Antibiotic resistance surveillance systems: A review

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ABSTRACT

Objective:

Epidemiological surveillance is one critical approach to estimate and fight against the burden of antibiotic resistance (AR). Herein, we summarize the characteristics of surveillance systems devoted to the surveillance of AR worldwide and published in literature.

Methods:

We performed a systematic review of the literature available on PubMed from January 2007 to July 2019 (12.5 years). The key words (“surveillance system" OR "laboratory-based surveillance" OR "syndromic surveillance" OR "sentinel surveillance" OR "integrated surveillance" OR "population-based surveillance") AND ("antibiotic resistance" OR "antimicrobial resistance") were used. This research was completed with antibiotic resistance monitoring systems available on websites.

Results:

We identified 71 antibiotic resistance surveillance systems described by 90 publications from 35 countries: 65 (91.5%) national surveillance systems and 6 (8.5%) multinational. Two regions accounted for 73% of admissions: European region (37; 52.9%), and region of the Americas (14; 20.2%). Fifty-three focused on AR suveillance in human, 12 studied both humans and animals, and 3 focused only on animals.

The two most common bacterial species reported were *Staphylococcus aureus* (42; 59.2%) and *Escherichia coli* (39; 54.9%). Twenty out of 71 (28.2%) antibiotic resistance surveillance systems used prevalence as indicator, 3 (4.2%) used incidence and 7 (9.9%) both. Methicillin-resistant *S. aureus*, vancomycin resistance for *Enterococcus spp*, *S. aureus* and *Streptococcus pneumoniae,* penicillin-resistant-*S. pneumoniae,* Extended Spectrum Beta-Lactamase and carbapenem resistance for *E. coli* and *Klebsiella pneumoniae* were monitored.

Conclusion:

Our results showed heterogeneous surveillance systems. A "one health approach" is needed to monitor antibiotic resistance, with reference to the WHO Global Action Plan.

Keywords: Antibiotic resistance, surveillance systems, Clinical microbiology laboratories

INTRODUCTION

The 20th century was considered as the "golden age" of antibiotics, as they have been extensively used in humans and animals [1,2]. These antibiotics have contributed to a dramatic decrease in morbidity and mortality due to infectious diseases worldwide [3–6]. This antibiotic consumption has continued to increase in the 21st century, probably due to better acces of low- and middle-income countries to antibiotics. In addition global antibiotic consumption increased by 65% between 2000 and 2015 worldwide, which is inversely correlated with the decrease in deaths from infectious diseases [4,7].

However, the massive use of antibiotics also led to the selection of resistant bacterial strains [7,8]. A study in the USA has a positive correlation between the use of macrolides and the proportion of resistance in *Streptococcus pneumoniae* isolates (Spearman's ρ =64%, IC 95% 41% - 80% [9]. Increasing AR complicates infection management by limiting the number of active antibiotics available and results in difficult-to-treat cases of infections and situations where recommended and available antibiotics are no longer active. This situation has led some investigators to design mathematical models predicting several million death, due-to bacterial resistance-[10–12]. The European Center for Disease Prevention and Control (ECDC) estimated the number of extra deaths due to multidrug resistant (MDR) to be 25,000 humans deaths per year in the European countries in 2009 [12]. In 2013, the Center for Disease Control and Prevention (CDC) published a report estimating the number of extra deaths due to AR to reach 23 000 people per year in the USA [13]. The Burden study estimated that MDR bacteria were responsible for 12 500 extra deaths every year in France [14]. Finally, in 2016, the team of Lord Jim O'Neill published a report estimating that antimicrobial resistance could be responsible for 10 million deaths per year globally, by 2050 [11].

These reports have considerable caveats as they extrapolate through mathematical models on estimates and do not used objective epidemiological counts [8,10,15,16]. Therefore, one solution to collect antimicrobial resistance data is to implement an antibiotic resistance (AR) surveillance system [17]. Moreover, AR highly varies from one region to another according to the incidence and prevalence of infectious diseases, the panels of antibiotics used and antibiotic susceptibility tests performed. The future AR surveillance system implemented would ensure should take these disparities into account to propose an indicator (Incidence or Prevalence), which antibiotics are used and which tests for used. AR surveillance systems are defined as "a structured and systematic procedure to measure the prevalence or incidence of antibiotic resistance through continuous or periodical surveillance performed with a defined methodology and with specified indicators" [18]. The data collected by such systems can then be used to design empirical therapy and implementation of local and national antibiotic treatment guidelines [19]. Besides, AR can also be detected in animals and in the environment [20]. Several studies have already shown, for example, that people in contact with livestock, especially calves and pigs, have an increased risk of MRSA [21]. It is in this context that the WHO has implemented the concept of "one health". The latter notably advocates surveillance of AR in humans, in animals, and in the environment with a multi-sectoral partnership between different research teams [22]. AR surveillance systems can differ considerably regarding their methods and exhaustivity, which can limit the interpretation, comparison and extrapolation of their data. These surveillance systems are not uniformly implemented throughout the world. Some authors have already listed the different surveillance systems in Europe [23] and in low and middle-income countries [24]. However, there have been no studies of AR surveillance systems listed worldwide. The purpose of this review is to identify and to detail the different AR surveillance systems in the world. To this end, we will first inventory all different AR surveillance systems in the world, then identify the different

bacterial species monitored, as well as the critical phenotypes, and finally determine the incidence and/or prevalence of the major phenotypes by surveillance system.

MATERIAL AND METHODS:

1- Systematic review of the literature

We performed a systematic review of the literature available on PubMed to search for publications describing AR surveillance systems collecting and analyzing incidence and/or prevalence data on AR. To do so, we used the following words/terms “surveillance system", "laboratory-based surveillance", "syndromic surveillance", "sentinel surveillance", "integrated surveillance", "population-based surveillance", "antibiotic resistance" and "antimicrobial resistance". This research was conducted from January 2007 and July 2019 and papers written in English and French were included.

The Mendeley references manager was used to de-duplicated the search results. This PubMed search was completed by adding AR surveillance systems included reports published by learned societies or others not indexed in PubMed. References from relevant articles were also screened. Articles that do not mention a surveillance system, a surveillance program or a surveillance study were excluded after reading their abstracts. After reading the articles, only articles describing a surveillance system or a surveillance program in humans, animals and / or environment were retained.

Studies were included if they reported a surveillance system and provided incidence and/or prevalence data for at least a 1-year period since 2007.

The data collected included: surveillance systems, bacterial species, antimicrobials, geographical areas, antibiotic resistance patterns, system updates, incidence and/or prevalence.

2- Definition

An AR surveillance system was considered to be up to date when the system complied with the publication of reports (weekly, monthly or annual) that it had prepared or when the system published at least one report in the last 3 years. As example, we considered that ISIS-AR ('Infectious Diseases Surveillance Information System for Antimicrobial Resistance') to be up to date because the last report was dated 2017 and so was the EARS-NET network, while the last report was dated 2017.

We used the definition given by each system for a given AR phenotype without a re-interpretation of the antibiotic susceptibility test(s) when available. For the prevalence and/or incidence of AR, we simply used data from the different reports without modification.

Inclusion criteria: A surveillance system having a structured and systematic procedure for analyzing prevalence and/or incidence data, reporting data periodically or continuously, or having reported data at least a 1-year period since 2007.

