BMJ Open

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

Fanny Pandolfi ,[1,2] Didier Guillemot,[1,2,3] Laurence Watier,[1,2] Christian Brun-Buisson[1,2]

To cite: Pandolfi F, Guillemot D, Watier L, *et al*. Trends in bacterial sepsis incidence and mortality in France between 2015 and 2019 based on National Health Data System (Système National des données de Santé (SNDS)): a retrospective observational study. *BMJ Open* 2022;**12**:e058205. doi:10.1136/bmjopen-2021-058205

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-058205).

LW and CB-B contributed equally.

Received 13 October 2021
Accepted 03 May 2022

For numbered affiliations see end of article.

Correspondence to
Dr Fanny Pandolfi;
fanny.pandolfi@pasteur.fr

ABSTRACT

Objective This study aims to provide a case definition of sepsis of presumed bacterial aetiology based on 10th revision of the International Classification of Diseases (ICD-10) codes, to assess 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 between 2015 and 2019.

Participants Between 2015 and 2019, 1 224 433 patients with sepsis of presumed bacterial aetiology were selected from the French National Hospital Discharge Database (Programme de Médicalisation des Systèmes d'Information) and were identified from corresponding ICD-10 codes for explicit sepsis or implicit sepsis.

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

Results The sex-standardised and age-standardised incidence per 100 000 (95% CI) increased from 357 (356.0 to 359.0) in 2015 to 403 (401.9 to 405.0) in 2019 and remained higher for males compared with females. Children under 1 year and patients over 75 years consistently had 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 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 infections during the COVID-19 pandemic.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study uses nationwide data, including hospitalised patients with presumed bacterial infection, from the anonymised French National Hospital Discharge Database (Programme de Médicalisation des Systèmes d'Information).
⇒ 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 10th revision of the International Classification of Diseases (ICD-10) codes of explicit sepsis and a more stringent selection criteria for implicit sepsis compared with previous studies.
⇒ This methodology may require further validation by comparing the results with clinical data.

INTRODUCTION

Sepsis is a complex disorder associated with long-term morbidity and major economic impact, 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 Systemic Inflammatory Response Syndrome (SIRS) criteria and the previous Sepsis-2 definition.[6–10] However, the successive changes in sepsis definition made it difficult to identify the true incidence of

sepsis and to assess the variation in incidence over time and across countries.[1 2]

In 2017, concerned by the amount of sepsis-related deaths and recognising the potential to mitigate the burden and impact of sepsis, the 70th 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 the WHO guidelines.[11] In France, a report commissioned by the French General Director of Health, in response to the WHO resolution, identifies new measures and proposes a clear framework for future actions, including the analysis and 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 databases 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 International Classification of Diseases (ICD) codes used to identify sepsis in medico-administrative databases may change or be partially replicated in different studies, leading to varying estimates.[14–16] Moreover, disparities were identified in sepsis incidence based on medico-administrative data compared with clinical data.[17 18] As no consensus exists regarding sepsis identification based on ICD codes and acknowledging that sepsis has no pathological 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 this period.[19 20] The aims of this study are to provide a case definition of sepsis based on ICD-10 codes, to assess 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 anonymised French National Hospital Discharge Database (Programme de Médicalisation des Systèmes d'Information, PMSI) issued from the French healthcare database (Système National des Données de Santé) and outpatient healthcare consumption (Données de Consommation Inter-Régimes)[21] (see online supplemental appendix A: eMethods). Therefore, only the incidence of sepsis of presumed bacterial aetiology (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 aetiologies among all sepsis cases (see online supplemental appendix A: eMethods and eTable 1). Demographic data were obtained from the French Census of the National Institute of Statistics and Economic Studies.[22]

Study population and selection of hospital stays with sepsis

The study population included all patients hospitalised with sepsis between 1 January 2015 and 31 December 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.

Similar 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 aetiology was defined as a stay with one of the selected ICD-10 codes for sepsis as primary diagnosis (PD: condition requiring hospitalisation), related diagnosis (RD: adds information to PD) or significant associated diagnosis (SAD: complications and comorbidities potentially affecting the course or cost of hospitalisation). Implicit sepsis of presumed bacterial aetiology 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: intensive care unit (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 supplemental eTable 1, Sepsis of presumed bacterial aetiology).

