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ORIGINAL ARTICLE

Clinical and economic outcomes of infective endocarditis

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Abstract

Background: In France, the estimated annual incidence of infective endocarditis (IE) is 33.8 cases per million residents. Valvular surgery is frequently undergone. We report an epidemiological and economic study of IE for 2007–2009 in a French region, using the hospital discharge database (HDD). *Methods:* The population studied concerned all the patients living in Centre region, France, hospitalized for IE. We extracted hospital stay data for IE from the regional HDD, with a definition based on IE-related diagnosis codes. The predictive positive value (PPV) and sensitivity (Se) of the definition were 87.4% and 90%, respectively, according to the Duke criteria (definite IE frequency 74.4%). Hospitalization costs were estimated, taking into account the fixed hospital charges of the diagnosis-related group (DRG) and supplementary charges due to intensive care unit (ICU) stay. *Results:* The analysis included 578 patients. The annual average incidence was 45.4 cases per million residents. Valvular surgery was performed in 19.4% of cases. The hospital mortality was 17.6%. Multivariate analysis identified as risk factors for mortality an age ≥ 70 years (odds ratio (OR) = 3.03, 95% confidence interval (CI) = 1.78–5.18), staphylococcal IE (OR = 3.3, 95% CI = 1.9–5.7), chronic renal insufficiency (OR = 2.04, 95% CI = 1.00–4.15), ischemic stroke (OR = 2.55, 95% CI = 1.19–5.47), and hemorrhagic stroke (OR = 5.7, 95% CI = 1.9–17.3). The average cost per episode was $20 103 (€15 281). *Conclusions:* We report a higher incidence of IE than described by the French national study of 2008. Valvular surgery was considerably less frequent than in the published data, whereas mortality was similar. IE generates substantial costs.

Keywords: *Infective endocarditis, epidemiology, surgery, mortality, cost*

Introduction

In France, the estimated annual incidence of infective endocarditis (IE) is 33.8 cases per million residents. This incidence was calculated from a survey conducted in 2008 in seven French regions (covering 15.3 million inhabitants). It was an observational study based on notification and included only adults with definite IE according to the Duke criteria [1]. Major changes have recently been observed in the epidemiology of IE, with an increase of healthcare-associated IE and of *Staphylococcus aureus* IE [1–7].

IE is a highly morbid disease; hospital mortality is reported to be approximately 10–20% and hospitalization in intensive care units (ICUs) is frequent [1,3,8,9]. In the 2008 French study, 44.9% of patients with IE underwent valvular surgery [1].

The economic costs of IE have been rarely studied [10]. However, it is likely to be costly due to the long

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duration of intravenous antimicrobial treatment required, the frequent need for valvular surgery, severe complications (e.g. neurological), and ICU admission, giving prolonged hospital stays. For these reasons, outpatient treatment is difficult to consider, and in the rare cases where it is possible, it is recommended to wait until after 14 days of hospitalization.

In France, every hospital discharge (HD) must be registered in the French Hospital Discharge Database (FHDD) whatever the hospitalization sector. Each administrative area has a Regional Hospital Discharge Database (RHDD), containing data about all the stays of its inhabitants in both local and other establishments everywhere in France. The RHDD is therefore a useful medico-administrative database that can be consulted for epidemiological studies.

The objective of this study was to describe the epidemiology and the clinical and financial outcomes of IE in the Centre region, using the RHDD for the years 2007–2009.

Material and methods

Study design

A historic descriptive study was performed using data collected from the RHDD between 2007 and 2009. Data for all patients hospitalized for IE were extracted from HDD of a French administrative area of 2.53 million inhabitants (4% of the French population, 38 private and public hospitals). This region is representative of the French population in terms of demographic characteristics (age distribution and sex ratio of the population). We used the unique and encrypted patient numbers to link multiple hospitalizations to anonymized patient data, and thereby obtain the patient database. Hospital discharge data were used to describe hospitalizations and economic outcomes, and the patient database was used to describe the epidemiology of IE cases.

Case definition of IE

The French HDD is based on the mandatory notification of each hospital stay, through coded summary, for all French hospitals, public or private. The patients were selected on the basis of an HD algorithm developed by experts specializing in infectious diseases and in medical information systems. Cardiologists agreed this HD algorithm. Each stay with a principal or secondary diagnosis code (International Classification for Diseases – ICD 10) of IE appearing alone or in combination with either microbial or associated complication codes (the ICD codes are listed in the Supplementary Section S1 available online at http://informahealthcare.com/doi/abs/10.3109/00365548.2014.968608 version of the journal). Ambulatory stays (< 24 h) were excluded from the analysis. If the same patient had several hospital stays, we considered them as the follow-up of the same episode of IE (due to the short study period we assumed that it was the same IE), in order not to overestimate the incidence of IE.

