

1 **TITLE PAGE**

2 **Title:**

3 The causative agents in Infective Endocarditis: a systematic review comprising 33,214 cases

4 **Running head:**

5 Infective Endocarditis cause

6 **Corresponding Author:**

7 Leonidas Palaiodimos, MD MSc

8 1955 Williamsbridge Road, 10461 Bronx, NY, USA

9 Email: palaiodimos@sni.gr, tel. (+1) 9294285997

10 **Authors & Affiliations:**

11 Christiana T. Vogkou*^{1,2}, Nikolaos I. Vlachogiannis*^{1,2}, Leonidas Palaiodimos^{1,3}, Antonis A. Kousoulis^{1,4}

12 ¹ Society of Junior Doctors, Athens, Greece

13 ² School of Medicine, National and Kapodistrian University of Athens, Greece

14 ³ Department of Medicine, Jacobi Medical Center / Albert Einstein College of Medicine, Bronx, NY, USA

15 ⁴ Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, Lon-
16 don, UK

17 *These authors contributed equally to the manuscript

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ABSTRACT

Purpose: Infective Endocarditis (IE) incidence remains high with considerable fatality rates; guidelines for prophylaxis against IE are currently under review in some settings which highlights the importance of maintaining up-to-date epidemiological estimates about the most common microbial causes. The objective of this systematic review, following PRISMA guidelines, was to identify the most common microbial causes of IE in recent years.

Methods: Medline was searched from January 1, 2003 to March 31, 2013 for all articles containing the term “infective endocarditis”. All relevant studies reporting diagnostic results were included. Special patient sub-populations were assessed separately.

Results: 105 studies were included, from 36 countries, availing data on a total of 33,214 cases. *Staphylococcus aureus* was found to be the most common microorganism, being the most frequent in 54.3% of studies (N=57) (and in 55.4% of studies using Duke’s criteria for diagnosis (N=51)). Viridans group streptococci (VGS), coagulase-negative staphylococci (CoNS), *Enterococcus* spp and *Streptococcus bovis* were among the most common causes. *S. aureus* was the most common pathogen in almost all population subgroups, however, this was not the case in patients with implantable devices, prosthetic valves, or immunocompromised non-HIV, as well as in the sub-group from Asia, emphasizing that a global one-size-fits-all approach to the management of suspected IE is not appropriate.

Conclusions: This review provides an evidence-based map of the most common causative agents of IE, highlighting *S. aureus* as the leading cause in the 21st century. The changing epidemiology of IE in some patient sub-groups in the last decade and the very high number of microbiologically undiagnosed cases (26.6%) suggest the need to revisit IE prophylaxis and diagnostic strategies.

1. Introduction

Infective endocarditis (IE) remains one of the most serious conditions in medicine in the 21st century [1,2]. The introduction of antibiotics in its treatment has decreased the mortality rates of the disease, however these can reach up to 20% in hospital and can be even higher on 1-year follow up (up to 40%) [3]. Fatality rates of IE remain high and 2.7% of patients suffer an unexpected sudden death at 6 months during or after treatment [4]. After the near eradication of rheumatic fever in the western world, infective endocarditis accounts for the vast majority of cases of endocarditis with an incidence ranging between 1.7 and 11.2 cases per 100.000 people/year [5]. Overall, the male to female ratio is estimated at around 2 but outcomes tend to be worse in women [6].

Incidence of IE is higher in elderly patients (reaching 14.5 cases per 100.000 person/years) [7] as well as among specific sub-populations such as injectable drug user(s) (IDUs), [8] where clinical characteristics of the disease also differ from the general population. [8] Diabetes mellitus, invasive techniques, haemodialysis [6,10] and implantable cardiac devices [11] have caused a shift in the most commonly identified infective microorganisms in the past decades significantly increasing the prevalence of staphylococcal infections [12] which generally had shown higher mortality rates when compared to streptococcal infections.[6,10,13] As a result, many studies have emphasized the need to better understand the mechanism of infection in cardiac devices and reinforce preventive measures of health-care associated staphylococcal bacteraemia in an effort to decrease IE incidence. [11,13]

