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Antimicrobial Stewardship (AL Pakyz, Section Editor)

The Legislative Momentum of Antimicrobial Stewardship: An International Perspective

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Opinion statement

In the USA, two million people fall ill with antimicrobial-resistant infections every year; with at least 23,000 dying as a result. Global estimates reveal that more than 700,000 die worldwide yearly of antibiotic-resistant infections and an extra 10 million people across the world could die every year by 2050 due to antibiotic resistance if this is not addressed. Antimicrobial stewardship programs have been shown to be effective in both combating antibiotic resistance and health-care cost containment. This has recently led to US governmental and organizational mandates for antimicrobial stewardship targeting health-care institutions; but in our global community, these regulations will do little without international support. This article will review international antimicrobial stewardship legislation and point out gaps or areas still needing attention.

The emerging global health problem of antimicrobial-resistant organisms

In the USA, two million people fall ill with antimicrobial-resistant infections every year; with at least 23,000 dying as a result [1]. Antibiotic-resistant infections are an unnecessary cost to the US health-care system accounting for an estimated excess direct annual health-care cost of 20 billion dollars as well as the additional cost to society in terms of loss of productivity secondary to impaired workforce participation on the order of 35 billion dollars a year [1]. Global estimates of antibiotic-resistant infections are more difficult to measure, but it has been estimated that more than 700,000 die worldwide yearly of antibiotic-resistant infections, and an extra 10 million people across the world could die every year by 2050 due to antibiotic resistance if this is not addressed [2]. This left alone, by 2050 the world cost estimate would be around $100 trillion in lost

output, a cost larger than the size of the current economy [2]. Antimicrobial-resistant infection deaths are approaching numbers seen in epidemics such as HIV where by the end of 2014 between 980,000–1.6 million people died from AIDS-related illnesses according to UNAIDS [3].

The etiologies of antimicrobial resistance and the One Health approach

There are many factors contributing to the rise of antimicrobial resistance, including antibiotic overuse and misuse, availability without prescription, counterfeiting, use in animals, food, and agriculture, release into wastewater, and the contribution of inadequate access to clean water and lack of sanitation to the need for antimicrobial therapy to treat infections. In addition, globalization with its travel, migration, and trade risks disseminating resistance through closer interaction between humans and various environments. Urbanization and rising population density can lead to increased antibiotic resistance by, for example, interaction between environmental bacterial genes and human pathogens in collections of water like lakes and ponds. Despite the dire need for new classes of effective antibiotics, research and development have dramatically decreased over the last decades. Without intervention, we are facing an increase in resistant human pathogens; increasing multidrug-resistant bacterial infections; increasing health-care costs; and costly drug development with fleeting utility as new resistance evolves.

Drug-resistant infections must be tackled by a One Health approach. One Health is the concept of linking the health of people, animals, and the environment [4]. With respect to the antimicrobial resistance crisis a One Health approach would include the following: adequate antimicrobial stewardship (AMS); infection control practices; improved global sanitation and waste management; animal and agricultural antibiotic regulations and surveillance; regulation and monitoring of antibiotics in the food industry; a variety of complex environmental surveillance and management systems, new drugs, rapid point of care testing systems, and vaccines. Antimicrobial stewardship programs have been shown to be effective in both combating antibiotic resistance and health-care cost containment. This has recently led to US governmental and organizational mandates for antimicrobial stewardship targeting health-care institutions; but in our global community, these regulations will do little without international support. This article will review international antimicrobial stewardship legislation and point out gaps or areas still needing attention.

The WHO's global action plan on antimicrobial resistance and GLASS

A global action plan was published by the World Health Organization (WHO) in May 2015 urging member states to develop national strategic plans to combat antimicrobial resistance [5••]. The global action plan is

