Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 59, No. 22, 2012
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2012.02.029

Temporal Trends in Infective Endocarditis in the Context of Prophylaxis Guideline Modifications

Three Successive Population-Based Surveys

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Objectives The goal of this study was to evaluate temporal trends in infective endocarditis (IE) incidence and clinical characteristics after 2002 French IE prophylaxis guideline modifications.

Background There are limited data on changes in the epidemiology of IE since recent guidelines recommended restricting the indications of antibiotic prophylaxis of IE.

Methods Three 1-year population-based surveys were conducted in 1991, 1999, and 2008 in 3 French regions totaling 11 million inhabitants age ≥20 years. We prospectively collected IE cases from all medical centers and analyzed age- and sex-standardized IE annual incidence trends.

Results Overall, 993 expert-validated IE cases were analyzed (323 in 1991; 331 in 1999; and 339 in 2008). IE incidence remained stable over time (95% confidence intervals given in parentheses/brackets): 35 (31 to 39), 33 (30 to 37), and 32 (28 to 35) cases per million in 1991, 1999, and 2008, respectively. Oral streptococci IE incidence did not increase either in the whole patient population (8.1 [6.4 to 10.1], 6.3 [4.8 to 8.1], and 6.3 [4.9 to 8.0] in 1991, 1999, and 2008, respectively) or in patients with pre-existing native valve disease. The increased incidence of *Staphylococcus aureus* IE (5.2 [3.9 to 6.8], 6.8 [5.3 to 8.6], and 8.2 [6.6 to 10.2]) was not significant in the whole patient population ($p = 0.228$) but was significant in the subgroup of patients without previously known native valve disease (1.6 [0.9 to 2.7], 3.7 [2.6 to 5.1], and 4.1 [3.0 to 5.6]; $p = 0.012$).

Conclusions Scaling down antibiotic prophylaxis indications was not associated with an increased incidence of oral streptococcal IE. A focus on avoidance of *S. aureus* bacteremia in all patients, including those with no previously known valve disease, will be required to improve IE prevention. (J Am Coll Cardiol 2012;59:1968–76) © 2012 by the American College of Cardiology Foundation

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Infective endocarditis (IE) is a rare but severe disease with an in-hospital mortality rate of around 20% and a 5-year mortality rate of 40% (1,2). It also has a high morbidity rate and cost burden: its treatment requires prolonged hospitalization, 1 out of 2 patients is operated on during the acute phase of the disease, and quality of life and return to work are compromised in some patients (3,4). Therefore, IE antibiotic prophylaxis strategies have been proposed for years worldwide to patients with cardiac diseases at risk for IE undergoing invasive procedures responsible for bacteremia (5).

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Because no randomized clinical trial had been conducted to demonstrate the efficacy of such a strategy and because case-control studies had not found any relationship between dental procedures and IE (6–8), IE prophylaxis guidelines were altered toward a drastic reduction in antibiotic indications, in France as early as 2002 and in other countries in 2007 to 2009 (5,9–13). This change led to restricting the use of antibiotic prophylaxis to patients with the highest risk of poor outcomes from IE (i.e., patients with prosthetic valves, complex congenital heart disease, previous IE). For example, antibiotic prophylaxis is no longer recommended for dental procedures in patients with previously known native valve disease such as mitral valve prolapse or bicuspid aortic valve. In parallel, general recommendations were made regarding patients with previously known valve disease, encouraging better oral and general hygiene and limiting the use of skin-breaking procedures or indwelling catheters to limit the risk of staphylococcal IE, the rate of which has reportedly been increasing (3,14,15). More recently, National Institute for Health and Clinical Excellence guidelines even recommended discontinuing IE antibiotic prophylaxis altogether (16).

The evaluation of the impact of this drastic change in IE prophylaxis strategy on clinical and epidemiological characteristics is complicated by several factors. Due to the disease's polymorphic presentation, patients with IE are managed by physicians of different specializations in secondary and/or tertiary care hospitals. Patients with the most severe form of the disease and those needing cardiac surgery are referred to tertiary care hospitals, where they are overrepresented (17,18). In addition, the use of administrative coding of discharge data in this evaluation may be misleading because the data generally represent nonexpert-validated IE cases and may reflect financial considerations rather than those of diagnostic precision (19,20). Recording IE characteristic changes with accuracy therefore requires large comprehensive population-based studies, which describe the whole IE patient population and are less subject to referral bias (17,18,21).

