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Towards a global antibiotic resistance surveillance system: a primer for a roadmap

HAJO GRUNDMANN

Department of Medical Microbiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Abstract

The need for global data about the scale of antibiotic resistance (ABR) in a geographical explicit and timely manner has been identified by many stakeholders, including the World Health Organization. This primer should help defining the objectives, scale, scope, and structure of possible future efforts. Stakeholders and their expected information demands were identified to generate an inventory of surveillance objectives. For simplification, an original approach was chosen to bundle sets of objectives that represent common demands and can be addressed by common subject areas, which fall into three areas. Subject area I addresses clinical demands and focuses on patients; subject area II addresses public health demands by focusing on meta-populations; subject area III addresses infection control demands and focuses on pathogens. A division into these areas leads to a separation of surveillance activities suggesting a modular approach which can provide complementary information. Moreover, the modules address the conundrum of ABR at the complementary levels of 1) patient, 2) population, and 3) pathogen, which—rather conventionally—follow the operational and professional fault-lines of the main disciplines involved, namely clinical medicine, public health, and biology. Essential features that define different surveillance systems have been listed and taken into consideration when suggesting templates for future efforts. Putting ABR on the global health map is a daunting task as it requires acceptance, agreements, and engagement but also concessions at many different levels. Given the existing gaps in the global diagnostic service landscape only a step-wise approach which defines achievable aims, objectives, and milestones will succeed to produce a sustainable system of international co-operative surveillance of ABR.

Key words: *Antibiotic resistance, bacterial infections, capacity building, epidemiology, global health, public health, surveillance, whole-genome sequencing*

Introduction

The remarkable discoveries of antibiotic agents between the 1930s and 1960s provided mankind with medicines that could for the first time cure bacterial infections with somewhat predictable success (1). Although far from equitably available, access to antibiotics has increasingly become democratized over the last 20 years. This is the result of the bulk manufacturing of generic antibiotic compounds in emerging market communities, making antibiotics more available and affordable. However, this honeymoon period is likely to come to an end through a continuous erosion of antimicrobial effectiveness. Three contemporaneous developments are held responsible for the current decay: 1) large-scale selection for antibiotic-resistant bacteria by appropriate and inappropriate antibiotic use, 2) dispersal by international high-volume transport, and 3) failure of the market to address dwindling drug resources, causing a lack of compensatory innovation and development. In order to monitor the current situation and adjust to the trajectories of this disquieting transition, the need for global data about the scale of antibiotic resistance (ABR) in a geographically explicit and timely manner has been identified by many

Correspondence: Professor Hajo Grundmann, Department of Medical Microbiology, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands. E-mail: h.grundmann@umcg.nl

stakeholders including the World Health Organization (WHO) who has been committed to ABR surveillance since 1982 (2-5) but with little success. Therefore, there have been repeated calls for international collaboration on ABR surveillance which have lately been reiterated on World Health Day 2011 (6).

With this primer, a prioritization process about strategic choices on how to forge an international collaboration that monitors the spread of ABR through surveillance should be facilitated. This primer should also help defining the objectives, scale, scope, and structure of possible future efforts and prepare the arguments for the discussions that would lead to an informed consent.

By listing the relevant stakeholders and their expected information demands an inventory of surveillance objectives was created. A pragmatic approach was chosen to address different sets of objectives by suitable approaches that would give form to emerging surveillance efforts to be introduced over global geographic scales.

