



Original article

Mandatory surveillance and outbreaks reporting of the WHO priority pathogens for research & discovery of new antibiotics in European countries

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ABSTRACT

Objectives: In 2017 the WHO published a global priority list of 12 antibiotic-resistant bacteria (ARB) in urgent need of new antibiotics. We aimed to identify and assess publicly accessible mandatory surveillance systems and outbreaks reporting for these pathogens in the 28 European Union and four European Free Trade Association member states.

Methods: Compulsory reporting was mapped by reviewing national documents without applying language restrictions and through expert consultation. Information on surveillance targets, indicators, metrics and dissemination modalities was extracted and a qualitative assessment was performed for open access systems only.

Results: Twenty-one countries (66%) had a mandate to survey at least one among the 12 WHO priority pathogens; 15 provided access to surveillance frameworks. These systems covered most frequently carbapenem-resistant *Enterobacteriales* (12; 38%), methicillin-resistant *Staphylococcus aureus* (12; 38%), and vancomycin-resistant enterococci (8; 25%). None of the European countries required reporting of resistance in *Salmonella*, *Campylobacter*, *Helicobacter pylori* and *Neisseria gonorrhoeae*. High heterogeneity was observed in data collection, reporting and dissemination among countries with clinical outcomes and risk factors being reported in less than half (22% and 25%). Only six countries (19%) implemented mandatory surveillance of outbreaks due to at least one WHO priority pathogen.

Conclusions: Our review shows that despite the increasing burden of ARB on the European population, very few countries implemented mandatory surveillance and outbreak reporting of the WHO priority pathogens. International efforts are needed to define the effectiveness of implementing mandatory reporting of these pathogens and to assess their role in reducing the spread of ARB in health-care and community settings. **N. Babu Rajendran, Clin Microbiol Infect 2020;26:943.e1–943.e6**

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Introduction

Surveillance in infectious diseases includes the monitoring and recording of the occurrence of an infection and the frequency with which it occurs, enriched by additional data such as environmental

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and patient factors that could influence incidence and spread of the disease. This process carried out in a systematic way together with timely analysis of data provides the evidence for decision-makers to organize effective infection control measures. In addition, surveillance of antibiotic-resistant bacteria (ARB) more specifically provides essential choices for appropriate empirical therapy of infections [1–3]. Data collected within the national and local surveillance systems could drive the usage of antibiotics in hospital and community settings and so can impact the resistance rates in the future [4].

International surveillance programmes are an important means of tracking significant threats at a global level, while local surveillance systems (such as in health-care facilities) are pivotal for the implementation of infection control measures and locally tailored therapeutic guidelines [5]. Data for surveillance systems may be collected by voluntary and/or mandatory participation. Mandatory reporting usually follows significant observed increases in rate of resistance and/or society or patients' clinical burden. A typical example is the mandatory surveillance implemented in 2001 in England after a significant increase in bloodstream infections due to methicillin-resistant *Staphylococcus aureus* (MRSA). Improvement of surveillance was one of the executive pillars that contributed to a significant decrease in MRSA bloodstream infections [6,7].

Travels and transfers of patients among countries play a significant role in the spread of resistance [8], and the European Union (EU) has called for united policies and strategies across borders to combat public health threats [9]. Since 2010, the European Centre for Disease Prevention and Control has been building up a voluntary network of national public health organizations and institutions to define risk of antimicrobial resistance (AMR) at local level and inform policy-makers [10]. However, a recent systematic review that mapped 42 voluntary regional and national systems in the 28 EU and 4 European Free Trade Association member states collecting data on resistance in humans showed persisting high heterogeneity of reporting among systems, and a lack of incidence-based indicators, clinical outcomes and risk factors data [11]. The WHO recently prioritized ARB according to the burden in hospital and community, the availability of infection control measures, and the need for new, effective antibiotics. The list included 12 pathogens, and multidrug-resistant *Enterobacteriales*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* were categorized as critical priority [12]. Although surveillance of infectious diseases associated with a high risk of burden and spreading such as tuberculosis, influenza and rabies is mandatory in all European countries, national policies for reporting of multidrug-resistant bacteria responsible for high morbidity in many European countries are still unclear and no guidelines are currently available.