Exclusion criteria: We excluded all articles referring to case-control studies, prevalence studies and cross-sectional study.

RESULTS:

1. Literature search

Our literature search enabled us to firstly identify 299 articles in PubMed. Of these articles, 90 (30.1%) met our inclusion criteria (Fig 1). These articles ultimately allowed us to clearly identify 71 AR surveillance systems. More details about these systems are summarized on Supplementary Table 1.

2. Localisation

Seventy-one AR surveillance systems from 35 countries were described, of which 65 (91.5%) were national surveillance systems and 6 (8.5%) were multinational (Table S.1). Two regions accounted for approximately 73% of admissions, European (37; 52.9%) and region of the

Americas (14; 20.2%). Other regions were: Western pacific region (12; 17.4%), African region (3; 4.3%), South East Asia region (3; 4.2%) and Eastern Mediterranean region (2; 2.8%). The most represented country was the USA with 7 out of 71 (9.9%) AR surveillance systems. 26 out of 71 (36.6%) surveillance systems were considered up to date; 45 out of 71 (63.4%) surveillance systems were not. 19 out of 71 (26.8%) are monitoring systems for which no report was found; 26 out of 71 (36.6%) are monitoring systems with at least one report found. 25 out of 26 (96.2%) had published at least one report in the past five years. Three out of 26 (11.5%) of them are real-time monitoring systems and have an alarm detection system for critical phenotypes (Marseille Antibiotic Resistance Surveillance System (MARSS), EPIdemiological Surveillance and Alert Based on MICrobiological Data (EPIMIC) and Swedish Surveillance of Antimicrobial Resistance (SVEBAR)). Nine out of 71 (12.7%) have an interactive database in which one could collect information on the percentage of resistance of specific antibiotics and/or phenotypes for a given period. Thirty out of 52 (57.7%) reports are written in English, 14 out of 52 (26.9%) in a local native language, 8 out of 52 (15.4%) in both English and local native language.

3. Bacterial species and phenotypes monitored

Sixty-three of 71 (88.7%) surveillance systems monitor 48 bacterial species and/or genera, and the others (11.3%) did not provide information on the bacterial species and/or genera being monitored. Table 1 shows the main species and/or genera monitored by the different AR surveillance systems. The most common bacterial species and/or genera reported were: *Staphylococcus aureus* (42; 59.2%), *Escherichia coli* (39; 54.9%), *S. pneumoniae* (30; 42.3%), *Pseudomonas aeruginosa* (26; 36.6%), *Klebsiella pneumoniae* (24; 33.8%), *Enterococcus faecalis* (19; 26.8%), *Salmonella* spp. (18; 25.4%), *Enterococcus faecium* (17; 23.9%), *Haemophilus influenzae* (15; 21.1%), and *Neisseria gonorrhoeae* (14; 19.7%). The surveillance system that had the greatest number of bacterial species and / or genus monitored

was ANRESIS (Swiss Antibiotic Resistance Surveillance database) with 26 species and / or genus. Eleven of 71 (15.5%) surveillance systems monitored one single bacterial species; the most common bacterium monitored was *N. gonorrhoeae* (3; 27.3%), followed by *Helicobacter pylori* (2; 18.2%). One of 11 (9.1%) is up to date (National TB surveillance system (NTSS)), 2 of 11 (18.2%) provided at least a 5-year report (European Gonococcal Surveillance Program (EURO-GASP), Gonococcal Isolate Surveillance Project (GISP)), and the remaining 9 (81.8%) have no reports found. Of these 71 surveillance systems, only 38 (54.3%) simultaneously monitored a critical antibiotic resistance phenotype. The most frequently monitored critical phenotypes were: methicillin-resistant *S. aureus* (MRSA) (30; 42.3%), carbapenem-resistant *Enterobacteriaceae* (19; 26.8%), vancomycin-resistant *Enterococci* (18; 25.4%), Extended Spectrum Beta-Lactamase for *Enterobacteriaceae* (16; 22.5%), *Staphylococcus* resistant to vancomycin (6; 8.5%) and streptococci resistant to penicillin (5; 7.0%).

4. Human vs Animals

Among the 71 surveillance systems, 53 (74.64%) were exclusively from human isolates, 12 (16.90 %) targeted both humans and animals, and 3 (4.22%) focused on the surveillance of AR in animals (Figure 1). The latter 6 surveillance systems monitored bacteria of zoonotic origin, including *Campylobacter* spp., *Salmonella* spp. and commensal bacteria (*E. coli*) according to the European Union (EU) legislation on monitoring and reporting of AR in zoonotic and commensal bacteria (2013/652/EU). As an example, the surveillance of AR and Antibiotic Usage in Animals in the Netherlands (MARAN) was launched in 2008 for the surveillance of AR data routinely produced by a network of 42 medical microbiological laboratories and one veterinary laboratory for the animal data. The medical microbiological laboratories were distributed as follows: four of these laboratories exclusively serve a university hospital, two exclusively serve general practitioner (GP) practices, obstetrician

practices, long-term care facilities and public health facilities, 36 serve both general hospitals and GP practices. [19]. *Campylobacter* spp. and *Salmonella* spp. isolates were sampled from food animals, meat and from humans with clinical enteral infections/acute gastroenteritis. The results of the antibiotic susceptibility testing (AST) were collected monthly from a laboratory information system that automatically generates reports. The data showed that there was no carbapenemase in the different *Salmonella* spp strains tested in 2017, whereas colistin resistance gene *mcr-1* was identified at low-level in *E. coli* from livestock (1.2%) and at higher levels in retail meat from chicken (7.7%), but not in *Salmonella*.

The Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM) was launched in 1999. The purpose of the JVARM antibiotic-resistance surveillance system is to monitor the susceptibility of foodborne pathogenic (*Campylobacter jejuni*, *Campylobacter coli* and *Salmonella* spp) and commensal bacteria (*E. coli*, *E. faecium* and *Enterococcus faecalis*) from production animals to antimicrobials agents. Data from the JVARM showed a slight increase of the prevalence of *mcr-1* in *E.coli* over the years [25].

5. Incidence and/or Prevalence of critical phenotypes

Twenty out of 71 (28.2%) antibiotic resistance surveillance systems for which data are available use prevalence as an indicator whereas 3 (4.2%) use incidence, and 7 (9.9%) use both prevalence and incidence. Table 2 shows the raw prevalence and/or incidence of the main phenotypes of the different antibiotic resistance surveillance systems. For Gram positive bacteria, only MRSA, vancomycin resistance for *Enterococcus spp*, *S. aureus*, *S. pneumoniae* and penicillin resistant for *S. pneumoniae* were found, and for Gram negative bacteria, Extended-spectrum-Beta-Lactamases (ESBL) for *E. coli*, *K. pneumoniae*, carbapenem resistant for *E. coli* and *K. pneumoniae* were monitored.