ABR and its clinical significance and epidemiology

The loss of antibiotic effectiveness threatens the success of modern medical interventions at all levels of health care (primary, secondary, and tertiary). At all administrative levels (local, regional, national, continental, and global), this creates a set of specific challenges for diagnostic, therapeutic, and public health interventions that need to be addressed by graded responses (7). Ignoring HIV, tuberculosis (TB), and malaria for the time being (for which dedicated surveillance systems are already in place), the clinically and epidemiologically most important pathogens that have become resistant against available anti-infective drugs consist of common bacteria, most of which are characterized by a predominantly opportunistic behaviour (8,9). The health effects they have on the vulnerable segments of societies, i.e. the young, the elderly, and patients in hospitals, have not been quantified and certainly accrue a significant burden of disease globally (2). Another feature that sets antibiotic-resistant bacteria apart from other perceived threats to public health (such as emerging infections, zoonoses, bioterrorism, and pandemic influenza) is the accelerating dynamic which makes this health threat (in contrast to the threats mentioned before) even more predictable. Yet there are vast discrepancies with respect to the prevalence and degree of resistance within and between health care systems. Hospitals generally see higher rates of infections caused by ABR bacteria than community care practices. Larger or more specialized hospitals see more than smaller hospitals (10). Countries with largely unregulated dispensing and high antimicrobial consumption seemingly grapple with more resistance than countries where drug use is more restricted (11). Moreover, there are many other determinants that are not yet understood, and these may include demographic and socio-economic conditions, health care utilization patterns, health care reimbursement structures, antimicrobial use in farm animals, environmental contamination, and lack of appropriate sanitation and hospital hygiene. All this may explain the enormous geographic variation exemplified by extremes where at the high end half of all hospital patients are infected with micro-organisms that are not responding to last-line drugs (12,13) and, at the other end, countries that only sporadically report resistant isolates of any kind (14). It is therefore clear that there is an urgent need for global surveillance of ABR bacterial infections in order to address these pertinent issues.

Objectives of ABR surveillance

Stakeholders, i.e. individuals that have a stake in antibiotic effectiveness be it for personal, medical, economic, social, political, scientific, or corporate reasons, can be broadly divided into two categories, representing 1) individuals who are immediately affected by adverse health care outcomes, and 2) individuals who may be impacted by the wider repercussions of adverse health care outcomes caused by ABR. The first group consists of current and future patients (and their families), doctors, clinical microbiologists, prescribers, and drug dispensers (pharmacists). Their immediate interest lies in the clinical outcome of individual cases. The second group consists of politicians, policy-makers, economists, public health experts, health insurance companies, health managers, and infection control practitioners who are concerned because they are judged for their response to the population effects of ABR. And yet a third group can be defined, consisting of 3) scientists and researchers, pharmaceutical industry, funding bodies, and global health donors who share a wider societal or corporate responsibility. Although coming from different angles, all stakeholders have a demand for accurate and comparable surveillance data. Some of these demands can be addressed by common objectives, but the majority is quite diverse and difficult to reconcile and at times are even mutually exclusive and can probably never be addressed by a single unified surveillance approach.

For this reason and in order to simplify further discussions, an original approach was chosen to bundle sets of objectives that address demands that are common to certain groups of stakeholders. It was felt that

this approach helps clarifying the relevant issues during the prioritization process and when choices have to be made about the scale, scope, and structure (for definition see Glossary) of future collaborative surveillance efforts. In the following, a non-exhaustive inventory of surveillance objectives is presented addressing many of the common but also highly specific stakeholder demands. As can be seen, the objectives are multi-faceted but were tentatively bundled into three main subject areas and consist of the following: area I addresses clinical demands (patients); area II addresses public health demands by focusing on meta-populations (populations); area III addresses infection control demands (pathogens).

Area I: Surveillance objectives addressing clinical demands (patient-centred)

- identifying drugs with remaining effectiveness
- improving access and availability to effective drugs
- assessing prescribing patterns
- reducing indiscriminate or irrational prescribing
- reducing exposure to unreliable, ineffective, substandard, and/or potentially toxic drugs
- improving empiric treatment for better clinical outcomes

Area II: Surveillance objectives addressing policy demands (population-centred)

- quantifying the occurrence of ABR (incidence and/or prevalence)
- comparing the occurrence of ABR over time and across geographical, administrative, and/or national boundaries (trends and benchmarking)
- identifying the emergence of ABR (horizon scanning)
- estimating the impact of ABR on public health and economy (burden of disease, BoD)
- creating the appropriate awareness among stakeholders and the public (awareness)
- helping decision-makers make informed decisions about prioritization and allocation of scarce health care resources (advocacy)
- exploring market and marketing opportunities (market research)
- quantifying the consumption of antibiotics (pharmaco-epidemiology)
- identifying the determinants for ABR emergence and spread (causal inference)
- informing prevention, control, and drug policies (intervention)
- monitoring the effect of interventions (guidelines and policies)

Area III: Surveillance objectives addressing infection control demands (pathogen-centred)

- identifying and mapping of high-risk clones (HiRiCs; see Glossary) and high-risk elements (HiRiEs; see Glossary) including novel resistance traits for early warning, descriptive, and interventional approaches
- understanding the routes of transmission and the role and behaviour of vectors in the dissemination of HiRiCs
- understanding the role of different sources or reservoirs and the diffusion across interfaces between environmental, animal, and human habitats
- understanding the ecologic constraints that govern the dynamics of HiRiCs and HiRiEs

