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

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Title Page

Trends in sepsis incidence and mortality in France between 2015 and 2019 Fanny Pandolfi, PhD^{1,2}, Didier Guillemot, PhD^{1,2,3}, Christian Brun-Buisson, PhD^{1,2,*}, Laurence Watier, PhD ^{1, 2,*} ¹ Epidemiology and Modeling of bacterial Evasion to Antibacterials Unit (EMEA), Institut Pasteur - Paris (France) ² Le Centre de recherche en Epidémiologie et Santé des Populations (CESP), Institut National de la Santé et de la Recherche Médicale (INSERM), Université de Versailles Saint Quentin-en-Yvelines/ Université Paris Saclay - Paris (France) ³ AP-HP, Hôpital Raymond-Poincaré - Garches (France) *Equal contribution Corresponding author: Fanny Pandolfi email: fanny.pandolfi@pasteur.fr Manuscript words count: 2878

hospital stays.

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

Design : Nationwide, population based cohort study.

Setting : Metropolitan France and between 2015 and 2019.

25 Participants : Sepsis cases of presumed bacterial etiology were selected from the French
 26 National Hospital Discharge Database (PMSI) were identified from corresponding ICD-10
 27 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.

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

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43 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

53 Introduction

Sepsis is a complex disorder, associated with long term morbidity and major economic 54 55 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 56 International Consensus Definition of sepsis (Sepsis-3) defined sepsis as a "life-threatening" 57 organ dysfunction due to a dysregulated host response to infection." ⁵. Indeed, organ 58 59 dysfunction, was found to have better ability to predict in-hospital mortality or to target 60 patients with higher risk of adverse outcomes than the original SIRS criteria and the previous sepsis-2 definition⁶⁻¹⁰. However, the successive changes of sepsis definition made it difficult 61 62 to identify the true incidence of sepsis and to assess of the variation of incidence over time and across countries ^{1,2}. 63

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

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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.

83 Methods

84 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). Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

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

93 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

98 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).

109 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. Page 7 of 33

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113 Description of patients, hospital stays and site of infection

Sex, age, Charlson index and detailed comorbidities were described for all patients²². 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 90day mortality were also assessed.

127 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 CochranArmitage 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 inhospital, 30-day and 90-day mortalities as a binary dependent variable and adjusting for sex,
age, comorbidities, septic shock and infection sites.

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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

- 57 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 58

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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%)

The overall in-hospital death fate slightly deenlied between 2015 (25.770) and 2017 (25.070)

as well as 30-day and 90-day mortality which approximated 26% and 33% respectively in

- ⁸ 182 2015 and 23% and 31% respectively in 2019 (all P<0.001) (see online supplementary
- ¹ 183 appendix A : eTable 6). Adjusting for sex, age, comorbidities, septic shock and infection sites,

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184	the odds ratios for the variable "year" progressively declined between 2016 and 2019,
185	confirming the decreasing trend for mortality. In 2019, the odds ratio for 2019 compared to
186	2013 was 0.904 [0.891-0.917] for in-hospital mortality, 0.938 [0.924-0.952] for 30-day
187	mortality and 0.918 [0.905-0.930] for 90-day mortality. In hospital mortality was 10% higher
188	for explicit (25.5% in 2019) compared to implicit sepsis (15.9% in 2019). In-hospital
189	mortality increased with age classes. In 2019, the mortality rate was under 10% for patients
190	aged up to 30 but reached 33.9% for patients above 85 years. Mortality rate also increased
191	with Charlson index (in 2019, 16.0% for Charlson index=0 and 38.3% for Charlson index>5)
192	and was also higher for patients with septic shock (49.5% with septic shock, 16.8% without
193	septic shock in 2019) or transferred to ICU (26.2% with ICU, 20.4% without ICU). The
194	proportion of death was highest for patients with unknown source of infection (33.0% in
195	2019) and those with multiple sites of infection (23.7% in 2019) (Figure 2). Among those
196	with a unique site of infection recorded, skin and soft tissues (31.8% in 2019), lower
197	respiratory tract (28.3% in 2019), and gastrointestinal and abdominal infections (21.1% in
198	2019) were associated with the highest mortality rates.

Discussion

201 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

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

211 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 cases²¹. A recent study in US also found a higher incidence compared to previous studies²⁷. 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).

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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

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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 sepsis²⁷. However, the proportion of patients having ICU admission^{16,21} or the percentage of septic shock²⁷ 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%.

2 255 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

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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 coding¹⁶. 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

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278 Conclusion

279 Medico-administrative databases can be used to provide nationwide estimates of the incidence 280 of sepsis and also allow to study healthcare pathways but further validation with detailed 281 clinical data is required. Our data should be complemented by the re-assessment of the

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

284 Our results confirm the high burden of sepsis in France. Patient characteristics could be

285 considered in quality-improvement programs and new individualized management strategies.

286 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

282 to describe sepsis in medico-administrative database.

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293 **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
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305 Competing interest : None

306 Ethics approval : The study, analysis and data extraction were approved by the French Data
307 Protection Agency (CNIL, approval DE-2016–176). Informed consent is waived for the use of

308 these anonymised secondary data, as mentioned in the Social Security Code, Article L161–

- 309 28-1. All methods were performed in accordance CNIL regulations and with REporting of
- 310 studies Conducted using Observational Routinely-collected Data (RECORD) guideline.
- 311 **Data sharing statement :** No additional data are available
- 0 312 **Patient and Public Involvement :** No patient involved

