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의학석사 학위논문

Epidemiology of invasive bacterial  
infections in immunocompetent  
children in Korea (1996–2020)

면역 기능이 정상인 소아에서 발생한 침습 세균  
감염의 국내 역학 (1996–2020)

2022년 2월

서울대학교 대학원

의학과 소아과학 전공

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# Epidemiology of invasive bacterial infections in immunocompetent children in Korea (1996–2020)

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# Abstract

**Background:** Invasive bacterial infection (IBI) causes significant burden in mortality and morbidity in children. Due to the impact of the coronavirus disease (COVID-19) pandemic on the epidemiology of many infectious diseases, a new epidemiological trend of IBI is expected in the post COVID-19 era. With this background, this study was performed to establish the epidemiology of IBI from 1996 to 2020 to serve as baseline epidemiologic data for monitoring future trend of IBI in children.

**Methods:** We retrospectively surveyed IBI in immunocompetent children caused by nine major bacteria, namely *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Neisseria meningitidis*, *Staphylococcus aureus*, *Streptococcus agalactiae*, *Streptococcus pyogenes*, *Listeria monocytogenes*, *Salmonella* species, and *Escherichia coli* that were diagnosed at the 29 university-affiliated hospitals from 2011 to 2020. The temporal trends of relative proportion of each pathogen were analyzed from 1996 to 2019 in children older than 3 months of age and from 2006 to 2019 in infants under 3 months of age, using the two previously published data. The Spearman rank correlation ( $r_s$ ) test was performed for

the trend analysis.

**Results:** A total of 2255 cases were identified. In infants < 3 months of age, *S. agalactiae* (46.5%), *E. coli* (36.7%), and *S. aureus* (14.1%) were the most common pathogens, *E. coli* was the most prevalent cause of bacteremia without localizing signs and *S. agalactiae* was the major cause of meningitis and pneumonia in this age group. In children 3 to 59 months of age, *S. pneumoniae* (35.3%), *S. aureus* (30.3%), and *Salmonella* species (17.1%) were the most common pathogens. *S. pneumoniae* was the most common cause of bacteremia without localizing sign, pneumonia, and meningitis in this age group. In children  $\geq 5$  years of age, *S. aureus* (60.0%) was the common pathogen, followed by *Salmonella* species (15.8%) and *S. pneumoniae* (9.9%). In infants < 3 months of age group, the relative proportion of *S. aureus* ( $r_s = -0.850$   $P < 0.01$ ) decreased significantly over the 14-year period (2006–2019), while that of *S. agalactiae* increased ( $r_s = 0.781$   $P < 0.01$ ). In infants and children > 3 months of age group, there is a trend toward a decrease in the relative proportions of *S. pneumoniae* ( $r_s = -0.430$   $P = 0.036$ ), *H. influenzae* ( $r_s = -0.922$ ,  $P < 0.001$ ) during the 24-year period, while trend toward an increase in the relative proportion of *S. aureus* ( $r_s = 0.850$ ,  $P < .001$ ), and *S.*

*agalactiae* ( $r_s = 0.615$ ,  $P = .001$ ).

**Conclusions:** In infants < 3 months of age group, IBI due to *S. agalactiae* increased significantly over the 14-year period. In children > 3 months of age, the relative proportion of *S. pneumoniae* and *H. influenzae* showed decreasing trend over the 24 years. These findings can be used as the baseline data to navigate the trend in the epidemiology of pediatric IBI in the post COVID-19 era.

**Keyword :** Invasive bacterial infections; Epidemiology; COVID-19; Children; *Streptococcus pneumoniae*

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# Introduction

Invasive bacterial infections (IBIs) are leading cause of childhood morbidity and mortality. Epidemiology of causative bacterial organism in children varies by age and time. To monitor these changes closely, multicenter surveillance system for pediatric IBI has been maintained from 1996 in Korea and two retrospective studies of IBI in children were published in 2011 and 2018, respectively<sup>1,2</sup>. In the first study, *Streptococcus pneumoniae* and *Haemophilus influenzae* were responsible for 66% of invasive bacterial diseases in children 3 to 59 months of age. The follow up study revealed that *S. pneumoniae* and *S. aureus* accounted for 75% of all invasive bacterial infections in same age group. These findings led to important consensus for empirical antibiotic treatment and vaccine policy.

The Korean National Immunization Program (NIP) provides 17 species of vaccine for free to children under 12 years of age. The 7- valent pneumococcal conjugate vaccine (PCV7) was introduced in 2003, and the PCV10 and PCV13 replaced PCV7 in 2010. In addition, PCV10 and PCV13 were introduced in NIP in 2014. The *Haemophilus influenzae* type b (Hib) vaccine was licensed to use in 1996 and was included in routine immunization schedule in March

2013<sup>3</sup>. This study period (2011–2020), after Hib and PCV 13 vaccines introduction, provides data on the epidemiological changes of IBI influenced by them.

The outbreak of coronavirus disease 2019 (COVID–19) has spread to many countries worldwide and the first pediatric case of COVID–19 in Korea was reported in February 2020<sup>4</sup>. To slow down the transmission of severe acute respiratory syndrome coronavirus 2 (SARS–CoV–2), many countries implemented non-pharmaceutical interventions such as containment, school closing, wearing facemasks, and handwashing. These led to reduction in the incidence of transmissible infectious disease among children including respiratory viral infections<sup>5–8</sup>. Moreover, these policies led to decrease in the number of IBI including *S. pneumoniae*, *H. influenzae*, and *N. meningitidis*, which were transmitted via the respiratory route<sup>9,10</sup>.

Due to profound impact of the COVID–19 pandemic on the epidemiology of diverse infectious diseases, a new epidemiological trend of IBI is expected in post COVID–19 era. This study details the epidemiology of IBI in children for the recent 10 years from 2011 to 2020 and establishes the epidemiology of IBI for the 25 years from 1996 to 2020 to serve as the baseline data for

monitoring future trend in the epidemiology of pediatric IBI.

# Methods

## Participating hospitals

Twenty-nine university-affiliated hospitals participated in this study. The geographic distribution of the 29 hospitals is shown in Figure 1. : 17 hospitals are located in the national capital region (Seoul St. Mary's hospital, Kyung Hee Medical center, Seoul National University Children's Hospital, Severance Children's hospital, Samsung Medical Center, Nowon Eulji Medical center, Ewha Womans University Medical Center, Hanyang University Hospital, Seoul Asan Medical center, Inha University Hospital, Gachon University Gil Medical Center, Hallym University Medical Center, Inje University Ilsan Paik Hospital, Korean University Ansan Hospital, St. Vincent's Hospital, Seoul National University Bundang Hospital, and CHA Bundang Medical Center, Ajou University Hospital), and 12 hospitals are located in the regional central cities of provinces (Gangwon-do: Wonju Christian Hospital, Chungcheongbuk-do: Chungbuk National University Hospital, Chungcheongnam-do: Dankook University Hospital, Chungnam National University Hospital, Jeollabuk-do: Chonbuk National University Hospital, Gwangju/Jeollanam-do: Chonnam National University Hospital, Daegu/Gyeongsangbuk-do: Keimyung

University Dongsan Medical Center, and Busan/Gyeongsangnam-do: Pusan National University Yangsan Hospital, Gosin University Gospel Hospital, and Changwon Fatima Hospital, Jeju-do: Jeju National University Hospital).