The suggested bundling of objectives into these three groups also offers an opportunity to reduce the complexity of the public health conundrum that ABR currently presents. It allows for a dissection into three complementary subject areas which—rather conventionally—follow the operational and professional fault-lines of the main disciplines involved, namely clinical medicine, public health, and biology. But probably even more important, if translated into appropriate task bundles it could lead to a separation of surveillance activities that could provide complementary information about possible improvements in case management, about the public health consequences of ABR and targeted interventions, and about the forces that shape the emergence of ABR in a more intuitive manner.

Scale, scope, and structure of ABR surveillance systems

Most existing and extinct ABR surveillance systems differ in scale, scope, and structure which makes it often *impossible to reconcile* the information that has been collected. Importantly, however, *all ABR surveillance systems can be described* by a set of simple attributes. These attributes describing their scale, scope, and structure are summarized below.

Scale

Type of surveillance. Type of surveillance distinguishes population-based from laboratory-based surveillance. In this context, laboratory-based surveillance collects susceptibility test results from microbiological specimens taken for diagnostic purposes from patients presenting with health problems, whereas population-based surveillance would draw samples

from people of defined populations such as community, hospital patients, etc.

Geo-administrative level. Geo-administrative level can be divided into surveillance that is local, national, international, continental, or global.

Sampling approach. Sampling approach can be divided into *active surveillance* through active bacteriological screening of populations or patients on a sample or more comprehensive basis (on the occasion of household visits, school admissions, visits to health centres, or on a single day in the hospital, etc.) or *passive surveillance* based on clinical specimen submitted to microbiological laboratories for diagnostic purposes.

Choice of surveillance sites. In comprehensive surveillance all possible reporting sites are requested to collect information (e.g. for national mandatory reporting), whereas in case of sentinel surveillance only a chosen set of sites (GPs, health centres, or laboratories) provide information.

Scope

Operational unit of surveillance (OUS). Operational unit of surveillance (OUS) is the marker or determinant for a health state which is recorded and reported. For laboratory-based ABR surveillance the conventional OUS consists of the proportion of isolates of a defined bacterial species resistant to a particular antibiotic compound (percentage resistance per pathogen compound combination). This can be stratified per type of infection to guide recommendations for empiric antibiotic treatment. In population-based surveillance, individuals (i.e. cases) affected or colonized with resistant bacteria may represent the OUS using a case definition and then counted to obtain incidence and prevalence figures for a defined population. For antibiotic consumption it is the amount of any antibiotic compound dispensed or administered to patients or animals. There are many other additional metrics that can be considered.

Species and compound. Species and compound refer to which named species of bacteria or which antibiotic compound or class is included into the reporting scheme. The selection may contain all bacteria isolated from clinical specimens (or all antibiotics dispensed or administrated) or a subgroup of indicator bacteria or compounds. The latter lends itself to an easier standardization of protocols, quality control, and

external quality assessment. The former provides a more comprehensive picture and can be used to calculate drug resistance or effectiveness indices. The same applies to the susceptibility patterns that should be recorded. In existing surveillance schemes there is often an agreed protocol describing for which antibiotic compounds susceptibility data should be recorded.

Anatomical site. Anatomical site refers to the selective reporting of bacteria isolated from defined anatomical origins. In this manner a distinction between clinically relevant (infection-causing) bacteria and potential colonizers or contaminants may be easier especially if bacteria from primarily sterile anatomical sites are selected (such as blood, cerebral-spinal fluid, puncture fluids, mid-stream or catheter urine).

Primary isolates. Primary isolates refer to an elimination of redundancy by reporting only isolates of bacteria identified for the first time per patient per time period. For simplicity the European Antibiotic Resistance Surveillance Network (EARS-Net) treats primary isolates as first bacterial isolate per species, per patient, per year.

Data. Data refer to the agreement on which data (per bacterial isolate and patient) will be reported and included into the database.

Structure

Aggregation level. Systems with data aggregation at different levels are possible. However, fully anonymized, non-aggregated data are the preferred data set as this allows for the testing of data consistency, biological plausibility, and the elimination of redundancy before acceptance and synchronization with a central database.