Validation of case definition

The case definition was validated in two steps in the three largest hospitals of the region (public hospitals of Tours, Orléans, and Bourges).

In a first step, we randomly selected 243 stays consistent with the HD definition from the local HDD of these hospitals. Medical records were considered as gold standard and the true episodes of IE were validated and considered as true IE based on the Duke criteria [11]. All the medical records of these patients were reviewed by an infectious diseases specialist. These stays corresponded to 198 patients. According to the Duke criteria, 173 patients had IE, giving a positive predictive value (PPV) of 87.4% (95% confidence interval (CI) = 82.8–92.0%) for the case definition. In all, 128 of these 173 IE were classified ‘definite’ and 44 as ‘possible’ (one patient could not be classified because of insufficient data). The frequency of definite IE was thus 74.4% (95% CI = 67.9–80.9%).

In the second step, we measured the reliability of the definition with a sample of 492 randomized patients who underwent valvular surgery, transesophageal echocardiography or pacemaker removal in one of these three hospitals. The case definition had a negative predictive value (NPV) of 99.4%, a PPV of 100%, a sensitivity of 90.0% (95% CI = 87.4–92.6%), and a specificity of 100% (95% CI = 99.2–100%).

Study variables

Variables used in the epidemiological analysis included: age (mean, median, and categorized into 10-year age groups), sex, comorbidities, causative pathogens, valve status of patients (native valve, prosthetic valve, presence of pacemaker or defibrillator), ICU stays, valve surgery, and in-hospital mortality. We calculated the annual mean incidence of IE, standardized for age and sex, adjusted for PPV, and frequency of definite IE. The incidence was calculated using population data for 2008 from the French National Institute of Statistics and Economic Studies (http://www.insee.fr/fr/default.asp).

Variables used in the economic analysis included: total length of stay, discharge destination, and total billed charges. Hospital costs were evaluated as the direct hospitalization cost to society (all expenses directly attributable to patient care), taking into account the fixed hospital charges of the diagnosis-related group (DRG) of the stay and supplementary charges due to ICU stay.

Statistical analysis

Results are presented as frequencies or as means and medians with range. The chi-squared test or Fisher's test was used to compare categories. Relative risk (RR) and 95% CIs were calculated. The means of continuous variables were compared using the *t* test (parametric) and the Wilcoxon (nonparametric) test. Binary logistic regression analysis was performed to analyze the factors associated with in-hospital mortality. All possible explanatory variables were first tested in a univariate model. The criterion for inclusion in the multivariate analysis was $p < 0.2$ in the univariate analysis. In the final logistic regression analysis, the variables were tested one at a time with adjustment for age, diabetes, cancer, kidney insufficiency, and infection with *Staphylococcus* spp.

SAS software, version 9.2, for Microsoft Windows (SAS Institute, Cary, NC, USA) was used for statistical analysis.

Results

Between 2007 and 2009, 807 HDs met the criteria for IE according to the case definition. These HDs involved 578 patients (194 in 2007, 185 in 2008, and 199 in 2009).

Epidemiology

The male:female sex ratio was 2.32. The overall mean age of IE cases was 68.2 years (median 73 years); males were significantly younger than females (mean age 66.8 vs 71.3 years, $p = 0.002$). The distribution and the incidence by sex and age category are presented in Figure 1.

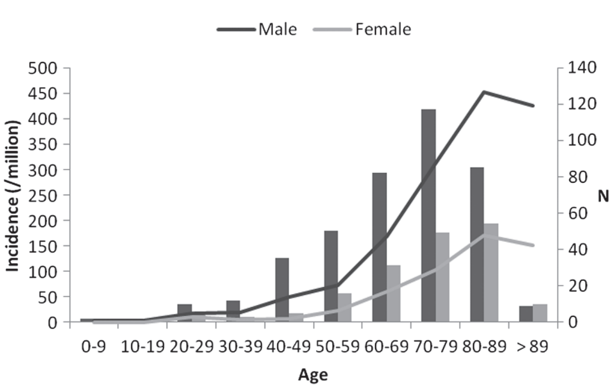

Figure 1. Distribution (bars) and mean annual incidence (curves) of infective endocarditis (IE) by sex and age category.

