Pediatric infective endocarditis: Has *Staphylococcus aureus* overtaken viridans group streptococci as the predominant etiological agent?

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BACKGROUND: Viridans group streptococci (VGS) have traditionally been the most common etiological agents of infective endocarditis (IE). Advances in cardiovascular surgery and the increasing use of long-term central venous catheters may have altered the epidemiology of pediatric IE.

METHODS: A chart review of children younger than 17 years of age with IE was completed at the Stollery Children's Hospital (Edmonton, Alberta) between 1985 and 2004. The literature was reviewed to look for changes over time in the most common etiological agents of pediatric IE.

RESULTS: There were 31 cases of definite IE and nine cases of possible IE at the Stollery Children's Hospital, 19 of which were nosocomial. Thirty cases (75%) had congenital heart disease. The etiological agents were *Staphylocccus aureus* (n=16), VGS (n=5), coagulase-negative staphylococci (n=3), enterococcus (n=3), other streptococci (n=8), *Enterobacter cloacae* (n=1) and *Stenotrophomonas maltophilia* (n=1), while three cases were culture negative. Two deaths were due to *S aureus* IE. Review of the literature identified an increasing number of case series in which *S aureus* was the predominant etiological agent, but VGS still predominated in some recent series.

CONCLUSION: Congenital heart disease remains the primary risk factor for pediatric IE. Prospective population-based studies are required to determine whether *S aureus* has become the predominant pathogen.

Key Words: *Cardiac; Endocarditis;* Staphylocccus aureus*; Viridans group streptococci*

Endocardite infectieuse pédiatrique : *Staphylococcus aureus* supplante-t-il les streptocoques du groupe *Viridans* comme agent étiologique prédominant?

HISTORIQUE : Les streptocoques du groupe *Viridans* (SGV) ont longtemps été les agents étiologiques les plus souvent impliqués dans l'endocardite infectieuse (EI). Mais les progrès de la chirurgie cardiovasculaire et l'emploi croissant des cathéters veineux centraux à demeure pourraient avoir modifié l'épidémiologie de l'EI pédiatrique.

MÉTHODE : Une analyse des dossiers d'enfants de moins de 17 ans atteints d'EI a été effectuée au Stollery Children's Hospital (Edmonton, Alberta) entre 1985 et 2004. Une revue de la littérature a permis de retracer les changements quant aux agents étiologiques les plus couramment rencontrés dans l'EI pédiatrique au fil des ans.

RÉSULTATS : Trente-et-un cas d'EI avérée et neuf cas d'EI possible ont été dénombrés au Stollery Children's Hospital; 19 étaient d'origine nosocomiale. Trente cas (61 %) souffraient de maladie cardiaque congénitale. Les agents étiologiques étaient *Staphylococcus aureus* (n = 16), les SGV (n = 5), le staphylocoque coagulase-négatif (n = 3), les entérocoques (n = 3), d'autres streptocoques (n = 8), *Enterobacter cloacæ* (n = 1) et *Stenotrophomonas maltophilia* (n = 1), tandis que trois cas ont obtenu des résultats de culture négatifs. Deux décès ont été attribuables à une EI à *S. aureus*. La revue de la littérature a permis de relever un nombre croissant de séries de cas dans lesquels *S. aureus* était l'agent étiologique prédominant, mais le GSV restait prépondérant dans certaines séries récentes.

CONCLUSION : La maladie cardiaque congénitale reste le principal facteur de risque d'EI pédiatrique. Il faudra réaliser des études de population prospectives pour déterminer si *S. aureus* est devenu l'agent pathogène prédominant.

Infective endocarditis (IE) occurs predominantly in children with congenital heart disease (CHD), with viridans group streptococci (VGS) traditionally being the most frequent causative pathogen (1). With advances in cardiovascular surgery and improved intensive care management, children are surviving cardiac surgeries that would not have been attempted in the past. However, these surgeries often constitute incomplete repairs. This, combined with the increased use of long-term central venous catheters (CVCs) in children with and without CHD, creates a new patient population at long-term risk for IE. The objective of the present study was to determine whether this change in host factors had altered the etiological agents of pediatric IE.