Organizational structure. Organizational structure refers to the degree of centralization of surveillance systems. Fully centralized systems collect data and isolates (for confirmation purposes) in central facilities, whereas fully distributed systems collect only aggregated information at defined time intervals. There are different degrees of compromise between these extremes. EARS-Net, for example, uses a hierarchically distributed system requiring only a defined data set (consisting of fully anonymized, non-aggregated data) for reporting to central level and leaving the reference laboratory work, data ownership,

and data management to institutes at national level (federated approach).

Funding sources. Funding sources can be public, private, or mixed in the form of private–public partnerships.

Surveillance addressing clinical demands: module 1, the patient-centred approach

Strategic aim

The aims of this type of surveillance consist of improving patient treatment by optimizing the empirical antibiotic treatment choices. This should lead to a reduction of inappropriate antibiotic administration and at the same time enable the critical appraisal of the availability of essential drugs. Patient-level surveillance is the most pervasive argument for patient safety, which can guide antibiotic treatment by local epidemiology (15). Obviously for the data to be relevant for treatment decisions, they need to be generated locally (laboratory-based), in a timely fashion, and should be stratified by type of infection.

Operational unit of surveillance (OUS)

The OUS is the proportion resistance encountered per type of infection and antibiotic compound (see above). This is obtained by measuring the proportion (percentage) resistance per pathogen compound combination stratified by the etiologic fraction of pathogens associated with the infection under surveillance. A variation of this scheme is the drug resistance index which factors local antibiotic use and availability into the equation (see text box 1).

Scale

Principally conceived as a tool for local epidemiology, this approach should consist of laboratory-based passive surveillance providing representative data for the catchment of a single health centre or health care collective (see Glossary).

Scope

In order to exploit the full potential of this surveillance approach, local data collection should include isolates from all anatomical sites as well as a comprehensive range of antibiotic susceptibility test results covering all antimicrobials available for treatment in that centre. Local data management can also easily record antibiotic prescribing patterns allowing for the calculation of the drug resistance index (DRI), if desired.

Structure

Modern information technology would allow regional or indeed national linkage of data through real-time collection of authorized test results with laboratory-specific national data aggregation and feedback via individualized and password-protected web access. This has been already achieved in many countries such as Denmark, Sweden, the Netherlands, and the UK. The data form the decision basis for needs-adapted and locally relevant treatment guidelines which are essential for optimized and rational antimicrobial prescribing. National networking of local data at this scale is, however, technically and managerially rather demanding. It requires agreements on IT interfaces, data fields, and semantic standards (see Glossary). If achievable at a higher geo-administrative level, these data become a rich source that can inform standard treatment guidelines and essential drug lists. Given that the DRI can approximate the fraction of infections that cannot be treated successfully at the current level of access and resistance, it can also be used as a crude indicator for the expected burden of disease (BoD) at any given geo-administrative level.

Text box 1: The drug resistance index

Quantifying antibiotic resistance for each pathogen compound combination separately is only understood by experts. A more meaningful way of defining the burden of antibiotic resistance would aggregate this information into a single index. Such a drug resistance index (DRI) has been recently suggested (16). It combines the antibiotic resistance against all available compounds into an average, weighted by each compound's use. In this manner, a single value can describe the average effectiveness of antibiotic treatment administered in a single facility. The observed prescribing pattern typically adapts to the local antibiotic resistance when antibiotic susceptibility test results are reported to clinicians by a microbiological laboratory. Thus, the index would represent an 'adaptive drug resistance index' that takes into account prescribing which adjusts to the local resistance patterns. It would assume values between 0 and 1, whereby 1 indicates the extreme that current prescribing would be 100% ineffective given the local resistance pattern. The elegance of indexing lies in the ability to describe the decay of antibiotic effectiveness over time as the antibiotic prescribing pattern can be fixed to a baseline year, i.e. if prescribing had not adapted to a changing antibiotic resistance pattern ('fixed DRI'). Moreover, an additional index can be determined in situations where treatment options are restricted by availability or access, or by public health decisions such as an essential drug list or an existing standard treatment guideline. This 'restricted DRI' determines the treatment effectiveness given these constrains in drug use. Indexing therefore provides a compelling tool for influencing decisions at various levels of health care and the public health cascade: at the bedside, for local drug and therapeutics committees, and at the highest policy and public health management level

Surveillance addressing public health demands: module 2, the population-centred approach