During the period 2007–2009, the mean annual incidence of IE in the Centre region, standardized for age and sex, adjusted for PPV and frequency of definite IE was 45.8 cases per million inhabitants (65 per million inhabitants for males and 27 per million inhabitants for females).

A substantial proportion of the population was affected by comorbidities, the most frequent being chronic cardiac insufficiency (19.6%), diabetes (16.1%), and cancer (12.1%).

A valvular prosthesis (VP) was coded for 115 (19.9%) patients. The valvular status was unknown for 36 patients (6.2%): we were not able to determine whether or not the VP code was noted because of the valvular surgery. Finally, 427 patients were classified as native valve (NV) IE. Seventy-three patients had a pacemaker (PM) (Table I).

The distributions of the main comorbidities and of valve status did not differ significantly between sexes, excepted for chronic renal insufficiency, which was more frequent in males ($p = 0.02$) (Figure 2).

Table I. Characteristics of patients with infective endocarditis (IE) ($n = 578$).

Characteristic	*n* (%)
Male gender	404 (69.9)
Age (years), mean (median, 25%, 75%)	68.2 (73, 60, 80)
Predisposing diseases	
Chronic cardiac insufficiency	113 (19.6)
Diabetes mellitus	93 (16.1)
Cancer	70 (12.1)
Chronic renal insufficiency	58 (10.0)
Chronic respiratory insufficiency	35 (6.1)
Intravenous drug user	11 (1.9)
Hemodialysis dependence	10 (1.7)
Valve status	
Native valve	427 (73.9)
Valve prosthesis	115 (19.9)
Unknown	36 (6.2)
Pacemaker	73 (12.6)
Microorganism	
Monomicrobial	249 (43.1)
Streptococci	123 (49.4)
Staphylococci	90 (36.1)
Gram-negative bacilli	32 (12.9)
Candida	3 (1.2)
Coxiella burnetii	1 (0.4)
Polymicrobial	26 (4.5)
Not documented	303 (52.4)
No microbiological code	269 (88.8)
Code for nonspecified organism	34 (11.2)
Complication	
Cardiogenic shock	37 (6.4)
Stroke	83 (14.4)
Ischemic stroke	46 (8.0)
Hemorrhagic stroke	16 (2.8)
Unspecified stroke	21 (3.6)
Acute ischemia of lower limb	13 (2.5)
Vertebral osteomyelitis	22 (3.8)
Valvular surgery	112 (19.4)
In-hospital death	102 (17.6)

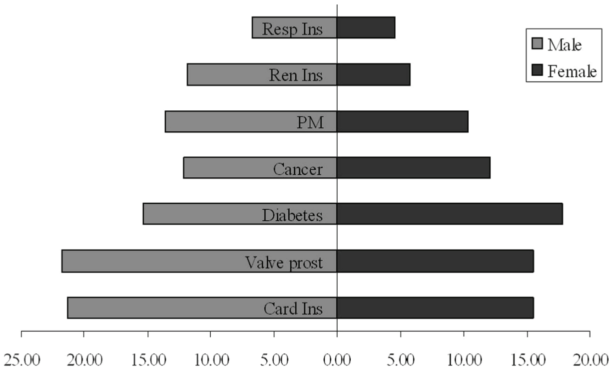

Figure 2. Comorbidities by sex for infective endocarditis (IE). Gray bars, males; black bars, females. Card Ins, chronic cardiac insufficiency; Valv prost, valve prosthesis; PM, pacemaker; Ren Ins, Renal insufficiency; Resp Ins, respiratory insufficiency. *$p < 0.05$.

Microbiology

A microbiological code was reported in the records for 309 patients (53.5%): 34 patients (11.2%) had a code for non-specified bacterial infection, 26 had several microbiological codes, defining polymicrobial IE (19 staphylococci, 15 streptococci, 16 gram-negative bacilli, 5 *Candida*, and 1 *Bartonella henselae*), and 249 patients had a single microbiological code (monomicrobial IE), with a predominance of streptococci (49.4%) and staphylococci (36.1%).

Among the 138 coded streptococci, 11 (8%) were group A streptococci, 8 (5.8%) were group B streptococci, 36 (26.1%) were group D streptococci, and 11 (8%) were pneumococci; 72 streptococci (52.2%) were unspecified.

Among the 109 coded staphylococci, there were 78 (71.6%) *Staph. aureus* and 32 (29.4%) coagulase-negative staphylococci.

Surgical management of IE (Table II)

Valve surgery was performed for 112 patients (19.4%), including 99 valve replacements and 13 valve repairs.

