A framework for global surveillance of antibiotic resistance

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\textbf{Abstract}

The foreseen decline in antibiotic effectiveness explains the needs for data to inform the global public health agenda about the magnitude and evolution of antibiotic resistance as a serious threat to human health and development. Opportunistic bacterial pathogens are the cause of the majority of community and hospital-acquired infections worldwide. We provide an inventory of pre-existing regional surveillance programs in the six WHO regions which should form the underpinning for the consolidation of a global network infrastructure and we outline the structural components such as an international network of reference laboratories that need to be put in place to address the void of these crucial data. In addition we suggest to make use of existing Health and Demographic Surveillance Sites (HDSS) to obtain crucial information from communities in resource limited settings at household level in low- and middle-income countries in Asia and Africa. For optimising the use of surveillance data for public health action i.e. priority setting for new drug development, comparative quantification of antibiotic effectiveness at local, national, regional and global level and identification of the action gaps can be helpful.

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And indeed, everything that one can discern has numbers, hence it is impossible to grasp or recognize anything without them.
Philolaos of Kroton, 440 BC

1. Introduction

Trends in antibiotic resistance and their consequences for health, welfare and the economy are rapidly changing (ECDC, 2010a). Antibiotic resistance threatens the success of medical interventions at all levels of health care and creates a set of specific challenges for clinical, therapeutic and public health interventions with local, national, and global dimensions.

Bacteria that belong to the normal flora in humans become indiscriminately exposed to antibiotic compounds every time antibiotics are used. Therefore, the most significant resistance has been emerging among these microorganisms. Since most of them are truly opportunistic pathogens, the most vulnerable segment of societies i.e. the young, elderly and immune-compromised are likely to face infections and the consequences of failing antibiotic effectiveness. Moreover (and this is in contrast to other infectious diseases perceived as threats to public health like zoonoses, bioterrorism and pandemic influenza), the trajectory of antibiotic resistance is rather predictable. Still, no surveillance system exists that would allow measuring the magnitude of antibiotic resistance as a threat to global health.

We argue that inequalities and market forces facilitate and accelerate the critical decline of antibiotic effectiveness and that
within the next 5–10 years untreated (or next-to-untreatable) community- as well as hospital-acquired infections will become widespread. This relentless dynamic is caused by often unwanted consequences of the evolving socio-political and physical environment in which we live. Current volume, speed and reach of travel and migration are unprecedented. Increasing civil unrest, food shortages and natural disasters leave vulnerable individuals under crowded conditions. Other economic and behavioural changes also impact on the pattern of antibiotic consumption worldwide. As the result of global medicalisation in the wake of the expansion of the HIV/AIDS pandemic and successful prevention campaigns that followed, recent patient generations around the world have been brought up with the tacit conviction that microbes are causing disease. This has lead to an overwhelmingly changed pattern of health seeking behaviour especially in poorer societies. It explains the growing demand for antibiotic chemotherapy, which, at the same time, is met by the availability of generic compounds produced in emerging market communities. Thus, it will come as no surprise that there will be a massive increase in antibiotic consumption while antibiotics become commodities in unregulated markets. In the following chapter we will describe in more detail how market forces contribute to the decay of antibiotic effectiveness and why a global surveillance effort is urgently needed.

2. Engines of resistance

Antibiotic resistance is driven by the density of antibiotic use, combined with the level of compliance with infection control measures to prevent spread of resistant bacteria. At the population level, several studies have shown a correlation between outpatient use of an antibiotic class and the percentage of bacterial isolates resistant to this class (Albrich et al., 2004; van de Sande-Bruinsma et al., 2008). This relationship between antibiotic use and resistance has also been demonstrated at the hospital level, for example for the carbapenems (Lepper et al., 2002; Lopez-Lozano et al., 2000).

Herrmann developed a dynamic, bio-economic model to better understand the pricing policy of a company which holds the monopoly for an antibacterial compound (Herrmann, 2010). This model revealed three phases: (i) under patent protection when the monopolist endogenously manages the level of antibiotic efficacy (quality) and the infected population (market size); (ii) approaching the end of patent protection when the monopolist behaves more and more short-sightedly, leading to a continuous decrease in the price of the antibiotic; and (iii) after patent expiration when the monopolist behaves competitively in a generic industry, which results in a discontinuous fall of price of the antibacterial (Herrmann, 2010).

