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Title Page

Trends in sepsis incidence and mortality in France between 2015 and 2019

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Abstract

Objective : This study aims to provide a case definition of sepsis of presumed bacterial etiology based on ICD-10 codes, to assess the trends in sepsis incidence and mortality between 2015 and 2019 in France and to describe the characteristics of affected patients and hospital stays.

Design : Nationwide, population based cohort study.

Setting : Metropolitan France and between 2015 and 2019.

Participants : Sepsis cases of presumed bacterial etiology were selected from the French National Hospital Discharge Database (PMSI) were identified from corresponding ICD-10 codes for explicit sepsis or implicit sepsis.

Main outcomes measures : Annual overall and age- and gender-specific incidences and 95% confidence intervals as well as trends in sepsis incidence and mortality were estimated. Comorbidities, length of hospital stay and outcomes were described.

Results : The incidence per 100 000 [95% CI] increased from 345.6 [344.2-347.0] in 2015 to 403.5 [401.9-405.0] in 2019 and remained higher for men compared to women. Children under 1 year and patients over 75 years had consistently the highest incidence. The most common comorbidities were cancer and chronic heart failure. The median hospital length of stay was 12 days. Most patients came from home but only half of them returned home after their hospital stay and approximately 15% were discharged to long term care. In-hospital mortality was about 25% and declined along the study period.

Conclusions : Medico-administrative databases can be used to provide nationwide estimates of the in-hospital burden of bacterial sepsis. The results confirm the high burden of sepsis in France. These data should be complemented by estimating the additional burden associated with fungal and viral infection during the COVID-19 pandemic.

Strengths and limitations of this study

- **The study uses nationwide data from the anonymized French National Hospital Discharge Database (PMSI)**
- A case definition of sepsis based on ICD-10 codes reflecting the Sepsis-3 definition is provided
- The study provides trend in sepsis incidence for the most recent years and shows a trend for reduced mortality after adjusting for sex, age, comorbidities, septic shock and infection sites
- This methodology may require further validation by comparing our results with clinical data

Introduction

Sepsis is a complex disorder, associated with long term morbidity and major economic impacts, responsible for several millions of deaths per year worldwide [1–4]. The challenge of defining sepsis led to several revised definitions over the past decades. In 2016, the Third International Consensus Definition of sepsis (Sepsis-3) defined sepsis as a "life-threatening organ dysfunction due to a dysregulated host response to infection." [5]. Indeed, organ dysfunction, was found to have better ability to predict in-hospital mortality or to target patients with higher risk of adverse outcomes than the original SIRS criteria and the previous sepsis-2 definition[6–10]. However, the successive changes of sepsis definition made it difficult to identify the true incidence of sepsis and to assess of the variation of incidence over time and across countries [1,2].

In 2017, concerned by the amount of sepsis related deaths and recognizing the potential to mitigate the burden and impact of sepsis, the seventieth World Health Assembly adopted a resolution to improve the prevention, diagnosis, and management of sepsis, urging Member

States to collect information and to initiate actions in accordance with WHO guidelines [11]. In France, a report commissioned by the French General Director of Health, in response to WHO resolution, identifies new measures and proposes a clear framework for future actions; including the analysis and the reporting of epidemiological data [12].

Clinical data or medico-administrative database can be used to assess sepsis incidence. Large scale studies generally rely on medico-administrative data which is a cost-effective way to study large cohorts [13]. However, the range of ICD codes used to identify sepsis in medico-administrative databases may change or be partially replicated in the different studies, leading to varying estimates [13–15]. Moreover, disparities were identified in sepsis incidence based on medico-administrative data compared to clinical data [16,17]. As no consensus exists regarding sepsis identification based on ICD codes and acknowledging that sepsis has no pathologic gold standard, a careful selection of explicit and implicit sepsis codes has been suggested, with the objective of maintaining good specificity and sensitivity [13,14,16].

This study aims to provide a case definition of sepsis based on ICD-10 codes, to assess the trends in sepsis incidence and mortality between 2015 and 2019 in France and to describe the characteristics of patients and hospital stays.

Methods

Data

The study consisted of a secondary data analysis of a cohort of all patients with bacterial infections and registered in the anonymized French National Hospital Discharge Database (PMSI) issued from the French health care database (SNDS)[18] (see online supplementary appendix A : eMethods). Therefore, only the incidence of sepsis of presumed bacterial etiology (referred to herein as sepsis) was estimated. The study, analysis and data extraction were approved by the French Data Protection Agency (CNIL, approval DE-2016–176).

Demographic data were obtained from the French Census of the National Institute of Statistics and Economic Studies [19].

Study population and selection of the hospital stays with sepsis

The study population included all patients hospitalized with sepsis between January 1st, 2015 and December 31st, 2019 in metropolitan France. Only hospital stays longer than 1 day were considered in the analysis. For patients with multiple stays per year, only one stay was considered for the descriptive analysis, to estimate in-hospital mortality and to estimate annual incidence.

Similarly to previous studies[1,20,21] sepsis was defined as either explicit sepsis or implicit sepsis (referred to hereafter as selection type). Explicit sepsis was defined as a stay with one of the selected ICD-10 codes for sepsis as primary diagnosis (PD: condition requiring hospitalization), related diagnosis (RD: adds information to PD) or significant associated diagnosis (SAD: complications and co-morbidities potentially affecting the course or cost of hospitalization). In the absence of specific sepsis ICD-10 codes, implicit sepsis was defined as a stay with one of the selected ICD-10 codes for infection as PD, RD or SAD with two associated conditions: 1/ ICU admission 2/ One of the selected ICD-10 codes for organ dysfunction or a code for organ support from the Common Classification of Medical Acts (CCAM) (see online supplementary appendix A : eTable 1).

Incidence

Annual overall incidence and age and gender specific incidence and 95% confidence intervals were calculated from 2015 to 2019 and expressed as the number of cases per 100 000 inhabitants.

Description of patients, hospital stays and site of infection

Sex, age, Charlson index and detailed comorbidities were described for all patients[22]. A total of 15 sites of infection was identified using the ICD-10 codes list defined by Opatowski et al.[23] : Bones and joints, Ears, nose and throat, Eyes, Gastrointestinal and abdomen, Heart and mediastinum, Lower respiratory tract, Medical devices, Nervous system, Newborn, Pregnancy, Skin and soft tissues, Urinary and genital tracts, Multiple sites and Unknown. Details for site classification are described in the eMethods in the supplementary appendix A online. Admission source, hospital discharge, yearly number of hospital stays as well as the percentage of septic shock and admission to ICU were also described. As admission to ICU and organ dysfunction/support were part of the selection criteria for implicit sepsis, the percentage of admission to ICU and the percentage of organ dysfunction/support were also described for explicit sepsis only. In-hospital death was assessed for explicit and implicit sepsis and according to age, ICU admission and the presence of septic shock; 30-day and 90-day mortality were also assessed.

Statistical analysis

No statistical tests to describe patients and hospital stays characteristics over time or confidence intervals were used, as the data cover the national population[24,25]. A Cochran-Armitage Test for Trend was use to assess the change of incidence and in-hospital mortality, 30-day and 90-day mortality over time. Three additional logistic regressions were used to assess the odds ratio for the ordinal variable "year" (using 2013 as reference), considering in-hospital, 30-day and 90-day mortalities as a binary dependent variable and adjusting for sex, age, comorbidities, septic shock and infection sites.

Results

Number of cases and characteristics of sepsis patients

For metropolitan France, there were 222 232 cases of sepsis of presumed bacterial etiology in 2015, which increased slightly up to 261 499 in 2019 (Table 1, Figure 1). This increase appears essentially due to a gradual increasing incidence of explicit sepsis between 2015 (169 419 cases) and 2019 (208 510 cases), whereas implicit sepsis remained stable (respectively 52 813 and 52 989 cases) (Figure 1).

Patient's characteristics were stable between 2015 and 2019 (Table 1). Men accounted each year for a 15% higher proportion of sepsis than women. In 2019, people aged over 55 years represented 78.6% of the sepsis cases. More than one third of the patients had a Charlson index of 0, whereas less than 30% had a Charlson index above 2. Cancer, chronic heart failure, renal disease and chronic pulmonary disease were the most frequent comorbidities, respectively associated with 23.0%, 20.9%, 13.2% and 11.2% of sepsis cases in 2019.

Incidence

The global incidence per 100 000 [95% CI] of sepsis increased from 2015 (345 [344.2-347.0]) to 2019 (403 [401.9-405.0]) (P<0.001) (Table2, Figure 1). The annual incidence remained higher for males (480 [477.5-482.3] in 2019) compared to females (332 [329.9-333.8] in 2019) and was markedly higher for people <1 and >75 years (Table 2).

Sites of infection

The distribution of infection sites was quite similar over the 5-year study period. A substantial proportion of stays had no site identified (20.2% in 2019) or multiple sites recorded (21.3% in 2019) (see online supplementary appendix A : eTable2). Most patients with no site identified had primary bacteremia (88%). Overall, the most common sites of infection for patients having a single site identified were the lower respiratory tract, urinary and genital tracts and

gastrointestinal and abdomen, followed by heart and mediastinum and skin and soft tissues (19.6%, 15.0%, 6.0%, 5.1% and 4.6% in 2019 respectively) (see online supplementary appendix A : eTable 2). Urinary and genital tracts infection predominated in women (19.0% in 2019) whereas lower respiratory tract infection predominated in men (21.3% in 2019).

About three fourth of sepsis were associated with bacteremia. Overall, about 20% of patients had primary bacteremia (17.7% in 2019), whereas more than 50% had secondary bacteremia (58.8% in 2019) (see online supplementary appendix A : eTable 3).

Hospital stays of patients with sepsis

A minority of the patients had more than one hospital stay per year related to sepsis (10% in 2019) (see online supplementary appendix A : eTable 4). As mentioned in the methods section, the description in Table 3 considers only one hospital stay per year per patient but a description of all hospital stays associated with sepsis (All stays of all patients) is available in the eTable 5 in the supplementary appendix A online and showed similar results. The median length of stay was 13 days in 2015 and 12 days in 2019. The percentage of septic shock varied from 22.6% in 2015 to 20.7% in 2019. Considering only explicit sepsis, the percentage of ICU admission varied from 45.9% in 2015 to 42.5% in 2019 and the percentage of organ dysfunction varied from 67.9% % in 2015 to 66.6% in 2019. While the large majority of patients came from home (85.6% in 2019) and only about 2% were admitted from long-term care, less than 50% returned home after the hospital stay, whereas nearly 15% were discharged to long term care.

In-hospital mortality, 30-day and 90-day mortality

The overall in-hospital death rate slightly declined between 2015 (25.7%) and 2019 (23.6%) as well as 30-day and 90-day mortality which approximated 26% and 33% respectively in 2015 and 23% and 31% respectively in 2019 (all P<0.001) (see online supplementary appendix A : eTable 6). Adjusting for sex, age, comorbidities, septic shock and infection sites,

the odds ratios for the variable "year" progressively declined between 2016 and 2019, confirming the decreasing trend for mortality. In 2019, the odds ratio for 2019 compared to 2013 was 0.904 [0.891-0.917] for in-hospital mortality, 0.938 [0.924-0.952] for 30-day mortality and 0.918 [0.905-0.930] for 90-day mortality. In hospital mortality was 10% higher for explicit (25.5% in 2019) compared to implicit sepsis (15.9% in 2019). In-hospital mortality increased with age classes. In 2019, the mortality rate was under 10% for patients aged up to 30 but reached 33.9% for patients above 85 years. Mortality rate also increased with Charlson index (in 2019, 16.0% for Charlson index=0 and 38.3% for Charlson index>5) and was also higher for patients with septic shock (49.5% with septic shock, 16.8% without septic shock in 2019) or transferred to ICU (26.2% with ICU, 20.4% without ICU). The proportion of death was highest for patients with unknown source of infection (33.0% in 2019) and those with multiple sites of infection (23.7% in 2019) (Figure 2). Among those with a unique site of infection recorded, skin and soft tissues (31.8% in 2019), lower respiratory tract (28.3% in 2019), and gastrointestinal and abdominal infections (21.1% in 2019) were associated with the highest mortality rates.

Discussion

Methodological approach

This study represents a first important step in the evaluation of sepsis burden in France, accounting for the new definition of sepsis. Our selection of patients attempted to use the new Sepsis-3 definition [5] and our methodology identified sepsis cases through explicit and implicit sepsis as previously suggested[1,20]. However, the list of ICD-10 codes used varied across the different studies and is prone to over or underestimate sepsis incidence [1,2,13,26]. While attempting to not under or overestimate implicit sepsis, organ dysfunction was identified through both ICD-10 and organ support (CCAM) but also based on the need for intensive care

unit (ICU) stay. Indeed, the expert panel has presented ICU care as a typical outcome for patients with sepsis [5].

Incidence and changes over time

The incidence of sepsis was substantially higher compared to the study of Rudd *et al* which used the Global Burden of Disease database (GBD)[1]. However, the authors acknowledged a difference between their results and previous published works, possibly due to unrecorded explicit sepsis or organ dysfunction. We also found a substantially higher incidence of sepsis compared to the study conducted in France between 2010 and 2015 but our selection criteria probably also captured less severe cases[21]. A recent study in US also found a higher incidence compared to previous studies[27]. Similarly to other studies, we observed a slight increase of sepsis incidence over time [1,21,27]. This could be due to a real increase or to changes in coding practices[1,27]. Indeed, population ageing and advanced therapies has impacted overall patients survival and are likely to increase sepsis incidence [2,27], but this may also be explained by the development of campaigns that increase the awareness, the screening, the diagnosis of sepsis[2,16,27] or due to the recommendations issued in 2014 issued by the French Technical Agency for Hospital Information (ATIH).

Characteristics of patients and hospital stays

Similarly to other studies, higher incidence was observed for men compared to women, for very young infants or elderly and for patients with comorbidities[20,21,27–30]. Indeed, ageing is associated with increased prevalence of chronic diseases and impaired immune system, thus increasing the risk of sepsis [29]. Some studies, which include low-income countries or different study population, found higher or similar incidence in women compared to men but the sepsis related mortality was higher in men[1,20]. As shown in previous studies, lower respiratory tract and urinary - genital tracts were the most common sites of infection with urinary - genital tracts more common for women and respiratory tract for men [20,27,31]. Fewer episodes of sepsis

of respiratory origin might partially explain the lower incidence of sepsis in women compared to men [20]. Additionally, several studies showed than men have more chronic comorbidities than women, which may impair their ability to combat infection [29,32,33]. Indeed, comorbidities and septic shock substantially increased in-hospital sepsis related death similarly to a previous study [21]. However, our study showed that more than one third of the patients had no comorbidity recorded, suggesting the influence of other risk factors and possibly the inclusion of less severe sepsis cases.

Only half of all patients returned home, which emphasize the high mortality rate and mid- and long-term burden of sepsis through the requirements of care in nursing homes or intermediate care facilities [27]. The percentage of patients returning home was higher compared to another recent study which also captured mild cases of sepsis[27]. However, the proportion of patients having ICU admission[16,21] or the percentage of septic shock[27] was in line with previous studies. The median length of stays was 12 days in 2019, which is much higher than the usual length of stay in acute care units. Comparatively to previous studies, in-hospital mortality slightly declined over time[15,34]. Moreover, the concomitant increase of the most severe sepsis cases (explicit sepsis) suggests a real decline of the mortality rate. In-hospital mortality rate was around 25% and was comparable to the results obtained in previous studies where sepsis related death rates ranged from 15% to 30% [2,20,27,31,34,35] and confirms the high mortality risk associated with sepsis, although in-hospital mortality was lower than the 34% rate reported in the 2010-2015 study of Dupuis et al. [21]. Sepsis-related deaths also occurred outside of the hospital [36]. Indeed, 90-days mortality reached about 30%.

Limitations of the study

The changes in sepsis definition and the different approaches in sepsis selection in medico-administrative databases across studies limit the comparability with other studies [13–15,27]. Moreover, identifying the incidence of sepsis with an ICD code-based approach may show

some discrepancies with clinical data. Therefore, this methodology may requires further validation [13,16].

While the number of implicit sepsis cases barely changed between 2015 and 2019, we observed a slight increase of explicit sepsis cases. Indeed, the coding practice might have experienced some changes over time and impacted sepsis incidence, especially following new instructions for sepsis coding[16]. However, the use of medico-administrative databases represents the only cost effective way to obtain a large population coverage and this type of data are largely used to benchmark the incidence of sepsis or other pathologies in the national population [13,14,36].

The majority of the patients had only one episode of sepsis over the year but around 10% experienced multiple stays. While we adapted our methodology to compare hospital stays and patients with single and multiple stays, patients with sepsis having multiple stays over the year could be further characterized.