Incidence

The annual overall incidence (crude and sex-adjusted and age-adjusted based on 2019 population distribution) and age-specific and gender-specific incidence and 95% CI 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 were identified using the ICD-10 code list defined by Opatowski *et al*,[25] who conducted a study on the same data set: 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 the definitions of the variables and infection site classification are described in online supplemental appendix A: eMethods. 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 presence of septic shock; 30-day and 90-day mortality were also assessed. To describe the characteristics of patients and hospital stays, no CIs were used as the data cover the national population.[26 27]

Statistical analysis

A Cochran-Armitage test for trend was used to assess change in incidence and mortality. Three additional logistic regressions were used to assess the OR 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.

Patient and public involvement

No patients were involved.

RESULTS

Number of cases and characteristics of patients with sepsis

For metropolitan France, there were 222 232 cases of sepsis of presumed bacterial aetiology 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).

Patients' characteristics were stable between 2015 and 2019 (table 1). Males accounted each year for a 15% higher proportion of sepsis than females. In 2019, people aged over 55 years represented 78.6% of 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 aetiology (without concomitant sepsis of presumed bacterial aetiology) among all cases of sepsis was 1.7% (range 1.55%–1.92%).

Incidence

The global sex-standardised and age-standardised incidence per 100 000 of sepsis increased from 2015 (357, 95% CI 356.0 to 359.0) to 2019 (403, 95% CI 401.9 to 405.0). A significant increasing trend was observed using Cochran-Armitage test (p<0.001) (table 2, figure 1). The annual incidence remained higher for males (480, 95% CI 477.5 to 482.3, in 2019) compared with females (332, 95% CI 329.9 to 333.8, in 2019) and was markedly higher for people <1 year 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 supplemental eTable 2). Most patients with no site identified *had* primary bacteraemia (88%). Overall, the most common sites of infection in patients with 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 supplemental eTable 2). Urinary and genital tract infection predominated in females (19.0% in 2019), whereas lower respiratory tract infection predominated in males (21.3% in 2019).

About three-fourths of sepsis were associated with bacteraemia. Overall, about 20% of patients had primary bacteraemia (17.7% in 2019), whereas more than 50% had secondary bacteraemia (58.8% in 2019) (see online supplemental eTable 3).

Hospital stays of patients with sepsis

A minority of patients had more than one hospital stay per year related to sepsis (10% in 2019) (see online supplemental 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 online supplemental eTable 5 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 hospital stay, whereas nearly 15% were discharged to long-term care.

In-hospital, 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 the 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 supplemental eTable 6). Adjusting for sex, age, comorbidities, septic shock and infection sites, the OR for the variable 'year' progressively declined between 2016 and 2019, confirming the decreasing trend for mortality. In 2019, the OR for 2019 compared with 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 supplemental eTable 7). In-hospital mortality was 10% higher for explicit sepsis

