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Original article

Estimating the number and incidence of carbapenemase-producing *Enterobacterales* infections in France in 2020: A capture-recapture study

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ABSTRACT

Objectives: Even though France faces few severe infections due to carbapenem-producing Enterobacterales (CPE), inter-regional epidemic stages render their dissemination a cause for considerable concern. CPE reporting relies in France on three non-exhaustive monitoring systems (MS): an early-alert system, a nationwide passive surveillance system and the National Reference Centre. We aim to estimate the number and incidence of CPE-related infections in France in 2020 and to identify any overlap between the three systems to determine whether their continued use still serves a purpose.

Methods: Data on clinical CPE isolates in 2020 were extracted from the three MS databases. Screening samples were excluded. Datasets were manually merged, isolate by isolate, so as to identify in which system(s) each isolate was reported. A system-participant was defined as any declarant reporting at least one isolate in an MS. Using our matched dataset, we performed Bayesian model averaging for capture-recapture estimations.

Results: All in all, 1722 CPE isolates were reported through the monitoring systems in 2020. We estimated that the number of CPE infections was almost twice this number, corresponding to incidence of 0.031 CPE/1000 hospital-days [CI95% 0.015–0.057/1,000 hospital-days], with regional disparities taken into account. Among participating the laboratories, 86% were involved in only one of the systems. Among clinical CPE isolates, 56% were isolated from urine.

Conclusion: Regarding this rare infection, surveillance based only on passive surveillance from voluntary hospitals does not reflect actual epidemiology. We recommend maintaining the three monitoring systems and improving the participation of hospitals' nationwide surveillance, the objective being to more accurately capture the real incidence of CPE infections.

1. Introduction

The spread of carbapenemase-producing *Enterobacterales* (CPE) is a major public health concern, since these emerging bacteria are resistant to most last-resort antibiotics. A recent report [1] estimated that the number of carbapenem-resistant *Klebsiella pneumoniae* infections in Europe increased by 47 % between 2016 and 2020.

In France, surveillance of CPE infections occurs through the nationwide network known as Surveillance and Prevention of Antibiotic Resistance in hospitals (SPARES), which collects data from the laboratories of voluntary participating hospitals (coverage of 55 % of total hospital-days in 2020) [2]. Clinical microbiology laboratories can send their suspected CPE isolates for microbiological expertise to the associated National Reference Center (NRC) for antimicrobial resistance specialized in CPEs [3]. Since 2001, infection prevention and control teams in all healthcare facilities have been urged to notify cases of CPE bacterial infection or colonization to the national Healthcare-Associated Infections Early Warning and Response System (HAI-EWRS), using a specific report form [4].

Since 2001, only sporadic cases or limited outbreaks of CPE have

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been reported in France [5,6]. In the first 10 years, while most outbreaks were linked with an imported case from another country, some regional diffusion was likewise described [4,7,8]. In 2018, a European study of patients colonized by CPE [9] showed that France had entered an inter-regional epidemic stage, which is the final stage prior to the endemic phase. Owing to a strict "search and control" strategy [10], CPE infections nevertheless remain rare in France. For several years, carbapenem resistance in Enterobacterales isolated from blood or cerebrospinal fluid culture has remained below 1 % [11]. However, the nationwide SPARES surveillance network recently documented an upward trend in CPE infection incidence, from 0.010/1,000 hospital-days in 2019 to 0.015/1000 hospital-days in 2021 [2]. Data from the NRC also revealed a sharp increase in the annual number of CPE isolates received for analysis: 3031 isolates in 2019 compared with 2012 (n = 343) and 2015 (n = 1272) [12]. That is why CPE diffusion is currently a major cause for concern, and a comprehensive overview of French CPE infection epidemiology is clearly called for.

The three nationwide data sources on CPE epidemiology have different purposes: surveillance (the SPARES network), microbiological expertise (NRC) and alerts (HAI-EWRS). Furthermore, as they are based on voluntary participation, they are non-exhaustive in their reporting of clinical CPE isolates. The number of unreported cases of CPE infection is consequently open to question. Capture-recapture, which is a method using several sources of information from the same population to estimate (a) the number of cases not identified by any of the sources, and (b) the total number of cases of a disease [13], appears to be the optimal design for our study. In addition, the overlapping of the three data sources has never been estimated, and the number of laboratories participating in at least one of these monitoring systems is unknown. Lastly, we question the usefulness of the specific CPE HAI-EWRS form with regard to constantly evolving epidemiology.