Abbreviation and Acronym

IE = infective endocarditis

We had the unique opportunity of having data from 2 previous national population-based surveys with expert-validated IE cases, performed in 1991 and 1999 before the modification of IE prophylaxis policy in 2002. We were thus able to conduct a third survey along the same model and on the same population pool after the guideline modifications and then to compare the results of all 3 studies. The objective was to evaluate temporal trends in IE incidence, clinical characteristics, and prognosis following the 2002 French IE prophylaxis guideline modifications. Particular attention was paid to oral streptococcal IE incidence, particularly in patients with previously known native valve disease, and to staphylococcal IE incidence. The working hypothesis was that a significant increase in the incidence of IE after scaling down prophylaxis use would be in favor of its efficacy, whereas a stable or a decreased incidence of IE would tend to support the appropriateness of prophylaxis guideline modifications.

Methods

Population-based survey methods. All three 1-year surveys (1991, 1999, and 2008) were conducted using the same methods (2,22). Survey participation packets were sent out by mail to all physicians potentially involved in IE patient care, to echocardiographers, and to microbiologists working in the 3 regions' hospitals. French societies for infectious diseases, cardiology, cardiac surgery, and microbiology also informed their members of the survey. All medical professionals were asked to report in real time any case of IE, regardless of diagnostic certainty, and were regularly reminded of the study throughout the study period. Duplicate reports were identified and excluded. Medical professionals were reminded by "study newsletter" to report regularly. For each patient age ≥20 years treated for IE, a specific case report form was filled out at the hospital and validated by the primary care physician. Institutional review board authorization was received from the Comité de Protection des Personnes de Besançon on December 19, 2007.

Case report forms included data on patients' medical history (including previously identified cardiac diseases at risk of IE, procedures at risk of IE performed within the previous 3 months, and use of antibiotic prophylaxis) and IE characteristics. Investigators were provided with standard definitions of all variables. Recent dental procedures were recorded based on patient report.

Microbiologists completed a form with detailed information on the identification and susceptibility of the

Microbiology and Infectious Diseases, and by Novartis Laboratories. The sponsor was the Département à la Recherche Clinique et à l'innovation (French Ministry of Health), Hôpital Universitaire de Besançon. The sponsor supported the research but had no access to the data. Dr. Iung is a consultant for Boehringer-Ingelheim, Bayer, Valtech, Servier, and Abbott; and has received speaker fees from Edwards Lifesciences and Sanofi-Aventis. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received November 2, 2011; revised manuscript received February 10, 2012, accepted February 14, 2012.

causative microorganism. Identification of streptococcal and staphylococcal strains was confirmed in the respective National Reference Centers. All strains were identified at the species level by genetic methods using gene sequencing (23,24).

Study populations. The same 3 French regions (Greater Paris, Lorraine, and Rhône-Alpes) participated in the 3 surveys. They accounted for an 11 million inhabitant population (24% of the French population age ≥20 years). Only patients ≥20 years of age with a first hospitalization between January 1 and December 31 of each year and residing in these 3 regions were kept in the analysis for standardized incidence calculations.

Case validation. All case report forms were checked for accuracy and validated by 3 independent regional assessment committees each composed of an infectious diseases specialist, a cardiologist, a cardiac surgeon, and a microbiologist. A modified von Reyn classification taking into account echocardiographic data was used in the 1991, 1999, and 2008 cases (22,25). Duke classification was also applied in the 1999 and 2008 cases and the modified Duke classification in 2008 (26,27). Each patient was also assigned to a category in the 3 classifications (modified von Reyn, Duke, and modified Duke) using a specific applet. Any discrepancies between computerized and specialists' classifications were resolved by consensus. The modified von Reyn classification being the only available classification for all 3 surveys was chosen to describe the changes over the 3 periods (22). Definite, probable, and possible cases of IE were considered and compared among the 3 surveys. Sensitivity analyses were performed, one considering only modified von Reyn definite cases and probable cases, the other considering the definite cases of the Duke classification for the 1999 and 2008 cases.

Calculation of incidence and statistical analysis. Incidence rates, expressed as number of cases per million inhabitants, were calculated by dividing the number of cases recorded within the study year in the 3 regions by the number of individuals age ≥20 years living in these regions. For each period, incidence rates were standardized to the sex-by-age distribution of the French population age ≥20 years. Population references were obtained from the National Institute of Statistics and Economic Studies on January 1, 2008, based on the nationwide 2007 census. IE standardized incidence rates were also estimated by preplanned subgroups: causative micro-organisms (streptococci, staphylococci), previously known pre-existing cardiac condition (previously known native underlying heart disease, prosthetic valve, no previously known underlying heart disease, and other IE classification criteria (definite and probable cases according to modified von Reyn classification, definite cases according to Duke and modified Duke classifications). Incidence rates were compared within the 3 surveys using a Poisson regression. Age-and-sex specific incidences were also calculated for each period. With 300 patients, an incidence of 30 cases per million, and α 2-sided risk of 5%, a difference of 7 cases per million between surveys can be detected with a power of 80%.