Finally, the cohort available narrowed our study to the assessment of sepsis of presumed bacterial etiology. While sepsis of viral and fungal etiology (without concomitant sepsis of presumed bacterial etiology) was estimated at only 2.5% of all sepsis cases in the period studied (data not shown) (see online supplementary appendix A : eMethods and eTable1), this should be reassessed during the Covid-19 pandemic period

Conclusion

Medico-administrative databases can be used to provide nationwide estimates of the incidence of sepsis and also allow to study healthcare pathways but further validation with detailed clinical data is required. Our data should be complemented by the re-assessment of the

relative proportion of sepsis with a bacterial, fungal and especially of viral etiology during the COVID-19 pandemic.

Our results confirm the high burden of sepsis in France. Patient characteristics could be considered in quality-improvement programs and new individualized management strategies. Concomitant changes of the coding practices and of the incidence itself, challenge the assessment of changes over time. This highlights the urgent need for a long-lasting consensus to describe sepsis in medico-administrative database.

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Contributors :

Fanny Pandolfi, Laurence Watier, Christian Brun-Buisson, Didier Guillemot conceived the study. Laurence Watier obtained the funding for the study. Fanny Pandolfi, Laurence Watier, Christian Brun-Buisson organized the data collection and conducted the analysis. Fanny Pandolfi, Laurence Watier, Christian Brun-Buisson drafted the manuscript. Fanny Pandolfi, Laurence Watier, Christian Brun-Buisson, Didier Guillemot contributed to the critical revision of the manuscript.

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Competing interest : None

Ethics approval : The study, analysis and data extraction were approved by the French Data Protection Agency (CNIL, approval DE-2016–176). Informed consent is waived for the use of these anonymised secondary data, as mentioned in the Social Security Code, Article L161–28-1. All methods were performed in accordance CNIL regulations and with REporting of studies Conducted using Observational Routinely-collected Data (RECORD) guideline.

Data sharing statement : No additional data are available

Patient and Public Involvement : No patient involved

References

1. Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. *Lancet Lond Engl*. 2020;395(10219):200-211. doi:10.1016/S0140-6736(19)32989-7

2. Cecconi M, Evans L, Levy M, Rhodes A. Sepsis and septic shock. *Lancet Lond Engl*. 2018;392(10141):75-87. doi:10.1016/S0140-6736(18)30696-2

3. Paoli C, Reynolds M, Sinha M, Gitlin M, Crouser E. Epidemiology and Costs of Sepsis in the United States-An Analysis Based on Timing of Diagnosis and Severity Level. *Crit Care Med*. 2018;46(12). doi:10.1097/CCM.0000000000003342

4. Tiru B, DiNino EK, Orenstein A, et al. The Economic and Humanistic Burden of Severe Sepsis. *PharmacoEconomics*. 2015;33(9):925-937. doi:10.1007/s40273-015-0282-y

5. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315(8):801-810. doi:10.1001/jama.2016.0287

6. Seymour CW, Liu VX, Iwashyna TJ, et al. Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315(8):762-774. doi:10.1001/jama.2016.0288

7. Freund Y, Lemachatti N, Krastinova E, et al. Prognostic Accuracy of Sepsis-3 Criteria for In-Hospital Mortality Among Patients With Suspected Infection Presenting to the Emergency Department. *JAMA*. 2017;317(3):301-308. doi:10.1001/jama.2016.20329

8. Eriksson J, Eriksson M, Brattström O, et al. Comparison of the sepsis-2 and sepsis-3 definitions in severely injured trauma patients. *J Crit Care*. 2019;54:125-129. doi:10.1016/j.jcrc.2019.08.019

9. Shahsavarinia K, Moharramzadeh P, Arvanagi RJ, Mahmoodpoor A. qSOFA score for prediction of sepsis outcome in emergency department. *Pak J Med Sci*. 2020;36(4):668-672. doi:10.12669/pjms.36.4.2031

10. Takauji S, Hayakawa M, Fujita S. A Nationwide Comparison Between Sepsis-2 and Sepsis-3 Definition in Japan. *J Intensive Care Med*. 2020;35(12):1389-1395. doi:10.1177/0885066618823151

11. WHO. WHA70.7, Agenda item 12.2. Improving the prevention, diagnosis and clinical management of sepsis. Published online May 29, 2017.

12. Annane D. Sepsis - tous unis contre un fléau méconnu. Rapport Au Directeur Général De La Santé. Published online 2019. https://solidarites-sante.gouv.fr/IMG/pdf/rapport_sepsis_dgs_130919.pdf

13. Jolley RJ, Sawka KJ, Yergens DW, Quan H, Jetté N, Doig CJ. Validity of administrative data in recording sepsis: a systematic review. *Crit Care Lond Engl*. 2015;19:139. doi:10.1186/s13054-015-0847-3

14. Gaieski DF, Edwards JM, Kallan MJ, Carr BG. Benchmarking the incidence and mortality of severe sepsis in the United States. *Crit Care Med*. 2013;41(5):1167-1174. doi:10.1097/CCM.0b013e31827c09f8

15. Fleischmann-Struzek C, Mellhammar L, Rose N, et al. Incidence and mortality of hospital- and ICU-treated sepsis: results from an updated and expanded systematic review and meta-analysis. *Intensive Care Med*. 2020;46(8):1552-1562. doi:10.1007/s00134-020-06151-x

16. Rhee C, Jentzsch MS, Kadri SS, et al. Variation in Identifying Sepsis and Organ Dysfunction Using Administrative Versus Electronic Clinical Data and Impact on Hospital Outcome Comparisons. *Crit Care Med*. 2019;47(4):493-500. doi:10.1097/CCM.0000000000003554

17. Liu YZ, Chu R, Lee A, et al. A surveillance method to identify patients with sepsis from electronic health records in Hong Kong: a single centre retrospective study. *BMC Infect Dis*. 2020;20(1):652. doi:10.1186/s12879-020-05330-x

18. Tuppin P, Rudant J, Constantinou P, et al. Value of a national administrative database to guide public decisions: From the système national d'information interrégimes de l'Assurance Maladie (SNIIRAM) to the système national des données de santé (SNDS) in France. *Rev Epidemiol Sante Publique*. 2017;65 Suppl 4:S149-S167. doi:10.1016/j.respe.2017.05.004

19. INSEE. Institut national de la statistique et des études économiques. Population par sexe et âge 2015, 2016, 2017, 2018 & 2019. https://www.insee.fr/fr/statistiques

20. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med*. 2001;29(7):1303-1310. doi:10.1097/00003246-200107000-00002

21. Dupuis C, Bouadma L, Ruckly S, et al. Sepsis and septic shock in France: incidences, outcomes and costs of care. *Ann Intensive Care*. 2020;10(1):145. doi:10.1186/s13613-020-00760-x

22. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol*. 2011;173(6):676-682. doi:10.1093/aje/kwq433

23. Opatowski M, Tuppin P, Cosker K, et al. Hospitalisations with infections related to antimicrobial-resistant bacteria from the French nationwide hospital discharge database, 2016. *Epidemiol Infect*. 2019;147:e144. doi:10.1017/S0950268819000402

24. Ioannidis JPA. What Have We (Not) Learnt from Millions of Scientific Papers with P Values? *Am Stat*. 2019;73(sup1):20-25. doi:10.1080/00031305.2018.1447512

25. Lin M, Lucas Jr. HC, Shmueli G. Too big to fail: Large samples and the p-value problem. *Inf Syst Res*. 2013;24(4):906-917. doi:10.1287/isre.2013.0480

26. Wilhelms SB, Huss FR, Granath G, Sjöberg F. Assessment of incidence of severe sepsis in Sweden using different ways of abstracting International Classification of Diseases

codes: difficulties with methods and interpretation of results. *Crit Care Med*. 2010;38(6):1442-1449. doi:10.1097/CCM.0b013e3181de4406

27. Wardi G, Tainter CR, Ramnath VR, et al. Age-related incidence and outcomes of sepsis in California, 2008-2015. *J Crit Care*. 2021;62:212-217. doi:10.1016/j.jcrc.2020.12.015

28. Fay K, Sapiano MRP, Gokhale R, et al. Assessment of Health Care Exposures and Outcomes in Adult Patients With Sepsis and Septic Shock. *JAMA Netw Open*. 2020;3(7):e206004. doi:10.1001/jamanetworkopen.2020.6004

29. Cillóniz C, Dominedò C, Ielpo A, et al. Risk and Prognostic Factors in Very Old Patients with Sepsis Secondary to Community-Acquired Pneumonia. *J Clin Med*. 2019;8(7):E961. doi:10.3390/jcm8070961

30. Davis JS, He V, Anstey NM, Condon JR. Long term outcomes following hospital admission for sepsis using relative survival analysis: a prospective cohort study of 1,092 patients with 5 year follow up. *PloS One*. 2014;9(12):e112224. doi:10.1371/journal.pone.0112224

31. Karlsson S, Varpula M, Ruokonen E, et al. Incidence, treatment, and outcome of severe sepsis in ICU-treated adults in Finland: the Finnsepsis study. *Intensive Care Med*. 2007;33(3):435-443. doi:10.1007/s00134-006-0504-z

32. Gipson SAY, Hall MD. The evolution of sexual dimorphism and its potential impact on host-pathogen coevolution. *Evol Int J Org Evol*. 2016;70(5):959-968. doi:10.1111/evo.12922

33. Zuk M. The Sicker Sex. *PLOS Pathog*. 2009;5(1):e1000267. doi:10.1371/journal.ppat.1000267

34. Imaeda T, Nakada T-A, Takahashi N, et al. Trends in the incidence and outcome of sepsis using data from a Japanese nationwide medical claims database-the Japan Sepsis Alliance (JaSA) study group. *Crit Care Lond Engl*. 2021;25(1):338. doi:10.1186/s13054-021-03762-8

35. Fleischmann C, Scherag A, Adhikari NKJ, et al. Assessment of Global Incidence and Mortality of Hospital-treated Sepsis. Current Estimates and Limitations. *Am J Respir Crit Care Med*. 2016;193(3):259-272. doi:10.1164/rccm.201504-0781OC

36. Melamed A, Sorvillo FJ. The burden of sepsis-associated mortality in the United States from 1999 to 2005: an analysis of multiple-cause-of-death data. *Crit Care Lond Engl*. 2009;13(1):R28. doi:10.1186/cc7733

37. Rochoy M, Chazard E, Bordet R. [Epidemiology of neurocognitive disorders in France]. *Geriatr Psychol Neuropsychiatr Vieil*. 2019;17(1):99-105. doi:10.1684/pnv.2018.0778

Tables

Table 1- Characteristics of patients with sepsis, France 2015-2019

Characteristics	N (%) Years									
	2015 (n=222232)		2016 (n=236314)		2017 (n=245780)		2018 (n=258608)		2019 (n=261499)	
Gender										
Men	128090	(57.6)	135613	(57.4)	141113	(57.4)	148650	(57.5)	150507	(57.6)
Women	94142	(42.4)	100701	(42.6)	104667	(42.6)	109958	(42.5)	110992	(42.4)
Age										
<1	12193	(5.5)	11321	(4.8)	11193	(4.6)	11052	(4.3)	10547	(4.0)
1-15	4137	(1.9)	4588	(1.9)	4287	(1.7)	4681	(1.8)	4786	(1.8)
16-30	6492	(2.9)	7050	(3.0)	7023	(2.9)	7441	(2.9)	7252	(2.8)
31-45	11993	(5.4)	12599	(5.3)	12691	(5.2)	13370	(5.2)	13078	(5.0)
46-55	18601	(8.4)	19046	(8.1)	19595	(8.0)	20392	(7.9)	20299	(7.8)
56-65	36585	(16.5)	38174	(16.2)	38539	(15.7)	40736	(15.8)	40349	(15.4)
66-75	45078	(20.3)	50052	(21.2)	54125	(22.0)	58989	(22.8)	61672	(23.6)
76-85	54256	(24.4)	56725	(24.0)	58052	(23.6)	59528	(23.0)	59679	(22.8)
>85	32897	(14.8)	36759	(15.6	40275	(16.4)	42419	(16.4)	43837	(16.8)
Charlson index[22]										
0	82175	(37.0)	87080	(36.8)	89599	(36.5)	94792	(36.7)	95465	(36.5)
1-2	76140	(34.3)	81113	(34.3)	84603	(34.4)	89191	(34.5)	90600	(34.6)
3-4	31656	(14.2)	33947	(14.4)	35485	(14.4)	36824	(14.2)	37358	(14.3)
>5	32261	(14.5)	34174	(14.5)	36093	(14.7)	37801	(14.6)	38076	(14.6)
Comorbidities										
Cancer	51042	(23.0)	54810	(23.2)	56581	(23.0)	59648	(23.1)	60064	(23.0)
Congestive heart failure	46324	(20.8)	49394	(20.9)	51912	(21.1)	54511	(21.1)	54553	(20.9)
Renal disease	27960	(12.6)	30091	(12.7)	32119	(13.1)	33252	(12.9)	34554	(13.2)
Chronic pulmonary disease	24941	(11.2)	26110	(11.1)	27097	(11.0)	28513	(11.0)	29249	(11.2)
Metastatic carcinoma	20619	(9.3)	22408	(9.5)	23516	(9.6)	24915	(9.6)	25331	(9.7)
Diabetes with chronic complications	13104	(5.9)	13690	(5.8)	14212	(5.8)	14558	(5.6)	14598	(5.6)
Paraplegia or hemiplegia	11535	(5.2)	12463	(5.3)	13238	(5.4)	14416	(5.6)	14496	(5.5)
Dementia	12265	(5.5)	13035	(5.5)	13825	(5.6)	14247	(5.5)	14123	(5.4)
Mild liver disease	11560	(5.2)	12002	(5.1)	12837	(5.2)	13134	(5.1)	13440	(5.1)
Moderate or severe liver disease	5844	(2.6)	5922	(2.5)	6266	(2.6)	6318	(2.4)	6335	(2.4)
Rheumatologic disease	2691	(1.2)	2807	(1.2)	2866	(1.2)	3071	(1.2)	3128	(1.2)
AIDS	1044	0.5)	1016	(0.4)	1104	(0.5)	1020	(0.4)	1006	(0.4)

428 Table 2- Overall sepsis incidence by gender and age, France 2015-2019[a]

Age	N [CI] Years				
	2015 (n=222232)	2016 (n=236314)	2017 (n=245780)	2018 (n=258608)	2019 (n=261499)
Men					
<1	1862 [1818.2-1905.0]	1771 [1728.5-1814.0]	1809 [1765.0-1852.3]	1808 [1763.6-1853.]	1755 [1711.2-1798.6]
1-15	37 [35.7-38.8]	42 [40.1-43.4]	39 [37.4-40.6]	43 [41.4-44.9]	44 [42.8-46.1]
16-30	53 [51.1-54.8]	55 [53.2-57.0]	56 [53.8-57.7]	59 [56.9-60.9]	58 [55.9-59.9]
31-45	104 [101.4-106.5]	108 [105.4-110.6]	111 [107.9-113.2]	116 [113.0-118.4]	114 [111.7-117.2]
46-55	266 [261.6-271.4]	273 [267.7-277.7]	279 [273.7-283.7]	288 [282.6-293.1]	283 [277.6-287.6]
56-65	618 [610.4-626.0]	643 [635.2-651.1]	646 [638.2-654.2]	673 [664.9-681.2]	670 [661.8-678.0]
66-75	1095 [1082.1-1107.1]	1159 [1146.8-1171.9]	1196 [1183.3-1208.3]	1250 [1237.5-1262.]	1260 [1248.0-1272.7]
76-85	1942 [1920.6-1963.6]	2022 [1999.9-2043.7]	2070 [2047.5-2091.7]	2159 [2136.7-2182.1]	2170 [2147.1-2192.5]
>85	2855 [2809.2-2901.5]	3060 [3013.3-3106.9]	3283 [3235.4-3330.5]	3393 [3344.8-3440.3]	3435 [3387.6-3482.3]
All Men	411 [409.1-413.6]	434 [432.2-436.8]	451 [448.7-453.4]	472 [469.5-474.3]	480 [477.5-482.3]
Women					
<1	1481 [1441.4-1520.9]	1385 [1346.6-1424.2]	1375 [1335.8-1413.8]	1381 [1341.6-1420.3]	1347 [1307.4-1386.0]
1-15	33 [31.4-34.4]	36 [34.6-37.7]	34 [32.4-35.4]	36 [34.6-37.8]	38 [36.4-39.6]
16-30	61 [58.8-62.9]	69 [66.9-71.2]	68 [66.1-70.5]	72 [69.6-74.6]	71 [68.8-73.2]
31-45	89 [87.1-91.8]	96 [93.9-98.7]	97 [94.1-99.0]	103 [100.2-105.3]	102 [99.2-104.3]
46-55	166 [162.4-170.0]	170 [166.0-173.7]	175 [171.5-179.3]	182 [177.8-186.7]	184 [179.9-187.8]
56-65	302 [296.7-307.2]	318 [312.5-323.3]	323 [317.9-328.8]	349 [343.6-354.9]	343 [337.3-348.5]
66-75	520 [511.6-527.8]	553 [544.9-561.1]	578 [569.4-585.7]	603 [594.6-611.9]	610 [602.2-618.3]
76-85	1018 [1005.0-1030.8]	1074 [1061.0-1087.7]	1107 [1093.2-1120.4]	1149 [1135.0-1163.0]	1151 [1137.0-1165.2]
>85	1590 [1567.2-1612.5]	1731 [1707.5-1754.0]	1825 [1801.0-1848.2]	1915 [1891.2-1939.5]	1919 [1895.5-1943.3]
All Women	303 [300.9-304.7]	303 [300.9-304.7]	314 [311.9-315.7]	328 [326.1-330.0]	332 [329.9-333.8]
Total population	346 [344.2-347.0]	367 [365.1-368.0]	380 [378.7-381.7]	398 [396.2-399.3]	403 [401.9-405.0]