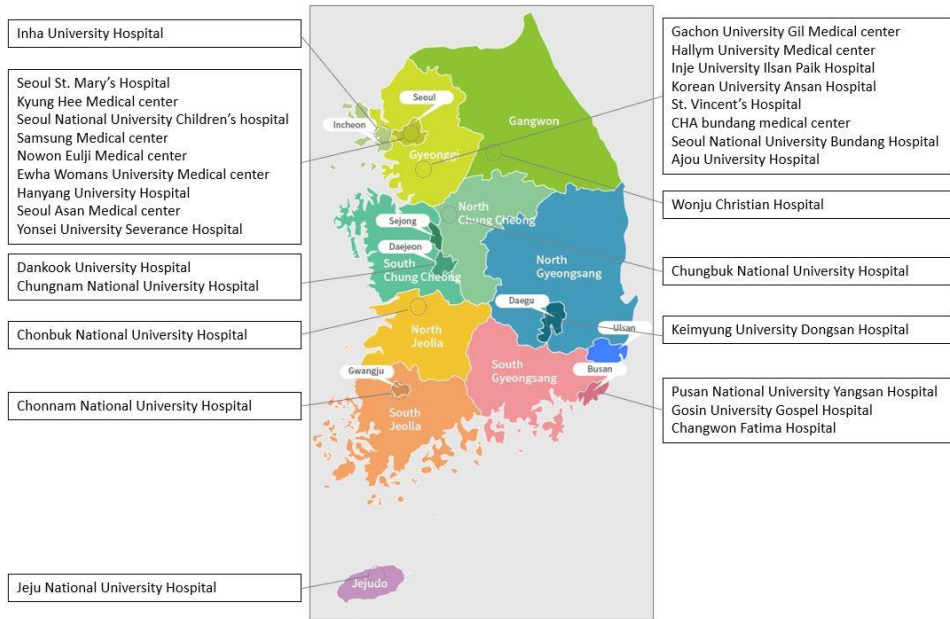


Figure 1. Geographic distribution of the 29 university-affiliated hospitals

## **Data collection**

The survey was conducted from January 2011 to December 2020. This study included children and adolescents younger than 18 years of age and neonates and infants born after 37 weeks of gestation who were treated with invasive bacterial infections. We extracted data from hospital discharge records and reviewed retrospectively. Initially, cases with positive results for the target organisms were selected and then, investigators reviewed the medical records of the cases and determined whether each case should be included in the study based on the case definition of the study protocol. A case report form was used to record the demographic characteristics, causative organisms, site(s) of bacterial isolation, clinical manifestations. The final clinical outcomes were categorized as follows: full recovery, recovery with sequelae, death, or hopeless discharge. Cases classified as ‘discharge against medical advice, expected not to die’ and ‘transfer to another hospital’ were considered missing data and they were excluded. The mortality was calculated for each pathogen. The distribution of bacterial pathogens was analyzed according to age, clinical diagnosis, and time.

Due to its retrospective nature, this study was approved with a waiver for the requirement of obtaining informed consent by the



Institutional Review Board at Seoul National University Hospital (No. 1706-125-861).

### **Case definition**

An ‘invasive bacterial infection’ was defined as isolation of a bacterial organism from a usually sterile site, such as blood, cerebrospinal fluid (CSF), pleural fluid, pericardial fluid, joint fluid, bone aspirate, or a deep tissue abscess<sup>11</sup>. The causative organisms were limited to nine major pediatric bacterial pathogens: *S. pneumoniae*, *S. aureus*, *H. influenzae*, *N. meningitidis*, *S. agalactiae*, *S. pyogenes*, *Listeria monocytogenes*, *Salmonella* species, and *E. coli*. If the same pathogen was found in another sample taken within 30 days of the previous positive sample or during the same admission period, the episode was considered as a single case. The organisms were obtained by culture, polymerase chain reaction or latex agglutination test. Cases with medical conditions vulnerable to invasive bacterial infections, such as congenital or acquired immunodeficiency, prematurity, steroid or cancer chemotherapy, and infections associated with anatomic abnormalities were excluded<sup>12</sup>. Urinary tract infections without bacteremia were excluded because culture results for specimens which were

collected by the bag method are not reliable.

An invasive infection was sorted based on clinical symptoms and the isolation of pathogens from the specimens. 'Bacteremia without localizing signs' was defined as cases in which no identifiable focus was identified, and the bacterium was isolated only from blood. A clinical diagnosis with a localizing lesion such as 'meningitis', 'pneumonia', 'arthritis', 'osteomyelitis', 'peritonitis', or 'deep tissue abscess' was defined if the bacterium was isolated from the equivalent body fluid, such as CSF, pleural fluid, joint fluid, bone aspirate or abscess, or if the bacterial organism was isolated only from blood, but the clinical symptoms were compatible with the diagnosis.

### **Statistical analysis**

The age groups were classified as follows: < 3 months of age, 3 to 23 months of age, 24 to 59 months of age, and  $\geq$  5 years of age. The temporal changes in the relative proportions of each causative pathogen for invasive bacterial infections in infants < 3 months of age group and children  $\geq$  3 months of age group were analyzed using the Spearman rank correlation ( $r_s$ ) test for trends. All tests were 2-tailed, and  $P < 0.05$  was considered statistically significant.

All data management and statistical analysis were performed using IBM SPSS version 26.0 (SPSS Inc.; Chicago, IL).

# Results

## Etiology of IBI from 2011 to 2020

A total of 2255 episodes of invasive bacterial infections were identified from 2011 to 2020. There are 5 co-infections, which were defined as the identification of more than 2 pathogens in the same episode. The source of the identified bacteria was the blood 64.8% (1466/2262) and sterile body fluids 19.1% (431/2262). Of them, 346 causative organisms were detected in CSF.

The male to female ratio was 1.5:1. 11.6% of patients had previously diagnosed underlying disease. Overall, *S. aureus* was the most frequently isolated organism (n=698, 30.8%), followed by *S. agalactiae* (n=545, 24.1%), *E. coli* (n=395, 17.5%), and *S. pneumoniae* (n=270, 11.9%). There were few cases of *L. monocytogenes* (n=10) and *N. meningitidis* (n=4) infections.

Of the 196 *Salmonella* isolates, serogroup data were available for the 194 cases. Among these, 17 (8.8%) isolates were *Salmonella typhi* and 177 isolates were non-typhoidal *Salmonella*.

## Distribution of causative bacterial organisms by age from 2011 to 2020

The number of cases were highest in < 3 months of age group

(n=1073, 47.4%), followed by > 5 years of age group (n= 628, 27.8%), 3–23 months of age group (n=335, 14.8%), and 24–59 months of age group (n=226, 10.0%). Infants and children younger than 5 years accounted for 72.2% of all cases. The distribution of causative organisms is shown in Table 1.

Difference in the distribution of causative bacterial organisms by age group was shown in this study. In infants < 3 months of age group, *S. agalactiae* (46.5%) and *E. coli* (36.7%) were the two most frequently identified pathogens, followed by *S. aureus* (14.1%); these three organisms were responsible for 97.3% of invasive bacterial infections in this age group.

*S. pneumoniae*, *S. aureus* and *Salmonella* species were isolated frequently in infants and children 3 months of age or older. *S. pneumoniae* (36.4%) and *S. aureus* (33.1%) showed predominance, followed by *Salmonella* species (11.3%) in 3–23 months of age group. The same trend was found in 24–59 months of age group and these three organisms accounted for 33.6%, 26.1% and 25.7%, respectively. In contrast, *S. pneumoniae* (9.9%) was the third most frequent cause of invasive bacterial infections in children older than 5 years of age.

*S. aureus* was the leading cause of invasive bacterial infections in

children older than 5 years of age. The percentage of *S. aureus* increased gradually to 30.3% in children between the ages of 3 months and 5 years of age and to 60.0% in children older than 5 years of age.

Identified species of bacteria	Age group, No. (%)					Total
	< 3months	3-59 months			> 5 years	
		3-23 months	24-59 months	Subtotal		
<i>Staphylococcus aureus</i>	151 (14.1)	111 (33.0)	59 (26.1)	170 (27.1)	377 (36.0)	698(30.9)
<i>Streptococcus pneumoniae</i>	10 (0.9)	122 (36.3)	76 (33.6)	198 (31.5)	62 (9.9)	270 (11.9)
<i>Streptococcus agalactiae</i>	499 (46.5)	32 (9.5)	1 (0.4)	33 (5.3)	13 (2.1)	545 (24.1)
<i>Salmonella</i> spp.	1 (0.1)	38 (11.3)	58 (25.7)	96 (15.3)	99 (15.8)	196 (8.7)
<i>Haemophilus influenzae</i>	5 (0.5)	13 (3.9)	10 (4.4)	23 (3.7)	18 (2.9)	46 (2.0)
<i>Streptococcus pyogenes</i>	5 (0.5)	18 (5.4)	18 (8.0)	36 (5.7)	58 (9.2)	99 (4.4)
<i>Neisseria meningitidis</i>	1 (0.1)	1 (0.3)	1 (0.4)	2 (0.3)	1 (0.2)	4 (0.2)
<i>Listeria monocytogenes</i>	7 (0.7))	0	3 (0.5)	3 (0.5)	0	10 (0.4)
<i>Escherichia coli</i>	394 (36.7)	<sup>a</sup> NA	NA	NA	NA	394 (17.4)
Total	1073	335	226	561	628	2262

NA – not applicable.