Limited understanding of the disease pathogenesis and progression is reflected upon different guidelines for prophylaxis among countries in recent years.[14] Identifying the most common microbial agents in IE is of particular current interest, following publication of new research at the American Heart Association meeting in Chicago in November 2014 showing increase in the incidence of infective endocarditis and the subsequent launch of a review of the guidance on Prophylaxis for Infective Endocarditis by the National Institute for Health and Care Excellence, in the UK (<http://www.nice.org.uk/news/press-and-media/nice-to-review-its-guidance-on-the-use-of-antibiotics-to-prevent-infective-endocarditis>). As far as treatment is con-

cerned, IE remains a therapeutic challenge to date primarily due to the changing epidemiology of the causative pathogens together with the lack of knowledge on the exact mechanism of the disease and the insufficiency of diagnostic and therapeutic methods.[1] Early surgical therapy is increasingly becoming more popular with studies showing superior outcomes when compared to conventional treatment.[15]

In this context, the objective of this study was to systematically review the literature to identify and prioritize the most common microbial factors causing IE in recent years and provide insight on special subpopulations. The rationale was that if more definitive conclusions on microbial associations could be drawn, these could inform prevention and treatment strategies. In this context, the study followed an inclusive approach to record study results predicting the most common microbial diagnosis for the patients presenting with IE.

2. Methods

2.1. Search strategy

This systematic review adopted the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[16] Eligible articles were identified by a systematic search of Pubmed bibliographical database for studies published from January 1, 2003 to March 31, 2013 by three investigators (CV, NV, LP) working independently. All articles derived from a search with the term “infective endocarditis” were assessed. In addition, all references of eligible articles retrieved by the search were scanned. Whenever full text was not available or additional data information was required, an e-mail was sent to the corresponding authors.

Study eligibility was based on the following inclusion criteria: (1) observational studies in patients with infective endocarditis and explicit mention of the pathogens related to the disease, (2) more than five patients with infective endocarditis reported in the article. Discrepancies were discussed until complete agreement was reached; an additional reviewer (AK) gave input where required to reach consensus. The selection process excluded: (1) reviews and secondary research, (2) case reports, (3) missing full text or key data, also excluding articles that only commented on a single pathogen, (4) overlapping populations, (5) irrelevant articles, ie articles not reporting on the etiologic agents of IE(6) articles published in languages other than

English. In the interest of not excluding clinically important case series, no formal quality assessment of eligible articles was undertaken.

2.2. Data extraction

The following variables were extracted and tabulated for each eligible study: first author's name, year of publication, study design, country of origin, study site, patients' age (mean, standard deviation, median, and age range or InterQuartile Range if available), reported use of Duke's diagnostic criteria, number of cases, number of unidentified microbes, numbers of cases reported per microbe, as well as special patient subpopulations. Due to the anticipated high heterogeneity of the included studies and the inclusive character of the search strategy, the five most frequent microbes associated with each study were recorded (with polymicrobial and unspecified cases included when being numerically among the five main causes) and sensitivity analyses were performed. A purely descriptive approach was adopted (i.e. data expressed as non-weighted means whenever possible) concerning continuous variables. Microbial causes results and all descriptive variables were treated in numerical values of totals or means. No further statistical analysis was undertaken.

The species was recorded where available, otherwise the genus was used.

3. Results

3.1. Eligible articles

The initial search of the Pubmed database yielded 3,397 potentially relevant articles, 2,313 of which were excluded as irrelevant and 477 as not written in English. For the remaining 607 articles, the full-text was studied. Further exclusion reasons comprised 345 case reports, and 107 secondary research papers. Fourteen were excluded on account of overlapping populations (by majority relating to the International Collaboration on Endocarditis Prospective Cohort Study), results from 23 studies could not be included because they only described one pathogen, while for 13 studies, though requested through repeat correspondence, data could not be retrieved, in part, because there was no response from the corresponding authors. Four authors provided additional data on their studies [17–20].

Eventually, 105 studies were included in this review (Figure 1) availing data for a total of **33,214 cases** of infective endocarditis. Although the mean age of patients was not available in all studies, virtually all age groups were represented, with age ranging from 6 days to 100 years. However, paediatric patients were un-

129 der-represented compared to adults. Ninety-two studies (87.6%) used the Duke's criteria or modified Duke's
130 criteria for case selection.

131 As shown in Table 1, the majority of included studies (92.4%, N=97) used a cohort design (prospective: 30 /
132 retrospective: 67), and only 5 were cross-sectional (4.8%) and 3 case-control (2.9%).