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Tables

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

3 —		N (*	%)									
, 0	Charactoristics	Yea	ırs									
1		2015 (n=222232)		2016 (n=236314)		2017 (n=245780)		201	8	2019		
2 _								(n=258608)		(n=261499)		
3	Gender											
4	Men	128090	(57.6)	135613	(57.4)	141113	(57.4)	148650	(57.5)	150507	(57.6)	
5	Women	94142	(42.4)	100701	(42.6)	104667	(42.6)	109958	(42.5)	110992	(42.4)	
0 7	Age											
, 8	<1	12193	(5.5)	11321	(4.8)	11193	(4.6)	11052	(4.3)	10547	(4.0)	
9	1-15	4137	(1.9)	4588	(1.9)	4287	(1.7)	4681	(1.8)	4786	(1.8)	
0	16-30	6492	(2.9)	7050	(3.0)	7023	(2.9)	7441	(2.9)	7252	(2.8)	
1	31-45	11993	(5.4)	12599	(5.3)	12691	(5.2)	13370	(5.2)	13078	(5.0)	
2	46-55	18601	(8.4)	19046	(8.1)	19595	(8.0)	20392	(7.9)	20299	(7.8)	
5 4	56-65	36585	(16.5)	38174	(16.2)	38539	(15.7)	40736	(15.8)	40349	(15.4)	
5	66-75	45078	(20.3)	50052	(21.2)	54125	(22.0)	58989	(22.8)	61672	(23.6)	
5	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)	
3	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	13104	(5.9)	13690	(5.8)	14212	(5.8)	14558	(5.6)	14598	(5.6)	
	complications		× - /		< - J	-			× -)		()	
	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)	

				ding	
-	N [CI]			y for	
Age	Years				
	2015 (n=222232)	2016 (n=236314)	2017 (n=245780)	2018 (n=2586 083 ₹	2019 (n=261499)
Men				elate	
<	1862 [1818.2-1905.0]	17/1 [1728.5-1814.0]	1809 [1765.0-1852.3]		1/55 [1/11.2-1/98.6
1-15	37 [35.7-38.8]	42 [40.1-43.4]	39 [37.4-40.6]	43 [41.4-44. 6] 1	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. Single Dia	58 [55.9-59.9]
31-45	104 [101.4-106.5]	108 [105.4-110.6]	111 [107.9-113.2]		114 [111.7-117.2]
46-55	266 [261.6-271.4]	273 [267.7-277.7]	279 [273.7-283.7]		283 [277.6-287.6]
56-65	618 [610.4-626.0]	643 [635.2-651.1]	646 [638.2-654.2]	673 [664.9-68 5 5	670 [661.8-678.0]
66-75	1095 [1082.1-1107.1]	1159 [1146.8-1171.9]	1196 [1183.3-1208.3]	1250 [1237.5-1282]	1260 [1248.0-1272.7
76-85	1942 [1920.6-1963.6]	2022 [1999.9-2043.7]	2070 [2047.5-2091.7]	2159 [2136.7-2]	2170 [2147.1-2192.5
>85	2855 [2809.2-2901.5]	3060 [3013.3-3106.9]	3283 [3235.4-3330.5]	3393 [3344.8-34≱0.3	3435 [3387.6-3482.3
All Men	411 [409.1-413.6]	434 [432.2-436.8]	451 [448.7-453.4]	472 [469.5-47 4]3]	480 [477.5-482.3]
Women				ning	
<1	1481 [1441.4-1520.9]	1385 [1346.6-1424.2]	1375 [1335.8-1413.8]	1381 [1341.6-14] 0.3	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 9	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. 4] o	71 [68.8-73.2]
31-45	89 [87.1-91.8]	96 [93.9-98.7]	97 [94.1-99.0]	103 [100.2-10 듏 3] 드	102 [99.2-104.3]
46-55	166 [162.4-170.0]	170 [166.0-173.7]	175 [171.5-179.3]	182 [177.8-18 5 7] 🗟	184 [179.9-187.8]
56-65	302 [296.7-307.2]	318 [312.5-323.3]	323 [317.9-328.8]	349 [343.6-35 4 9] גע	343 [337.3-348.5]
66-75	520 [511.6-527.8]	553 [544.9-561.1]	578 [569.4-585.7]	603 [594.6-61 6 9] 8	610 [602.2-618.3]
76-85	1018 [1005.0-1030.8]	1074 [1061.0-1087.7]	1107 [1093.2-1120.4]	1149 [1135.0-11 7 3.0 5	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] 9	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] o	403 [401.9-405.0]

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

Variables	2 (N=2	015 222232)	20 (N=2))16 36314)	20 (N=24)17 45780)	20 (N=25	18 58608)	2 (=2	019 61499)
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	{3-3
Septic shock ^c , N (%)										
Yes	50145	(22.6)	49948	(21.1)	51964	(21.1)	53635	(20.7)	54145	(20.)
No	172087	(77.4)	186366	(78.9)	193816	(78.9)	204973	(79.3)	207354	(79.
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.
Hospital discharge, N (%)										
Home	106133	(47.8)	113812	(48.2)	119069	(48.5)	127894	(49.5)	130250	(49.
Acute care ^a	25992	(11.7)	29436	(12.5)	30904	(12.6)	31329	(12.1)	30784	(11.
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	(23.0

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 $^{b}\ Follow-up$ 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

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

129x76mm (300 x 300 DPI)

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

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Supplementary Appendix A

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

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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 S1². 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.

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		Implicit se	epsis ^{b,c,d} ຜຼັ ຊ
	Infection codes ^a	1 st associated condition	ວັກ ^d associated condition
Sepsis of presumed bacterial ef	tiology		s reig
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 sing an dystunction : A483, D65, D689, D695, D696, D767, 886, E872, F05.0-F05.9, F09, I460, G934, I469, I959, 3959, J80, J81, J952, J969, K72.0, K72.9, N08.0, N98, N16.0, N17.0-N17.9, N19, R09.2, R17.0-17.9, R34, 840.0-R40.28, R39.2, R41.0, R41.8, R55, R65.1, R57, a, R57.2, R57.8, R57.9 AND CCAM codes for an an support : EQLF003, EQLF002, EQMF002, DKN D061, DKMD002, FELF003, GLLP004, GLLD003, GLL D012, JVJF005, JVJB002, JVJF006,
			JVJF007
Sepsis of presumed viral ou fur B00.7, B37.7, B44.7, B45.7, B46.4, B50.8	Agal etiology 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, N08.8, N16.0, N17.0-N17.9, N19, R09.2, R17.0-17.9, R33, R30.0-R40.28, R39.2, R41.0, R41.8, R55, R65.1, R57.1, F57.2, R57.8, R57.9 AND CCAM codes for organ support : EQLF003, EQLF002, EQMF002, DKM D001, DKMD002, FELF003, GLLP004, GLLD003, GLL 018, GLLD008, GLLD004, GLLD015, JVJF003, JVJF 02, JVJF005, JVJB002, JVJF006, JVJF007

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

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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 stav	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