<sup>a</sup>NA denotes data were not collected.

**Table 1. Distribution of causative organisms for invasive bacterial infection from 2011 to 2020, by age group.**

## Distribution of etiologic organisms according to clinical diagnosis from 2011 to 2020

Among the 2262 invasive bacterial infections identified, bacteremia without localizing signs was most frequent, accounting for 51.2% (n=1158) of cases, followed by arthritis and osteomyelitis (n=442, 19.5%), meningitis (n=396, 17.5%), pneumonia with bacteremia or empyema (n=149, 6.6%), and deep organ abscess (n=66, 2.9%). Other diseases not assigned to one of the above clinical entities accounted for 2.3%.

There were age-related differences in the distribution of causative bacterial organism among patients presenting with bacteremia without localizing signs, meningitis and bacteremic pneumonia or pneumonia with empyema. Detailed age-specific distribution of causative organisms according to clinical diagnosis are presented in Figure 2. For bacteremia without localizing signs, *E. coli* (49.1%) was the most common organism in infant younger than 3 months of age, followed by *S. agalactiae* (36.0%). *S. pneumoniae* (32.9%) was the most frequent causative organism in patients 3 to 23 months of age, while *Salmonella* spp. was the most prevalent organism in patients older than 24 months of age. For meningitis and pneumonia, *S. agalactiae* was the leading cause of meningitis in



infants younger than 3 months of age and *S. pneumoniae* in patients older than 3 months of age.

*S. aureus* was the most predominant causative organism of bone and joint infection in all age groups, causing 64.6% of cases in < 3 months of age, 82.9% of cases in 3 - 24 months of age, 70.5% in 24 - 59 months of age, and 86.1% in > 5 years of age group.

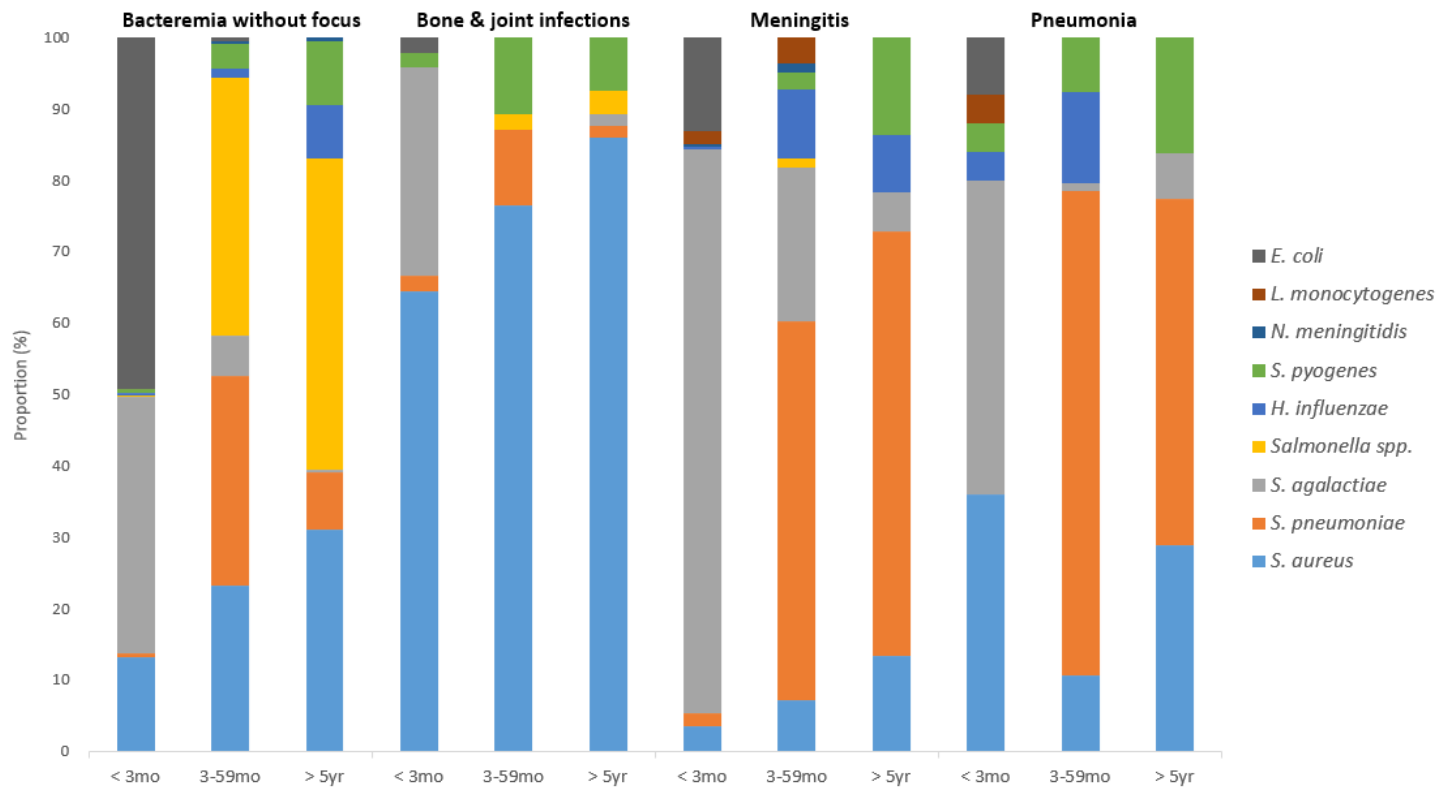


Figure 2. Distribution of causative bacterial organisms in invasive infections in immunocompetent children according to age group and clinical diagnosis (2011–2020)

## Clinical outcomes from 2011 to 2020

Clinical outcome data were available for 1975 cases (87.3%). The Overall case–fatality rate was 3.3% (66/1975). When the data was analyzed according to clinical diagnosis, meningitis showed highest case–fatality rate (6.3%, 23/365) followed by pneumonia with bacteremia or empyema (6.2%, 9/145) and bacteremia without localizing signs (2.2%, 24/1083). Analyzed according to age groups, infants < 3 months of age group showed highest case–fatality rate (4.1%, 39/956), followed by 24–59 months of age group (3.7%, 10/203), 3–23 months of age group (2.7%, 8/291) and older than 5 years of age group (1.7%, 9/538).

Among the bacteria studied, *N. meningitidis* was associated with highest case–fatality rate of 25% (1/4), followed by *H. influenzae* of 5.1% (2/39).; however, the overall number of cases of *N. meningitidis* and *H. influenzae* infection were relatively small. When bacteria that were isolated more than 50 cases were analyzed, we found that *S. pneumoniae* had the highest case fatality of 6.6% (15/229), followed by *S. agalactiae* with a case fatality rate of 4.6% (22/476). *E. coli*, *S. pyogenes* and *S. aureus* had case fatality of 3.9% (14/361), 3.2% (3/95), and 1.3% (8/600), respectively. No fatalities associated with *L. monocytogenes* and *Salmonella* spp.

infection were identified during the study period.

In terms of frequency of sequelae associated with meningitis cases, *H. influenzae* had a very high sequelae rate of 36.4% (4/11). Sequelae associated with meningitis caused by the other common infective organisms, namely *S. agalactiae*, *E. coli* showed similar trends compared to the case fatality rates and were 28.8% (59/205) and 27.6% (6/34), respectively. *S. pneumoniae* showed high case fatality rate, while frequency of sequelae was low (24.6%, 15/61).