These results were recently confirmed by Jensen et al. (2010) who reported on the effects of patent loss and generic entry on ciprofloxacin price, sales and resistance in Denmark. The Danish study showed that, within one year following patent loss, the number of formulations of ciprofloxacin increased from 3 to 10 and the median price per defined daily dose (DDD) decreased by 53%. During the four years following patent loss, outpatient consumption of ciprofloxacin increased by more than 250% and the proportion of *Escherichia coli* from urine samples that were resistant to ciprofloxacin increased by 200% (Jensen et al., 2010). In Europe, outpatient consumption of antibacterials is significantly correlated with the number of antibacterial trade names (Monnet et al., 2005). This relationship was found both in situations where the antibacterials were still protected by a patent and in situations where the market was opened to generic copies of original agents (Monnet et al., 2005).

Consumption of antibacterials varies widely between countries (Goossens et al., 2007) and is significantly correlated with per capita gross domestic product (GDP)/(ReAct, unpublished data). Countries with a low per capita GDP also report low average consumption of antibacterials per capita, which is likely due to poor access to these medicines or only access through informal channels because of low individual resources and poor infrastructures. However, the United Nations report that per capita GDP is growing rapidly in many low per capita GDP countries such as China and India but also Brazil, Indonesia, Mexico and Turkey (UN, 2010). In emerging markets, this results in an increase in the sales of pharmaceuticals in general (IMS, 2010) and of antibacterials in particular (LeadDiscovery, 2009).

Newly industrialized countries increasingly contribute to the production of antibacterials and research-based companies and global generic manufacturers have been reported to sign agreements with or invest in generic companies and production facilities in newly industrialized countries (Biospectrum Asia, 2009; Morey, 2010; Singer, 2010). Several last-line, intravenous antibacterials, including the carbapenems imipenem–cilastatin and meropenem, and the penicillin-beta-lactamase inhibitor combination piperacillin–tazobactam, recently lost patent protection and are now available as cheaper, generic presentations from manufacturers in newly industrialized countries. The manufacturers already received approval or have filed applications for their generics in the United States (FDA, 2011; Golikera, 2010) and in European countries (IMS, 2010).

The data presented above describe a gloomy scenario for antibiotic resistance in the near future: increasing availability of lower priced, generic presentations of last-line, intravenous antibiotics such as the carbapenems will result in increasing use in most countries, which in turn will result in increasing resistance of these antibiotics. In regions of the world with low sanitation coverage and sub-optimal hospital infection control practices, this will promote spread of almost totally resistant bacteria such as carbapenemase-producing *Enterobacteriaceae*. Global travel, global healthcare and medical tourism, will further contribute to global spread of these almost totally resistant bacteria.

This scenario started to unfold in 2010 with the report of cases of New Delhi metallo-beta-lactamase-1 (NDM-1)-producing *Enterobacteriaceae* in patients in the United Kingdom, mainly associated with travel or healthcare contact in the Indian subcontinent (Kumarasamy et al., 2010). NDM-1-producing *Enterobacteriaceae* have since been reported from many countries, in particular in North America, Europe and Asia (CDC, 2010; Chihara et al., 2011; Mulvey et al., 2011; Struelens et al., 2010; Wu et al., 2010). The rapid spread of another carbapenemase, OXA-48, reported in Mediterranean countries, in Europe and recently in Sub-Saharan Africa represents another example of this scenario (Carrer et al., 2010; Moquet et al., 2011). In the latter report from Senegal, five patients died from their infection before antimicrobial susceptibility testing could be completed and proper therapy administered. These recent developments clearly illustrate the urgent need for a global surveillance data that can inform clinicians, public health experts, policymakers and pharmaceutical companies about the dynamic spread of antibiotic-resistant pathogens in a geographical explicit and timely manner.

3. Surveillance of antibiotic resistance: the emerging opportunity for a global network infrastructure

The WHO Global Strategy for Containment of Antibiotic Resistance (UN, 2001) recognized laboratory-based surveillance of antibiotic resistance as a “fundamental priority” for the development of strategies to contain antibiotic resistance and for assessment of the impact of interventions. In face of the above mentioned dimensions of antibiotic resistance as a threat to public health, many countries have established national and regional
Table 1
Estimate of WHONET software use by WHO region.

