics used and how they are used contribute to the development of resistance.

In 1994 a 'threshold' hypothesis proposed that resistance could be curtailed if total antibiotic use in a particular environment stayed below a critical quantitative level (11). The proposal was founded on the natural competition among bacteria and the potential for the return of susceptible flora after antibiotic treatment – a possibility that decreased as antibiotic consumption in a particular environment increased. Definition of the threshold values for different antibiotics would be important in controlling bacterial resistance.

Using population genetic methods and epidemiological observations, Austin et al (12) reported an analysis of the influence of the selective pressure imposed by the volume of drug use on temporal changes in resistance. The analyses indicated that the time scale for emergence of resistance under a constant selective pressure is typically much shorter than the decay time after cessation or decline in the volume of drug use and that significant reductions in resistance require equally significant reductions in drug consumption. These results highlighted the need for early intervention once resistance is detected.

In this context, implementation of antibiotic reduction policies in local environments,

such as hospitals, has been followed by a successful decrease in antibiotic resistance. The incidence of resistance in Staphylococcus aureus hospital isolates was affected by different antibiotic policies, e.g. restriction in the use of erythromycin resulted in significant decreases in erythromycin resistance among Staphylococcus aureus isolates (13). A multidrug resistant Klebsiella aerogenes outbreak in a neurosurgical ICU was only controlled when the use of all antibiotics was suspended (14). A significant decrease in antibiotic consumption, paralleled by a significant reduction in bacterial resistance, followed implementation of an antibiotic restriction policy program in a Greek hospital (15).

Surveillance of antimicrobial resistance (16)

The decision to undertake the surveillance and microbiological testing of pathogens for resistance will be determined, in part, by the extent to which resistance impacts on therapy. Establishment of surveillance systems is essential for improving appropriate antimicrobial use and containing the threat of antimicrobial resistance.

Ideally, surveillance of antimicrobial resistance should involve the collection and collation of both clinical and microbiological data. By establishing surveillance systems that integrate clinical and laboratory data, not only can the necessary data be captured but the

strengths of both data sets can be combined.

There are two general approaches to surveillance. *Comprehensive surveillance* which means the surveillance of a specified pathogen in the whole population at risk, involves the capture of data on all cases of infection. *Sentinel surveillance* is characterized by collection of data from a limited area or population to serve as indicator data for the rest of the population. Sentinel surveillance is generally more suitable where prolonged, ongoing and detailed data collection is required. Normally, the sentinel population should be representative of the total population, but in certain circumstances where the primary objective is to detect the emergence of resistance, a targeted approach may be more appropriate. Surveillance may be *continuous* or *episodic* (i.e. undertaken over limited periods of time). Episodic surveillance may be suitable in resource-limited situations or for diseases that are predictably seasonal. Surveillance may be defined as *passive*, where reports are awaited and no attempt is made to seek reports actively from the primary data collector in the surveillance system, or *active* where reports are sought from the primary data collector in the surveillance system on a regular basis. Surveillance may be *routine* (the regular systematic collection of a specified data set), or e*nhanced* (the collection of additional data about cases reported under routine surveillance, under predetermined and specified circumstances).

Collection and processing of specimens

The collection and processing of specimens for surveillance purposes should be undertaken in a consistent way and to the appropriate quality standard. Wherever possible, the procedure for obtaining specimens should be readily understood and acceptable to the patient (simple, quick and, where possible, non-invasive) and should minimize the risk of false negative and false positive results, particularly from contamination by commensal or other organisms.

Tests on specimens obtained from normally sterile sites, which may involve invasive procedures (e.g. blood, CSF), normally have a higher positive predictive value for infection than those from other sites (e.g. throat swab, sputum and skin).