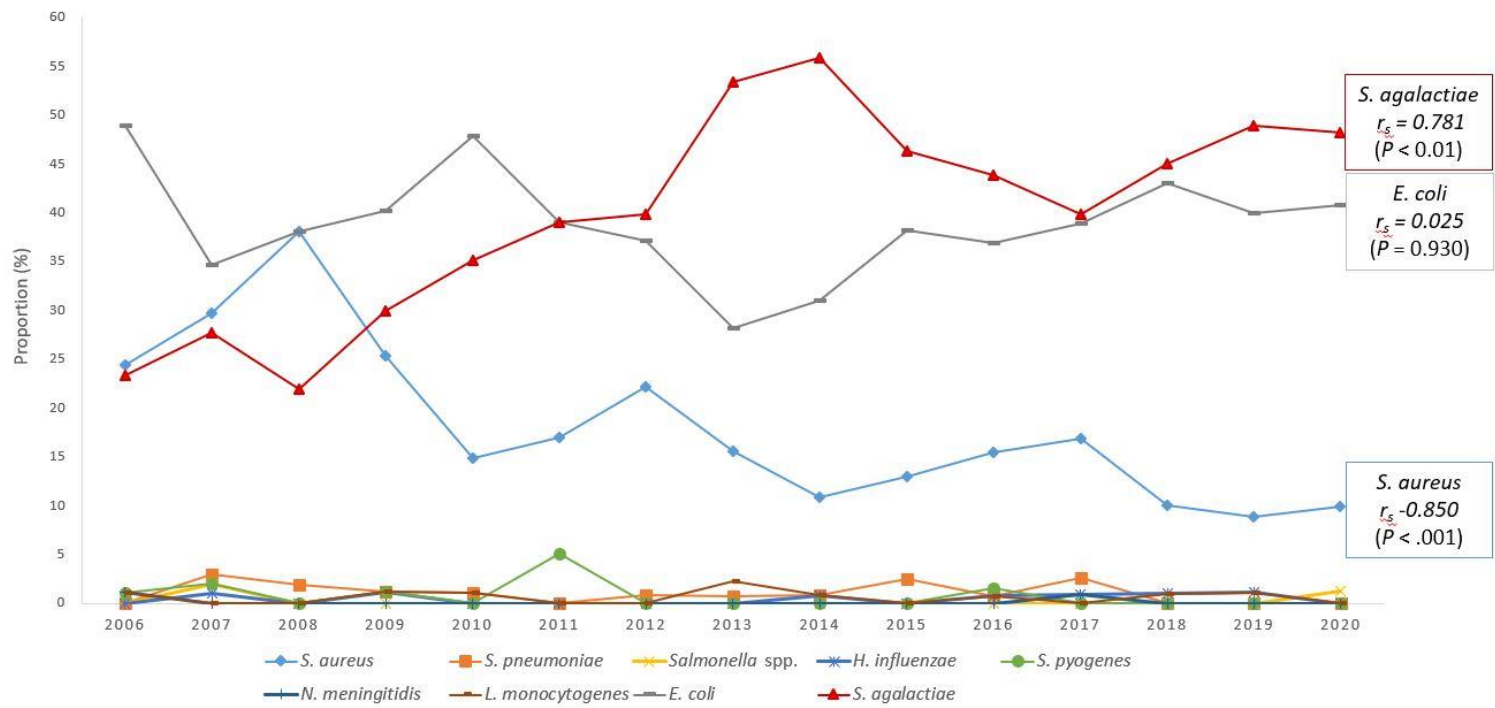
#### **Changes in the relative proportion of bacterial organisms over time from 1996 to 2020**

In this trend analysis over time, the proportion of IBI in 2020 were excluded because the distribution of causative organism in 2020 was quite different from previously shown trend. Total 3873 cases were analyzed for annual trend analysis of the relative proportion of bacterial organisms from 1996 to 2019: 768 cases from 1996 - 2005, 995 cases from 2006–2010 and 2103 cases from 2011 to 2019. In addition, as *E. coli* was not included in the first study period (1996–2005), the trend in infants < 3 months of age was analyzed from 2006 to 2019.

Figure 3 shows the temporal changes in the relative proportions of

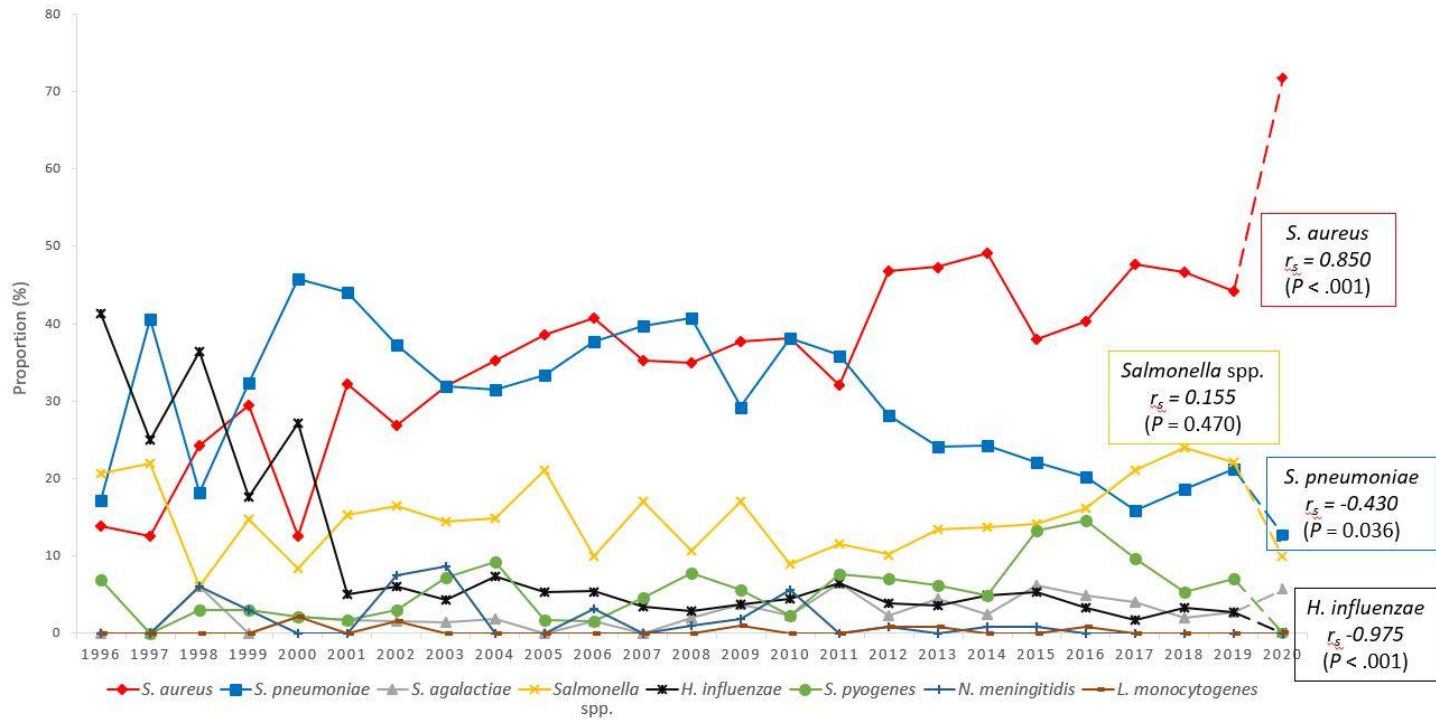
the nine causative bacterial organisms of invasive infections in infants younger than 3 months of age. Over 14 years, three organisms, *E. coli*, *S. agalactiae* and *S. aureus* accounted for most of the invasive bacterial infections in this age group. There was a decreasing trend in the relative proportion of *S. aureus* ( $r_s = -0.82$ ,  $P < .001$ ), while that of *S. agalactiae* showed increasing trend ( $r_s = 0.792$ ,  $P = .001$ ). No significant changes in the trends were observed for other seven organisms.

The overall trends in the relative proportions of the eight causative bacterial organisms in infants and children older than 3 months of age from 1996 to 2019 are shown in Figure 4. Statistical analysis revealed a significant decrease in the percentage of *S. pneumoniae* ( $r_s = -0.43$ ,  $P = 0.036$ ), *H. influenzae* ( $r_s = -0.975$ ,  $P < .001$ ) and increase in that of *S. aureus* ( $r_s = 0.85$ ,  $P < .001$ ), and *S. agalactiae* ( $r_s = 0.615$ ,  $P < .001$ ). The percentage of *Salmonella* spp. had not significantly changed over 24 years, however showed increasing trend from 2010 to 2019 ( $r_s = 0.976$ ,  $P < .001$ ).