For MRSA, the prevalence of resistance was <5% in 4 out of 20 (20%) antibiotic resistance surveillance systems in the Netherlands (ISIS-AR), United Kingdom (BSAC), Finland (FIRE)

and Sweden (SVEBAR), 5-15% in 6 out of 20 (30%) antibiotic resistance surveillance systems in Switzerland (ANRESIS), Australia (AURA), EARS-NET, Bulgaria (BulSTAR), Croatia (ISKRA), Germany (ARMIN) and Japan (JANIS), >15% in 8 out of 20 (40%) antibiotic resistance surveillance systems in South Korea (KOR-GLASS), Argentina (WHONET-Argentina), Germany (SARI), Greece (WHONET-GREECE), France (ONERBA), CAESAR, Thailand (NARST), and Philippines (ARSP). The prevalence of carbapenem resistance was less than 1% in the majority of surveillance systems except for Thailand antibiotic resistance surveillance system (NARST) for *E. coli*, likewise for *K. pneumoniae*, the prevalence was <5% in 17 out of 24 (70.8%) , > 5% in 5 antibiotic resistance surveillance systems (Ears-net,), in Argentina (WHONET-Argentina), Thailand (NARST), Greece (WHONET-GREECE), CAESAR and Philippine (ARSP).

6. Advantages and disadvantages of different antibiotic resistance surveillance systems

The data collected by the various AR surveillance systems have the advantage of providing information on the actual burden of resistance at the local, national and international levels. For instance, in Marseille, the antibiotic resistance surveillance system (MARSS) has shown between 2001 and 2016 an increase of resistance to third-generation cephalosporins for *E. coli* invasive strains (0% vs 17.8%; $p<10^{-5}$) and *K. pneumoniae* (8% vs 35.4%; $p=0.001$), along with a decrease of MRSA strains (31% vs 19.8%; $p=0.006$) [26]. In Europe, according to the 2017 EARST-NET report, the EU and EEA weighted average percentage of MRSA has decreased (19.6% in 2014 to 16.9% in 2017) [27]. In the Netherlands, the antibiotic resistance surveillance system (ISIS-AR) has shown that the level of resistance to colistin in *E. coli* and *K. pneumoniae* remained stable over the last 5 years [19].

Different AR surveillance systems have different objectives, which imply a data collection methodology tailored to each objective. As example, the antibiotic resistance Surveillance

System (DANMAP) collects data on the consumption and AR of indicator bacteria, zoonotic bacteria and pathogenic bacteria of animal, food and human origin, to determine the association between consumption and resistance development, and modeling the transmission of AR to humans. The system ISIS-AR collects data on antibiograms and some epidemiological data in humans and animals.

AR surveillance systems do not use the same rule of interpretation, which makes comparison between them very difficult. In the USA, NARMS uses the Clinical and Laboratory Standards Institute (CLSI) interpretation rule and in Europe, EARS-NET uses the European Committee for Antimicrobial Susceptibility Testing (EUCAST) criteria. It has been shown that the change in interpretation tools from CLSI to EUCAST has increased the number of strains classified as multidrug-resistant (MDR) including *K. pneumoniae* (2.2%), *Enterobacter cloacae* (1.1%), *P. aeruginosa* (0.7%) and *E. coli* (0.4%) [28]. For some bacteria-antibiotic couple, such as *E. coli*-ciprofloxacin and *K. pneumoniae*, the agreement between CLSI and EUCAST was 77.8% and 61.5% respectively [28]. Patient clinical data are unavailable in most antibiotic resistance surveillance systems, and genotyping is almost absent in these systems. This is due on the one hand to the regulatory provisions of countries such as in European countries were privacy laws are increasingly defended. On the other hand, to obtain clinical information, it will be necessary to have a unique identifier for each patient, which is difficult for countries that do not have a medical information system in place.

DISCUSSION

We performed a review of antibiotic resistance systems available worldwide. In this review we attempted to be comprehensive, encompassing all AR surveillance systems in the world. It also provides information on the phenotypes and different bacterial species monitored. It

284 shows the value of the "one health" concept and describes the future surveillance system for
285 AR.
286 The seventy AR surveillance systems were mainly human surveillance systems. The bacterial
287 species monitored were those responsible for the main bacterial infections in humans (*S.*
288 *aureus*, *E. coli*, *K. pneumoniae*, *S. pneumoniae*, *H. influenzae*). However, few systems
289 monitor AR in animals (*Salmonella spp*, *Campylobacter spp*) and commensal (*E. coli*, *E.*
290 *faecium* and *E. faecalis*) bacterial species.
291 The data used by the different AR surveillance systems are very heterogeneous and difficult
292 to compare (selection of bacterial species to be monitored, choice of antibiotics, monitored
293 phenotypes, methods of antibiotic susceptibility determination, the fact that they use different
294 antibiotics to define the same phenotype is an example of heterogeneity). There are several
295 scenarios; some AR surveillance systems use cefoxitin, oxacillin and/or flucloxacillin to
296 define MRSA. The Dutch national antibiotic resistance surveillance system (ISIS-AR)
297 includes cefoxitin results to define MRSA and if this antibiotic is not available, oxacillin
298 and/or flucloxacillin are used [19]. The Canadian antibiotic resistance Surveillance System
299 (CARSS), however, uses methicillin, oxacillin and cefazolin to define this same phenotype
300 [29]. Another obstacle to compare data between different AR surveillance systems is the use
301 of different epidemiological indicators between systems and sometimes even within the same
302 AR surveillance system. Thus, the European network (EARS-NET), uses prevalence as an
303 indicator to estimate the burden of AR per pathogen [30,31], while the CNISP (Canadian
304 Nosocomial Infection Surveillance Program) antibiotic uses incidence [29]. The DANMAP
305 uses both prevalence and incidence in estimating the burden of bacterial AR [32]. These
306 limitations are related to a lack of international coordination, inadequate standardization of
307 epidemiological definitions, samples and data collected, culture media used, microbiological
308 testing methods, and publication of reports years after data collection [23]. The diversity of

sources of bacterial isolates considered is another limitation of some AR surveillance systems. Some surveillance systems focus only on invasive clinical specimens (blood and cerebrospinal fluid) while others include all types of clinical samples. This is a crucial aspect in estimating the burden of AR. Including all strains without regarding the sample nature allow to have a global snapshot of antibiotic resistance prevalence, even if it is just carriage. Having this information still give the possibility to make further analyses such as the prevalence of AR in invasive samples and allow to evaluate relation between AR carriage and infections. Focusing only on invasive samples could give a better idea of the impact of AR on mortality but the link between bacteria isolated in samples, even invasive ones, and mortality remains difficult to establish.

Therefore, a system collecting only blood cultures at a small sample size can hardly be compared to a system that collects all types of samples. The simple fact of considering only samples from invasive specimens could bias the weight estimate of AR, as De Kraker et al. have shown [16]. For example, in the various reports estimating mortality due to antibiotic resistance in Europe, only invasive samples are available; to obtain resistance in the other samples, a ratio has been applied, which has the effect of biasing the weight of resistance.

The other aspect that should be considered is the coverage by the antibiotic resistance surveillance system of the different laboratories and hospitals at a local, national, and global level. As an example, EARS-NET (European Antibiotic Resistance Surveillance Network) covers only tertiary hospitals in different countries and generalizes the burden of AR for specific pathogens. The French disease burden study estimated that mortality due to resistance in France was 12 500 deaths, but covered only 18% of French laboratories, and that they had only invasive samples, the others were obtained by applying ratios from the literature [8,14,16].

