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Integrated Multilevel Surveillance of the World's Infecting Microbes and Their Resistance to Antimicrobial Agents

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INTRODUCTION

We have long known that the infectious diseases that we recognized by their signs and symptoms, such as plague, cholera, or influenza, came to different places at different times. Over the last century microbiology has also shown the spread of less distinctive infectious diseases by enabling laboratories anywhere to identify the microbes that cause these diseases.

The advent 70 years ago of amazingly effective antibacterial agents and the emergence then of bacteria resistant to them gave those microbiology laboratories a new task. They began to test *in vitro* the resistance of the bacteria that they isolated from infected patients to each agent so that they could report which agents could still cure which patients (32).

The increasing prevalence of resistance to penicillin in isolates of *Staphylococcus aureus* proved to be due largely to the global spread of a strain that was phage typed as 80/81 (99). Resistance to multiple antibacterial agents in an outbreak strain of *Shigella* in Japan was found to be encoded on a plasmid that was able to transfer to other bacteria (128). Such examples began to show the complex epidemiology driving the spread of bacteria and of their resistance.

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Since then, newer antibacterial agents have come into use after various intervals. Genes expressing resistance to each agent eventually emerged under selection by it, spread through multiple bacterial species, and combined to make strains of some species wholly untreatable until a new rescuing agent came into use (47, 78). The tracking of these processes and protecting patients from them increasingly require oversight by surveillance (76).

Such surveillance may be seen as the ongoing generation, capture, assembly, and analysis of all information on the evolving nature, spread, and distribution of infecting microbes and their resistance to antimicrobial agents and its full use for actions to improve health. This review does not catalog all such surveillance projects but rather delineates their different types and uses and explores their potential synergies.

The resources for such surveillance can be seen to have developed over this period even faster than the problem. The power of nucleotide sequencing to discriminate resistance genes and resistant strains and the power of information technology to trace their movements have each expanded exponentially, while the volume and detail of routine laboratory phenotype data that can interrelate the two have continued to grow.

What has lagged has been the full integration and real-time application of the resources to the full range of the problem, due in part to its underrecognition as one interrelated global public health problem. Many surveys of resistant bacteria continue to appear as random, one-time, one-place, and often one-issue print-delayed publications that apply part of the available information to part of the problem's complexities.

History of Surveillance of Microbes for Public Health

People monitor the spread of any contagious illnesses to try to get out of its way or stop it. A cholera outbreak in London in 1835 slowed when residents began to flee the area and then stopped when John Snow took the pump handle from the well that served the area (16). Yellow fever prompted the affluent to abandon New Orleans each summer to avoid it and then the founding of the U.S. Public Health Service to contain it (18).

Microbiology laboratories distinguished different infectious diseases with similar clinical syndromes by identifying the microbes that caused each disease. The laboratories then delineated outbreaks of each disease that might have been obscured if lumped together by syndrome. Finally, by finding microbes that are able to cause diseases such as tuberculosis or typhoid in people who were not sick, microbiology laboratories began to find silent carriers that spread them (61).

Public health authorities thus first used microbiology to greatly reduce morbidity and mortality from infections by detecting epidemics and containing them with quarantine, immunization, clean food and water, and personal hygiene, etc. As microbiology laboratories multiplied to test microbes infecting individual patients to guide their care, however, the fraction of the world's total microbial data that public health authorities produce or see has become miniscule.

Patient care laboratories usually report only patients with diagnoses on a list of mostly rare infections with epidemic potential to public health authorities, representing perhaps a percent or less of all infected patients or microbial data (18,

71). In some public health programs, such as the National Healthcare Safety Network (NHSN) or Active Bacterial Core (ABC) surveillance programs of the U.S. Centers for Disease Control and Prevention, more data, e.g., total counts and clinical details of methicillin-resistant *Staphylococcus aureus* (MRSA) infections, are now reported. Overall, however, very little patient care microbiology data are currently mined to inform public health (41).

History of Surveillance of Microbial Resistance to Antimicrobials

The developers of penicillin soon found strains resistant to it, which had an enzyme that destroyed it (57). Manufacturers of later antibacterial agents explored and reported their spectra of use by testing resistance to them in infecting microbes collected from many places, and similar testings of agents not brought to market may have gone unpublished (110).

After patient care laboratories began to test the resistances of bacteria infecting their patients to antibacterials, new uses emerged for analyses of their accumulating reports. Caregivers wanted to know local rates of resistance to predict the best drugs for patients for whom an infecting microbe was not found or not yet tested (117). Hospital infection control programs sought the locations of patients with resistant strains to focus efforts to contain them (7). Surveys of reports from multiple laboratories guided regional antibacterial use policies (114).

Early surveillance studies avoided the resistance testing errors of patient care laboratories by retesting their isolates in more controlled reference laboratories (58). As more training, standardizing, accrediting, and proficiency testing programs have come into place to improve testing by patient care laboratories, however, their routine reports are being increasingly used for surveillance. The resulting increased volume of free reports surveyed reduces the per-isolate cost of surveillance and gives its analyses greater epidemiological detail (103).

Paper-based data made initial resistance surveillance tedious and limited its analyses. Computers facilitated data acquisition and more types of analysis. Early applications included computer graphic displays of resistance measurements, discrimination of resistance mechanisms, resistance time trends, and international comparisons of prevalences of resistance (79, 81). A working group of the World Health Organization (WHO) in 1982 reviewed work with computer-based surveillance of resistance to antibacterial agents and outlined its methods and types of analyses (3). This working group also noted that the personal computer, just introduced that year, could make surveillance widespread and cheap.

Many types of antibacterial resistance surveillance are currently in use. Reference laboratories retest isolates from multiple patient care laboratories for detailed resistance testing to position new antibacterial agents, establish testing standards, or survey serotypes to support vaccine development (77, 101). Hospitals survey their laboratories' data to guide local infection control practices and antimicrobial stewardship, and some hospitals share data to support national drug use policies. Moreover, over the past decade, Europe, Asia, and Latin America have built multinational networks to survey resistance in their regions (1, 2).

MICROBES TO SURVEY

Infecting Microbes

In the decades after Koch isolated *Bacillus anthracis* in 1876, a small number of workers identified most of the bacteria infecting people and animals, and discoveries continued through the 20th century (27). Microbiology laboratories proliferated in developed countries to identify the microbes that were infecting individual patients until such routine patient care laboratories came to produce most of the world's total microbiology data.

Such patient care laboratories intend to report microbes that are infecting the patients from whom they obtain samples. Infecting microbes belong to species called pathogens because they can infect but are highly varied fractions of them, as seen with *Neisseria* species. Most *Neisseria gonorrhoeae* cells infect while nearly all *N. meningitidis* cells only colonize healthy nasopharynges, and only a tiny subpopulation ever infects anyone (67). A laboratory thus reports pathogens that it finds at anatomical sites which they are likely to infect.