Antimicrobial susceptibility tests

Antimicrobial susceptibility tests are undertaken to assist the clinician in selecting the most appropriate antimicrobial to use in the treatment of an individual patient suffering from infection. Appropriate specimens taken from the patient are submitted for culture. Organisms cultured from these specimens are further examined to determine the extent to which a particular drug inhibits the growth of the organism identified. The methods normally used for susceptibility tests are either the dilution test, which can be used to define the minimum inhibitory concentration (MIC) of the antimicrobial, or the diffusion test utilizing discs impregnated with the antimicrobial under examination.

Choice of antimicrobials for surveillance

Since the primary reason for determining the susceptibility of organisms is to guide clinical management, the choice of drugs for surveillance needs to take this into account. It is suggested that the number of antimicrobials for which susceptibility testing is requested for surveillance purposes should be three or at a maximum four. Different antimicrobials will be necessary for different groups of organisms (e.g. Gram-positive and Gram-negative).

Setting up an antimicrobial resistance surveillance system

If there is no current antimicrobial resistance surveillance system in the country/ region, one of the challenges will be to establish a network of laboratories and sufficient logistical support for the transfer of data and bacterial strains. The chance of success is probably higher if the system is implemented on a smaller scale, but capable to provide a country or region with important information to describe the level of resistance in a limited number of pathogens of public health importance, and expanded later. When the basic surveillance system is operating effectively, other relevant pathogens may be added to the list, depending on local priorities.

Hospital laboratories and antimicrobial resistance surveillance system

Most hospitals have laboratory facilities for microbiological diagnosis. Many of these

laboratories already perform some antimicrobial susceptibility testing of clinical specimens. However, at many hospitals, this information is used only for guiding treatment of individual patients, and is not kept in a format suitable for resistance surveillance. For surveillance purposes in the hospital setting, additional parameters to be added to the basic data set include: patient group and health care facility, day of admission (or whether the specimen has been taken >48 hours after admission, distinguishing community acquired and nosocomial infections) and, preferably, the antimicrobial treatment during the hospital stay. The level of resistance in isolates collected at the hospital less than 48 hours after admission reflects resistance levels in the community. The recommended 48 hour limit does not account for specimens originating from patients that had been transferred from another hospital.

Relevant pathogens to be considered include *Pseudomonas aeroginosa*, *Klebsiella pneumoniae*, *E. Coli* and/ or *Staphylococcus aureus* from urinary tract infections, septicaemia and pneumonia cases.

Surveillance of antibiotic consumption

Assessment of antimicrobial use patterns over time enables mapping of trends in dosing, which may assist in the development of strategies to prevent antimicrobial resistance when

use and resistance data are compared. It is important to note that different methods of assessing antimicrobial use and of comparing use and resistance data may lead to different results. In addition to data from international studies, data from local antimicrobial use surveillance studies are useful in that information obtained in one nation may assist other nations in determining likely resistance mechanisms that may occur as a consequence of specific types of antimicrobial use (17).

Surveillance of antibiotic consumption in hospitals

Hospital antimicrobial use can be quantified accurately using *patient-level surveillance*. This

involves collection of data concerning the dose, dosage interval and duration of therapy. When other patient-specific data are collected, such as demographics, underlying disease states, pathogens involved and outcomes of antibiotic use, the appropriateness of antibiotic therapy can also be assessed (18,19). In contrast, population-level surveillance refers to the collection of aggregate antibiotic use data, summarized at the level of a hospital or a ward. Aggregate data should then provide a reliable estimate of antibiotic consumption. In most instances, population-level surveillance is the only realistic alternative for ongoing and systematic monitoring of antibiotic use (20).

Surveillance of antibiotic consumption in community

For investigating drug use in health facilities WHO/ INRUD methodology may be used to determine the quantity of data to be collected. The number of prescribing encounters per facility and the number of facilities which should be examined will depend on the objective of the study. If the objective of the study is to describe drug use problems in a sample of facilities that is representative of a majority, then at least 30 prescribing encounters in each of 20 facilities (a total of 600 prescribing encounters) should be examined. If fewer health facilities are examined, then more prescribing encounters should be examined.

