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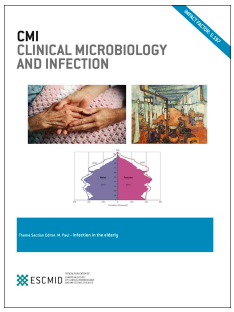

The Methodology of Surveillance for Antimicrobial Resistance and Healthcare-Associated Infections in Europe (SUSPIRE): A Systematic Review of Publicly Available Information

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The Methodology of Surveillance for Antimicrobial Resistance and Healthcare-Associated Infections in Europe (SUSPIRE): A Systematic Review of Publicly Available Information.

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ABSTRACT

Objectives: Surveillance is a key component of any control strategy for health-care associated infections (HAIs) and antimicrobial resistance (AMR), and public availability of methodological aspects is crucial for the interpretation of the data. We sought to systematically review publicly available information for HAIs and/or AMR surveillance systems organised by public institutions or scientific societies in European countries.

Methods: A systematic review of scientific and grey literature following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines was performed. Information on HAIs and/or AMR surveillance systems published until October 31, 2016 were included.

Results: 112 surveillance systems were detected; 56 from 20 countries were finally included. Most exclusions were due to lack of publicly available information. Regarding antimicrobial resistance, the most frequent indicator was the proportion of resistant isolates (27 of 34 providing information, 79.42%); only 18 (52.9%) included incidence rates; the data were only laboratory-based in 33 of the 42 providing this information (78.5%). Regarding HAIs in intensive care units, all 22 (100%) the systems providing data included central line-associated bloodstream infections, and 19 (86.3%) ventilator-associated pneumonia and catheter-associated urinary tract infections; incidence density was the most frequent indicator. Regarding surgical site infections, the most frequent procedures included were hip prosthesis, colon surgery and caesarean section (21 out of 22, 95.5% of the systems).

Conclusions: Publicly available information about the methods and indicators of the surveillance system is frequently lacking; despite the efforts of ECDC and other organisations, there is still a wide heterogeneity in procedures and indicators.

Registration: The SUSPIRE protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) on 12 February 2016. Protocol registration number: CRD42016033867.

Keywords: Antimicrobial resistance; healthcare-associated infections; surveillance; epidemiology; systematic review

INTRODUCTION

Health-care associated infections (HAIs) are well recognised causes of avoidable morbidity, mortality, and costs of care [1]. Additionally, the emergence and spread of antimicrobial resistance (AMR) is now considered a global public health threat [2, 3]. Both problems, HAIs and AMR are intrinsically related and may act synergistically within hospitals. Surveillance of HAIs and AMR are key parts of any control strategy [4]. Surveillance data have been traditionally used to detect problems, prioritise resources, evaluate control programmes and provide feedback. Appropriate descriptions of the methodology used and assessment of quality of data are critical to adequately interpret the information provided by surveillance; however, to our knowledge, the public availability of methodological information of the surveillance systems and their appropriateness has not been systemically reviewed. Additionally, during the last decades, surveillance data are been increasingly used and demanded for benchmarking and public reporting [5], which is controversial due to heterogeneity in methodology, inadequate control of confounders and different quality of data. Significant methodological heterogeneity in surveillance activities was shown by the European Centre for Disease Control and Prevention (ECDC) in 2008 [6]. In 2009, the European Council recommended to establish or strengthen active surveillance systems at national or regional level [7]; ECDC is leading a huge effort through the establishment of HAI-Net, a network of national/regional networks collecting surveillance data across Europe. Despite these efforts, heterogeneity in national surveillance methods and activities might still be important among European countries.

An additional potential result of surveillance activities might be to inform the burden of specific syndromes caused by resistant pathogens (e.g., the incidence rate of pneumonia caused by carbapenemase-producing Enterobacteriaceae) in order to better identify priorities

for research. Additionally, the identification of the patients' features would contribute to more efficient recruitment in randomised controlled trials by choosing sites with higher rates and patient population at higher risk of the target infections. To our knowledge, whether present surveillance systems provide useful information for these purposes has not been analysed.

The objectives of this work were: (a) to catalogue, review and summarise the information publicly available from active, official surveillance systems in European countries or regions; (b) to identify the main differences in methodological aspects and indicators used; and (c) to analyse the potential gaps to inform next steps in harmonisation processes. This study was performed under the auspices of EPI-Net, an epidemiological network for antimicrobial resistance and healthcare-associated infections formed as an outcome of the COMBACTE-MAGNET project, funded by the Innovative Medicines Initiative (IMI).