The objectives of this study were as follows:

To provide, using a capture-recapture method, a more accurate estimation of the number and incidence of CPE-related infections in France in 2020;
To estimate the overlap between the three monitoring systems and to determine whether continued use of the three systems still serves a purpose.

2. Methods

2.1. Data sources

2.1.1. The nationwide SPARES surveillance system

Individual anonymized microbiology records of clinical samples obtained from the laboratories of voluntary participating hospital laboratories are exhaustively collected on an annual basis. Collected data include the anonymous identification number of the patient, identification of the laboratory and hospital, date and type of sampling, microorganism, antimicrobial susceptibility profile (phenotypic data) and specific resistance mechanism (carbapenemase production…). Based on specimen types, the SPARES surveillance system targets clinical isolates. Some screening samples (rectal swabs…) are systematically excluded during data collection.

The SPARES database was searched using the following inclusion criteria:

– confirmed carbapenemase-producing Enterobacterales;
– sampling date between 1 January and 31 December 2020.

A case of CPE-related infection in the SPARES data was defined as: Enterobacterales isolate with a mention of carbapenemase production. Duplicates were defined according to the SPARES methodology as isolates from one patient for whom an isolate of a similar species with the same antibiotic susceptibility profile had already been identified during the study period in the same specimen type; they were removed from the database.

2.1.2. NRC for antimicrobial resistance

On a voluntary but recommended basis, clinical microbiology laboratories send Enterobacteriale isolates presenting decreased susceptibility to carbapenems to NRC for expertise to search for carbapenemase production. It is recommended to send the first isolate of each patient suspected of CPE. As the data source relies on the goodwill of laboratories, it is non-exhaustive. While it is difficult to evaluate coverage of the system, in 2020, 86 out of 101 French departments sent at least one isolate to the NRC (a total of 3289 isolates received in 2020, of which 67.1 % were confirmed CPE from either clinical or screening samples). The sending form included the pseudonymized number of the patient, identification of the laboratory, and the date and type of sampling. All isolates received for expertise were identified by MALDI-TOF mass spectrometry (Microflex, Bruker Daltonics). For all Enterobacteriale isolates, susceptibility testing was performed by disc diffusion on Mueller–Hinton (Bio-Rad) according to the Antibiogram Committee of the French Microbiology Society guidelines. Carbapenemase activity was searched using the Carba NP test [14]. The five major families of carbapenemases (KPC, NDM, VIM, IMP, and OXA-48-like) were detected using lateral flow immunochromatographic assay, NG-Test Carba5 (NG-Biotech), as previously described [15].

The NRC database was searched using the following inclusion criteria:

– confirmed carbapenemase-producing Enterobacterales isolate;
– sampling date between 1 January 2020 and 31 December 2020.

The specimen type was manually declared by the laboratory, with a clear distinction made between screening (mostly rectal swabs) and clinical samples. In line with the scope of our study, we excluded all screening samples from our analyses. A case of CPE-related infection in the NRC data source was defined as any patient with an Enterobacterales isolate with confirmed carbapenemase production.

2.1.3. HAI-EWRS notifications

Since 2001, the HAI-EWRS has been implemented in France to quickly detect unusual and emerging events in hospitals, facilitate outbreak investigations and implement control measures. Notification is performed by the healthcare setting's infection prevention and control team, in collaboration with the laboratory. It is strongly recommended to record all cases of CPE bacterial infection or colonization, but due to its voluntary nature, data are not exhaustive. For users, a specific report form for CPE bacteria notification has facilitated data entry since September 2017. The report form provides, among other variables, data on healthcare facilities and laboratories (name and location), aggregated total number of infected cases in the outbreak (when no secondary cases have occurred, total number of cases is one), and microbiological information for the first case (microorganism(s) identified, mechanism of resistance, and type of specimen).