Strategic aim

Instead of providing the fine-scale information at a per patient per infection level, the aim of this approach is to generate reliable estimates about how far ABR has already encroached on populations determining the size of ABR as a national and international public health problem. This should furnish the means to put ABR not only into the context with other public health threats but also to identify population-level determinants that can be linked to ABR emergence. Information can be used for benchmarking and monitoring of the effects of interventions. Feedback to stakeholders will create the necessary awareness and the recognition of antimicrobial effectiveness as a scarce or non-renewable resource influencing consumer choices, policies, and investment into drug development. Some of today's continental networks (such as EARS-Net, and Red Latinoamericana de Vigilancia a las Resistencias Antimicrobianas, ReVALA) already collect and report these types of data and have had a documented and measurable impact on national strategies (17).

Scale

Obviously, the gold standard for population-level surveillance would be active, population-based screening for carriage or infection with ABR bacteria allowing for the quantification of ABR prevalence. However, experience with existing systems has shown that laboratory-based passive surveillance at a selected number of sentinel sites satisfies the information needs if the sampling condition remains constant and the sample is representative for a defined target population. The downside of this approach is that a population incidence or prevalence cannot be easily established because the population denominators are difficult or impossible to assess. The degree of granularity, i.e. the geographic resolution of measurements, depends on the number of laboratories that can be recruited into the surveillance scheme. Low numbers scattered over wide geographical regions will decrease the confidence in the estimates. Selection of merely tertiary care institutions will most probably increase the resistance proportions. Experience with the EARS-Net, however, shows that national surveillance networks are quite resilient to sample variation and only a small number of sentinel sites (less than 20% of national hospitals) are required in order to provide relatively robust estimates of average national ABR proportions Ciccoilni et al. (unpublished data).

Scope

The principal OUS is the proportion resistance per pathogen compound combination expressed as a percentage. However, as a concession to practicality, decisions should be taken about the scope of data to be recorded. It has been shown that restrictions, i.e. limiting the data, reduce the workload for designated sentinel laboratories and thus improve acceptability, conciseness, comparability, and coverage of the surveillance initiative.

An agreement about limiting the reporting to a few indicator bacteria and indicator compounds would be a worthwhile consideration. Restricting the reporting of susceptibility data to the clinically and epidemiologically most important COBPs (cosmopolitan opportunistic bacterial pathogens; see Glossary) provides meaningful information for public health purposes. This simplifies the implementation of standard diagnostic protocols, of quality assurance and assessment schemes, and therefore improves diagnostic quality, data validity, and comparability. Globally, COBPs are responsible for the fastest expansion of resistance and arguably cause the highest burden of disease associated with ABR. Moreover, their cosmopolitan nature makes them versatile markers for local differences in resistance. This advantage would probably outweigh the drawback that some important obligate pathogens such as TB and *N. gonorrhoeae* would have to remain the remit of existing dedicated surveillance systems. A clear disadvantage would be that an emergence of ABR in species other that indicator organisms may be missed.

Susceptibility data can be reported for bacteria isolated from normally sterile anatomical sites (invasive isolates), which excludes the majority of unwanted contaminants or colonizers of bacteria of doubtful clinical significance. This could minimize the introduction of heterogeneity and improve comparability between reporting laboratories. Moreover, laboratories are more likely routinely to carry out susceptibility testing of invasive isolates over non-invasive ones as they attain clinical priority. The disadvantage would be that some bacteria causing other important infections such as upper and lower airway infections, or diarrhoeal disease, remain excluded.

To report only routinely generated susceptibility data could be another concession to practicality. The main advantage lies in data availability and potential ease of reporting. These data have public health relevance as they are a reflection of the ABR problems that become visible and to which doctors adjust their prescribing. However, there are also disadvantages. Susceptibility data are mostly from patients treated in hospitals. Although they represent the vulnerable

patients who frequently attend hospitals and develop infections with COBPs, they are not necessarily representative for patients in the community and often harbour hospital-acquired bacteria which are more resistant. Moreover, there are issues of health care utilization, sampling frequency, and diagnostic habits. Unequal sampling represents the most important threat to data comparability and needs to be addressed by agreed diagnostic protocols according to good diagnostic standards, regular reporting of sampling density, and audit.

