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Why surveillance of antimicrobial resistance needs to be automated and comprehensive

Thomas F. O'Brien, Adam Clark, Rob Peters, John Stelling*

Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

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ABSTRACT

Objectives: Surveillance of antimicrobial resistance (AMR) can now be automated to analyse the reports of microbiology laboratories continually without operator assistance. It can also be made comprehensive to monitor all the reports of all the world's microbiology laboratories.
Methods and results: As illustrated through examples provided in this work, each clinical report can be scanned automatically by algorithms to suspect emerging problems and to prompt sampling to confirm such problems, now increasingly by nucleotide sequencing. An emerging problem may be an excess (clustering) of similar microbes owing to their spread among patients who are interrelated in some way, as by shared locations, caregivers or food products. Or it might be a microbe new to an area or to a laboratory but already seen nearby, such as *Elizabethkingia anophelis* or *mcr-1*-positive *Escherichia coli*. Automated early alerting of responders enables them to contain spread sooner and to avert infections downstream. 'Big Data' informatics now also enables surveillance of AMR to be made comprehensive, to monitor all reports of all the world's microbiology laboratories. Such orders of magnitude increase in analysed data would accordingly increase its granularity and thus detect many more global problems sooner. It would also reduce surveillance-blind areas where problems may now emerge and spread undetected.
Conclusions: The world's microbiology laboratories need to integrate and analyse all of their reports for surveillance to make their own patients safer from existing and approaching problems otherwise hard to notice. Making automated surveillance an easy-to-adopt laboratory standard of care can make it comprehensive.

1. Introduction

Antimicrobial resistance (AMR) is a recent phenomenon. We began only 75 years ago to use antimicrobials widely and to inadvertently disturb microbial populations that had been evolving all over the world for billions of years. After wide use of each new antimicrobial agent, a gene expressing resistance to it eventually emerged in a microbe somewhere and then spread to other microbes and other places, and linked to other resistance genes [1].

How each antimicrobial was used and where genes expressing resistance to it emerged and how they spread have differed. These differences have spread resistance genes irregularly among the world's microbes and led each antimicrobial to fail to cure patients more often in some places [2,3]. We need to track all such spread to see it coming, to avoid and treat it, and to keep it from spreading further and killing more patients. We have a unique resource for doing this in the already paid for reports of the world's tens of thousands of microbiology laboratories, the only places that can observe microbes [4].

These reports are often tallied once annually by a laboratory to summarise for its caregivers the overall percentage resistance to each antimicrobial of a few priority microbes tested over the prior year. Samples of such reports from samples of laboratories are also used to estimate how much some specific types of resistance or how much resistance overall, e.g. the World Health Organisation's (WHO) Global Antimicrobial Resistance Surveillance System (GLASS), had changed over the prior year. We explore here how advancing informatics can now automate surveillance of AMR in detail and integrate it across the world to be comprehensive in near-real-time.

Microbiology laboratories measure and record the level of resistance of a microbe to an antimicrobial in one of two ways. One is by growing it in multiple concentrations of each antimicrobial and recording (or for some automated systems, estimating) the

* Corresponding author.
E-mail address: jstelling@whonet.org (J. Stelling).

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lowest concentration (the minimum inhibitory concentration or MIC) that inhibits its growth. The other records the diameter (in mm) of the zone of inhibition around a paper disk containing that antimicrobial in a lawn of growth of that microbe on an agar plate.

The measurements, their interpretive categories, and the species or subspecies identification of the tested microbe are made by laboratory workers and instruments and are sent as paper or electronic reports to each patient's record to guide that patient's therapy. In many facilities the results are stored in paper log books and consequently are unavailable for supporting data analysis and data sharing, but in high-, medium- and, increasingly, low-resource settings, reports are stored in the electronic files of a laboratory information system (LIS) integrated with other clinical reporting services.

Each of the world's microbiology laboratories thus has years of files of all the identities and levels of resistance to antimicrobials it reported for the microbes from patients that it tested. Those files have all we can know of the ongoing shifts in microbial populations everywhere that continue to build the world's AMR. They are a largely unused and unshared representation of the past and ongoing progression of AMR.

Data files extracted from participating laboratories are used for national and multinational programmes to estimate the accumulation of selected types of AMR. Automated analyses can now facilitate such reporting but also track and alert in real-time, in detail, all of the reported resistant microbes spreading among local and global communities.

Full surveillance of AMR needs now also to integrate with growing data from nucleotide sequencing to confirm and detail interrelationships that full surveillance can suggest and then to extrapolate those interrelationships back to the world's ongoing infections.

The obstacles to surveillance of microbiology laboratory files were their inaccessibility in diverse paper and electronic codes and formats as well as a lack of shared analytical software. Successive versions of the WHONET software [5] were made to enable any microbiology laboratory to survey the problems of its patients and to join with others for country or multicountry surveillance. The WHONET package includes BacLink, a data capture and conversion utility that translates the diverse codes and formats of each laboratory into those of WHONET [6]. WHONET is now used to support surveillance in over 2300 laboratories in over 120 countries [6]. In addition to its use at local and national levels worldwide, WHONET is an integral component of the successful regional and global surveillance programmes ReLAVRA (Latin America) [7], EARS-Net (European Union) [8], CAESAR (Central Asia and Eastern Europe) [9] and GLASS [10].