Although most of the AR surveillance systems listed in this review publish reports, the majority do so with a time frame of at least one year, which should be corrected by putting the data online in real-time. Thus, the publication of reports with real-time data makes it possible to update knowledge on emerging resistance events and mechanisms and detect an epidemic [19,23]. In addition, some AR surveillance systems, such as the Danish Integrated Antimicrobial Resistance Monitoring and Research Program (DANMAP) combine phenotypic identification with genotypic identification to identify *mecA* or even *mecC* genes in MRSA strains using whole genome sequencing (WGS) [32]. EUCAST members recommend to associate phenotypic surveillance with WGS since 2016 as a routine tool in clinical microbiology [33]. This method is as accurate to predict AR phenotype as phenotypic tests in *S. aureus* [34,35], *E. coli*, *K. pneumoniae* [36], *Salmonella* [37] and *Mycobacterium tuberculosis* [35,38]. The overall concordance rate was 90% between phenotypic tests and WGS according to the bacteria [33]. This tool is particularly useful in case of infections caused by slow-growing bacteria, such as Mycobacteria as it is faster than culture and allows informed and timely clinical decisions about antibiotic treatment strategies in patients [39]. Several recommendations suggested the implementation of surveillance of AR and antibiotic consumption in humans, animals and the environment [40].

In the light of our results, we find that no current system for monitoring AR takes into account the concept of “one health”, because of the absence of the environment component, the fauna in the data collected, but also because most current AR surveillance systems precede the concept of “one health” [40].

The fact that bacterial strains of animal or related origin have been identified in humans without direct exposure to animals, by linking them to food consumption and/or food handling, confirms the need for greater integration between human and animal surveillance systems [41]. For example, it has already been demonstrated by sequencing the entire genome

that MRSA in cattle has evolved from MRSA in humans [42]. Voss et al have also demonstrated that farm animals frequently transmit MRSA of animal origin to exposed humans [21]. The concept of “one health” recommends monitoring AR in humans, animals and the environment with multisectoral teams and international collaboration between different AR surveillance systems (or networks) [43]. It is in this same context that the WHO in its global plan of action against AR advocates a reinforcement of knowledge from the precise data from the surveillance. It would allow to deepen the knowledge on the real weight of the AR, its prevalence, incidence and geographical disparities among others, but also to optimize the use of antibiotics in human and animal health [44]. In addition, these data would allow us to know the actual number of deaths due to antibiotic resistance, which is currently being done in Marseille [8,10] .

The application of molecular techniques allows the detection and recognition of epidemic clones of resistant bacteria [45,46]. The integration of molecular technique could facilitate the detection of resistance mechanisms such as colistin [20]. Unfortunately, most current surveillance systems do not monitor colistin resistance while this antibiotic is a resort for the treatment of Gram-negative bacterial infections resistant to carbapenems. Thus, new mechanisms of colistin resistance have emerged in recent years around the world [20].

PERSPECTIVES AND FUTURE ACTIONS

Current computer systems and networks collect, analyze and transmit data at a large scale as we entered the period of big data. This should lead to collect, homogenize, analyze and report data at the broadest scale on the basis of true counts/measurements, rather than to lose ourselves in estimates, extrapolation and models. It is absolutely necessary to involve the various actors in the surveillance of antibiotic resistance (doctors, epidemiologists, veterinary surgeons, pharmacists) in the framework of "one health", in order to set up effective systems adapted to the current reality (Figure 2). Indeed, an ideal surveillance system would be a

system that combines from various sources/laboratories data from humans, animals and environments, analyzes the results of antibiotic susceptibility tests phenotypically, and combines molecular analysis by WGS to determine the distribution of high-risk clones and resistance mechanisms. These analyses must generate data available in the freely accessible public domain and export them in a standardized data exchange format. These antibiotic resistance surveillance systems must be scalable and extensible, reports must be available. In addition, given the disparity between the different methods of analysis and antibiotics tested, it is clearly identified that there is an urgent need to harmonize AST (Antibiotic Susceptibility Testing) techniques, to have minimal inhibitory concentration (MIC) for antibiotics to homogenize interpretations, and merge these collected data with a register of deaths due to AR. In the future, the various surveillance systems should have, in addition to microbiological data, demographic data and clinical data to facilitate understanding of the phenomenon of AR. This data, once collected, would allow us to monitor the evolution of antibiotic resistance. However, new legislation on general data protection regulations limits access to this data and this is a barrier to public health decision-making. In addition, these data could make it possible to set up registers of deaths due to antibiotic resistance necessary to avoid the fear caused by alarming published studies and reports.

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Figures and Tables

Figures: 2

Figure 1. Flowchart of the selection of the studies

Figure 2. Future Antibiotic Resistance Surveillance System

Tables: 2

Table 1: Summary of the different species and/or genera monitored by antibiotic resistance surveillance systems around the world.

Table 2 Prevalence and/or incidence of phenotypes monitored by the different antibiotic resistance surveillance systems

Supplementary data: 1

Table S1: Summary of different antibiotic resistance surveillance systems around the world