	N ('	%)								
	Ye	ar								
Variables	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 *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
Mortality according to a	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 ind	ex			
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	r absence of s	eptic 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 admissio	on			
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 t	type of selec	tion			
Explicit sepsis	28.5	27.1	26.6	26	25.5
Implicit sepsis	16.6	16.1	15.9	15.3	15.9

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References

- Tuppin P, Rudant J, Constantinou P, et al. Value of a national administrative database to guide public 1. 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

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

	Item No	Recommendation	Page No
Title and abstract	1	(<i>a</i>) Indicate the study's design with a commonly used term in the title or the	1
		abstract	
		(b) Provide in the abstract an informative and balanced summary of what was	
		done and what was found	
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being	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	5
U		recruitment, exposure, follow-up, and data collection	
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of	5
1		participants. Describe methods of follow-up	
		(b) For matched studies, give matching criteria and number of exposed and	
		unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and	5-6
		effect modifiers. Give diagnostic criteria, if applicable	
Data sources/	8*	For each variable of interest, give sources of data and details of methods of	4
measurement		assessment (measurement). Describe comparability of assessment methods if	
		there is more than one group	
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	6
		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	
		(<u>e</u>) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially	7
		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	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social)	7-9
		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)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	7-9

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Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and	7-9
		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	
Other analyses	17	Report other analyses done-eg analyses of subgroups and interactions, and	supplement
		sensitivity analyses	
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	11-12
		imprecision. Discuss both direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations,	9-12
		multiplicity of analyses, results from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	9-12
Other informati	on		·
Funding	22	Give the source of funding and the role of the funders for the present study and, if	14
		applicable for the original study on which the present article is based	

*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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Primary Subject Heading :	Infectious diseases
Secondary Subject Heading:	Intensive care, Infectious diseases, Epidemiology, Public health
Keywords:	INFECTIOUS DISEASES, INTENSIVE & CRITICAL CARE, PUBLIC HEALTH, Epidemiology < INFECTIOUS DISEASES





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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 Fanny Pandolfi, PhD^{1,2}, Didier Guillemot, PhD^{1,2,3}, Laurence Watier, PhD^{1,2,*}, Christian Brun-Buisson, PhD 1, 2,* ¹ Epidemiology and Modeling of bacterial Evasion to Antibacterials Unit (EMEA), Institut Pasteur - Paris (France) ² Le Centre de recherche en Epidémiologie et Santé des Populations (CESP), Institut National de la Santé et de la Recherche Médicale (INSERM), Université de Versailles Saint Quentin-en-Yvelines/ Université Paris Saclay - Paris (France) ³ AP-HP, Hôpital Raymond-Poincaré - Garches (France) *Equal contribution Corresponding author: Fanny Pandolfi email: fanny.pandolfi@pasteur.fr Manuscript words count: 3208

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19 Abstract

20 **Objective:** This study aims to provide a case definition of sepsis of presumed bacterial

21 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

23 hospital stays.

24 **Design:** Nationwide, population based retrospective observational study.

25 **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.

32 **Results:** The sex and age-standardized incidence per 100 000 [95% CI] increased from 2015

33 357 [356.0-359.0] in 2015 to 403 [401.9-405.0] in 2019 and remained higher for men

34 compared to women. Children under 1 year and patients over 75 years had consistently the

35 highest incidence. The most common comorbidities were cancer and chronic heart failure.

36 The median hospital length of stay was 12 days. Most patients came from home but only half

37 of them returned home after their hospital stay and approximately 15% were discharged to

38 long term care. In-hospital mortality was about 25% and declined along the study period.

39 **Conclusions:** Medico-administrative databases can be used to provide nationwide estimates

40 of the in-hospital burden of bacterial sepsis. The results confirm the high burden of sepsis in

41 France. These data should be complemented by estimating the additional burden associated

42 with fungal and viral infection during the COVID-19 pandemic.

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44	Strengths and limitations of this study
45	• The study uses nationwide data including hospitalized patients with presumed
46	bacterial infection, from the anonymized French National Hospital Discharge
47	Database (PMSI)
48	• Patients with sepsis and viral or fungal infection only were not included, but their
49	proportion among all sepsis cases estimated on a representative sample from the same
50	database
51	• Sepsis cases were selected using ICD-10 codes of explicit sepsis and a more stringent
52	selection criteria for implicit sepsis compared to previous studies.
53	• This methodology may require further validation by comparing our results with
54	clinical data
55	Introduction
56	Sepsis is a complex disorder, associated with long term morbidity and major economic

term morbidity and major economic clated with Ig impacts, responsible for several millions of deaths per year worldwide ^{1–4}. The challenge of 57 58 defining sepsis led to several revised definitions over the past decades. In 2016, the Third 59 International Consensus Definition of sepsis (Sepsis-3) defined sepsis as a "life-threatening 60 organ dysfunction due to a dysregulated host response to infection." ⁵. Indeed, organ 61 dysfunction, was found to have better ability to predict in-hospital mortality or to target 62 patients with higher risk of adverse outcomes than the original SIRS criteria and the previous 63 sepsis-2 definition⁶⁻¹⁰. 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 64 across countries ^{1,2}. 65

In 2017, concerned by the amount of sepsis related deaths and recognizing the potential to 66 67 mitigate the burden and impact of sepsis, the seventieth World Health Assembly adopted a Page 5 of 42

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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 only¹³.

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 2014¹⁹. 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. Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

91 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 Studies²².