For descriptive analysis, quantitative variables were expressed as their mean ± SD and qualitative variables expressed as percentages. The chi-square test or Fisher exact test for qualitative variables, and tests stemming from 1-way analysis of variance or Kruskal-Wallis test for quantitative variables were used for comparisons over the 3 periods. When a significant difference was observed for variables available for the 3 periods, a trend test was performed (Cochran-Armitage trend test for binary variables and linear trend test for quantitative variables). First, factors associated with in-hospital mortality were searched for according to bivariable analysis (logistic regression), first within each study year and then in the whole 3-study population. The tested variables were those already identified as associated with in-hospital mortality in the literature (i.e., age, microorganisms, prosthetic valve, cerebral emboli, cardiac surgery) (1,28–32). Second, 4 multivariable forward stepwise logistic regression models were built with an enter p value of 0.2 and a remove p value of 0.05. The calendar year effect (1991, 1999, or 2008) was forced in the analysis on the global population. Odds ratios and their 95% confidence intervals were calculated. The validity of the models was checked using the Hosmer and Lemeshow goodness-of-fit test. All statistical analyses were performed using SAS version 9.2 (SAS institute, Inc., Cary, North Carolina).

Results

Figure 1 shows the case selection process in each of the 3 surveys. There were 323, 331, and 339 patients with a definite, probable, or possible IE according to the modified von Reyn classification, aged ≥20 years, living in the studied regions, and hospitalized during the survey year in 1991, 1999, and 2008, respectively. Using the Duke criteria, there were 323 and 332 definite cases in 1999 and 2008, respectively.

Characteristics of IE among the 3 surveys. DEMOGRAPHICS, UNDERLYING HEART DISEASE, AND AT-RISK DENTAL PROCEDURES. Mean age increased over time from 58 to 62 years ($p = 0.013$) (Table 1). IE predominated in males in all 3 surveys; the sex ratio increased significantly over time. The IE incidence rate varied differently according to age and sex in the 3 surveys (Online Fig. 1). The distribution of underlying heart diseases is summarized in Table 1. The rate of patients with no previously known heart valve disease increased from 34% in 1991 to 49% in 1999 and remained stable in 2008 (47%) ($p < 0.001$). Between 1999 and 2008, the proportion of patients with prosthetic valves and with pacemakers increased, as did the proportion of patients with hypertension and diabetes mellitus. The proportion of intravenous drug users remained stable. The rate of patients reporting having had at-risk dental procedures was low and not statistically different between 1999 and 2008 (5.1% and 4.7%, respectively). Other background characteristics and