429 [a] *Data are shown as number per 100,000 population, with 95% CI*

Table 3 – Characteristics of hospital stays with sepsis, France 2015-2019

Variables	2015 (N=222232)		2016 (N=236314)		2017 (N=245780)		2018 (N=258608)		2019 (=261499)	
Admission source, **N (%)**										
Home	194616	(87.6)	202500	(85.7)	210221	(85.5)	221543	(85.7)	223879	(85.6)
Acute care [a]	22651	(10.2)	28743	(12.2)	30312	(12.3)	31483	(12.2)	32093	(12.3)
Long term care [b]	4965	(2.2)	5071	(2.2)	5247	(2.1)	5582	(2.2)	5527	(2.1)
Length of stay (days), **N (%)**										
<7	53135	(23.9)	58561	(24.8)	61192	(24.9)	68677	(24.6)	69367	(24.9)
7-14	65184	(29.3)	70842	(30.0)	75365	(30.7)	89195	(32.0)	89297	(32.0)
15-30	62373	(28.1)	65549	(27.7)	67988	(27.7)	78123	(28.0)	77442	(27.8)
>30	41540	(18.7)	41362	(17.5)	41235	(16.8)	43187	(15.4)	42771	(15.3)
Length of stay, **Median {P10-P90}**	13	{3-43}	13	{3-41}	13	{3-41}	13	{3-40}	12	{3-39}
Septic shock [c], **N (%)**										
Yes	50145	(22.6)	49948	(21.1)	51964	(21.1)	53635	(20.7)	54145	(20.7)
No	172087	(77.4)	186366	(78.9)	193816	(78.9)	204973	(79.3)	207354	(79.3)
ICU admission [d], **N (%)**										
Yes	130587	(58.8)	134181	(56.8)	137025	(55.8)	142001	(54.9)	141685	(54.2)
No	91645	(41.2)	102133	(43.2)	108755	(44.3)	116607	(45.1)	119814	(45.8)
Hospital discharge, **N (%)**										
Home	106133	(47.8)	113812	(48.2)	119069	(48.5)	127894	(49.5)	130250	(49.8)
Acute care [a]	25992	(11.7)	29436	(12.5)	30904	(12.6)	31329	(12.1)	30784	(11.8)
Long term care [b]	33035	(14.9)	34958	(14.8)	36198	(14.7)	38010	(14.7)	38891	(14.9)
Death	57072	(25.7)	58108	(24.6)	59609	(24.3)	61375	(23.7)	61574	(23.6)

[a] *Acute care unit in medicine, surgery or obstetrics or psychiatry unit*

[b] *Follow-up and rehabilitation care unit, long-term care unit or home care*

[c] *ICD-10 code R57.2, R57.8 as primary diagnosis, related diagnosis or significant associated diagnosis*

[d] *Including implicit sepsis for which ICU admission is part of the selection criteria*

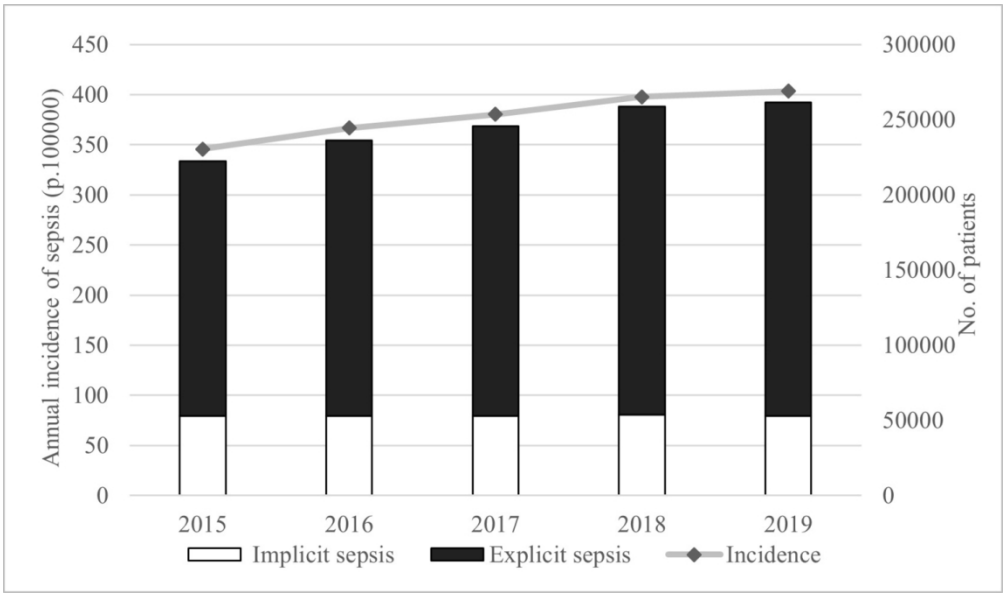


Figure 1 - Sepsis incidence per 100 000 inhabitants and number of cases between 2015 and 2018 in metropolitan France

129x76mm (300 x 300 DPI)

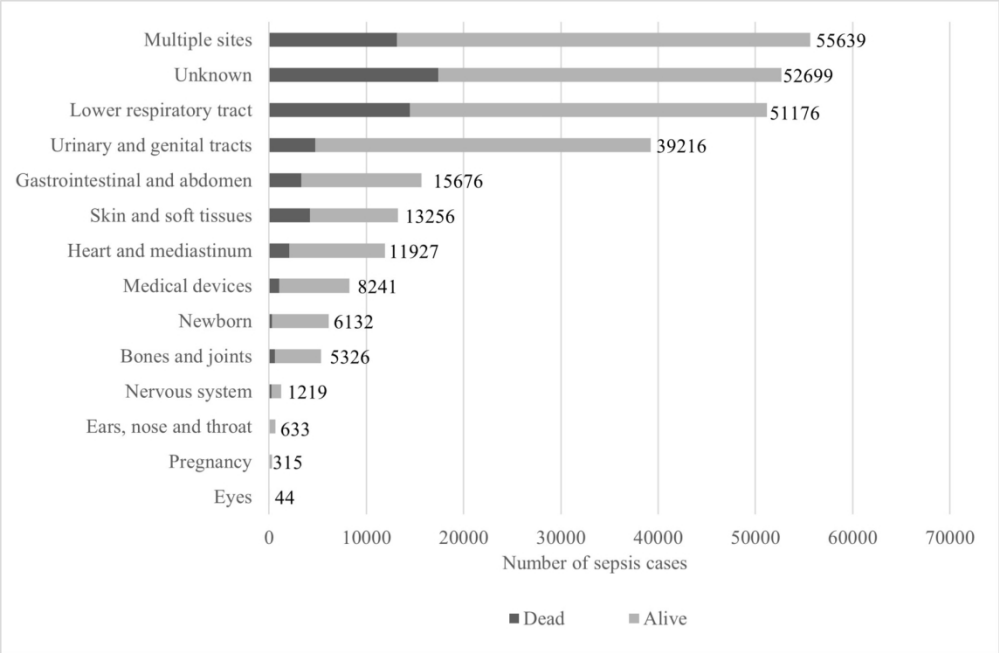


Figure 2 – Number of patients with sepsis in 2019 and associated number of in-hospital deaths by infection site.

160x104mm (300 x 300 DPI)

Supplementary Appendix A

Pandolfi F, Guillemot D, Watier L, Brun-Buisson C, Trends in sepsis incidence and mortality in France between 2015 and 2019

eMethods

eTable1

eTable2

eTable3

eTable4

eTable5

eTable6

eMethods

Description of the French National Hospital Discharge Database (PMSI)

The study, analysis and data extraction were approved by the French Data Protection Agency (CNIL, approval DE-2016–176). Informed consent is waived for the use of these anonymised secondary data, as mentioned in the Social Security Code, Article L161–28-1. All methods were performed in accordance CNIL regulations and with REporting of studies Conducted using Observational Routinely collected Data (RECORD) guideline. For acute-care facilities PMSI data includes all discharge summaries of hospitalization and covers all hospital stays in publicly funded and private institutions including acute-care facilities (medicine, surgery or obstetrics units: MSO)[1]. For each stay, the diagnoses are coded with ICD-10-codes as primary diagnosis (PD: condition requiring hospitalization), related diagnosis (RD: adds information to PD) and significant associated diagnosis (SAD: complications and co-morbidities potentially affecting the course or cost of hospitalization). While PD and RD are unique for each stay, several SAD can be attributed per stay. Additional information is available about the patients, such as sex or age and about the hospital stays as entry and exit date, admission source, hospital discharge or medical procedures.

Assessment of the proportion of sepsis cases of presumed fungal and viral etiology

Since the database analyzed in this study included only infections of presumed bacterial etiology, the EGB (Generalist sample of beneficiaries is a sample representative of the beneficiaries of the health insurance (Survey at the 97th percentile of the French health insurance beneficiaries) was used to estimate the proportion of sepsis of viral or fungal etiologies among all sepsis cases. The breakdown per sex and age class is similar to that of the overall population. The data were available from 2015 to 2018 and were used to estimate the overall number of sepsis cases and the percentage of sepsis cases of presumed fungal and viral etiology. The percentage of sepsis cases of presumed fungal and viral etiology (without associated sepsis of presumed bacterial etiology) was assessed for each year. Sepsis of presumed fungal or viral etiology were identified by explicit sepsis codes and implicit sepsis codes (eTable 1)

Methodology to define the site of infection

First, the site of infection was identified based on the list of specific ICD-10 codes used by Opatowski et al. in Supplementary Table S1[2]. The sites of infection included: Bones and joints, Ears, nose and throat, Eyes, Gastrointestinal and abdomen, Heart and mediastinum, Lower respiratory tract, Medical devices, Nervous

system, Newborn, Pregnancy, Skin and soft tissues, Urinary and genital tracts, Multiple sites and Unknown site. (mainly represented by primary bacteremia).

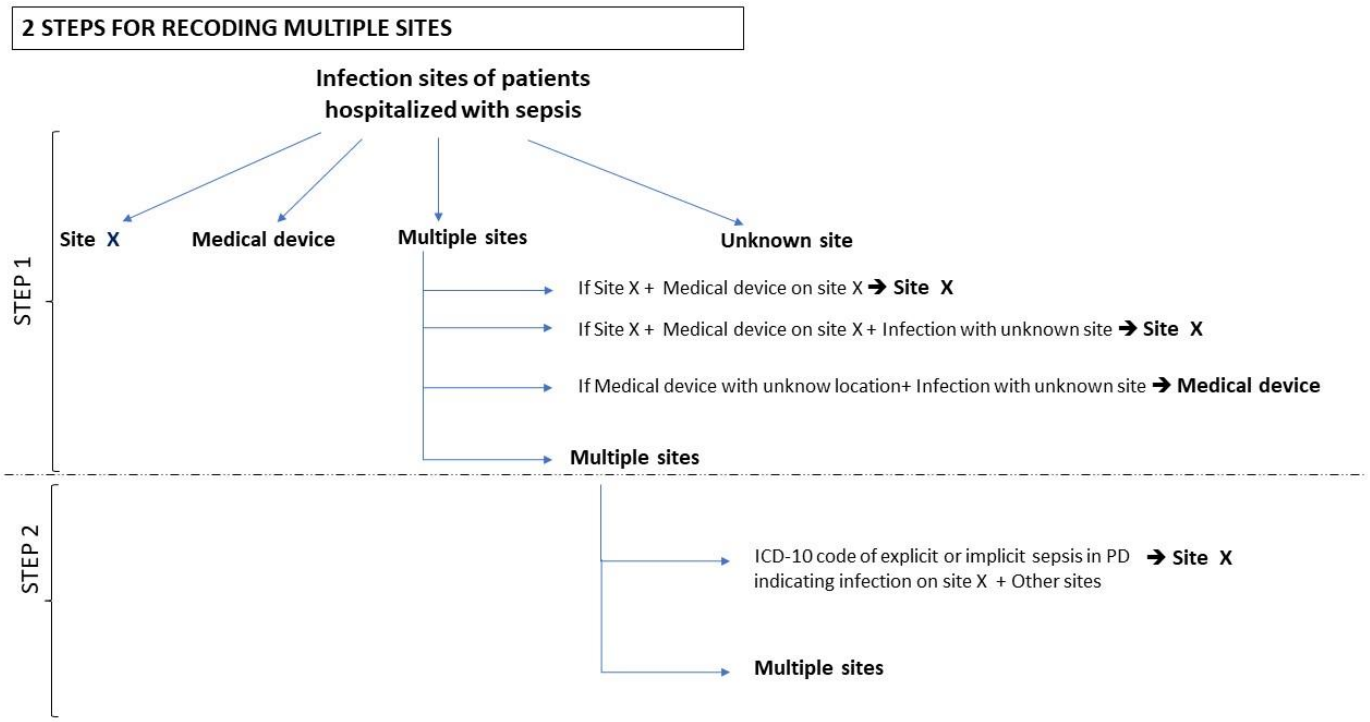
As, the ICD-10 codes for infection could be coded as PD, RD or SAD and multiple site locations were found for part of the patients, a "Two steps" recoding method was used to identify the main site of infection:

FIRST STEP

- When the medical device could be identified as located in the urinary tract, heart or bones and joints, the site of the medical device was prioritized over the medical device. Therefore, « medical devices » sites only include medical devices of unknown location.
- When an infection site (associated or not to an infection on medical device on the same site) and an infection of unknown location were identified, the infection site was prioritized over the unknown location and considered as the single site of infection. When medical devices of unknown location and an infection of unknown location were identified, the medical device was considered as the single site of infection. As a result, "unknown" site only included primary bacteremia or few unidentified sites of infection not located on a medical device.