METHODS

A systematic scientific and grey literature search and review of surveillance systems for HAIs and/or AMR developed or endorsed by official institutions in Europe was performed. The study protocol and methodology, which followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline [8], was previously published [9].

Information Sources and searching strategies

Two independent strategies were followed. First, peer-reviewed literature (PubMed, EMBASE and Scopus) was systematically searched. References from the retrieved articles were also reviewed for potential additional articles. No language restrictions were applied. An example for the search strategy designed for the peer-reviewed literature for AMR is

"Antimicrobial resistan*" OR "Antibiotic resistan*" OR "Multidrug resistan*" AND Surveillance NOT reviews AND ("last 10 years"[PDat]); ((Surveillance [MeSH Terms]) AND Spain [MeSH Terms]) AND "Antimicrobial resistan*"; "epidemiology"[Mesh] AND "antimicrobial resistance" NOT animals.

Second, a comprehensive grey literature search included Google search engine and websites from the ministries of health, healthcare services, institutes of public health, European Centre for Disease Prevention and Control (ECDC), World Health Organization (WHO), scientific societies in the field (including the European Society of Clinical Microbiology and Infectious Diseases [ESCMID], the International Society for Infectious Diseases [ISID]; the International Epidemiological Association [IEA], the European Society of Intensive Care Medicine [ESICM] and the European Respiratory Society [ERS]). The search strategy used the following terms in English and local languages: "Antimicrobial resistance" AND/OR "Hospital-associated" OR "Hospital-acquired" OR "Nosocomial" AND "Surveillance" AND "epidemiology" OR "prevalence" OR "incidence". The time period was until October 31, 2016. Also, after the data were reviewed, the national representatives of the European Committee on Infection Control (EUCIC) of ESCMID were consulted as additional source to detect specific publicly available documents that might have been missed with our search strategy and for helping with the translation of specific terms. Anyway, only data from publicly available information was included in the review.

Eligibility criteria

We selected the information related to the 32 European countries, including the 28 European Union member states and the four countries from the European Free Trade Association (EFTA) (Iceland, Liechtenstein, Norway and Switzerland).

A HAIs or AMR surveillance system was defined as a structured and systematic procedure to measure the prevalence or incidence cases of HAIs and/or AMR, performed continuously or periodically, with a defined methodology and specified indicators. The inclusion criteria were: data were reported for at least one year period since 2006; the methodology was publicly available for review; and the system was promoted or endorsed by a regional, national or transnational official health organisations or scientific society. Surveillance systems referring their methodology to transnational systems (like those promoted by ECDC) were included.

Exclusion criteria were: systems exclusively declaring/notifying individual cases of a specific disease or pathogen (e.g., compulsory reporting of individual cases) not to be reported as proportion of cases, or cases per person or person-days at risk (rates); systems providing only animal, environmental or food data; surveillance data promoted by private companies; and outbreaks reports. Regional systems using the same methodology as national systems were also excluded.

Three independent reviewers (MNN, MDN and NBR) performed a two-step selection process. Titles and abstracts of the retrieved documents were initially assessed and non-relevant documents excluded. For data from grey literature, executive summaries, table of contents and documents (whichever was available) were screened. The full text of potentially eligible documents were then obtained and assessed for relevance or duplication against predefined selection criteria. When available, national experts were contacted to clarify protocol details.

Data extraction and analysis

Data extraction was limited to publicly available information, and was performed by the same authors. Disagreements were resolved by review and consensus with other co-authors (JRB and ET).

The data collected included the scope, population covered, quality assessment, dates of the information available; for AMR systems, pathogens, antimicrobials, definitions, inclusion criteria, risk factors, and indicators; for HAI surveillance systems in intensive care units (ICUs), risk factors, indicators for device related-infections (central line-associated bloodstream infections [CLABSI], ventilator-associated pneumonia [VAP] and catheter-associated urinary tract infection [CAUTI]); and outcome data; and for surgical site infections, inclusion of urgent interventions, antibiotic prophylaxis, procedure indicators, and the interventions included. Variables for which information was not specified or was not available were computed as "not reported/unknown".

We did not seek ethical approval for this study because data collected is not linked to individuals. The data are shown in a descriptive manner and stratified whenever possible by country/region, scope, population, settings, and major outcome (HAI and/or AMR control).