133 3.2. Most common microorganisms

134 Overall *Staphylococcus aureus* was found to be the most common microorganism causing infective endo-
135 carditis being isolated as one of the five most common microorganisms in 99 out of 105 studies (94.3%),
136 and being the most frequent in more than half of the studies (N=57, 54.3%), and second in a further third of
137 the studies (N=32, 30.5%). 35 of the above-mentioned 99 studies report data regarding MRSA strains;
138 MRSA was isolated in the 4.5% to 51.1% of *S. aureus* infective endocarditis cases, while the median per-
139 centage was 28.1 Viridans group streptococci (VGS) were the second most commonly reported microorgan-
140 isms, being the primary cause in over a fifth (21.9%) of all studies (N=23), and second in 24 studies (22.9%)
141 or third in 10. Coagulase-negative staphylococci (CoNS) were the most common not otherwise specified
142 group recorded, isolated as the most frequent cause in 8.6% of studies (N=9), and reported as one of the five
143 most common in 73.3% (N=77) of studies. *Enterococcus* spp was only rarely the most common microbe re-
144 ported (N=3), but it appeared consistently among the 5 most frequent in the majority of all studies (78.1%,
145 N=82). Cases of *Streptococcus bovis* were also frequently reported, being the most common cause in 3 stud-
146 ies. The top decile of our studies (N=11) comprised 18,065 cases. Of these studies, when using Duke's crite-
147 ria, all but one had *S. aureus* as the most commonly diagnosed microbe. Only Day et al included a special
148 sub-group: pediatric patients. This study contributes 61.6% of the sample of this sub-group, substantially
149 shifting the most common result towards *S. aureus*, as 4/7 studies report other microbes as most common.
150 However, absolute sum of the results still points towards *S. aureus*, accounting for 45.4% of all cases.

151 Table 2 summarises the most common pathogens per population category.

153 3.3. Special populations

154 Congenital heart defects: Five cohort studies (2 from Asia, 3 from Europe) examined 672 patients with con-
155 genital heart defects. *S. aureus* and VGS were almost equally identified among the most common pathogens

156 in all five studies. Alpha hemolytic streptococci [21] and *S. bovis* [22] were also reported. All patients were
157 included irrespective of the type of their congenital heart disease and whether they had undergone surgical
158 correction or not. Patients were not stratified by age and effect of surgery

159 Prosthetic valve: Three cohort studies reported exclusively 994 patients with prosthetic valve endocarditis.
160 CoNS were the most commonly isolated microorganisms being the primary cause in one study and among
161 the three most common microorganisms in the other two studies. *S. aureus* was the primary cause in one
162 study and among the four most common pathogens in the other two studies. VGS were the main pathogen in
163 the study authored by Lalani et al [23] *Enterococcus* spp. was the 3rd most common microorganism in two
164 out of three studies. Finally, *Propionibacterium acnes* appeared as the second most common causative agent
165 in one study but not among the 5 most common microorganisms in the other two studies [24].

166 Paediatric patients: Seven retrospective cohort studies (3 from N. America, 3 from Asia and 1 from Oceania)
167 referred to 1,026 paediatric patients, their age ranging from 3 days to 20 years. *S. aureus* was again found to
168 be the most commonly isolated microorganism responsible for the disease (1st in 3 studies and 2nd in 4), fol-
169 lowed by VGS (1st in 3 studies and 2nd in 2). CoNS ranked as the 3rd most common pathogen in 5 out of 7
170 studies. Two studies found *Candida albicans* to be the 2nd and 3rd most common pathogen respective-
171 ly,[25,26] while cases of *Enterococcus* spp were also reported.

172 Injectable drug user(s) (IDUs): Four retrospective cohort studies (N. America: 2, Asia: 1, Europe: 1) com-
173 prising a total of 580 cases examined the characteristics of IE among populations of IDUs. As expected, *S.*
174 *aureus* was by far the most commonly isolated microorganism (1st in 4 out of 5 studies). Three studies report
175 MRSA strains, which were isolated in 11.4%, 45.2%, and 46.4% of *S. aureus* infective endocarditis cases,
176 respectively VGS followed (2nd in 2 studies and 3rd in 1 more study) and CoNS completed the triad of the
177 most commonly isolated microorganisms (3rd in 2 studies). *Enterococcus* spp (4th in 2 studies) and *C. albi-*
178 *cans* (2nd and 5th in 2 studies respectively) were also reported.