The HAI-EWRS database was searched using the following inclusion criteria:

– all notifications involving at least one CPE reported at the national level based on the 'microorganism' item of the CPE form.
– notifications made between 1 January and 31 December 2020.

Notifications reporting only CPE isolated from screening samples, as declared by the declarant in "type of specimen", were excluded.

We analyzed the following variables:

- microorganism(s) identified (up to three different microorganisms for a given patient);
- mechanism(s) of resistance (up to two mechanisms per microorganism);
- type of specimen.

2.1.4. Denominator data to estimate incidence

The activity of each French healthcare facility is declared annually in an exhaustive compulsory administrative survey [16]. From this database, we extracted the number of hospital-days in 2020 for each hospital with declarants.

2.2. Combining the three datasets

The three datasets do not include the personal identifiers or common unique anonymized numbers of patients. Therefore, we had to consider the probability of two records relating to the same isolate based on a set of variables. To be considered identical, the following criteria had to be met:

1) two isolates involving the same bacterial species;

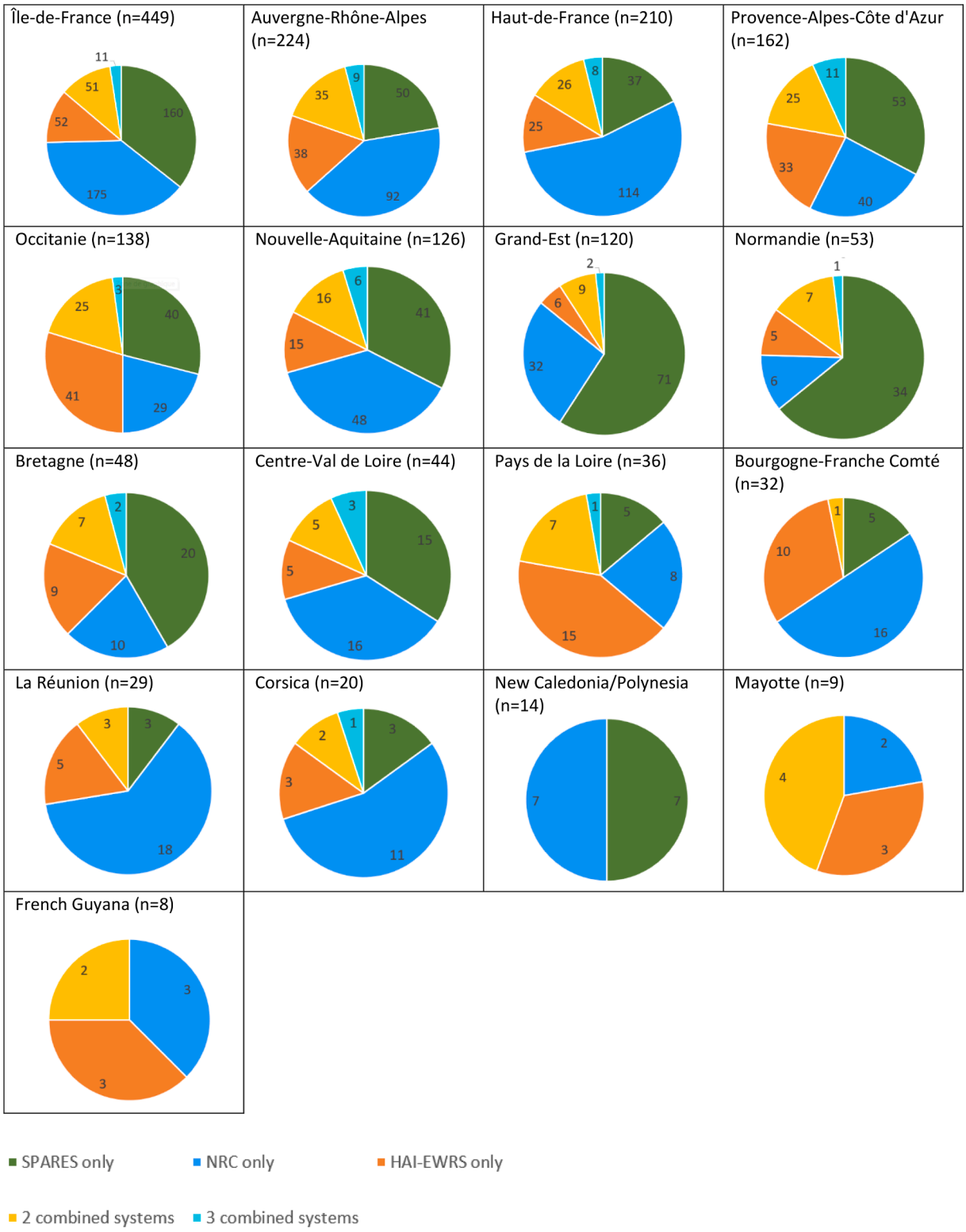

Fig. 1. Number of reported carbapenemase-producing clinical *Enterobacterales* isolates according to monitoring system and region, France, 2020 (n = 1722). *HAI-EWRS: Healthcare-Associated Infections Early Warning and Response System. NRC: National Reference Centre. SPARES: Surveillance and Prevention of Antibiotic Resistance in hospitals.*

2) AND slightly different specimen types, as the thesaurus of the three systems is not identical.
3) AND sampling dates having occurred within a 2-week period (expert consensus) considering that two systems (NRC and HAI-EWRS) manually report the sampling date, with the recording potentially delayed by a few days

Duplicated reports were combined in a matched dataset.

A declarant (laboratory or infection control team) was considered as a system-participant when reporting at least one isolate using this system during the study period.

2.3. Analysis

The total number of laboratories having reported at least one isolate in one of the monitoring systems, as well as the number isolates reported in each system, and the total number of unique isolates in France were analyzed. We estimated the overlapping of the reporting system by determining the number of laboratories participating in one system in proportion to the total number of laboratories having participated in at least one system.

We defined teaching hospitals as tertiary hospitals, local hospitals as secondary hospitals, and local private clinics as primary hospitals.