Figure 1. Flowchart of the selection of the studies

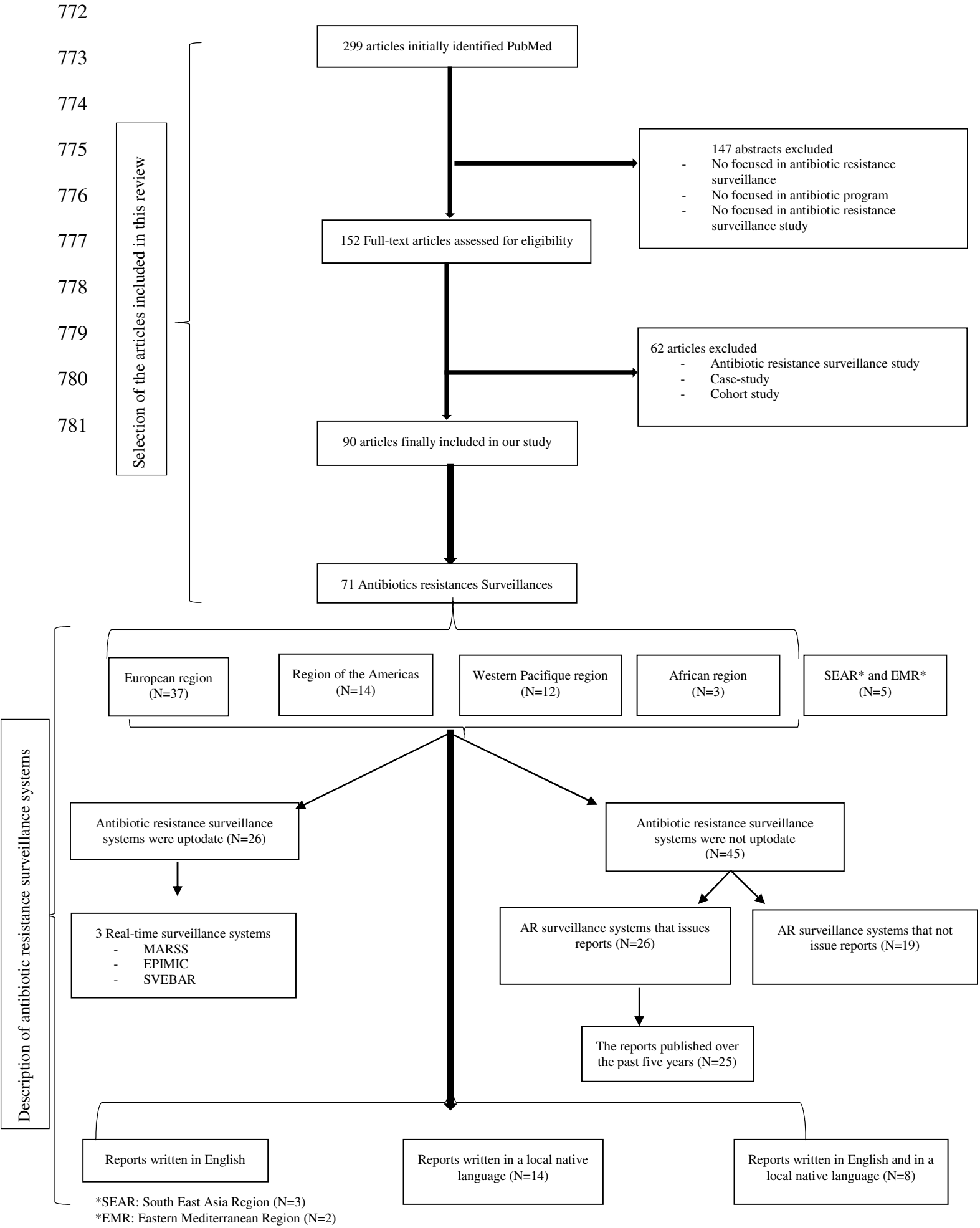
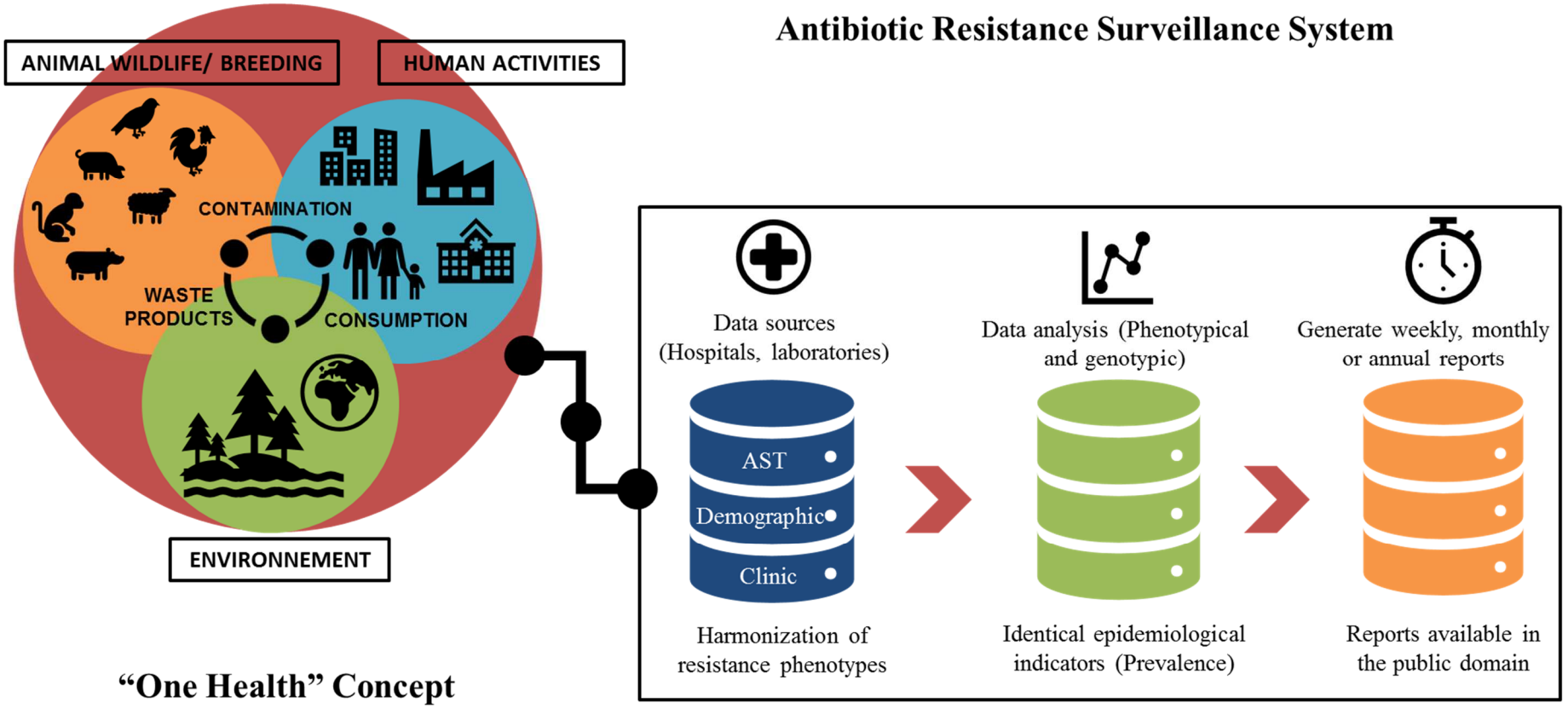
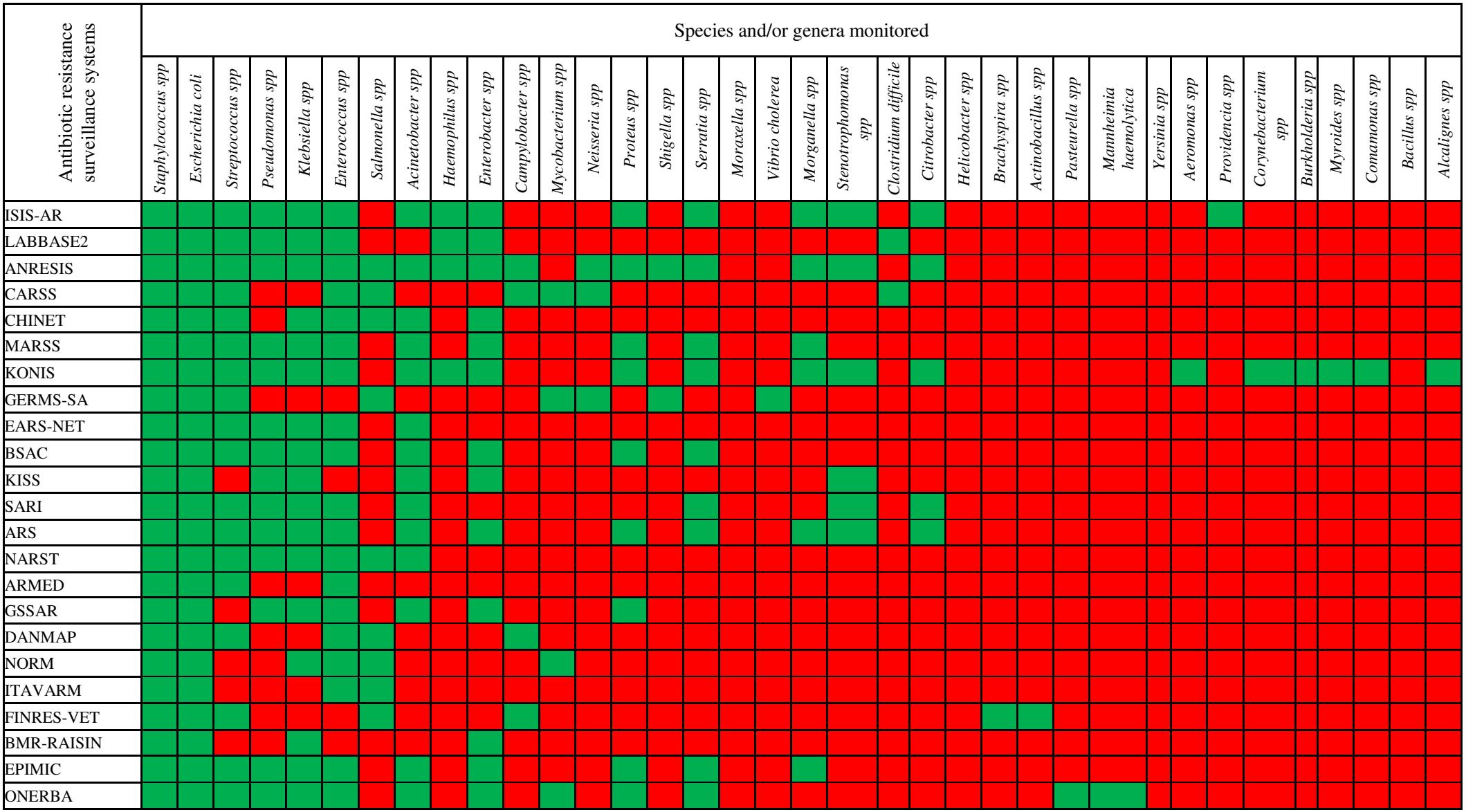
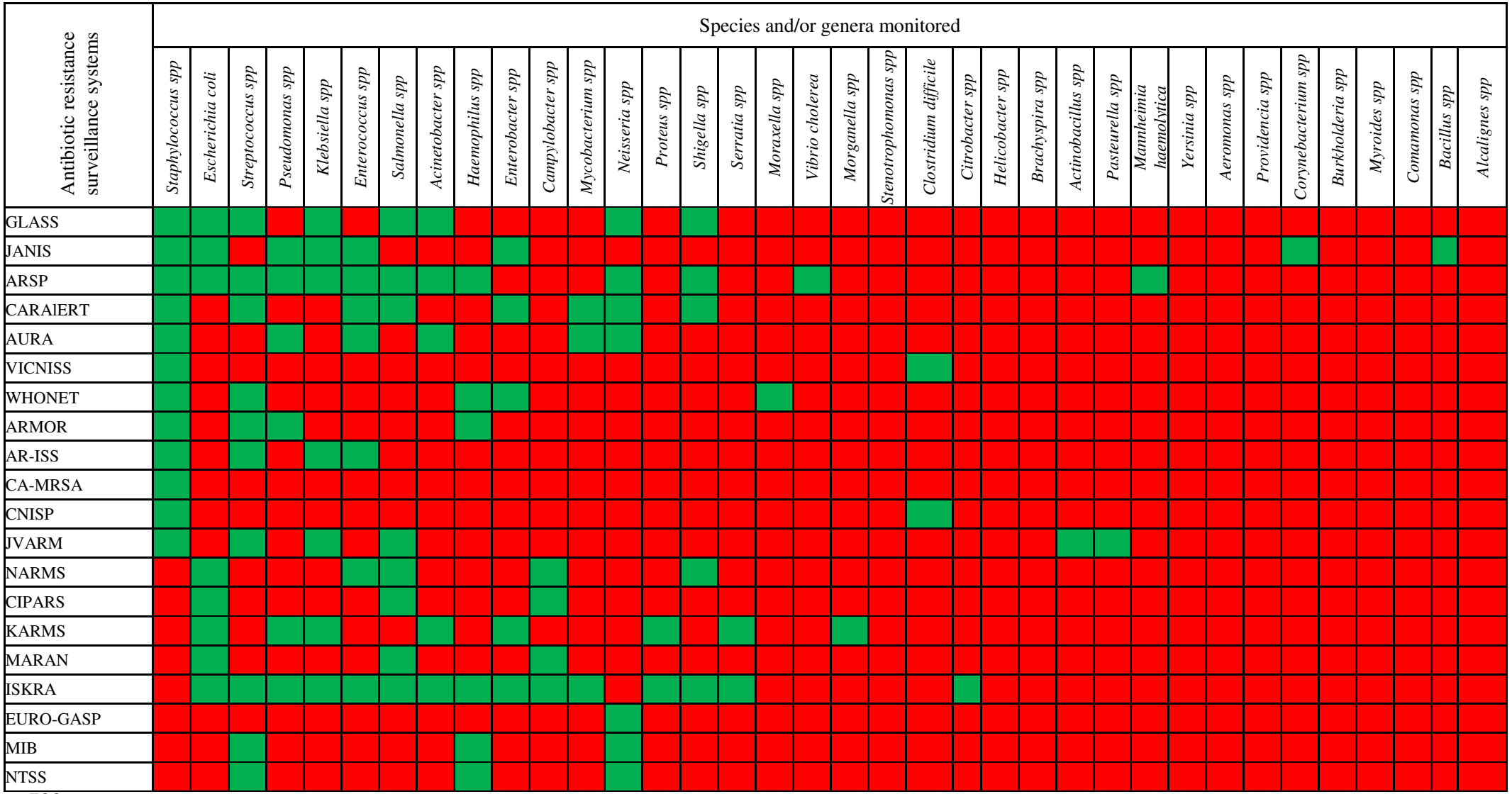