Study population and selection of the hospital stays with sepsis Study population and selection of the hospital stays with sepsis

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

- ⁵⁰ 111 estimate in-hospital mortality and to estimate annual incidence.
- $^{53}_{54}$ 112 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
 Explicit sepsis of presumed bacterial etiology was defined as a stay with one of the selected
- ⁶⁰ 115 ICD-10 codes for sepsis as primary diagnosis (PD: condition requiring hospitalization),

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2 3 4	116	related diagnosis (RD: adds information to PD) or significant associated diagnosis (SAD:
5 6	117	complications and co-morbidities potentially affecting the course or cost of hospitalization).
7 8	118	Implicit sepsis of presumed bacterial etiology was defined as a stay with one of the selected
9 10 11	119	ICD-10 codes for infection (other than those defining explicit sepsis) as PD, RD or SAD with
12 13	120	two associated conditions: ICU admission and at least one of the selected ICD-10 codes for
14 15	121	organ dysfunction or one or more of the codes for organ support from the Common
16 17	122	Classification of Medical Acts (CCAM) (see online supplementary appendix A: eTable
18 19 20	123	1(Sepsis of presumed bacterial etiology)).
21 22 23	124	Incidence
24 25	125	Annual overall incidence (crude and sex and age-adjusted based on 2019 population
26 27	126	distribution) and age and gender specific incidence and 95% confidence intervals were
28 29 30	127	calculated from 2015 to 2019 and expressed as the number of cases per 100 000 inhabitants.
31 32 33	128	Description of patients, hospital stays and site of infection
34 35	129	Sex, age, Charlson index and detailed comorbidities were described for all patients ²⁴ . A total
36 37	130	of 15 sites of infection was identified using the ICD-10 codes list defined by Opatowski et
38 39 40	131	al. ²⁵ who conducted a study on the same dataset: Bones and joints, Ears, nose and throat,
40 41 42	132	Eyes, Gastrointestinal and abdomen, Heart and mediastinum, Lower respiratory tract, Medical
43 44	133	devices, Nervous system, Newborn, Pregnancy, Skin and soft tissues, Urinary and genital
45 46 47	134	tracts, Multiple sites and Unknown. Details on definitions of the variables and infection site
49 49	135	classification are described in the eMethods in the supplementary appendix A online.
50 51	136	Admission source, hospital discharge, yearly number of hospital stays as well as the
52 53	137	percentage of septic shock and admission to ICU were also described. As admission to ICU
54 55 56	138	and organ dysfunction/support were part of the selection criteria for implicit sepsis, the
54 55 56 57 58	138 139	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
54 55 56 57 58 59 50	138 139 140	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

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sepsis and according to age, ICU admission and the presence of septic shock; 30-day and 90-

142 day mortality were also assessed. To describe patients and hospital stays characteristics no

143 confidence intervals were used, as the data cover the national population 26,27 .

144 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

151 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

155 (169 419 cases) and 2019 (208 510 cases), whereas implicit sepsis remained stable

156 (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.

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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%).

166 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).

172 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).

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185 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.

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⁴ 198 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

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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.

220 Discussion

221 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

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comparability with the previous French sepsis incidence Study conducted between 2010 and
2015¹³, 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}.

239 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 cases¹³. A recent study in US also found a higher incidence compared to previous studies³⁰. 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).

46 253 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

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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 men²³. 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 sepsis³⁰. However, the proportion of patients having ICU admission^{13,17} or the percentage of septic shock³⁰ 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

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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%.

288 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 review14,17,29,45.

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 coding¹⁷. 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}. Page 15 of 42

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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

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333 assessment of changes over time. This highlights the urgent need for a long-lasting consensus

to occurrences

to describe sepsis in medico-administrative database.

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339 **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,
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351 **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–

355 28-1. All methods were performed in accordance CNIL regulations and with REporting of

356 studies Conducted using Observational Routinely-collected Data (RECORD) guideline.

357 **Data sharing statement:** No additional data are available

³⁵⁸ **Patient and Public Involvement:** No patient involved

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Tables

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

_		N (*	%)								
0	Characteristics	Yea	ırs								
1		2015		20	16	2017		201	18	20	19
2 _		(n=22)	(n=222232)		(n=236314)		(n=245780)		(n=258608)		1499)
3	Gender										
4	Men	128090	(57.6)	135613	(57.4)	141113	(57.4)	148650	(57.5)	150507	(57.6)
5	Women	94142	(42.4)	100701	(42.6)	104667	(42.6)	109958	(42.5)	110992	(42.4)
о 7	Age										
3	<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)
I	31-45	11993	(5.4)	12599	(5.3)	12691	(5.2)	13370	(5.2)	13078	(5.0)
2	46-55	18601	(8.4)	19046	(8.1)	19595	(8.0)	20392	(7.9)	20299	(7.8)
5 1	56-65	36585	(16.5)	38174	(16.2)	38539	(15.7)	40736	(15.8)	40349	(15.4)
r	66-75	45078	(20.3)	50052	(21.2)	54125	(22.0)	58989	(22.8)	61672	(23.6)
5	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)
3							· /		· /		
)	Charlson index ²⁴ Median (IOR)	2	(0-3)	2	(0-3)	2	(0-3)	2	(0-3)	2	(0-3)
		82175	(37.0)	87080	(36.8)	89599	(36.5)	94792	(367)	95465	(36.5)
	1-2	76140	(343)	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	(143)
	>5	32261	(14.5)	34174	(14.5)	36093	(14.7)	37801	(14.6)	38076	(14.6)
	Comorbidities	02201	(1.1.0)	0.17	(1.1.0)		(1)	0,001	(1)	20070	(1)
	Cancer	51042	(23.0)	54810	(23.2)	56581	(23.0)	59648	(23.1)	60064	(23.0)
	Congestive heart failure	46324	(20.8)	49394	(20.2)	51912	(23.0) (21.1)	54511	(23.1) (21.1)	54553	(20.0)
	Renal disease	27960	(20.0)	30091	(20.7)	32119	(21.1)	33252	(21.1) (12.9)	34554	(20.7)
	Chronic nulmonary disease	2/900	(12.0)	26110	(12.7)	27007	(13.1)	28512	(12.7)	202/0	(13.2)
	Metastatic carcinome	24741 20610	(11.2)	20110	(11.1)	27097	(11.0)	20313	(11.0)	29249	(11.2)
	Dispatas with abrania	12104	(5.3)	12600	(9.3)	14212	(5.0)	14550	(9.0)	23331 14509	(5.1)
	complications	13104	(3.9)	13090	(3.8)	14212	(3.8)	14338	(3.0)	14398	(3.0)
	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)