As the clinical microbiology laboratories of hospitals reporting a HAI-EWRS notification are encouraged to send the isolates to the NRC, possible interaction between these two datasets was taken into account. With regard to the matched dataset, we applied a Bayesian model averaging method for capture-recapture estimations, as dependence is best managed with this type of model [17,18]. Because we suspected heterogeneity of capture in the data related to a given region, the dataset was stratified into subgroups according to French regions. Population size was estimated for the subgroups and added up to obtain the national estimate. Analysis was performed using the free Shinyrecap application [19].

2.4. Ethical statementt

Pseudonymous surveillance data were collected from laboratories and healthcare settings only for the public interest mission of the French public health agency or its partners, in accordance with the French data protection authority. Analyses were performed in agreement with the European and French regulations on personal data protection (GDPR).

3. Results

3.1. Number of participating laboratories

In 2020, 521 out of the 3915 French laboratories [20] reported at least one clinical CPE isolate in at least one of the three monitoring systems for CPE. Out of these 521 laboratories, 27 % were involved only in the SPARES surveillance, 31 % sent isolates only to the NRC, and 28 % reported CPE in the HAI-EWRS alone. Consequently, 86 % of participating laboratories were involved in only one of the three CPE monitoring systems existing in 2020, while 12 % were involved in two systems and 2 % in all three. The different French regions showed substantial heterogeneity in their choice of monitoring system (Fig. 1). In eight regions, the NRC was the monitoring system used to report the majority of CPE isolates, whereas SPARES surveillance and HAI-EWRS predominated in four and two regions, respectively.

3.2. Number of reported clinical CPE isolates

In 2020, a total of 730 clinical CPE isolates were reported through the SPARES, 863 through the NRC and 469 through the HAI-EWRS. The distribution of these isolates by region is shown in Fig. 1. The number of unique cases after matching was 1722. Overlapping between monitoring systems is shown in Fig. 2. Among the 1722 reported unique isolates, 1438 (83.5 %) were reported in only one of the monitoring systems, while 228 unique isolates (13.2 %) were reported in two monitoring systems, and 56 (3.3 %) in the three systems. As expected, the largest overlap was found between the HAI-EWRS and NRC: 32,8 % (154/469) of the isolates reported to the HAI-EWRS were also reported to the NRC. The smallest overlap was found between SPARES and the HAI-EWRS: 14.1 % (103/730) of the isolates reported to the SPARES were also reported to the HAI-EWRS.