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

Characteristics	n (%)				
	Years				
	2015 (n=222 232)	2016 (n=236 314)	2017 (n=245 780)	2018 (n=258 608)	2019 (n=261 499)
Gender					
Male	128 090 (57.6)	135 613 (57.4)	141 113 (57.4)	148 650 (57.5)	150 507 (57.6)
Female	94 142 (42.4)	100 701 (42.6)	104 667 (42.6)	109 958 (42.5)	110 992 (42.4)
Age					
<1	12 193 (5.5)	11 321 (4.8)	11 193 (4.6)	11 052 (4.3)	10 547 (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	11 993 (5.4)	12 599 (5.3)	12 691 (5.2)	13 370 (5.2)	13 078 (5.0)
46–55	18 601 (8.4)	19 046 (8.1)	19 595 (8.0)	20 392 (7.9)	20 299 (7.8)
56–65	36 585 (16.5)	38 174 (16.2)	38 539 (15.7)	40 736 (15.8)	40 349 (15.4)
66–75	45 078 (20.3)	50 052 (21.2)	54 125 (22.0)	58 989 (22.8)	61 672 (23.6)
76–85	54 256 (24.4)	56 725 (24.0)	58 052 (23.6)	59 528 (23.0)	59 679 (22.8)
>85	32 897 (14.8)	36 759 (15.6	40 275 (16.4)	42 419 (16.4)	43 837 (16.8)
Charlson index,[24] median (IQR)	2 (0–3)	2 (0–3)	2 (0–3)	2 (0–3)	2 (0–3)
0	82 175 (37.0)	87 080 (36.8)	89 599 (36.5)	94 792 (36.7)	95 465 (36.5)
1–2	76 140 (34.3)	81 113 (34.3)	84 603 (34.4)	89 191 (34.5)	90 600 (34.6)
3–4	31 656 (14.2)	33 947 (14.4)	35 485 (14.4)	36 824 (14.2)	37 358 (14.3)
>5	32 261 (14.5)	34 174 (14.5)	36 093 (14.7)	37 801 (14.6)	38 076 (14.6)
Comorbidities					
Cancer	51 042 (23.0)	54 810 (23.2)	56 581 (23.0)	59 648 (23.1)	60 064 (23.0)
Congestive heart failure	46 324 (20.8)	49 394 (20.9)	51 912 (21.1)	54 511 (21.1)	54 553 (20.9)
Renal disease	27 960 (12.6)	30 091 (12.7)	32 119 (13.1)	33 252 (12.9)	34 554 (13.2)
Chronic pulmonary disease	24 941 (11.2)	26 110 (11.1)	27 097 (11.0)	28 513 (11.0)	29 249 (11.2)
Metastatic carcinoma	20 619 (9.3)	22 408 (9.5)	23 516 (9.6)	24 915 (9.6)	25 331 (9.7)
Diabetes with chronic complications	13 104 (5.9)	13 690 (5.8)	14 212 (5.8)	14 558 (5.6)	14 598 (5.6)
Paraplegia or hemiplegia	11 535 (5.2)	12 463 (5.3)	13 238 (5.4)	14 416 (5.6)	14 496 (5.5)
Dementia	12 265 (5.5)	13 035 (5.5)	13 825 (5.6)	14 247 (5.5)	14 123 (5.4)
Mild liver disease	11 560 (5.2)	12 002 (5.1)	12 837 (5.2)	13 134 (5.1)	13 440 (5.1)
Moderate or severe liver disease	5844 (2.6)	5922 (2.5)	6266 (2.6)	6318 (2.4)	6335 (2.4)
Rheumatological 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)

(25.5% in 2019) compared with implicit sepsis (15.9% in 2019). In-hospital mortality increased with age classes. In 2019, the mortality rate was under 10% in patients aged up to 30 but reached 33.9% in 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 the 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

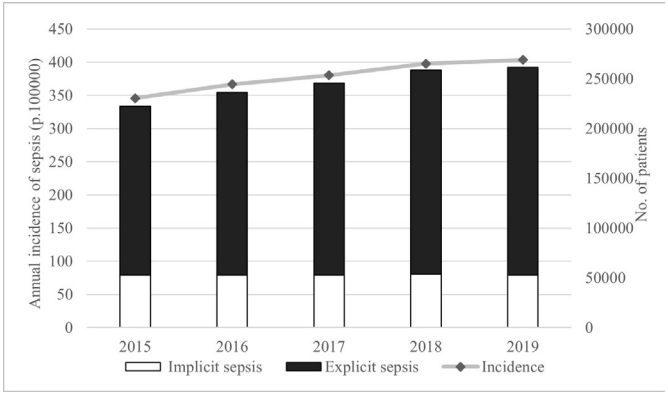

Figure 1 Sepsis incidence per 100 000 inhabitants and number of cases between 2015 and 2019 in metropolitan France.

as previously suggested.[1 23] However, the list of ICD-10 codes used varied across different studies and is prone to overestimating or underestimating sepsis incidence.[1 2 14 28] While attempting to not underestimate or overestimate implicit sepsis, organ dysfunction was identified through both ICD-10 and organ support (CCAM) but also based on the need for 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 Fleischmann-Struzek *et al*.[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 aetiology only) limit comparability with a 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 with the study of Rudd *et al*,[1] which used the Global Burden of Disease database. However, the authors acknowledged a difference between their results and previous published work, possibly due to unrecorded explicit sepsis or organ dysfunction. We also found a substantially higher incidence of sepsis compared with the study conducted in France between 2010 and 2015, but our selection criteria probably also captured less severe cases.[13] A recent study in the USA also found a higher incidence compared with previous studies.[30] Similar to other studies, we observed a slight increase in 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 have impacted overall patient survival and are likely to increase sepsis incidence,[2 30] but this may also be explained by the development of campaigns that increase awareness, screening and diagnosis of sepsis[2 17 30] or due to the recommendations issued in 2014 by the French Technical Agency for Hospital Information.