METHODS

The present study was approved by the Health Research Ethics Board of the University of Alberta, Edmonton, Alberta. A retrospective chart review was completed of children younger than 17 years of age who were admitted to the Stollery Children's Hospital (a major centre for pediatric cardiac surgery in Edmonton, Alberta, with over 200 open cases per year) between January 1, 1985 and February 29, 2004, with one or

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TABLE 1
Organisms isolated from blood cultures or heart tissues in 40 children with infective endocarditis

Isolate	n (%)
Staphylococci	
Staphylococcus aureus	16 (40)
Coagulase-negative staphylococci	3 (7.5)
Streptococci	
Viridans	5 (12.5)
Enterococci	3 (7.5)
Pneumococci	3 (7.5)
Beta-hemolytic (group A [n=2]; group B [n=1])	3 (7.5)
Other streptococci*	2 (5)
Gram-negative organisms	
Enterobacter cloacae	1 (2.5)
Stenotrophomonas maltophilia	1 (2.5)
Other	
Culture negative	3 (7.5)

*Aerococcus *(n=1),* Abiotrophia *(n=1)*

more of the following *International Classification of Disease – Ninth Revision* clinical modification codes: 036.42, meningococcal endocarditis; 083.0, Q fever; 098.84, gonococcal endocarditis; 112.81, candidal endocarditis; 115.94, histoplasmosis endocarditis; 421.0, acute and subacute bacterial endocarditis; 421.1, acute and subacute infective endocarditis in disease classified elsewhere; or 421.9, acute endocarditis, unspecified.

Cases were included in the study if:

- They had a diagnosis of definite IE according to the modified Duke criteria or
- They had possible IE defined as:
  - CHD, fever, and two or more blood cultures positive for VGS,
  - CHD and two or more blood cultures positive for coagulase-negative staphylococci that did not resolve within 24 h of removal of CVCs,
  - No CHD, fever, two or more blood cultures positive for coagulase-negative staphylococci that did not resolve within 24 h of removal of CVCs, and either immunological or vascular phenomena, or
  - CHD, two or more blood cultures positive for any organism, in which removal of all intravascular catheters did not result in resolution of the bacteremia and a noncardiac source of bacteremia was not identified.

Children were excluded if they fit the case definition of IE, but were apparently cured with less than seven days of antibiotics or ultimately had a more convincing alternate diagnosis. Nosocomial IE was defined as the onset of symptoms of IE in a hospitalized patient more than 48 h after admission.

Data were collected on underlying medical conditions including CHD, recent surgery or cardiac catheterization, and blood culture results. The presence or absence of a CVC was recorded in children without CHD who developed IE. Cases of IE in children younger than six months of age were analyzed separately to determine whether the etiological agents varied in this age group. Data were collected on the presence and duration of a fever (temperature higher than 38.2°C) or the presence of a secondary fever (defined as recurrence of fever after being afebrile for more than 48 h) and the suspected reason for the fever. The need for surgery to treat IE, the duration and route of antibiotic administration and survival to hospital discharge were recorded. More detailed outcome data could not be collected because many patients were discharged to distant hospitals.

MEDLINE, EMBASE and evidence-based medicine reviews (including Cochrane Database of Systematic Reviews, ACP Journal Club, Database of Abstracts of Reviews of Effects, and Cochrane Central Register of Controlled Trials) were searched from 1966 to 2003 inclusive for case series of pediatric IE with no language restriction. Studies were excluded if they contained incomplete data on pathogens, included only patients with specific pathogens or only patients requiring surgery for IE. Underlying cardiac conditions, causative agents, surgical rates and mortality related to IE were recorded from each study. Because many of the studies spanned more than 10 years, it was not possible to statistically compare the causative agents by the year of occurrence of IE.

RESULTS

Demographics

The *International Classification of Disease – Ninth Revision* codes at the Stollery Children's Hospital identified 75 patients, 40 of whom fit the inclusion criteria (23 boys and 17 girls ranging from two weeks to 16 years of age, with a median age of two years). There were 31 cases of definite IE (10 based on pathological criteria and 21 on clinical criteria) and nine cases of possible IE.