Tertiary and secondary hospitals reported a majority of the 1722 CPE isolates, with 26 % (n = 450) and 37 % (n = 645), respectively. Primary care hospitals reported 11 % (n = 188) and long-term care facilities 4 % (n = 65). CPE isolates originated from 348 healthcare facilities: 28 tertiary hospitals, 209 secondary hospitals, 71 primary hospitals, and 40 long-term care facilities. In addition, 22 % (n = 374) of the CPE isolates were of unknown origin, because they were analyzed by a private community laboratory that did not declare whether the patients were hospitalized or not.

Most of the clinical CPE isolates (56 %, n = 973) were isolated from urine (Fig. 3). A non-negligible portion (9 %, n = 156) were isolated from blood culture and 10 % (n = 166) from the respiratory tract.

Among these clinical CPE isolates, the most prevalent bacterial species were *Klebsiella pneumoniae* (38 %, n = 648), *Escherichia coli* (22 %, n = 378), and *Enterobacter cloacae complex* (10 %, n = 168). In blood culture, the same species were likewise the most prevalent: *Klebsiella pneumoniae* (40 %, n = 62), *Enterobacter cloacae* (22 %, n = 35), and *Escherichia coli* (21 %, n = 32).

For 1177 among the 1722 isolates, the mechanism of resistance was recorded: the most prevalent was OXA-48-like (69 %, n = 809, of which 686 were OXA-48), followed by NDM (18 %, n = 211), VIM (9 %, n = 101), KPC (3 %, n = 45), IMI ((0,7%, n = 8) and IMP (0,3%, n = 3). SPARES surveillance does not collect resistance mechanisms.

3.3. Estimation of the total number of CPE-related infections

The capture-recapture methodology applied to our three datasets estimated that the total number of clinical CPE isolates in France in 2020 was 3287 [$CI_{95\%}$ 1.566–6.096], corresponding to an incidence of 0.031 CPE/1000 hospital-days [$CI_{95\%}$ 0.015–0.057/1000 hospital-days]. The estimated regional incidences are shown in Fig. 4.

4. Discussion

This is the first study to estimate the total number of CPE-related infections in France, using a capture-recapture design. We confirm that CPE infections are rare (0.031 CPE/1000 hospital-days [$CI_{95\%}$ 0.015–0.057/1000 hospital-days]), especially when compared with other drug-resistant bacteria such as extended spectrum beta-lactamase-producing Enterobacterales (EBLSE), which had an estimated incidence of 0.52 EBLSE / 1000 hospital days in clinical samples in 2021 [2].

The estimated CPE incidence of 0.032 CPE/1,000 hospital-days found in our study is three times higher than that estimated by the national SPARES surveillance system in 2020 (0.013 CPE/1000 hospital-days). Two explanations may be given for this underestimated incidence by the SPARES surveillance. Firstly, we have shown that CPE-related infections are rare in France with pronounced regional disparity, and only around one-third of French hospitals participated in the SPARES surveillance in 2020. Secondly, some large tertiary hospitals did not participate in this surveillance. For these rare infections, the surveillance of incidence based only on passive surveillance from voluntary hospitals does not appropriately reflect actual epidemiology. It therefore remains necessary to continue using the EWRS system to alert health authorities whenever an outbreak occurs, and to draw upon the expertise of the NRC to investigate new resistance mechanisms and compare isolates. The best way to calculate real incidence would be to increase the number of participants in the SPARES surveillance system,