RESULTS

We detected 112 surveillance programmes/activities from 27 countries/regions. After reviewing the available data, 56 surveillance programmes were included (online supplementary Table S1). Noteworthily, information was not publicly available for the surveillance systems in 12 (21.4%) countries (Bulgaria, Cyprus, Czech Republic, Estonia, Iceland, Latvia, Liechtenstein, Luxembourg, Malta, Poland, Romania and Slovenia).

Of the 56 surveillance systems included, 33 (58.9%) target HAIs and 45 (80.3%) target AMR; 22 target both. The general features of the systems are shown in the online

supplementary Table S2. In summary, the coverage of the systems was national in 35, regional in 17 and transnational in 4. Among the national systems, 8 (22.5%) were focused on HAI only, 16 (45.7%) in AMR only, and 11 (31.4%) in both; external quality audits were applied or recommended in 13 systems (37.1%), and some type of internal quality assessment was reported in 5 (14.2%).

Surveillance systems for AMR

Data were available for 42 systems from 20 countries, and for the 4 transnational systems. The features of the 46 national, regional and transnational system are specified in online supplementary Table S3; the aggregated data for the 42 regional and national systems are summarised in Table 1. Among the latter, information about the susceptibility interpretative criteria used was available for 26 systems (61.9%); among these, the European Committee for Antimicrobial Susceptibility Testing (EUCAST) breakpoints were used in 22 (84.6%); in 9 of them, Clinical Laboratory Standards Institute (CLSI) breakpoints were used for some pathogens; in 3 (11.5%) and 1 (3.8%), local and CLSI criteria were the only used, respectively.

Data on the indicators used were available in 34 systems (80.9%). Among them, the most frequent indicator was the percentage of resistant isolates to specific drugs (27 systems, 79.4%; 64.2% of all systems); this was the only indicator in 16 (47.0%; 38.0% of all systems); 18 (52.9%; 42.8% of all systems) included indicators based on incidence (either as cumulative incidence or incidence density) as indicators. It is also important to notice that outcome data were not included in any system.

Regarding the pathogens, most of the systems included data on *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Enterococcus* spp., *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii;* online supplementary

Tables S4 and S5 show the antibiotics considered per pathogen in each system, and the aggregated data are summarised in Table 2. As regards specific mechanisms of resistance, 11 (55%) countries had at least one surveillance system reporting actively data on extended spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae* and 9 (45%) on carbapenemase-producing *Enterobacteriaceae. Clostridium difficile* was also included in most of them. Overall, there was a marked heterogeneity regarding the types of microbiological samples considered (online supplementary Tables S4 and S5).

Surveillance of HAI in intensive care units (ICUs)

A description of key features and indicators used in each surveillance systems of HAIs in ICU patients is showed in online supplementary Table S6. Overall, 32 systems plus one transnational system were included. Information about indicators was provided in 22 systems (68.6%). The most frequent indicators specified for device related-infections were density of incidence (all 22 providing information about indicators [100%] for CLABSI, and 19 [86.3%] for VAP and CUTI); 14 systems (63.6%) also included the device utilization rates. When all systems were considered, individual predisposing factors were collected in 20 systems overall (62.5%); as outcome measures, 16 (48.5%) included mortality during ICU stay, and 4 (12.1%) also included the length of ICU stay.

Surveillance of surgical site infections (SSI)

The features of the 32 systems for SSI plus the transnational ECDC programme are also shown in online supplementary Table S6. Data about stratification according to risk were provided by 19 systems (57.6%) and included the NNIS risk index in all of them; urgent procedures were included in 17 (51.5%) and data on antibiotic prophylaxis were collected in 16 (48.5%). For the 22 surveillance systems providing the type of interventions, the most

commonly included were: hip prosthesis, colon surgery and caesarean section in 21 systems (95.5%); cholecystectomy in 20 (90.9%); knee prosthesis in 19 (86.4%); coronary artery by-pass grafting in 18 (81.8%); cardiac valve replacement in 13 (59.1%); and laminectomy in 9 (40.9%). Data on procedure indicators such as checklist were included only in 17 systems overall (51.5%).

DISCUSSION

The most important findings in this systematic review of surveillance systems for HAIs and AMR in Europe are: (a) publicly available information on important methodological aspects and indicators measured are frequently lacking; (b) methodological heterogeneity across countries/regions was found in many aspects; and (c) in the case of AMR, there is a low frequency of systems including indicators based on incidence and clinical information.