Infecting microbes have been the main focus of surveillance because infection is what sickens and kills patients but also because patient care laboratories generate huge numbers of reports, which have already been paid for, about infecting microbes. The reports were mostly of bacteria but are now increasingly adding data on the identification and resistance testing of fungi and viruses, which may now be usefully added to the surveillance of infecting microbes.

Colonizing Microbes

The historic emphasis of clinical care laboratories on culturable infecting microbes led them to focus on pathogens at infected sites, ignore nonpathogens at any site, and be largely unaware of unculturable microbes, with *Treponema pallidum* being an early exception (19, 67). Genetic methods to identify all bacteria, as now in the human microbiome initiative, are greatly expanding earlier estimates of the numbers and diversity of microbes that colonize us (19).

One use for a survey of the prevalence of the subtypes or the antibiotic resistance of a type of bacterium colonizing people in a geographic area has been to estimate their likely prevalence among the bacteria of that type that are actually infecting people in that area, which may be more difficult to collect. Surveys of serotypes or antibacterial resistances of *Streptococcus pneumoniae* colonizing nasopharynges of uninfected children, for example, have been used to predict those of the more difficult-to-obtain strains that infect children at that time and region (125). Surveys of such resistance in *Escherichia coli* colonizing stools of people in a geographic area have been used in a similar way to predict the resistance of *E. coli* bacteria infecting urinary tracts there and to estimate the sizes of reservoirs of resistance to antibacterial agents in different parts of the world (64).

Hospital microbiology laboratories are now being asked to survey uninfected patients for the silent carriage of pathogens, such as MRSA or vancomycin-resistant enterococci (VRE), so that carriers of such colonizing pathogens can be isolated or decontaminated before they can disseminate those strains or become infected by them (38, 39, 68). This addition of pathogens that are only colonizing isolates to surveillance systems enables the resulting amplified surveillance systems to find more links in the spread of those pathogens (69).

RANGE		
Support	Private	Public
Laboratory	Reference	Patient-care
Report inclusion	Selective	Comprehensive
Microbial typing	Phenotype	Genotype
Level of surveillance	Local	Multi-center
Levels of analysis	One + Summaries	All levels
Types of analysis	One (annual % RIS)	Many, ongoing
Integration of analyses	Routine micro only	Link to other databases
Automation of anlyses	None, only operator-driven	Multiple, automated
Participation	Partial	Complete, all laboratories

FIG. 1. Descriptors of elements of microbial surveillance systems.

Other Microbes

Resistance genes appearing anew in infecting microbes are increasingly being found to have been in, and likely mobilized from, more obscure microbes (38, 108). Exploration and genetics are now also revealing an enormous and enormously diverse world microbial biomass, with a correspondingly huge potential to carry such genes. It will be useful to survey this global microbiome for genes encoding resistance to current or future antimicrobials (108).

ELEMENTS OF MICROBIAL SURVEILLANCE

Microbial surveillance programs vary in their elements and methods. Figure 1 outlines and this section discusses a list of suggested descriptors for the elements of such programs. Any program falls somewhere along the range of terms projected for each descriptor in Fig. 1, and its positions on those ranges characterize the program.

Support

Support for surveillance is how its work is paid for. The vast bulk of data available for microbial surveillance, however, are already paid for before surveillance begins. Each of the reports from thousands of laboratories on microbes from millions of patients was produced to benefit one of the patients and was paid for by that patient or a health care system. Such reports are now being reused for surveillance with little or no further cost to some laboratories and could be so used in all laboratories.

When such reports are used for surveillance, the costs of that surveillance then begin as paid time for laboratory staff to tabulate percentages of microbes resistant to antimicrobials, to do analyses for hospital infection control, and to send mandated reports to public health agencies. Infection control staff also spend paid time searching the files for data on microbial spread (66). This local surveillance work by two staffs in thousands of hospitals around the world is seen as patient care,

however, which tends to hide its total cost and the potential savings of doing it more efficiently.

Support for other microbial surveillance work ranges from private to public. Private funding, often from pharmaceutical companies, supports surveillance by specialized reference laboratories (e.g., SENTRY [91], MYSTIC [121], TRUST [119], and SMART [14]). They usually retest the resistance to antimicrobial agents of the isolates selected and shipped from patient care laboratories, using strict controls, full-range dilutions, and/or molecular testing to delineate breakpoints, mechanisms of resistance, or the best use of new agents (101).

Private companies now offer surveillance services to hospitals. Focus Technologies (52, 102) extracted, analyzed, reported back, and published data from multiple hospitals at no cost to the hospitals, with support from pharmaceutical companies. Other companies (e.g., TheraDoc, MedMine, Vecna, and Premier) charge hospitals to extract and analyze their microbial and demographic data for them, essentially outsourcing part of the local surveillance work of the two hospital staffs mentioned above.

Government public health agencies have traditionally supported reference laboratories for the specialized testing of uncommon or potentially epidemic pathogens, e.g., serotyping of enteric pathogens or resistance testing of mycobacteria, from clinical care laboratories in their jurisdictions. This public surveillance is supplemented by required reports to the agencies by the patient care laboratories of identifications of listed reportable pathogens (6).

National public health agencies support programs to survey samples of particular pathogens, such as *N. gonorrhoeae* or food chain contaminants for resistance or *S. pneumoniae* for serotype and resistance, or to track the efficacy of programs for the control of particular problems, such as methicillin-resistant *Staphylococcus aureus*. Some types of antimicrobial-resistant microbes are also included in more general public health surveillance programs, such as the NHSN of the U.S. Centers for Disease Control and Prevention (29).

Supranational public health organizations have advocated and variably supported surveillance initiatives. Since its 1982 working group on the surveillance of antimicrobial resistance, the WHO has advocated surveillance in successive reports, including its 2001 global strategy for the containment of antimicrobial resistance and its current movements toward designating antimicrobial resistance a global patient safety challenge (4).

In the 1990s, the Western Pacific Regional Office of the WHO supported an antimicrobial resistance program that reviewed resistance test results of selected medical centers in each of its countries at an annual meeting, but the program has not resumed since its efforts were diverted by outbreaks of severe acute respiratory syndrome (SARS) and avian influenza earlier in this century. Two other WHO regional offices, the Pan-American Health Organization (PAHO) (2) and its European office, in collaboration with the European Union (26), each now support the growing surveillance networks described below. In addition to these regional programs to survey resistance infections broadly, the WHO also support networks to survey resistance in specific pathogens, such as *Mycobacterium tuberculosis* (96) and *N. gonorrhoeae* (116).