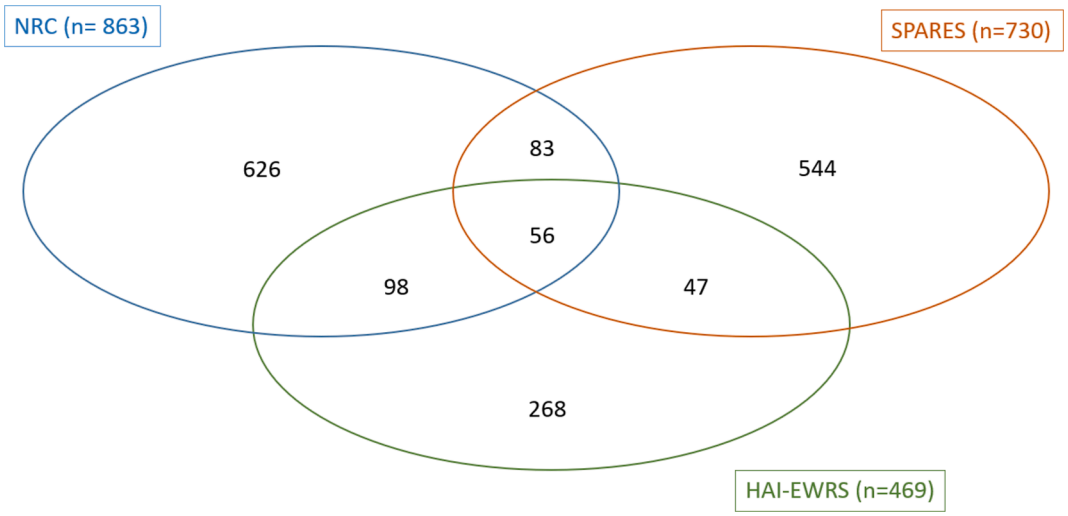

Fig. 2. Number of reported carbapenemase-producing Enterobacterales isolates isolated from clinical samples, according to monitoring system, France, 2020 (n = 1,722). *HAI-EWRS: Healthcare-Associated Infections Early Warning and Response System. NRC: National Reference Centre. SPARES: Surveillance and Prevention of Antibiotic Resistance in hospitals.*

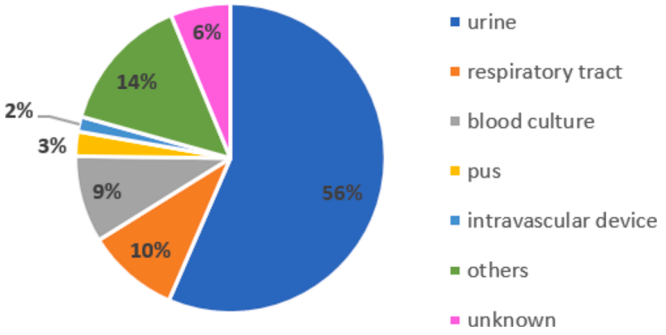

Fig. 3. Type of clinical samples for the reported carbapenemase-producing Enterobacterales isolates, France, 2020 (n = 1,722).

especially in tertiary hospitals. We therefore recommend incentivizing the participation of hospitals in the national SPARES surveillance so as to improve routine monitoring of CPE infection incidence in France.

Similar to susceptible Enterobacterales, clinical CPE isolates originated mostly from urinary samples (56 %). Isolates from blood cultures were rare (9 %). This distribution of CPE according to specimen type is similar to that observed for ESBL-producing Enterobacterales [2]. One limitation of our study is that the majority (56 %) of CPE isolates came from urine and, in some circumstances (presence of a urinary catheter…), it is difficult to distinguish true infection from carriage. The same holds true for isolates from the respiratory tract, especially if the patient is intubated in the intensive care unit. We may therefore have slightly overestimated the number of CPE infections.

The three most prevalent CPE species (*Klebsiella pneumoniae, Enterobacter cloacae* and *Escherichia coli*) identified in our study accounted for 70 % of the clinical CPE isolates. This is consistent with previous French studies or surveillance reports [12].

We uncovered regional disparity in CPE incidence, with regional incidences ranging from 0.010 to 0.053 CPE/1000 hospital-days. The regions with the highest incidence (Ile-de-France, French overseas territories) have numerous interactions with foreign countries with comparably high CPE incidence. That much said, other explanations may be explored. Firstly, the level of participation in SPARES surveillance and HAI-EWRS and the tendencies of laboratories to send isolates to the NRC differ between regions. Secondly, infection control practices may vary from one region to another. Surprisingly, Corsica, which is an insular region, has high estimated incidence. The majority of isolates reported in this region in 2020 originated from private laboratories, probably from patients previously hospitalized in the nearby Provence-Alpes-Côte d'Azur region.