<table>
<thead>
<tr>
<th>WHO region</th>
<th>Number of countries</th>
<th>Number of laboratories</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFRO = WHO Regional Office for Africa</td>
<td>13</td>
<td>69</td>
</tr>
<tr>
<td>EMRO = WHO Regional Office for the Eastern Mediterranean</td>
<td>15</td>
<td>64</td>
</tr>
<tr>
<td>EURO = WHO Regional Office for Europe</td>
<td>39</td>
<td>505</td>
</tr>
<tr>
<td>AMRO/PAHO = WHO Regional Office for the Americas/Pan American Health Organization</td>
<td>25</td>
<td>466</td>
</tr>
<tr>
<td>SEARO = WHO Regional Office for South-East Asia</td>
<td>6</td>
<td>105</td>
</tr>
<tr>
<td>WPRO = WHO Regional Office for the Western Pacific</td>
<td>13</td>
<td>568</td>
</tr>
<tr>
<td>Total</td>
<td>111</td>
<td>1777</td>
</tr>
</tbody>
</table>

* In some countries, figures reflect the estimated number of laboratories which use the WHONET software, while in others figures reflect the estimated number of laboratories managed with WHONET at the national level.

surveillance collaborations, others have not. Furthermore, there is no formal framework for collaboration among surveillance programs worldwide. This lack of a global framework for collaborative surveillance of antibiotic resistance hobbles efforts to track emerging resistance challenges; to identify, characterize, and contain new threats; and to systematically compare and evaluate the value of national resistance containment activities.

Fortunately, key components of a global surveillance collaboration already exist, and much more has been accomplished worldwide than is generally appreciated. In this chapter, we will highlight current and past surveillance initiatives in the six world regions defined by the World Health Organization. The initial focus of this discussion will be on antibiotic resistance among common community- and healthcare-associated bacterial pathogens including *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Escherichia coli*, and others. This will be followed by a survey of WHO-affiliated disease- and pathogen-specific programs, such as those organized for tuberculosis, malaria, HIV/AIDS, and foodborne pathogens.

3.1. Surveillance of antibiotic resistance at national level

A number of early WHO meetings recommended the establishment of local, national, and regional/global surveillance programs (WHO, 1981, 1982, 1994). At national level, priority objectives identified include: monitoring trends in infection and resistance, development of standard treatment guidelines, assessment of resistance containment interventions, early alert for novel resistant strains, and prompt identification and control of outbreaks. A national view permits benchmarking of experiences by facility and geographic distribution, particularly valuable when supplemented by information on pathogen population dynamics, antibiotic use, infection control measures, and patient population demographics. National coordinators also have a critical role in mentoring network participants in quality improvement and use of data to support local action and therapeutic guideline decisions.

To support surveillance at multiple levels, the WHO Collaborating Centre for Surveillance of Antibiotic Resistance in Boston has developed and supported the WHONET software for the management and sharing of microbiology laboratory test results since 1989 (WHO, 1999; www.whonet.org/DNN). At present, WHONET is used in over 110 WHO Member States to support local and/or national surveillance in over 1700 clinical, public health, food, and veterinary laboratories. In most of these countries, the WHONET software is used as a core component of the national surveillance program. Estimates of WHONET use by region are provided in Table 1, and a global map is depicted in Fig. 1.

Data can be entered manually or downloaded into WHONET from existing laboratory information systems, laboratory diagnostic instruments, or desktop applications using the BacLink utility distributed with WHONET. In most laboratories and countries, WHONET is used to manage results for all positive culture results from all specimen types from all microbial species identified by the laboratory. In some instances, data collection is limited to a few so-called indicator pathogens.

The more comprehensive approach to data collection – with information on all species identified, specimens processed, and antibiotics tested – has several advantages over a narrow view of a few priority issues: a broad view of emerging microbial threats, identification of novel strains, detection of hospital and community

Fig. 1. WHONET use around the world, from http://www.whonet.org/DNN/.
outbreaks with any microbial pathogen, and adaptability as new issues are identified. When data can be downloaded from existing microbiology information systems, a comprehensive approach for data acquisition is simpler than a narrower filtered view of certain indicator pathogens.

### 3.2. Surveillance of antibiotic resistance at regional level

A summary of regional surveillance programs in the six WHO regions is provided in Table 2. Regional activities have been launched in five of the six WHO regions, while in the remaining region (SEARO) the regional strategy for containment of antibiotic resistance published in June 2010 made a commitment to establishing national and regional surveillance over the next few years. Three of the regions (AMRO/PAHO, EURO, and AFRO) continue to be active to this day in resistance surveillance. Two regions (EMRO and WPRO) were active in the past, and WPRO has recently established a new Working Group which has identified surveillance of resistance as a regional priority.