Characteristics of patients and hospital stays

Similar to other studies, a higher incidence was observed for males compared with females, 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 populations found higher or similar incidence in females compared with males, but sepsis-related mortality was higher in males.[1 23] As shown in previous studies, lower respiratory tract and urinary and genital tracts were the most common sites of infection, with urinary and genital tracts more common among females and respiratory tract among males.[23 30 34] Fewer episodes of sepsis of respiratory origin might partially explain the lower incidence of sepsis in females compared with males.[23] Additionally, several studies showed than males have more chronic comorbidities than females, 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 2, similar to other studies.[13 33] However, our study showed that more than one-third of patients had no comorbidities recorded. Patients with sepsis without comorbidities were also identified in other studies.[23 37 38] This suggests the influence of other risk factors such as as excess alcohol use, trauma, other issues in neonates or immunosuppression.[33 39 40]

Only half of all patients returned home, which emphasises the high mortality rate and the mid-term 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 with another recent study which also captured mild cases of sepsis.[30] However, the proportion of patients with 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 be considered as the most severe sepsis cases, could suggest a real decline in mortality rate. However, changes in coding practices might have increased 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 with 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

Table 2 Overall sepsis incidence by gender and age, France 2015–2019*

	n (CI)				
	Years				
Age	2015 (n=222 232)	2016 (n=236 314)	2017 (n=245 780)	2018 (n=258 608)	2019 (n=261 499)
Male					
<1	1862 (1818.2 to 1905.0)	1771 (1728.5 to 1814.0)	1809 (1765.0 to 1852.3)	1808 (1763.6 to 1851.5)	1755 (1711.2 to 1798.6)
1–15	37 (35.7 to 38.8)	42 (40.1 to 43.4)	39 (37.4 to 40.6)	43 (41.4 to 44.7)	44 (42.8 to 46.1)
16–30	53 (51.1 to 54.8)	55 (53.2 to 57.0)	56 (53.8 to 57.7)	59 (56.9 to 60.9)	58 (55.9 to 59.9)
31–45	104 (101.4 to 106.5)	108 (105.4 to 110.6)	111 (107.9 to 113.2)	116 (113.0 to 118.4)	114 (111.7 to 117.2)
46–55	266 (261.6 to 271.4)	273 (267.7 to 277.7)	279 (273.7 to 283.7)	288 (282.6 to 292.7)	283 (277.6 to 287.6)
56–65	618 (610.4 to 626.0)	643 (635.2 to 651.1)	646 (638.2 to 654.2)	673 (664.9 to 681.2)	670 (661.8 to 678.0)
66–75	1095 (1082.1 to 1107.1)	1159 (1146.8 to 1171.9)	1196 (1183.3 to 1208.3)	1250 (1237.5 to 1262.5)	1260 (1248.0 to 1272.7)
76–85	1942 (1920.6 to 1963.6)	2022 (1999.9 to 2043.7)	2070 (2047.5 to 2091.7)	2159 (2136.7 to 2182.1)	2170 (2147.1 to 2192.5)
>85	2855 (2809.2 to 2901.5)	3060 (3013.3 to 3106.9)	3283 (3235.4 to 3330.5)	3393 (3344.8 to 3440.3)	3435 (3387.6 to 3482.3)
All male	411 (409.1 to 413.6)	434 (432.2 to 436.8)	451 (448.7 to 453.4)	472 (469.5 to 474.3)	480 (477.5 to 482.3)
Female					