The aim of this study was to map and describe publicly accessible mandatory reporting of infections, colonization and outbreaks in humans due to the WHO priority pathogens within the European region and to identify gaps and potential needs to be addressed in the European surveillance networks.

Methods

The target bacteria were the 12 high and critical WHO priority pathogens, selected based on the results of a multicriterion decision analysis incorporating several criteria including mortality, hospital and community transmissibility, and treatment options [12]. Mandatory surveillance was defined as the process of compulsory reporting of occurrence of WHO priority pathogens by laboratories and/or health-care facilities as stipulated by national laws or regulations. Mandatory notifications required by regional, i.e. state or administrative divisions within a country, were not included in this study. Using this definition, mandatory reporting in

Europe (defined as EU member states and European Free Trade Association countries) was mapped using a combination of search terms. Key words included 'obligatory', 'mandatory', 'reporting', 'notification', 'infectious disease', 'registry', 'antibiotic', 'antimicrobial', 'resistance'. These terms were used in various combinations together with the country name, for example, 'mandatory reporting infectious disease AND Estonia' OR 'mandatory reporting resistance AND Estonia' OR 'mandatory notification infectious disease AND Estonia'. The search was performed using the Google search engine in regional languages, and results were screened to identify country-specific public health agencies, ministries of health or official websites with mandates on infectious disease notifications. When no mandatory notification and outbreaks reporting was identified through the web-based search strategy, the European Committee on Infection Control (EUCIC; with national committees in 23 European countries devoted to prevention of infections) [13] was contacted. For the five countries without a EUCIC national committee, the national public health authorities were contacted. Qualitative assessment to evaluate surveillance frameworks was performed only for those countries that provided open access to surveillance protocols and results. Variables for mandatory surveillance included: target ARB, resistance definition, notification criteria, data providers, notification period, notification method, setting, sampling, specimen, infections monitored, microbiology laboratory details, demographics, risk factor, outcome, public feedback. Variables for outbreaks reporting included: target ARB, resistance definition, notification period, notification method, data

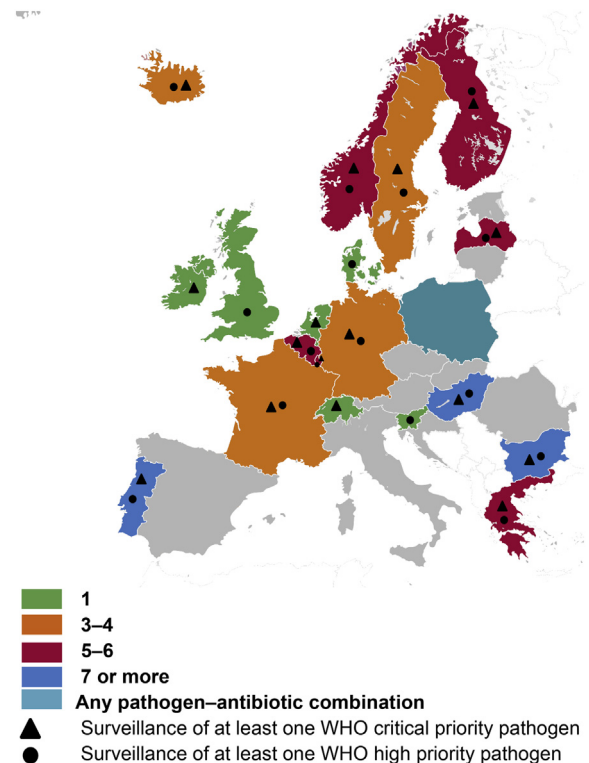


Fig. 1. European countries with mandatory surveillance of antibiotic resistant bacteria included as high and critical priorities for research and discovery of new antibiotics by WHO [12]. Colours indicate notifications by number of WHO priority pathogens. Countries with publicly accessible mandatory surveillance include: Belgium, Denmark, Finland, Germany, Greece, Hungary, Iceland, Ireland, Latvia, Norway, Portugal, Sweden, Switzerland/Liechtenstein, United Kingdom (Scotland and England only). *The Netherlands: law under implementation at the time of study. Poland requires reporting of infections due to bacteria resistant to selected antibiotics; specifications on the pathogen–antibiotic combination were unavailable.