Figure 2. Future Antibiotic Resistance Surveillance System




Antibiotic resistance surveillance systems
Species and/or genera monitored
Staphylococcus spp
Escherichia coli
Streptococcus spp
Pseudomonas spp
Klebsiella spp
Enterococcus spp
Salmonella spp
Acinetobacter spp
Haemophilus spp
Enterobacter spp
Campylobacter spp
Mycobacterium spp
Neisseria spp
Proteus spp
Shigella spp
Serratia spp
Moraxella spp
Vibrio cholerea
Morganella spp
Stenotrophomonas spp
Clostridium difficile
Citrobacter spp
Helicobacter spp
Brachyspira spp
Actinobacillus spp
Pasteurella spp
Mannheimia haemolytica
Yersinia spp
Aeromonas spp
Providencia spp
Corynebacterium spp
Burkholderia spp
Myroides spp
Comamonas spp
Bacillus spp
Alcaligines spp
ISIS-AR
LABBASE2
ANRESIS
CARSS
CHINET
MARSS
KONIS
GERMS-SA
EARS-NET
BSAC
KISS
SARI
ARS
NARST
ARMED
GSSAR
DANMAP
NORM
ITAVARM
FINRES-VET
BMR-RAISIN
EPIMIC
ONERBA

787 **Table 1:** Summary of the different species and/or genera monitored by antibiotic resistance surveillance systems around the world.