\*The Spearman rank correlation ( $r_s$ ) test was performed using the 2-tailed t test to reject the null hypothesis that  $r_s = 0$ .

**Figure 3. Temporal changes in the relative proportions of the causative bacterial organisms of invasive infections in infants younger than 3 months of age (2006–2020).**



\*The Spearman rank correlation ( $r_s$ ) test was performed using the 2-tailed t test to reject the null hypothesis that  $r_s = 0$ .  
**Figure 4.** Temporal changes in the relative proportions of the causative bacterial organisms of invasive infections in immunocompetent children 3 months of age or older (1996–2020).

## Discussion

The purpose of this study was to investigate the epidemiology of invasive bacterial infections in a pediatric population in Korea through a retrospective multicenter review of hospital data and to compare the relative proportions of causative bacteria over 25 years, from 1996 to 2020. This study includes the largest episodes of IBI in children in Korea, and it is of great significance in continuous the multicenter – based monitoring of invasive bacterial infection in children from 1996 till 2020. An expanded number of episodes and hospitals were included in this study compared to the 1996–2005 and 2006–2010 period: 768 episodes in 18 hospitals was included in the 1996–2005 study, 1005 episodes in 25 hospitals included in the 2006–2010 study, while 2252 episodes in 29 hospitals were comprised the 2011–2020 period study.

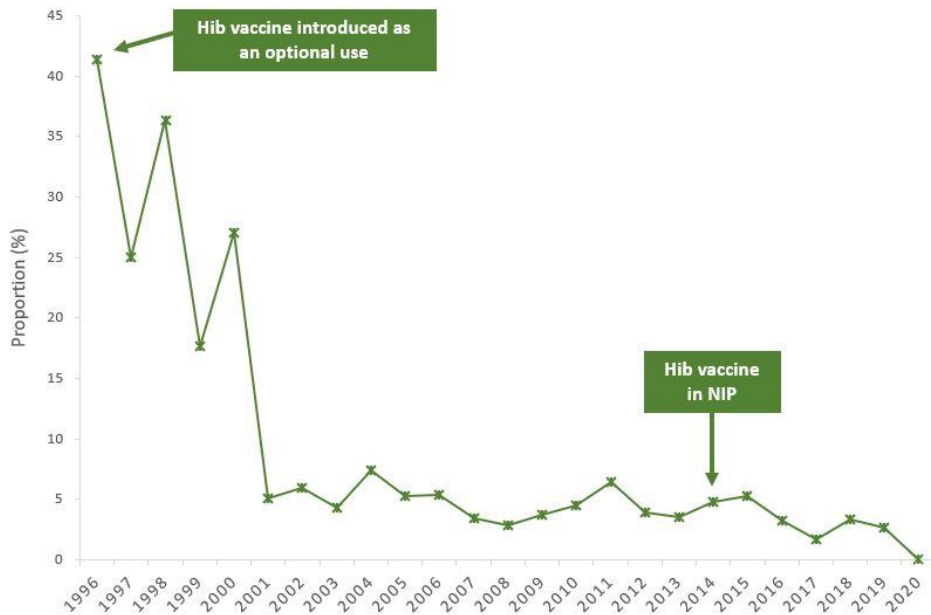
The major causative organism of invasive bacterial infection differed according to age. For patients under 3 months of age, *S. agalactiae* (46.5%), *E. coli* (36.7%) and *S. aureus* (14.1%) were most prevalent. *S. pneumoniae*, *S. aureus* and *Salmonella* species predominated in patients 3 to 59 months of age. *S. aureus* (60.0%) was the most common pathogen in patients over 5 years of age, followed by *Salmonella* species (15.8%) and *S. pneumoniae* (9.9%).



In infants younger than 3 months of age, the relative proportion of *S. agalactiae* showed significant increasing trend from 2006 to 2019. The relative proportion of *S. pneumoniae* and *H. influenzae* showed decreasing trend from 1996 to 2019 in infants and children older than 3 months of age.

*Haemophilus influenzae* is one of the major causes of epiglottitis, pneumonia, meningitis, arthritis, pericarditis and other infections in infant and children over 3 months of age<sup>13</sup>. *H. influenzae* type b (Hib) is the most virulent type and causes invasive diseases in children. The relative proportion of *H. influenzae* in children 3 months of age or older from 1996 to 2020 and introduction of Hib immunization are shown in Figure 5. After introduction of conjugated Hib vaccine, decline of invasive infections due to Hib vaccine in children was observed in worldwide, including Japan where is the nearest country in Korea<sup>14,15</sup>. In Korea, Hib vaccine has been available since 1996 and has introduced into the National Immunization Program in 2013. Following the implementation of Hib vaccination program, decline of *H. influenzae* in invasive bacterial infection patients older than 3months of age were observed (20.1% in the 1996–2000 period, 4.5% in the 2001–2005 period, 3.3% in the 2006–2010 period, 2.3% in the 2011–2015 period and 1.7% in

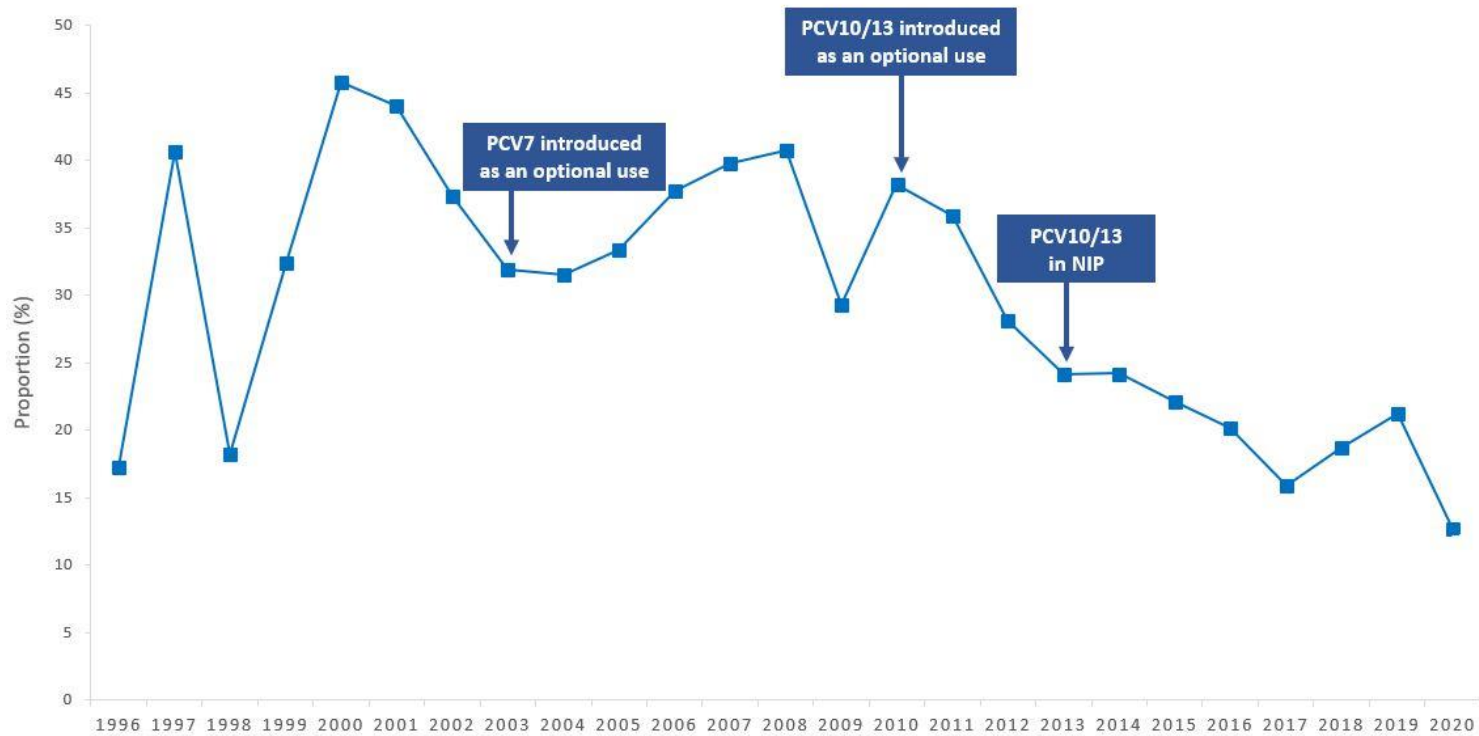
the 2016–2020 period)<sup>1,2</sup>.