In 2020, 348 out of the estimated 3000 French healthcare facilities reported at least one clinical CPE isolate via the monitoring systems. Coverage of the systems is difficult to estimate, as non-participating healthcare facilities may simply not have had any CPE isolates in clinical samples in 2020, meaning that they did not meet the inclusion criteria, or that while they may have had some clinical CPE isolates, they chose not to participate. However, among the 31 French tertiary hospitals, which are the most likely to encounter patients with CPE-related infections, 28 participated in at least one of the three systems, leading us to assume a high rate of participation.

CPE infections remain an emerging public health threat in France, and strong control measures, including surveillance, are still necessary to prevent their spread. However, monitoring systems should be regularly reviewed so as to ensure that they adequately correspond to current epidemiological situations and that data reporting remain adequate. Unfortunately, a lack of unique isolate identifiers in the three datasets renders the task of matching exceedingly difficult and time-consuming. A study similar to our own cannot be routinely repeated. Since 86 % of participating laboratories reported data through only one monitoring system, the co-existence of three different monitoring systems for CPE isolates in France seems necessary in view of optimally monitoring CPE epidemiology and preventing the spread of infection in France. We therefore recommend, at least in the short term, maintaining the three systems, especially insofar as they have complementary objectives: maintaining nationwide epidemiologic surveillance with the SPARES, ensuring microbiological expertise with the NRC, and alerting healthcare facilities with the HAI-EWRS.

As regards other European countries with similar CPE epidemiology, Germany has likewise implemented three complementary monitoring systems with distinct objectives. The German Antimicrobial Resistance Surveillance System collects routine data on antimicrobial susceptibility testing from voluntarily participating laboratories across the country. Since 2016 reporting for CPE infections and colonization is mandatory. Early identification and notification of cases to local public health authorities is aimed at enabling rapid implementation of control measures to prevent further spread. In England, as an increasing number of local laboratories are adopting methods to detect carbapenemase activity locally, the need to send specimens to the national reference laboratory

