Editorial

Surveillance of Antibiotic Resistance: Learning to Live With Bias

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The introduction of antibacterial drug therapy in the 1940s led to a dramatic reduction in illness and death from infectious diseases over the next 50 years. Worldwide, antimicrobial drugs have saved the lives of hundreds of millions of people for whom premature death or crippling complications would have been unavoidable. However, the emergence of drug-resistant bacteria, fungi, and viruses is reversing the miracles of the previous 50 years. As we approach the 21st century, the choices of effective therapy for common infections will be more limited, much more expensive, or, in some cases, simply absent. We may be faced with the specter of hospital wards with patients dying of common, untreatable, infectious diseases.

In recent years, a series of developments have highlighted the emergence of drug-resistant organisms. These include the following:

- Once exquisitely susceptible to penicillin, drug-resistant *Streptococcus pneumoniae* infections have become common in some communities. *S pneumoniae* is the cause of at least 7,000,000 cases of middle ear infection in children, 500,000 cases of pneumonia, 50,000 cases of bacteremia, and 3,000 cases of meningitis; this pathogen causes at least 40,000 deaths per year in the United States. The proportion of strains with high levels of resistance to penicillin increased 60-fold between 1987 and 1992.[1] In some regions of the United States, the proportion of strains resistant to penicillin is as high as 30%.[2,3]
- Antimicrobial resistance to penicillins and tetracyclines has emerged in *Neisseria gonorrhoeae,* the causative agent of gonorrhea, to the extent that expensive agents such as broad-spectrum cephalosporins and fluoroquinolones currently are recommended for the treatment of uncomplicated gonorrhea.[4]
- Hospital-acquired (nosocomial) infections affect approximately 2 million hospitalized patients in the United States, contributing to 80,000 deaths each year. Drug-resistant nosocomial pathogens are making some of these infections difficult (as with *Staphylococcus aureus)* or impossible (vancomycin-resistant *Enterococcus)* to treat and are driving up costs of hospital care and mortality.[5]
- Foodborne diseases cause millions of illnesses each year in the United States. Periodic monitoring of *Salmonella* has shown a steady increase in the prevalence of antimicrobial resistance in this pathogen from 17% in 1980 to 31% in 1990.[6] Epidemic dysentery due to *Shigella dysenteriae* type 1 is now a major threat in southern Africa.[7] This disease caused over 20,000 deaths 20 years ago in Latin America, where it could reemerge. Antimicrobial therapy for *S dysenteriae* can be life-saving, but widespread prevalence of drug-resistant strains makes treatment expensive or impossible in some developing countries.

This list could go on to discuss fungi, viruses, mycobacteria, and other microorganisms developing antimicrobial resistance. How do we know these

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numbers? The answer pushes us squarely into the field of public health surveillance.

The definition of surveillance, as defined by CDC,[8] is *the ongoing, systematic collection, analysis, and interpretation of health data essential to the planning, implementation, and evaluation of public health practice, closely integrated with the timely dissemination of these data to those who need to know.*

Few people need to be persuaded that antimicrobial resistance is a public health concern. However, reports in the media of a "super germ" certainly seem sensationalistic. How do we interpret available data to give the public and the medical community a picture that is reasonable? What can we do to make the available data better?

In the current issue of the journal, Dr. Victor Lorian suggests a need for surveillance for antimicrobial resistance.[9] Dr. Lorian suggests that, for quite a few organisms, resistance has not been increasing at a dramatic rate. He cites a study of 10 million strains 12 years ago that showed little change in bacterial resistance.[10] He also cites other published studies and his review of MEDLINE as evidence that the hospitals that report resistance data in the literature are, in general, systematically different from hospitals that do not publish such data. Reports from single hospitals, despite providing illustrative information, do not provide "randomized, nonselective, multicenter data necessary to determine the scope of the resistance problem." He comments that geographic location of hospitals, hospital bed size, and affiliation with managed care organizations also could affect interpretation of data. One of Dr. Lorian's proposed solutions would include a comprehensive surveillance system, comprised of all medical microbiology laboratories, on eight species of bacteria. He cites an alternative approach to extend an already-existing surveillance system, ie, the National Nosocomial Infections Surveillance (NNIS) System, by reporting all bacterial susceptibility data, not just data on nosocomial infections.

