

Surveillance of Antibiotic Resistance Gene Epidemics**

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Summary

Initially, each new antibiotic cured almost all bacterial infections. However, infecting bacteria then began to acquire genes that blocked the antibiotic's action. Such resistance genes arose somewhere by mutation or by transfer from obscure bacteria to an infecting strain, and were then driven from their origin by antibiotic use through genetic elements, bacterial strains, animals, and people, to different hospitals and continents. Such epidemics of resistance genes and the bacteria that carry them have spread resistant strains throughout the world. As these genes have spread through the global population of infecting bacteria, successive antibiotics have become ineffective and patients have died as a result.

Efforts to control antibiotic resistance have not adapted to its epidemic spread. While caregivers at the local level make efforts to track and contain resistance in the hospital as a component of infection control, there is little tracking at state, national, or international levels. Hospitals do not know what can be expected from another local hospital or from hospitals elsewhere in the country. Public health agencies, traditionally responsible for detecting and minimizing epidemics, lack data for tracking resistance. Yet, abundant data is already collected at the clinical level that could be utilized for surveillance of resistance.

Tens of thousands of laboratories worldwide distinguish phenotypes of infecting bacteria daily with biochemical and antibiotic tests and are now genotyping more strains, but the reports go to the requesting clinical staff. New informatics now enable us to translate the reports from diverse file codes, extract them with confidential/secure protocols, aggregate, integrate, and search them on Web servers continuously to find events, trends, and epidemics in real time and alert predesignated responders automatically. We should do all of these things now. The current method of using publication to disseminate resistance data obscures actionable information and delays its effective use to protect the effectiveness of the antibiotics.

Current realities

The world's bacteria evolved and diversified over billions of years into massive populations. Only a tiny fraction of these bacteria can infect people, but these infecting bacteria shortened human lives more than any other cause. Then, 80 years ago, we began making antibiotics. These small molecules could diffuse through tissues of infected patients, kill any bacteria within the tissue and, astonishingly, cure any infections caused by the bacteria. No drug is ever likely to save as much life as penicillin did in 1943. However, the miracle did not last. Antibiotics failed to cure more and more infections because infecting bacteria became resistant to the antibiotics. New antibiotics were then discovered and also cured most infections, until bacteria became resistant to them too. However, few new antibiotics are being discovered now.

An antibiotic kills a bacterium by binding to a target site within the bacterium to block an essential function at that site. A strain of bacteria becomes resistant to the agent by acquiring a resistance gene expressing a product that keeps an antibiotic from blocking its target site. A strain of bacteria may get a resistance gene from a mutation in one of its own genes or if a gene is transferred to it from another strain. However, the antibiotic resistance conferred by these resistance genes is only beneficial if selective pressure is applied by exposure to antibiotics. Many such resistance genes

would thus previously have disappeared or stayed too rare to notice, until they began to be enormously amplified due to selection by widespread use of antibiotics 70 years ago. A gene expressing resistance to an antibiotic has often been first noticed only after the antibiotic was used for years or even decades, and then only in one or a few parts of the world, from which it eventually spread widely.

The resistance gene that makes a patient's treatment fail today may have thus emerged years earlier on another continent and travelled to this patient in a strain of bacteria, or a genetic element moving between strains, through a long chain of hosts colonized or infected by the bacterium. Such travel is driven mostly by antibiotic selection. When a resistant bacterium lands on a host, it is a tiny part of that host's total bacteria and has only a tiny chance of being among those that host transfers to the next potential host. But, if an antimicrobial kills the host's other bacteria, the resistant bacterium will multiply exponentially, as will its chances of getting to the next host.

The antibiotic resistance genes that cause the most treatment failure, morbidity, and mortality today, and the genetic elements and strains of bacteria carrying them, can now be seen to have emerged and spread through a succession of antibiotic-driven global epidemics. Penicillin-insensitive pneumococci first appeared in South Africa and began to spread in Europe a decade later with derivative strains being spread from Spain, one to Iceland, and others to the Americas. Methicillin-resistant *Staphylococcus aureus* (MRSA) circulated for a decade in Europe before first being seen in a few United States hospitals and then moving into the community more widely. Vancomycin-resistant enterococci (VRE) appeared in animals in Europe and then became widespread in intensive care units in the U.S., and later in many other countries.