Laboratory Type

Microbiology laboratories range from the tens of thousands of patient care laboratories that diagnose and guide the therapy of individual infected patients to the far-fewer but more specialized reference laboratories. Microbiology for patient care is done in laboratories at most medical centers, but more centers now share a laboratory, and large commercial laboratories support much of the office-based patient care. Despite the growing numbers of types of tests and complexity of the instruments for the performance of these tests in affluent countries, the identification, resistance testing, and reporting terms and formats for infecting bacteria remain basically similar throughout the world. Those laboratory reports can thus be extracted, aggregated, and analyzed globally (85).

The diversity of the testing capabilities of different types of reference laboratories, such as serotyping, more quantitative resistance testing of common microbes, special testing for difficult-to-test microbes, and genetic definition of resistance mechanisms, is highly informative in itself but also has great potential for the cross-validation and interpretation of patient care laboratory surveillance data (65).

Report Inclusion

Microbial surveillance programs range from selective programs that survey reports from participating laboratories of only certain types of microbes or certain kinds of specimens to comprehensive programs that survey all of them. Selective sampling can overview broad trends over wide areas. Comprehensive surveillance has far more samples from any place, however, and thus better resolution to focus local containment by infection control teams and to detect outbreaks and the incursion of new types of resistance sooner (105).

Microbial Typing

Microbes may be typed by phenotyping or genotyping. Microbiology laboratories traditionally named isolates of bacteria to the genus or species level by their microscopic and colonial morphology and staining plus a few biochemical tests (27). Many laboratories now routinely use panels of as many as 48 biochemical tests as well as measurements of resistance to 6 to 18 antimicrobial agents. Results of these tests may be accessed by surveillance to screen for phenotypes with distributions suggesting the spread of a strain or a plasmid (84).

Some clinical care laboratories now do or ask reference laboratories to do genotyping of selected isolates. Often used among the many genotyping methods are specific gene probes (126), pulsed-field gel electrophoresis (56), multilocus sequence typing (MLST) (10, 88), and microarrays (62). The European Antimicrobial Resistance Surveillance System (EARSS) program is now using selective *spa* typing to delineate the finer-scale epidemiology of MRSA over a continent (88, 120). Falling costs of nucleotide sequencing also suggest full-genome sequencing as a future and definitive option that can also decode, and thus relate to, all of the other genotyping methods (92).

The detailed phenotypes of bacterial isolates that laboratories now generate in the process of identifying those isolates may be used to guide the best selective use of the more ex-
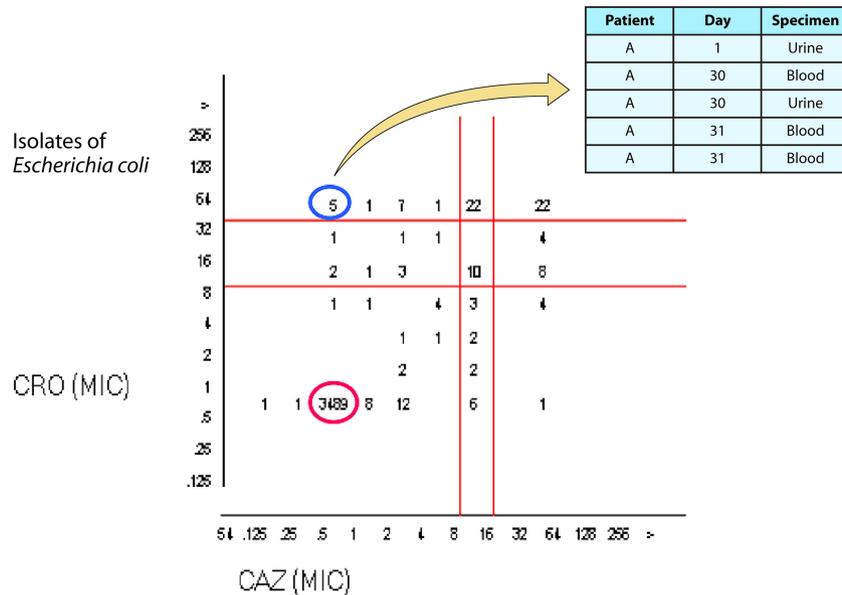
FIG. 2. WHONET scatter plot of MICs of ceftriaxone (CRO) and of ceftazidime (CAZ) for all isolates of *E. coli* at one hospital during 1 year. The red circle encloses the 3,489 isolates that had MICs of 0.5 µg/ml for both agents. Scattered single or double digits falling on intercepts representing varied 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 3 months earlier on another continent, which illustrates how the systematic screening of phenotypes may detect the incursion of a foreign strain.

pensive genotyping. The surveillance of such phenotypes may find clusters in time or space of isolates with distinctive bacterial phenotypes that the surveillance of bacterial species only would overlook. When isolates with such distinctive phenotypes are genotyped, they may be shown to belong to the same strain to confirm an outbreak (22).

Levels of Surveillance

Levels of microbial surveillance range from local, usually a medical center and the community it serves, through higher levels of multicenter networks that are national or even multinational (95). To facilitate both local and higher levels of analysis, the WHO has made available a free software program called WHONET. WHONET enables any laboratory to put its reports into a personal computer database for its local surveillance and also to merge its data easily with the then-common-language electronic data files of other WHONET laboratories into multicenter files for higher-level analyses (107, 112).

The attainment of such data file compatibility within and across levels of surveillance emerges as a major issue in this review. Microbial surveillance has usually been built at each level by different workers to meet their different immediate needs: guidance for local empirical therapy, antimicrobial stewardship or infection control, prevalence of resistance at the state or national level, trends, informing antimicrobial usage policy, and global epidemiology, etc. Such piecemeal objectives may overlook the efficiency of integrating the common data that they share, while separately improvised analytical schemes for each may preclude their integration (60).

Levels of Surveillance Analysis

Surveillance may analyze the data of just one laboratory and of a hospital or community served by it. Higher levels of surveillance may analyze data aggregated from the laboratories of an area of a country, from a whole country, or even from many countries. Earlier paper files not only restricted local data analysis but also limited analyses at higher levels to summaries of analyses at lower levels. Computer-based surveillance now allows full analyses of all isolates at all levels, although this is often not fully utilized. Higher-level analyses of only aggregated summaries of lower-level data may allow crude benchmarking and trend detection across a network, but full-detail analyses of isolates at all levels allow a finer dissection of either one and of their causes (35, 123). Higher-level full-detail analyses of all isolates also permit the identification of the first isolates at any center with distinctive phenotypes seen earlier at distant centers and may thus be able to trace epidemics over wide areas otherwise overlooked until the epidemic is too widespread to be contained (105) (Fig. 2).

Types of Analysis

Types of analysis range from analyses of a single type run once a year to ongoing analyses of multiple types. The one type now run routinely at many centers and networks yearly is the cumulative antibiogram, the percentage of isolates of each microbial species testing resistant, intermediate, and/or susceptible (%RIS) to each of a set of antimicrobial agents (42). Medical centers tabulate the %RIS of local isolates to guide local empirical therapy for patients whose infecting bacteria

are unknown or still being tested and to monitor trends (7, 44). Multicenter or multicountry networks (e.g., the PAHO and EARSS) use the %RIS to monitor trends and compare resistance across centers or nations (15, 44). Both uses for the %RIS analyses assume that rates of obtaining cultures from different anatomical sites at different places are roughly comparable, since the analyses are ratios of proportions without formal population denominators.