Table 1
Mandatory surveillance of WHO priority pathogens in 32 European countries: target antibiotic-resistant bacteria

	Publicly accessible n (%)	Experts consultation n (%)
Carbapenem-resistant Enterobacteriales	12 (38)	4 (13)
Carbapenem-resistant <i>Acinetobacter baumannii</i>	5 (16)	3 (9)
Carbapenem-resistant <i>Pseudomonas aeruginosa</i>	4 (13)	2 (6)
Third-generation cephalosporin-resistant Enterobacteriales	7 (22)	2 (6)
Fluoroquinolone-resistant <i>Salmonella</i>	0 (0)	0 (0)
Fluoroquinolone-resistant <i>Campylobacter</i>	0 (0)	0 (0)
Third-generation cephalosporin-resistant <i>Neisseria gonorrhoeae</i>	0 (0)	0 (0)
Fluoroquinolone-resistant <i>Neisseria gonorrhoeae</i>	0 (0)	0 (0)
Clarithromycin-resistant <i>Helicobacter pylori</i>	0 (0)	0 (0)
Methicillin-resistant <i>Staphylococcus aureus</i>	12 (38)	3 (9)
Vancomycin-resistant <i>Staphylococcus aureus</i>	3 (9)	2 (6)
Vancomycin-resistant Enterococci	8 (25)	2 (6)

■ WHO Critical pathogens ■ WHO High-priority pathogens.

providers, outbreak definition, outbreak setting, demographics, reporting of transmission mode, reporting of control/intervention measures, outcome, microbiology details, public feedback. Literature in languages other than English was translated by native speakers or with the Google Translate web application.

Results

Mandatory surveillance of WHO priority pathogens

Antibiotic resistance as primary surveillance target was part of the mandates in 21 European countries (66%) (Fig. 1, Table 1). Qualitative assessment was possible for 15 countries with public-access information. In the UK both Scotland and England have region-specific mandatory surveillance; for the analysis they were assessed as one surveillance system. Raw data extracted from all public-access mandatory AMR surveillances identified in this study are available in the Supplementary material, file S1.

Mandatory antibiotic resistance surveillance in gram-negative bacteria

Among the 13 mandatory surveillance systems identified for Gram-negative bacteria in 13 countries, carbapenem-resistant Enterobacteriales was monitored by 12 (38%). Third-generation cephalosporin-resistant Enterobacteriales (7; 22%), carbapenem-resistant *A. baumannii* (5; 16%), and carbapenem-resistant *P. aeruginosa* (4; 13%) were the other common pathogens under surveillance. Infections were monitored in 4 (13%), and both infections and colonizations were monitored in 8 (25%) (Table 2). Type of infection was specified by only three systems (two invasive, one bacteraemia). Data collection included resistance mechanism (5; 16%), antibiotic susceptibility testing MIC or disc diffusion (mg/mL or mm) (2; 6%) and antibiotic susceptibility testing interpretation (susceptible (S), intermediate (I), resistant (R)) (3; 9%) in a few systems. Age and gender data were included in a majority of the systems (11; 34%) whereas risk factors (invasive procedures, previous antibiotic use, previous hospitalization, co-morbidities) were

collected by only five systems (16%). Crude mortality was the only clinical outcome reported (7; 22%). Surveillance data were publicly available for nine systems (28%) and published either weekly (4; 13%) or yearly (5; 16%). Incidence as surveillance metric was used by six systems (19%).