Finally, susceptibility data should only be reported for primary isolates. In a very pragmatic manner, primary isolates can be defined as first isolates per species per patient per defined period. This excludes bias introduced by repeated sampling of frequent health care attendants, which also tends to contribute more resistant bacteria.

Structure

Surveillance addressing policy demands would follow the laboratory-based sentinel model. A minimum set of criteria would be required for a sentinel site to participate in a national network. The criteria would include health centres/laboratories which 1) provide health services to patients who are representative for a geo-demographically defined catchment population, 2) utilize microbiological laboratory services according to acceptable diagnostic standards, 3) adhere to agreed laboratory protocols, 4) use agreed clinical susceptibility breakpoints that are internationally recognized (Clinical Laboratory Standards Institute, CLSI; or European Committee for Antimicrobial Susceptibility Testing, EUCAST), 5) have in place an acceptable laboratory information management system, 6) have a dedicated data manager, and 7) participate in national/international quality assurance/assessment schemes. Sentinel sites report test results on a per isolate basis to national data portals. This allows for an exclusion of non-primary isolates, biological plausibility testing of reported susceptibility patterns, data quality control and monitoring of sampling density, and immediate feedback for quality improvement. National data managers will bundle local data and submit bundles at predefined intervals to central databases.

Surveillance addressing infection control demands: module 3, the pathogen-centred approach

Strategic aim

Pathogen level surveillance utilizes the genetic/genomic information to determine the ancestral relationship between any two micro-organisms. If place and sampling date can be included, it can be used to map and track bacteria at all geo-temporal scales. This is not only useful for the identification of transmission and outbreaks but also to uncover the reservoirs and origins of emerging high-risk clones (HiRiCs; see Glossary). Data at this level will provide answers about the relationship between the emergence of resistance in different ecological niches such as humans, animals, or the environment and their spread between hosts and across the interfaces between these respective habitats. Moreover, pathogen surveillance allows for the early detection of potential HiRiCs or high-risk genetic elements (HiRiEs; see Glossary) that convey antibiotic resistance, virulence, or transmissibility and is thus an essential part of surveillance for early warning and response.

Scale

Population snapshots for bacterial species can be generated for clinical isolates collected during structured surveys. These surveys take advantage of existing surveillance networks asking centres to collect isolates using a standardized sampling frame. With the enrolment of representative hospitals that provide services to sufficiently large catchment populations and a distribution that matches the geo-demographic structure of the participating country, data will provide meaningful information. This allows for an unbiased sample that informs the infection control audience about the geographic spread, transmission clusters (outbreaks), and importation of clones with particular public health importance. Moreover, isolates with unusual or novel properties identified during routine diagnostics or surveillance can also be collected and submitted and the information compared with existing population snapshots to determine their likely origin and date of emergence.

Scope

The principal operational unit of surveillance (OUS) is a measure of the genetic similarity between any two bacterial isolates determined by genetic typing. This can be accomplished in different ways using typing methods that provide biologically meaningful data (such as DNA sequences) that are robust, sufficiently discriminatory, and which are portable and unambiguous. Whole-genome sequencing (WGS) has recently emerged as the gold standard and is becoming increasingly affordable (see Text box 2). With this technique, similarity can be tabulated in evolutionary time-scales (time to the most recent common

ancestor), and resulting phylogenies can be super-imposed with epidemiological information.

Typing tools can be furnished at different levels of the ABR surveillance cascade and inform infection control experts about potential transmission and outbreak situations (18,19). More in-depth investigations will focus on particular species of COBPs that have been identified as important sources of HiRiCs and HiRiEs. Typical examples are *Staphylococcus aureus* known for the emergence of international clones of hospital-, community-, or livestock-associated MRSA, or *Klebsiella pneumoniae* which has been identified as one of the major reservoir hosts of extended-spectrum beta-lactamases (ESBLs) and carbapenemases.

Structure

This is a more advanced surveillance approach that requires a network of well-equipped reference laboratories. But considering the decrease of prices for WGS and the wealth of important public health information (about the origin and ecological forces that determine the success and abundance of HiRiCs) it can be expected that this technique will soon be regarded as crucial for international surveillance efforts in order to identify HiRiCs in a timely manner and inform early warning and response. Network participants reveal the required level of proficiency through their submission of sequence data that allow for simple quality assessment. To that end, databases need to be freely accessible to all relevant stakeholders, easy to use, and provide geographically explicit information.