Valvular surgery for IE was performed at a hospital of the Centre region for 48 patients (42.9%), and in hospitals of the Ile de France region (Paris) for most of the other patients.

The patients who underwent valve surgery were more frequently male than female (OR = 1.74, 95% CI = 1.06–2.85), were on average 8 years younger ($p = 0.001$) and had a higher frequency of infections with gram-negative bacilli (OR = 2.68, 95% CI = 1.27–5.65) than patients who were not operated. The valvular status, the staphylococcal infection, and the place of residence were not statistically differently distributed in both groups (univariate analysis).

There was no statistically significant difference of in-hospital mortality between patients who had

Table II. Risk factors of surgery: univariate analysis.

Factor	No surgery, *n* (%)	Surgery, *n* (%)	OR
Sex			
Female	150 (32.2)	24 (21.4)	**1**
Male	332 (67.8)	88 (78.6)	**1.74 (1.06–2.85)**
Age (mean, years)	69.7	61.8	**<0.001**
Valve status*			
Native valve	368 (79.1)	59 (76.6)	1
Prosthetic valve	97 (20.9)	18 (23.4)	1.16 (0.65–2.05)
Microbiology of IE†			
Staphylococcal	72 (30.1)	18 (24.0)	1.05 (0.60–1.84)
Streptococcal	93 (39.7)	30 (40.0)	1.47 (0.91–2.36)
Gram-negative bacilli	20 (8.5)	12 (16.0)	**2.68 (1.27–5.65)**
County of residence‡			
18	82 (17.6)	19 (17.0)	
28	61 (13.1)	21 (18.8)	
36	43 (9.2)	14 (12.5)	0.29
37	89 (19.1)	22 (19.6)	
41	68 (14.6)	9 (8.0)	
45	123 (26.4)	27 (21.1)	
In-hospital death	84 (18.1)	18 (16.1)	0.87 (0.49–1.52)

OR, odds ratio. Bold type relates to factors significantly associated with poor outcome.
*Patients with unknown status were excluded ($n = 36$).
†Microbiological variables are monomicrobial.
‡Départements (administrative areas): 18 = Cher; 28 = Eure-et-Loir; 36 = Indre; 37 = Indre-et-Loire; 41 = Loir-et-Cher; 45 = Loiret.

surgical management and those who had exclusively medical management (16.1% and 18.1%, respectively; $p = 0.62$).

Complications

During the 3 years studied, the global in-hospital mortality rate was 17.6% (102/578).

Eighty-three patients (14.4%) had a code for a brain stroke; 55% strokes were ischemic ($n = 46$), and the others were hemorrhagic ($n = 16$) or non-specified ($n = 21$). Twenty-two (3.8%) patients had a code for vertebral osteomyelitis, 37 (6.4%) for cardiogenic shock, and 13 (2.5%) for acute ischemia of the lower limbs (Table I).

The factors associated with in-hospital mortality are presented in Table III. An age ≥ 70 years (OR/year = 1.03, 95% CI = 1.02–1.05), staphylococcal IE (OR = 3.3, 95% CI = 1.9–5.7), chronic renal insufficiency (OR = 2.04, 95% CI = 1.00–4.15), ischemic stroke (OR = 2.55, 95% CI = 1.19–5.47), and hemorrhagic stroke (OR = 5.7, 95% CI = 1.9–17.3) were significantly associated with poor outcome. The valve status, the county (French administrative area; several to a 'Region') of residence, and the surgical management of IE were not factors associated with in-hospital death (multivariate analysis).

Economic analysis

The mean duration of hospitalization was 30 days (median 22.4 days). During their stay, 29.6% of patients were admitted to an ICU.

The average cost of hospital stays was €15 281 ($20 429) per patient, representing a mean annual cost for the region of €2 944 279 ($3 936 202). It increased by + 34.3% between 2007 (€12 938 = $17 613) and 2009 (€17 735 = $23 654).

Discussion

In this epidemiological study conducted in one representative French region, an elevated annual incidence of IE was estimated (45.8 cases per million inhabitants). The frequency of valvular surgery was low (20%) and the in-hospital mortality was 17%. The average cost of hospital stays was €15 281 ($20 429), resulting in a significant burden of IE for society.

One of the strengths of using HDDs for epidemiological investigations is that they are population-based. Their use requires a robust case definition and validation. The algorithm used in the present study to identify hospitalization for IE fulfilled this condition for the reliability parameters: Se 90%, Sp

Table III. Risk factors for in-hospital mortality: univariate and multivariate analysis.