Mandatory antibiotic resistance surveillance in gram-positive bacteria

Among the 12 mandatory notifications systems identified for Gram-positive bacteria in 12 countries, MRSA was monitored by all, vancomycin-resistant enterococci in 8 (25%) and vancomycin-resistant *S. aureus* in three systems (9%). Infections were monitored in 5 (16%), and both infections and colonizations were monitored in 6 (19%). Types of infections under surveillance were reported in only four systems (two bacteraemia, two invasive). Provisions for reporting laboratory results were available in a few surveillance systems: antibiotic susceptibility testing MIC or disc diffusion (mg/mL or mm) (2; 6%), antibiotic susceptibility interpretation (S, I, R) (3; 9%), and resistance mechanisms (5; 16%). Patient-based age and gender were reported by all but two systems (10; 31%), whereas risk factors and clinical outcome as crude mortality were collected by five systems (16%). Access to recent surveillance results was available for ten systems (31%), which published weekly (3; 9%), monthly (3; 9%) or yearly (4; 13%) updates. Incidence as a surveillance metric was used by 7 (22%) surveillance systems.

Mandatory reporting of outbreaks caused by WHO priority pathogens

Mandatory reporting of outbreaks was identified in nine European countries, of which only six provided public access (19%). Notification criteria and surveillance principles were diverse among these (Table 3) but all provided access to surveillance results with number of outbreaks being updated yearly (5; 16%) or weekly (1; 3%). Four countries (13%) allowed reporting of all outbreaks unrestricted by pathogens while two countries had indications on

Table 2
Framework of publicly accessible mandatory surveillance of WHO priority pathogens: Gram-negative bacteria versus Gram-positive bacteria in Europe

		Gram-negative (n = 13)	Gram-positive (n = 12)
		n (%)	n (%)
Data collection			
Notifying bodies	Health-care professional/facility	3 (9)	3 (9)
	Laboratory	4 (13)	4 (13)
Notification method	Laboratory and health-care professional/facility	6 (19)	5 (16)
	Notification forms	11 (34)	7 (22)
Case definitions	Web interface	5 (16)	6 (19)
	Infection	4 (13)	5 (16)
Infections monitored	Infection and colonization	8 (25)	6 (19)
	Invasive	2 (6)	2 (6)
	Bacteraemia	1 (3)	2 (6)
Resistance details	Health-care-associated	1 (3)	1 (3)
	Any	8 (25)	6 (19)
	Susceptibility results (MIC or Disc diffusion (mg/mL or mm))	2 (6)	2 (6)
Age and gender	Antibiotic susceptibility interpretation (S/I/R)	3 (9)	3 (9)
	Resistance mechanism	5 (16)	5 (16)
Risk factors ^a	Reported	11 (34)	10 (31)
	Device use (any)	1 (3)	4 (13)
Clinical outcome	Invasive procedures, including surgery	3 (9)	3 (9)
	Previous hospitalization	1 (3)	4 (13)
	Previous antibiotic use	1 (3)	1 (3)
	Factors for infection acquisition (travel, contact, etc.)	4 (13)	3 (9)
	Co-morbidities (any underlying condition)	3 (9)	3 (9)
	Mortality	7 (22)	5 (16)
Data dissemination			
Public access ^b	Available	9 (28)	10 (31)
	Not available	4 (13)	2 (6)
Publication frequency	Weekly	4 (13)	3 (9)
	Monthly	0 (0)	3 (9)
	Yearly	5 (16)	4 (13)
Data stratification	Age group and gender	4 (13)	6 (19)
	Sampling (infection or colonization)	1 (3)	3 (9)
	Specimen	2 (6)	2 (6)
	Type of infection	1 (3)	1 (3)
Indicators	Number of cases	8 (25)	9 (28)
	Incidence	6 (19)	7 (22)

Total identified = 15 surveillance systems in 15 countries.