divided into five objectives which together target a One Health approach with cross-disciplinary cooperation. The five objectives are as follows: "Improve awareness and understanding of antimicrobial resistance through effective communication, education and training; strengthen the knowledge and evidence base through surveillance and research; reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures; optimize the use of antimicrobial medicines in human and animal health; and develop the economic case for sustainable investment that takes into account the needs of all countries, increases investment in new medicines, diagnostic tools, vaccines and other interventions." [5••] The WHO's recommendation is a start, but some immediate problems needing attention are the lack of internationally agreed upon standards for collection of data and reporting on antimicrobial resistance, as well as the need for a global forum facilitating rapid sharing of information related to antimicrobial resistance [5••]. To address this, the Global Antimicrobial Resistance Surveillance System (GLASS) is an exciting new WHO initiative to support the global action plan. The GLASS initiative will be in early implementation phase from 2015 to 2019, with the aim to create standardized, comparable, and validated data on antimicrobial resistance (AMR) [6••]. With this long overdue, but excellent, WHO initiative follows the need for long-term financial planning and financial priority, both for the WHO, but also for the countries not yet ready to enroll in GLASS. A barrier to the global enrollment is the countries', especially developing countries', need for substantial changes in laboratory facility and capacity, education of staff, and technological advancements for surveillance systems to enroll. These tasks often require governmental support and political and financial priority, as well as potential redistribution of finances from other programs—a delicate task balancing consequences. We can expect a step-wise process as countries set up their capacity to enroll, but the need for financial investment and support should not be underestimated.

The WHO has committed to deliver biennial progress reports including an assessment of countries that have plans in place, their progress in implementation, and the effectiveness of action at regional and global levels [5••]. Lastly, how can WHO's global action plan and GLASS integrate with other established global organizations and partnerships working on the same or similar missions, for example, the global antibiotic resistance partnerships (GARP)? Can we avoid duplication of work, wastage of finances, and consolidation of knowledge, enthusiasm, skills, and global efforts to achieve success?

The antimicrobial stewardship legislative momentum in Europe

Antimicrobial stewardship policies and practices vary greatly across Europe. The European Centre for Disease Prevention and Control (ECDC) is responsible for the coordination of surveillance networks in the EU regarding antimicrobial resistance, antimicrobial consumption, and health-care association infection. The European Antimicrobial Resistance Surveillance Network (EARS-Net) is the

main EU surveillance system for AMR and includes 28 member states of the EU plus Norway and Iceland [7]. For the first time, in June of 2015, cooperation between the European Union (EU) and the United States (USA) on the issue of antimicrobial resistance via the Transatlantic Task Force on Antimicrobial Resistance (TATFAR) published indicators for antimicrobial stewardship programs allowing characterization of programs and comparisons among health-care systems in the EU and the USA [8]. In contrast to recent proposed regulations concerning antimicrobial stewardship programs in the USA [9], there are no such laws for the EU. A study of organization of infection control in European hospitals published in September 2015 by Hansen S. et al. reviewed data from 309 hospitals in 24 countries and found that while 96 % had defined infection control objectives, only 66 % of the hospitals had antibiotic stewardship programs [10]. The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) steers the European Study Group for Antibiotic Policies (ESGAP), a group promoting awareness about antimicrobial stewardship including the development of virtual learning community for health-care providers, and ongoing research within the field of antibiotic policies. In December 2015, the joint effort of ESGAP, the European Committee on Infection Control (EUCIC), and the European Committee on antimicrobial susceptibility testing (EUCAST) started a project surveying European countries to evaluate which countries have implemented selective reporting of antibiotic susceptibility testing, as well as their methodology [11]. This survey will likely enhance understanding of differences and gaps between and within countries which can assist in the process of European standardization of collection and reporting of antimicrobial resistance data.

Driving reinvestment in research and development and responsible antibiotic use (DRIVE-AB) is a project that began on October 2014 consisting of 16 public and 7 private partners from 12 countries in Europe funded by the Innovative Medicines Initiative (IMI). IMI is a joint undertaking between the European Union and the European Pharmaceutical Industry Association (EFPIA). Its mission, with an estimated project completion in 2017, is to reduce antimicrobial resistance through responsible antibiotic use and identify how, through new economic models, to incentivize the discovery and development of novel antibiotics for use now and in the future. These recommendations, to be presented to policymakers, and the general public, aim to estimate the value of new and existing antibiotics from an all aspect perspective [12]. Although this project will not make law or mandate, it may help inform future European antimicrobial stewardship program decisions.