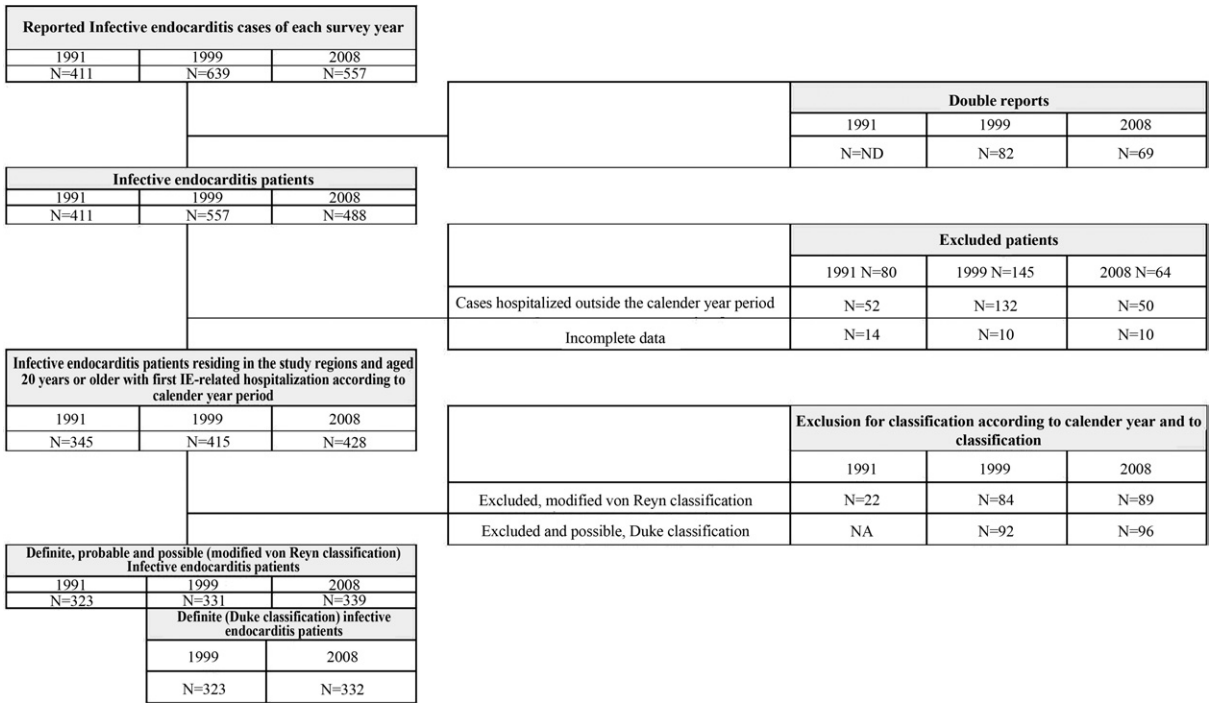

Figure 1 **Flowchart of the 1991, 1999, and 2008 Surveys**

IE = infective endocarditis; NA = not available; ND = not determined.

at-risk dental procedures are displayed in Table 1 and Online Table 1.

CLINICAL AND BIOLOGICAL EVENTS, LOCATION OF IE, AND ECHOCARDIOGRAPHY. Fever was reported significantly less frequently over time (Table 1). Severe congestive heart failure was common. At least one embolic event was reported in 38%, 37%, and 58%, respectively. The proportion of prosthetic valve IE did not differ significantly among the 3 surveys whereas that of pacemaker IEs increased significantly. Echocardiography yield increased significantly over time.

CAUSATIVE MICRO-ORGANISMS. Micro-organisms responsible for IE were identified in 87%, 93%, and 93% from 1991 to 2008 (Table 1). Streptococcaceae were the most frequent micro-organisms across the 3 surveys, but their proportion decreased over time. The proportion of group D streptococci evolved in 2 phases with a marked increase between 1991 and 1999 (17% to 25%, which explains the overall streptococci increase between 1991 and 1999) followed by a decrease in 2008 to below the 1991 level (12%; $p < 0.001$). The proportion of *Staphylococcus aureus* increased regularly and significantly (16%, 21%, and 26%; $p = 0.011$), as did that of coagulase-negative staphylococci (4%, 6%, and 10%; $p = 0.007$). The number of patients having had an oral procedure in the preceding 3 months and who developed an oral streptococci IE was low and did not differ between 1999 and 2008 (6 of 331 [1.8%] and 7 of 339 [2%], respectively).

OUTCOME. Mean hospital stay duration increased over time, although not significantly. The rate of cardiac surgery performed during the acute phase of the disease increased from 1991 to 1999 (31% to 50%) and then remained stable (50%) ($p < 0.001$). In-hospital death rates were not significantly different among the 3 periods (21%, 15%, and 21%, respectively).

Incidence of IE among the 3 surveys. Overall, the age- and sex-standardized annual IE incidence did not change significantly across the 3 surveys (Fig. 2, Online Table 2), but it decreased significantly in patients with previously known native heart valve disease. The incidence of oral streptococcal IE did not increase in the overall population or in the population of patients with previously known native heart valve disease, in whom it significantly decreased. The incidence of both *S. aureus* and coagulase-negative staphylococcal IE increased significantly in patients without previously known native heart valve disease.

Prognostic factors. Factors associated with in-hospital mortality are presented in Table 2. In multivariate analysis, considering the overall population of patients enrolled in the 3 surveys, calendar year was not associated with death, whereas increasing age, staphylococci, and cerebral emboli were associated with death. In the models considering the prognostic factors in each of the surveys, increasing age and staphylococcal IE were both independently associated with death in the 3 surveys.