2. Materials and methods

Here we provide examples of the analytical features available within WHONET to explore how routinely available clinical diagnostic laboratory results can generate insights and alerts needed for the development and implementation of resistance containment interventions. At a high-level, this relies on the recognition and tracking in space and time of evolving microbial subpopulations. Specific applications include support for the development of standard treatment guidelines, timely recognition and containment of emerging threats such as new multiresistant pathogens and infection outbreaks both in the community and hospital settings, and notifications of potential deficiencies in laboratory test practices.

To this end, data are presented here from one US hospital in one state as well as from most hospital microbiology laboratories of a network in another state in collaboration with the state health department. Our WHONET support team worked with facility staff to implement existing data extraction routines or to develop new ones in order to extract relevant patient, sample, location, organism identification and antimicrobial susceptibility test results from the facility LIS systems [11]. In instances where the availability of antimicrobial test results within the LIS was significantly limited by local 'antimicrobial suppression rules' to support local antimicrobial stewardship programmes, comprehensive susceptibility test results were downloaded directly from the laboratory's automated susceptibility test instruments. These simple text files were then transformed by the BacLink data import module of the WHONET package into standardised and intercompatible WHONET files for purposes of data sharing and data analysis.

WHONET files stored within the individual facilities were used for purposes of local interpretation and application, including monthly reporting to the US Centers for Disease Control and Prevention (CDC) National Healthcare Safety Network (NHSN) module for the reporting of Multidrug-Resistant Organisms and *Clostridiodes difficile* infection (MDRO/CDI). Copies of the data were also sent monthly through secure electronic data transfer to the data co-ordinating site to support integrated facility- and network-level analyses and feedback.

The analyses presented in this work include the standard WHONET analytical features 'Isolate listing and summary', '% Resistant, intermediate, susceptible and test measurement distributions', 'Scatterplot', 'Isolate alerts' and, finally, 'Cluster alerts' generated through integration of the free WHONET software with the free SaTScan™ software for detection of possible outbreaks both in space and time. Further details about the interpretation and value of these analyses is provided below in the Results. Routine daily, weekly, monthly and yearly analyses and notifications can be performed automatically using WHONET's macro and report features, whilst the analyses presented here were prepared interactively.

3. Results

The WHONET initiative has generated interoperable, common-format files of data from several thousand of the world's microbiology laboratories, many going back decades. It has also linked networks of microbiologists who analyse their files locally and link them into country and multicountry public-health surveillance networks. New informatics can now automate this surveillance of AMR to make it easier, more informative and open to all laboratories. We describe here the types of operator-driven analyses WHONET does now and why each needs to be automated and made comprehensive.

3.1. Isolate listing and summary

Specific isolates of microbes in any WHONET file may be characterised and filtered by one or many of over 100 descriptors, and the isolates and their filed descriptors then listed and summarised. Descriptors include patient identification (name or number), testing laboratory, department, hospital or other institution and date of patient admission, country or other georeferencing data, patient hospital location and patient hospital day when specimen was taken, specimen type, isolate identification, isolate BioNumber summarising its biochemical test results, and measurements of the susceptibility of each isolate to each of 8 to 18 antimicrobials by the MIC or disk diffusion test methods.

These descriptors let WHONET analyse discriminating subsets of filed microbial isolates from any specified patient or from patients of any age group, country or time period, etc. Similarly, they can subgroup for analysis filed microbes by species and by

resistance or by specific levels of resistance to one or multiple different antimicrobials and by laboratory or country and/or time period etc. These analytical options enable WHONET users to search for and examine specific deviations from expected distributions of any microbes or resistance genes occurring at any time or place.

3.2. Percentage resistant/intermediate/susceptible (RIS) and test measurement distributions

The proportion of a collection of a type or subtype of microbes that falls within each of these three categories of susceptibility to any antimicrobial is the most used analysis of AMR. Microbiology laboratories commonly report these values annually for each of the commonly isolated species of bacteria. Caregivers use these reports when selecting empirical therapy to predict the probability that an antimicrobial will cure an infection due to a microbe not yet reported but made probable by the patient's clinical picture.

The setting of the boundaries for these categories is done by expert groups reviewing measurements of the minimal concentrations of an antimicrobial that inhibit standard inocula of commonly infecting types of microbes, and they may be adjusted with clinical experience [12]. Problems dealt with include varied concentrations of drugs at different body sites as well as variable interpretation of whether the intermediate category is for values uncertain as predictors of cure or for values needing higher drug doses for cure.

Besides displaying the %RIS for each selected set of isolated microbes, WHONET also presents for each %RIS value its confidence interval, its MIC_{50} and MIC_{90} (the number or percent of tested isolates that fall within the more susceptible 50% or 90% of the total tested) and the total number tested. Finally, for any tested set of isolates, a histogram displays the percentage of the total tested found to have each measured diameter (in mm) for disk diffusion testing or each measured MIC value for the dilution test method.