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Antibiotic resistance surveillance systems	Species and/or genera monitored																																			
	Staphylococcus spp	*Escherichia coli*	*Streptococcus spp*	*Pseudomonas spp*	*Klebsiella spp*	*Enterococcus spp*	*Salmonella spp*	*Acinetobacter spp*	*Haemophilus spp*	*Enterobacter spp*	*Campylobacter spp*	*Mycobacterium spp*	*Neisseria spp*	*Proteus spp*	*Shigella spp*	*Serratia spp*	*Moraxella spp*	*Vibrio cholerea*	*Morganella spp*	*Stenotrophomonas spp*	*Clostridium difficile*	*Citrobacter spp*	*Helicobacter spp*	*Brachyspira spp*	*Actinobacillus spp*	*Pasteurella spp*	*Mannheimia haemolytica*	*Yersinia spp*	*Aeromonas spp*	*Providencia spp*	*Corynebacterium spp*	*Burkholderia spp*	*Myroides spp*	*Comamonas spp*	*Bacillus spp*	*Alcaligenes spp*
GISP																																				
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FIRE																																				
ARMIN																																				
SNARS																																				
SVEBAR																																				

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791 Green: the species or species monitored (we put the genus when we have several species of the same genus); Red: not monitored by the systems.

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793 **ISIS-AR:** Infectious Diseases Surveillance Information System for Antimicrobial Resistance; **LabBase2:** Health Protection Agency's voluntary;
794 **ANRESIS:** Swiss Antibiotic Resistance Surveillance database; **Euro-GASP:** European gonococcal antimicrobial surveillance programme;
795 **NARMS:** National Antimicrobial Resistance Monitoring System; **CARSS:** Canadian Antimicrobial Resistance Surveillance System; **CHINET:**
796 Surveillance system for bacterial epidemiology and resistance in China; **MARSS:** Marseille Antibiotic Resistance Surveillance System;
797 **KONIS :** Korean Nosocomial Infections Surveillance System; **GERMS-SA:** Group for Enteric, Respiratory and Meningeal Surveillance in
798 South Africa; **EARS-NET:** European Antimicrobial Resistance Surveillance Network; **BSAC:** Bacteraemia and Respiratory Resistance
799 Surveillance System; **KISS:** German national nosocomial infection surveillance system; **SARI:** Surveillance of Antibiotic-usage and bacterial
800 Resistance on Intensive Care Units; **ARS:** Antibiotic Resistance Surveillance System; **NARST:** Antimicrobial Resistance Surveillance Thailand;
801 **ARMED:** Antibiotic Resistance Surveillance & Control in the Mediterranean Region; **GSSAR:** Greek System for the Surveillance of
802 Antimicrobial Resistance; **DANMAP:** Danish Integrated Antimicrobial Resistance Monitoring and Research Programme; **ITAVARM:**Italian
803 Veterinary Antimicrobial Resistance Monitoring; **FINRES-VET:**Finnish Veterinary Antimicrobial Resistance Monitoring and Consumption of

Antimicrobial Agents report; **NORM:**Norwegian Surveillance System for Antimicrobial Drug Resistance; **BMR-RAISIN:**Bactéries MultiRésistantes-Réseau d'alerte d'investigation et de surveillance des infections nosocomiales; **EPIMIC:** EPIdemiological Surveillance and Alert Based on MICrobiological Data; **ONERBA:**National Observatory of Bacterial Resistance Epidemiology; **ENTERNET:**Italian surveillance system for foodborne and waterborne diseases; **BulSTAR:**Bulgarian Surveillance Trackling Antimicrobial Resistance; **ISKRA:**Intersectoral Coordination Mechanism for the Control of Antimicrobial Resistance; **FIRE:**Finnish Study Group for Antimicrobial Resistance; **ARMIN:**Monotoring antibiotic resistance in Niedersachsen; **AR-ISS:**Surveillance of antibiotic resistance; **SNARS:**Slovak National Antimicrobial Resistance Surveillance Sytem; **Svebar:**Swedish surveillance of antimicrobial resistance; **CA-MRSA:**CA-MRSA surveillance system; **CAESAR:**Central Asian and Eastern European Surveillance of Antimicrobial Resistance; **GLASS:** Global antimicrobial resistance surveillance system; **CNISP**:Canadian Nosocomial Infection Surveillance Programm; **JANIS:**Japan Nosocomial Infections Surveillance; **ARSP:**Phillipine Antimicrobial Resistance Surveillance Programm; **JVARM:**Japanese Veterinary Antimicrobial Resistance Monitoring System; **RELAVRA :**Latin American Surveillance Network of Antimicrobial Resistance; **MIB:**Invasive bacterial disease; **CARAlert:**National Alert System for Critical Antimicrobial Resistances; **AURA:**Antimicrobial Use and Resistance in Australia; **NTSS:**National TB surveillance system; **CIPARS:**Canadian Integrated Program for Antimicrobial Resistance Surveillance; **GISP:**Gonococcal Isolate Surveillance Project ; **KO-GLASS:**Korean Antimicrobial Resistance Monitoring System; **VICNISS:**Victorian Healthcare Associated Infection Surveillance System; **WHONET-Argentina**:National Argentine network for monitoring antimicrobial resistance; **ARMOR:**Antibiotic Resistance Monitoring in Ocular micRorganisms; **MARAN:**Monitoring of Antimicrobial Resistance and Antibiotic Usage in Animals in the Netherlands;

NB: Only systems with at least one species and/or genus monitored have been represented in this table.

823 **Table 2** Prevalence and/or incidence of phenotypes monitored by the different antibiotic resistance surveillance systems
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Antibiotic Resistance Surveillance Systems	Year	MRSA (Prevalence and/ or Incidence)	ESBL_*E.* (Prevalence and/ or Incidence))	ESBL_*K. pneumoniae* (Prevalence and/ or Incidence)	*E. coli* resistant to Carbapenem (Prevalence and/ or Incidence)	*K. pneumoniae* resistant to carbapenem (Prevalence and/ or Incidence)	*E. faecalis* resistant to vancomycin (Prevalence and/ or Incidence)	E. faecium resistant to vancomycin (Prevalence and/ or Incidence)	S. aureus resistant to vancomycin (Prevalence and/ or Incidence)	S. pneumoniae resistant to vancomycin (Prevalence and/ or Incidence)	S. pneumoniae resistant to penicillin (Prevalence and/ or Incidence)
ISIS-AR	2017	55963 (2.0)	177230 (4.5)	27322 (7.6)	176884 (0)	27285(0,2)	26385(0.3)	5406(1.1)	53075(0)	3024(0)	5351(4.7)
ANRESIS	2016	18763(6.7)	NA	NA	82118(0.3)	13598(1.8)	9867(0.2)	2861(4.8)	20212(0.1)	NA	1896(3.0)
AURA	2017	18551(13.5)	12	7	0.5	0.5	10424(0.5)	2 511(52.36)	NA	NA	4262(3.7)
CARSS	2017	3.13/10000	NA	NA	NA	NA	0.43	NA	NA	0	1132(10)
DANMAP	2016	3550(62.2/1000)	NA	NA	51618(<1)	15652(<1)	692(0)	692(7.3)	NA	NA	714(6.2)
KOR-GLASS	2015	390(53)	NA	NA	1104 (0)	422(2.0)	NA	NA	NA	NA	NA
EARS-NET	2017	56606(10.9)	121674(12.4)	30192(25.7)	120175(0.1)	29892(6.1)	18520(0.93)	12282(11.8)	NA		15402(6.9)
WHONET-ARGENTINE	2016	3046(45)	2170(17)	1903(48)	2170(1)	1903(14)	590(2)	226(64)	3046(0)	NA	732(25)
BSAC	2017	478(0.4)	496(8.7)	186(14.5)	496(0.2)	186(1.1)	105(1.0)	127(27.6)	478(0)	220(0)	220(8.2)
SARI	2017	23	16.3	15.7	NA	1.6	13.3	NA	NA	NA	NA