Predisposing cardiac conditions

Twenty-eight of 40 IE patients (70%) had previously diagnosed CHD (ventricular septal defect [VSD], n=3; VSD with other defects, n=17; coarctation of the aorta, n=2; bicuspid aortic valve, n=2; pulmonary stenosis, n=2; transposition of the great arteries, n=1 and mitral valve prolapse [MVP], n=1), two (5%) had previously undiagnosed CHD (MVP and VSD) and 10 (25%) had a normal heart. Of the 10 cases with a normal heart, four had no IE risk factors and the other six had a severe burn, an infected cystic hygroma with a CVC, Crohn's disease with a CVC, cerebral palsy with recurrent pneumococcal bacteremia, excoriated skin from infected eczema and necrotizing enterocolitis. None of the patients had a history of intravenous drug use. Previous cardiac surgery had been performed in 21 of 30 children with CHD (70%), with 16 of these 21 children having surgery within six months before the onset of IE. The cardiac lesions in the eight children with known CHD but no previous cardiac surgery included VSD (n=4), MVP and mitral regurgitation (n=1), pulmonary stenosis (n=1), bicuspid aortic valve and aortic stenosis (n=1), and Tetralogy of Fallot (n=1).

Etiological agents

Blood cultures were positive for the suspected etiological agent in 37 of 40 cases (93%) of IE (Table 1), with 16 (40%) due to methicillin-sensitive *Staphylococcus aureus* and none due to methicillin-resistant *S aureus*. There were three cases of culture-negative IE. The etiological agents in the 10 children with normal

TABLE 2
Features of children with *Staphylococcus aureus* infective endocarditis (IE) compared with those with other etiological agents. All P values are not significant at the 0.05 level

	S aureus (n=16)	Other organisms (n=24)
<6 months of age, n (%)	5 (31)	6 (25)
Male, n (%)	10 (63)	13 (54)
Nosocomial, n (%)	10 (63)	9 (38)
CHD, n (%)	13 (81)	17 (71)
Surgery required before IE, n (%)	3 (19)	8 (33)
Median duration of fever before IE (25th percentile, 75th percentile)	4.0 (1, 7)	4.0 (1, 7)

CHD Congenital heart disease

TABLE 3
Incidence of infective endocarditis by five-year blocks

Years	Total cases (n)	Cases due to *Staphylococcus aureus* n (%)
1985–1989	2	2 (100)
1990–1994	9	3 (33)
1995–1999	11	3 (27)
2000–2004*	18	8 (44)

**Data collected only up until February 29, 2004*

hearts were *S aureus* (n=3), enterococcus (n=1), VGS (n=1), *Abiotrophia* (n=1), pneumococcus (n=1), group A streptococcus (n=1) and *Enterobacter cloacae* (n=1). The features of children with *S aureus* IE are compared with those with other etiological agents in Table 2, with there being a trend toward an increased incidence of nosocomial infections in those with *S aureus* IE. Over the 19 years of the study, there was an increase in the number of cases of IE but no significant change in the incidence of *S aureus* IE (Table 3).

Eleven cases of IE occurred in children younger than six months of age (10 of whom had CHD), with the etiological agents being *S aureus* (n=4), enterococcus (n=3), coagulase-negative staphylococci (n=2), *Streptococcus agalactiae* (n=1) and *Stenotrophomonas* (n=1). All were nosocomial. The only statistically significant difference from older children was that the incidence of enterococcal IE was higher (P=0.017).

Nosocomial infection

Seventeen of 28 cases (61%) in children with known CHD were nosocomial (*S aureus* [n=10], coagulase-negative staphylococci [n=3], enterococcus [n=2], *Stenotrophomonas* [n=1], and culture negative [n=1]), with IE occurring a median of eight days (range zero to 72 days) following cardiac surgery or cardiac catheterization – eight cases occurring within eight days of cardiac surgery, seven cases occurring 14 to 73 days after cardiac surgery, and two cases (both with *S aureus*) occurring within four days after diagnostic cardiac catheterization.

Hospital course and outcome

Fever occurred in 37 of 40 patients for a median of four days before diagnosis and for a median of one day after appropriate antibiotics were started (range zero to 21 days). Among the 12 patients who had fever daily for five or more days after appropriate antibiotics were started, eight had complicated courses (seven had possible emboli and one had an aortic ring abscess). Their etiological agents were *S aureus* (n=4), VGS (n=1), pneumococcus (n=1), *E cloacae* (n=1) and culture negative (n=1). Secondary fever occurred in seven cases and was never attributed to IE.