3.3. Scatterplot

For any subset of microbial isolates selected by any of the above parameters, WHONET can plot the measurements (MIC or inhibition zone diameter) or interpretive categories of susceptibility to one antimicrobial on one axis against those of another on the other axis. A two-dimensional display then discriminates isolates with varying levels of resistance to each of the drugs. By preselecting for this analysis isolates that have tested resistant (or susceptible) to a third antimicrobial, the plot can be made essentially to distinguish subpopulations varying in susceptibility to any of the three.

The first example of a scatterplot shown here (Fig. 1) plots the diameters of zones of inhibition (in mm) around the oxacillin disk on the horizontal scale against the MICs of penicillin extrapolated

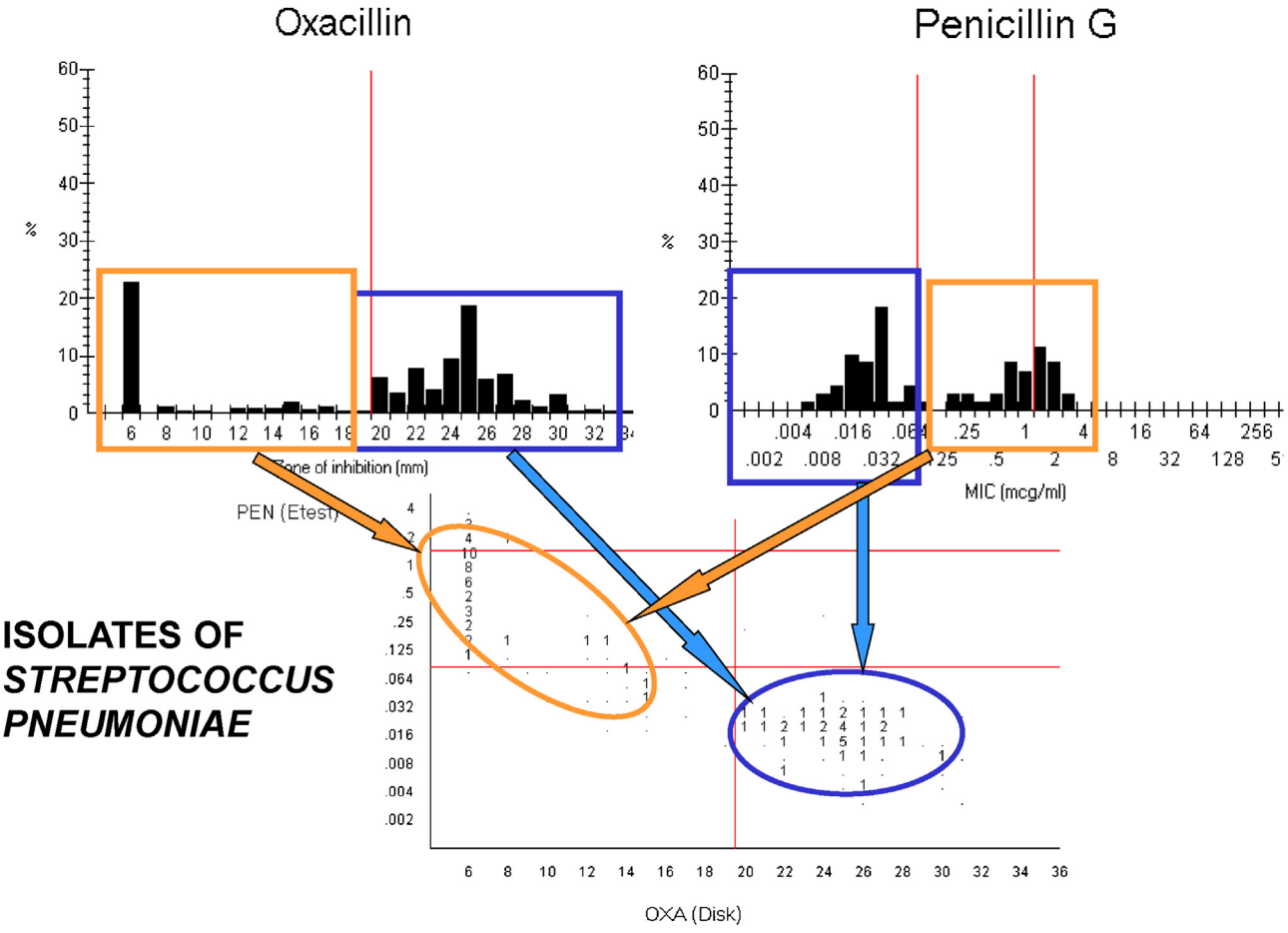

Fig. 1. WHONET-generated plots comparing the diameters (in mm) of zones of inhibition of isolates of *Streptococcus pneumoniae* around CLSI-standardised oxacillin disks with the minimum inhibitory concentrations (MICs) of penicillin for the same isolates determined by Etest. The upper graphs plot distributions of the diameters of the oxacillin disk inhibition zones (left) and the Etest MICs (right) against corresponding CLSI breakpoints for susceptible categories. The lower graph scatterplots correlation between those distributions. Susceptible isolates have been enclosed in blue boxes, whilst non-susceptible isolates are demarcated in orange. CLSI, Clinical and Laboratory Standards Institute.

from Etest on the vertical scale for a collection of *Streptococcus pneumoniae* isolates. The distributions distinguish larger populations of isolates that appear most susceptible and most resistant by both tests as well as smaller populations intermediate to one or both. The results show correlation between the test methods that supports quality of testing, but with some divergence at intermediate concentrations.