^a Individual risk factor definitions vary from system to system.^b Refers to electronic literature published on surveillance websites, excludes publication in peer-reviewed journals and scientific conferences.**Table 3**
Framework of publicly accessible mandatory notification of outbreaks due to WHO priority pathogens in Europe

		N (%)
Data collection		
Target resistance	Any (unrestricted to pathogen)	4 (13)
	Methicillin-resistant <i>Staphylococcus aureus</i>	2 (6)
	Vancomycin-resistant Enterococci	1 (3)
	Carbapenem-resistant <i>Enterobacteriales</i>	1 (3)
	Third generation-resistant <i>Enterobacteriales</i>	1 (3)
Surveillance structure	Mandatory notification of outbreaks	3 (9)
	Mandatory notification of health-care-associated outbreaks	2 (6)
Notification period	Mandatory notification of clusters	1 (3)
Notification method	Immediate	2 (6)
	Notification forms	5 (16)
Outbreak setting	Web interface	5 (16)
	Phone	1 (3)
	Hospital	1 (3)
Transmission mode	Health-care facility	1 (3)
	Health-care facility and community	4 (13)
Control/intervention measures to tackle outbreaks	Reported	5 (16)
	Reported	3 (9)
Clinical outcome	Mortality	3 (9)
Data dissemination		
Publication frequency	Weekly	1 (3)
	Yearly	5 (16)

Total identified = 6 surveillance systems in 6 countries.

ARB-specific outbreaks. Data on outbreaks included information on transmission mode in five (16%), while prevention/intervention measures undertaken to control outbreaks were reported by only three (9%) surveillance systems.

Discussion

Our review shows that, although the burden of AMR at global level has been clearly recognized, fewer than half of the European countries (47%) implemented publicly accessible mandatory surveillance of at least one ARB among the 12 pathogens identified by WHO as in urgent need of new therapies [12]. Twelve countries target at least one 'critical' bacterium (most frequently carbapenem-resistant *Enterobacteriales*) and one 'high priority' bacterium (most frequently MRSA). Surveillance of 'high priority' fluoroquinolone-resistant *Salmonella*, *Campylobacter*, *Neisseria gonorrhoeae*, third-generation cephalosporin-resistant *N. gonorrhoeae*, and clarithromycin/metronidazole-resistant *Helicobacter pylori* was not mandatory in any European country. Notably, the type of data collected and disseminated differed between the 15 mandatory surveillance systems. Significant differences included heterogeneous definition of clinical samples, screening and type of specimen included. Epidemiologically relevant findings on resistance mechanisms, patient-based risk factors and clinical outcomes data were collected by only half the systems. Although surveillance results were frequently published as weekly or monthly numbers on new cases, stratification of data by

specimen, infection type, risk factors and clinical outcomes was not commonly in practice.

Mandatory notifications of outbreaks due to the WHO priority pathogens seem also limited at European level. These notifications could overcome publication bias associated with reporting of outbreaks in peer-reviewed journal [14]. According to our study, only six countries integrate publicly accessible outbreak reporting for ARB and only one country provides numbers on outbreaks every week. Reliable and timely surveillance data of outbreaks should help to identify new patterns of resistance and could drive early definition of effective infection control measures and interventions necessary to reduce the spread of resistance [15].

This study has limitations. It focused only on high and critical WHO priority pathogens without covering medium-priority pathogens. Although the authors believe that surveillance systems should cover all WHO priority pathogens, the choice was based on the values of the criteria used for the prioritization exercise, which included, for high and critical priorities, lack of effective infection control measures and treatments, and high mortality. Data were extracted from openly available literature only. It is possible that there are countries with mandatory reporting that do not provide publicly accessible data. To overcome this gap, EUCIC members and national surveillance representatives were contacted. No further mandatory surveillances fitting the study objective could be included. Some experts underlined that in their country they were in the process of implementing the necessary infrastructure. For example, in the Netherlands a law to make the reporting of carbapenem-resistant *Enterobacteriales* mandatory is in preparation. In Italy, the recently developed national action plan is under implementation and will include mandatory surveillance of most relevant antibiotic resistance. Likewise in Malta, dedicated regulations included in the national strategy will be formalized soon. The design of national mandatory surveillance systems is carried out to meet national objectives and action plans. Consequently, global, i.e. inter-country, comparisons could introduce a bias in the quality of surveillance methodologies and data dissemination. Of note, *Salmonella* and *Campylobacter* are under mandatory surveillance in many European countries and notifications are not defined by resistance to any target antibiotic. In countries such as Finland and Croatia, isolates must be sent to national reference laboratories, whereas Germany and Switzerland/Liechtenstein specify that they must be sent on request. If indeed susceptibility testing is performed (in local or national laboratories), resistance data for these pathogens might not be included in the surveillance results.