Additional types of analyses can be useful. The record that a laboratory files for each bacterial isolate which it reports usually includes fields with the identifying number and/or name, age, and sex of the patient whose specimen yielded that isolate as well as the date on which the specimen was taken and the patient's location on that date. The laboratory fills additional fields with the microbe's quantity and identity, 2 to 48 tested biomarkers, and measurements of resistance to each of 6 to 18 antimicrobial agents. Selected isolates sent to reference laboratories gain fields for more measurements of resistance to more agents or other biomarkers or genotypes. Examples follow of the many possible types of analyses between the values in those record fields.

To manage hospital-associated infections (HAIs), the infection control staff needs analyses of local isolate files, such as the locations of patients with strains of MRSA, vancomycin-resistant enterococci (VRE), or certain multiresistant bacteria, in order to look for their sources and routes of spread and to focus their containment (115). Similar analyses are requested increasingly to monitor and/or report rates of particular kinds of infections, e.g., those of inserted prostheses or vascular catheter-associated bloodstream infections (59).

Other types of analyses have further uses. Differing ratios of measured levels of resistance to two related antimicrobial agents may represent different mechanisms of resistance, e.g., different aminoglycoside-inactivating enzymes or extended-spectrum β-lactamases (ESBLs) and so infer different genes expressing resistance to agents of those classes. Since these genes may prevail in different places, the appearance of one gene that has been uncommon there at any place, as shown in Fig. 2, may signal the incursion there of a new resistant strain or plasmid (43, 83, 105).

The finding of multiple isolates of a bacterial species with similar and uncommon sets of levels of resistance to each of a tested series of antimicrobial agents, that is, similar and distinctive resistance phenotypes, suggests that those isolates may belong to the same strain or, if in multiple species, carry the same plasmid (83). To optimize the observation of such similar phenotypes, WHONET provides a "profile" analysis. This routine puts all of the tests and measurements of each isolate in a row, sorts the rows by grouping rows of isolates that are resistant to the same combinations of agents, and sorts the lines of the isolates within each such group by the patients who had yielded them and by the dates on which their specimens were taken (112). An analyst or an automated program scanning this output to see when and where patients had isolates with the same resistance phenotypes can find clusters of the same strains suggesting outbreaks (Table 1) (46).

To minimize the analysis time needed to do these different types of analyses routinely, ways of doing them automatically are being explored. These include time scan analyses that

TABLE 1. Segment of a WHONET profile analysis of 1,056 isolates of *Klebsiella pneumoniae* isolated from one hospital over a 1-year period[a]

Patient	Ward	Specimen	Date (mo/day)	Antibiotype
A	32	Sputum	4/26	M FZ L
	32	Sputum	5/05	M FZ L
	32	Sputum	6/03	M FZ L
B	78	Tissue	9/04	M P LTH
C	22	Pleural fluid	6/05	M P LTH
	EW	Sputum	7/08	M P LTH
D	22	Pleural fluid	4/22	M P LTH
	22	Other	4/25	M P LTH
E	87	Tissue	6/13	M Z P LT
F	77	Urine	6/16	M Z P LT

[a] The analysis sorts isolates by their antibiotypes, the combinations of antimicrobial agents to which each isolate tested resistant. Each isolate's antibiotype is displayed by capital letters representing the antibiotics to which it tested resistant, with spaces left for those to which it tested susceptible. The analysis sorts isolates with the same antibiotype by patient and by the date on which the specimen was taken. Multiple isolates with the same antibiotype from the same patient are thus listed in descending order by date within a block adjacent to blocks of isolates of other patients with the same antibiotype. In this extracted segment of the analysis, patient A, over a 5-week period, had three sputum isolates that tested resistant to 4 (designated M FZ L) of the 11 tested agents and was the only patient with isolates of that antibiotype that year. Patient B had one and patients C and D each had two isolates that were the only ones that year with the antibiotype designated M PLTH. One of those isolates from patient C and both isolates from patient D were from specimens obtained within a 6-week period, during which each patient had been on the same one of the hospital's 56 wards. Patients E and F each had one of the only two isolates that year with the antibiotype designated M Z P LT within a 3-day period while on adjacent floors of the hospital. The examples illustrate how such analyses may alert surveillance to time and space clusters of multiresistant isolates. Patient and ward designations and antibiotypes are not identified here, for the purpose of confidentiality. EW, emergency ward.

screen data sets for statistically unlikely groupings of isolates in time which may represent outbreaks. More recently, the incorporation of a time-space scanning program, SatScan, into WHONET software has enabled it to detect clusters of hospital-associated infections at a U.S. hospital and of *Shigella* infections in Argentina (46, 98, 111). Additionally, many rule-based screens to detect and report a wide variety of known troublesome phenotypes can be run successively on large data sets, and any phenotype not encountered previously can be noted whenever it first shows up (83, 84, 105).

Integration of Analyses

Two types of analyses that may be run separately on surveillance data may be more informative if ways can be found to integrate them. Earlier reporting of a calculated mean patient-hospital day obtained for specimens yielding the isolates within each resistance phenotype of a profile analyses, its "in-day" index, indicated the likelihood of its nosocomial spread (82). Time-space algorithms, as mentioned above, detected more clusters of cases in both the U.S. hospital and Argentina when they screened isolates that had been sorted by species and antibiotype than when isolates were sorted by species only (111).

It has also been recommended that data from the more quantitative and extended resistance or genotype testing by a reference laboratory of isolates selected from patient care laboratories be integrated into their patient care surveillance databases. Such an integration could "cross-validate" their testing methods and match mechanisms of resistance discovered by the reference laboratory to resistance phenotypes, the local distributions of which could be traced in the reports of the patient care laboratory (65).

Besides the integration of different types of analyses done on microbiology reports of individual patients, there is also value in analyses that integrate data from those reports with other types of patient care data, for example, pharmacy records of antibiotic usage by those same patients, to develop programs that support both antimicrobial selection and infection control (17). The large-scale integration and multicenter analyses of those data files could give more detailed insights into all of the relationships between area antimicrobial usage and resistance. It also adds a tool for antibiotic stewardship by monitoring each prescriber's treatments of patients infected with specific microbes resistant to specific antibiotics (63).

Integration with microbiology files of data in a hospital's admission-discharge-transfer (ADT) files or files recording individual patient intubations or catheterizations also eases reporting by infection control workers of specific types of nosocomial infections, such as catheter-associated bloodstream infections or ventilator-associated pneumonia (12, 28). These types of integrations may be underutilized now because a lack of informatic standards has allowed the separate data files to develop with incompatible structures and coding and therefore require expensive translation software, "middleware," to allow cross talk between them (109).