					<u>in 05</u>	
	_	N [CI]			clud 0	
Age	-	Years	2016 (22/214)	2015 (245500)		2010 (2(1400
Mon		2015 (n=222232)	2016 (n=236314)	2017 (n=245780)	$\frac{1}{2018}$ (n=258608)	2019 (n=261499
< 1		1862 [1818 2-1905 0]	1771 [1728 5-1814 0]	1809 [1765 0-1852 3]	© m≧ ®®™1763 6-1851 5]	1755 [1711 2-1798
1-15		37 [35 7-38 8]	42 [40 1-43 4]	39 [37 4-40 6]		44 [42 8-46 1]
16-30		53 [51 1-54 8]	55 [53 2-57 0]	56 [53 8-57 7]		58 [55 9-59 9]
31-45		104 [101 4-106 5]	108 [105 4-110 6]	111 [107 9-113 2]		114 [111 7-117 2
46-55		266 [261 6-271 4]	273 [267 7-277 7]	279 [273 7-283 7]	6 7 485 782 6-292 7]	283 [277 6-287 6
40 55 56-65		618 [610 4-626 0]	643 [635 2-651 1]	646 [638 2-654 2]		670 [661 8-678 (
66-75		1095 [1082 1-1107 1]	1159 [1146 8-1171 9]	1196 [1183 3-1208 3]		1260 [1248 0-1272
76-85		1942 [1920 6-1963 6]	2022 [1999 9-2043 7]	2070 [2047 5-2091 7]		2170 [2147 1-2192
>85		2855 [2809 2-2901 5]	3060 [3013 3-3106 9]	3283 [3235 4-3330 5]		3435 [3387 6-348]
All Men		411 [409 1-413 6]	434 [432 2-436 8]	451 [448 7-453 4]		480 [477 5-482 3
Women						100 [177.5 102.
<1		1481 [1441 4-1520 9]	1385 [1346 6-1424 2]	1375 [1335 8-1413 8]	B 81 9 1341 6-1420 31	1347 [1307 4-138
1-15		33 [31 4-34 4]	36 [34 6-37 7]	34 [32 4-35 4]	n . 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]	u u u u u u u u u u	71 [68 8-73 2]
31-45		89 [87 1-91 8]	96 [93 9-98 7]	97 [94 1-99 0]	n_{10}^{2} [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]	≅1820[177 8-185 7]	184 [179 9-187
56-65		302 [296 7-307 2]	318 [312 5-323 3]	323 [317 9-328 8]	\mathbf{H}_{3}^{102}	343 [337 3-348
66-75		520 [511 6-527 8]	553 [544 9-561 1]	578 [569 4-585 7]	a 60 3 [594 6-610 9]	610 [602 2-618
76-85		1018 [1005 0-1030 8]	1074 [1061 0-1087 7]	1107 [1093 2-1120 4]	ម្ភី49ឆ្លំ1135 0-1163 01	1151 [1137 0-116
>85		1590 [1567 2-1612 5]	1731 [1707 5-1754 0]	1825 [1801 0-1848 2]	6 15 8 1891 2-1939 51	1919 [1895 5-194]
All Women		303 [300.9-304.7]	303 [300.9-304.7]	314 [311.9-315.7]	G 328 [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]	3980[396 2-399 3]	403 [401 9-405 (
rotar population	explicit only	263 [262 2-264 7]	284 [283 1-285 7]	298 [296 7-299 4]	31 4 [313 5-316 2]	322 [320 3-323]
	implicit only	82 [81 4-82 8]	82 [81 5-82 9]	82 [81 5-82 9]	89 [82 2-83 6]	82 [81 1-82 5]
ser and age-s	tandardized ^b	357 [356 0-359 0]	376 [374 2-377 2]	386 [384 6-387 7]	40 ⁵ 5 401 6-404 71	403 [401 9-405 (
506 a Data are shown as num	her per 100 000 por	wlation with 95% CI	510 [514.2 511.2]	500 [504.0 507.7]	o	