In three of the regional networks (AMRO/PAHO, AFRO, and WPRO), programs were coordinated by WHO staff, while in the other two (EURO and EMRO), activities were led by the initiative of individual institutes and funded by the European Commission (EARSS, Dutch National Institute for Public Health and the Environment, RIVM, until 2009 for EURO and ARMed St. Lukes Hospital, Malta, until 2007 for EMRO). Since January 2010 EARSS, now under the name EARS-Net, has been coordinated by the European Centre for Disease Prevention and Control (ECDC). The EARSS/EARS-Net, ARMed, and AFRO surveillance networks focus on a limited number of pathogens and specimen types of public health importance, while the other regional programs (AMRO/PAHO, WPRO, and proposed EMRO program) have a broader scope for data collection (all organisms, specimens, antibiotics) and targeted data analyses of certain issues of regional importance.

### 3.3. External quality assurance programs at regional level

Strategies for ensuring and maintaining the quality of laboratory test results are critical to the value of surveillance initiatives. All facilities should have procedures for ongoing assessment of the quality of test reagents and test performance by laboratory technicians. In addition to internal quality control practices, laboratories should also participate in national and/or external quality assurance (EQA) programs. As highlighted in Table 3, all six WHO regions currently have regional EQA initiatives which address routine organism identification and antibiotic susceptibility testing. Three of these (AMRO/PAHO, AFRO, EMRO) are coordinated by WHO offices in collaboration with high-quality microbiology laboratories in the region, while the remaining three (EURO, SEARO, WPRO) are coordinated by independent organizations dedicated to training and/or quality assurance for laboratories in the region.

### 3.4. Disease- and pathogen-specific networks

The above description has covered surveillance of resistance in a broad range of common, primarily bacterial, pathogens. In addition to these surveillance initiatives, a number of additional WHO-affiliated regional and global surveillance networks have developed over time to support the technical, epidemiological, and strategic needs of specific disease control programs. Details on several dedicated networks coordinated by or affiliated with the World Health Organization are provided in Table 4.

### 4. Core components for global collaboration

Since most WHO regions are already primed for surveillance for antibiotic resistance, a global collaborative network should be achievable and affordable. However, core tasks and responsibilities need still to be addressed, implemented or harmonized. For operational purposes, we suggest to distinguish between some of these core tasks which include (i) reference work, (ii) quality assurance, and (iii) surveillance. All of these tasks are essential for surveillance and may be accomplished by single but more often separate institutions. Moreover, all three core activities need to be functional at both national and at regional level.

#### 4.1. National level framework

At national level, we envisage that national reference laboratories for antibiotic resistance, national centres for external quality assessment, and a national surveillance centre could coexist in the same institution or consist of different centres that could cater for these functions. Whatever solution fits the country’s needs, a close communication and collaboration between the centres would be key. Moreover, it would be the remit of all centres to iden-
Table 3
Regional programs for external quality assurance in common bacterial pathogens.