Antibiotic usage and resistance data have been integrated at a multinational level, however, in a large and influential study that integrated national data from both the European Antimicrobial Resistance Surveillance System (EARSS) and the European Survey of Antimicrobial Consumption (ESAC). Those analyses showed a correlation across 31 European countries between total national antimicrobial consumption and overall national levels of antimicrobial resistance, and their conclusions prompted efforts that have reduced both consumption and resistance (36, 37, 72, 75, 122).

Automation of Analyses

Analyses of microbial surveillance data range from being nonautomated and operator driven, as most are now, to being nearly fully automated, which seems a realistic future possibility. Microbial surveillance now often consists of an operator performing one type of analysis, such as the %RIS; at intervals, such as yearly; and at one level of surveillance, such as a local hospital or country network. Centers and networks, however, often lack operators with the support, time, or skills to perform additional useful types of analyses.

Advancing informatics is now beginning to open the potential for ongoing automated integrated analyses of data at multiple levels. Previously mentioned experiences with the time-space algorithm detecting clusters of similar isolates revealing potential outbreaks indicate that they could be made to run continuously (46, 111). A system of this type could alert ap-
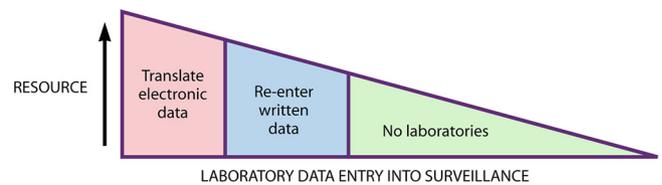

FIG. 3. Transmission of microbiology laboratory reports into microbial surveillance systems along the world's gradient of available resources.

propriate responders at each level automatically to events such as the appearance of a new type of resistance, trends such as a significantly increasing resistance of any type of microbe to any agent or to multiple agents, or epidemics of resistant genes or strains.

Participation

The participation of an area or country in microbial surveillance programs ranges from participation by only one or a few of its medical centers or reference laboratories to participation by all of them. Participation has commonly been sparse in the past years when paper records and separate data entry made it burdensome for a center to participate and limited analyses benefitted the program more than its participants, but both are now changing. The wider use of electronic laboratory information systems (LISs) and data security systems can make more centers' reports available to area surveillance networks continuously with less effort. Benchmarking and epidemiologic alerting across networks to detect epidemics and to protect patients from them at participating centers can also now be seen (30, 90). Finland now includes reports from all of its medical centers in national surveillance, and the laboratories in Ireland that participate in the EARSS serve more than 90% of its people (9, 97).

Participation in surveillance could be measured not just by the proportion of an area's laboratories that participate but also by the proportion of its seriously infected patients whose infecting microbes are identified, tested for resistance, and included in surveillance data. This ratio, a significant health care metric, might vary more than 100-fold along the world's gradient of available resources, as depicted in Fig. 3 and as discussed below.

At the affluent end of the available-resource gradient depicted in Fig. 3, laboratories identify and test an infecting microbe in many or most seriously infected patients. Their reports may enter an LIS, but those are so diverse that they usually then need translation by a data extraction program before they can be uploaded into a surveillance database. Along the middle of the resource gradient, fewer laboratories identify microbes in fewer of the infected patients, and they must then reenter data from each of their usually paper reports into a computer to build a surveillance database.

However, at the lowest end of the available-resource gradient, vast areas have essentially no functioning laboratory, and almost no infecting microbes are identified for patient care, and therefore, no microbes are identified for surveillance either (5). This makes two major global health care inequities. It is one inequity to have no laboratory available to determine

what microbe is infecting a seriously infected patient and what drug could cure that infection. It is another to have no laboratory anywhere in that patient's region to determine for surveillance what microbes treatable by what drugs are infecting anyone in the region and, therefore, perhaps that patient also (106).

Increasing participation across the whole gradient can be seen as the major challenge going forward for the global surveillance of infecting microbes. Advancing informatics have facilitated the growth of surveillance to this point by both lowering the threshold of effort for entry into participation and increasing its benefits. Newer informatics can continue to drive the improvement of and participation in microbial surveillance, but it will have to meet different needs in each segment of the global resource gradient.

For the affluent segment the major work for informatics is to continue to circumvent an unnecessary obstacle. LIS systems and, indeed, patient care informatics generally were allowed to grow without uniform file coding standards, and the implementation of efforts to retrofit standards, for example, HL-7, LOINC, and SNOMED, etc., have lagged (21, 55, 127). Accordingly, the file structure and coding of the LIS output vary, even among installations by the same vendor, and therefore, each file needs to be extracted and translated into uniform files for surveillance. For this purpose, the WHO offers a free data conversion utility, BacLink, to facilitate translations into globally uniform WHONET files (111). A repeat of the problem might be avoided if the growing diverse commercial software products for infection control were to adopt a uniform export format.

Patient care laboratories along the middle segment of the resource gradient have different informatics needs. Most cannot afford any of the LISs of the affluent segment, which also have some laboratory operating system (LOS) functionality. They thus have to continue managing their day-to-day workflow, reporting, and billing, etc., with paper records and then reenter their reports into a computer if they are to participate in surveillance. This problem may, however, conceal an opportunity. If a free standard LOS were available to them, for example, as a modular addition to the WHONET LIS, their use of the LOS/LIS to manage their workflow could generate a uniform output into a standardized surveillance database now used worldwide without the extraction and translation needed for the affluent segment.

The lowest-resource segment of the gradient needs more than informatics, but it needs informatics too. Necessary attention to such major infectious diseases as HIV, malaria, and tuberculosis may overshadow the aggregate prevalence, morbidity, and mortality of dozens of other infecting microbes that should be identified and tested for resistance in at least some patients in vast areas of the resource-limited world to guide therapy for all.

A way needs to be found to make a sentinel laboratory perform simple essential microbiology tests in a vast area now without any and to put data from all of its reports into a surveillance database that will begin to guide therapy in the area and reveal its part in the world's shifting microbial populations. An LOS/LIS as described above but modified to meet the segment's special needs could help such a laboratory. The LOS could aid in managing supplies, advising each step of the

workflow, and, if Web-based, allowing a distant supervisor to monitor workflow and help with problems. Some sites may have Web access now, and more may have access with cell phone technology (31).

COMPARISON OF ELEMENTS OF THE PAHO AND EARSS SURVEILLANCE SYSTEMS

The use of the above-described 10 descriptors to characterize surveillance systems may be illustrated by attempting to apply each of them to two existing large surveillance programs, those supported by the PAHO in the Western Hemisphere and the EARSS program in Europe, which is now becoming the European Antimicrobial Surveillance Network (EARS-Net) at the European Center for Disease Prevention and Control (ECDC).