Genotyping and now genome sequencing have enabled precise identification of different genes expressing resistance to one antibiotic, and as a result have enabled more precise tracking of the epidemics of each gene. A gentamicin resistance gene (*aad2*^r) first seen in Paris was thus shown to have spread on an epidemic plasmid (a transferable DNA element) through hospitals in Venezuela and the U.S. over the following decade and, after a single entry, to have converted a hospital with no resistance to gentamicin to ones with it prevalent in many infections by many bacterial species. Reports are now growing of single incursions into multiple countries from an apparent base in India of the recently discovered New Delhi M1 (NDM1) gene, which is now making infecting bacteria resistant to all effective antibiotics.

Scientific opportunities and challenges

Recognition of such successive epidemics of antibiotic resistance genes has been delayed. Thus, chances for early detection and containment have been lost because the potential observers, mostly based in separate hospitals and with few surveillance tools, see only parts of the epidemics and communicate primarily through publications in scientific journals. Genotyping of resistant bacteria is increasingly being reported but rarely related to the context of local resistance phenotypes. What is most needed to fill these gaps is the traditional surveillance for epidemics by public health agencies, overseeing and responding to all information across laboratories, hospitals, and communities and coordinating containment for their regions. Until now, these agencies have lacked data for such surveillance and response, but newer informatics can now provide this data.

Modern informatics has enormous potential to track and focus containment of the global spread of antibiotic resistance. Tens of thousands of microbiology laboratories around the world each day issue millions of reports of richly detailed identification and antibiotic resistance phenotypes of bacteria infecting patients. These reports, which already are paid for, contain everything we can know about the kinds of bacteria, their antibiotic resistance, which patients they are infecting and where, and where this information suggests these bacteria may be heading next. Informatics technology for

accessing, aggregating, and analyzing such reports has been lacking, but is now increasingly available. In addition to antibiotic resistance tests, the reports include other tests valuable to public health epidemiology (e.g., *Clostridium difficile*, HIV viral load, viral influenza), that could be accessed as well.

While these reports are primarily produced to guide care of individual infected patients, their reuse for overview across regions for trend discernment, epidemic detection, and containment can be seen as a new and under-recognized public health opportunity. Networks for such surveillance of antibiotic resistance exist in several regions of the world but underutilize newer informatics and gather only a tiny fraction of the available reports that could enrich these networks. A systematic effort to enhance, extend, integrate, and fully analyze and use such surveillance would be the most cost-effective component of any initiative to control antibiotic resistance.

Policy Issues

Since all levels of public health, infection control, and patient care should coordinate their responses to global resistance epidemics, there is a need for global public health funding to develop and deploy shared, automated informatics to speed and integrate the surveillance and alerting required by healthcare organizations. Policies are needed to:

- Implement the translation, extraction, secure transmission, and aggregation of reports from multiple clinical microbiology laboratories onto dedicated Web servers.
- Develop and solicit statistical and other algorithms to search these aggregated Web databases continuously for events, trends, and epidemics in antibiotic resistance.
- Develop automated, prompt alerting of preselected public health and local responders to detected events, trends, and epidemics for which they can begin containment measures.
- Extend automated searches of aggregated Web databases beyond antibiotic-resistance to findings of other reported pathogens (e.g., *Clostridium difficile*, HIV viral load, viral influenza) and for links with other data (e.g. genome sequences).

There is also concurrent need to encourage and prepare public health, infection control, and patient caregivers to utilize this new level of surveillance information with skilled responses to alerts generated by such information.