<1	1481 (1441.4 to 1520.9)	1385 (1346.6 to 1424.2)	1375 (1335.8 to 1413.8)	1381 (1341.6 to 1420.3)	1347 (1307.4 to 1386.0)
1–15	33 (31.4 to 34.4)	36 (34.6 to 37.7)	34 (32.4 to 35.4)	36 (34.6 to 37.8)	38 (36.4 to 39.6)
16–30	61 (58.8 to 62.9)	69 (66.9 to 71.2)	68 (66.1 to 70.5)	72 (69.6 to 74.0)	71 (68.8 to 73.2)
31–45	89 (87.1 to 91.8)	96 (93.9 to 98.7)	97 (94.1 to 99.0)	103 (100.2 to 105.3)	102 (99.2 to 104.3)
46–55	166 (162.4 to 170.0)	170 (166.0 to 173.7)	175 (171.5 to 179.3)	182 (177.8 to 185.7)	184 (179.9 to 187.8)
56–65	302 (296.7 to 307.2)	318 (312.5 to 323.3)	323 (317.9 to 328.8)	349 (343.6 to 354.9)	343 (337.3 to 348.5)
66–75	520 (511.6 to 527.8)	553 (544.9 to 561.1)	578 (569.4 to 585.7)	603 (594.6 to 610.9)	610 (602.2 to 618.3)
76–85	1018 (1005.0 to 1030.8)	1074 (1061.0 to 1087.7)	1107 (1093.2 to 1120.4)	1149 (1135.0 to 1163.0)	1151 (1137.0 to 1165.2)
>85	1590 (1567.2 to 1612.5)	1731 (1707.5 to 1754.0)	1825 (1801.0 to 1848.2)	1915 (1891.2 to 1939.5)	1919 (1895.5 to 1943.3)
All female	303 (300.9 to 304.7)	303 (300.9 to 304.7)	314 (311.9 to 315.7)	328 (326.1 to 330.0)	332 (329.9 to 333.8)
Total population					
Crude	346 (344.2 to 347.0)	367 (365.1 to 368.0)	380 (378.7 to 381.7)	398 (396.2 to 399.3)	403 (401.9 to 405.0)
Explicit only	263 (262.2 to 264.7)	284 (283.1 to 285.7)	298 (296.7 to 299.4)	315 (313.5 to 316.2)	322 (320.3 to 323.1)
Implicit only	82 (81.4 to 82.8)	82 (81.5 to 82.9)	82 (81.5 to 82.9)	83 (82.2 to 83.6)	82 (81.1 to 82.5)
Sex-standardised and age-standardised†	357 (356.0 to 359.0)	376 (374.2 to 377.2)	386 (384.6 to 387.7)	403 (401.6 to 404.7)	403 (401.9 to 405.0)

*Data are shown as number per 100 000 population, with 95% CI.
†Based on population distribution by sex and age in 2019.

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

Variables	2015 (n=222 232)	2016 (n=236 314)	2017 (n=245 780)	2018 (n=258 608)	2019 (n=261 499)
Admission source, n (%)					
Home	194 616 (87.6)	202 500 (85.7)	210 221 (85.5)	221 543 (85.7)	223 879 (85.6)
Acute care*	22 651 (10.2)	28 743 (12.2)	30 312 (12.3)	31 483 (12.2)	32 093 (12.3)
Long-term care†	4965 (2.2)	5071 (2.2)	5247 (2.1)	5582 (2.2)	5527 (2.1)
Length of stay (days), n (%)					
<7	53 135 (23.9)	58 561 (24.8)	61 192 (24.9)	68 677 (24.6)	69 367 (24.9)
7–14	65 184 (29.3)	70 842 (30.0)	75 365 (30.7)	89 195 (32.0)	89 297 (32.0)
15–30	62 373 (28.1)	65 549 (27.7)	67 988 (27.7)	78 123 (28.0)	77 442 (27.8)
>30	41 540 (18.7)	41 362 (17.5)	41 235 (16.8)	43 187 (15.4)	42 771 (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‡, n (%)					
Yes	50 145 (22.6)	49 948 (21.1)	51 964 (21.1)	53 635 (20.7)	54 145 (20.7)
No	172 087 (77.4)	186 366 (78.9)	193 816 (78.9)	204 973 (79.3)	207 354 (79.3)
ICU admission§, n (%)					
Yes	130 587 (58.8)	134 181 (56.8)	137 025 (55.8)	142 001 (54.9)	141 685 (54.2)
No	91 645 (41.2)	102 133 (43.2)	108 755 (44.3)	116 607 (45.1)	119 814 (45.8)
Hospital discharge, n (%)					
Home	106 133 (47.8)	113 812 (48.2)	119 069 (48.5)	127 894 (49.5)	130 250 (49.8)
Acute care*	25 992 (11.7)	29 436 (12.5)	30 904 (12.6)	31 329 (12.1)	30 784 (11.8)
Long-term care†	33 035 (14.9)	34 958 (14.8)	36 198 (14.7)	38 010 (14.7)	38 891 (14.9)
Death	57 072 (25.7)	58 108 (24.6)	59 609 (24.3)	61 375 (23.7)	61 574 (23.6)