SECOND STEP

- For the remaining stays with multiple infection sites after the first step, the PD was used to identify a single site. In cases where an ICD-10 code of explicit sepsis was found in PD (except if the PD was an infection with unknown location), this ICD-10 code was used to identify a single site of infection.
- After these different steps process, if a single site of infection could not be identified, the patient was classified as having multiple infection sites.



eTable 1. ICD-10 codes used to identify sepsis of presumed bacterial, viral and fungal etiology according to type of selection

Explicit sepsis codes[a,b,d]	**Implicit sepsis** [b,c,d]		
	Infection codes[a]	**1st associated condition**	**2nd associated condition**
Sepsis of presumed bacterial etiology			
A02.1, A40.0-A40.9, A41.0-A41.9, A48.0, A48.3, O85, O88.3, P36.00, P36.10, P36.20, P36.30, P36.40, P36.50, P36.80, P36.90, R57.2, R57.8, R65.1	A04.0-A04.9, A39.0-A39.9, G00.0-G00.9, I33.0, J06.8, J13, J14, J15.0-J15.9, J16.0-J16.8, J18.0-J18.9, J86.9, K65.0, K65.9, K81.0, K83.0, L02.2, L08.9, M00.0-M00.99, M46.20-M46.29, M60.00-M60.09, M86.00-M86.09, M86.90-M86.99, N13.6, N39.0, P00.2, T79.3, T80.2, T81.1, T81.4, T82.7, T84.5, T85.7	Transfer to ICU/ resuscitation	ICD-10 codes for organ dysfunction : A483, D65, D689, D695, D696, D762, E86, E872, F05.0-F05.9, F09, I460, G934, I469, I959, I959, J80, J81, J952, J969, K72.0, K72.9, N08.0, N08.6, N16.0, N17.0-N17.9, N19, R09.2, R17.0-17.9, R34, R40.0-R40.28, R39.2, R41.0, R41.8, R55, R65.1, R57.1, R57.2, R57.8, R57.9 AND CCAM codes for organ support : EQLF003, EQLF002, EQMF002, DKMD001, DKMD002, FELF003, GLLP004, GLLD003, GLLD012, GLLD008, GLLD004, GLLD015, JVJF003, JVJF002, JVJF005, JVJB002, JVJF006, JVJF007
Sepsis of presumed viral ou fungal etiology			
B00.7, B37.7, B44.7, B45.7, B46.4, B50.8	A86, A87.0-A87.9, A91, A92.0-A92.9, A94, A96.0-A96.9, A98.0-A98.9, A99, B009, B01.1-B01.9, B17.9, B25.0-B25.9, B27.0-B27.9, B33.4, B34.1, B38.0-B38.9, B39.0-B39.9, B40.0-B40.9, B44.0-B44.9, B45.0-B45.9, B47.8, B49, B50.0-B50.9, B58.0-B58.9, B59, B78.7, J09, J10.0-J10.8, J11.0-J11.8, J12.0-J12.9, U04.9	Transfer to ICU/ resuscitation	ICD-10 codes for organ dysfunction : A483, D65, D689, D695, D696, D762, E86, E872, F05.0-F05.9, F09, I460, G934, I469, I959, I959, J80, J81, J952, J969, K72.0, K72.9, N08.0, N08.6, N16.0, N17.0-N17.9, N19, R09.2, R17.0-17.9, R34, R40.0-R40.28, R39.2, R41.0, R41.8, R55, R65.1, R57.1, R57.2, R57.8, R57.9 AND CCAM codes for organ support : EQLF003, EQLF002, EQMF002, DKMD001, DKMD002, FELF003, GLLP004, GLLD003, GLLD012, GLLD008, GLLD004, GLLD015, JVJF003, JVJF002, JVJF005, JVJB002, JVJF006, JVJF007

[a] *One of the ICD-10 code as primary diagnosis (PD: condition requiring hospitalization), related diagnosis (RD: adds information to PD) or significant associated diagnosis (SAD: complications and co-morbidities potentially affecting the course or cost of hospitalization)*

.[b] *Sepsis = sepsis explicit sepsis + implicit sepsis*

[c] *Implicit sepsis= ICD-10 code of infection + transfer to ICU or resuscitation+ organ dysfunction/support*

[d] *Stays shorter than 24h hours without death were excluded from our selection*

eTable 2. Distribution of infection sites (reported as % of sepsis cases) recorded in patients hospitalized with sepsis of presumed bacterial etiology in metropolitan France between 2015 and 2019

Sites[a]	% Year				
	2015	2016	2017	2018	2019
Unknown[b]	21.7	21.3	20.7	20.4	20.2
Multiple sites	19.9	20.2	20.6	21.2	21.3
Lower respiratory tract	21.4	20.6	20.2	19.9	19.6
Urinary and genital tracts	13.2	14.2	14.6	14.7	15.0
Gastrointestinal and abdomen	5.8	6.0	5.9	6.0	6.0
Heart and mediastinum	4.6	4.8	4.8	5.0	5.1
Skin and soft tissues	4.6	4.6	4.5	4.5	4.6
Medical devices[c]	3.7	3.1	2.8	2.6	2.3
Newborn	2.9	2.9	3.1	3.2	3.2
Bones and joints	1.6	1.7	1.9	2.0	2.0
Nervous system	0.5	0.5	0.5	0.5	0.5
Ears, nose and throat	0.2	0.2	0.3	0.2	0.2
Pregnancy	0.1	0.1	0.1	0.1	0.1
Eyes	0.0	0.0	0.0	0.0	0.0

[a] *Based on the classification of the infection site detailed in Supplementary file*

[b] *Sepsis without primary site identified (88% primary bacteremia and 12% sepsis with no infection site recorded)*

[c] *Medical devices of unknown location. When the location of the medical could be identified, the site of the medical device was prioritized*

eTable 3. Primary and secondary bacteremia (reported as % of sepsis cases) in patients hospitalized with sepsis of presumed bacterial etiology in metropolitan France between 2015 and 2019

Bacteremia	% Year				
	2015	2016	2017	2018	2019
Primary bacteremia[a]	19.2	18.9	18.3	18.0	17.7
Secondary bacteremia[b]	53.2	55.3	56.8	58.1	58.8
No bacteremia	27.6	25.8	24.8	24.0	23.5

[a] *Bacteremia without other infection site identified*

[a] *Bacteremia with another infection site identified*

eTable 4. Yearly number of hospital stays (reported as % of sepsis cases) for patients hospitalized with sepsis of presumed bacterial etiology in metropolitan France between 2015 and 2019

Number of stay	%				
	Year				
	2015	2016	2017	2018	2019
1	91.6	90.6	90.3	90.2	90.0
2	7.0	7.8	8.0	8.0	8.2
>2	1.4	1.7	1.8	1.7	1.8

eTable 5. Description of all hospital stays for sepsis of presumed bacterial etiology in metropolitan France between 2015 and 2019

Variables	N (%)									
	Year									
	2015 (N=250 642)		2016 (N=270 013)		2017 (N=281 882)		2018 (N=296 460)		2019 (=300 925)	
Admission source										
Home	218497	(87.2)	230057	(85.2)	239568	(85.0)	252447	(85.2)	256079	(85.1)
Acute care [a]	26459	(10.6)	34048	(12.6)	36165	(12.8)	37526	(12.7)	38344	(12.7)
Long term care [b]	5686	(2.3)	5908	(2.2)	6149	(2.2)	6487	(2.2)	6502	(2.2)
Length of stay (days)										
<7	61364	(24.5)	69278	(25.7)	72622	(25.8)	77430	(26.1)	79094	(26.3)
7-14	72757	(29.0)	79888	(29.6)	85214	(30.2)	90597	(30.6)	92597	(30.8)
15-30	69629	(27.8)	73810	(27.3)	76882	(27.3)	80359	(27.1)	81094	(27.0)
>30	46892	(18.7)	47037	(17.4)	47164	(16.7)	48074	(16.2)	48140	(16.0)
Septic shock [c]										
Yes	56441	(22.5)	57152	(21.2)	59356	(21.1)	61534	(20.8)	62290	(20.7)
No	194201	(77.5)	212861	(78.9)	222526	(78.9)	234926	(79.2)	238635	(79.3)
ICU admission [d]										
Yes	146153	(58.3)	152065	(56.3)	155784	(55.3)	161631	(54.5)	161761	(53.8)
No	104489	(41.7)	117948	(43.7)	126098	(44.7)	134829	(45.5)	139164	(46.3)
Hospital discharge										
Home	118601	(47.3)	127525	(47.2)	133574	(47.4)	143340	(48.4)	146239	(48.6)
Acute care [a]	37903	(15.1)	44798	(16.6)	47526	(16.9)	48651	(16.4)	48945	(16.3)
Long term care [b]	37010	(14.8)	39542	(14.6)	41126	(14.6)	43039	(14.5)	44128	(14.7)
Death	57128	(22.8)	58148	(21.5)	59656	(21.2)	61430	(20.7)	61613	(20.5)

[a] *Acute care unit in medicine, surgery or obstetrics or psychiatry unit*

[b] *Follow-up and rehabilitation care unit, long-term care unit or home care*

[c] *ICD-10 code R57.2, R57.8 as primary diagnosis, related diagnosis or significant associated diagnosis*

[d] *Including implicit sepsis for which ICU admission is part of the selection criteria*

eTable 6. In-hospital mortality (reported as % of sepsis cases) by age class, Charlson index, according to the presence/absence of septic shock, ICU admission, type of selection and 90-day mortality for patients hospitalized with sepsis of presumed bacterial in metropolitan France between 2015 and 2019

Variables	%				
	Year				
	2015	2016	2017	2018	2019
In-hospital mortality	25.7	24.6	24.3	23.7	23.6
30-day mortality	24.8	24.0	23.9	23.4	23.2
90-day mortality	32.6	31.7	31.4	30.9	30.7
Mortality according to age class					
<1	5.0	5.2	5.8	6.1	5.8
1-15	5.1	4.1	4.2	4.6	3.9
16-30	6.3	6.0	6.3	6.2	5.8
31-45	11.5	11.0	11.0	10.7	11.2
46-55	19.3	18.2	17.7	17.2	17.5
56-65	23.6	23.0	22.3	21.9	21.4
66-75	26.3	25.3	24.7	24.5	24.4
76-85	32.0	30.2	29.6	28.7	28.1
>85	39.5	36.6	35.5	34.5	33.9
Mortality according to Charlson index					
0	18.1	17.0	16.8	16.4	16.0
1-2	25.8	24.6	23.9	23.2	23.1
3-4	31.5	30.0	29.7	29.0	28.8
>5	39.1	38.5	38.3	38.2	38.3
Mortality according the presence or absence of septic shock					
Shock	52.1	48.5	51.3	50.6	49.5
No shock	18.0	17.4	17.0	16.7	16.8
Mortality according to ICU admission					
ICU	27.5	26.8	26.7	26.3	26.2
No ICU	23.0	21.7	21.2	20.7	20.4
Mortality according to type of selection					
Explicit sepsis	28.5	27.1	26.6	26	25.5
Implicit sepsis	16.6	16.1	15.9	15.3	15.9

References

1. Tuppin P, Rudant J, Constantinou P, et al. Value of a national administrative database to guide public decisions: From the système national d'information interrégimes de l'Assurance Maladie (SNIIRAM to the système national des données de santé (SNDS in France. *Rev Epidemiol Sante Publique*. 2017;65 Suppl 4:S149-S167. doi:10.1016/j.respe.2017.05.004

2. Opatowski M, Tuppin P, Cosker K, et al. Hospitalisations with infections related to antimicrobial-resistant bacteria from the French nationwide hospital discharge database, 2016. *Epidemiol Infect*. 2019;147:e144. doi:10.1017/S0950268819000402

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	6
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	7-9
Outcome data	15*	Report numbers of outcome events or summary measures over time	7-9

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7-9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	supplement
Discussion			
Key results	18	Summarise key results with reference to study objectives	9-12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11-12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	9-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Trends in bacterial sepsis incidence and mortality in France between 2015 and 2019 based on National Health Data System (SNDS): retrospective observational study

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Title Page

Trends in bacterial sepsis incidence and mortality in France between 2015 and 2019 based on National Health Data System (SNDS): retrospective observational study

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Abstract

Objective: This study aims to provide a case definition of sepsis of presumed bacterial etiology based on ICD-10 codes, to assess the trends in sepsis incidence and mortality between 2015 and 2019 in France and to describe the characteristics of affected patients and hospital stays.

Design: Nationwide, population based retrospective observational study.

Setting: Metropolitan France and between 2015 and 2019.

Participants: Between 2015 and 2019 1 224 433 patients with sepsis of presumed bacterial etiology were selected from the French National Hospital Discharge Database (PMSI) and were identified from corresponding ICD-10 codes for explicit sepsis or implicit sepsis.

Main outcomes measures: Annual overall and age- and gender-specific incidences and 95% confidence intervals as well as trends in sepsis incidence and mortality were estimated. Comorbidities, length of hospital stay and outcomes were described.

Results: The sex and age-standardized incidence per 100 000 [95% CI] increased from 2015 357 [356.0-359.0] in 2015 to 403 [401.9-405.0] in 2019 and remained higher for men compared to women. Children under 1 year and patients over 75 years had consistently the highest incidence. The most common comorbidities were cancer and chronic heart failure. The median hospital length of stay was 12 days. Most patients came from home but only half of them returned home after their hospital stay and approximately 15% were discharged to long term care. In-hospital mortality was about 25% and declined along the study period.

Conclusions: Medico-administrative databases can be used to provide nationwide estimates of the in-hospital burden of bacterial sepsis. The results confirm the high burden of sepsis in France. These data should be complemented by estimating the additional burden associated with fungal and viral infection during the COVID-19 pandemic.

Strengths and limitations of this study

- The study uses nationwide data including hospitalized patients with presumed bacterial infection, from the anonymized French National Hospital Discharge Database (PMSI)
- Patients with sepsis and viral or fungal infection only were not included, but their proportion among all sepsis cases estimated on a representative sample from the same database
- Sepsis cases were selected using ICD-10 codes of explicit sepsis and a more stringent selection criteria for implicit sepsis compared to previous studies.
- This methodology may require further validation by comparing our results with clinical data

Introduction

Sepsis is a complex disorder, associated with long term morbidity and major economic impacts, responsible for several millions of deaths per year worldwide [1–4]. The challenge of defining sepsis led to several revised definitions over the past decades. In 2016, the Third International Consensus Definition of sepsis (Sepsis-3) defined sepsis as a "life-threatening organ dysfunction due to a dysregulated host response to infection." [5]. Indeed, organ dysfunction, was found to have better ability to predict in-hospital mortality or to target patients with higher risk of adverse outcomes than the original SIRS criteria and the previous sepsis-2 definition[6–10]. However, the successive changes of sepsis definition made it difficult to identify the true incidence of sepsis and to assess the variation of incidence over time and across countries [1,2].

In 2017, concerned by the amount of sepsis related deaths and recognizing the potential to mitigate the burden and impact of sepsis, the seventieth World Health Assembly adopted a

resolution to improve the prevention, diagnosis, and management of sepsis, urging Member States to collect information and to initiate actions in accordance with WHO guidelines [11]. In France, a report commissioned by the French General Director of Health, in response to WHO resolution, identifies new measures and proposes a clear framework for future actions; including the analysis and the reporting of epidemiological data [12]. The last French Study about sepsis incidence was conducted on data collected between 2010 and 2015, for adults only[13].

Clinical data or medico-administrative database can be used to assess sepsis incidence. Large scale studies generally rely on medico-administrative data which is a cost-effective way to study large cohorts [14]. However, the range of ICD codes used to identify sepsis in medico-administrative databases may change or be partially replicated in the different studies, leading to varying estimates [14–16]. Moreover, disparities were identified in sepsis incidence based on medico-administrative data compared to clinical data [17,18]. As no consensus exists regarding sepsis identification based on ICD codes and acknowledging that sepsis has no pathologic gold standard, a careful selection of explicit and implicit sepsis codes has been suggested, with the objective of maintaining good specificity and sensitivity [14,15,17].

The study was conducted from 2015, following new recommendations of coding practices in France for sepsis in 2014[19]. This study spans from 2015 to 2019, to assess the incidence of sepsis before the COVID-19 pandemic, and as recommendations regarding coding practices did not change during that period [19,20] . The aims of this study are to provide a case definition of sepsis based on ICD-10 codes, to assess the trends in sepsis incidence and mortality between 2015 and 2019 in France and to describe the characteristics of patients and hospital stays.

Methods

Data

The study consisted of a secondary data analysis of a cohort of all patients with bacterial infections and registered in the anonymized French National Hospital Discharge Database (Programme de Médicalisation des Systèmes d'Information: PMSI) issued from the French health care database (Système National des Données de Santé: SNDS) and outpatient health care consumption (Données de Consommation Inter-Régimes: DCIR) [21] (see online supplementary appendix A : eMethods). Therefore, only the incidence of sepsis of presumed bacterial etiology (referred to herein as sepsis) was estimated. The EGB (Generalist sample of beneficiaries, a sample representative of the national health insurance beneficiaries) was used to estimate the proportion of sepsis of viral or fungal etiologies among all sepsis cases (see online supplementary appendix A: eMethods and eTable 1). The study, analysis and data extraction were approved by the French Data Protection Agency (CNIL, approval DE-2016–176). Demographic data were obtained from the French Census of the National Institute of Statistics and Economic Studies [22].

Study population and selection of the hospital stays with sepsis

The study population included all patients hospitalized with sepsis between January 1st, 2015 and December 31st, 2019 in metropolitan France (thus excluding overseas territories). Hospital stays shorter than 1 day where the patient did not die were excluded. For patients with multiple stays per year, only the last stay was considered for the descriptive analysis, to estimate in-hospital mortality and to estimate annual incidence.

Similarly to previous studies[1,13,23], sepsis was defined as the combination of the two mutually exclusive categories of explicit or implicit sepsis (referred to hereafter as selection type). Explicit sepsis of presumed bacterial etiology was defined as a stay with one of the selected ICD-10 codes for sepsis as primary diagnosis (PD: condition requiring hospitalization),

related diagnosis (RD: adds information to PD) or significant associated diagnosis (SAD: complications and co-morbidities potentially affecting the course or cost of hospitalization). Implicit sepsis of presumed bacterial etiology was defined as a stay with one of the selected ICD-10 codes for infection (other than those defining explicit sepsis) as PD, RD or SAD with two associated conditions: ICU admission and at least one of the selected ICD-10 codes for organ dysfunction or one or more of the codes for organ support from the Common Classification of Medical Acts (CCAM) (see online supplementary appendix A: eTable 1(Sepsis of presumed bacterial etiology)).

Incidence

Annual overall incidence (crude and sex and age-adjusted based on 2019 population distribution) and age and gender specific incidence and 95% confidence intervals were calculated from 2015 to 2019 and expressed as the number of cases per 100 000 inhabitants.