Both systems are publicly supported, by the PAHO and the European Union.

The laboratory type providing the data for both programs is patient care laboratories.

Report inclusion differs. The EARSS files isolates of seven bacterial species (*S. pneumoniae*, *S. aureus*, *E. coli*, *Enterococcus faecium*, *Enterococcus faecalis*, *K. pneumoniae*, and *Pseudomonas aeruginosa*) only from blood and cerebrospinal fluid (CSF) cultures from survey laboratories in each of its participating countries (1). PAHO surveillance more comprehensively files all bacterial isolates tested for resistance from all specimen types from its participating laboratories.

Microbial typing to discriminate phenotypes includes the serotyping of enteric pathogens in the PAHO program (104). Both programs use resistance phenotypes to summarize the prevalence of resistance to antimicrobials in the types of microbes which they survey but not routinely to detect occasional unusual strains. Some EARSS investigators now use molecular *spa* typing to trace MRSA clones (113).

Levels of surveillance include local, national, and regional surveillance for each program. The more comprehensive surveillance of all bacteria tested for resistance from all specimens tested in the laboratories of the PAHO program, however, makes more data available for local hospital or multicenter infection control programs than does the more selective filing of only blood and cerebrospinal fluid isolates of seven microbial species by the EARSS program.

Levels of surveillance analysis differ in that each country in the PAHO program now analyzes its own data, and the PAHO collates their summaries centrally, while the EARSS analyzes files for all isolates both nationally and centrally for the whole program (1). Both programs post their results on websites.

The types of analyses appear to be similar in that each analysis appears to use mostly the %RIS to overview the prevalence of resistance of each tested species to each tested antimicrobial to make comparisons between countries and over time.

The integration of analyses differs by the above-noted accomplishment of the EARSS in correlating the prevalence of antimicrobial resistance in participating countries with national data on antimicrobial usage by patients in the same countries to show a correlation between the two that appears to have then influenced usage widely in the region (75).

Automation of analyses seems not to be used much by either

program, nor does either program now approach real-time data management. Country data are required quarterly by the EARSS and yearly by the PAHO, which would allow multinational infection control and surveillance to be only retrospective now. Those PAHO-participating centers that do now file all their resistance test results by computer daily or nearly daily can now use those files for real-time local infection control and could utilize automation for it. The limited subset (seven species from blood and CSF specimens only) of its isolates that participating centers report to the EARSS program for its multicountry-level surveillance, however, omits the majority of the isolates that their local infection control programs would need to monitor.

Participation has grown steadily in both programs over the approximate decade of their existence, to a recent total of more than 300 centers in the PAHO program and 1,578 centers in the EARSS, due to the continuing efforts of both program managers and medical center participants. Each program, however, still surveys only a minority of the laboratories in its participating countries.

Summary of PAHO and EARSS Program Comparisons

The comparisons between these two multinational surveillance programs show differences for a number of the listed descriptors. For report inclusion, for example, the PAHO files isolates of all species and specimen types, while the EARSS files only blood and CSF isolates of seven species. For levels of surveillance analysis the EARSS analyzes isolate-level data in country and centrally, while the PAHO collates centrally only summaries of country-level analyses. These differences may reflect differences in original intent. The EARSS may have sought more to overview variances and their causes among national levels of antimicrobial resistance, and the PAHO may have sought more to support its local management.

These differences, however, are mostly in the completeness of descriptor categories. As programs become more complete for a descriptor, e.g., by the EARSS including more of each laboratory's reports and the PAHO analyzing isolate-level data centrally, as are likely, they become more capable and similar. Such growing comparability would empower them to collaborate, benchmark trends and details across their regions, and more fully exemplify the potential of global microbial surveillance.

USES OF MICROBIAL SURVEILLANCE

Surveillance Assists Patient Diagnosis

The identity of the microbe that is infecting a patient is usually uncertain when the patient first seeks care. Initial diagnoses are inferred in part from the rates at which various microbes have been infecting other people at that time and place. Caregivers get a sense of these through informal surveillance from their own and shared experiences, but explicit surveillance of all microbes infecting patients locally and regionally can refine their impressions (23). Caregivers without laboratories can learn less from their experience and need some surveillance to be done and broadcast by at least one sentinel laboratory somewhere in their region.

Surveillance Guides Treatment of Individual Patients

The initial therapy for an infected patient needs to be guided by surveillance more than does the initial diagnosis. Initial diagnosis is essentially a short list of the kinds of microbes likely to be infecting that patient chosen from all the kinds of microbes infecting others locally at that time and by clues from the patient's signs and symptoms. Each microbe on that list, however, then requires that an antimicrobial agent that can still kill it be chosen from among a dozen or more antimicrobials, most of which often cannot kill the microbe, and the only clues for that otherwise blind choice come from an essentially recycled surveillance of local or regional microbial resistance.

A cycle starts when a laboratory reports the identity and antimicrobial resistance of the microbe infecting a patient. That report reveals the best antimicrobial to replace the one that had been chosen empirically to treat that patient during the 1- to 2-day wait for the report. That report, paid for by the patient or a health care system, can then be recycled into a free surveillance database to estimate the probable best empirical treatment for each succeeding patient's first days or entire course, if no infecting microbe is identified (86).

This treatment-predictive surveillance, expressed as a %RIS antibiogram, is the most widely used type of surveillance, as mentioned above. It recognizes the critical need for the best initial treatment. It also addresses the variances in the prevalence of microbes and their resistance with location and especially between hospitals that differ in their antimicrobial usages and nosocomial strains. This surveillance thus needs to be based locally, but any center would also benefit by multicenter integration that would let it gauge how bad its problems are through benchmarking with others and be warned of new trends and new problems appearing at others, and in regions without resources where courses of antimicrobial therapy must be determined empirically throughout, such %RIS guidance can come only from a sentinel laboratory (48).

Surveillance Informs Local and National Drug Policies and Guidelines

As microbial surveillance data guide an individual caregiver who empirically selects an initial antimicrobial agent for an individual patient, as described above, it also supports pharmacy committees and national policy makers who must also address other needs, such as cost and antibiotic stewardship. Such groups may thus determine which agents are available for the caregiver to select from and which agents will be recommended for each type of infection in guidelines circulated to caregivers in the area (24).

Surveillance Focuses Local Infection Control in Hospitals and Communities

Patients become infected in a hospital because they are impaired by their illnesses, injuries, incisions, inserted catheters, tracheotomies, and other foreign bodies. The microbes that then infect these patients are often the more antimicrobial-resistant and virulent nosocomial strains, e.g., MRSA and VRE, that circulate in that hospital. Infection control workers need microbial surveillance to both identify and report infec-

tions in hospitals but also now to trace and stop the spread of such nosocomial strains to the patients who can become infected (74).