Two examples of European antimicrobial stewardship and legislation

UK/England

In 2013, the Department of Health and Public Health England released antimicrobial prescribing and stewardship competencies with the goal to improve the quality of antimicrobial treatment and stewardship. These

competencies, which are as yet optional but could be used by regulators, target certain groups of providers and are suggested as standards, guidance, and methods of demonstrating compliance with the Code of Practice [13, 14]. In August 2015, a guideline on the use of antimicrobials in all publically funded health and social care was published. Commissioned, or provided, by NHS organizations, local authorities in England, and independent organizations or contractors, it was put forward as an official national recommendation (NICE guidelines) [15]. The NHS has the capability to access and compare prescribing rates through the NHS Prescription Services [16], and this could also allow for assessment of adherence to the NICE guidelines, and potential sanctions for inappropriate prescribing.

Norway

Despite Norway having low antimicrobial resistance relative to most other nations, the resistance trend is also rising there. The first national action plans to combat antibiotic resistance were published in 2000 (Action Plan to Prevent Antibiotic Resistance 2000–2004) and have been updated regularly since. The national strategy for prevention of infections in the health service and antibiotic resistance (2008–2012), a cooperation between the Ministry of Labour and Social Inclusion, the Ministry of Fisheries and Coastal Affairs, the Ministry of Agriculture and Food, the Ministry of the Environment, and the Ministry of Health and Care Services, outlines a One Health approach to tackle antimicrobial resistance [17]. An updated Norwegian action plan is in process; this plan will likely include mandatory components such as antimicrobial stewardship programs and audits.

Antimicrobial stewardship programs with implemented accreditation legislation

Canada

The Public Health Agency of Canada has two national surveillance programs monitoring antimicrobial use and antimicrobial resistance in hospitalized patients (Canadian Nosocomial Infection Surveillance Program—CNISP), and in humans, animals and the food supply (Canadian Integrated Program for Antimicrobial Resistance Surveillance—CIPARS), and these are planned to be joined into The Canadian Antimicrobial Resistance Surveillance System (CARSS) to consolidate all antimicrobial resistance data, track antimicrobial resistance at a national level, and expand surveillance activities at the hospital and also community level. The Canadian government regulates antimicrobial use to public health and health professionals, food producers, veterinarians, and the Canadian public; a goal stated in the report from 2014 regarding antimicrobial resistance and use in Canada is to work more closely with the professional organizations to strengthen and promote responsible use of antimicrobials [18]. After 2012, the number of

Canadian antimicrobial stewardship programs has steadily increased as it became a national requirement for accreditation of organizations providing inpatient acute care, inpatient cancer, inpatient rehabilitation, and complex continuing care [19–21].

Australia

The Australian Commission on Safety and Quality in Health Care (ACSQHC) recommended AMS programs to be established in all Australian hospitals in 2011 and in 2013 AMS became an accreditation standard for all hospitals, both regional and rural [22, 23]. As this has been in effect for a few years in Australia, other countries could benefit from reviewing the Australian as well as the Canadian successes and battles, especially regarding rural hospital outreach.

Status of antimicrobial stewardship program legislation in countries with the highest antibiotic consumption

According to a 2014 Lancet article by Boeckel et al. that reviewed the global antibiotic consumption, a 36 % increase in antibiotic consumption was seen globally from 2000 to 2010 with India, China, Brazil, Russia, and South Africa accounting for 76 % of the increase [24•].

India

Prior to August 2012, India had no national antibiotic policy to address antimicrobial resistance; but with the Chennai Declaration in 8/2012, efforts to formulate a national policy to control the rising trend of antimicrobial resistance began [25]. In March 2014, the Union Health and Family Welfare Ministry of India released an amendment to the Drugs and Cosmetics Act of 1940 restricting over-the-counter antibiotics and drugs used for tuberculosis [26]. Also in 2014, the Global Antibiotic Resistance Partnership-India (GARP-India) held a workshop followed by a policy forum focusing on antibiotic resistance and stewardship in Indian hospitals. As a result of this workshop, planning has begun for mandatory reporting of emerging resistance in hospitals, providing uniform training on infection control for health-care practitioners, establishing a surveillance network, creating a national prescription database, and implementing regular pharmacy audits [27, 28]. Earlier this year (2016), the state of Kerala announced the start of the country's first antibiotic stewardship program which will cover both public and private health services. Kerala will serve as a trial state prior to dissemination to other states [29].