Table 1 Temporal Trends in Characteristics of IE (Definite, Probable, and Possible IE Using Modified von Reyn Classification)

Characteristic	1991 (n = 323)*			1999 (n = 331)*			2008 (n = 339)*			p Value†	p Value‡
	n	%/Mean	SD	n	%/Mean	SD	n	%/Mean	SD		
Background characteristics											
Age (yrs)	323	57.9	16.6	331	59.8	16.5	339	61.6	16.3	**0.013**	**0.021**
Sex										**0.040**	**0.011**
Men	212	65.6		231	69.8		253	74.6			
Women	111	34.4		100	30.2		86	25.4			
Diabetes mellitus	NA	NA		44	13.3		72	21.2		**0.006**	NA
Dialysis	NA	NA		12	3.6		6	1.8		0.137	NA
Intravenous drug users	18	5.6		21	6.3		16	4.7		0.655	NA
Previously known underlying heart diseases											
Previously known underlying heart disease	212	65.6		168	50.8		179	52.8		**0.002**	**0.001**
Native valve disease	170	52.6		113	34.1		74	21.8		**<0.001**	**<.001**
Mitral valve prolapse	17	5.3		7	2.1		25	7.4		**0.006**	0.195
Prosthetic valve	73	22.6		58	17.5		84	24.8		0.065	
Pacemaker	10	3.1		21	6.3		51	15.0		**<0.001**	**<.001**
IE at-risk dental procedures or situations											
Dental oral at risk	NA			17	5.1		16	4.7		0.8034	NA
Dental oral at risk in oral streptococci IE patients	NA			6	9.8		7	10.0		0.9750	NA
Dental oral at risk with antibioprophylaxis	NA			3	17.6		6	37.5		0.2587	NA
Clinical and biological events											
Fever	300	94.0		292	89.0		281	83.9		**0.002**	**<.001**
Cerebral emboli	46	23.2		50	15.1		78	23.0		**0.017**	0.680
Cerebral hemorrhage	NA			4	1.2		24	7.1		**0.001**	NA
Other emboli	30	15.1		74	22.4		121	35.7		**<0.001**	**<0.001**
Echocardiography											
Transesophageal echocardiography				303	91.5		307	90.6		**0.657**	
Positive echocardiography	249	77.1		296	89.4		300	88.5		**<0.001**	**<0.001**
Vegetation	228	70.6		281	84.9		287	84.7		**<0.001**	**<0.001**
Perforation	NA			24	7.3		71	20.9		**<0.001**	NA
Location of IE											
Left heart IE	289	89.5		265	80.1		260	76.7		**<0.001**	**<0.001**
Pacemaker IE	NA			11	3.3		19	5.6		0.153	NA
Prosthetic valve IE	66	20.4		45	13.6		62	18.3		0.061	
Micro-organisms											
Streptococcaceae	180	55.7		195	58.9		167	49.3		**0.037**	0.089
Streptococci	144	44.6		160	48.3		128	37.8		**0.019**	0.071
Oral streptococci	77	23.8		61	18.4		70	20.6		0.232	
Group D streptococci	54	16.7		83	25.1		40	11.8		**<0.001**	0.087
Staphylococcaceae	67	20.7		90	27.2		122	36.0		**<0.001**	**<0.001**
Staphylococcus aureus	52	16.1		70	21.1		87	25.7		**0.010**	**0.002**
Coagulase-negative staphylococci	14	4.3		20	6.0		35	10.3		**0.007**	**0.002**
Outcome											
Cardiac surgery	99	31.3		166	50.2		168	49.6		**<0.001**	**<0.001**
In-hospital death	63	20.7		51	15.4		72	21.2		0.110	

Values given in **bold** reflect statistically significant difference. *Considering definite, probable, and possible IE cases according to modified von Reyn classification taking into account echocardiographic data (22). †Chi-square test or Fisher exact test for qualitative variables, test stemming from a 1-way analysis of variance or Kruskal-Wallis test for quantitative variables. ‡Trend test only for variables with 3 measures and significant difference in bivariate analysis with an alpha level of 0.05. Cochran-Armitage trend test calculated for binary variables and linear trend test for quantitative variable.
IE = infective endocarditis; NA = not available data.

Discussion

Despite marked modifications of IE prophylaxis recommendations between 1999 and 2008 toward a reduction of antibiotic use, we did not identify any increase either in the overall incidence rate of IE or in that of oral streptococcal IE incidence rate. We also observed an increase of staphylococcal IE in a population of patients not identified as at risk for IE. To our knowledge, this is the first study using a large population-based survey, which analyzes IE epidemi-