Surgery for IE was performed in 11 cases (27.5%) (four valve replacement, one VSD homograft replacement, four valve repair and two vegetation removal), a median of 17 days (range three days to nine months) following diagnosis of IE. The etiological agent was *S aureus* in three of these 11 cases. Death occurred in two patients with *S aureus* IE (a two-month-old girl who developed IE following cardiac catheterization and a nineyear-old boy who had a mitral valve vegetation diagnosed eight days following cardiac surgery and died of intracranial hemorrhage five days later).

All survivors received a minimum of four weeks intravenous antibiotics (range 28 to 90 days), with the longest course being in a child with infected prosthetic material that could not be removed. Antibiotics were administered via a peripheral intravascular catheter only (n=2) or primarily by a conventional CVC (n=24), a peripherally inserted CVC (n=11) or both kinds of CVC (n=3). There were no recurrences of IE, although a patient with *S agalactiae* (group B streptococcus) IE received 14 days of intravenous antibiotics for group B streptococcus bacteremia 44 days before the diagnosis of IE. Oral antibiotics were not used for therapy of IE, except for long-term suppression in the child with the infected prosthetic material with long-term follow-up not being available. Six of the 40 patients were in the intensive care unit at the time of diagnosis for a median intensive care unit stay of 16 days (range three to 27 days) after diagnosis of IE.

Literature review

The 17 previous case series (2-18) of pediatric IE that fit the study criteria are shown in Table 4, along with the current study for a total of 18 studies. Looking for trends in etiological agents is confounded by the fact that many of the studies spanned decades, and some included only infants (8). However, of the seven studies ending in the 1970s and/or 1980s, all showed VGS to be the most common pathogen. Of the studies ending in the 1990s, VGS predominated in four and *S aureus* in three, while of the studies ending in the 2000s, VGS and *S aureus* predominated in two each.

DISCUSSION

IE remains a relatively rare pediatric disease with approximately two cases identified per year at Stollery Children's Hospital. The majority of children with IE had CHD, which is consistent with previous reviews of CHD where at least 50% of children with IE had CHD. The one exception is a study (2) from Pakistan in which rheumatic heart disease predominated (Table 4). The number of cases of IE increased in the last five years of the present study, and the median age of the patients was only two years. Because this is a cardiac referral centre, the majority of cases were nosocomial; the bulk of complete repairs are now performed at the youngest possible age. An older median age might be expected for IE in the general pediatric population.

The predominance of *S aureus* in the current case series and in several newer case series (12,13,15,17) suggests that

TABLE 4
Episodes of pediatric infective endocarditis in published case series listed in order of year the study ended

Reference	3	4	5	6	7	8	9	10	11	12	13
Years of study	1933–1972	1970–1979	1971–1980	1965–1984	1977–1985	1987*	1950–1989	1979–1990	1958–1992	1977–1992	1988–1992
Number of children	149	26	64	35	23	44	25	48	76	62	16†
CHD with no previous surgery, n (%)	NR‡	8 (31)	49 (77)	1 (28)	NR§	18 (41)	NR¶	24 (50)	14 (19)	18 (29)	5 (31)
CHD with previous surgery, n (%)	NR‡	14 (54)	14 (22)	7 (20)	NR§	26 (59)	NR¶	24 (50)	48 (66)	22 (35)	4 (25)
RHD, n (%)	14 (9)	1 (4)	1 (2)	0 (0)	1 (4)	0 (0)	0 (0)	0 (0)	4 (5)	3 (5)	0 (0)
Normal heart, n (%)	17 (11)	3 (11)	0 (0)	0 (0)	2 (9)	0 (0)	3 (12)	0 (0)	7 (10)	19 (31)	7 (44)
Staphylococcus aureus, n (%)	41 (27)	3 (11)	12 (19)	6 (17)	8 (35)	14 (32)	2 (18)	13 (27)	24 (31)	24 (39)	7 (29)
VGS, n (%)	64 (45)	13 (50)	23 (36)	16 (46)	9 (39)	17 (39)	9 (40)	14 (29)	29 (38)	22 (35)	0 (0)
Culture negative, n (%)	19 (13)	1 (4)	19 (30)	10 (28)	1 (4)	3 (7)	3 (12)	5 (10)	5 (6)	4 (6)	0 (0)
Other organisms, n (%)	25 (15)	9 (35)	10 (15)**	3 (9)	5 (22)	10 (23)	11 (44)	16 (33)††	19 (25)‡‡	12 (19)	17 (70)§§