The surveillance of a hospital's microbiology isolates can identify most of the patients who are infected but may overlook some who did not yield a plausible isolate and find one in others who are only colonized by it. The correction of either situation before reporting to the hospital and/or public health agency has been done by examination and clinical judgment. Microbiology files are now being integrated with other patient files, such as the presence of central vascular line insertions and ADT data, etc., to explore the reporting of nosocomial infections by automated surveillance (8).

The surveillance of the individual microbial isolates of a hospital's patients focuses the containment of its nosocomial strains by identifying, isolating, and decolonizing patients who carry these microbes. Until recently, the only strains surveyed were isolated from infected patients for their diagnosis and treatment. The realization that uninfected patients colonized with a nosocomial strain may be silent links in its spread, however, is now prompting many hospitals to improve the resolution of surveillance by also taking samples from uninfected patients (33, 45). Health care workers are included in such surveillance in a few places where rare carriage makes the findings manageable (13, 50).

Surveillance data to support control by local public health workers of infections in the community, e.g., food-borne and contagious respiratory infections, etc., may be obtained from the local hospital laboratory that also supports inpatient infection control but also from other laboratories serving ambulatory health care centers over wide areas. Integrating files of such overlapping services in comprehensive surveillance would optimize the detection and management of community outbreaks, as in the above-described example of the *Shigella* outbreaks in Argentina (111).

Surveillance Enables Infection Control To Be Regional, National, and Global

A nosocomial multidrug-resistant microbial strain or plasmid or clone that circulates among the patients in a hospital can often be shown to have emerged years earlier in another part of the world and to have spread through a chain of hosts, human or animal, until someone ultimately brought it to the hospital. This has been true for major problems such as MRSA and VRE, etc., as well as many other multidrug-resistant microbes (54, 70, 83, 93, 100).

As such a clone then spreads nosocomially in hospitals, its infections increase morbidity, mortality, and cost; its containment becomes the major work of hospital infection control staff; and its menace is a major concern of public health agencies, such as the Centers for Disease Control and Prevention (CDC) and state health departments, etc., and, ultimately, the press and even legislatures (40). When public health agencies respond, however, they have tended to focus on the hospitals' infection control efforts by providing training and advice for their work and supporting and/or mandating additional reporting of their problems (87).

What seems to be overlooked is the possibility of public health agencies assuming for these global epidemics of resis-

tant microbial clones the overview tracking and management role that they have performed for other epidemics of infectious diseases for a century and for which they were created. As useful as their help is to local infection control staff to slow the patient-to-patient spread of such clones in hospitals where they are already endemic, it would also be useful for public health agencies to track all isolates of new epidemic clones coming into their jurisdictions and work to stop their hospital-to-hospital spread.

The core problem can be seen as resistance gene convergence. Hundreds of different resistance genes have been emerging in different parts of the world and spreading irregularly into locally varied distributions, and therefore, the numbers ultimately converging in clones in any area continue to grow. Early examples of such convergence were aminoglycoside resistance genes (73), macrolide resistance genes (53), and others ubiquitous in hospitals now, but more are imminent, such as more clones of MRSA (25, 54), extended-spectrum β-lactamases (ESBLs) (20, 25), and carbapenemases (e.g., KPC) (94). The monitoring and managing of such invasions would be a major task for multicenter, regional, national, or global infection control programs.

Existing microbial surveillance programs commonly compare overall levels of resistance to antimicrobials in infecting microbes, but their data could also be used to track newer resistance mechanisms for infection control for their regions. Strains or plasmids with a new level of resistance to an antimicrobial agent have a new resistance phenotype and may have additional distinctive markers as well. More comprehensive and inclusive surveillance programs would have finer-scale tracking, and those closer to real-time automated analysis would have quicker responsiveness, for new problems in their regions.

Surveillance Can Improve Testing in Patient Care Laboratories

The earlier view that patient care laboratories should not participate in surveillance programs until their test quality is certain is offset now by the realization that useful information can be gained earlier and that the programs themselves bring improvement. Surveillance programs commonly establish internal and external proficiency testing where they were not mandated or available before and bring training, teaching material, and the routine review of test results that previously had no outside scrutiny (51, 118).

Some surveillance programs have evolved a laboratory improvement program that collects and analyzes all identifications and resistance measurements of all clinical isolates and quality control strains from participating laboratories, analyzes them in multiple ways, reviews all the results in a multiday meeting of representatives from all of the laboratories, and repeats the process each year. This process resembles the "continuous quality improvement" management programs that use extensive analyses of ongoing measurements of all processes to display variances, collegial discussions of the results by the workers, motivated improvements, and continuing repetitions of the cycle (80).

Where resources are fewer, there are fewer hospitals with fewer microbiologists doing their specialized work nearly alone

without the helpful collegiality and supervision found in larger laboratories. Participation in the standards, benchmarking, feedback, contacts, and shared information of a fully functioning surveillance network lessens this isolation now, and newer informatics could bring a network closer to being one virtual laboratory. A nearly free derived use of the aggregated results of tests done for individual patients can thus be recycled to improve that testing and, through it, the safety of those patients.

Surveillance Supports Sentinel Laboratories in Areas with Minimal Resources

Where resources are fewest, there are few functioning laboratories, and establishing one requires special assistance (5). The support for laboratory proficiency provided by some surveillance networks, described above, is needed but not sufficient for minimal-resource regions. Additionally supportive would be a Web-based program for as-needed teaching, supply chain management, workflow, real-time advice by remote mentors or supervisors, and analysis of test results and their conversion into treatment guidelines for what may be, except for that sentinel laboratory, a vast microbe-blind area.

Surveillance Enhances Safety of Patients in Participating Centers

Each of the benefits of microbial surveillance cited in this section in some way enhances patient safety, and some, such as its support of empirical antimicrobial therapy and infection control in a particular center, specifically enhance the safety of patients in that center. Beyond that, however, data from other participating centers enhance the safety of patients in a participating center by benchmarking to indicate and prioritize its relatively more prevalent problems and by monitoring to warn of new problems entering the area (11, 34).

The Addition of Participating Centers Anywhere Adds to Patient Safety Everywhere

The addition of participating centers to a surveillance network increases the number of surveyed isolates in its area and so allows it to discriminate more trends and outbreaks sooner. It also reduces blind spots where new resistance clones can emerge and spread unseen (130). Each of the nine vancomycin-resistant MRSA isolates reported to date appears to have been contained at its index patient, possibly because their likely preconditions and large reservoirs of donor transposon (Tn*1546*) and recipient strains coexisted peculiarly in a country (United States) where high rates of culturing aid early detection (89). Past resistance clones, in contrast, may have spread widely in regions where laboratories are sparse before being noticed.