China

China has more than 1.3 billion people [30], and by health-care reform China aims to secure basic medical security for all by 2020 [31, 32].

China is second to India in antibiotic consumption [24•], and antibiotic resistance is rampant despite more than 10 years of authority-promoted antibiotic guidelines for rational use [31]. The Ministry of Health National Antimicrobial Resistance Investigation Net (MOHNARIN) conducts the surveillance [33]. In 2011, coupled with health-care reforms, the Chinese Ministry of Health supported a campaign to reorganize the rational use of antimicrobials in health-care settings including "establishing mandatory administrative strategies for the rational use of antimicrobials, setting targets for antimicrobial management, organizing task forces, developing audit and inspection systems, and investigating and reassigning responsibility to hospital management staff who violate rational use policies." [34] The campaign was enacted in August 2012 by the Chinese Ministry of Health signing a responsibility agreement with major hospital authorities. This included details on consequences to be faced by providers and hospitals failing to meet targets, such as the hospital becoming downgraded to a lower classification level, leaders being dismissed, or loss of antibiotic prescribing privileges by staff members, revocation of professional qualifications, or even prosecution [31]. This law has resulted in public announcement of hospital, leadership, and clinician compliance, including the consequences of not complying such as leadership dismissal, economic sanctions of the clinicians, or suspension of prescription rights [31]. A major drop in antibiotic sales and antibiotic prescribing has since been noted, and compliance with antibiotic duration for standard pre-operative antibiotic prophylaxis increased [31]. Enforcement of the Chinese antimicrobial stewardship mandate seems efficient and effective and in some measure bears semblance to the recently enacted US mandate of hospital antimicrobial stewardships which is expected to be enforced by CMS and via the joint commission hospital accreditation process; however, one does wonder if a punitive strategy is really the only and/or best way to achieve success in combating the problem of global antimicrobial resistance. At any rate, we must strive to keep quality of care as the primary goal while preserving medical ethics. Theory- and evidence-based interventions are important to achieve lasting individual, institutional, and societal behavioral change. Education, implementation of guidelines with constructive feedback, and non-punitive strategies including positive incentives are, for example, alternatives to strict punitive actions.

Brazil and the pan american health organization antimicrobial action plan, 2015

Brazil is the biggest and most populous country in Latin America with a population more than 208 million [35] and antibiotic resistance much higher than Europe and US with laws allowing for over-the-counter antibiotic sales until as recently as October 2010 [36]. In 2013, antibiotics were included in the National Controlled Substances Management System (SNGPC) to improve the supervision of their consumption [37]. Brazilian resistance data are collected by the Latin American Network for

Antimicrobial Resistance Surveillance (RELAVRA) and the Surveillance System for the Bacterial Agents Responsible for Pneumonia and Meningitis (SIREVA Laboratory Network), coordinated by the Pan American Health Organization [38]. The 67th session of the regional committee of WHO for the Americas, agenda item 4.9, the Plan of Action of Antimicrobial Resistance, was published in October 2015 [37]. This action plan is the recognition of antimicrobial resistance as a priority for the Pan American Health Organization (PAHO) region, and includes a list of required action objectives with current country status as of 2015, and goals for 2020. PAHO member states include all 35 countries in the Americas. The plan includes an attempt to increase the number of countries providing laboratory-based data on antimicrobial resistance annually. The scope will expand from the current number of 20 countries in 2015 to 35 countries in 2020. Only two countries in the region currently report and analyze the use of antimicrobial drugs in humans and animals, and only three countries have multi-sectoral collaboration mechanisms to implement integrated antimicrobial resistance surveillance programs; this will be a major focus moving toward 2020. No country in this region has a regional research agenda on public health actions to contain antimicrobial resistance. Three countries have a written strategy for containing antimicrobial resistance, and five countries have funded national inter-sectoral groups to promote the appropriate use of antimicrobial drugs and prevent the spread of infections. A mere five countries have produced, through a funded national inter-sectoral group, reports and recommendations to promote the appropriate use of antimicrobial drugs and prevent the spread of infections. Furthermore, 15 countries in the PAHO region are still struggling to prevent the sale nonprescription antibiotics, despite regulations to the contrary [38]. Brazil and the remaining of the PAHO region has yet a long way to go, but the first step in terms of progress has been made by outlining the gaps, and creating goals to be achieved.