Reference	14	15	16	2	17	18	Current series	Total
Years of study	1984–1993	1971–1994	1990–1995	1997–2000	1990–2002	1997–2004	1985–2004	
Number of infants	30	98	43	45	57	27	40	908¶¶
CHD with no previous surgery, n (%)	21 (75)	37 (38)	NR***	NR†††	14 (25)	NR‡‡‡	9 (23)	
CHD with previous surgery, n (%)	0 (0)	39 (40)	NR***	NR†††	32 (56)	NR‡‡‡	21 (53)	
RHD, n (%)	3 (11)	0 (0)	11 (26)	24 (53)	0 (0)	1 (4)	0 (0)	
Normal heart, n (%)	4 (14)	22 (22)	0 (0)	1 (2)	11 (19)	2 (7)	10 (25)	
Staphylococcus aureus, n (%)	7 (23)	32 (33)	2 (5)	6 (29)	12 (21)	5 (20)	16 (40)	234 (26)
VGS, n (%)	14 (47)	16 (16)	6 (14)	9 (43)	9 (16)	7 (28)	5 (13)	282 (31)
Culture negative, n (%)	4 (13)	14 (14)	27 (63)	24 (53)	5 (9)	5 (20)	3 (8)	152 (17)
Other organisms, n (%)	5 (16)§§§	36 (37)	8 (18)¶¶¶	6 (29)	31 (54)****	9 (36)††††	16 (40)	247 (27)

**Years of study not reported (NR) so publication year reported; †Only infants younger than three months of age enrolled; ‡118 children (79%) had congenital heart disease (CHD), but it is not specified how many had surgery; §20 children (87%) had CHD, but it is not specified how many had surgery; ¶22 children (88%) had CHD, but it is not specified how many had surgery; **Coagulase-negative staphylococci n=4 (6%), pneumococcus n=3 (5%),* Candida albicans *n=2 (3%),* Acinetobacter *n=1 (1%); ††3 (6%) were fungi; ‡‡One case died before blood cultures sent and two cases had two organisms each; §§Coagulase-negative staphylococci n=6 (25%),* Candida *n=6 (25%), enterococcus n=2 (8%),* Klebsiella *n=1 (4%),* Serratia *n=1 (4%),* Citrobacter *n=1 (4%); ¶¶Total 916 rather than 908 because etiological agents were NR for three children (11,18) and nine children had two pathogens each (11,13); ***34 children (74%) had CHD, but it is not specified how many had surgery; †††20 children (45%) who had CHD, but it is not specified how many had surgery; ‡‡‡24 children (89%) had CHD, but it is not specified how many had surgery; §§§Corynebacterium species n=2 (7%), enterococcus n=1 (3%), coagulase-negative staphylococci n=1 (3%), pneumococcus n=1 (3%); ¶¶¶*Candida *n=3 (7%),* Pseudomonas *n=1 (2%),* Aspergillus *n=1 (2%),* Staphylococcus albus *n=2 (5%),* Salmonella *n=1 (2%); ****Enterococcus n=9 (16 %), other streptococci n=8 (14%), Gram-negative n=7 (12%), coagulase-negative staphylococci n=4 (7%);* Candida *n=3 (5%); ††††Coagulase-negative staphylococci n=2 (8%), pneumococcus n=2 (8%), group A streptococcus n=1 (4%), group B streptococcus n=1 (4%), HACEK (*Haemophilus *species [*H parainfluenzae*,* H aphrophilus *and* H paraphrophilus*],* Actinobacillus actinomycetemcomitans*,* Cardiobacterium hominis*,* Eikenella corrodens *and* Kingella *species) n=1 (4%),* Aspergillus *n=1 (4%), NR (n=2). RHD Rheumatic heart disease; VGS Viridans group streptococci*