The second example of a scatterplot shown here (Fig. 2) plots the MICs of ceftazidime on the horizontal scale against the MICs of ceftriaxone on the vertical scale for all unrepeated ciprofloxacin-non-susceptible isolates of *Escherichia coli* at a US medical centre during 2007 and again during 2013. During this relatively short 7-year period, the number of patients with isolates susceptible to ceftazidime and non-susceptible to ceftriaxone (dashed line box) and to ciprofloxacin became six times more prevalent, and the subset of these with the highest MICs to ceftriaxone and the lowest to ceftazidime (dashed line circle) had a similar increase, also evident in the isolate listing summary, as described earlier, in Fig. 3.

A resistance profile summary, described further below (Table 1), shows that at the end of this 7-year period such isolates of *E. coli* susceptible to ceftazidime and non-susceptible to ceftriaxone and to ciprofloxacin were approaching 1% of nearly 20 000 isolates of *E. coli* surveyed by WHONET across nearly all of the medical centres of one US state. This is the resistance phenotype often expressed by *E. coli* sequence type (ST) 131, now known to have spread over this period to become approximately as prevalent as WHONET shows it to be here and in Fig. 2 [13]. It thus shows how a fully automated WHONET could scan for beginning shifts in distributions of any phenotypes and alert laboratories to save specific isolates for molecular testing in order to identify them early.

3.4. Resistance profiles

Microbiology laboratories now commonly test the antimicrobial susceptibility of microbes to 8–18 antimicrobials. Listing those to which each microbe has tested as resistant or non-susceptible (resistant or intermediate) assigns to it a resistance profile. Such antibiotypes are the only way most of the routinely reported isolates of a species can now be distinguished from one another using routine test results.