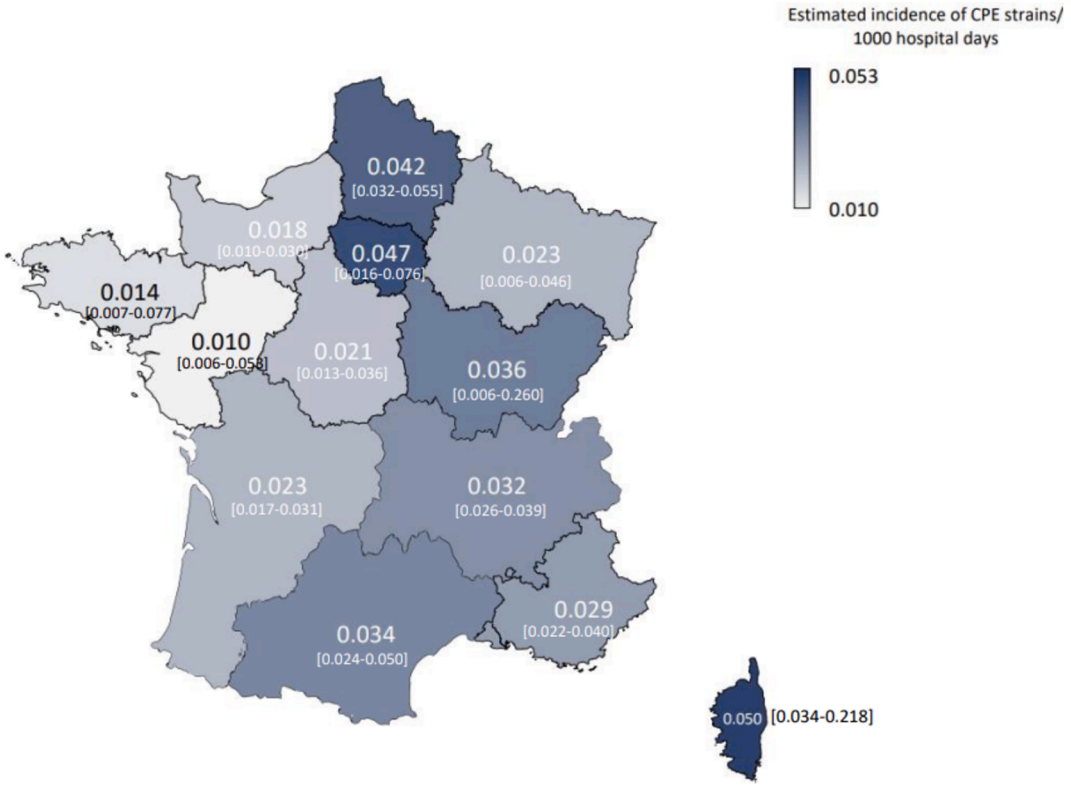

Fig. 4. Estimated incidence of carbapenemase-producing Enterobacterales (CPE) isolates from clinical samples, by region, France, 2020. *French overseas territories:* French Guyana: 0.036 [0.032–0.079]. Reunion Island – Mayotte: 0.053 [0.034–0.218].

has decreased, leading to gaps in data capture and reporting. To address this issue, England updated its Health Protection Regulations in October 2020, making it a legal requirement for local laboratories to report carbapenemase-producing Gram-negative bacteria to the national public health agency.

One limit of our study is that only for the first case of each CPE report does the HAI-EWRS data provide information on type of specimen and species. If more than one case is reported in the form, only the first one is taken into account in our capture-recapture study. Therefore, overlap with the NRC data or the SPARES mission data may have been slightly underestimated. We assume this to be a minor gap; in 2020, only 13 % of the notifications reported more than one case [21].

Another limitation of our study is its use of data from 2020, which was heavily marked by the COVID-19 pandemic. Hospital activity sharply decreased that year, as a large number of non-urgent procedures were postponed [22,23]. Since the overall number of patients admitted to hospital decreased, the data from 2020 do not reflect usual data. While the impact of the pandemic on resistant bacteria diffusion at the national level was partially reported, some authors showed that measures to prevent COVID-19 did not always decrease the incidence of multidrug-resistant bacteria, with several outbreaks having been described [24,25]. That year, the number of HAI-EWRS CPE notifications and CPE isolates received by the NRC decreased for the first time in quite a while. This may be associated with the COVID-19 pandemic, given that i) the increased workload of infection and prevention control teams in regions with high COVID incidence probably led to under-notification of CPE cases, and ii) the number of screening samples analyzed by laboratories decreased. Indeed, the proportion of isolates from screening samples among all CPE isolates sent to the NRC decreased in 2020 compared to previous years: 65.3 % in 2020, 70.1 % in 2019, 69.3 % in 2018 and 68.3 % in 2017 [12]. Accordingly, the estimated incidence of CPE infections may have been slightly underestimated in our study.

5. Conclusion

Our study confirms that while CPE infections are rare in France, estimated CPE incidence is three times higher than that calculated by the national SPARES surveillance system. We believe our study may be useful to other countries that face the same increasing trend in CPE referrals.Monitoring systems should be regularly reviewed with regard to evolving epidemiology, and our methods and findings may arouse interest and provide inspiration.

Author contributions

Mélanie Colomb-Cotinat conceived and designed the study, conducted the analysis, contributed to interpretation of the results, and wrote the original manuscript;

Amélie Jouzeau, Aurélie Chabaud, Christian Martin and Lory Dugravot provided the national surveillance data, and contributed to interpretation of the results;

Gaëlle Pedrono contributed to the data analysis, interpretation of the results and revised the manuscript;

Isabelle Poujol provided the early-alert system data, contributed to interpretation of the results, and revised the manuscript;

Sylvie Maugat contributed to interpretation of the results;

Catherine Dumartin and Loic Simon contributed to interpretation of the results, and revised the manuscript;

Laurent Dortet, provided the National Reference Centre data, conceived and designed the study, contributed to interpretation of the results, and revised the manuscript.

Anne Berger-Carbonne, conceived and designed the study, contributed to interpretation of the results, and revised the manuscript.

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