Implementation

The challenge to put ABR on the global health map is to make the invisible visible. This has been a daunting

task, conceptually and practically. Conceptually it calls for the unconditional acceptance of germ theory and the principles of antimicrobial chemotherapy, the recognition of natural selection (or, more appropriate in this context, artificial selection), and the acknowledgement that laboratory-based analysis of specimens taken from patients can improve the understanding of disease processes. Practically it is daunting because it requires skills and competences and advanced equipment that is typically only present in diagnostic laboratories associated with well-equipped health care centres. It is for these reasons that networks for the surveillance of ABR operative at a global scale cannot be built instantaneously but require a guided developmental process.

Considering the potential demands and the gaps in the diagnostic service landscape especially in low- and middle-income countries (LMICs) a step-wise approach edging towards a full-fledged international surveillance initiative is the most likely scenario. Not all regions need to move at the same speed.

This step-wise approach would entail an agreement on prioritization of objectives and strategic aims. In this respect the modular approach suggested above may serve as a model. It should be emphasized that the modules suggested above are by no means the final conclusion but represent a workable solution to a conundrum that very unlikely will be addressed by a single system. All modules can be implemented independently or in a step-wise manner, whereby module 2 requires the least initial investment in terms of structure and capacity building. Conversely, it could be envisaged that in underserved regions some health centres/laboratories start implementing local data collection according to module 1 and then consider networking towards module 2. Clearly, module 3 requires a network of reference laboratories as suggested elsewhere before (20). Whatever the choice, all planning steps should detail the visions

Text box 2: Whole-genome sequencing.

Whole-genome sequencing (WGS) is the only way reliably to describe the genetic background and genetic repertoire including resistance and virulence markers of bacterial pathogens. The current epidemic of ABR is caused by the spread of HiRiCs or mobile genetic elements that encompass antibiotic resistance genes. Acquisition of these mobile genetic elements does not always raise minimal inhibitory concentrations (MICs) above the accepted clinical breakpoints (defined as susceptible = S, intermediate = I, or resistant = R), meaning that conventional susceptibility testing may miss the presence of HiRiEs in non-permissive genetic backgrounds. If the origins and reservoirs of emerging ABR are to be reliably identified and mapped on a global scale, there will be no other choice than searching the genetic contents of bacteria as the spread of certain extended-spectrum beta-lactamase genes (ESBL) and carbapenemase genes could otherwise be missed. Phenotypic methods based on internationally accepted breakpoints (S,I,R methods) are a good guidance for clinical treatment but have a limited epidemiological sensitivity. Sequencing provides not only information about presence and absence about genes or mutations associated with antibiotic resistance but is the most precise method to determine the genetic relatedness of different isolates which allows for a reconstruction of the population history and identifying the origins of HiRiCs and HiRiEs on geo-temporal scales

While the prices for WGS are decreasing, the amount of data generated increases in an exponential fashion that dwarfs the development of personal computing power during the last 20 years (Moore's law). Indeed, dynamics are four times faster. Results are quickly generated using bench-top equipment, and pipelines are under development which can deal with the amount of data, to zoom in swiftly on targets of choice. The price for sequencing at the time of writing is about $100 per whole bacterial genome at specialized genome centres but also using third-generation personalized genome sequencing equipment

for the layout of the total network, and it may be worthwhile to consider three different stages: 1) the near future (achievable within 2–5 years), 2) the medium term (achievable within 5–10 years), and 3) the long term (achievable within 10–15 years).

Based on agreed objectives and strategic aims, a criteria catalogue needs to be set up that describes the minimum requirements for the enrolment of diagnostic laboratories as potential sentinel sites and for the national and regional structures that need to be realized. These criteria will also clarify to what extent already existing surveillance networks can be utilized. To be able to assess the capability of existing networks to form part of a future international network alliance, a detailed inventory of the scale, scope, and structures of existing initiatives is an important first step.

Following the appraisal of existing networks with regard to the set objectives, strategic aims, and minimum requirements, the outline of the 'near-future' achievable network should become visible. It will then be the task to define realistic goals/milestones per country and/or region. This will allow for tallying upgrading and investment demands with respect to the structure of national and regional surveillance networks, external quality assessment exercises, reference services, and resource procurement. Budgeting should include the near-future funding demands, but also medium- and long-term volumes for investment.