the etiological agents of pediatric IE may be changing. The 2000 modification of the Duke criteria added community-acquired *S aureus* bacteremia as a major criteria (19) (the original version accepted only nosocomial *S aureus* bacteremia as a major criteria) – recognizing that many cases of *S aureus* IE are now community acquired, including six of the 16 *S aureus* cases in the current study. A registry of cases of adult IE between 2000 and 2003, from 16 developed countries, showed *S aureus* to be the predominant pathogen, accounting for 558 of 1779 cases (31.4%) (20). Recent IE guidelines mentioned that the incidence of *S aureus* IE seems to be increasing, and postulated that this could be secondary to more invasive surgical procedures being performed for correction of CHD (21). However, a population-based study (22) in Minnesota, USA, showed no change in the causative agents of adult IE from 1970 to 2000, with VGS still being predominant. Therefore, it is possible that *S aureus* IE is over-represented in studies, such as the present one, in which many of the cases of IE occurred in the postoperative period.

Blood cultures were positive in almost all cases in the present study, versus rates as low as 37% in previous pediatric studies (16). However, these differences are likely accounted for by variation in the definition chosen for IE, and it is possible that cases of culture-negative IE were missed by our definition. In an adult study (23) of 105 valves excised due to IE, pathogens were identified by polymerase chain reaction in 64 valves but by culture in only 14 valves, likely because patients had received effective antibiotics that sterilized the valve or had pathogens that were difficult to culture. Determining the etiological agent of IE is likely to be more accurate once molecular testing of blood or excised tissue for multiple organisms becomes more practical. As has been previously described, enterococcal IE occurred only in children younger than

24 months of age (17). It is not clear why this organism causes IE in this young age group.

Approximately 50% of all IE patients and three-quarters of patients with CHD and IE in the present study had previously had cardiac surgery, and almost 50% of the cases of IE were nosocomial (19 of 40), with another two cases possibly being nosocomial because they occurred after hospital discharge but within six months of cardiac surgery. Two of the 40 cases occurred within four days of cardiac catheterization. Antibiotic prophylaxis is not recommended for diagnostic cardiac catheterization because the risk of IE is thought to be negligible, but in a previous study, seven of 73 children underwent cardiac catheterization within two months before their IE diagnosis, although six had other risk factors (including recent surgery in four cases) (11). It is possible that the risk of IE following cardiac catheterization is higher in children (especially infants) than in adults because the procedure is technically more difficult. Contrary to a previous study (12) in which 11 of 62 children with IE had normal hearts, right-sided IE and a CVC, the presence of a CVC in the absence of CHD did not appear to be an important risk factor for IE with only two cases occurring over the 19-year study period (definite IE with a tricuspid vegetation and possible IE with no vegetation seen), despite extensive use of CVCs in this large tertiary care hospital.

Surgical intervention was required in 28% of cases of IE in the current study compared with 130 of 550 (24%) in previous studies (Table 4). Indications for surgery in pediatric IE are extrapolated from adult recommendations (21), with definite indications and ideal timing of surgery remaining controversial. The combined mortality rate of IE in all previous studies in Table 4 is 163 of 811 (20%), with the rate of 5% in the current study being comparable with that in other recent studies. Mortality is lower in adults with *S aureus* IE managed surgically than in those managed medically, but this could be because surgery is avoided in the most high-risk patients (24). Both deaths in the present study were due to *S aureus* IE, three other patients with *S aureus* required surgery, but another 11 cases of *S aureus* IE were successfully managed medically.

The definitions used for IE are not uniform across pediatric studies, although most recent studies apply the Duke criteria. Although these criteria have been shown to be more sensitive than previous criteria for the diagnosis of definite pediatric IE (25), the specificity of a diagnosis of possible IE by Duke criteria in children with CHD may be low. All children with CHD, fever and a single positive blood culture are classified as having possible IE by the Duke criteria. In a cardiac surgical centre, this includes a large number of children recovering from complex cardiac surgery – it seems likely that the vast majority of these children have contaminated blood cultures, CVC-related bacteremia or surgical site infections rather than IE, and may have a different array of pathogens than do patients with IE. In the current study, the decision was made to use the Duke criteria for definite IE, but to require stricter criteria for a diagnosis of possible IE because the primary goal was to look at causative pathogens.

CONCLUSION

Pediatric IE still occurs predominantly in the setting of CHD and is rarely associated with the presence of a CVC alone in the absence of CHD. *S aureus* was the predominant pathogen in many recent studies, including the current one, but a prospective population-based study would be necessary to determine whether this apparent change in etiological agents is a real phenomenon.

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