Description of patients, hospital stays and site of infection

Sex, age, Charlson index and detailed comorbidities were described for all patients[24]. A total of 15 sites of infection was identified using the ICD-10 codes list defined by Opatowski et al.[25] who conducted a study on the same dataset: Bones and joints, Ears, nose and throat, Eyes, Gastrointestinal and abdomen, Heart and mediastinum, Lower respiratory tract, Medical devices, Nervous system, Newborn, Pregnancy, Skin and soft tissues, Urinary and genital tracts, Multiple sites and Unknown. Details on definitions of the variables and infection site classification are described in the eMethods in the supplementary appendix A online. Admission source, hospital discharge, yearly number of hospital stays as well as the percentage of septic shock and admission to ICU were also described. As admission to ICU and organ dysfunction/support were part of the selection criteria for implicit sepsis, the percentage of admission to ICU and the percentage of organ dysfunction/support were also described for explicit sepsis only. In-hospital death was assessed for explicit and implicit

sepsis and according to age, ICU admission and the presence of septic shock; 30-day and 90-day mortality were also assessed. To describe patients and hospital stays characteristics no confidence intervals were used, as the data cover the national population[26,27].

Statistical analysis

A Cochran-Armitage Test for Trend was used to assess the change of incidence and mortality. Three additional logistic regressions were used to assess the odds ratio for the ordinal variable "year" (using 2015 as reference), considering in-hospital, 30-day and 90-day mortalities as a binary dependent variable and adjusting for sex, age, comorbidities, septic shock and infection sites.

Results

Number of cases and characteristics of sepsis patients

For metropolitan France, there were 222 232 cases of sepsis of presumed bacterial etiology in 2015, which increased slightly up to 261 499 in 2019 (Table 1, Figure 1). This increase appears essentially due to a gradual increasing incidence of explicit sepsis between 2015 (169 419 cases) and 2019 (208 510 cases), whereas implicit sepsis remained stable (respectively 52 813 and 52 989 cases) (Figure 1).

Patient's characteristics were stable between 2015 and 2019 (Table 1). Men accounted each year for a 15% higher proportion of sepsis than women. In 2019, people aged over 55 years represented 78.6% of the sepsis cases. More than one third of the patients had a Charlson index of 0, whereas less than 30% had a Charlson index above 2. Cancer, chronic heart failure, renal disease and chronic pulmonary disease were the most frequent comorbidities, respectively associated with 23.0%, 20.9%, 13.2% and 11.2% of sepsis cases in 2019.

Between 2015 and 2018, the estimated mean percentage of sepsis of viral and fungal etiology (without concomitant sepsis of presumed bacterial etiology) among all sepsis was 1.7% (range 1.55% to 1.92%).

Incidence

The global sex and age-standardized incidence per 100 000 [95% CI] of sepsis increased from 2015 (357 [356.0-359.0]) to 2019 (403 [401.9-405.0]). A significant decreasing trend was observed using Cochran-Armitage test (P<0.001) (Table2, Figure 1). The annual incidence remained higher for males (480 [477.5-482.3] in 2019) compared to females (332 [329.9-333.8] in 2019) and was markedly higher for people <1 and >75 years (Table 2).

Sites of infection

The distribution of infection sites was quite similar over the 5-year study period. A substantial proportion of stays had no site identified (20.2% in 2019) or multiple sites recorded (21.3% in 2019) (see online supplementary appendix A : eTable2). Most patients with no site identified had primary bacteremia (88%). Overall, the most common sites of infection for patients having a single site identified were the lower respiratory tract, urinary and genital tracts and gastrointestinal and abdomen, followed by heart and mediastinum and skin and soft tissues (19.6%, 15.0%, 6.0%, 5.1% and 4.6% in 2019 respectively) (see online supplementary appendix A : eTable 2). Urinary and genital tracts infection predominated in women (19.0% in 2019) whereas lower respiratory tract infection predominated in men (21.3% in 2019).

About three fourth of sepsis were associated with bacteremia. Overall, about 20% of patients had primary bacteremia (17.7% in 2019), whereas more than 50% had secondary bacteremia (58.8% in 2019) (see online supplementary appendix A : eTable 3).

Hospital stays of patients with sepsis

A minority of the patients had more than one hospital stay per year related to sepsis (10% in 2019) (see online supplementary appendix A : eTable 4). As mentioned in the methods section, the description in Table 3 considers only one hospital stay per year per patient but a description of all hospital stays associated with sepsis (All stays of all patients) is available in the eTable 5 in the supplementary appendix A online and showed similar results. The median length of stay was 13 days in 2015 and 12 days in 2019. The percentage of septic shock varied from 22.6% in 2015 to 20.7% in 2019. Considering only explicit sepsis, the percentage of ICU admission varied from 45.9% in 2015 to 42.5% in 2019 and the percentage of organ dysfunction varied from 67.9% % in 2015 to 66.6% in 2019. While the large majority of patients came from home (85.6% in 2019) and only about 2% were admitted from long-term care, less than 50% returned home after the hospital stay, whereas nearly 15% were discharged to long term care.

In-hospital mortality, 30-day and 90-day mortality

The overall in-hospital death rate slightly declined between 2015 (25.7%) and 2019 (23.6%) as well as 30-day and 90-day mortality which approximated 26% and 33% respectively in 2015 and 23% and 31% respectively in 2019. A significant decreasing trend was observed using Cochran-Armitage test (P<0.001) (see online supplementary appendix A: eTable 6). Adjusting for sex, age, comorbidities, septic shock and infection sites, the odds ratios for the variable "year" progressively declined between 2016 and 2019, confirming the decreasing trend for mortality. In 2019, the odds ratio for 2019 compared to 2015 was 0.904 [0.891-0.917] for in-hospital mortality, 0.938 [0.924-0.952] for 30-day mortality and 0.918 [0.905-0.930] for 90-day mortality (see online supplementary appendix A: eTable 7). In hospital mortality was 10% higher for explicit (25.5% in 2019) compared to implicit sepsis (15.9% in 2019). In-hospital mortality increased with age classes. In 2019, the mortality rate was under

10% for patients aged up to 30 but reached 33.9% for patients above 85 years. Mortality rate also increased with Charlson index (in 2019, 16.0% for Charlson index=0 and 38.3% for Charlson index>5) and was also higher for patients with septic shock (49.5% with septic shock, 16.8% without septic shock in 2019) or transferred to ICU (26.2% with ICU, 20.4% without ICU). The proportion of death was highest for patients with unknown source of infection (33.0% in 2019) and those with multiple sites of infection (23.7% in 2019) (Figure 2). Among those with a unique site of infection recorded, skin and soft tissues (31.8% in 2019), lower respiratory tract (28.3% in 2019), and gastrointestinal and abdominal infections (21.1% in 2019) were associated with the highest mortality rates.

Discussion

Methodological approach

This study represents a first important step in the evaluation of sepsis burden in France, accounting for the new definition of sepsis. Our selection of patients attempted to use the new Sepsis-3 definition [5] and our methodology identified sepsis cases through explicit and implicit sepsis as previously suggested[1,23]. However, the list of ICD-10 codes used varied across the different studies and is prone to over or underestimate sepsis incidence [1,2,14,28]. While attempting to not under or overestimate implicit sepsis, organ dysfunction was identified through both ICD-10 and organ support (CCAM) but also based on the need for intensive care unit (ICU) stay. Indeed, the expert panel has presented ICU care as a typical outcome for patients with sepsis [5] and the potential overestimation of implicit sepsis based only on the combination of infection and organ dysfunction was illustrated in the study by Fleishmann et al. (2018)[29]. Conversely, our more stringent selection criteria for implicit sepsis may have led to an underestimation of implicit sepsis cases, managed exclusively within wards. While our methodological choices and our database (sepsis of bacterial etiology only) limits the

comparability with the previous French sepsis incidence Study conducted between 2010 and 2015[13], our methodological choice is in line with the conclusions of recent studies which suggest better estimation of sepsis incidence by combining a larger set of explicit sepsis cases and a careful selection of implicit sepsis cases[1,14,17,29].

Incidence and changes over time

The incidence of sepsis was substantially higher compared to the study of Rudd *et al* which used the Global Burden of Disease database (GBD)[1]. However, the authors acknowledged a difference between their results and previous published works, possibly due to unrecorded explicit sepsis or organ dysfunction. We also found a substantially higher incidence of sepsis compared to the study conducted in France between 2010 and 2015 but our selection criteria probably also captured less severe cases[13]. A recent study in US also found a higher incidence compared to previous studies[30]. Similarly to other studies, we observed a slight increase of sepsis incidence over time [1,13,30]. This could be due to a real increase or to changes in coding practices[1,30]. Indeed, population ageing and advanced therapies has impacted overall patients survival and are likely to increase sepsis incidence [2,30], but this may also be explained by the development of campaigns that increase the awareness, the screening, the diagnosis of sepsis[2,17,30] or due to the recommendations issued in 2014 issued by the French Technical Agency for Hospital Information (ATIH).

Characteristics of patients and hospital stays

Similarly to other studies, higher incidence was observed for men compared to women, for very young infants or elderly and for patients with comorbidities[13,23,30–33]. Indeed, ageing is associated with increased prevalence of chronic diseases and impaired immune system, thus increasing the risk of sepsis [32]. Some studies, which include low-income countries or different study population, found higher or similar incidence in women compared to men but the sepsis related mortality was higher in men[1,23]. As shown in previous studies, lower respiratory tract

and urinary - genital tracts were the most common sites of infection with urinary - genital tracts more common for women and respiratory tract for men [23,30,34]. Fewer episodes of sepsis of respiratory origin might partially explain the lower incidence of sepsis in women compared to men [23]. Additionally, several studies showed than men have more chronic comorbidities than women, which may impair their ability to combat infection [32,35,36]. Indeed, comorbidities and septic shock substantially increased in-hospital sepsis related death similarly as previously shown [13]. The median Charlson score was of 2, similar to other studies[13,33]. However, our study showed that more than one third of the patients had no comorbidity recorded. Septic patients without comorbidities were also identified in other studies[23,37,38]. This suggests the influence of other risk factors, as excess alcohol use, trauma, other issues in neonates or immunosuppression[33,39,40].

Only half of all patients returned home, which emphasize the high mortality rate and mid- and long-term burden of sepsis through the requirements of care in nursing homes or intermediate care facilities [30]. The percentage of patients returning home was higher compared to another recent study which also captured mild cases of sepsis[30]. However, the proportion of patients having ICU admission[13,17] or the percentage of septic shock[30] was in line with previous studies. The median length of stays was 12 days in 2019, which is much higher than the usual length of stay in acute care units. Comparatively to previous studies, in-hospital mortality slightly declined over time[16,41]. Moreover, the concomitant increase of explicit sepsis, which could been considered as the most severe sepsis cases, could suggest a real decline of the mortality rate. However, changes in coding practices might have increase explicit sepsis due to the inclusion of less severe sepsis cases in this category, making the decline of mortality artificial[19,42]. In-hospital mortality rate was around 25% and was comparable to the results obtained in previous studies where sepsis related death rates ranged from 15% to 30% [2,23,30,34,41,43] and confirms the high mortality risk associated with sepsis, although in-hospital

mortality was lower than the 34% rate reported in the 2010-2015 study of Dupuis et al. [13]. Sepsis-related deaths also occurred outside of the hospital [44]. Indeed, 90-days mortality reached about 30%.

Limitations of the study

The methodology used is similar to previous studies identifying sepsis in medico-administrative database based on explicit and implicit sepsis[1,13]. However, coding practices, databases and the ICD-code used to select sepsis cases might vary across studies and countries, which can limit the comparability with other studies [14–16,30]. Therefore, this methodology of selection should be reproduced on other time-period in France, and eventually other countries, in order to compare our results with similar studies and limit comparison bias. Moreover, identifying the incidence of sepsis with an ICD code-based approach may show some discrepancies with clinical data[17,29]. Indeed, several studies have demonstrated high specificity but low sensitivity of explicit sepsis and lower specificity but higher sensitivity of implicit sepsis when compared to clinical data[17,29]. Validating medico-administrative data to avoid misclassification bias is an important step and our study would requires further validation against clinical charts and/or electronic health records review[14,17,29,45].

While the number of implicit sepsis cases barely changed between 2015 and 2019, we observed a slight increase of explicit sepsis cases. Indeed, the coding practice might have experienced some changes over time and impacted sepsis incidence, especially following new instructions for sepsis coding[17]. However, the use of medico-administrative databases represents the only cost effective way to obtain a large population coverage and this type of data are largely used to benchmark the incidence of sepsis or other pathologies in the national population [14,15,46].

The majority of the patients had only one episode of sepsis over the year but around 10% experienced multiple stays. While we adapted our methodology to compare hospital stays and patients with single and multiple stays, patients with sepsis having multiple stays over the year could be further characterized.

Finally, due to administrative and regulation hurdles and the time required to obtain access to all hospitalization of the PMSI, the cohort available narrowed our study to the assessment of sepsis of presumed bacterial etiology. However, sepsis of viral and fungal etiology (without concomitant sepsis of presumed bacterial etiology) was estimated at only 1.7% of all sepsis cases in the period studied. Therefore, we believe having obtained a reasonable estimate of the overall sepsis incidence in France for the period considered. The incidence of sepsis of all etiologies should be further assessed, using our proposed methodology for the time period both before and during the Covid-19 pandemic. Moreover, in order to estimate the percentage of deaths attributable to sepsis, causes of death records could be used but the estimation will also depend upon the coding practices.

Conclusion

Medico-administrative databases can be used to provide nationwide estimates of the incidence of sepsis and also allow to study healthcare pathways but further validation with detailed clinical data is required. Our data should be complemented by the re-assessment of the relative proportion of sepsis with a bacterial, fungal and especially of viral etiology during the COVID-19 pandemic.

Our results confirm the high burden of sepsis in France. Patient characteristics could be considered in quality-improvement programs and new individualized management strategies. Concomitant changes of the coding practices and of the incidence itself, challenge the

assessment of changes over time. This highlights the urgent need for a long-lasting consensus to describe sepsis in medico-administrative database.

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Contributors:

Fanny Pandolfi, Laurence Watier, Christian Brun-Buisson, Didier Guillemot conceived the study. Laurence Watier obtained the funding for the study. Fanny Pandolfi, Laurence Watier, Christian Brun-Buisson organized the data collection and conducted the analysis. Fanny Pandolfi, Laurence Watier, Christian Brun-Buisson drafted the manuscript. Fanny Pandolfi, Laurence Watier, Christian Brun-Buisson, Didier Guillemot contributed to the critical revision of the manuscript.

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References

1. Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. *Lancet Lond Engl*. 2020;395(10219):200-211. doi:10.1016/S0140-6736(19)32989-7

2. Cecconi M, Evans L, Levy M, Rhodes A. Sepsis and septic shock. *Lancet Lond Engl*. 2018;392(10141):75-87. doi:10.1016/S0140-6736(18)30696-2

3. Paoli C, Reynolds M, Sinha M, Gitlin M, Crouser E. Epidemiology and Costs of Sepsis in the United States-An Analysis Based on Timing of Diagnosis and Severity Level. *Crit Care Med*. 2018;46(12). doi:10.1097/CCM.0000000000003342

4. Tiru B, DiNino EK, Orenstein A, et al. The Economic and Humanistic Burden of Severe Sepsis. *PharmacoEconomics*. 2015;33(9):925-937. doi:10.1007/s40273-015-0282-y

5. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315(8):801-810. doi:10.1001/jama.2016.0287

6. Seymour CW, Liu VX, Iwashyna TJ, et al. Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315(8):762-774. doi:10.1001/jama.2016.0288

7. Freund Y, Lemachatti N, Krastinova E, et al. Prognostic Accuracy of Sepsis-3 Criteria for In-Hospital Mortality Among Patients With Suspected Infection Presenting to the Emergency Department. *JAMA*. 2017;317(3):301-308. doi:10.1001/jama.2016.20329

8. Eriksson J, Eriksson M, Brattström O, et al. Comparison of the sepsis-2 and sepsis-3 definitions in severely injured trauma patients. *J Crit Care*. 2019;54:125-129. doi:10.1016/j.jcrc.2019.08.019

9. Shahsavarinia K, Moharramzadeh P, Arvanagi RJ, Mahmoodpoor A. qSOFA score for prediction of sepsis outcome in emergency department. *Pak J Med Sci*. 2020;36(4):668-672. doi:10.12669/pjms.36.4.2031

10. Takauji S, Hayakawa M, Fujita S. A Nationwide Comparison Between Sepsis-2 and Sepsis-3 Definition in Japan. *J Intensive Care Med*. 2020;35(12):1389-1395. doi:10.1177/0885066618823151

11. WHO. WHA70.7, Agenda item 12.2. Improving the prevention, diagnosis and clinical management of sepsis. Published online May 29, 2017.