Nevertheless, the data reported suggest important improvements in the homogeneity of surveillance activities with regard to previous reports [6] probably as a consequence of ECDC activities. First, the number of countries/regions with comprehensive systems has increased; in 2008, only 16 of 32 countries (50%) had surveillance programmes for surgical site infections and 10 (31.2%) for ICU-acquired infections. And second, for ICU infections and SSI the indicators are reasonably homogeneous. However, there are still important differences in the surgical procedures included in each country/region, which might be primarily be related to specific objectives, requirements in a given geographical area and in many occasions, in the available resources in each hospital

Of note, the inclusion of most procedures is voluntary in many systems. Additionally, surveillance of adherence to process indicators is still lacking in most surveillance protocols. Implementation of successful prevention bundles including assessment of the adherence to the

measures included in the bundle has been associated with reduced rates of CLABSI and SSI [10, 11], but some studies have found contradictory results [12]. Such activities have a strong rationale but require more resources. Homogeneous inclusion of such indicators in national or regional systems would benefit from guidance and consensus on the specific indicators, definitions and monitoring system. We did not collect information about other types of HAIs such as CLABSI, CUTI or healthcare-associated pneumonia outside ICUs. Information about these infections are being collected within the HAI-Net module for point prevalence surveys performed yearly [13].

There seem to be more heterogeneity in surveillance activities for AMR. In 2000, Monnet reviewed the international AMR surveillance initiatives in Europe [14], and detected four supported by public funding (WHO/AR, EARSS, INSPEAR and ESAR) and two with corporate funding (TSN and SENTRY). As in 2016, all countries participated in EARS-Net (the continuation of EARSS) and some also in the WHO initiatives (GLASS and CAESAR). However, only a few collect incidence-based indicators and even fewer collect data on specific infections and risk factors. The information provided by EARS-Net is of upmost importance from many perspectives, but it should be noted that it is a population-based system, do not provide incidence rates, and do not differentiate between nosocomial and community-onset episodes; in fact, wrong interpretations of these data may be misleading, as some authors recently suggested when analysing the conclusions obtained with extrapolation of the EARS-Net data (among other sources of information) to predict the expected burden of disease cause by resistant bacteria during future years [15]. Also, information about the type of infections caused by the resistant bacteria, outcomes and specific risk factors are usually lacking. As a consequence, the information about the real burden of specific infections caused by AMR pathogens or their health impact is very limited. The increasing availability of

automated information may improve this in the near future [16], but again guidance is needed to help decide the data to collect and the operational definitions.

The use of surveillance data for benchmarking is unavoidable despite all the present limitations of the systems. Therefore, the centres may be reluctant to provide real data to national or regional systems, but quality assessment of the data is mostly lacking. One of the biggest problems of many systems is the fact that reporting of results are performed yearly, which makes them useless in terms of real time action. Therefore, such surveillance systems would need to be able to provide data within an appropriate time frame, or ideally, in real time.

We were surprised to see the difficulties for accessing to the protocols of HAIs and AMR surveillance activities in many countries. For some countries the protocols could not be found and in many others, the protocols were not detailed enough. Therefore the fact that for many data we could not obtain information is one of the limitations of this review; while the available information strongly suggest that more homogeneity is needed, we acknowledge that part of the observed heterogeneity in the methodology of surveillance might actually be more related to an inadequate public reporting of detailed information. Nevertheless, this also reflects a lack of transparency in the procedures recommended and performed in many areas. The fact that surveillance data are not frequently made public further challenge the collection of informative data.

Finally, the information provided by the surveillance systems with the reported methodologies does not seem to be useful for the design of future randomised trials with older or newer drugs. If there is a drug potentially useful against several pathogens, which are causing different types of infections, it would be useful to know which of those infections are more frequent, in which populations they predominantly occur, and which are their clinical implications in order to decide the priority target for a trial and in which regions or countries

and patient population should the trial be performed. We do think that surveillance may provide useful information in this regard, so that research investment are efficiently aiming to the real problems. Of course, such efforts require more resources, and therefore the feasibility and sustainability is to be considered. This is one of the areas in which EPI-Net is working and will try to help and built a complementary surveillance structure to fill this need.

This study has limitations that should be considered when interpreting the data. First, despite the fact that we used different sources of information, we may have been unable to find or adequately interpret relevant publicly available information about some surveillance systems. Second, we already stated the problem regarding the fact that the available information was sometimes not detailed enough which may not reflect problems in the methodology but in reporting. Finally, the structured format used to collect the data might not have been able to perfectly capture the information provided in some systems.