<table>
<thead>
<tr>
<th>WHO region</th>
<th>Program name</th>
<th>Coordinating institutions</th>
<th>Participants</th>
<th>Years of activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFRO, EMRO, SEARO</td>
<td>WHO AFRO/NICD Microbiology EQA Programme in Africa</td>
<td>WHO/HQ-Lyon and National Institute for Communicable Diseases, South Africa (Routine bacteriology, plague, TB microscopy and malaria)</td>
<td>Total = 50 countries in 45 countries in AFRO, 4 in EMRO, 1 in SEARO Number of laboratories Microbiology – 81 TB microscopy – 82 Malaria microscopy – 69 Plague – 18</td>
<td>2002–present</td>
</tr>
<tr>
<td>EMRO</td>
<td>1. ARMed = Antimicrobial resistance in the Mediterranean</td>
<td>National External Quality Assurance Scheme (NEQAS), United Kingdom</td>
<td>9 countries</td>
<td>2001–2005</td>
</tr>
<tr>
<td></td>
<td>2. EMRO Regional Microbiology External Quality Assessment Scheme</td>
<td>WHO/HQ-Lyon and EMRO and Central Public Health Laboratory, Oman (Bacteriology) Health Reference Laboratories, Iran (Seroology, mycology, parasitology)</td>
<td>27 laboratories</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. ARMed = Antimicrobial resistance in the Mediterranean</td>
<td>WHO/HQ-Lyon and EMRO and Central Public Health Laboratory, Oman (Bacteriology) Health Reference Laboratories, Iran (Seroology, mycology, parasitology)</td>
<td>22 countries 27 laboratories</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. EMRO Regional Microbiology External Quality Assessment Scheme</td>
<td>WHO/HQ-Lyon and EMRO and Central Public Health Laboratory, Oman (Bacteriology) Health Reference Laboratories, Iran (Seroology, mycology, parasitology)</td>
<td>22 countries 27 laboratories</td>
<td></td>
</tr>
<tr>
<td>EURO</td>
<td>National External Quality Assurance Scheme (NEQAS)</td>
<td>National External Quality Assurance Scheme (NEQAS), United Kingdom</td>
<td>33 countries 917 laboratories 110 million citizens</td>
<td>1999–2009</td>
</tr>
<tr>
<td></td>
<td>In collaboration with 1. EARSS = European Antimicrobial Resistance Surveillance System</td>
<td>1. Institute for Public Health and the Environment (RIVM), Netherlands</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. EARS-Net = European Antimicrobial Resistance Surveillance Network</td>
<td>2. European Centre for Disease Prevention and Control (ECDC), Sweden</td>
<td>28 countries 886 laboratories</td>
<td>2010–present</td>
</tr>
<tr>
<td>AMRO/PAHO</td>
<td>ReLAVRA = red Latinoamericana de Vigilancia a las Resistencias Antimicrobianas</td>
<td>Pan American Health Organization in collaboration with Malbrán Institute, Argentina</td>
<td>18 countries 18 national reference laboratories which provide EQA to 500 sentinel laboratories</td>
<td>1997–present</td>
</tr>
<tr>
<td>AFRO, EMRO, SEARO, WPRO</td>
<td>RCPA Quality Assurance Programs Pty Limited</td>
<td>Royal College of Pathologists of Australia (RCPA)</td>
<td>4 countries 35 laboratories in AFRO 3 countries 51 laboratories in EMRO 3 countries 3 laboratories in SEARO 12 countries 395 laboratories in Australia and New Zealand 85 laboratories in other WPRO countries</td>
<td>2002–present</td>
</tr>
<tr>
<td>WPRO, SEARO</td>
<td>REQA = Regional External Quality Assessment Programme</td>
<td>Pacific Paramedical Training Center, New Zealand – WHO Collaborating Centre for External Quality Assessment in Health Laboratory Services</td>
<td>17 countries 22 laboratories in WPRO 2 countries 2 laboratories in SEARO</td>
<td>1991–present</td>
</tr>
</tbody>
</table>

tify and recruit diagnostic microbiological laboratories as reporting laboratories that would report routine antimicrobial susceptibility test results to a national surveillance centre. Until now, laboratory capacity remains critical in many parts of the world, however surprisingly large amounts of quality data are generated but remain underutilized. There are also emerging options to built diagnostic capacity for simple sentinel surveillance around recently established diagnostic centres for HIV, TB and Malaria. The national reference laboratories should fulfil functions stipulated by a recently published ECDC technical report (ECDC, 2010a,b). This should include species confirmation and the ability to repeat phenotypical antibiotic susceptibility tests, as well as
the determination of minimum inhibitory concentrations (MIC). A repertoire of phenotypic tests indicating the presence of certain resistance mechanisms would be especially useful if molecular characterisation would not yet be available.

External quality assessment (EQA) could be provided in two forms, (i) by supporting a genuine national EQA scheme, whereby highly characterised isolates are distributed to reporting laboratories at regular intervals for species identification and susceptibility testing, or (ii) by assisting of the regional EQA schemes in the regular distribution of isolates provided by regional EQA centres (Bronzwaer et al., 2002; Tenover et al., 2001).

The collection of routine AST results would be the remit of the national surveillance centre. This centre would not need to be a laboratory but could be hosted at national health agency. Important for the surveillance centre however, would be competence to evaluate the collected data for consistency and biological plausibility as well as skills in data management.

For countries where the above mentioned infrastructure is absent, centres at regional level may substitute for any or all of these tasks.

### 4.2. Regional level framework

Each region should be free to set up its own surveillance framework. The overall structure would be the classical network of network approach as in the EARSS/EARS-net and ReAVRA of AMRO/PAHO networks (federated structure). In analogy with national level surveillance the three core tasks may be divided between separate centres.

#### 4.2.1. Reference work

Recognizing the global need to strengthen laboratory capacity for the determination of antibiotic resistance, we also propose a network of reference labs at regional level linked electronically among each other and to a roster of international excellence centres. Regional reference laboratories should be equipped to receive a stream of isolates from their national counterparts that fulfil a set of criteria indicating public health importance or probable public health importance (to be defined). They should be able to carry out a repertoire of confirmatory tests incl. molecular identification of genetic resistance determinants to detect emerging resistance.