12. Annane D. Sepsis - tous unis contre un fléau méconnu. Rapport Au Directeur Général De La Santé. Published online 2019. https://solidarites-sante.gouv.fr/IMG/pdf/rapport_sepsis_dgs_130919.pdf

13. Dupuis C, Bouadma L, Ruckly S, et al. Sepsis and septic shock in France: incidences, outcomes and costs of care. *Ann Intensive Care*. 2020;10(1):145. doi:10.1186/s13613-020-00760-x

14. Jolley RJ, Sawka KJ, Yergens DW, Quan H, Jetté N, Doig CJ. Validity of administrative data in recording sepsis: a systematic review. *Crit Care Lond Engl*. 2015;19:139. doi:10.1186/s13054-015-0847-3

15. Gaieski DF, Edwards JM, Kallan MJ, Carr BG. Benchmarking the incidence and mortality of severe sepsis in the United States. *Crit Care Med*. 2013;41(5):1167-1174. doi:10.1097/CCM.0b013e31827c09f8

16. Fleischmann-Struzek C, Mellhammar L, Rose N, et al. Incidence and mortality of hospital- and ICU-treated sepsis: results from an updated and expanded systematic review and meta-analysis. *Intensive Care Med*. 2020;46(8):1552-1562. doi:10.1007/s00134-020-06151-x

17. Rhee C, Jentzsch MS, Kadri SS, et al. Variation in Identifying Sepsis and Organ Dysfunction Using Administrative Versus Electronic Clinical Data and Impact on Hospital Outcome Comparisons. *Crit Care Med*. 2019;47(4):493-500. doi:10.1097/CCM.0000000000003554

18. Liu YZ, Chu R, Lee A, et al. A surveillance method to identify patients with sepsis from electronic health records in Hong Kong: a single centre retrospective study. *BMC Infect Dis*. 2020;20(1):652. doi:10.1186/s12879-020-05330-x

19. ATIH. Fascicule de Codage pour Le PMSI : Maladies infectieuses. Published online 2014. http://www.departement-information-medicale.com/wp-content/uploads/2014/12/fascicule_codage_mal_infect_2014.pdf

20. ATIH. Guide Méthodologique De Production Des Informations Relatives A L'activité Médicale Et A Sa Facturation En Médecine, Chirurgie, Obstétrique Et Odontologie _Version provisoire 2021. Published online 2021. https://www.atih.sante.fr/guide-methodologique-mco-2021-v2

21. Tuppin P, Rudant J, Constantinou P, et al. Value of a national administrative database to guide public decisions: From the système national d'information interrégimes de l'Assurance Maladie (SNIIRAM) to the système national des données de santé (SNDS) in France. *Rev Epidemiol Sante Publique*. 2017;65 Suppl 4:S149-S167. doi:10.1016/j.respe.2017.05.004

22. INSEE. Institut national de la statistique et des études économiques. Population par sexe et âge 2015, 2016, 2017, 2018 & 2019. https://www.insee.fr/fr/statistiques

23. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med*. 2001;29(7):1303-1310. doi:10.1097/00003246-200107000-00002

24. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol*. 2011;173(6):676-682. doi:10.1093/aje/kwq433

25. Opatowski M, Tuppin P, Cosker K, et al. Hospitalisations with infections related to antimicrobial-resistant bacteria from the French nationwide hospital discharge database, 2016. *Epidemiol Infect*. 2019;147:e144. doi:10.1017/S0950268819000402

26. Ioannidis JPA. What Have We (Not) Learnt from Millions of Scientific Papers with P Values? *Am Stat*. 2019;73(sup1):20-25. doi:10.1080/00031305.2018.1447512

27. Lin M, Lucas Jr. HC, Shmueli G. Too big to fail: Large samples and the p-value problem. *Inf Syst Res*. 2013;24(4):906-917. doi:10.1287/isre.2013.0480

28. Wilhelms SB, Huss FR, Granath G, Sjöberg F. Assessment of incidence of severe sepsis in Sweden using different ways of abstracting International Classification of Diseases codes: difficulties with methods and interpretation of results. *Crit Care Med*. 2010;38(6):1442-1449. doi:10.1097/CCM.0b013e3181de4406

29. Fleischmann-Struzek C, Thomas-Rüddel DO, Schettler A, et al. Comparing the validity of different ICD coding abstraction strategies for sepsis case identification in German claims data. *PloS One*. 2018;13(7):e0198847. doi:10.1371/journal.pone.0198847

30. Wardi G, Tainter CR, Ramnath VR, et al. Age-related incidence and outcomes of sepsis in California, 2008-2015. *J Crit Care*. 2021;62:212-217. doi:10.1016/j.jcrc.2020.12.015

31. Fay K, Sapiano MRP, Gokhale R, et al. Assessment of Health Care Exposures and Outcomes in Adult Patients With Sepsis and Septic Shock. *JAMA Netw Open*. 2020;3(7):e206004. doi:10.1001/jamanetworkopen.2020.6004

32. Cillóniz C, Dominedò C, Ielpo A, et al. Risk and Prognostic Factors in Very Old Patients with Sepsis Secondary to Community-Acquired Pneumonia. *J Clin Med*. 2019;8(7):E961. doi:10.3390/jcm8070961

33. Davis JS, He V, Anstey NM, Condon JR. Long term outcomes following hospital admission for sepsis using relative survival analysis: a prospective cohort study of 1,092 patients with 5 year follow up. *PloS One*. 2014;9(12):e112224. doi:10.1371/journal.pone.0112224

34. Karlsson S, Varpula M, Ruokonen E, et al. Incidence, treatment, and outcome of severe sepsis in ICU-treated adults in Finland: the Finnsepsis study. *Intensive Care Med*. 2007;33(3):435-443. doi:10.1007/s00134-006-0504-z

35. Gipson SAY, Hall MD. The evolution of sexual dimorphism and its potential impact on host-pathogen coevolution. *Evol Int J Org Evol*. 2016;70(5):959-968. doi:10.1111/evo.12922

36. Zuk M. The Sicker Sex. *PLOS Pathog*. 2009;5(1):e1000267. doi:10.1371/journal.ppat.1000267

37. Devendra Prasad K, Abhinov T, Himabindu K, Rajesh K, Krishna Moorthy D. Modified Shock Index as an Indicator for Prognosis Among Sepsis Patients With and Without Comorbidities Presenting to the Emergency Department. *Cureus*. 13(12):e20283. doi:10.7759/cureus.20283

38. Fleischmann-Struzek C, Mikolajetz A, Schwarzkopf D, et al. Challenges in assessing the burden of sepsis and understanding the inequalities of sepsis outcomes between National Health Systems: secular trends in sepsis and infection incidence and mortality in Germany. *Intensive Care Med*. 2018;44(11):1826-1835. doi:10.1007/s00134-018-5377-4

39. Mas-Celis F, Olea-López J, Parroquin-Maldonado JA. Sepsis in Trauma: A Deadly Complication. *Arch Med Res*. 2021;52(8):808-816. doi:10.1016/j.arcmed.2021.10.007

40. Born S, Dame C, Matthäus-Krämer C, et al. Epidemiology of Sepsis Among Children and Neonates in Germany: Results From an Observational Study Based on Nationwide Diagnosis-Related Groups Data Between 2010 and 2016. *Crit Care Med*. 2021;49(7):1049-1057. doi:10.1097/CCM.0000000000004919

41. Imaeda T, Nakada TA, Takahashi N, et al. Trends in the incidence and outcome of sepsis using data from a Japanese nationwide medical claims database-the Japan Sepsis Alliance (JaSA) study group. *Crit Care Lond Engl*. 2021;25(1):338. doi:10.1186/s13054-021-03762-8

42. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. *JAMA*. 2010;304(16):1787-1794. doi:10.1001/jama.2010.1553

43. Fleischmann C, Scherag A, Adhikari NKJ, et al. Assessment of Global Incidence and Mortality of Hospital-treated Sepsis. Current Estimates and Limitations. *Am J Respir Crit Care Med*. 2016;193(3):259-272. doi:10.1164/rccm.201504-0781OC

44. Melamed A, Sorvillo FJ. The burden of sepsis-associated mortality in the United States from 1999 to 2005: an analysis of multiple-cause-of-death data. *Crit Care Lond Engl*. 2009;13(1):R28. doi:10.1186/cc7733

45. Benchimol EI, Manuel DG, To T, Griffiths AM, Rabeneck L, Guttmann A. Development and use of reporting guidelines for assessing the quality of validation studies of health administrative data. *J Clin Epidemiol*. 2011;64(8):821-829. doi:10.1016/j.jclinepi.2010.10.006

46. Rochoy M, Chazard E, Bordet R. [Epidemiology of neurocognitive disorders in France]. *Geriatr Psychol Neuropsychiatr Vieil*. 2019;17(1):99-105. doi:10.1684/pnv.2018.0778

Tables

Table 1- Characteristics of patients with sepsis, France 2015-2019

Characteristics	N (%)									
	Years									
	2015 (n=222232)		2016 (n=236314)		2017 (n=245780)		2018 (n=258608)		2019 (n=261499)	
Gender										
Men	128090	(57.6)	135613	(57.4)	141113	(57.4)	148650	(57.5)	150507	(57.6)
Women	94142	(42.4)	100701	(42.6)	104667	(42.6)	109958	(42.5)	110992	(42.4)
Age										
<1	12193	(5.5)	11321	(4.8)	11193	(4.6)	11052	(4.3)	10547	(4.0)
1-15	4137	(1.9)	4588	(1.9)	4287	(1.7)	4681	(1.8)	4786	(1.8)
16-30	6492	(2.9)	7050	(3.0)	7023	(2.9)	7441	(2.9)	7252	(2.8)
31-45	11993	(5.4)	12599	(5.3)	12691	(5.2)	13370	(5.2)	13078	(5.0)
46-55	18601	(8.4)	19046	(8.1)	19595	(8.0)	20392	(7.9)	20299	(7.8)
56-65	36585	(16.5)	38174	(16.2)	38539	(15.7)	40736	(15.8)	40349	(15.4)
66-75	45078	(20.3)	50052	(21.2)	54125	(22.0)	58989	(22.8)	61672	(23.6)
76-85	54256	(24.4)	56725	(24.0)	58052	(23.6)	59528	(23.0)	59679	(22.8)
>85	32897	(14.8)	36759	(15.6	40275	(16.4)	42419	(16.4)	43837	(16.8)
Charlson index[24] **Median (IQR)**	2	(0-3)	2	(0-3)	2	(0-3)	2	(0-3)	2	(0-3)
0	82175	(37.0)	87080	(36.8)	89599	(36.5)	94792	(36.7)	95465	(36.5)
1-2	76140	(34.3)	81113	(34.3)	84603	(34.4)	89191	(34.5)	90600	(34.6)
3-4	31656	(14.2)	33947	(14.4)	35485	(14.4)	36824	(14.2)	37358	(14.3)
>5	32261	(14.5)	34174	(14.5)	36093	(14.7)	37801	(14.6)	38076	(14.6)
Comorbidities										
Cancer	51042	(23.0)	54810	(23.2)	56581	(23.0)	59648	(23.1)	60064	(23.0)
Congestive heart failure	46324	(20.8)	49394	(20.9)	51912	(21.1)	54511	(21.1)	54553	(20.9)
Renal disease	27960	(12.6)	30091	(12.7)	32119	(13.1)	33252	(12.9)	34554	(13.2)
Chronic pulmonary disease	24941	(11.2)	26110	(11.1)	27097	(11.0)	28513	(11.0)	29249	(11.2)
Metastatic carcinoma	20619	(9.3)	22408	(9.5)	23516	(9.6)	24915	(9.6)	25331	(9.7)
Diabetes with chronic complications	13104	(5.9)	13690	(5.8)	14212	(5.8)	14558	(5.6)	14598	(5.6)
Paraplegia or hemiplegia	11535	(5.2)	12463	(5.3)	13238	(5.4)	14416	(5.6)	14496	(5.5)
Dementia	12265	(5.5)	13035	(5.5)	13825	(5.6)	14247	(5.5)	14123	(5.4)
Mild liver disease	11560	(5.2)	12002	(5.1)	12837	(5.2)	13134	(5.1)	13440	(5.1)
Moderate or severe liver disease	5844	(2.6)	5922	(2.5)	6266	(2.6)	6318	(2.4)	6335	(2.4)
Rheumatologic disease	2691	(1.2)	2807	(1.2)	2866	(1.2)	3071	(1.2)	3128	(1.2)
AIDS	1044	(0.5)	1016	(0.4)	1104	(0.5)	1020	(0.4)	1006	(0.4)

505 Table 2- Overall sepsis incidence by gender and age, France 2015-2019[a]

Age	N [CI] Years				
	2015 (n=222232)	2016 (n=236314)	2017 (n=245780)	2018 (n=258608)	2019 (n=261499)
Men					
<1	1862 [1818.2-1905.0]	1771 [1728.5-1814.0]	1809 [1765.0-1852.3]	[1763.6-1851.5]	1755 [1711.2-1798.6]
1-15	37 [35.7-38.8]	42 [40.1-43.4]	39 [37.4-40.6]	[41.4-44.7]	44 [42.8-46.1]
16-30	53 [51.1-54.8]	55 [53.2-57.0]	56 [53.8-57.7]	[56.9-60.9]	58 [55.9-59.9]
31-45	104 [101.4-106.5]	108 [105.4-110.6]	111 [107.9-113.2]	[113.0-118.4]	114 [111.7-117.2]
46-55	266 [261.6-271.4]	273 [267.7-277.7]	279 [273.7-283.7]	[282.6-292.7]	283 [277.6-287.6]
56-65	618 [610.4-626.0]	643 [635.2-651.1]	646 [638.2-654.2]	[664.9-681.2]	670 [661.8-678.0]
66-75	1095 [1082.1-1107.1]	1159 [1146.8-1171.9]	1196 [1183.3-1208.3]	[1237.5-1262.5]	1260 [1248.0-1272.7]
76-85	1942 [1920.6-1963.6]	2022 [1999.9-2043.7]	2070 [2047.5-2091.7]	[2136.7-2182.1]	2170 [2147.1-2192.5]
>85	2855 [2809.2-2901.5]	3060 [3013.3-3106.9]	3283 [3235.4-3330.5]	[3344.8-3440.3]	3435 [3387.6-3482.3]
All Men	411 [409.1-413.6]	434 [432.2-436.8]	451 [448.7-453.4]	[469.5-474.3]	480 [477.5-482.3]
Women					
<1	1481 [1441.4-1520.9]	1385 [1346.6-1424.2]	1375 [1335.8-1413.8]	[1341.6-1420.3]	1347 [1307.4-1386.0]
1-15	33 [31.4-34.4]	36 [34.6-37.7]	34 [32.4-35.4]	[34.6-37.8]	38 [36.4-39.6]
16-30	61 [58.8-62.9]	69 [66.9-71.2]	68 [66.1-70.5]	[69.6-74.0]	71 [68.8-73.2]
31-45	89 [87.1-91.8]	96 [93.9-98.7]	97 [94.1-99.0]	[100.2-105.3]	102 [99.2-104.3]
46-55	166 [162.4-170.0]	170 [166.0-173.7]	175 [171.5-179.3]	[177.8-185.7]	184 [179.9-187.8]
56-65	302 [296.7-307.2]	318 [312.5-323.3]	323 [317.9-328.8]	[343.6-354.9]	343 [337.3-348.5]
66-75	520 [511.6-527.8]	553 [544.9-561.1]	578 [569.4-585.7]	[594.6-610.9]	610 [602.2-618.3]
76-85	1018 [1005.0-1030.8]	1074 [1061.0-1087.7]	1107 [1093.2-1120.4]	[1135.0-1163.0]	1151 [1137.0-1165.2]
>85	1590 [1567.2-1612.5]	1731 [1707.5-1754.0]	1825 [1801.0-1848.2]	[1891.2-1939.5]	1919 [1895.5-1943.3]
All Women	303 [300.9-304.7]	303 [300.9-304.7]	314 [311.9-315.7]	[326.1-330.0]	332 [329.9-333.8]
Total population *crude*	346 [344.2-347.0]	367 [365.1-368.0]	380 [378.7-381.7]	[396.2-399.3]	403 [401.9-405.0]
explicit only	263 [262,2-264,7]	284 [283,1-285,7]	298 [296,7-299,4]	[313,5-316,2]	322 [320,3-323,1]
implicit only	82 [81,4-82,8]	82 [81,5-82,9]	82 [81,5-82,9]	[82,2-83,6]	82 [81,1-82,5]
sex and age-standardized[b]	357 [356.0-359.0]	376 [374.2-377.2]	386 [384.6-387.7]	[401.6-404.7]	403 [401.9-405.0]