IMPROVING TOOLS FOR MICROBIAL SURVEILLANCE

More Discriminating Phenotyping

By testing to identify a patient's bacterial isolate to the genus or species level and its resistance to each of a set of antimicrobials, patient care laboratories inform caregivers of the cause and best therapy for that patient's infection. The filed

values of the increasing numbers of tests employed also generate increasingly detailed phenotypes for each isolate. These may serve occasionally to alert infection control or public health authorities to the unusual prevalence of a phenotype, suggesting an outbreak of a strain or clone, as shown in Table 1, or the earliest appearance of a novel phenotype, suggesting the incursion of a new strain or clone, as shown in Fig. 2. This use is made more valuable by the fact that the strains more likely to be detected in this way are often, as described here, the more resistant or more novel strains, the spread of which may be most dangerous.

Clones of a species may differ in the clinical characteristics of the infections that they cause or in their propensity to acquire resistance (54), and ultimately, it is a strain and not a species that spreads from one host to another. Local infection control could observe the movement of a strain between patients that is now obscured by all the other strains that we lump together as species. Regional infection control programs could detect the first incursion of a new clone into its region, track its early spread, and organize its containment, while global infection control programs might have observed the initial emergence of that clone in another part of the world.

In fact, the tests that laboratories perform to identify each isolate and test its resistance now yield enough information to further subtype the isolate into many antibiotypes and identity subtypes. The need to find effective antimicrobials has made laboratories test resistance to more of them, and instruments now test as many as 48 biomarkers and resistance to each of 18 antimicrobials at several levels. Such discriminating phenotyping has had limited use for patient diagnosis, e.g., negative sorbital correlation with *Escherichia coli* O157, but can have more uses for surveillance (67).

For example, a patient often has a bacterial isolate with a resistance phenotype seen in no other isolate of that species in the hospital that year. Some patients, moreover, have such an isolate repeatedly and so show its phenotype's reproducibility. If other patients begin to have isolates with that previously rare phenotype, as shown in Table 1, it suggests an outbreak that would be overlooked if surveillance monitored species only and ignored phenotypes. A similar use of isolates' identity phenotypes, their biotypes, seems even less explored but might at least correlate with or further subdivide antibiotypes.

Another application for the surveillance of the resistance phenotypes of bacterial isolates compares their levels of resistance to different members of a family of antimicrobial agents to distinguish different mechanisms of resistance to them. This is especially useful when it can, as shown in Fig. 2, detect the first incursion or track the early spread of a new resistance gene in a hospital or region before it spreads beyond containment.

Genotyping To Distinguish Resistance Genes, Genetic Elements, and Strains

A succession of innovative technologies for detecting specific sequences or determining longer sequences of nucleotides is allowing genotyping to identify microbes to the strain level and to identify the genes and genetic elements that encode the resistance of those microbes to antimicrobial agents. These technologies began with the electrophoretic sizing of nucleo-

tide chain segments between sites cut by restriction digestion enzymes, first of plasmids and later with pulsed-field gel electrophoresis of whole bacterial chromosomes. It has progressed through nucleotide probes, PCR, and the sequencing of single genes (*spa*) or multilocus sets (MLST) (124) of genes and now begins to include whole-genome sequencing.

Such methods are now used mostly by reference laboratories and not much yet to bring real-time surveillance in detail to hospital or regional infection control programs.

The various methods developed explore diverse applications, but their diversity may also impair comparisons of data from studies done with differing technologies. A solution for this may come from full-genome sequencing, because it is comprehensive, can decode and therefore interrelate data from the other methods, and can be rooted in the full delineated genealogy of a species rather than a narrow or arbitrary view of it (54). The future of genotyping may hinge largely on the rate at which the cost of full-genome sequencing continues to decrease and its role as a translator or even a replacement for the other methods inversely increases. What may come sooner is the full-genome sequencing of a small number of isolates from a new problem to guide the design of a specific genotyping test for such isolates. That test would need to be cheap enough to use widely to monitor the extent to which the phenotype still tracks the spread of the problem and its variants in large laboratory-generated data sets.

Integration of Genotyping and Phenotyping To Refine Surveillance

The phenotypes of patients' bacterial isolates are available from patient care laboratories for reuse in surveillance essentially for free. Genotypes are now available occasionally for special studies by public health laboratories at no cost or at cost by private reference laboratories. Some phenotypes are so distinctive as to likely represent strains or clones, and clusters of these may presumptively identify outbreaks which selective genotyping could then confirm. The screening of surveillance data for such "low-hanging-fruit" outbreaks of distinctive phenotypes is rarely done systematically now but could be managed with existing informatics.

More challenging is the teasing out of epidemic strains or clones from endemic blocks of isolates that appear to have the same phenotype. A major example now is MRSA in most hospitals. When U.S. hospitals began to acquire MRSA 3 decades ago, the strains were probably monoclonal initially, but reinvasions and recombination have likely made most strains polyclonal now, as genotyping into USA 100, USA 200, and USA 300 or *mec* cassette typing, etc., has demonstrated (49). More applicable genotyping, more discriminating phenotyping, or an integrated use of both that could delineate some of these clones would not only help track their spread now but might also have detected their separate pandemics sooner (54).

Approaches to this challenge are to make more use of the discriminating phenotyping that is available, to make genotyping more available, and to integrate both optimally. While a large portion of the MRSA isolates at a hospital may, for example, have the same qualitative resistance pattern (resistance category for the same drugs), their measured levels of resistance or their biotypes may differ, and a larger portion may have a variety of different qualitative resistance patterns. The exploitation of such differences may await the clustering of one or another of them to suggest a spreading clone or genotyping to identify which of such phenotypes represent one or a few clones (129). These approaches may be more applicable to multiresistant Gram-negative bacilli, which generally have more diverse phenotypes with smaller percentages of total isolates in each.

Informatics

Advances in informatics over recent decades have driven the development of microbial surveillance networks by reducing the work of participation and expanding its benefits. Even so, surveillance still appears to use little of today's rapidly expanding informatic technology and thus likely has many opportunities for improvement. Secure, Web-based data capture and processing, for example, will give surveillance ongoing automated real-time analyses with prompt alerting of responders at all levels and therefore will further incentivize participation (21). Just-in-time information prompts and images and step-by-step workflow advice from remote colleagues via the Web, with possible cell phone extension, can bring the needed support and collegiality to the critically important but isolated workers in sentinel laboratories in severely resource-limited and underserved areas.

Integrating Levels of Surveillance

The review of microbial surveillance activities finds them existing at multiple levels for different applications that range from local guidance for treatment and hospital infection control through reference laboratory specialty testing; professional-, pharmaceutical-, or public health-supported multicenter networks; and several multicountry networks. The overall participation, range of analyses, and integration between levels, however, still seem to be a small fraction of their potential and to provide a small fraction of their possible uses and benefits. What might most accelerate surveillance is the recognition by those doing it at any level that the data that they must extract, secure, and analyze are the same data needed for other levels of surveillance and that integrating and performing all levels fully and linking them in supportive networks would make microbial surveillance far more efficient and effective for patient safety and public health.

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