*Acute care unit in medicine, surgery or obstetrics or psychiatry unit.
†Follow-up and rehabilitation care unit, long-term care unit or home care.
‡10th revision of the International Classification of Diseases (ICD-10) codes R57.2 and R57.8 as the primary diagnosis, related diagnosis or significant associated diagnosis.
§Including implicit sepsis for which ICU admission is part of the selection criteria.
ICU, intensive care unit.

deaths also occurred outside of the hospital.[44] Indeed, 90-day mortality reached about 30%.

Limitations of the study

The methodology used is similar to previous studies identifying sepsis in medico-administrative databases 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 comparability with other studies.[14–16 30] Therefore, this methodology of selection should be reproduced in other time periods in France, and eventually other countries, in order to compare the 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 the high specificity but low sensitivity of explicit sepsis and the lower specificity but higher sensitivity of implicit sepsis when compared with clinical data.[17 29] Validating medico-administrative data to avoid misclassification bias is an important step and our study would require 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 is 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 with multiple stays over the year could be further characterised.

Finally, due to administrative and regulation hurdles and the time required to obtain access to all hospitalisation

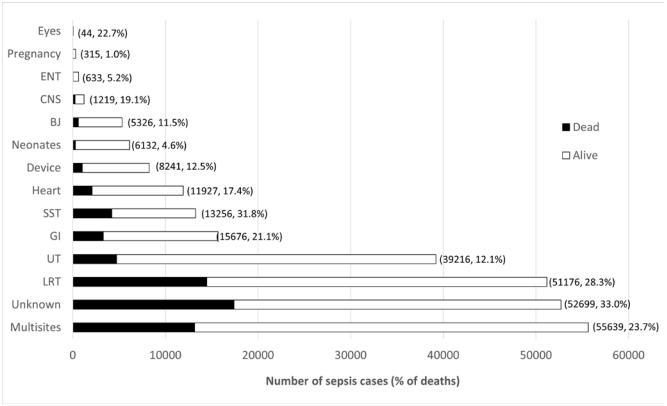

Figure 2 Number of patients with sepsis in 2019 and the associated percentage of in-hospital deaths by infection, n (%). Eyes, Eyes infections; Pregancy, Pregancy-associated infections; ENT, Ear, nose and throat infections; CNS, Central nervous system infections; BJ, Bones and joints infections; Neonates, Neonatal infections; Device, Device-associated infections; Heart, Heart and mediastinum infection; SST, Skin and soft tissues infections; GI, Gastro-intestinal and abdominal infections; UT, Urinary and genitals tracts infections; LRT, Lower respiratory tract infections; Unknow, Infections of unknow location; Multisites, Multiple sites of infection

of the PMSI, the cohort available narrowed our study to the assessment of sepsis of presumed bacterial aetiology. However, sepsis of viral and fungal aetiology (without concomitant sepsis of presumed bacterial aetiology) 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 aetiologies 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 on coding practices.

CONCLUSION

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

Our results confirm the high burden of sepsis in France. Patient characteristics could be considered in quality improvement programmes and new individualised management strategies. Concomitant changes of 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 databases.