506 a *Data are shown as number per 100,000 population, with 95% CI*

507 *b Based on the population distribution by sex and age in 2019*

508 Table 3 – Characteristics of hospital stays with sepsis, France 2015-2019

Variables	2015 (N=222232)		2016 (N=236314)		2017 (N=245780)		2018 (N=258608)		2019 (=261499)	
Admission source, **N (%)**										
Home	194616	(87.6)	202500	(85.7)	210221	(85.5)	221543	(85.7)	223879	(85.6)
Acute care [a]	22651	(10.2)	28743	(12.2)	30312	(12.3)	31483	(12.2)	32093	(12.3)
Long term care [b]	4965	(2.2)	5071	(2.2)	5247	(2.1)	5582	(2.2)	5527	(2.1)
Length of stay (days), **N (%)**										
<7	53135	(23.9)	58561	(24.8)	61192	(24.9)	68677	(24.6)	69367	(24.9)
7-14	65184	(29.3)	70842	(30.0)	75365	(30.7)	89195	(32.0)	89297	(32.0)
15-30	62373	(28.1)	65549	(27.7)	67988	(27.7)	78123	(28.0)	77442	(27.8)
>30	41540	(18.7)	41362	(17.5)	41235	(16.8)	43187	(15.4)	42771	(15.3)
Length of stay, **Median {P10-P90}**	13	{3-43}	13	{3-41}	13	{3-41}	13	{3-40}	12	{3-39}
Septic shock [c], **N (%)**										
Yes	50145	(22.6)	49948	(21.1)	51964	(21.1)	53635	(20.7)	54145	(20.7)
No	172087	(77.4)	186366	(78.9)	193816	(78.9)	204973	(79.3)	207354	(79.3)
ICU admission [d], **N (%)**										
Yes	130587	(58.8)	134181	(56.8)	137025	(55.8)	142001	(54.9)	141685	(54.2)
No	91645	(41.2)	102133	(43.2)	108755	(44.3)	116607	(45.1)	119814	(45.8)
Hospital discharge, **N (%)**										
Home	106133	(47.8)	113812	(48.2)	119069	(48.5)	127894	(49.5)	130250	(49.8)
Acute care [a]	25992	(11.7)	29436	(12.5)	30904	(12.6)	31329	(12.1)	30784	(11.8)
Long term care [b]	33035	(14.9)	34958	(14.8)	36198	(14.7)	38010	(14.7)	38891	(14.9)
Death	57072	(25.7)	58108	(24.6)	59609	(24.3)	61375	(23.7)	61574	(23.6)

509 [a] *Acute care unit in medicine, surgery or obstetrics or psychiatry unit*

510 [b] *Follow-up and rehabilitation care unit, long-term care unit or home care*

511 [c] *ICD-10 code R57.2, R57.8 as primary diagnosis, related diagnosis or significant associated diagnosis*

512 [d] *Including implicit sepsis for which ICU admission is part of the selection criteria*

513

514 **Figure caption**

515 Figure 1 - Sepsis incidence per 100 000 inhabitants and number of cases between 2015 and
516 2019 in metropolitan France

517 Figure 2 - Number of patients with sepsis in 2019 and associated number of in-hospital deaths
518 by infection (N (%))

519

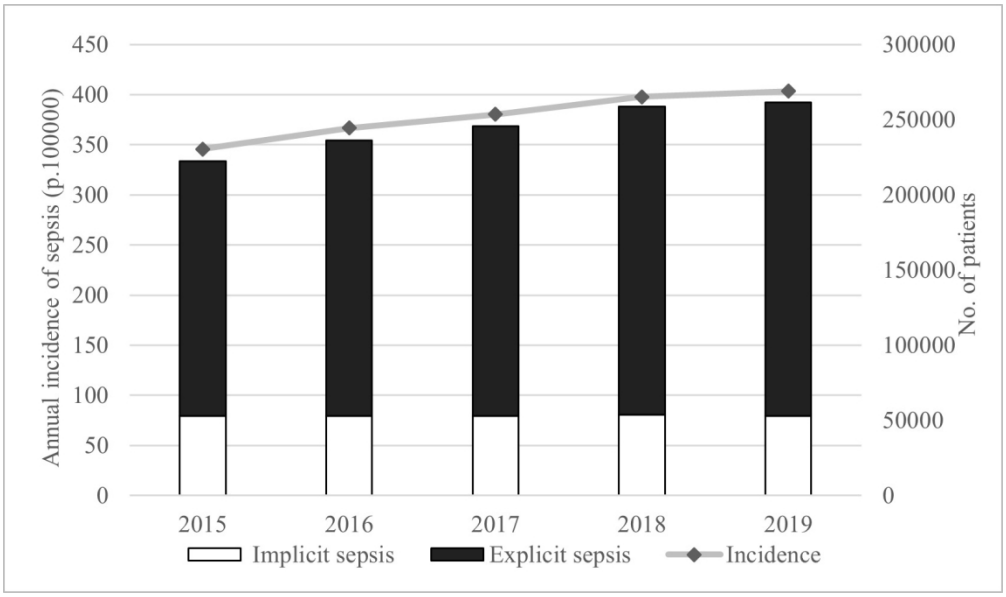


Figure 1 - Sepsis incidence per 100 000 inhabitants and number of cases between 2015 and 2019 in metropolitan France

129x76mm (330 x 330 DPI)

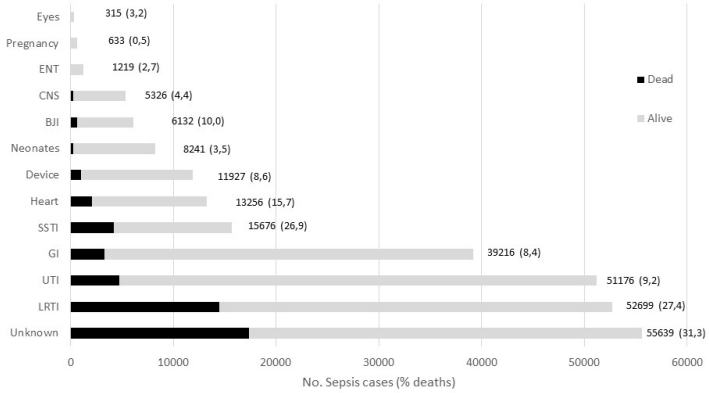


Figure 2 - Number of patients with sepsis in 2019 and associated number of in-hospital deaths by infection (N (%))

338x190mm (96 x 96 DPI)

Supplementary Appendix A

Pandolfi F, Guillemot D, Watier L, Brun-Buisson C, Trends in bacterial sepsis incidence and mortality in France between 2015 and 2019 based on National Health Data System (SNDS): retrospective observational study

eMethods

eTable1

eTable2

eTable3

eTable4

eTable5

eTable6

eMethods

Description of the French National Hospital Discharge Database (PMSI)

The study, analysis and data extraction were approved by the French Data Protection Agency (CNIL, approval DE-2016–176). Informed consent is waived for the use of these anonymised secondary data, as mentioned in the Social Security Code, Article L161–28-1. All methods were performed in accordance CNIL regulations and with REporting of studies Conducted using Observational Routinely collected Data (RECORD) guideline. The SNDS (Système national des données de santé) essentially contains individual data used for billing and reimbursement of outpatients health care consumption (Données de Consommation Inter-Régimes: DCIR) and private and public hospital data (Programme de médicalisation des systèmes d'information: PMSI) by the Agence technique de l'information sur l'hospitalisation (ATIH)[1].

For acute-care facilities, PMSI data includes all discharge summaries of hospitalization and covers all hospital stays in publicly funded and private institutions including acute-care facilities (medicine, surgery or obstetrics units: MSO)[1]. For each stay, the diagnoses are coded with ICD-10-codes as primary diagnosis (PD: condition requiring hospitalization), related diagnosis (RD: adds information to PD) and significant associated diagnosis (SAD: complications and co-morbidities potentially affecting the course or cost of hospitalization). While PD and RD are unique for each stay, several SAD can be attributed per stay. Additional information is available about the patients, such as sex or age and about the hospital stays as entry and exit date, admission source, hospital discharge or medical procedures.

Regarding mortality, in-hospital mortality was calculated based on the data of PMSI and 30 and 90-days mortality was calculated based on death records of the beneficiaries in the DCIR.

Recommendations about coding practices are regularly published by the ATIH. Recommendations on coding practices for sepsis were published in 2014 especially concerning the use of R65.1 and R57.2 ICD-10 codes combined with infection codes in order to better identify organ dysfunction and septic shock[2]. Further recommendations about coding practices for sepsis were updated in 2021[3].

Assessment of the proportion of sepsis cases of presumed fungal and viral etiology

Since the database analyzed in this study included only infections of presumed bacterial etiology, the EGB (Generalist sample of beneficiaries), a sample representative of the beneficiaries of the health insurance for which INSERM has a permanent access, was used to estimate the proportion of sepsis of viral or fungal etiologies among all sepsis cases. The breakdown per sex and age class is similar to that of the overall population. The data were available from 2015 to 2018 and were used to estimate the overall number of sepsis cases and the percentage of sepsis cases of presumed fungal and viral etiology. The percentage of sepsis cases of presumed fungal and viral etiology (without associated sepsis of presumed bacterial etiology) was assessed for each year and for all the study period. Sepsis of presumed fungal or viral etiology were identified by explicit sepsis codes and implicit sepsis codes (eTable 1).

Methodology to define the site of infection

First, the site of infection was identified based on the list of specific ICD-10 codes used by Opatowski et al. in Supplementary Table S1[4]. The sites of infection included: Bones and joints, Ears, nose and throat, Eyes, Gastrointestinal and abdomen, Heart and mediastinum, Lower respiratory tract, Medical devices, Nervous system, Newborn, Pregnancy, Skin and soft tissues, Urinary and genital tracts, Multiple sites and Unknown site. (mainly represented by primary bacteremia).

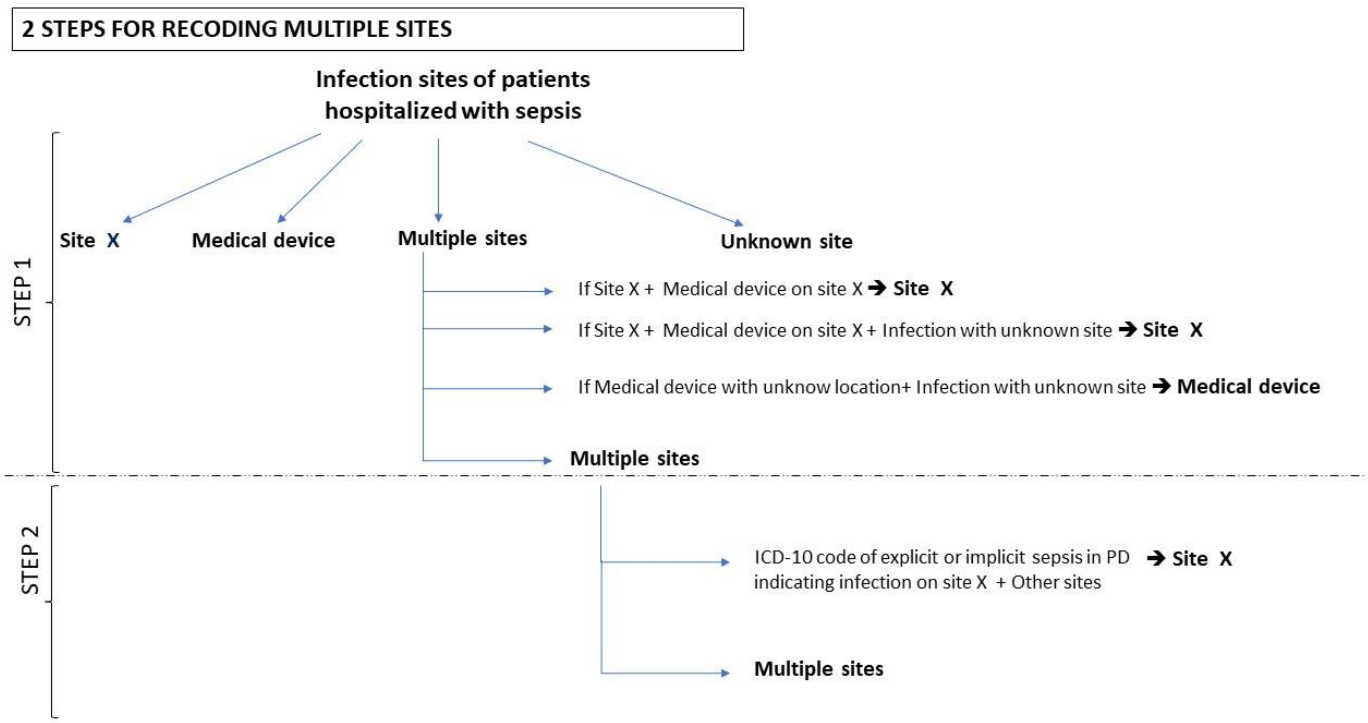
As, the ICD-10 codes for infection could be coded as PD, RD or SAD and multiple site locations were found for part of the patients, a “Two steps” recoding method was used to identify the main site of infection:

FIRST STEP

- When the medical device could be identified as located in the urinary tract, heart or bones and joints, the site of the medical device was prioritized over the medical device. Therefore, « medical devices » sites only include medical devices of unknown location.
- When an infection site (associated or not to an infection on medical device on the same site) and an infection of unknown location were identified, the infection site was prioritized over the unknown location and considered as the single site of infection. When medical devices of unknown location and an infection of unknown location were identified, the medical device was considered as the single site of infection. As a result, “unknown” site only included primary bacteremia or few unidentified sites of infection not located on a medical device.

SECOND STEP

- For the remaining stays with multiple infection sites after the first step, the PD was used to identify a single site. In cases where an ICD-10 code of explicit sepsis was found in PD (except if the PD was an infection with unknown location), this ICD-10 code was used to identify a single site of infection.
- After these different steps process, if a single site of infection could not be identified, the patient was classified as having multiple infection sites.



Definition of the variables

Variables	Sub-categories
Gender	*Male, Female*
Age	*<1, 1-5, 6-15, 16-25, 26-35, 36-45, 46-55, 56-65, 66-75, 75-85, >85*
Charlson Index	*0, 1-2, 3-4, ≥5 based on the classification of Quan et al. (2011)*[5]
Selection code	*Explicit sepsis case, Implicit sepsis case (see eTable 1)*
In-hospital death	*Dead, Alive*
Septic shock	*Yes: ICD-10 code R57.2, R57.8 as primary diagnosis, related diagnosis or significant associated diagnosis, No: No ICD-10 code R57.2, R57.8 as primary diagnosis, related diagnosis or significant associated diagnosis*
Intensive care unit (ICU) admission	*Yes: recorded in one of the following medical unit: Intensive care unit (ICU), Pediatric ICU, Neonatal ICU, Other ICU, Coronary care unit, Neuro-intensive care; No: not recorded in one of the above listed units*

Admission source	*Acute care: From a short hospital stay in medicine, surgery or obstetrics ward, after a transfer for or after a medical procedure or from psychiatry unit; Long term care: From follow-up and rehabilitation care unit or from long term care unit or home care; Home.*
Hospital discharge	*Acue care: To a short hospital stay in medicine, surgery or obstetrics units (included after a transfer for or after a medical procedure or from psychiatry unit); Long term care: To follow-up and rehabilitation care unit or from long term care unit or home care; Home; Death.*
Length of stay (days)	*As Date of discharge - date of admission, further stratified in 4 groups <7days, 7-14 days, 15-30 days, >30 days*
Infection site	*Lower respiratory tract, Urinary and genital tracts, Abdomen and digestive tract, Heart and mediastinum, Skin and soft tissues, Associated with medical device, Newborn infections, Bones and joints, Nervous system, Ears nose and throat, Infections during pregnancy, Eyes, Multiple site, unknown (Sepsis without primary site identified: primary bacteremia or sepsis with no infection site recorded). See methodology for site identification in eMethods.*

eTable 1. ICD-10 codes used to identify sepsis of presumed bacterial, viral and fungal etiology according to type of selection