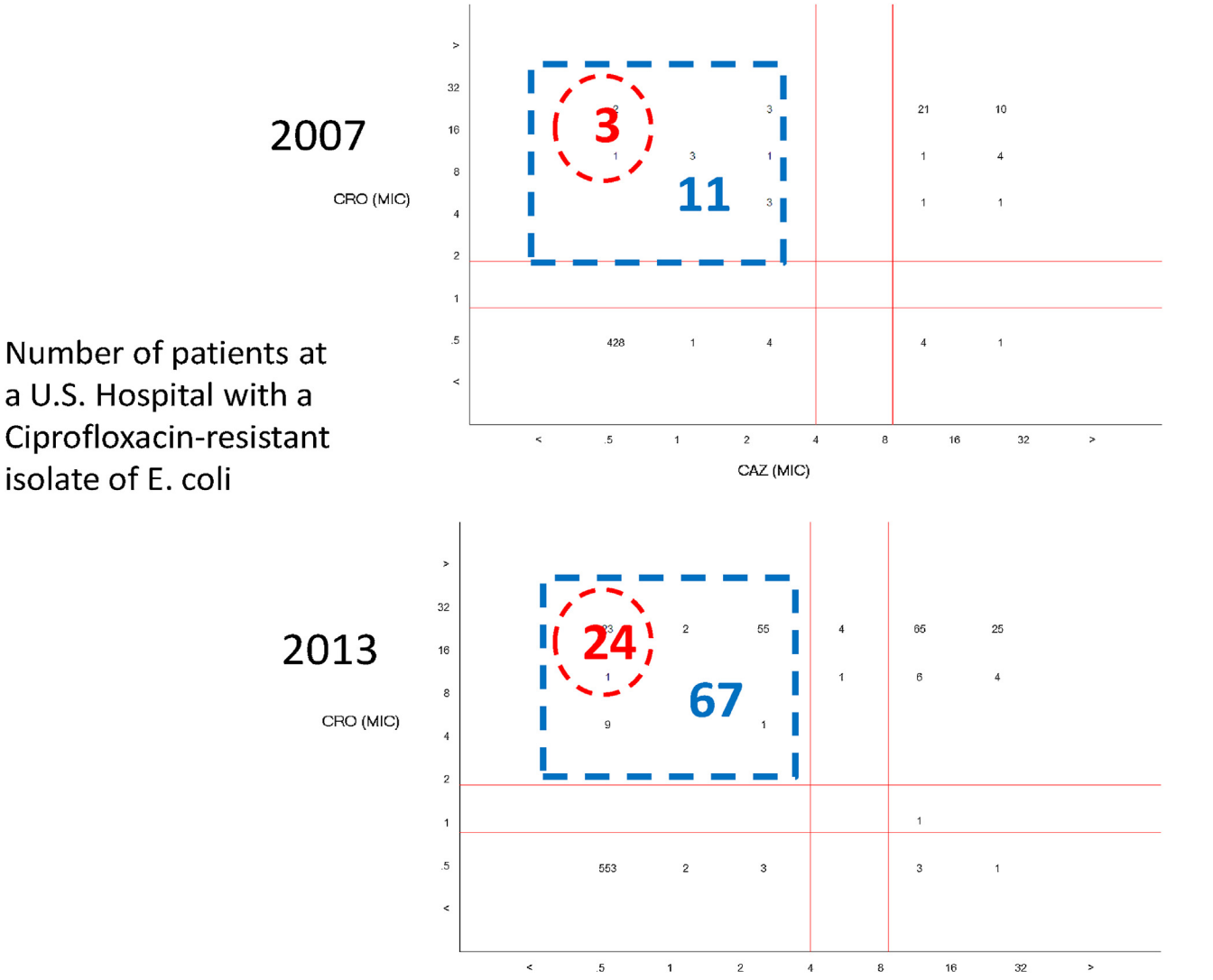

Fig. 2. WHONET-generated scatterplot of number of patients at one US medical centre who had ciprofloxacin-resistant isolates of *Escherichia coli* with each combination of minimum inhibitory concentrations (MICs) of ceftazidime (CAZ) and ceftriaxone (CRO) during the first and last years of a 7-year period. The dash-enclosed squares include all isolates classified as resistant to CRO and susceptible to CAZ, whilst the dash-enclosed circles include all those with the highest MICs to CRO and lowest MICs to CAZ. Vertical and horizontal solid lines delimit MICs that categorise isolates as resistant, intermediate or susceptible to either drug by Clinical and Laboratory Standards Institute (CLSI) standards.

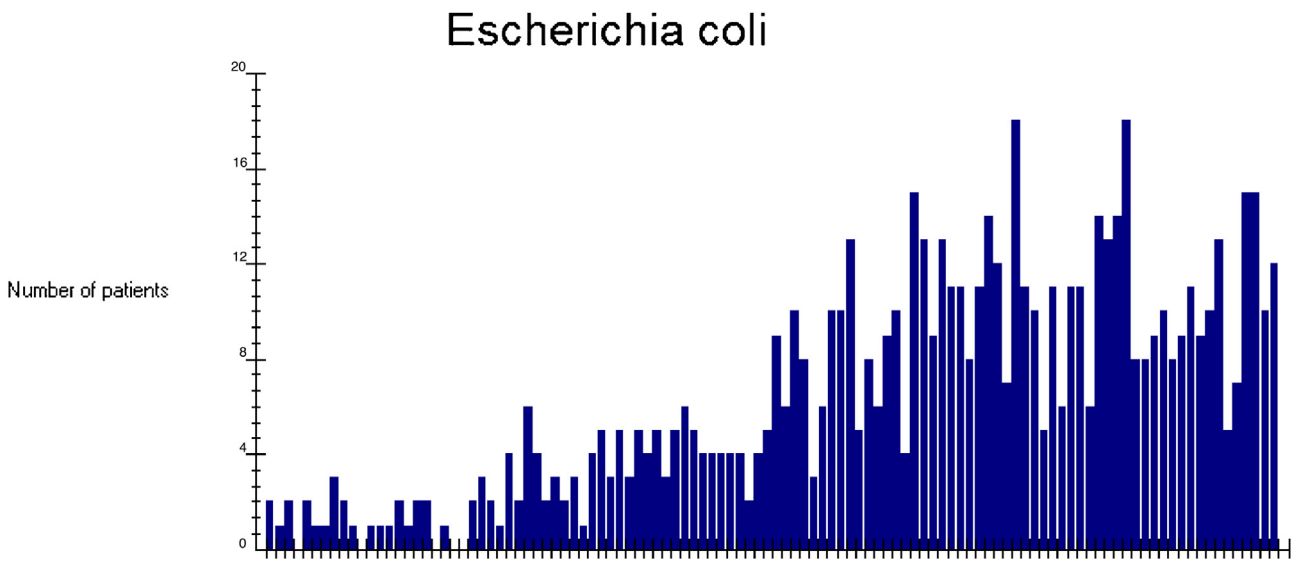

Fig. 3. WHONET-generated plot of the number of patients at the centre in Fig. 2 who had an isolate of *Escherichia coli* that was susceptible to ceftazidime and non-susceptible to ceftriaxone and ciprofloxacin in each month of that 7-year period.

Table 1
Prevalence of separate and combined resistance to three antimicrobials in several recent years among *Escherichia coli* isolates at all 12 laboratories of a small US state (19 389 isolates from 14 591 patients). Isolates in the first row are susceptible to the three antimicrobials indicated; subsequent rows indicate the number of patients non-susceptible to the antimicrobials displayed.

Resistance profile	No. (%) of isolates	No. (%) of patients
Susceptible	16 023 (82.6)	12 761 (87.5)
CIP	2635 (13.6)	1589 (10.9)
CRO	61 (0.3)	51 (0.3)
CAZ	35 (0.2)	29 (0.2)
CRO/CIP[a]	169 (0.9)	128 (0.9)
CAZ/CIP	20 (0.1)	16 (0.1)
CAZ/CRO	212 (1.1)	185 (1.3)
CAZ/CRO/CIP	234 (1.2)	145 (1.0)

CIP, ciprofloxacin; CRO, ceftriaxone; CAZ, ceftazidime.
[a] Isolates with the resistance profile of CRO/CIP match those of the isolates in Fig. 3 of a medical centre in an adjacent state.