179 Implantable heart devices: Six cohort studies examined 505 cases in patients with implantable heart devices.
180 *S. aureus* and CoNS were isolated with equal frequency as the primary causative agents of the disease and
181 were consistently found in the top 5 microorganisms causing IE in this special population. *Enterococcus* spp

and Gram-negative bacteria, though not usually found among the 3 most common pathogens, comprised a big number of cases accounting as the 4th or 5th most common microbial agent isolated.

Fungal Endocarditis: Sixteen studies (2,145 cases), fifteen cohort and one cross-sectional, reported fungi as one of the five most frequent microbes causing infective endocarditis. These studies came primarily from Europe (N=9) and Asia (N=5), with 1 additional in USA and 1 in Latin America. Fungi were reported as the third cause in one study, fourth in 2 studies and fifth in 2 studies. *Candida* species are reported in two studies as the fourth most common cause of endocarditis. *C. albicans* was the most frequently isolated fungus, as it is found in 6% of studies (N=7), thrice as the second cause, twice as the third and once as the fourth and fifth cause. Finally, *Aspergillus fumigatus* and *Candida parapsilosis* were isolated in only one study.

Using Duke's criteria: A sensitivity analysis was performed among the 92 studies reporting use of the Duke's criteria for diagnosis of IE and accounting for 22,081 cases of IE. The five most common pathogens were, in order of decreasing frequency, *S.aureus*, VGS, CoNS, *Enterococcus* spp and *Streptococcus* spp. *S.aureus* was found in a total of 5,546 cases and was the most common pathogen in 51 of these studies and second in 29. VGS were the second most common cause, found in a total of 2,694 cases, and it was the first cause in 24 studies and second in 22. CoNS followed, accounting for 1,765 cases of IE in total, being first in 5 studies and second in 9. *Enterococcus* spp was the fourth most common cause, isolated in 1,543 cases, and being the second common pathogen in 4 studies. Finally, *Streptococcus* spp was the fifth leading cause of IE, isolated in 1,145 patients in total, being the most common cause in 7 studies and second in 6.

3.4. Results per continent

Forty-nine studies (46.7%, N=12,752 patients) originate from European countries, 29 from Asia (27.6%, N=12,105), 14 from North America (13.3%, N=1,918), 4 from Africa (3.8%, N=602). 4 from Oceania (3.8%, N=1,681 patients), 2 from South America (1.9%, N=452), and three were multi-continent (2.9%, N=3,704 patients). Table 3 summarizes the main microbial causes per continent.

4. Discussion

4.1. General population

As presented above, our study concluded that the five most common pathogens causing infective endocarditis in the 21st century are by order of frequency: *S. aureus*, viridans group streptococci (VGS), coagulase-

209 negative staphylococci (CoNS), *Enterococcus* spp and, *S. bovis*. *S. aureus* was the most common microor-
210 ganism in over half of the studies included in our research.

211 Our results highlight the change in the epidemiology of the causative agents of IE throughout time, as they
212 contrast studies from the 1990s reporting streptococcal infections outnumbering staphylococcal [27,28], but
213 are consistent with more recently published literature: Slipczuk et al report a significant increase in *S. aureus*
214 IE which may associate with increasing numbers of IDUs in North America.[29] Also, in a review pub-
215 lished in 2006 streptococci and staphylococci were found to account for the vast majority of infective endo-
216 carditis cases.[30] Enterococci have been found to be the third leading cause of IE in other studies as well.
217 [13,31] On the other hand, quite surprisingly, a recent study carried out across 11 years in France identified
218 *S. bovis* to be responsible for 149 of 847 cases (17.6%) [4]. These changes in the pattern of the pathogens of
219 IE can be attributed to several factors, such as modern cardiology invasive techniques, non-nosocomial
220 health care acquisition, the growing importance of the central line associated blood stream infections
221 (CLABSIs), the percentage of colonization by MRSA in cardiac surgery patients, the aging population and
222 the rise of enterococci and *S. bovis*. Of note, frequency of identified microbes was not identified in the same
223 pattern in Asia, strongly emphasizing that a global one-size-fits-all approach to the management of IE pa-
224 tients is not appropriate.