Antibiotic Resistance Surveillance Systems	Year	MRSA (Prevalence and/or Incidence)	ESBL_E. coli (Prevalence and/or Incidence)	ESBL_*K. pneumoniae* (prevalence and/or Incidence)	*E. coli* resistant to Carbapenem (Prevalence *and/or Incidence)*	*K. pneumoniae* resistant to carbapenem (Prevalence and/ or Incidence)	*E. faecalis* resistant to vancomycin ((Prevalence and/ or Incidence)	E. faecium resistant to vancomycin ((Prevalence and/ or Incidence)	S. aureus resistant to vancomycin (Prevalence and/ or Incidence)	S. pneumoniae resistant to vancomycin (Prevalence and/ or Incidence)	S. pneumoniae resistant to penicillin (Prevalence and/ or Incidence)
NARST	2017	30.8	50	48	2.16	8,83	0.7	8.3	9.6	0.8	37.8
WHONET-GREECE	2017	1716(33,16)	4938(10.9)	2138(60.56)	NA	2612(54.9)	2284(10.7)	2284(10.7)	NA	NA	NA
MSIS	2017	2538(49/ 100000)	3561(8.8)	1484(9.7)	3561(0)	1484(0)	421(0.2)	162(1.2)	2604(0)	NA	976(6.8)
NORM	2017	2538(49/ 100000)	3561(8,8)	1484(9,7)	3561(0,0)	1484(0,0)	421(0,2)	162(1,2)	2604(0,0)	NA	976(6.8)
BMR-RAISIN	2016	5180(0.24/1000)	8811(0.41/1 000)	3805(0.18/1 000)	NA	NA	NA	NA	NA	NA	NA
ONERBA	2015	11345(18.0)	34462(6.2)	18,3	0,37	0,18	3317(0)	624(0)	11303(0.1)	16.9	65(16.9)
BulSTAR	2016	222(13.0)	205(40.0)	NA	205(0)	95(3.0)	107(0)	41(15)	NA	NA	35(23.0)
ISKRA	2016	3 958(14.0)	19339(7.0)	4823(34)	19303(0.0)	4802(1.0)	5457(0.0)	826(15)	NA	NA	2130(22.0)
FIRE	2012	35997(3.00)	125655(8.6)	13950(2.5)	3306(0)	557(0)	23431(0)	4484(0.26)	NA	NA	1890(1.5)
ARMIN	2017	39847(14.4)	107680(14.2)	15410(16.9)	93436(0)	16401(0.2)	30498(0.1)	438(8.2)	37521(0)	NA	2508(12.4)
SVBAR	2016	3032(1.9)	NA	NA	4245(0.1)	1136(0.11)	NA	NA	NA	NA	NA

Table 2

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Antibiotic Resistance Surveillance Systems	Year	MRSA (Prevalence and/ or Incidence)	ESBL_*E.* (Prevalence and/ or Incidence)	ESBL_*K. pneumoniae* (Prevalence and/ or Incidence)	*E. coli* resistant to Carbapenem (Prevalence and/ or Incidence)	*K. pneumoniae* resistant to carbapenem (Prevalence and/ or Incidence)	*E. faecalis* resistant to vancomycin (Prevalence and/ or Incidence)	E. faecium resistant to vancomycin (Prevalence and/ or Incidence)	S. aureus resistant to vancomycin (Prevalence and/ or Incidence)	S. pneumoniae resistant to vancomycin (Prevalence and/ or Incidence)	S. pneumoniae resistant to penicillin (Prevalence and/ or Incidence)
CAESAR	2016	4732(24.7)	NA	NA	9420(28.00)	4934(22.5)	2566(2.9)	2184(15.7)	4950(0.3)	31(0)	861(26.7)
CNISP	2016	2241(2.3/1000)	NA	NA	24(0.10/1000)	49(0.10/1000)	299(0,32/1000)	299(0,32/1000)	NA	NA	NA
JANIS	2016	177,768(6.48)	NA	NA	284,316(0,00)	143,813(0.5)	124,305(0)	49,618(1.47)	181,288(0)	134(0)	36100(2.06)
ARSP	2017	5882(57.0)	3488(41.0)	6239(41.0)	8194(5.00)	11409(11.0)	1447(2.0)	791(5.0)	4250(2.0)	NA	421(10.0)
LABBASE	2017	NA	NA	NA	40272(0.07)	4000(1.5)	NA	NA	NA	NA	NA

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829 **ISIS-AR:** Infectious Diseases Surveillance Information System for Antimicrobial Resistance; **LabBase2:** Health Protection Agency's voluntary;
830 **ANRESIS:** Swiss Antibiotic Resistance Surveillance database; **NARMS:** National Antimicrobial Resistance Monitoring System;
831 **CARSS:** Canadian Antimicrobial Resistance Surveillance System; **EARS-NET:** European Antimicrobial Resistance Surveillance Network;
832 **BSAC:** Bacteremia and Respiratory Resistance Surveillance System; **SARI:** Surveillance of Antibiotic-usage and bacterial Resistance on
833 Intensive Care Units; **ARS:** Antibiotic Resistance Surveillance System; **NARST:** Antimicrobial Resistance Surveillance Thailand; **ARMED:**
834 Antibiotic Resistance Surveillance & Control in the Mediterranean Region; **DANMAP:** Danish Integrated Antimicrobial Resistance Monitoring
835 and Research Programme; **NORM:** Norwegian Surveillance System for Antimicrobial Drug Resistance; **BMR-RAISIN:** Bactéries

MultiRésistantes-Réseau d'alerte d'investigation et de surveillance des infections nosocomiales; **ONERBA:** National Observatory of Bacterial Resistance Epidemiology; **BulSTAR:** Bulgarian Surveillance Tackling Antimicrobial Resistance; **ISKRA:** Intersectoral Coordination Mechanism for the Control of Antimicrobial Resistance; **FIRE:** Finnish Study Group for Antimicrobial Resistance; **AR-ISS:** Surveillance of antibiotic resistance; **SNARS:** Slovak National Antimicrobial Resistance Surveillance System; **Svebar:** Swedish surveillance of antimicrobial resistance; **CA-MRSA:**CA-MRSA surveillance system; **CAESAR:** Central Asian and Eastern European Surveillance of Antimicrobial Resistance; **GLASS:** Global antimicrobial resistance surveillance system; **CNISP**: Canadian Nosocomial Infection Surveillance Program; **JANIS:** Japan Nosocomial Infections Surveillance; **ARSP:** Philippine Antimicrobial Resistance Surveillance Program; **AURA:** Antimicrobial Use and Resistance in Australia; **NTSS:** National TB surveillance system; **CIPARS:** Canadian Integrated Program for Antimicrobial Resistance Surveillance; **GISP:** Gonococcal Isolate Surveillance Project ; **KO-GLASS:** Korean Antimicrobial Resistance Monitoring System; **WHONET-Argentina**: National Argentine network for monitoring antimicrobial resistance;