<table>
<thead>
<tr>
<th>Program name</th>
<th>Subject</th>
<th>Countries</th>
<th>Coordinator</th>
<th>Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFN = Global Foodborne Infections Network (formerly Global Salm. Surv.)</td>
<td>Foodborne pathogens include Salmonella, Campylobacteria, and others</td>
<td>Global 180 countries 1633 laboratories The focus to date has been on capacity-building and quality assurance. As part of the current 5-year strategy, surveillance will be added as an important component of the determination of antibiotic resistance, we also propose a network of reference labs at regional level linked electronically among each other and to a roster of international excellence centres. Regional reference laboratories should be equipped to receive a stream of isolates from their national counterparts that fulfil a set of criteria indicating public health importance or probable public health importance (to be defined). They should be able to carry out a repertoire of confirmatory tests incl. molecular identification of genetic resistance determinants to detect emerging resistance.</td>
<td>Danish Technical University, Denmark</td>
<td>2000–present</td>
</tr>
<tr>
<td>WHO Global HIV Drug Resistance (HIVDR) Surveillance Strategy and WHO HIVResNet</td>
<td>HIV Global 60 countries are implementing HIVDR surveillance 24 laboratories at national, regional and specialized level constitute the Global HIVDR Laboratory Network</td>
<td>World Health Organization</td>
<td>2004–present</td>
<td></td>
</tr>
<tr>
<td>WHO Global Malaria Programme</td>
<td>Malaria Global 72 countries</td>
<td>World Health Organization</td>
<td>1996–present</td>
<td></td>
</tr>
<tr>
<td>WHO Global Malaria Programme and</td>
<td>Malaria Global 92 countries in literature survey</td>
<td>World Health Organization and Literature survey</td>
<td>1975–present</td>
<td></td>
</tr>
<tr>
<td>WWARN = WorldWide Antimalarial Resistance Network</td>
<td></td>
<td>WWARN Executive Management Team</td>
<td>WWARN is establishing a network of centres for patient-level resistance surveys</td>
<td></td>
</tr>
<tr>
<td>Global Project on Anti-tuberculosis Drug Resistance Surveillance</td>
<td>M. tuberculosis 119 countries with national laboratories 29 Supranational Reference Laboratories</td>
<td>World Health Organization</td>
<td>1994–present</td>
<td></td>
</tr>
<tr>
<td>WHO GASP for WPRO and SEARO GASPS: Gonococcal Antimicrobial Surveillance Programme</td>
<td>N. gonorrhoeae 23 countries/jurisdictions 28 laboratories</td>
<td>WHO Collaborating Centre for STD, Prince of Wales Hospital, Sydney, Australia University of Ottawa, Canada</td>
<td>1994–present</td>
<td></td>
</tr>
<tr>
<td>SIREVA = Sistema Regional de Vacunas</td>
<td>Vaccine-preventable pathogens including S. pneumoniae, H. influenzae, and N. meningitidis Latin America 20 countries 471 laboratories</td>
<td>World Health Organization 1996–present</td>
<td>1993–present</td>
<td></td>
</tr>
<tr>
<td>LCDC/PAHO Collaborative project on Surveillance of the Antibiotic Resistance in Salmonella, Shigella, and Vibrio cholera</td>
<td>S. Typhi, S. paratyphi, S. flexneri, Shigella, V. cholera</td>
<td>Laboratory Centre for Disease Control, Canada</td>
<td>1995–present</td>
<td></td>
</tr>
</tbody>
</table>
threats and rapidly expedite confirmation tests for novel resistance mechanisms.

As the emergence of novel resistance determinants is a function not only of selection but also of the expansion of clones harbouring these determinants, reference labs also need expertise in methods of molecular epidemiology. Considering molecular typing as essential for the understanding of clonal dissemination, the limitations in portability of conventional molecular epidemiological typing data should be understood and sequence-based typing may be favoured as the preferable option (Grundmann et al., 2010).

Regional centres shall support national reference laboratories and reporting laboratories with protocol implementation, training and capacity building. Standardisation as well as protocol development should be referred to reference laboratory working groups. This approach has successfully worked for the EARSS which profited largely from European expert experience.