For antibiotic use, prescription data (especially that for calculating the percentage of antibiotic containing prescriptions) is probably the most reliable. While this indicates the prevalence of antibiotic use, it does not provide much information on the extent of use, and in particular on the quantity of antibiotic used. This latter factor is expected to be important in determining the degree of ecological pressure exerted, which will inevitably result in antimicrobial resistance. A more specific measure of utilization is therefore provided by the number of DDDs prescribed per unit of population. Since data on DDD prescribed per 1000 patients help to provide insight into antibiotic use, efforts must be made to collect these data.

The challenge in settings where only a sample of prescriptions/sales can be measured is to decide on an appropriate denominator for this calculation. The total number of patients seen in the time required to generate the antibiotic containing prescriptions captured can be used. Utilization is therefore expressed as the number of DDDs of a specific antibiotic prescribed per 100 patients seen, at a

particular point in time. Data can be collected retrospectively at time intervals from prescriptions or clinic records, or prospectively by interviewing patients as they exited from facilities. Data may be collected from public sector primary health-care facilities, private general practitioners and pharmacies.

The appropriate method for exit interviews would be for one person to count the total number of patients and identify those with antibiotics and a second person to interview those with antibiotics. An alternative method could be to examine the records retained in facilities (whether computerized or paper based, prescriptions or duplicate bills) and to extract numerator (antibiotic prescriptions) and denominator (total prescriptions).

Mixed methods, whereby the numerator is collected from patient exit interviews and the denominator from facility records, risk error and may result in apparently very low antibiotic use. Therefore, special care has to be taken to standardize the method used and to train the data collectors accordingly.

The ATC classification

Countries and hospitals vary widely in the classification systems used for pharmaceuticals.

The most widely used, and most useful, classification system for the expression of drug utilization is the Anatomical Therapeutic Chemical (ATC) classification system.

The ATC system which initiated in 1970, is now coordinated by the World Health Organization (WHO) Collaborating Centre for Drug Statistics Methodology, established in Oslo in 1982. The centre revises the ATC codes as necessary and maintains an online database and published index. Drugs are divided into different groups according to the organ or system on which they act and/ or their therapeutic and chemical characteristics. Each drug is assigned at least one ATC code, which are classified into groups at five different levels.

Defined daily dose

To facilitate the ability to compare consumption information across time and geography, a technical unit of measurement was created for use in conjunction with the ATC classification. It is referred to as the Defined Daily Dose (DDD) and assigned to each drug at the 5th level (chemical substance) classification. It is defined by the ATC as the assumed average maintenance dose per day for a drug used for its main indication in adults and is assigned by the WHO Collaborating Centre using established principles. Because the ATC/ DDD system is continuously being modified, it is essential that the version (year) of ATC classification in use is clearly identified. By convention, the most recent classification is usually used. However, one must be aware of changes in the classification or DDD assignment when comparing with historic information (21,22).

Expressing consumption information - Rates

Most commonly, drug consumption is expressed as a rate. Common units for antibiotic consumption include DDD per 1000 inhabitant-days for outpatient data and DDD per 100 bed-days in hospitals. For expressions of antibiotic consumption at the level of a country, province or large region, census population estimates are appropriate.

Major Surveillance Programs/ Projects

Alexander Project. The Alexander Project was an international study that began in 1992. It was designed to provide surveillance data on adult community-acquired respiratory tract infections. From 1996, the study focused on infections caused by Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis (23). Throughout the 10 years of the study (1992–2001), strains isolated from patients in a total of 27 countries were assessed for susceptibility to a wide range of antimicrobials. Data were used for multiple purposes, such as identification of factors influencing resistance, mechanisms of resistance, clinical relevance of resistance, strategies to reduce resistance, changes in susceptibility over time, geographic variations in the prevalence of resistance (23).

SENTRY Antimicrobial Surveillance Program. The SENTRY Program is an ongoing international surveillance program that was initiated in 1997 to monitor the occurrence and antimicrobial susceptibility of bacterial pathogens causing

nosocomial and community acquired infections (e.g. bloodstream infections, inpatient and outpatient lower respiratory tract infections, urinary tract infections [UTIs], and skin and soft tissue infections). Sentinel sites are present in more than one hundred countries worldwide. The SENTRY Program also explores pathogen resistance mechanisms (24).