Hib, *Haemophilus influenzae* type b; NIP, national immunization program

Figure 5. The relative proportion of *H. influenzae* in children 3 months of age or older (1996–2020) and introduction of *H. influenzae* type b immunization.

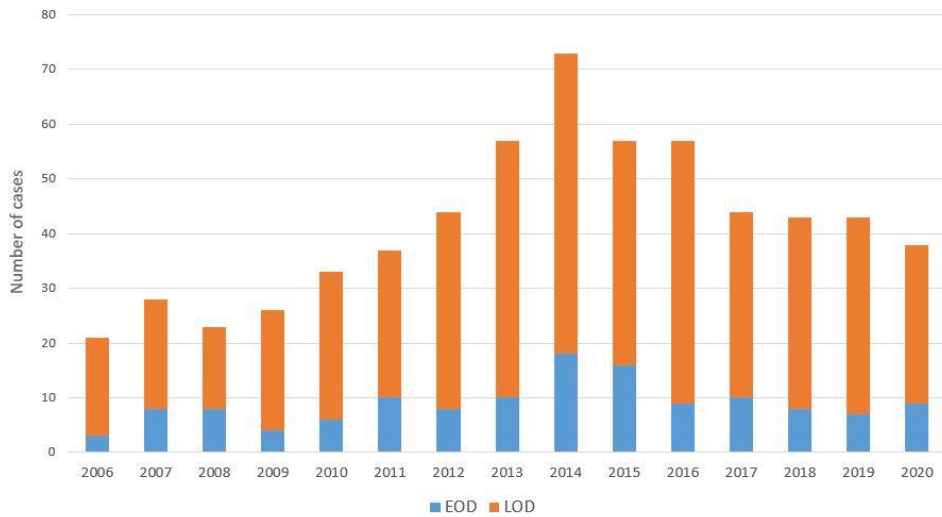
*Streptococcus pneumoniae* remains as a major etiologic organism of invasive bacterial infections in children. *S. pneumoniae* accounted for 45.3% of infections occurred among 3 to 59 months of age in 1996–2005 and 54.4% in 2006–2010. In this study, *S. pneumoniae* accounted for 35.3% of invasive bacterial infections, followed by *S. aureus* (33.3%). The most common clinical diagnosis in this age group were bacteremia without localizing signs (37.9%, 77/198), followed by pneumonia (31.8%, 63/198), and meningitis (22.2%, 44/198). In Korea, 7-valent pneumococcal conjugate vaccine (PCV7) was introduced in 2003, PCV10 and PCV13 was introduced in 2010 and NIP implemented PCV10 and PCV13 in 2014. The proportion of *S. pneumoniae* (1996–2020) and introduction of PCVs are shown in Figure 6. After the introduction of PCV7 in 2003, the trend in decreased proportion of *S. pneumoniae* was not seen immediately. The reduction in proportion of *S. pneumoniae* was seen after 2010 when PCV10 and PCV13 were introduced. This finding suggest that the trend change of *S. pneumoniae* was different from that of Hib. Replacement with nonvaccine serotypes among invasive pneumococcal disease after the introduction of PCVs may be responsible for the difference<sup>16</sup>.



PCV, Pneumococcal–conjugated vaccine; NIP, national immunization program

Figure 6. The relative proportion of *S. pneumoniae* in children 3 months of age or older (1996–2020) and introduction of pneumococcal immunization.

*Streptococcus agalactiae*, known as group B Streptococcus (GBS), is a major pathogen causing invasive bacterial infections in neonates and infants. In infants < 3 months of age group, *S. agalactiae* was the most common causative pathogen and this finding is consistent with previous studies<sup>1,2</sup>. GBS can cause early-onset disease (day 0–6) or late onset disease (day 7 – 90). Early-onset disease (EOD) can be acquired from colonized mother during delivery, while late-onset disease (LOD) is contributed to infection from mother, breast milk or environmental sources<sup>17, 18</sup>. The number of cases presenting with EOD and LOD due to GBS is presented in Figure 7. The relative proportion of EOD does not show certain tendency. The colonization rate of GBS in pregnant women tended to increase in Korea ranging from 1.96% in 2000 and 11.6% in 2015<sup>19–21</sup>. The increase in GBS colonization may explain the increased in invasive bacterial infection caused by GBS in infant in recent years.

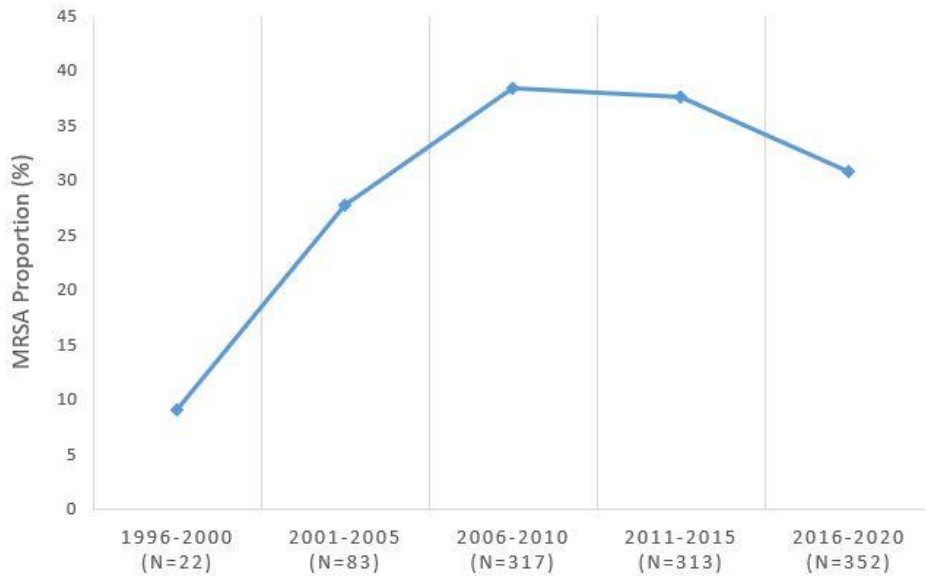


EOD, early-onset disease; LOD, late-onset disease  
**Figure 7.** The number of cases of invasive *Streptococcus agalactiae* disease in infants younger than 3 months of age (2006–2020).

*Staphylococcus aureus* can cause various illnesses, range from skin infection to life-threatening disease such as bacteremia, osteomyelitis, pneumonia, and endocarditis. *S. aureus* remains a major cause of infection and causes significant mortality and morbidity in pediatric populations<sup>22-24</sup>. An increase in relative proportion of *S. aureus* infections in infant and children > 3 months of age is observed during whole period of this study. The relative proportion of *S. aureus* occupied more than 60% of bone and joint infection in patients of any age. In infants younger than 3 months of age and children over 5 years of age, *S. aureus* was the second most frequent organism (36.0%, 29.0%) in patients presenting with pneumonia. In this study, we found the most frequent cause of bacterial infection in children older than 3 months of age was *S. aureus*. However, we don't know whether the incidence of *S. aureus* has increased, or relative proportion of *S. aureus* has increased without true increase. Based on this study and previous report, *S. aureus* bacteremia should be considered in febrile infants when initiating empirical antibiotics therapy, as vaccine-preventable causes of bacteremia decline<sup>25</sup>. The rate of oxacillin susceptibility of *S. aureus* from 1996 to 2020 is shown in Figure 8. Compared to the Methicillin-resistant *Staphylococcus aureus*



(MRSA) rate 9.1% in 1996–2000, the MRSA rate ranged between 27–38% through 2001 to 2020. However direct comparison of MRSA rate during the study period should be interpreted in caution because the case number in early period (1996–2000) was small. As the MRSA occupied significant portions, antibiotics such as vancomycin or clindamycin should be considered in empiric guidelines for treatment of febrile infants<sup>23,24</sup>.