To identify the regional reference laboratories, the technical expertise and the willingness to serve the role as a resource for the region should be considered. For each region the key laboratories which meet these criteria would be publicised, thereby giving national reference labs a set of options among which they can select the laboratory which they consider to be most appropriate for their needs and preferences. For each regional reference laboratory, the network would identify the specific technical capacities and tests that individual laboratories have and set about to fill the gaps, for example in PCR, PFGE, and sequencing. This kind of information could be made available through a dedicated network and shared through WHO's GLaDMap initiative – Global Laboratory Directory at www.gladmap.org.

A network of reference labs, proficient in molecular and phenotypic approaches to detecting resistance and clonality in key pathogens is an urgent and affordable goal. These reference laboratories will enable further knowledge and quality improvement in their regions but may or may not be responsible for external quality assessment depending on the region.

4.2.2. External Quality Assessment

Regional EQA programs currently exist in all six WHO regions, and in three regions (AFRO, EURO, and AMRO/PAHO), these EQA activities are integrated with the regional antibiotic resistance surveillance initiatives. Ideally, and for reasons of consistency, a single centre per region should be awarded the task for EQA for routine bacterial identification and susceptibility testing. These programs have demonstrated a track record and capacity for batch production of the required number of specimen to be distributed throughout the regional network. The participation of all reporting laboratories in regular EQA is crucial for antibiotic resistance surveillance for three reasons. (1) EQA assesses the ability of the reporting laboratories to identify antibiotic resistance of clinical and public health importance. (2) It allows the evaluation of qualitative and quantitative susceptibility test results received from reporting laboratories. (3) Results of the EQA decide over comparability of routinely reported test results between different laboratories and countries and thus provide the means for justifying the pooling and comparison of antimicrobial susceptibility test (AST) results across the region.

We would also suggest the implementation a global EQA program to ensure that references laboratories are carrying out the specific confirmatory tests with sufficient accuracy. Global EQA would concentrate on the molecular confirmation tests and for these exercises it would suffice to dispatch DNA extracts. Global EQA should be provided by the roster of international excellence centres which connect to regional reference centres on a routine basis.

4.2.3. Surveillance

Primarily responsible for ongoing routine surveillance would be the Regional Centre for Surveillance, which in practice is often a regional public health authority, not a laboratory, e.g. WHO in the case of AMRO/PAHO (North/South America) and WPRO (Western Pacific) or the ECDC for Europe.

Focusing the surveillance aspect on human infections and clinical isolates is advisable. Possible initial indicator organisms could consist of S. pneumoniae, S. aureus, E. coli, K. pneumoniae, Pseudomonas aeruginosa, and Acinetobacter baumannii. The decision on the final selection of organisms may be left to the surveillance working group and network participants. Different ecological, socio-economic and epidemiological circumstances (e.g. Africa vs. China) may require a different set of priority pathogens. If the expertise and capacity of the regional antibiotic resistance reference laboratory allows for the analysis of samples from food, water and veterinary sources, there is no reason to object to their inclusion but care should be taken not to overburden the capacities and one should not make this a remit of the regional reference laboratories. There is a system already in place for global surveillance of food and animal isolates GFN (Global Foodborne Infections Network). So for food/animal/human enteric pathogens issues, we propose to treat them in a way similar to HIV, TB, and malaria. We recognize the significant accomplishments of the global networks dedicated to these specific pathogens and the existing expertise in these areas. The scope of the suggested global framework could be inclusive, but for our present recommendation we focus on the human clinical isolates which consist of the cosmopolitan opportunistic pathogens mentioned in the introduction and are missing from current global collaborative efforts.

5. In-depth surveillance using health and demographic surveillance sites in low- and middle-income countries

The global problem of antibiotic resistance is particularly pressing in low- and middle-income countries (LMICs), where the high infectious disease burden is aggravated by erratic access to antibiotics. Here weak antibiotic policies and a lack of capacity for antibiotic resistance surveillance means that the build-up of antibiotic resistance contributing to global pool of difficult-to-treat-infections is impossible to fathom (Blomberg et al., 2005; Okeke et al., 2005). The prevalence of antibiotic resistance varies greatly between and within countries and between different pathogens. Multidrug-resistant microorganisms, which in developed countries could still be treated by expensive alternative drugs cause infections that become untreatable in resource limited settings. Data from Pakistan indicate that, because of the development of resistance to first line antibiotics, 70% of hospital-acquired neonatal infections could not be successfully treated by using WHO's recommended regimen (Zaidi et al., 2005). Factors described in the first chapter above contribute to the worldwide emergence and spread of antibiotic resistance which is epitomized by the steady stream of pan-resistant hospital infections emerging from Asian, African, and Latin American countries.