In summary, while some harmonisation has been reach, there is still much room for improvement in surveillance systems in European countries regarding the quality of surveillance and homogeneity of indicators and procedures.

***Other members of the EPI-NET, COMBACTE-MAGNET and EUCIC group for SUSPIRE are (alphabetical order):** Francesco Burkert, Elena Carrara, Maja von Cube, Lubos Drgona, Kim Gilchrist, Herman Goossens, Stephan Harbarth, Delphine Hequet, Hasan Jafri, Gunnar Kahlmeter, Stefan Kuster, Christine Luxemburger, Mike McCarthy, Milan Niks, Abdel Oualim, Mario Poljak, Oana Sandulescu, Alexander Schweiger, Cuong Vuong, Irith Wiegand, Andreas Widmer, Anne Therese Witschi, Giorgio Zanetti and Walter Zingg.

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Authors' contributions

JRB conceived the study, led the development of the manuscript, provided supervision and mentorship to MNN who wrote the first draft, coordinated and integrated comments from coauthors and together with JRB is the guarantor of the review. MDN, NBR and PG contributed with data extraction and review of variables and information sources. VP assisted on data extraction. MS and MDT provided specific expertise on paediatric and Surgical Site Infections variables respectively. AV contributed with the selection of variables and FS contributed with development of the protocol and variables selection. ET provided specific expertise on epidemiology, contributed to data management and contributed to the development of the manuscript. All authors critically reviewed successive drafts of the manuscript, provided important intellectual input and approved the final version for publication.

Transparency declaration

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Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation or in manuscript development. This manuscript has been seen and approved by all members of the COMBACTE-MAGNET consortia before submission.

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Table 1. Features of 42 national and regional surveillance systems on antimicrobial resistance included in the review.

Variable		**Systems (percentage)**
Source of data	Laboratory only	33 (78.5)
	Laboratory and patients' charts	8 (19.0)
	Unknown/not reported	1 (2.3)
Duplicates policy	Duplicates excluded	25 (59.5)
Case definition	Isolates from clinical samples	22 (52.3)
	Infections	10 (23.8)
	Unknown/not reported	10 (23.8)
Indicators	Proportion of resistant isolates*	27 (64.2)
	Cumulative incidence*	11 (26.1)
	Incidence density*	12 (28.5)
	Unknown/not reported	8 (19.0)
Pathogens specified	*Streptococcus pneumoniae*	32 (76.1)
	Staphylococcus aureus	41 (97.6)
	Enterococcus spp.	31 (73.8)
	Escherichia coli	38 (90.4)
	Klebsiella pneumoniae	36 (85.7)
	Pseudomonas aeruginosa	34 (80.9)
	Acinetobacter baumannii	35 (83.3)
	Clostridium difficile	22 (52.3)

*Not mutually exclusive

Table 2. Drugs or drug families included in the 42 national and regional antimicrobial resistance surveillance systems

Pathogen	**Antimicrobial agent/s**	**Systems (percentage)**
Streptococcus pneumoniae	Penicillin	24 (58.1)
	Cefotaxime/ceftriaxone	19 (45.2)
	Fluroquinolones	19 (45.2)
	Macrolides	21 (50.0)
Staphylococcus aureus	Oxacillin	34 (80.9)
	Fluroquinolones	19 (45.2)
	Vancomycin	22 (52.3)
	Linezolid	18 (42.8)
	Aminoglycosides	15 (35.7)
Enterotococcus spp.	Ampicillin	26 (61.9)
	Vancomycin	30 (71.4)
	Aminoglcosides*	18 (42.8)
Escherichia coli / *Klebsiella pneumoniae*	Amoxicillin-clavulanate	24 (57.1)
	3rd gen. cephalosporins	29 (69.0)
	Carbapenems	28 (66.6)
	Fluoroquinolones	24 (57.1)
	Aminoglycosides	21 (50.0)
Pseudomonas aeruginosa	Ceftazidime/cefepime	28 (66.6)
	Carbapenems	28 (66.6)
	Piperacillin-tazobactam	26 (61.9)
	Fluoroquinolones	25 (59.5)
	Aminoglycosides	23 (54.7)
Acinetobacter baumannii	Carbapenems	26 (61.9)
	Colistin	26 (61.9)
	Tigecycline	14 (33.3)
	Sulbactam	14 (33.3)