The examples here show use of resistance profiles to detect possible outbreaks. Essentially in these examples, a place such as a medical centre or a location within one has more isolates of a microbial species with a particular antibiotype than seen there previously or seen at comparable places over a comparable time period. Such isolates might belong to the same strain spread to many patients by a common source, such as a contaminated instrument, a healthcare worker who is a carrier, or a food product. An excess common resistance profile may not fully discriminate among such problems, but alerts to them early.

Five patients at 1 medical centre had isolates of *Klebsiella pneumoniae* non-susceptible to ceftazidime within a 4-month period, whilst no patients at any of 11 other medical centres in that state had one during that 2-year observation period (Table 2). In the second example (Table 3), nine patients at 1 medical centre had isolates of *Staphylococcus aureus* non-susceptible to oxacillin (more commonly described as methicillin-resistant *S. aureus* or MRSA), erythromycin, ciprofloxacin and gentamicin, six of them within 2 months, whilst only one patient each at only 3 of the other 11 hospitals surveyed in that state had such an isolate. In a third example (Table 4), a centre with less than half as many isolates of *Pseudomonas aeruginosa* as three others with which it could be compared had more than three times as many resistant to ceftazidime, ciprofloxacin and gentamicin.

3.5. SaTScan in WHONET

SaTScan, a software program designed to detect changes in the spatial distribution of events over time, has been incorporated into WHONET to enable it to detect and locate significant shifts over time in the distributions of AMR phenotypes reported from a geographical area. In WHONET data of a 750-bed US medical centre from 2002 to 2006, WHONET-SaTScan found 59 cluste[rs] involving 2–27 patients (median 4 patients). Most of these clusters were judged by reviewing epidemiologists to be worth investigating and more than one-quarter of them to have needed intervention [4].

4. Discussion

Many thousands of microbiology laboratories around the world are paid to report which kind of microbe is infecting each of many millions of patients and which antibiotics could kill each strain and cure the patient it is infecting. Beyond this one-time one-person use, such already paid for data accumulating in the files of those laboratories has other uses for patients and public health that informatics can now support.

Unlike the other clinical laboratories, such as biochemistry or haematology, which test analytes mostly confined within each patient, microbiology tests free-living microbes that move between people, sometimes in global epidemics, and often carry harmful genetic elements that can move between the microbes. Everything we can know about these spreading dangers has to come from microbiology laboratories, which it does now, not automatically and completely, but largely through sporadic infrequent noticing of a few priority issues by various observers.

Such observers may promptly notice changes in well-recognised problems, such as MRSA, but less promptly other emerging issues not yet emphasised, as in the example of *E. coli* ST131 above or locally endemic strains resistant to a set of antibiotics, such as the multiresistant *S. aureus* prevalent above in just one hospital.

Table 2
Prevalent *Klebsiella pneumoniae* resistance phenotypes at a US medical centre. Five different patients demarcated in the dashed box at one medical centre over a 4-month period during a 3-year observation of isolates at 12 medical centres in a small US state had an isolate of *K. pneumoniae* with a resistance phenotype (non-susceptible solely to CAZ among the antimicrobials included in the analysis) otherwise not seen in that or any of the other centres. Dates have been shifted for confidentiality.

Patient	Centre	Location	Specimen date	Specimen type	Resistance profile	MIC					
						OXA	GEN	CIP	ERY	SXT	TCY
A	A	Long-term care	11/04/2013	Genital	OXA/CIP/ERY/SXT	>2	≤0.5	>4	>4	>8	≤1
B	B	Outpatient	12/10/2014	Wound	OXA/GEN/CIP/ERY	>2	>8	>4	>4	≤0.5	≤1
C	C	Home health	09/01/2015	Other	OXA/GEN/CIP/ERY	>2	>8	>4	>4	≤0.5	≤1
D	D	Outpatient	02/21/2014	Leg	OXA/GEN/CIP/ERY	>2	>8	>4	>4	≤0.5	≤1
E	E	Outpatient	12/10/2014	Wound	OXA/GEN/CIP/ERY	>2	8	>2	4	≤2	≤4
F	E	Outpatient	01/26/2015	Respiratory	OXA/GEN/CIP/ERY	>2	>8	>2	>4	≤2	≤4
G	E	Outpatient	10/03/2014	Urine	OXA/GEN/CIP/ERY	>2	8	>2	>4	≤2	≤4
H	E	Outpatient	05/20/2014	Respiratory	OXA/GEN/CIP/ERY	>2	>8	>2	>4	≤2	≤4
I	E	Outpatient	12/14/2014	Wound	OXA/GEN/CIP/ERY	>2	>8	>2	>4	≤2	≤4
J	E	Outpatient	12/20/2014	Respiratory	OXA/GEN/CIP/ERY	>2	8	>2	>4	≤2	≤4
K	E	Outpatient	01/17/2015	Wound	OXA/GEN/CIP/ERY	>2	8	>2	>4	≤2	≤4
L	E	Outpatient	04/15/2014	Respiratory	OXA/GEN/CIP/ERY	>2	>8	>2	>4	≤2	≤4
M	E	Outpatient	12/18/2014	Wound	OXA/GEN/CIP/ERY	>2	>8	>2	>4	≤2	≤4
N	E	Outpatient	11/01/2014	Wound	GEN/CIP/ERY/SXT/TCY	1	>8	>2	>4	>2	>8

Table 3
Distinctive prevalent *Staphylococcus aureus* resistance phenotype in medical facilities in a small US state. Twelve isolates of a distinctive *S. aureus* resistance phenotype were found during the analysed time period, non-susceptible to four antimicrobials (OXA/GEN/CIP/ERY). Nine of the isolates were found at a single medical centre, whilst one isolate was found in each of three medical centres in the state. The remaining eight medical centres had no isolates with this antibiotype.