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

Admission source, $N(\%)$ Home 194616 (87.6) 202500 (85.7) 210221 (85.5) 221543 (85.7) 223879 (85. Acute care * 22651 (10.2) 28743 (12.2) 30312 (12.3) 31483 (12.2) 32093 (12. Long term care * 4965 (2.2) 5071 (2.2) 5247 (2.1) 5582 (2.2) 5257 (2.1) Length of stay (days), $N(\%)$ <7 53135 (23.9) 58361 (24.8) 61192 (24.9) 68677 (24.6) 69367 (24.7) 7.14 65184 (29.3) 70842 (30.0) 75365 (30.7) 89195 (32.0) 89297 (32. 15.30 62373 (28.1) 65549 (27.7) 67988 (27.7) 78123 (28.0) 77442 (27.7) >30 41540 (18.7) 41362 (17.5) 41235 (16.8) 43187 (15.4) 42771 (15. Length of stay, Median (13. (3-43) 13 (3-41) 13 (3-41) 13 (3-40) 12 (3-3) Septic shock *, $N(\%)$ Yes 50145 (22.6) 49948 (21.1) 51964 (21.1) 53635 (20.7) 54145 (20. No 172087 (77.4) 186366 (78.9) 193816 (78.9) 204973 (79.3) 207354 (79.1) CU admission ⁴ , $N(\%)$ Yes 130587 (58.8) 134181 (56.8) 137025 (55.8) 142001 (54.9) 141685 (54. No 91645 (41.2) 102133 (47.8) 113812 (48.2) 119069 (48.5) 127894 (49.5) 130250 (49. Acute care ⁴ 25992 (11.7) 29436 (12.5) 30904 (12.6) 31329 (12.1) 30784 (11. Long term care ³ 33035 (14.9) 34988 (14.8) 36198 (14.7) 38010 (14.7) 38891 (14. Death 57072 (25.7) 58108 (24.6) 59609 (24.3) 61375 (23.7) 61574 (23.7) Super shock spice are unit in medicine, surgery or obseries or psychetry unit 510 ⁴ Faltow-up and relativitation-care unit domescare biometric or psychiatry unit 510 ⁴ Faltow-up and relativitation-care unit domescare are unit in medicine. Surgery or obseries or psychetry unit 510 ⁴ Faltow-up and relativitation-care unit domescare are unit in medicine. Surgery or obseries or psychetry unit 510 ⁴ Faltow-up and relativitation-care unit of home care unit in medicine. Surgery or obseries or psychetry unit 510 ⁴ Faltow-up and relativitation-care unit of home care to 30.335 (14.9) 3498 (14.8) 36198 (14.7) 38010 (14.7) 38010 (14.7) 38891 (14. 20. 2019) in metropolitan France Figure 2 - Number of patients with sepsis in 2019 and associated number of in-hospital deaths 518 by i	Variables		2 (N=2	2015 (N=222232)		2016 (N=236314)		2017 (N=245780)		2018 (N=258608)		2019 (=261499	
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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. 7.14 65184 (29.3) 70842 (30.0) 75365 (30.7) 89195 (32.0) 89297 (32. 15.30 62373 (28.1) 65549 (27.7) 67988 (27.7) 78123 (28.0) 7742 (27. >30 41540 (18.7) 41362 (17.5) 41235 (16.8) 43187 (15.4) 42771 (15. Length of stay, Median (P10-P9) Septic shock *, N(%) Yes 50145 (22.6) 49948 (21.1) 51964 (21.1) 53635 (20.7) 54145 (20. No 172087 (77.4) 186366 (78.9) 193816 (78.9) 204973 (79.3) 207354 (79. ICU admission ⁴ , N(%) Yes 130587 (58.8) 134181 (56.8) 137025 (55.8) 142001 (54.9) 141685 (54. No 91645 (41.2) 102133 (43.2) 108755 (44.3) 116607 (45.1) 119814 (45. Hospital discharge, N(%) Home 106133 (47.8) 113812 (48.2) 119069 (48.5) 127894 (49.5) 130250 (49. Acute care * 25992 (11.7) 29436 (12.5) 30904 (12.6) 31329 (12.1) 30784 (11. Long term care ^b 33035 (14.9) 34958 (14.8) 36198 (14.7) 38010 (14.7) 3889 (14. Death 57072 (25.7) 58180 (24.6) 59609 (24.3) 61375 (23.7) 61574 (23. * Acute care with in medicine, surgery or obstration protein with * CD-0 code R57.2, R57.8 as primary diagnosis, related diagnosis or significant associated diagnosis * Figure 2.1. Surgers in cidence per 100 000 inhabitants and number of cases between 2015 and 2019 [*] Acute care with in medicine, surgery or obstration or criteria * Dialoging inplicit segris for whick <i>ICU</i> admission is part of the selection criteria * CD-10 code R57.2, R57.8 as primary diagnosis, related diagnosis or significant associated diagnosis * Pilon-up and rehabilitation care with or home care * Figure 2. Number of patients with sepsis in 2019 and associated number of in-hospital deaths * S019 * S019 * S019 * S019 * S019 * S019 * S010 (N (%)) * S010 (N (%))	Acute	care ^a	22651	(10.2)	28743	(12.2)	30312	(12.3)	31483	(12.2)	32093	(12.	
Length of stay (days), N (%) <7 53135 (23.9) 58561 (24.8) 61192 (24.9) 68677 (24.6) 69367 (24.7) <7 53135 (23.9) 58561 (24.8) 61192 (24.9) 68677 (24.6) 69367 (24.7) <7 530 62373 (28.1) 65549 (27.7) 67988 (27.7) 78123 (28.0) 77422 (27.7) >30 41540 (18.7) 41362 (17.5) 41235 (16.8) 43187 (15.4) 42771 (15.7) = regth of stay, Median 13 (3-43) 13 (3-41) 13 (3-41) 13 (3-40) 12 (3-5) Septic shock ⁴ , 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 (79.7) $= 120 4 mission ^4$, N (%) Yes 130587 (58.8) 134181 (56.8) 137025 (55.8) 142001 (54.9) 141685 (54.7) No 19165 (41.2) 102133 (43.2) 108755 (44.3) 116007 (45.1) 119814 (45.7) Home 106133 (47.8) 113812 (48.2) 119069 (48.5) 127894 (49.5) 130250 (49.7) Acute care ⁴ 25992 (17.7) 29436 (12.5) 30904 (12.6) 31329 (12.1) 30784 (11.7) Long term care ^b 33035 (14.9) 34958 (14.5) 36198 (14.7) 38010 (14.7) 38891 (14.7) $> 10^{-1}$ Follow-up and rehabilitation care unit, long-term care unit in medicine, superv or busices or probative or probati	Long	term care ^b	4965	(2.2)	5071	(2.2)	5247	(2.1)	5582	(2.2)	5527	(2.1	