MRSA, Methicillin-resistant *Staphylococcus aureus*  
Figure 8. The relative proportion of MRSA in children 3 months of age or older (1996–2020).

*Salmonella* infection causes mostly acute diarrhea, while some patients may have serious complications such as bacteremia, meningitis, osteomyelitis or arthritis and these diseases are associated with high mortality<sup>26,27</sup>. The relative proportion of *Salmonella* spp. during the study period is shown in Figure 9. Studies in 1996–2010 showed a decreasing of *Salmonella* infection, while increasing trend was observed in current study period (2011–2020)<sup>1, 2</sup>. The case number of typhoidal *Salmonella* and nontyphoidal *Salmonella* (1996–2020) is shown in Figure 10 and the increasing trend of nontyphoidal *Salmonella* is observed. It is interesting to note that higher average temperature and increase poultry consumption may contribute to increase of nontyphoidal *Salmonella*.<sup>28,29</sup> The increased of poultry consumption in Korea may be responsible for the increase of nontyphoidal *Salmonella*<sup>30</sup>.

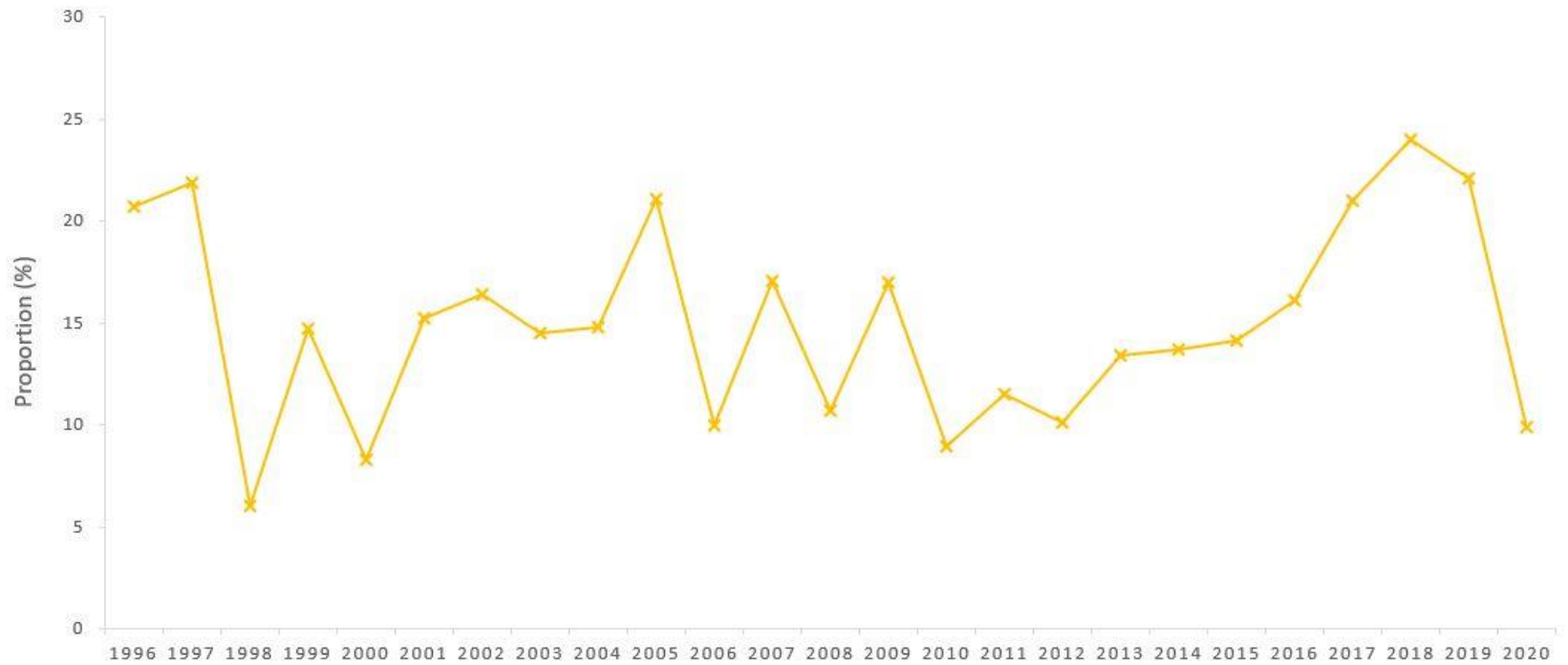


Figure 9. The relative proportion of *Salmonella* spp. in children 3 months of age or older (1996–2020).

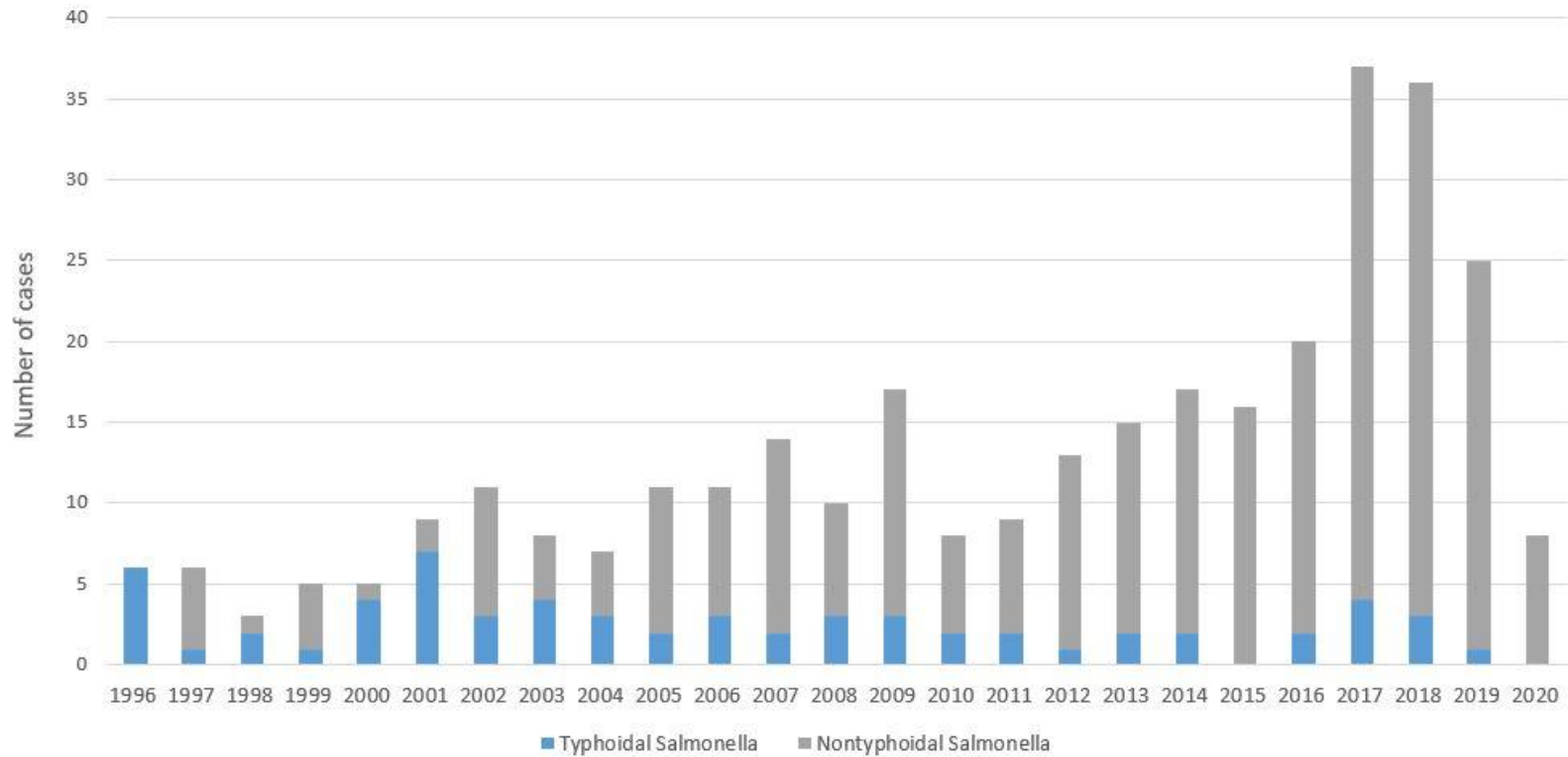


Figure 10. The number of cases of Typhoidal *Salmonella* and Nontyphoidal *Salmonella* in children 3 months of age or older (1996–2020).