225 4.2. Special groups

226 This is the first study that has systematically assessed the cause of IE in several special patient groups of im-
227 portance. Our study found that those with congenital heart defects did not differ significantly compared to
228 the general IE population as far as causative microorganisms are concerned. *S. aureus* and VGS were the
229 most commonly isolated microorganisms. Of interest, patients with bicuspid aortic valve were more prone to
230 perivalvular abscess formation particularly when *S. aureus* was the causative microorganism of IE [22] and
231 surgical intervention was required in a big number of cases- ranging between 26-72% - to treat infective en-
232 docarditis.[21,22,32,33] Taking into consideration that oral hygiene and dental prophylaxis seem to be of
233 vital importance among these patients[32,34] and that incidence of IE after reparative surgery has been in-
234 creasing [34] revision of the current guidelines regarding patients with CHD is crucial. Similarly, among

235 paediatric patients *S. aureus* was the most common pathogen, followed by VGS, CoNS, *C. albicans* and *En-*
236 *terococcus* spp. This is in accordance with a recent study which reported increasing frequencies of *S. aureus*,
237 CoNS and fungal IE among children. [35] A large proportion of the affected children had underlying heart
238 disease as described in all the included studies. Of interest, Marom et al. noted that children with no predis-
239 posing factors exhibited a more aggressive form of the disease with *S. aureus* and *S. pneumoniae* being sig-
240 nificantly more frequent among these patients.[25] On the other hand, patients with prosthetic valves were
241 found positive for CoNS in the majority of cases, while *S. aureus* appeared second and VGS third. Of inter-
242 est, CoNS infection conferred increased risk for perivalvular abscess development and heart failure com-
243 pared to *S.aureus* and VGS IE. [23] Also, proportion of patients with early death was higher among patients
244 with CoNS IE.[24] Thus, prompt attention should be given to antimicrobial prophylaxis against CoNS in
245 patients with prosthetic valves. Our study identified that *S. aureus* was the most commonly reported cause
246 of IE in IDUs and patients with implantable heart devices. Cases of CoNS and fungal endocarditis need to
247 be explored in these patients. The extensive use of invasive methods and implantable devices in the past
248 decades has changed the spectrum of microorganisms that tend to colonise the heart valves causing infective
249 endocarditis. Cabell et al described a 42% increase in the use of implantable heart devices between 1990 and
250 1999, especially depicting the increased frequency of the use of permanent pacemaker, and leading to a
251 124% increase in device infections and 50% increase in infective endocarditis prevalence.[11] Thanavaro et
252 al suggested that the increased mortality and morbidity due to implantable cardiac devices infection can be
253 partly attributed to the increased age of the patients and comorbidities [36]. Taking this evidence into ac-
254 count, revisions in guidelines regarding chemoprophylaxis after such procedures could be explored.

255 4.3. Limitations and strengths

256 Though inclusive, significant heterogeneity and a number of poorly designed studies among the included is
257 the primary limitation of this review [37]. For example, a large cohort study from Thailand that reported
258 non-fermentative Gram-negative rods as the leading cause is subject to various limitations, such as lack of
259 use of the modified Duke's criteria for patient selection and failure to identify a causative agent in 86.59%
260 of cases.[38] Also, the included studies used different ways to record the pathogens; some agents are reported by
261 genera, others by subgenera and others by species making presentation of data inconsistent in terms of nomen-

clature. Notably, evidence of MRSA infection was only recorded in 35 out of 99 studies in which *S. aureus* was identified as 1 of the 5 most common microorganisms, and evidence of vancomycin-resistant *S. epidermidis* (VRSE) only in 1 study implicating enterococcal infections. A large number of studies routinely did not specify the species of fungi or Gram-negative microorganisms. Another possible limitation of this study is that the world population is represented disproportionately with the cases included in this review, as cases from Europe and Asia represent a 74.28% of the total cases displayed. Also, excluding case reports and case series may lead to negative reporting bias for emerging pathogens and excluding non English literature may lead to selection bias.

Finally, in one in four of our included cases (8,835/33,214, 26.6%) the causative agent was not identified. The above most likely reflect resource limited settings (or in a few cases poor laboratory techniques) and highlight the importance of the use of newer techniques, such as PCR, which may lead to increase in the detection of the etiologic agents of infective endocarditis.