Explicit sepsis codes[a,b,d]	**Implicit sepsis** [b,c,d]		
	Infection codes[a]	**1st associated condition**	**2nd associated condition**
Sepsis of presumed bacterial etiology			
A02.1, A40.0-A40.9, A41.0-A41.9, A48.0, A48.3, O85, O88.3, P36.00, P36.10, P36.20, P36.30, P36.40, P36.50, P36.80, P36.90, R57.2, R57.8, R65.1	A04.0-A04.9, A39.0-A39.9, G00.0-G00.9, I33.0, J06.8, J13, J14, J15.0-J15.9, J16.0-J16.8, J18.0-J18.9, J86.9, K65.0, K65.9, K81.0, K83.0, L02.2, L08.9, M00.0-M00.99, M46.20-M46.29, M60.00-M60.09, M86.00-M86.09, M86.90-M86.99, N13.6, N39.0, P00.2, T79.3, T80.2, T81.1, T81.4, T82.7, T84.5, T85.7	ICU admission	ICD-10 codes for organ dysfunction: A483, D65, D689, D695, D696, D762, E86, E872, F05.0-F05.9, F09, I460, G934, I469, I959, I959, J80, J81, J952, J969, K72.0, K72.9, N08.0, N08.6, N16.0, N17.0-N17.9, N19, R09.2, R17.0-17.9, R34, R40.0-R40.28, R39.2, R41.0, R41.8, R55, R57.1, R57.9 CCAM codes for organ support: EQLF003, EQLF002, EQMF002, DKMD001, DKMD002, FELF003, GLLP004, GLLD003, GLLD012, GLLD008, GLLD004, GLLD015, JVJB002, JVJF002, JVJF003, JVJF005, JVJF006, JVJF007
Sepsis of presumed viral or fungal etiology			
B00.7, B37.7, B44.7, B45.7, B46.4, B50.8	A86, A87.0-A87.9, A91, A92.0-A92.9, A94, A96.0-A96.9, A98.0-A98.9, A99, B009, B01.1-B01.9, B17.9, B25.0-B25.9, B27.0-B27.9, B33.4, B34.1, B38.0-B38.9, B39.0-B39.9, B40.0-B40.9, B44.0-B44.6, B44.8, B44.9, B45.0-B45.6, B45.8, B45.9, B47.8, B49, B50.0-B50.9, B58.0-B58.9, B59, B78.7, J09, J10.0-J10.8, J11.0-J11.8, J12.0-J12.9, U04.9	ICU admission	ICD-10 codes for organ dysfunction: A483, D65, D689, D695, D696, D762, E86, E872, F05.0-F05.9, F09, I460, G934, I469, I959, I959, J80, J81, J952, J969, K72.0, K72.9, N08.0, N08.6, N16.0, N17.0-N17.9, N19, R09.2, R17.0-17.9, R34, R40.0-R40.28, R39.2, R41.0, R41.8, R55, R57.1, R57.9 CCAM codes for organ support: EQLF003, EQLF002, EQMF002, DKMD001, DKMD002, FELF003, GLLP004, GLLD003, GLLD012, GLLD008, GLLD004, GLLD015, JVJF003, JVJF002, JVJF005, JVJB002, JVJF006, JVJF007

[a] *One of the ICD-10 code as primary diagnosis (PD: condition requiring hospitalization), related diagnosis (RD: adds information to PD) or significant associated diagnosis (SAD: complications and co-morbidities potentially affecting the course or cost of hospitalization)*

.[b] *Sepsis = explicit sepsis + implicit sepsis*

[c] *Implicit sepsis= ICD-10 code of infection + ICU admission (Intensive care unit (ICU), Pediatric ICU, Neonatal ICU, Other ICU, Coronary care unit, Neuro-intensive care) + organ dysfunction/support*

[d] *Stays shorter than 24h hours without death were excluded from our selection*

eTable 2. Distribution of infection sites (reported as % of sepsis cases) recorded in patients hospitalized with sepsis of presumed bacterial etiology in metropolitan France between 2015 and 2019

Sites[a]	% Year				
	2015	2016	2017	2018	2019
Unknown[b]	21.7	21.3	20.7	20.4	20.2
Multiple sites	19.9	20.2	20.6	21.2	21.3
Lower respiratory tract	21.4	20.6	20.2	19.9	19.6
Urinary and genital tracts	13.2	14.2	14.6	14.7	15.0
Gastrointestinal and abdomen	5.8	6.0	5.9	6.0	6.0
Heart and mediastinum	4.6	4.8	4.8	5.0	5.1
Skin and soft tissues	4.6	4.6	4.5	4.5	4.6
Medical devices[c]	3.7	3.1	2.8	2.6	2.3
Newborn	2.9	2.9	3.1	3.2	3.2
Bones and joints	1.6	1.7	1.9	2.0	2.0
Nervous system	0.5	0.5	0.5	0.5	0.5
Ears, nose and throat	0.2	0.2	0.3	0.2	0.2
Pregnancy	0.1	0.1	0.1	0.1	0.1
Eyes	0.0	0.0	0.0	0.0	0.0

[a] *Based on the classification of the infection site detailed in Supplementary file*

[b] *Sepsis without primary site identified (88% primary bacteremia and 12% sepsis with no infection site recorded)*

[c] *Medical devices of unknown location. When the location of the medical could be identified, the site of the medical device was prioritized*

eTable 3. Primary and secondary bacteremia (reported as % of sepsis cases) in patients hospitalized with sepsis of presumed bacterial etiology in metropolitan France between 2015 and 2019

Bacteremia[a]	% Year				
	2015	2016	2017	2018	2019
Primary bacteremia[b]	19.2	18.9	18.3	18.0	17.7
Secondary bacteremia[c]	53.2	55.3	56.8	58.1	58.8
No bacteremia	27.6	25.8	24.8	24.0	23.5

a Defined by ICD-10 codes: A40, A41, R57, R65.0, R65.1

b Bacteremia without other infection site identified

c Bacteremia with another infection site identified

eTable 4. Yearly number of hospital stays (reported as % of sepsis cases) for patients hospitalized with sepsis of presumed bacterial etiology in metropolitan France between 2015 and 2019

Number of stay	%				
	Year				
	2015	2016	2017	2018	2019
1	91.6	90.6	90.3	90.2	90.0
2	7.0	7.8	8.0	8.0	8.2
>2	1.4	1.7	1.8	1.7	1.8

eTable 5. Description of all hospital stays for sepsis of presumed bacterial etiology in metropolitan France between 2015 and 2019

Variables	N (%)									
	Year									
	2015 (N=250 642)		2016 (N=270 013)		2017 (N=281 882)		2018 (N=296 460)		2019 (N=300 925)	
Admission source										
Home	218497	(87.2)	230057	(85.2)	239568	(85.0)	252447	(85.2)	256079	(85.1)
Acute care [a]	26459	(10.6)	34048	(12.6)	36165	(12.8)	37526	(12.7)	38344	(12.7)
Long term care [b]	5686	(2.3)	5908	(2.2)	6149	(2.2)	6487	(2.2)	6502	(2.2)
Length of stay (days)										
<7	61364	(24.5)	69278	(25.7)	72622	(25.8)	77430	(26.1)	79094	(26.3)
7-14	72757	(29.0)	79888	(29.6)	85214	(30.2)	90597	(30.6)	92597	(30.8)
15-30	69629	(27.8)	73810	(27.3)	76882	(27.3)	80359	(27.1)	81094	(27.0)
>30	46892	(18.7)	47037	(17.4)	47164	(16.7)	48074	(16.2)	48140	(16.0)
Septic shock [c]										
Yes	56441	(22.5)	57152	(21.2)	59356	(21.1)	61534	(20.8)	62290	(20.7)
No	194201	(77.5)	212861	(78.9)	222526	(78.9)	234926	(79.2)	238635	(79.3)
ICU admission [d]										
Yes	146153	(58.3)	152065	(56.3)	155784	(55.3)	161631	(54.5)	161761	(53.8)
No	104489	(41.7)	117948	(43.7)	126098	(44.7)	134829	(45.5)	139164	(46.3)
Hospital discharge										
Home	118601	(47.3)	127525	(47.2)	133574	(47.4)	143340	(48.4)	146239	(48.6)
Acute care [a]	37903	(15.1)	44798	(16.6)	47526	(16.9)	48651	(16.4)	48945	(16.3)
Long term care [b]	37010	(14.8)	39542	(14.6)	41126	(14.6)	43039	(14.5)	44128	(14.7)
Death	57128	(22.8)	58148	(21.5)	59656	(21.2)	61430	(20.7)	61613	(20.5)

[a] *Acute care unit in medicine, surgery or obstetrics or psychiatry unit*

[b] *Follow-up and rehabilitation care unit, long-term care unit or home care*

[c] *ICD-10 code R57.2, R57.8 as primary diagnosis, related diagnosis or significant associated diagnosis*

[d] *Including implicit sepsis for which ICU admission is part of the selection criteria*

eTable 6. In-hospital mortality (reported as % of sepsis cases) by age class, Charlson index, according to the presence/absence of septic shock, ICU admission, type of selection and 30 and 90-day mortality for patients hospitalized with *sepsis* of presumed bacterial in metropolitan France between 2015 and 2019

Variables	%				
	Year				
	2015	2016	2017	2018	2019
In-hospital mortality	25.7	24.6	24.3	23.7	23.6
30-day mortality	24.8	24.0	23.9	23.4	23.2
90-day mortality	32.6	31.7	31.4	30.9	30.7
In-hospital mortality according to age class					
<1	5.0	5.2	5.8	6.1	5.8
1-15	5.1	4.1	4.2	4.6	3.9
16-30	6.3	6.0	6.3	6.2	5.8
31-45	11.5	11.0	11.0	10.7	11.2
46-55	19.3	18.2	17.7	17.2	17.5
56-65	23.6	23.0	22.3	21.9	21.4
66-75	26.3	25.3	24.7	24.5	24.4
76-85	32.0	30.2	29.6	28.7	28.1
>85	39.5	36.6	35.5	34.5	33.9
In-hospital mortality according to Charlson index					
0	18.1	17.0	16.8	16.4	16.0
1-2	25.8	24.6	23.9	23.2	23.1
3-4	31.5	30.0	29.7	29.0	28.8
>5	39.1	38.5	38.3	38.2	38.3
In-hospital mortality according to the presence or absence of septic shock					
Shock	52.1	48.5	51.3	50.6	49.5
No shock	18.0	17.4	17.0	16.7	16.8
In-hospital mortality according to ICU admission					
ICU	27.5	26.8	26.7	26.3	26.2
No ICU	23.0	21.7	21.2	20.7	20.4
In-hospital mortality according to type of selection					
Explicit sepsis	28.5	27.1	26.6	26	25.5
Implicit sepsis	16.6	16.1	15.9	15.3	15.9

eTable 7. Adjusted odds ratio (ORa) for in-hospital mortality, 30 and 90-day mortality for patients hospitalized with *sepsis of presumed bacterial* in metropolitan France between 2015 and 2019: multivariate logistic regression

	ORa[95% CI]		
	In-hospital mortality	**30-days mortality**	**30-days mortality**
Sexe (ref=men)	0.96 [0.95-0.97]	0.95 [0.97-0.97]	0.97 [0.97-0.96]
Age (ref=16-30)			
<1	1.45 [1.36-1.56]	1.36 [1.56-1.44]	1.56 [1.44-1.35]
1-15	0.73 [0.68-0.79]	0.68 [0.79-0.76]	0.79 [0.76-0.70]
31-45	1.59 [1.51-1.68]	1.51 [1.68-1.63]	1.68 [1.63-1.54]
46-55	2.36 [2.25-2.48]	2.25 [2.48-2.44]	2.48 [2.44-2.32]
56-65	3.01 [2.88-3.16]	2.88 [3.16-3.09]	3.16 [3.09-2.95]
66-75	3.76 [3.59-3.94]	3.59 [3.94-3.90]	3.94 [3.90-3.72]
76-85	5.51 [5.26-5.77]	5.26 [5.77-5.96]	5.77 [5.96-5.68]
>85	8.53 [8.14-8.94]	8.14 [8.94-10.27]	8.94 [10.27-9.80]
Charlson (ref=0)			
1-2	1.28 [1.26-1.29]	1.26 [1.29-1.22]	1.29 [1.22-1.20]
3-4	1.52 [1.50-1.55]	1.50 [1.55-1.38]	1.55 [1.38-1.36]
>=5	3.06 [3.02-3.11]	3.02 [3.11-2.67]	3.11 [2.67-2.64]
	0.00 [0.00-0.00]	0.00 [0.00-0.00]	0.00 [0.00-0.00]
Septic shock (ref=no)	5.09 [5.04-5.15]	5.04 [5.15-4.38]	5.15 [4.38-4.34]
Site (ref=lower respiratory tract)			
Gastrointestinal and abdomen	0.57 [0.55-0.58]	0.55 [0.58-0.57]	0.58 [0.57-0.55]
primary bacteremia	1.09 [1.07-1.10]	1.07 [1.10-1.17]	1.10 [1.17-1.16]
Bones and joints	0.42 [0.40-0.44]	0.40 [0.44-0.37]	0.44 [0.37-0.35]
Ears, nose, throat	0.31 [0.27-0.37]	0.27 [0.37-0.37]	0.37 [0.37-0.32]
Eyes	0.85 [0.56-1.30]	0.56 [1.30-0.95]	1.30 [0.95-0.63]
Heart and mediastinum	0.60 [0.58-0.61]	0.58 [0.61-0.59]	0.61 [0.59-0.58]
multiple sites	0.67 [0.66-0.67]	0.66 [0.67-0.50]	0.67 [0.50-0.49]
Medical devices	0.44 [0.42-0.45]	0.42 [0.45-0.46]	0.45 [0.46-0.44]
Nervous system	1.08 [1.00-1.16]	1.00 [1.16-1.04]	1.16 [1.04-0.97]
Newborn	0.57 [0.53-0.62]	0.53 [0.62-0.85]	0.62 [0.85-0.80]
Pregancy	0.07 [0.04-0.14]	0.04 [0.14-0.14]	0.14 [0.14-0.09]
Skin and soft tissues	0.98 [0.96-1.01]	0.96 [1.01-0.96]	1.01 [0.96-0.94]
Urinary and genital tracts	0.31 [0.30-0.32]	0.30 [0.32-0.34]	0.32 [0.34-0.34]
unknown	0.96 [0.93-0.99]	0.93 [0.99-1.13]	0.99 [1.13-1.10]
Year (ref=2015)*			
2016	0.96 [0.95-0.98]	0.95 [0.98-0.98]	0.98 [0.98-0.96]
2017	0.93 [0.92-0.95]	0.92 [0.95-0.96]	0.95 [0.96-0.95]
2018	0.92 [0.90-0.93]	0.90 [0.93-0.95]	0.93 [0.95-0.94]
2019	0.90 [0.89-0.92]	0.89 [0.92-0.94]	0.92 [0.94-0.92]
P-value for trend*	*<0.001*	*<0.001*	*<0.001*

** Cochran-Armitage test*

References

1. Tuppin P, Rudant J, Constantinou P, et al. Value of a national administrative database to guide public decisions: From the système national d'information interrégimes de l'Assurance Maladie (SNIIRAM) to the système national des données de santé (SNDS) in France. *Rev Epidemiol Sante Publique*. 2017;65 Suppl 4:S149-S167. doi:10.1016/j.respe.2017.05.004

2. ATIH. Fascicule de Codage pour Le PMSI : Maladies infectieuses (Instruction for PMSI coding practices: Infectious diseases). Published online 2014. http://www.departement-information-medicale.com/wp-content/uploads/2014/12/fascicule_codage_mal_infect_2014.pdf

3. ATIH. Fascicule de Codage pour Le PMSI : Maladies infectieuses (Instruction for PMSI coding practices: Infectious diseases). Published online 2021.https://www.atih.sante.fr/sites/default/files/public/content/1288/fascicule_atih_codage_mal_infectieuses_v2021_0.pdf

4. Opatowski M, Tuppin P, Cosker K, et al. Hospitalisations with infections related to antimicrobial-resistant bacteria from the French nationwide hospital discharge database, 2016. *Epidemiol Infect*. 2019;147:e144. doi:10.1017/S0950268819000402

5. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol*. 2011;173(6):676-682. doi:10.1093/aje/kwq433

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found		RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and time period within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Page 1
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported			Page 3-4
Objectives	3	State specific objectives, including any prespecified hypotheses			Page 4
Methods					
Study Design	4	Present key elements of study design early in the paper			Page 4-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection			Page 5

Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case		RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation is conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	Page 5 and eMethods and eTable1in the supplementary file
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.		RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Page 6, eMethods and eTable1in the supplementary file
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group			Page 4-6 eMethods and eTable1 in the supplementary file

Bias	9	Describe any efforts to address potential sources of bias			Page 5 and 10
Study size	10	Explain how the study size was arrived at			Page 4-5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why			Page 4-5
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses			Page 6-7
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.	Page 4-5, 13

				RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	Page 5 eMethods and eTable1 in the supplementary file
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	No data linkage
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram		RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Page 5-7 eMethods and eTable1 in the supplementary file
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)			Page 7-9
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time			Page 7-9

		Case-control study - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures			
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period			Page 7-9
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses			Supplementary files
Discussion					
Key results	18	Summarise key results with reference to study objectives			Page 10-12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Page 10 and 12-13

Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			Page 10-13
Generalisability	21	Discuss the generalisability (external validity) of the study results			Page 12-13
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based			Page 15
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Supplementary file

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.