$ \frac{7}{14} = \frac{53135}{12} (23.9) 58561 (24.8) 61192 (24.9) 68677 (24.6) 69367 (24.7) 7.14 (5184 (29.3) 70842 (30.0) 75365 (30.7) 89195 (32.0) 89297 (32.15-30) (52373 (28.1) 65549 (27.7) 67988 (27.7) 78123 (28.0) 77442 (27.3) 73123 (28.0) 77442 (27.3) 73123 (28.0) 77442 (27.3) 73123 (28.0) 77442 (27.3) 73123 (28.0) 77442 (27.3) 73123 (28.0) 77442 (27.3) 73123 (28.0) 77442 (27.3) 73123 (28.0) 77442 (27.3) 73123 (28.0) 77442 (27.3) 73123 (28.0) 77442 (27.3) 73123 (28.0) 77442 (27.3) 73123 (28.0) 77442 (27.3) 7312 (28.0) 77442 (27.3) 7312 (28.0) 77442 (27.3) 7312 (28.0) 77442 (27.3) 7312 (28.0) 77442 (27.3) 7312 (28.0) 77442 (27.3) 7312 (28.0) 77442 (27.3) 7312 (27.3) 7312 (27.3) 7312 (27.3) 7312 (27.3) 7312 (27.3) 7312 (27.3) 7313 (27.3) 734 (27.3) 733 (27.3) 73$	Lengt	h of stay (days), N (%)	× ,		. ,				× ,			
7-14 65184 (29.3) 70842 (30.0) 75365 (30.7) 89195 (32.0) 89297 (32.1) 15-30 62373 (28.1) 65549 (27.7) 67988 (27.7) 78123 (28.0) 77442 (27.7) >30 41540 (18.7) 41362 (17.5) 41235 (16.8) 43187 (15.4) 42771 (15.9) Length of stay, Median (PI0-Pop) 13 (3-43) 13 (3-41) 13 (3-41) 13 (3-40) 12 (3-3) Septic shock *, N (%) Yes 50145 (22.6) 49948 (21.1) 51646 (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 4, N (%) Yes 130587 (58.8) 134181 (56.8) 137025 (55.8) 142001 (54.9) 130250 (49.4) 110812 (48.5) 127894 (49.5) 130250 (49.4) 40150 137292 <td><7</td> <td></td> <td>53135</td> <td>(23.9)</td> <td>58561</td> <td>(24.8)</td> <td>61192</td> <td>(24.9)</td> <td>68677</td> <td>(24.6)</td> <td>69367</td> <td>(24.</td>	<7		53135	(23.9)	58561	(24.8)	61192	(24.9)	68677	(24.6)	69367	(24.	
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$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	15-30		62373	(28.1)	65549	(27.7)	67988	(27.7)	78123	(28.0)	77442	(27.	
Length of stay, Median (P10-P90) Septic shock ${}^{\circ}$, N(%) Yes 50145 (22.6) 49948 (21.1) 51964 (21.1) 53635 (20.7) 54145 (20. No 172087 (77.4) 186366 (78.9) 193816 (78.9) 204973 (79.3) 207354 (79. ICU admission d , N(%) Yes 130587 (58.8) 134181 (56.8) 137025 (55.8) 142001 (54.9) 141685 (54. No 91645 (41.2) 102133 (43.2) 108755 (44.3) 116607 (45.1) 119814 (45. Hospital discharge, N(%) Home 106133 (47.8) 113812 (48.2) 119069 (48.5) 127894 (49.5) 13020 (49. Acute care ${}^{\circ}$ 25992 (11.7) 29436 (12.5) 30904 (12.6) 31329 (12.1) 30784 (11. Long term care ${}^{\circ}$ 33035 (14.9) 34958 (14.8) 36198 (14.7) 38010 (17.7) 38891 (14. Death 57072 (25.7) 58108 (24.6) 59609 (24.3) 61375 (23.7) 61574 (23. 509 ${}^{\circ}$. Acute care unit in medicine, surgery or obstatries or psychiary unit 510 ${}^{\circ}$ Follow-up and relabilitation care unit. long-term care unit or home care 511 ${}^{\circ}$ ICU-0 code R57.2, R57.8 as primary diagnosis, related diagnosis or significant associated diagnosis 512 ${}^{\circ}$ Including implicit sepsis for which ICU admission is part of the selection criteria 513 ${}^{\circ}$ 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 (%))	>30		41540	(18.7)	41362	(17.5)	41235	(16.8)	43187	(15.4)	42771	(15.	
Septic shock *, 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 4, N(%) "Yes 130587 (58.8) 134181 (56.8) 137025 (55.8) 142001 (54.9) 141685 (54. No 91645 (41.2) 102133 (43.2) 108755 (44.3) 116607 (45.1) 119814 (45.1) Home 106133 (47.8) 113812 (48.2) 119069 (48.5) 127894 (49.5) 130250 (49. Acute care a 25992 (11.7) 29436 (12.5) 30904 (12.6) 31329 (12.1) 30784 (11. Long term care b 33035 (14.9) 34958 (14.8) 36198 (14.7) 38010 (14.7) 38891 (14. Death 57072 (25.7) 58108 (24.6) 59609	Lengt { P10-	h of stay, Median P90 }	13	{3-43}	13	{3-41}	13	{3-41}	13	{3-40}	12	{3-3	
Yes 50145 (22.6) 49948 (21.1) 51664 (21.1) 53635 (20.7) 54145 (20. 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 (54.8) No 91645 (41.2) 102133 (43.2) 108755 (44.3) 110812 (49.5) Home 106133 (47.8) 113812 (48.2) 119069 (48.5) 127894 (49.5) 130250 (49.4) Acute care " 25992 (11.7) 29436 (12.6) 36198 (14.7) 38010 (14.7) 38891 (14.8) Long term care b 33035 (14.9) 34958 (14.8) 36198 (14.7) 38010 (14.7) 38891 (14.7) Long term care b 33035 (14.9) 34958 (14.8) 36198 (14.7) 38010 (14.7) 38911<	Septic	c shock ^c , N (%)											
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ICU admission 4 , N (%) Yes 130587 (58.8) 134181 (56.8) 137025 (55.8) 142001 (54.9) 141685 (54.) No 91645 (41.2) 102133 (43.2) 108755 (44.3) 116607 (45.1) 119814 (45.) Hospital discharge, N (%) 10607 (45.1) 119814 (45.) 127894 (49.5) 130250 (49.) Acute care a 25992 (11.7) 29436 (12.5) 30904 (12.6) 31329 (12.1) 30784 (11.) Long term care b 33035 (14.9) 34958 (14.8) 36198 (14.7) 38010 (14.7) 38891 (14.3) Death 57072 (25.7) 58108 (24.6) 59609 (24.3) 61375 (23.7) 61574 (23.7) 510 * <i>ICD-10 code R57.2, R57.8 as primary diagnosis, related diagnosis or significant associated diagnosis</i> * * 102105 * * * * 511 < <i>ICD-10 code R57.2, R57.8 as primary diagnosis, related diagnosis or significant associated diagnosis</i> * <td>No</td> <td></td> <td>172087</td> <td>(77.4)</td> <td>186366</td> <td>(78.9)</td> <td>193816</td> <td>(78.9)</td> <td>204973</td> <td>(79.3)</td> <td>207354</td> <td>(79.</td>	No		172087	(77.4)	186366	(78.9)	193816	(78.9)	204973	(79.3)	207354	(79.	
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508 Table 3 – Characteristics of hospital stays with sepsis, France 2015-2019