*Escherichia coli* is a major invasive pathogen and frequently isolated in urinary tract infection in term infants. In United States, *E. coli* accounted for 42% of bacteremia in infants younger than 90 days and most of the patients had concurrent urinary tract infection<sup>31</sup>. *E. coli* was the most frequently isolated organism and accounted for 41.3% of isolated organism in neonates and infants under 3 months of age in the last study, while *E. coli* was the second common causative organism in same age group in this study. Considering urinary tract infection is the leading source of *E. coli* bacteremia and urogenital infections occur frequently in young infants, empirical antibiotic coverage should cover Gram-negative organism like current recommendation of ampicillin plus gentamicin or ampicillin plus third-generation cephalosporin. In current study, from 2011 to 2020, the case-fatality rate of *E. coli* was 3.9% (14/361), higher than previous study conducted from 2006 to 2010 (0.5%).

This study includes pre and post COVID-19 pandemic period. From 2012 to 2017, 250 bacterial infections occurred annually on average, while in 2019 and 2020, 203 and 152 bacterial infections occurred respectively. *S. aureus* showed a significant increasing trend and *Salmonella* showed a decreasing trend in 2020. In 2018,

the relative proportion of *S. aureus* infections was 46.7%, which rose to 71.8% in 2020. In 2018, the relative proportion of *Salmonella* species was 23.3%, which dropped to 9.9% in 2020. There were no cases of invasive bacterial infection due to *H. influenzae* and *N. meningitidis* and relative proportion of infection due to *S. pneumoniae* also declined and these findings are corresponded with worldwide trend<sup>10</sup>. Several studies revealed that containment measure and lockdown reduced invasive bacterial infection. The containment measures prevented invasive bacterial disease by blocking bacterial acquisition and colonization due to decreased person-to-person transmission<sup>9,10</sup>. Future study comparing the etiology of invasive bacterial infection in pediatric population before and after COVID-19 pandemic should be performed.

This study had several limitations. First, by targeting nine main bacterial organisms, bacteria with low pathogenicity and other Gram-negative organisms were ignored relatively. As bacteremia due to *Klebsiella pneumoniae*, *Enterobacter* spp. and *Enterococcus* spp. are reported worldwide in pediatric patients<sup>32, 33</sup>, further study could include other bacterial organisms. Second, as the number of hospitals differed and number of episodes increased explosively,

this may affect the trend of relative proportion of causative organisms. Furthermore, there are over one hundred university-affiliated hospitals in Korea and only 29 of them participated in this study. These hospitals do not represent nationwide epidemiology of invasive bacterial infection in Korea; however, this is the only available surveillance system for IBI in children which has been maintained for 25 years. At last, as the design of this study was focused on the relative proportion of each bacterial infection, the exact incidence of invasive bacterial infection caused by each organism was not evaluated. Further well-designed prospective studies which analyze annual incidence of bacterial infections are needed for more accurate description of the etiology of invasive bacterial infections. As surveillance system for invasive bacterial infections by the national immunization program include diphtheria, pertussis, tetanus, and *H. influenzae* type b only, continuing and reinforcing this multicenter study is indispensable to provide epidemiologic data of invasive bacterial infections in



## Conclusion

The 25-year study on the epidemiology of IBI in children revealed that *S. agalactiae* was the most common pathogen in infants younger than 3 months of age, *S. pneumoniae* in children between 3 to 59 months of age and *S. aureus* in children over 5 years of age. In infants < 3 months of age, the relative proportions of *S. agalactiae* increased significantly over recent 14 years (2006–2019), while that of *S. aureus* showed significant decreasing trend. The relative proportion of *S. pneumoniae* decreased and the proportion of *S. aureus* increased over 25-year study period in children > 3 months of age. As a new trend of invasive bacterial infections in children is expected due to emergence of SARS–COV–2, these findings can be used as baseline data before COVID–19 pandemic.

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## 요약 (국문초록)

**연구배경:** 항생제의 발달에도 불구하고 침습 세균 감염은 소아에서 중요한 소아 이환 및 사망의 중요한 원인으로 남아있다. 코로나바이러스 (COVID-19) 대유행이 많은 감염병의 역학에 미치는 영향 때문에, 소아에서의 침습 세균 감염의 새로운 역학 추세가 COVID-19 이후 시대에 예상된다. 이러한 배경에서, 본 연구는 1996년부터 2020년까지 소아 침습 세균 감염의 향후 추세를 모니터링하기 위하여, 기준 데이터 역할을 하는 침습 세균 감염의 역학을 확립하기 위해 수행되었다.

**연구방법:** 2011년 1월부터 2020년 12월까지 전국의 29개 대학병원에 서 진단된 면역 기능이 정상인 소아에서의 침습성 세균 감염 원인균을 후향적으로 조사하였다. 대표적인 9개의 세균감염 원인균은 다음과 같다. *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Neisseria meningitidis*, *Staphylococcus aureus*, *Streptococcus agalactiae*, *Streptococcus pyogenes*, *Listeria monocytogenes*, *Salmonella* species, *Escherichia coli*. 각 병원체의 상대적 비율에 대한 시간에 따른 추세 변화는 생후 3개월 이상 아동에서 1996년부터 2019년까지, 생후 3개월 미만 영아의 경우 2006년부터 2019년까지, 이전에 발표된 두 데이터와 종합하여 분석되었다. 추세 분석을 위해 Spearman 순위 상관관계( $r_s$ ) 검사를 시행하였다.

**연구결과:** 총 2255개의 사례를 분석하였다. 3개월 미만 영아에서는 *S. agalactiae* (46.5%), *E. coli* (36.7%), *S. aureus* (14.1%) 이 가장 흔한 원인균이었고 *E. coli*은 원인이 되는 국소부위가 없는 균혈증에서, *S. agalactiae*는 뇌수막염과 폐렴에서의 가장 흔한 원인균이었다. 3개월에서 59개월 사이의 소아에서는 *S. pneumoniae*(35.3%), *S. aureus*(30.3%), *Salmonella* spp. (17.1%)이 가장 흔하게 동정된 균이었다. 5세 이상의 소아에서 *S. aureus* (60%)은 가장 흔한 균이었고, *Salmonella* spp. (15.8%), *S. pneumoniae* (9.9%) 이 그 뒤를 이었다. 3개월 미만 영아들에서 14년간 (2006-2019) 3개월이 넘는 소아에서

25년의 기간 (1996–2020) 동안 *S. aureus* ( $r_s = -0.850$   $P < 0.01$ )의 상대분율은 통계적으로 유의하게 감소하였고 *S. agalactiae* ( $r_s = 0.781$   $P < 0.01$ )의 분율은 유의하게 증가하였다. 3개월 이상 소아에서 24년간 (1996–2019) of *S. pneumoniae* ( $r_s = -0.430$   $P = 0.036$ ), *H. influenzae* ( $r_s = -0.922$ ,  $P < 0.001$ ) 의 상대 분율은 유의하게 감소한 반면, *S. aureus* ( $r_s = 0.850$ ,  $P < .001$ ), 와 *S. agalactiae* ( $r_s = 0.615$ ,  $P = .001$ )의 분율은 유의하게 증가하였다.

**결론:** 이러한 연구 결과는 COVID-19 이후 시대에 소아 침습 세균 감염의 역학 추세를 탐색하기 위한 기준 데이터로 사용될 수 있다.

**주요어 :** 침습 세균 감염; 역학; COVID-19; 소아; *Streptococcus pneumoniae*

**학 번 :** 2020-25741