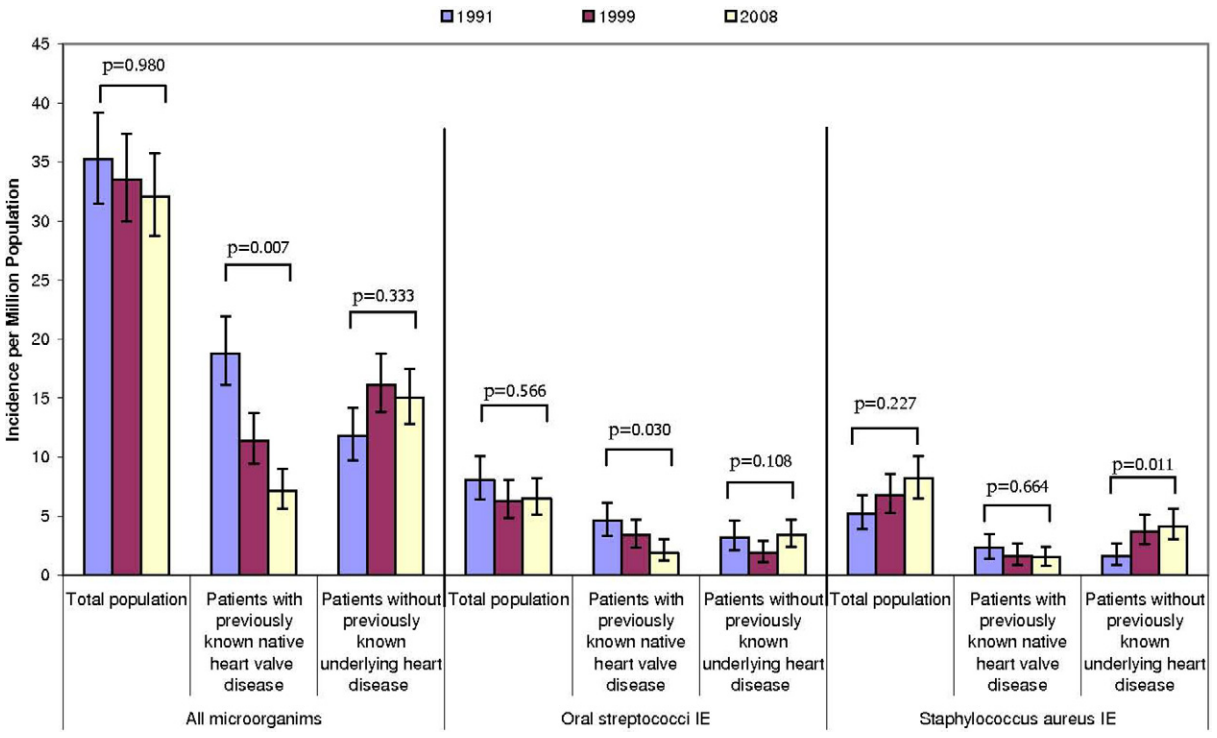

Figure 2 **Temporal Trends in IE Age- and Sex-Standardized Incidence for All Micro-Organisms and According to Underlying Heart Disease and Micro-organisms**

IE = infective endocarditis.

ology evolution after the recent drastic restrictions in IE prophylaxis indications.

Population-based surveys most accurately analyze IE characteristics because they avoid major referral bias (2,15). The rarity of this disease, concern about its diagnosis, and the diversity of physicians potentially involved make exhaustive data collection difficult. Studies describing temporal changes in IE characteristics necessitate either prolonged longitudinal follow-up of a predefined and usually small population pool or repeated temporal cross-sectional surveys providing an intensive, time-limited assessment of a larger population pool. We chose the latter approach to collect very large samples of IE cases (several hundred) among a population of 11 million (one fifth of the total French population) over three 1-year periods.

Increase in the incidence of staphylococci IE. This temporal comparison underlines the evolving nature of IE despite the stability of the incidence rate, with an aging population with increasing rates of comorbidities. On the contrary, the rate of patients with pre-existing native valve diseases has more than halved in 18 years (1 in 5 patients in 2008). This evolving nature of IE is also reflected by its microbiological profile. Whereas there are contradictory data on the evolution of micro-organisms responsible for IE, our study provides clear evidence of the increase of both *S. aureus* and coagulase-negative staphylococci IE rates and incidences. This increase may not be attributed to referral bias, to a modification of intravenous drug use prevalence (because its rate remained stable over time), or to an increase of *S. aureus* IE due to community-acquired methicillin-resistant clones (none were isolated in the 2008 survey). The increased incidence of staphylococci must be considered in the light of the increased number of patients with prosthetic valve IE, pacemaker IE, diabetes mellitus, all conditions associated with staphylococcal bacteremia. This is consistent with the significant increase in the rate of cerebral and peripheral emboli, identified as more frequent in patients with staphylococcal IE (33). When considering staphylococcal IE incidence change, the only statistically significant increase concerned staphylococcal IE cases occurring in patients with no previously known valvular diseases, a population not targeted by IE prophylaxis.