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

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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

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eMethods

eTable1

eTable2

eTable3

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eTable5

eTable6



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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 shock². Further recommendations about coding practices for sepsis were updated in 2021³.

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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 (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 S1⁴. 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.

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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.



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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

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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 stav	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

	N (%)								
	Ye	ar								
Variables	20 ⁻ (N=250	15 0 642)	20 ⁻ (N=27	16 D 013)	20 ⁻ (N=28 ⁻	17 1 882)	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 ac	cording to a	ge 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 ac	cording to C	harlson 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 ac	cording to th	e presence or	absence of se	ptic 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 ac	cording to IC	CU 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 ac	cording to ty	pe of selection	ı		
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]
Eves	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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BMJ Open BMJ Open Page 3 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 including for	Location in manuscript where items are reported
Title and abstra	ct		1		
	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	or tevie	RECORD 1.1: The type b for the used should be specified in the b for the databases used should b for the databases used should b for the databases used should b for the geographic region and time frame within which the study the for the study the should be reported in the transformer 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			-	d s	
Background rationale	2	Explain the scientific background and rationale for the investigation being reported		imilar tec	Page 3-4
Objectives	3	State specific objectives, including any prespecified hypotheses		2, 2025 at Innologies.	Page 4
Methods			1	Ag	
Study Design	4	Present key elements of study design early in the paper		ence B	Page 4-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection		libliographiqu	Page 5

9 of 42		BMJ Open	:ed by	
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 	RECORD 6.1: The methods of study population selection (such a codes or algorithms used to identity subjects) should be listed in details. If this is not possible, an explanation to be provided. RECORD 6.2: Any validation of the codes or algorithms are do select the population should be referenced. If validation of score conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study of a flow diagram or other graphical display to demonstrate the data finkage process, including the number of individuals with linked that at each stage.	Page 5 and eMethods and eTable1 in the supplementary file
Variables	7	controls per case 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, conformeders, and effect modifiers should be provided. If these cannot be reported and explanation should be provided.	Page 6, eMethe and eTable1in 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	Agence Bibliographiq	Page 4-6 eMethods and eTable1 in the supplementary file

			BMJ Open	36/bm	Page 4
Bias	9	Describe any efforts to address potential sources of bias		jopen-2	Page 5 and 10
Study size	10	Explain how the study size was arrived at		021-05 ght, inc	Page 4-5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why		8205 on 24 May ; Ense luding for uses	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) <i>Cohort study</i> - If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> - If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses 	ererie	2022. Downloaded from http://bmjopen.bmj.com/ on June 12, 2025 at eignement Superieur (ABES) . related to text and data mining, Al training, and similar technologies	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	Page 5
			provide information on the data	eMethods and
			cleaning methods used in the study	eTable1 in the
			inclus	supplementary
Linkage			RECORD 12.3: State whether the	No data linkag
C			study included person-level	
			institutional-level, or other data linkage	
			across two or more databases. The	
			methods of linkage and retained by the second secon	
			linkage quality evaluation \$\$	
			provided.	
Results	-		t SL	
Participants	13	(a) Report the numbers of	RECORD 13.1: Describe n Hetail the	Page 5-7
-		individuals at each stage of the	selection of the persons field ded in the	eMethods and
		study (e.g., numbers potentially	study (<i>i.e.</i> , study popula	eTable1 in the
		eligible, examined for eligibility,	including filtering based	supplementary
		confirmed eligible, included in	quality, data availability	file
		the study, completing follow-up,	The selection of included persons can	
		and analysed)	be described in the text and by	
		(b) Give reasons for non-	means of the study flow Hiagram.	
		participation at each stage.		
		(c) Consider use of a flow	an S	
		diagram	å å	
Descriptive data	14	(a) Give characteristics of study		Page 7-9
		participants (e.g., demographic,	art	
		clinical, social) and information	ect 1	
		on exposures and potential	11no	
		confounders	logi	
		(b) Indicate the number of	es. at	
		participants with missing data	Ag	
		for each variable of interest	anc	
		(c) <i>Cohort study</i> - summarise	α 	
		follow-up time (<i>e.g.</i> , average and	ib lic	
		total amount)	 <u></u>	
Outcome data	15	<i>Cohort study</i> - Report numbers	aph	Page 7-9
		of outcome events or summary	qu	
		measures over time	e	

Main results16(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 periodPage 7-9Page 7-9Other analyses17Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time periodSupplementary filesOther analyses17Report other analyses done— c.g., analyses of subgroups and interactions, and sensitivity analysesPage 10-12Discussion18Summarise key results with reference to study objectives taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential biasRECORD 19.1: Discussification specific research question(see relative reserved confounding, mgssing data, and changing eligibilitie over time, as they pertain to the study beingPage 10 and 12- 13			<i>Case-control study</i> - Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> - Report numbers of outcome events or summary measures		oen-2021-058205 on 2 opyright, including fo	
Other analyses17Report other analyses done— e.g., analyses of subgroups and interactions, and sensitivity analysesSupplementary filesDiscussionPage 10-12Key results18Summarise key results with reference to study objectivesRECORD 19.1: Discussable implications of using data, that were not potential bias or imprecision. Discuss both direction and magnitude of any potential biasRECORD 19.1: Discussification bias, unmeasured confounding, numerising data, and changing eligibility over time, as they pertain to the study being	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 	er teri	4 May 2022. Downloaded from http://bmjopen Enseignement Superieur (ABES) . r uses related to text and data mining, Al train	Page 7-9
Discussion Page 10-12 Key results 18 Summarise key results with reference to study objectives RECORD 19.1: Discuss the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Page 10 and 12-13 Image: Include of any potential bias Image: Include of any potential bias	Other analyses	17	Report other analyses done— e.g., analyses of subgroups and interactions, and sensitivity analyses	10	ing, and simi	Supplementary files
Key results18Summarise key results with reference to study objectivesPage 10-12Limitations19Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential biasRECORD 19.1: Discuss 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 beingPage 10-12	Discussion				lar t	
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 Height and the specific research question of misclassification bias, unmeasured confounding, nessing data, and changing eligibility over time, as they pertain to the sendy being	Key results	18	Summarise key results with reference to study objectives		e 12, 2 echno	Page 10-12
reported.	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 S implications of using data that were not created or collected to answar 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	с е	D 10.10
		interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	en-2021-058205 on 2 pyright, including fo	Page 10-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	4 May 202 Enseigu r uses rela	Page 12-13
Other Informatio	'n			
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	ownloaded from ent Superieur (<i>/</i> to text and data	Page 15
Accessibility of protocol, raw data, and programming code			RECORD 22.1: Authors and access any supplemental information such as the study protocol, raw datagor programming code.	Supplementar file
Reference: Benchi Committee. The RI n press. Checklist is protec	mol EI, Eporting	Smeeth L, Guttmann A, Harron K, Mohe g of studies Conducted using Observationa er Creative Commons Attribution (<u>CC BY</u>	D, Petersen I, Sørensen HT, von Elm E, Längen SM, the l l Routinely-collected health Data (RECORD) Statement.	RECORD Work PLoS Medicine 2
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