Author affiliations
[1]Epidemiology and Modeling of bacterial Evasion to Antibacterials Unit (EMEA), Institut Pasteur, Paris, France
[2]Centre de recherche en Epidémiologie et Santé des Populations (CESP), INSERM, Paris, France
[3]Hôpital Raymond-Poincaré, APHP, Paris, France

Correction notice The article has been corrected since it was published online. The second text under the heading 'Incidence' has been updated to 'A significant increasing trend was observed using Cochran-Armitage test (p<0.001) (table 2, figure 1)'. Also, supplemental table e7 has been revised as the authors found some errors in the data.

Acknowledgements We are grateful to DATAD department of the French National Health Insurance for providing the data.

Contributors FP, LW, CB-B and DG conceived the study. LW obtained funding for the study. FP, LW and CB-B organised the data collection and conducted the analysis. FP, LW and CB-B drafted the manuscript. FP, LW, CB-B and DG contributed to the critical revision of the manuscript. LW and CB-B act as guarantor for the final manuscript.

Funding This work was supported by Award RMA19183LLA from the French Ministry of Social Affairs and Health.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

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

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

ORCID iD
Fanny Pandolfi http://orcid.org/0000-0001-8318-3452

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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).

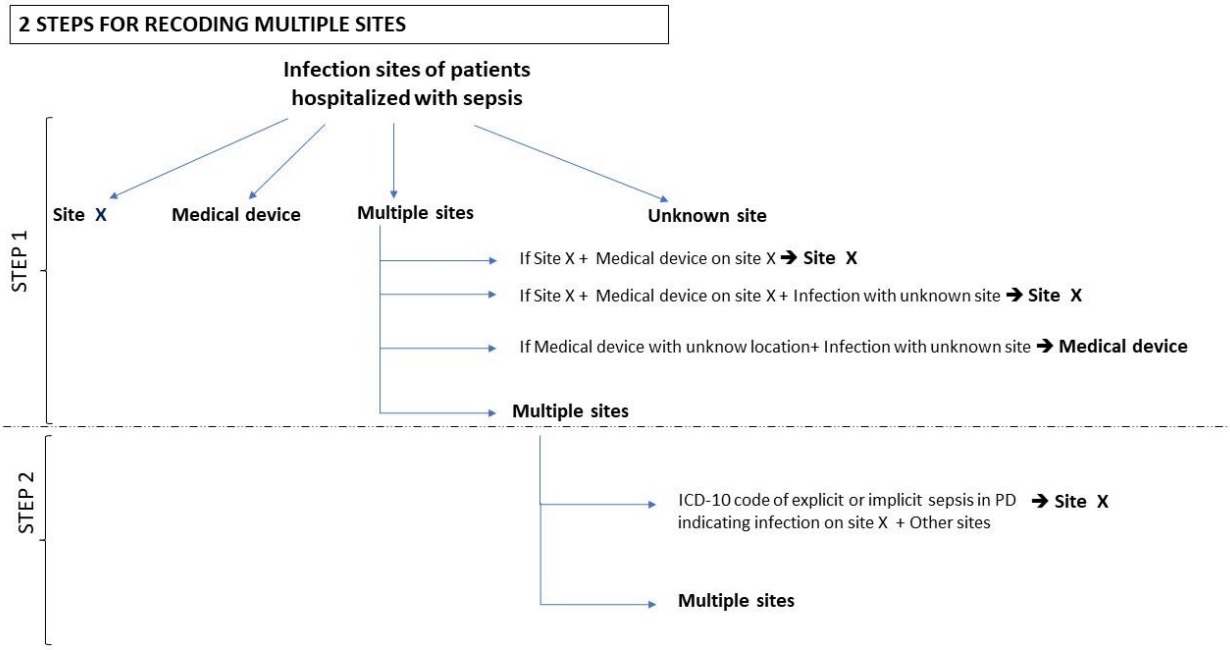
As, the ICD-10 codes for infection could be coded as PD, RD or SAD and multiple site locations were found for part of the patients, a “Two steps” recoding method was used to identify the main site of infection:

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, I950, I959, J80, J81, J952, J969, K72.0, K72.9, N08.0, N08.8, 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, I950, I959, J80, J81, J952, J969, K72.0, K72.9, N08.0, N08.8, 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 *s*epsis 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 *s*epsis 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*

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