Meropenem Yearly Susceptibility Test Information Collection* (*MYSTIC*) *Program.

The MYSTIC Program (initiated in 1997) is an international surveillance program that aims to determine the susceptibility of nosocomial pathogens to meropenem and comparator broad-spectrum antimicrobials (25). A unique feature of the MYSTIC Program is its use in conjunction with antimicrobial pharmacokinetic/ pharmacodynamic data in the Optimizing Pharmacodynamic Target Attainment using the MYSTIC Antibiogram (OPTAMA) Program.

Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin (PROTEKT) US.

PROTEKT is a global surveillance study that began in 1999 to obtain pathogen susceptibility data for telithromycin and other agents used to treat respiratory tract infections (e.g., pneumonia, acute bacterial exacerbation of chronic bronchitis or chronic obstructive airway disease, sinusitis, pharyngitis, and otitis media) (26). PROTEKT sites are worldwide and include more than 200 medical centers in 42 states in the United States; US participation began in 2000 as the sister PROTEKT US study.

ECO/SENS Project.

The ECO/ SENS Project was a prospective study that collected antimicrobial susceptibility data specific to pathogens that cause community-acquired UTIs in women. Initiated in 1999, it was a multinational project that involved 16 European countries and Canada. Midstream urine samples from women aged 18–65 years with symptoms of an uncomplicated UTI were collected for culture and analysis (27).

Surveillance of Antimicrobial Use and Antimicrobial Resistance in ICUs (SARI).

The SARI system was initiated in 2000, primarily to collect data on antimicrobial use for the treatment of nosocomial infections, on the incidence of antimicrobial-resistant nosocomial pathogens, and on relationships between antimicrobial use and pathogen resistance in Germany (28).

European Antimicrobial Resistance Surveillance System (EARSS).

The EARSS (29) was established in 1998, following increasing concern for the occurrence and spread of antimicrobial resistance, and was made up of national centers in 31 countries throughout Europe. On a quarterly basis, each center collected data from its country's clinical laboratories on the antimicrobial susceptibility of *S. pneumoniae*, *S. aureus*, *Enterococcus faecalis*, *Enterococcus faecium*, *E. coli*, *K. pneumoniae*, and *P. Aeruginosa* isolated from patients with invasive infections and submitted the data to an EARSS management team for review for consistency and subsequent publication. The clinical laboratories received patient samples from academic and nonacademic hospitals, tertiary referral hospitals, and nursing homes. By January 1st, 2010, the administration and coordination of EARSS was transferred from RIVM to the European Centre for Disease Prevention and Control (ECDC). The network was renamed to 'European Antimicrobial Resistance Surveillance Network (EARS-Net)'.

European Surveillance of Antimicrobial Consumption (ESAC) project.

The European Surveillance of Antimicrobial Consumption (ESAC) project is funded by the European Centre for Disease Prevention and Control (ECDC) to continue surveillance of antimicrobial agents in Europe. ESAC took start in November 2001 and managed to develop and maintain a continuous, comprehensive and comparable database on antibiotic use in Europe. Indicators of appropriate antibiotic prescribing in primary care were developed, and the ESAC data were used to explain the variation of antibiotic resistance in Europe and to assess the impact of interventions in the community. Until 30 September 2002, retrospective data (1997-2001) on antibiotic consumption was collected in the format available in each of the participating countries. The objective

was to convert the routine formats into the ATC/ DDD format and thus facilitate the prospective data collection which was launched in January 2003. The different systems of data collection were harmonized by means of an ATC/ DDD quality label. In 2006, 34 countries participated in ESAC, all 27 countries of the European Union, 2 applicant countries (Turkey, Croatia), and 5 other countries joined the project (Iceland, Israel, Norway, Russia and Switzerland).

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