South Africa and the African region

The African region has no overall unified collaborative surveillance of antibiotic resistance, and the region lacks laboratory standards, save for a few countries, even the capability to conduct susceptibility testing [39]. The lack of laboratory ability to detect or confirm suspected antimicrobial resistance also implies uncertainty of the true burden of the problem [39]. In addition, the logistical challenges of the antimicrobial delivery systems are dire. According to WHO, "The medicines supply and distribution systems in most countries of the Region are fragmented and weak. This situation increases the opportunities for infiltration of sub-standard/counterfeit medicines into the supply chain" [39].

South Africa has an essential drug list (EDL) and structured treatment guidelines (STGs) to guide prescribers, and these were combined into an algorithmic approach available to the providers as a part of the national South African Antibiotic Stewardship Program (SAASP) for all hospitals. It was started in 2012 and monitored by the Office of Health Standards and

Compliance [40, 41]. South Africa has even leveraged technology to increase convenience and availability of information to providers via a mobile "SAASP" application [41], an idea that should be adopted by other countries and regions. South Africa is also a member of the Global Antibiotic Resistance Partnership (GARP) arranged by Center for Disease Dynamics, Economics and Policy (CDDEP): a global alliance, currently spanning Africa, Asia, and North America, mainly focused on policy [42].

Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR)

The Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR) is a joint network initiative of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), the National Institute for Public Health and the Environment (RIVM) in the Netherlands, and the WHO. It was established to supply reliable information on AMR, contain and prevent emergence and spread of antibiotic resistance in the region for those countries that are not a part of the European AMR Surveillance Network (EARS-Net) coordinated by ECDC in the EU [43]. A total of 19 countries are participating in CAESAR: Albania, Armenia, Azerbaijan, Belarus, Bosnia and Herzegovina, Georgia, Kazakhstan, Kyrgyzstan, Montenegro, the Republic of Moldova, the Russian Federation, Serbia, Switzerland, Tajikistan, Yugoslav Republic of Macedonia, Turkey, Turkmenistan, Ukraine, Uzbekistan, and Kosovo [43]. A report published in October 2014 gives an update on the status of national plans regarding AMR for each of the participating countries, including some country-specific data on AMR [43]. A total of 47 % of the countries participating in the CAESAR network have an AMR reference laboratory in place, but only 26 % of the countries have a national AMR action plan developed [43]. The 2015 CAESAR manual contains information regarding data collection, laboratory protocols, and AMR case definitions and is intended to be used as a guideline by countries yet in the initial phase of obtaining national AMR capacity [44].

Barriers to achieving global implementation of antimicrobial stewardship programs

The lack of international standards for collection of data and reporting on antimicrobial resistance, and no current global forum facilitating rapid sharing of information of antimicrobial resistance, is a major barrier to a full understanding of the global resistance problem. The new WHO initiative—GLASS—will hopefully fill this gap, but time is of the essence. In addition, the majority of the world is lacking adequate and standardized laboratory facilities, capacity, and training to be able to report and analyze antimicrobial resistance, and this is the key foundation in establishing national action plans. Academia and government should collaborate with industry to develop rapid diagnostics which allow for accurate treatment plans. The fight against counterfeit drugs is ongoing, and there remains many areas of improvement for national and global regulation of antimicrobials. In addition,

drug shortages have not gained enough focus in areas of multidrug resistance. Lastly, antimicrobial stewardship is not only important in hospitals but also in our community and the countries which current national plans do not address this enough. A One Health approach to antimicrobial stewardship legislation globally is needed.

Compliance with Ethical Standards

Conflict of Interest
Drs. Tine Vindenes declares that she has no conflict of interest.
Kirthana R. Beaulac declares that she has no conflict of interest.
A. Pakyz declares that she has no conflict of interest

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by the authors.

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- • Of importance
- •• Of major importance

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