The review benefits from its strict methodology and the large number of studies and cases analysed. Sensitivity analyses were performed throughout. Notably, all five continents and various special subgroups are represented.

5. Conclusion

The current review is the largest epidemiological study regarding causative agents in IE including a collective cohort of 33,214 infective endocarditis cases. The results document the rapidly changing profile of IE etiology, especially among special sub-groups of patients, as well as the predominance of *S. aureus* as the leading cause for infective endocarditis in the 21st century. However, the most common agent differed among several special groups of patients (most notably implantable heart devices) as well as patients from Asia, showing the need to tailor patient prophylaxis and treatment. Also, our study showed that in an important percentage of IE cases the responsible agent remained unidentified, even in high-level reference laboratories; this stresses how newest techniques have the capacity to change the profile of IE diagnosis and prevention. The results further emphasize the need to revisit IE prophylaxis and management strategies, as well as improving the reporting of the causative agents in future studies..

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Table 2
Most common microbes in special populations

Special populations [cases]	Most common microbes
HIV [N=91]	<i>S. aureus</i> / <i>E. faecalis</i> / CoNS / VGS / <i>Pseudomonas</i> spp
Cardiac resynchronization therapy device [N=505]	<i>S. aureus</i> CoNS (equal rates) / <i>S. pneumoniae</i> / <i>E. faecalis</i>
Dialysis [N=233]	<i>S. aureus</i> / CoNS / <i>E. faecalis</i> / VGS / <i>P. aeruginosa</i>
Paediatric [N=1026]	<i>S. aureus</i> / VGS / CoNS / <i>Enterococcus</i> spp / <i>S. pneumoniae</i>
ICU [N=228]	<i>S. aureus</i> / Oral streptococci / Other Group D streptococci / <i>Enterococcus</i> spp / Gram (-) bacteria
Transplantation [N=27]	<i>Staphylococcus</i> spp / Polymicrobial / Fungi
Congenital heart defect [N=672]	VGS / <i>S. aureus</i> / CoNS / <i>S. bovis</i> / <i>Enterococcus</i> spp
Prosthetic valve [N=994]	CoNS / <i>S. aureus</i> / VGS / <i>Enterococcus</i> spp / <i>S. bovis</i>
Injectable drug user(s) (IDUs) [N=580]	<i>S. aureus</i> / VGS / CoNS / <i>Enterococcus</i> spp / <i>C. albicans</i>
Cross infection (healthcare associated) [N=495]	<i>S. aureus</i> / <i>E. faecalis</i> / VGS / <i>S. epidermidis</i> / <i>S. bovis</i>
Diabetic [N=309]	<i>S. aureus</i> / Other Group D streptococci / Oral streptococci / CoNS / <i>Enterococcus</i> spp
Critically ill [N=198]	<i>S. aureus</i> / <i>Streptococcus</i> spp / <i>Enterococcus</i> spp / CoNS / <i>Enterobacter</i> spp
Epidural abscess [N=6]	<i>S. aureus</i> / CoNS / <i>E. faecalis</i>
Immunocompromised (non HIV) [N=56]	<i>E. faecalis</i> / <i>S. aureus</i> / <i>Streptococcus</i> spp / <i>E. coli</i> / <i>K. ozaenae</i>

CoNS: coagulase-negative staphylococci

Table 3

Most common microbes per continent

Continent [cases]	Most common microbes
Europe [N=12,752]	<i>S. aureus</i> / VGS/ CoNS / <i>Enterococcus</i> spp / <i>S. bovis</i>
Asia [N=12,105]	VGS / <i>Streptococcus</i> spp / <i>S. aureus</i> / <i>Staphylococcus</i> spp
North America [N=1,918]	<i>S. aureus</i> / VGS/ CoNS / <i>Streptococcus</i> spp / <i>Enterococcus</i> spp
Oceania [N=1,681]	<i>S. aureus</i> / <i>Streptococcus</i> spp / <i>Enterococcus</i> spp / CoNS
Africa [N=602]	<i>S. aureus</i> / Oral streptococci / CoNS / <i>Streptococcus</i> spp
South America [N=452]	<i>S. aureus</i> / <i>Enterococcus</i> spp / CoNS / HACEK
Multi-continent [N=3,704]	<i>S. aureus</i> / VGS/ CoNS / <i>Enterococcus</i> spp / <i>S. bovis</i>

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Compliance with ethical standards

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Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

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