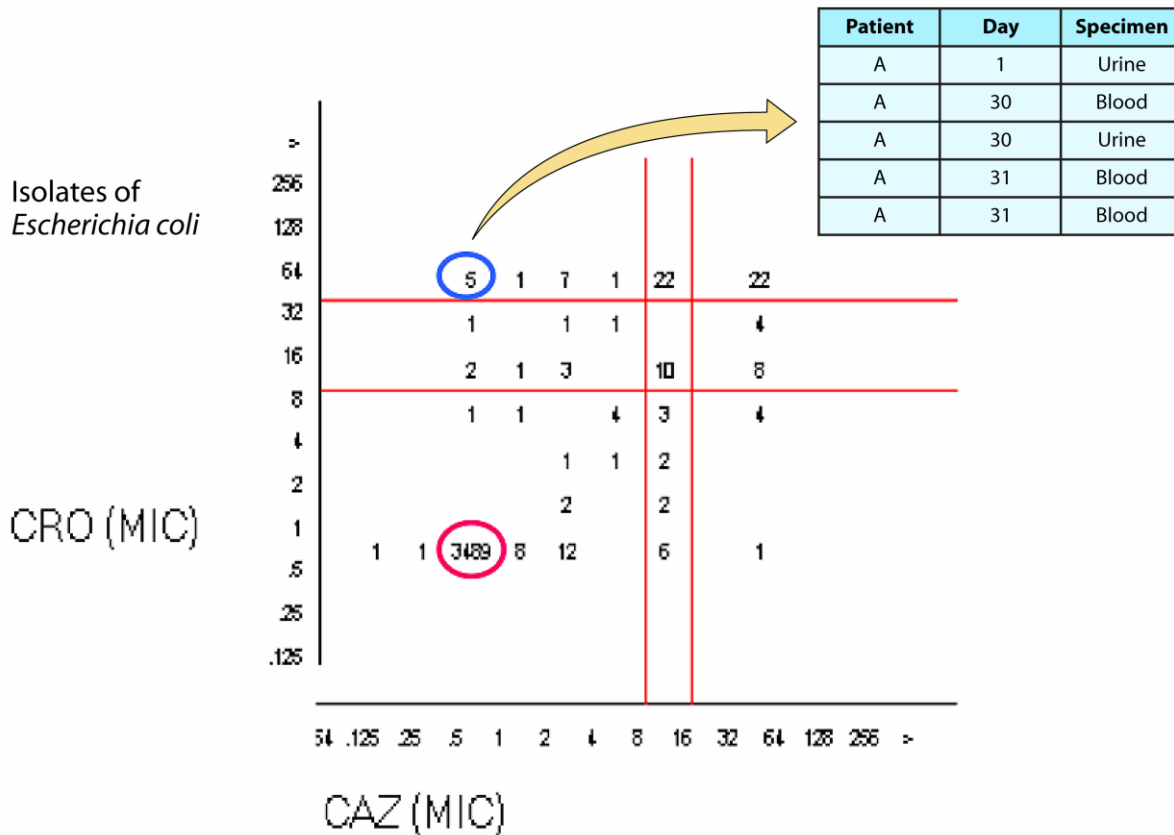
References

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Figure: Routine clinical laboratory results detect incursion of a distinctive resistance phenotype.



Scatterplot (by WHONET) of minimal inhibitory concentrations (MICs) of ceftriaxone (CRO) and of cefazidime (CAZ) for all isolates of *E. coli* at one hospital during one year.

The **red circle** encloses the 3,489 isolates that had MICs of 0.5 µg/ml for both agents. Scattered single or double digits falling on intercepts representing varied other MICs of the two agents indicate the numbers of isolates with each of those sets of MICs. The **blue circle** encloses the five isolates that had an MIC of 0.5 µg/ml for ceftazidime and an MIC of 64 µg/ml for ceftriaxone.

All five isolates were from patient A, who, as shown in the inserted table, had a urine isolate and a month later urine and blood isolates with that unique-for-the-year combination of MICs. The patient had received a kidney transplant three months earlier on another continent. Analyses of routine laboratory tests could thus detect incursion of an epidemic foreign resistance gene.

The distinctive phenotype of this patient’s five isolates was generated by measurements of its susceptibility to two antibiotics. Each isolate’s file, however, has measurements to 15 other antibiotics as well as results of an additional 48 biochemical tests - indicating their potential in combination to discriminate distinctive phenotypes.