Dr. Lorian's comments on the inadequate state of knowledge about the incidence of antimicrobial resistance are painfully accurate. The reasons for this inadequacy are many, but probably can be distilled into the fact that, until now, most people, including healthcare professionals, apparently believed the problem did not merit sufficient attention to devote the resources needed to improve the data. Perhaps people believed that the pharmaceutical industry always would have another new antimicrobial to bail us out of a problem with resistance. Perhaps some of the studies, such as the one by Atkinson and Lorian, suggested that resistance was not really a problem at all.[10] However, multidrug-resistant tuberculosis (MDR-TB) and vancomycin-resistant *Enterococci* (VRE) may be changing that view. For the first time in decades, we are facing clinical situations where there are *no* drugs on the shelf for patients with these diseases that previously were treated easily. But does resistance among a few pathogens merit the expenditure of limited resources when, for a number of pathogen-antimicrobial combinations, the incidence of resistance is low or unknown? This is a difficult question for society to answer, especially given the lack of data. However, MDR-TB and VRE demand that we try to answer the question, or we may find many more resistant organisms on the untreatable list. We first should examine the data we do have.

Is resistance increasing? Dr. Lorian indicates that the problem is overstated and that, with a few exceptions, antimicrobial resistance is not nearly the problem some people, including the media, make it out to be. Inherent in all of Dr. Lorian's comments, criticisms, and suggestions is one word—bias. All, not virtually all, but *all* surveillance systems are biased. Bias is evident in the published literature as well, as Dr. Lorian stated.[9] Understanding the source and direction of the bias is essential to interpret the data. It also is one of the goals of a surveillance system's evaluation.[11] However, bias does not negate the value of published reports or surveillance systems. Rather, bias colors our interpretation of the data or our ability to generalize the data beyond the study population.

In the case of antimicrobial resistance, the type of bias of greatest concern is *selection bias.* Selection bias refers to a distortion in the estimate of effect (ie, the percentage of a pathogen resistant to an antimicrobial agent) resulting from the manner in which subjects (or isolates) are *selected* for the study population. Let us examine one of the studies cited by Dr. Lorian, in which 10 million strains showed little change in bacterial resistance.[10] This study, which was based on data from the 1970s and early 1980s, examined an enormous number of isolates, largely from outpatients, and was unable to detect significant changes in resistance. How were these isolates selected for analysis? While the data seem accurate for this population of isolates, there was a significant selection bias. Imagine the scenario where one samples an enormous amount of water from the middle of the Pacific Ocean when testing for water pollution. One may be led to the conclusion that, despite a huge sample, there is no water pollution on Earth. Hidden within the enormous number of outpatient isolates in the study by Atkinson and Lorian could have been isolates from hospitalized or recently hospitalized patients where resistance was increasing. Stratified analyses were not provided.[10] Thus, the population of isolates *selected* may not be the ones on which to

plan, implement, and evaluate public health practice to control antimicrobial resistance. Returning to the analogy of water pollution, would it be desirable to wait until this large sample showed evidence of water pollution before determining that water pollution is a problem somewhere on Earth and requires preventive efforts? Clearly, the answer is no!

Stratification of data by attributes already known to be associated with resistance can reduce bias. In Atkinson and Lorian's study, stratification may have reduced the bias of the study. Such stratification was needed in many of the NNIS studies on antimicrobial resistance.[12-16] Even with the biased sample in these studies, ie, isolates associated with nosocomial infections, a hospital's affiliation with a medical school, bed size, or an isolates acquisition from a patient in an ICU were factors independently associated with resistance. Once we controlled for these factors using logistic regression analysis, the central question, "Is resistance increasing?" could be examined. Even after controlling for all these other factors, in virtually every case, resistance was increasing.

Analyses like those from the multicenter NNIS system led to determination of the "influential data point." This is data from a single hospital, which is correct, but so different from that of other hospitals that it tends to influence (bias) the entire dataset. Logistic regression analysis can control for this bias. However, in reading a paper about a single hospital's experience, it is difficult to determine if the hospital's experience is similar to many others or if it is an "influential data point." Allowing for this determination is an advantage of multicenter studies over single hospital reports, but the data must be examined for evidence of this influential data point and, if found, its influence controlled.