Over the past 15 years The International Network for the Demographic Evaluation of Populations and Their Health in Developing Countries (INDEPTH) has developed a series of novel and synergistic tools to measure, map and track the socio-demographic impact of cause-specific morbidity and mortality in difficult to access populations in LMICs (www.indepth-network.org). This has led to a fundamentally new understanding about the magnitude of health events and effectiveness of interventions from drug and vaccine trials to marketing of health products. Using household-based surveys and the totality of the catchment population surrounding central hospitals at so-called Health and Demographic Surveillance Sites
(HDSS), it has been possible to measure the extent of disease in the community against case counts in hospitals offering the means to translate hospital-based surveillance information into estimates on the burden of disease in the community. INDEPTH is a network currently comprising 37 Health Demographic Surveillance System Sites in 20 countries. The research sites are in Africa, Asia, and Oceania.

Through harnessing the ability of HDSS in these countries, it shall be possible

- to determine the true prevalence of antibiotic resistance
- to reconcile laboratory incidence figures from hospitals (reporting laboratories) with community prevalence
- to ascertain antibiotic use
- to understand major determinants of antibiotic resistance in the community including perceptions and health seeking behaviour
- to assess the burden of disease attributable to antibiotic resistance in LMICs

We suggest to recruit HDSS centres in different countries that could serve as focal points for the training and dissemination of laboratory and surveillance competences in these and surrounding countries as well as providing a reality check by in-depth investigations into the occurrence of antibiotic resistance and antibiotic use.

6. Conclusions

We identified mechanisms that are likely to aggravate the decay of antibiotic effectiveness in the near future. Free market economy is about choice and enhancing the ability of individuals and industry to make these choices. Industry has so far chosen not to invest in innovative antibacterials. Instead, companies recently priced several of the last line antibacterial compounds (such as carbapenems which are losing patent protection in the near future) to compete on the global generic market. Generic manufacturers in emerging market communities are ready to produce the active pharmaceutical ingredients, often in agreement with parent companies, at low price for world markets. Unregulated access to these drugs – especially in countries where opportunities for transmission and spread are abundant – will lead to the emergence and expansion of antibiotic resistance through migration, travel and trade.

We therefore believe that the need for a global surveillance system for antibiotic resistance is evident, especially as antibiotic resistance fulfills all criteria of health threats that typically warrant surveillance. The threat is emerging, urgent, geographically heterogeneous, transmissible and likely to expand in an epidemic fashion, but also amenable to interventions and effective control efforts. A systematic collection, consolidation and evaluation of the resistance data and their trends will help define the problem, inform national and international control activities and support the monitoring of their effectiveness. Crucially, valid data would provide incentives to invest into anti-infective strategies including novel drug development.

We therefore recommend utilizing and rehabilitating initiatives that have already been developed in the six WHO regions. Existing structures need to be harmonized and core competences need still to be addressed and allocated. For operational purposes, we suggest to separate reference work, quality assurance, and surveillance. All of these tasks are essential for the collection of reliable and consistent surveillance data and may be accomplished by single but more often separate institutions. Moreover, all of these tasks should be addressed by institutions with the appropriate competence at either national and at regional level.

Since the global problem of antibiotic resistance is particularly pressing in low- and middle-income countries (LMICs), where the infectious disease burden is high but access to antibiotics and laboratory service is erratic, we suggest to implement selective sentinel surveillance at research sites that have access to health and demographic surveillance systems (HDSS). Given that existing networks are able to provide the necessary structures, it will become possible to correlate antibiotic resistance in the community with hospital incidence and contextualize, in these low resource settings, the health care seeking behaviour which determines antibiotic use.

With the improvement of surveillance comes the obligation to communicate the findings in a timely fashion to policy and decision makers. This poses another challenge as long as the available information requires expert knowledge to grasp the medical and epidemiological ramifications. A comparative assessment of the average effectiveness of drugs available for a given infection can assist in comparing trends in antibiotic resistance between countries and regions. An example of this is the Drug Resistance Index that has recently been proposed as a ‘Dow Jones index’ for drug resistance (Enserink, 2010). This would be a true improvement in the democratic tradition, making the facts available also to a broader public who can hold policy makers accountable for their decisions, and as we have already learned “good surveillance does not necessarily ensure the making of the right decisions, but reduces the chance of wrong ones” (Langmuir, 1962).

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