Stability of streptococcal IE. Streptococcal IE incidence did not increase between 1999 and 2008, despite IE antibiotic prophylaxis indications being discontinued for most patients since 2002 in France. These results are consistent with those of a recent study conducted in the United Kingdom that excluded any large increase in the incidence of IE in the 2 years after the U.K. National Institute for Health and Clinical Excellence guideline modifications, which were implemented by dentists and physicians (20). This compliance with the modified guidelines

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Table 2 Factors Associated With In-Hospital Mortality in Each of the 3 Surveys (1991, 1999, and 2008) and in the Pooled Survey Population

		In-Hospital Death		Bivariate Regression			Multivariate Regression	
Factor	N	n	%	Odds Ratio	95% CI	p Value	Odds Ratio	95% CI
Age (yr)								
1991	305	63	20.7	1.03	1.01–1.05	0.003	1.03	1.00–1.05
1999	331	51	15.4	1.03	1.01–1.06	<0.001	1.04	1.02–1.07
2008	339	72	21.2	1.04	1.02–1.06	<0.001	1.05	1.02–1.07
1991–1999–2008	975	186	19.1	1.03	1.02–1.04	<0.001	1.04	1.03–1.05
Prosthetic valve								
1991	69	23	33.3	2.45	1.34–4.49	0.004	2.56	1.13–5.84
1999	58	13	22.4	1.79	0.88–3.62	0.118		
2008	84	20	23.8	1.22	0.68–2.19	0.510		
1991–1999–2008	211	56	26.5	1.76	1.23–2.52	0.002		
Staphylococcaceae*								
1991	62	23	37.1	2.99	1.62–5.55	<0.001	3.11	1.38–7.00
1999	90	27	30.0	3.88	2.09–7.18	<0.001	5.29	2.73–10.26
2008	122	43	35.2	3.53	2.06–6.05	<0.001	3.95	2.23–7.00
1991–1999–2008	274	93	33.9	3.36	2.41–4.68	<0.001	4.15	2.84–6.06
Cerebral emboli								
1991	43	14	32.6	2.25	1.04–4.83	0.042		
1999	50	8	16.0	1.05	0.46–2.40	0.900		
2008	78	26	33.3	2.34	1.32–4.13	0.004	2.90	1.55–5.42
1991–1999–2008	171	48	28.1	1.95	1.32–2.87	0.001	2.00	1.31–3.03
Cardiac surgery								
1991	94	21	22.3	1.15	0.64–2.08	0.643		
1999	166	17	10.2	0.44	0.23–0.82	0.008		
2008	168	30	17.9	0.67	0.39–1.13	0.130		
1991–1999–2008	428	68	15.9	0.69	0.49–0.95	0.023		
Survey year †								
1991	305	63	20.7	1.00		0.104	1.00	
1999	331	51	15.4	0.70	0.47–1.05		0.56	0.34–0.92
2008	339	72	21.2	1.04	0.71–1.52		0.65	0.40–1.05

Four statistical models were built, 1 for each of the 3 surveys and the last one for the pooled population of 975 patients. The survey year variable was only included in the last model. Blank cells correspond to nonsignificant characteristics in the multivariate regression model. *Staphylococcaceae group includes *Staphylococcus aureus,* coagulase-negative staphylococci, and other staphylococcaceae. †Variables analyzed only in the model pooling the 3 surveys.

CI = confidence interval.

was depicted by a drastic decrease in the number of prescribed antibiotic prophylaxis assessed through National Health Service medication reimbursement data. However, their data on IE incidence originated from codified discharge diagnosis data, not from expert-validated diagnostic classification, which presents several limitations. Notably, this method permits the description of broad general tendencies but is unable to provide precise analysis of epidemiological evolution including microbial modification.