Patient	Centre	Location	Specimen date	Specimen type	Resistance profile	MIC					
						OXA	GEN	CIP	ERY	SXT	TCY
A	A	Long-term care	11/04/2013	Genital	OXA/CIP/ERY/SXT	>2	≤0.5	>4	>4	>8	≤1
B	B	Outpatient	12/10/2014	Wound	OXA/GEN/CIP/ERY	>2	>8	>4	>4	≤0.5	≤1
C	C	Home health	09/01/2015	Other	OXA/GEN/CIP/ERY	>2	>8	>4	>4	≤0.5	≤1
D	D	Outpatient	02/21/2014	Leg	OXA/GEN/CIP/ERY	>2	>8	>4	>4	≤0.5	≤1
E	E	Outpatient	12/10/2014	Wound	OXA/GEN/CIP/ERY	>2	8	>2	4	≤2	≤4
F	E	Outpatient	01/26/2015	Respiratory	OXA/GEN/CIP/ERY	>2	>8	>2	>4	≤2	≤4
G	E	Outpatient	10/03/2014	Urine	OXA/GEN/CIP/ERY	>2	8	>2	>4	≤2	≤4
H	E	Outpatient	05/20/2014	Respiratory	OXA/GEN/CIP/ERY	>2	>8	>2	>4	≤2	≤4
I	E	Outpatient	12/14/2014	Wound	OXA/GEN/CIP/ERY	>2	>8	>2	>4	≤2	≤4
J	E	Outpatient	12/20/2014	Respiratory	OXA/GEN/CIP/ERY	>2	8	>2	>4	≤2	≤4
K	E	Outpatient	01/17/2015	Wound	OXA/GEN/CIP/ERY	>2	8	>2	>4	≤2	≤4
L	E	Outpatient	04/15/2014	Respiratory	OXA/GEN/CIP/ERY	>2	>8	>2	>4	≤2	≤4
M	E	Outpatient	12/18/2014	Wound	OXA/GEN/CIP/ERY	>2	>8	>2	>4	≤2	≤4
N	E	Outpatient	11/01/2014	Wound	GEN/CIP/ERY/SXT/TCY	1	>8	>2	>4	>2	>8

MIC, minimum inhibitory concentration; OXA, oxacillin; GEN, gentamicin; CIP, ciprofloxacin; ERY, erythromycin; SXT, trimethoprim/sulfamethoxazole, TCY, tetracycline.

Most observers view only one medical centre, moreover, and may have little way of recognising early emergence in their centre of a strain already widespread in another. Many national and regional surveillance networks exist, but the typical focus is annual data collection of percent susceptibility results on a few high-priority issues, and thus of little value in supporting real-time resistance containment interventions.

4.1. Why needed?

Over time, strains of microbes join or leave the many that live on each of us, our microbiomes. Some strains can infect us, and public-health containment efforts have kept those of many species, e.g. *Salmonella* Typhi, *Shigella*,*Vibrio cholerae*, etc., from spreading through the microbiomes of people in much of the world [14]. Other infecting strains, e.g. of *S. aureus* or *E. coli*, remain ubiquitous, and when they infect we need antimicrobials to kill them and to cure the infections they cause.

After each antimicrobial was widely used, however, a gene expressing resistance to it eventually emerged in a microbe somewhere and began to spread on genetic elements. Along the paths of spread of such resistance genes, antimicrobials failed to kill infecting strains with those genes and patients remained infected or died. We need to notice such spread in order to contain it and select treatment that circumvents it, and also to find common sources for the spread, such as food products or healthcare settings.

Surveillance of AMR rarely does either now. A laboratory often tallies and lists the percentage of its last year's isolates grouped by species that had tested resistant to each antimicrobial. A country may average reports from a sample of its laboratories to project its overall percentage resistance. The EARS-Net program of the European Union and the GLASS programme of the WHO, as mentioned above, average the past resistance of selected subsets of the reports of a sample of a country's laboratories.

Surveillance in detail and in near-real-time could do much more. Microbiology laboratories test and record the concentrations

Table 4
Prevalent *Pseudomonas aeruginosa* resistance phenotype at a medical centre. Twenty-six patients at Centre X had isolates of *P. aeruginosa* with a resistance phenotype seen in only eight of nearly two times as many patients at the other centres observed. Isolates in the first row are susceptible to the three antimicrobials indicated; subsequent rows indicate the number of patients non-susceptible to the antimicrobials displayed.