Well-known limitations of mandatory notifications include under-reporting and increased workload for public health authorities and expenditure [16–18]. In 2015 Bijkerk et al. [19] proposed a decision aid to help policy-makers weigh the necessity of implementing mandatory notification for any infectious disease under question. According to the authors however, their guide could not be applied to resistance monitoring because the disease to be surveyed (i.e. isolation of ARB) is not only associated to diseases but also to colonization which *per se* has no impact on an individual's health. A study on Swedish mandatory surveillance data on carbapenemase-producing *Enterobacteriales* indicates that inclusion of clinical and screening samples facilitates flexible analysis essential to understanding epidemiology of resistance [20].

Another issue to be considered is the difficulty in diagnosing some of the bacteria regardless of the susceptibility patterns. For example, testing for *H. pylori* can either be performed through the breath test or gastric fluid culture. In the first case, no analysis of resistance can be defined. However, even when cultured, susceptibility testing of *Helicobacter* usually happens in larger and more specialized laboratories. Another example is the *Neisseria* testing, which is sometimes done solely using molecular methods, without

testing for resistance, therefore decreasing the quality of data that could be collected for surveillance.

Current mandatory surveillance systems for ARB in Europe warrant improvement. Collection of data and meta-data needs to be standardized, otherwise subsequent analysis of the collected data, especially when comparing different countries, will remain difficult and external validity will be very low. Additionally, the frequency of publication of surveillance results needs to be harmonized. The detection of pathogens spreading over country borders will never be successful if, for example, surveillance data collected during January is reported by France in February and by Germany in August. Clonal spread of a resistant bacterium present in January in France and Germany might actually appear separated, solely due to the difference in time-point of reporting. Lastly, infection control measures necessary to stop such a spread would always be implemented too late [21].

The results of this review should push forward the debate on mandatory surveillance for high-priority ARB and restructuring of current surveillance strategies at national level in Europe. Making surveillance protocols and results freely accessible is considered a pillar of the European AMR strategy [22] and should be made an immediate priority. A platform to exchange experiences and outcomes between countries must be made available so that lessons learned from countries with a low endemicity for resistant bacteria can guide countries with high endemicity. The national plans should more clearly define the importance of mandatory surveillance and link the resistance rates with clinical data to develop effective, diagnostic and antibiotic stewardship policies. Technologies should be shared across Europe to make mandatory surveillance feasible for all nations. For difficult pathogens, particularly *H. pylori*, establishment of sentinel surveillance through national reference or special laboratories could be considered if establishment of mandatory surveillance is not possible but the data should be reported and published frequently to match the surveillance results of other priority pathogens. Major stakeholders should develop a European consensus on the role and significance of mandatory surveillance of AMR and define implementation, targets, indicators and dissemination measures. For Europe to serve as a model region, a common platform for data reporting will increase timeliness and effectiveness of infection control procedures.

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Transparency declarations

Frangiscos Sifakis is an employee of Boehringer Ingelheim Pharmaceuticals, Inc. Cuong Vuong is an employee of AiCuris Anti Infective Cures GmbH.

Author contributions

ET and NM conceived the study, provided expertise and contributed towards the review of the manuscript. NBR carried out data collection, analysis and drafting of the manuscript. GM, MC, FS, CV, AV and JRB critically reviewed the manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.cmi.2019.11.020>.

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