Variable	Univariate analysis, OR (95% CI)	Multivariate analysis OR (95% CI)
Sex		
Female	1	–
Male	1.04 (0.65–1.66)	
Age		
< 70 years	**1**	**–**
≥ 70 years	**2.53 (1.57–4.07)**	**3.03 (1.78–5.18)**
Predisposing diseases		
Diabetes mellitus	1.57 (0.92–2.68)	1.26 (0.67–2.37)
Chronic cardiac insufficiency	1.16 (0.69–1.97)	–
Chronic respiratory insufficiency	1.41 (0.62–3.21)	–
Chronic renal insufficiency	**1.92 (1.03–3.58)**	**2.04 (1.00–4.15)**
Cancer	1.45 (0.79–2.66)	1.32 (0.66–2.65)
Valvular status		
Valve prothesis	1	–
Native valve	0.64 (0.35–1.16)	0.56 (0.29–1.08)
Microorganism (monomicrobial IE)		
Streptococci	0.76 (0.44–1.32)	–
Staphylococci	**3.29 (2.00–5.43)**	**3.09 (1.77–5.40)**
Gram-negative bacilli	1.33 (0.56–3.16)	–
Cerebral complications		
Ischemic stroke	**2.48 (1.28–4.78)**	**2.55 (1.92–5.47)**
Hemorrhagic stroke	**4.98 (1.82–13.6)**	**5.77 (1.93–17.28)**
Unspecified stroke	1.10 (0.36–3.35)	–
Valvular surgery	0.87 (0.50–1.52)	–

CI, confidence interval; OR, odds ratio. Bold type relates to factors significantly associated with poor outcome.

100%, PPV 87.4%, and NPV 99.4%. The frequency of definite IE was 74.4%, lower than in previous published studies [12]. These studies were based on prospective data collection in referral centers allowing best descriptive results but possibly biased. In contrast, the present study, which was based on HD algorithm, could have overestimated the diagnosis of IE, but our population-based study could be more representative of the reality.

HDDs could be used to estimate the annual incidence of IE because the disease is not chronic; consequently, prevalent cases could be assimilated to incident cases. The mean annual incidence of IE, adjusted with the PPV for the definition used and the frequency of definite IE, was 45.8 cases per million residents in the region (39.6 cases per million with the lower values of 95% CIs of these adjustment variables). This incidence is higher than the incidence of IE reported in the study by Selton-Suty et al. (33.8 cases per million population) [1]. There are several possible explanations for this difference.

First, the sample of medical records reviewed to calculate the PPV and the frequency of definite IE may not have been representative of the population extracted from the RHDD. Thus, the incidence of IE may have been overestimated (IE may be encoded in excess, the fixed hospital charges of the DRG being financially advantageous). We believe that the size of our sample (34% of the population) would have tended to minimize this bias.

Second, the estimated incidence reported by Selton-Suty et al. was extracted from an observational study, based on the declaration of cases of IE by all the institutions of the area concerned [1]. Some cases may not have been declared to the investigators. By contrast, the HDDs we used have the advantage of being totally exhaustive.

The incidence of IE in our study is similar to that found in another population-based study in Italy [13].

The characteristics of our population were similar to those described in other studies. The population was old (mean age 68 years), and predominantly male. Thus, the incidence of IE in men aged from 80 to 89 years was 10 times greater than in the general population. It has not yet been well explained why, but higher incidence or prevalence of IE in male gender is a classic finding from epidemiological studies [1,4,14]. A protective role of estrogens for endothelial damage has been proposed [15]. In the older categories of age, the male:female sex ratio decreased to be reversed over 90 years. Comorbidities, particularly cardiac insufficiency, diabetes, renal insufficiency, and cancer, were frequent. The majority of IE occurred on native valves. Our observations confirm that the profile of IE has changed during the three last decades. This is probably a consequence of the aging of the population and medical progress. Thus, increasing numbers of people are carrying pacemakers, prosthetic valves, long-term central venous catheters or ports, and need chronic dialysis. The fact that our population is comparable to those in other studies increases the value of our results [1,2,4,5,13].

The microbiological results of our study are limited by the small percentage of patients with a code for microbial documentation (53.5%). This is probably because in 2009 hospital stays were not billed according to this type of code. Despite this limitation, the overall distribution of the pathogens identified is similar to that reported in other recent studies, with a predominance of *Staph. aureus* IE [1,3,4]. The frequency of group D streptococci was high, as reported elsewhere in Europe [4]; note that this may include enterococcal IE (there is no specific diagnosis code for this species). The frequency of documented gram-negative bacilli was also high (12% vs $<$8.5% in the study by Seton-Suty et al. [1]). This may be due to other infections during the hospital stay of patients (e.g. urinary tract infection) being coded (information bias).