We observed this reassuring absence of increases in streptococci IE incidence both in the overall population of IE patients and in patients with previously known native valve heart disease (i.e., those for whom IE prophylaxis was no longer recommended after the 2002 French IE prophylaxis guidelines). In addition, similar findings resulted using different case definitions (modified von Reyn or Duke classifications). Our evaluation of incidence evolution is based on a highly accurate estimation of streptococcal IE incidence. First, each streptococcal strain identification was cross-validated by the national reference center for streptococci. Second, all IE cases were checked by a multidisciplinary adjudication committee leading to the exclusion of a high number of cases initially considered as potential IE by the primary care physicians. This process underlines both the difficulty of IE diagnosis and, in epidemiological surveillance, the need for critical and careful appraisal of data from inpatient charts, which represent nonexpert-validated IE cases (19). In addition, the 3 surveys were conducted by the same group of investigators, using similar methods and classifications, thus limiting the risks of definition biases. We cannot definitely claim that IE prophylaxis modification did not lead to an increase in the incidence of oral streptococcal IE; given the low number of streptococcal IE in patients with previously known heart disease, the limited number of cases collected would have allowed us to detect only a major increase in IE incidence in this group of patients. Furthermore, the stability of streptococcal IE incidence despite IE antibiotic prophylaxis reduction for bucco-dental procedures could reflect practitioners' lack of compliance with these new recommendations. However, in

a survey of French cardiologists in 2007, 80% reported awareness of the 2002 IE prophylaxis recommendations and 60% declared having modified their use of prophylaxis accordingly.

IE prognosis evolution. Despite the general improvement in patients' medical care, IE prognosis did not improve between 1991 and 2008. The in-hospital mortality rate remained as high as 20%. When analyzing prognostic factors in the total population of 975 patients, mortality tended to be lower in 2008 and 1999 compared with 1991 in multivariate analysis. When considering each year in 3 distinct analyses, age and staphylococcal IE were independently associated with mortality in 1991, 1999, and 2008.

Study limitations. We must acknowledge some limitations to our study. First, underreporting is a potential limitation when relying on physician report and not on investigators' active search for cases. In our study, underreporting was minimized through reliance on 3 separate notification sources (physicians, echocardiographers, and microbiologists). The rate of unreturned case report was low in each survey, between 1% and 2%. To lighten physicians' work load and encourage reporting, specially trained clinical research assistants were assigned to facilitate the reporting procedure. Furthermore, the proportion of patients living within one of the study regions and treated for IE outside these regions was <5%, based on the French national database file of diagnosis-related groups as classified at hospital discharge. Second, the IE classification in use at the time of each survey was different and based partially on different data. Because retrospective classifying 1991 and 1998 surveys using the modified Duke classification was impossible, we categorized all our cases using the modified von Reyn classification to permit temporal comparisons. Because the same classification was used for the 3 surveys, it limited the risk of a differential bias. Furthermore, to validate our result, we took into account both comparisons based on broad case definitions and those based on more restricted case definitions; comparison of the 1999 to 2008 temporal trends (surrounding the 2002 guidelines modification) using both modified von Reyn and Duke classifications revealed no discrepancies (Online Tables 3 and 4). Of note, there was no statistically significant difference in the incidences of IE in 2008 using the different classifications. Third, the comparison of IE incidence between the 1991 and 2008 time intervals may be biased by an improvement in IE diagnosis performance due to medical progress (improvement in echocardiographic or microbiological techniques increasing their sensitivity and the diagnosis of IE), which could artificially inflate reported IE incidence. The stability in IE incidence observed in our study over time should therefore be interpreted with caution. Finally, differences among countries in the incidence of IE, in the proportion of the micro-organisms responsible, and in the IE prophylaxis guidelines may influence the generalizability of the study results. However, we think that the results may reasonably be extrapolated to most industrialized countries.

Conclusions

IE co-evolved with socioeconomic changes and medical progress, leading to an increase of onset age, co-morbidities, intracardiac devices, and of staphylococcal IE. A high and stable in-hospital mortality rate was associated with age and staphylococci, two characteristics which rates have both increased over the last 2 decades. Given the poor prognosis of *S. aureus* IE and its increasing incidence, *S. aureus* bacteremia prevention is necessary in patients with previously known valve diseases but also in patients without such disease in whom IE incidence has increased most. So far, changes in IE antibiotic prophylaxis guidelines have not given rise to an increase in oral streptococci IE, which supports a posteriori the reduction of its use. This fact should prompt a decrease in the unnecessary consumption of antibiotics, a source of ever-increasing bacterial resistance.

Acknowledgements

The authors are indebted to Hélène Coyart, Annick Billoet, Nicole Tavares, and Gislène Collobert for excellent technical assistance, and Marie-Line Erpelding for her statistical analysis. The authors are fully indebted to the physicians and microbiologists who participated in this survey.

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Key Words: epidemiology ■ infective endocarditis ■ population-based ■ prophylaxis ■ staphylococci.

APPENDIX

For supplementary materials (including study group members, author contributions, tables, and figures), please see the online version of this article.