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References

1. Greenwood D. Antimicrobial drugs. Chronicle of a twentieth century triumph. Oxford, UK: Oxford University Press; 2008.
2. Laxminarayan R, Duse A, Wattal C, Zaidi AK, Wertheim HF, Sumpradit N, et al. Antibiotic resistance-the need for global solutions. Lancet Infect Dis. 2013;13:1057–98.
3. WHO. 1981. WHO Meetings – Antimicrobial Resistance. Available at http://whqlibdoc.who.int/HQ/pre-wholis/WHO BVI PHA ANT 82.1.pdf.accessed 3 March 2014.
4. WHO. 1982. WHO Meetings – antimicrobial resistance. Available at http://whqlibdoc.who.int/hq/pre-wholis/BVI PHA ANT 82.2.pdf.accessed 3 March 2014.
5. WHO. 1994. WHO Meetings – antimicrobial resistance. Available at http://whqlibdoc.who.int/hq/1995/WHO CDS BVI 95.7.pdf.accessed 3 March 2014.
6. WHO. 2011. World Health Day – 7 April 2001. Antimicrobial resistance: no action today, no cure tomorrow. Available at http://www.who.int/world-health-day/2011/en/.accessed 3 March 2014.
7. WHO. 2001. Surveillance standards for antimicrobial resistance. Available at http://whqlibdoc.who.int/hq/2002/WHO_CDS_CSR_DRS_2001.5.pdf.accessed 3 March 2014.
8. Ashley EA, Lubell Y, White NJ, Turner P. Antimicrobial susceptibility of bacterial isolates from community acquired infections in Sub-Saharan Africa and Asian low and middle income countries. Trop Med Int Health. 2011;16:1167–79.
9. Zafar A, Hussain Z, Lomama E, Sibille S, Irfan S, Khan E. Antibiotic susceptibility of pathogens isolated from patients with community-acquired respiratory tract infections in Pakistan–the active study. J Ayub Med Coll Abbottabad. 2008;20:7–9.
10. Donker T, Wallinga J, Grundmann H. Patient referral patterns and the spread of hospital-acquired infections through national health care networks. PLoS Comput Biol. 2010;6: e1000715.
11. Goossens H, Ferech M, Vander Stichele R, Elseviers M; ESAC Project Group. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. Lancet. 2005;365:579–87.
12. Saleem AF, Ahmed I, Mir F, Ali SR, Zaidi AK. Pan-resistant Acinetobacter infection in neonates in Karachi, Pakistan. J Infect Dev Ctries. 2009;4:30–7.
13. Perry JD, Naqvi SH, Mirza IA, Alizai SA, Hussain A, Ghirardi S, et al. Prevalence of faecal carriage of Enterobacteriaceae with NDM-1 carbapenemase at military hospitals in Pakistan, and evaluation of two chromogenic media. J Antimicrob Chemother. 2011;66:2288–94.
14. ECDC, 2013. Surveillance report. Antimicrobial resistance surveillance 2012. Available at http://ecdc.europa.eu/en/publications/Publications/antimicrobial-resistance-surveillance-europe-2012.pdf.accessed 3 March 2014.
15. Paterson DL. The role of antimicrobial management programs in optimizing antibiotic prescribing within hospitals. Clin Infect Dis. 2006;42:S90–5.
16. Laxminarayan R, Klugman KP. Communicating trends in resistance using a drug resistance index. BMJ Open. 2011;1: e000135.
17. Allerberger F, Gareis R, Jindrák V, Struelens MJ. Antibiotic stewardship implementation in the EU: the way forward. Expert Rev Anti Infect Ther. 2009;7:1175–83.
18. Reuter S, Ellington MJ, Cartwright EJ, Köser CU, Török ME, Gouliouris T, et al. Rapid bacterial whole-genome sequencing to enhance diagnostic and public health microbiology. JAMA Intern Med. 2013;173:1397–404.
19. Harris SR, Cartwright EJ, Török ME, Holden MT, Brown NM, Ogilvy-Stuart AL, et al. Whole-genome sequencing for analysis of an outbreak of meticillin-resistant Staphylococcus aureus: a descriptive study. Lancet Infect Dis. 2013; 13:130–6.
20. Grundmann H, Klugman KP, Walsh T, Ramon-Pardo P, Sigauque B, Khan W, et al. A framework for global surveillance of antibiotic resistance. Drug Resist Updat. 2011;14: 79–87.

Supplementary material available online
Appendix: Glossary