In most of the studies on antimicrobial resistance, the factors associated with resistance usually varied, depending on which pathogen-antibiotic combinations were examined. For example, for methicillin-resistant *S aureus,* the hospital bed size was associated with resistance, but medical school affiliation of the hospital was not.[13,14] Conversely, for imipenem-resistant *Pseudomonas aeruginosa,* medical school affiliation was associated with resistance, but hospital bed size was not.[12] The reasons for these differences are open to conjecture. However, if one is attempting to collect comprehensive data on several pathogen-antibiotic combinations, several different factors may need to be collected for stratification to reduce bias, and the factors will vary depending on the pathogen-antibiotic combination.

Dr. Lorian proposes a comprehensive approach to a surveillance system that is laudable but may not be practical. Collecting data in an ongoing system from all medical microbiology laboratories is a goal that probably never can be reached entirely. There are inevitable cost issues involved in transferring data, even electronic data. Where would this money come from? What about laboratories that are not computerized? They comprise a small number to be sure, but excluding them from a "comprehensive" database creates a certain bias. What does one do if a laboratory chooses not to participate? Will they be required to participate? If so, is there sufficient money to offset their costs for testing antibiotics that the laboratory would not test ordinarily? Where would this money come from? What is the direct benefit to the individual laboratory providing the data? Will there be comparative data? If so, in what form? Who would provide it? Antimicrobial use is a major risk factor in antimicrobial resistance, which may account for much of the difference in resistance from one site to another. Will there be an attempt to control for antimicrobial use? Will there be any attempt to determine the clinical impact of resistance from all isolates (colonization versus infection)?

These are difficult questions, but attempts have been made to answer them. However, the approach to answering these questions has differed, as it must, according to the pathogen-antimicrobial combination. A "comprehensive" effort may not even be needed. A sample of sites with adequate knowledge of factors, such as geographic location and hospital bed size (or whether an isolate is from an outpatient), will be more practical, cost effective, and adequate to the task. For example, while the NNIS system may overrepresent hospitals affiliated with medical schools, there is no evidence that these hospitals differ significantly from teaching hospitals not reporting to the NNIS system. For some analyses, teaching affiliation was not even important.[13,14]

Some of the current approaches actively being pursued are strikingly similar to those suggested by Dr. Lorian. For example, CDC's Division of Bacterial and Mycotic Diseases (DBMD) has initiated a strategy to collect penicillin susceptibility data on all *S pneumoniae* from cerebrospinal fluid (CSF) and blood cultures in as many laboratories in the 50 states as possible. The Council of State and Territorial Epidemiologists has added drug-resistant *S pneumoniae* (DRSP) to the US list of reportable diseases such as AIDS and rabies (termed National Public Health Surveillance System). However, the investigators are under no illusion that they will have a comprehensive database. The investigators in DBMD chose CSF and blood cultures rather than all microbiology cultures with *S pneumoniae,* because the lat-

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ter may not have susceptibility results at all, introducing further bias. However, the development of the surveillance system for DRSP is long overdue. Pilot studies throughout the United States suggest that the incidence in outpatients may be as high as 30%, an alarming and unexpected finding.[2,3]

The Hospital Infections Program at CDC, in cooperation with Emory University's Rollins School of Public Health, has initiated Project ICARE (Intensive Care Antimicrobial Resistance Epidemiology) which, as Dr. Lorian suggests, collects data on all bacterial susceptibility, including data on outpatients, for certain pathogen-antimicrobial combinations and not just on pathogens associated with nosocomial infections. A pilot study was completed in the spring of 1995. Preliminary findings suggest that the focus of the study, intensive care units, is appropriate because resistance is consistently higher in ICUs compared with that in noncritical care wards and higher in hospitals than among outpatient isolates.[17]

These efforts to improve our knowledge of antimicrobial resistance will take time, but already are bearing some fruit. Improved methods of susceptibility testing, computerization of data with electronic transfer, and data collection and stratification using factors associated with resistance will reduce bias and improve our knowledge in the future.

One probably will never know the "true" incidence of resistance—only an estimate of "truth," ie, a biased estimate. Understanding the nature and direction of the bias of surveillance systems is what we must learn to live with, not bemoan. Nor should we dismiss an entire surveillance system because we have discovered that it is biased. Understanding the bias of a system, analyzing data in ways to reduce the bias, and collecting better information to reduce the bias should be the goal. Dr. Alexander Langmuir, the late director of CDC's Epidemiology Program Office, once said, "A good surveillance system does not guarantee you will make the right decisions, but it reduces the chances of making the wrong ones."[18]

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