The frequency of valve surgery in the present study was relatively low. This is the result that differs most from the study by Selton-Suty et al. [1] (19.4% vs 44.9%). Assuming that all patients who underwent valve surgery had 'definite' IE according to Duke criteria, the frequency of valve surgery, adjusted for the frequency of definite IE in our sample, was 26%. This result still differs from the frequency reported by Selton-Suty et al. (which addresses exclusively 'definite' IE) [1]. It has been demonstrated that patients with an indication for surgery but who do not undergo surgery have high in-hospital mortality, up to 80% [7,16–18]. In our population, in-hospital mortality was 17.6%. If all patients who died had a definite IE, in-hospital mortality would have been 23.7%, consistent with the in-hospital mortality reported by Selton-Suty et al. [1]. Thus, the difference in surgical management cannot be explained by non-compliance with the indications for valvular surgery. Possibly, the discrepancy is due to a difference in the populations studied: our population may have been non-representative, with less severe IE in our region than in the population studied by Selton-Suty et al. [1]. However, this is unlikely, because no geographical variation in the severity of IE has been described, and the population of the Centre region is globally representative of the French general population. Another possible explanation for the discrepancy is a referral bias. The main centers included in the study by Selton-Suty et al. specialize in IE [1]; in these hospitals, there is close collaboration between infectious disease teams, cardiologists, and heart surgeons. This may lead to easier access to surgery, with patients undergoing surgery despite not having formal indications for such interventions [19]. Two recent population-based studies found results similar to ours, with low rates of valve replacement and no excess of mortality [13,20].

The main factors associated with recourse to surgery were age, sex, and gram-negative infection (patients who underwent operations were younger, most frequently males, and they had a higher frequency of gram-negative IE than patients who were not operated). In other cohorts women underwent surgery less often than men, probably because of differences between genders in pre-existing conditions. However, a systematic bias (under referral of women with IE for valve surgery) has been discussed [21,21]. We did not find any significant difference regarding the valvular status, the Département of residence or mortality between patients who had valve surgery and those who did not. Note that these conclusions are limited by the fact that we did not perform a multivariate analysis.

In-hospital mortality was similar to that reported in the literature. Multivariate analysis identified five factors as being associated with mortality: age, chronic renal insufficiency, staphylococcal infection, and ischemic and hemorrhagic stroke. These factors have repeatedly been reported in previous studies [9,23–26].

The economic analysis confirmed that the costs of IE for society are large. During the 3 years studied, the average cost of a stay for IE increased by 34%, so our analysis probably underestimates the true cost of IE. If surgery had been more frequent than we observed in our study, and indeed as reported by Selton-Suty et al. [1], the global cost would have been even higher than we estimate here.

Our study has several limitations. Regarding its design, the inclusion of patients was based on passive surveillance. Some stays for IE may not have been encoded with a diagnostic code for IE, and therefore failed in the analyses. Specificity (as sensitivity) is normally not related to the sample. However, due to the low incidence of the IE in the sample selected for validation, if the sample size had been more greater the specificity would have been lower. Our case definition did not allow us to distinguish 'definite' or 'possible' IE according to the Duke criteria. As mentioned above, microbiological and clinical results are limited with missing data, due to a non-systematic coding of these data in HDD by clinicians. This could impact the results of our multivariate analysis. We only studied the in-hospital mortality. A 6-month mortality end point would have been more appropriate for the outcome analysis, notably because the benefit of surgery begins to be observed at this point [27]. Finally, the economic analysis did not include either the direct costs associated with rehabilitation care (notably post surgery) or the indirect costs caused by the disruption of often prolonged absences, which could substantially increase the burden of IE on society in terms of finance.

In conclusion, we report an epidemiological analysis of IE in a region of France, based on the analysis of HDD. The results are exhaustive and reliable due to a robust case definition, previously assessed and validated. However, the lowest frequency of definite IE (74%, according to the Duke criteria) constituted a limit. We tried to minimize it by adjusting our results on these data. Compared with the baseline study of IE in France, we found a higher frequency of IE in our population, less frequent surgical management, and similar in-hospital mortality. These results could be strengthened by a national analysis of HDD.

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Supplementary material available online

Supplementary information.