Resistance profile	No. of patients	
	Centre X	All other centres
Susceptible	393	940
GEN	69	67
CIP	78	134
CAZ	31	38
CIP/GEN	52	79
CAZ/GEN	22	5
CAZ/CIP	16	18
CAZ/CIP/GEN	26	8

GEN, gentamicin; CIP, ciprofloxacin; CAZ, ceftazidime.

of each of extended sets of antimicrobials needed to inhibit each microbe as well as its reactivity to sets of biochemical agents or mass spectrometry signal profiles to determine the microbial species. Taken together these tests can often distinguish from one another many different microbes that are now only lumped together under a species name in reports that also carry unused these data which might distinguish them. Such free subtyping and subdividing of reported microbes can be used to reveal dangerous grouping of subtypes not apparent at the species level.

A grouping or shift in the relative prevalence of a subtype needs to be noticed promptly to prevent progression of dangerous outbreaks from common sources, such as a particular food, healthcare worker or environment. Such groupings may be sensitive but not necessarily very specific reporters of outbreaks however, since some biotypes and/or multiresistant phenotypes may be common enough to cluster co-incidentally. This need not be a practical problem, however, as such alerts can usually be readily evaluated and dismissed or confirmed to identify early dangers that might have been noticed only later or not at all.

The likelihood that such an alert reveals a significant problem, moreover, could be included in the alerting message. In the example above of the nine patients at one centre in 1 year with isolates of *S. aureus* resistant to oxacillin, erythromycin, ciprofloxacin and gentamicin, it could be noted that only 73 patients in the eight centres over 5 years had isolates with that resistance phenotype, whilst 822 had isolates resistant to oxacillin, erythromycin and ciprofloxacin but not to gentamicin. The relative rarity in this area of resistance to gentamicin in oxacillin-resistant isolates of *S. aureus* could thus have made this cluster more likely to be significant.

One reason why alerts based on subtype clustering are becoming more useful now is the growing availability of molecular typing techniques, including whole-genome sequencing (WGS), to confirm that such a cluster is due to the spread of a strain [15]. The alert can prompt the laboratory to save the alerting isolates and the sequencing laboratory to receive them. To fully utilise genome sequencing to tease out detailed microbial epidemiology in near-real-time, however, may require a central agency to do more than store the sequences. They may also need to report promptly the molecular and geographical interrelationships of the newly submitted strain to all those previously sequenced anywhere.

4.2. Why automated?

The work of a human analyser needed to find the few examples of useful analyses presented here as well as the enormity of all the possible useful analyses of such data indicate why such analyses need to be automated. Essentially, microbes are complex living organisms, and microbiology laboratories delineate in detail the generally reproducible susceptibility and biochemical characteristics or mass spectrometry signal profiles of each one they report. The number of possibly insightful ways of interrelating these markers across space and time exceeds the time available from human analysers.

A model for automating surveillance of AMR may be seen in the growing examples of electronic sensor networks. These widely deploy sensors that record specific sets of observations and transmit them to a central database. Examples are buoys at sea recording ocean temperatures, seismic detectors recording earth tremors, bird watchers recording bird species' migrations, or chain store inventory monitors. Each database is monitored by algorithms to alert predesignated responders specific for that type of alert.

The microbiology laboratories of a country or the world are increasingly exquisite sensors of the movements of AMR genes, genetic elements and strains that spread to make antimicrobial treatments fail and treated patients remain infected or die. The Internet now enables us to link them in an electronic sensor network with monitoring algorithms to detect, track and contain such dangers early at all levels [16]. They might, for example, alert a centre's infection preventionist that a microbe is first of its phenotype there but seen at other centres, alert microbiology to save it for sequencing, and alert area public health that this centre is now added to the list of those with this phenotype.

4.3. Why comprehensive?

Current AMR surveillance protocols typically collect and analyse small microbiology laboratory data subsets annually usually in one way (%RIS for a few priority species) for a few priority pathogens and specimen types from a limited number of sentinel healthcare facilities in an area. It overviews magnitude and trends in AMR and can be used to guide antimicrobial selection. Advancing informatics, however, now enables surveillance of AMR not only in aggregate but also in rich comprehensive detail, including all microbes tested by all laboratories in a region.

AMR surveillance needs to include all laboratories to minimise blind areas. People in many parts of the world lack access to microbiology laboratories. They may know little about local causes of infection and resistance rates, and laboratory data from locally relevant surveillance sites would help. Even in areas with laboratories, including all data from all of them can detect sooner new problems arriving in any and enable that place to recognise it as new—no other place has had it—or as one that has arrived from elsewhere [17,18].

AMR surveillance needs to include all laboratories for patient safety. The examples here show how automated surveillance can detect early and help contain emerging hazards that might otherwise go unnoticed. This can be done with data from one centre but is better from a network that can discern automatically that a problem now emerging at one centre has just arrived at, and especially needs containment at, another. As these types of initiative go forward it may be seen that every microbiology laboratory needs to participate in automated multicentre near-real-time comprehensive surveillance of AMR to provide full safety for its patients.

These observations, taken together, point to a future facilitated by the growing availability of information technology in which any report by a microbiology laboratory to a patient about a microbe found in a specimen from that patient can be accompanied by an automated report of the characteristics and distribution of that particular microbe locally and globally. The newly established WHO GLASS initiative brings the concept of truly global collaboration closer to reality.

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Competing interests

None declared.

Ethical approval

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