J Korean Med Sci. 2025 Oct 20;40(40):e250
https://doi.org/10.3346/jkms.2025.40.e250
eISSN 1598-6357·pISSN 1011-8934

JKMS

Original Article
Infectious Diseases

Check for updates

Hospital-Based Surveillance of Pediatric Invasive Pneumococcal Diseases, 2016–2023 in Korea: Serotype Trends and Vaccination Policy

Dayun Kang,[1] **Ki Wook Yun**,[1,2] **Hyunju Lee**,[2,3] **Eun Song Song**,[4] **Jong Gyun Ahn**,[5] **Su Eun Park**,[6] **Taekjin Lee**,[7] **Hye-Kyung Cho**,[8] **Jina Lee**,[9] **Yae-Jean Kim**,[10] **Dae Sun Jo**,[11] **Hyun Mi Kang**,[12] **Joon Kee Lee**,[13] **Chun Soo Kim**,[14] **Dong Hyun Kim**,[15] **Jae Hong Choi**,[16] **Byung Wook Eun**,[17] **Nam Hee Kim**,[18] **Eun Young Cho**,[19] **Yun-Kyung Kim**,[20] **Han Wool Kim**,[21] and **Eun Hwa Choi**[1,2]

[1]Department of Pediatrics, Seoul National University Hospital, Seoul, Korea
[2]Department of Pediatrics, Seoul National University College of Medicine, Seoul, Korea
[3]Department of Pediatrics, Seoul National University Bundang Hospital, Seongnam, Korea
[4]Department of Pediatrics, Chonnam National University, Gwangju, Korea
[5]Department of Pediatrics, Severance Children's Hospital, Yonsei University College of Medicine, Seoul, Korea
[6]Department of Pediatrics, Pusan National University School of Medicine, Yangsan, Korea
[7]Department of Pediatrics, CHA Bundang Medical Center, CHA University, Seongnam, Korea
[8]Department of Pediatrics, Ewha Womans University Mokdong Hospital, Seoul, Korea
[9]Department of Pediatrics, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
[10]Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[11]Department of Pediatrics, Jeonbuk National University Medical School, Jeonju, Korea
[12]Department of Pediatrics, College of Medicine, The Catholic University of Korea, Seoul, Korea
[13]Department of Pediatrics, Chungbuk National University Hospital, Chungbuk National University College of Medicine, Cheongju, Korea
[14]Department of Pediatrics, Keimyung University School of Medicine, Daegu, Korea
[15]Department of Pediatrics, Inha University College of Medicine, Incheon, Korea
[16]Department of Pediatrics, Jeju National University School of Medicine, Jeju, Korea
[17]Department of Pediatrics, Nowon Eulji University Hospital, Eulji University School of Medicine, Seoul, Korea
[18]Department of Pediatrics, Inje University Ilsan Paik Hospital, Goyang, Korea
[19]Department of Pediatrics, Chungnam National University Hospital, Daejeon, Korea
[20]Department of Pediatrics, Korea University Ansan Hospital, Ansan, Korea
[21]Departement of Pediatrics, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang, Korea

OPEN ACCESS

Received: Dec 2, 2024
Accepted: Mar 18, 2025
Published online: Aug 22, 2025

Address for Correspondence:
Eun Hwa Choi, MD, PhD
Department of Pediatrics, Seoul National University Hospital, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea.
Email: eunchoi@snu.ac.kr

ORCID iDs
Dayun Kang
https://orcid.org/0000-0002-0314-9455
Ki Wook Yun
https://orcid.org/0000-0002-0798-6779
Hyunju Lee
https://orcid.org/0000-0003-0107-0724
Eun Song Song
https://orcid.org/0000-0003-1056-2165
Jong Gyun Ahn
https://orcid.org/0000-0001-5748-0015
Su Eun Park
https://orcid.org/0000-0001-5860-821X

ABSTRACT

Background: In Korea, the 10-valent and 13-valent pneumococcal conjugate vaccines (PCVs) were introduced into the national immunization program (NIP) in 2014 for the protection in children. A decade later, in 2024, PCV15 replaced PCV10 and was included in the NIP in April, while PCV20 was licensed for use in October. To inform optimal vaccination policy, this study aimed to analyze the current distribution of serotypes responsible for invasive pneumococcal diseases (IPDs) in children.

Methods: IPD cases from children under 19 years of age were collected from a prospective hospital-based surveillance study conducted at 20 hospitals between 2016 and 2023. Data on the changes in IPD case number and serotype distribution were compared between the pre-coronavirus disease 2019 (COVID-19) period (2016–2019) and the during/post-COVID-19 period (2020–2023).

Taekjin Lee
https://orcid.org/0000-0002-8912-6982
Hye-Kyung Cho
https://orcid.org/0000-0003-0990-1350
Jina Lee
https://orcid.org/0000-0002-3435-251X
Yae-Jean Kim
https://orcid.org/0000-0002-8367-3424
Dae Sun Jo
https://orcid.org/0000-0002-3141-9539
Hyun Mi Kang
https://orcid.org/0000-0003-3456-793X
Joon Kee Lee
https://orcid.org/0000-0001-8191-0812
Chun Soo Kim
https://orcid.org/0000-0003-3888-334X
Dong Hyun Kim
https://orcid.org/0000-0001-9883-0229
Jae Hong Choi
https://orcid.org/0000-0003-3284-9407
Byung Wook Eun
https://orcid.org/0000-0003-3147-9061
Nam Hee Kim
https://orcid.org/0000-0002-1793-1392
Eun Young Cho
https://orcid.org/0000-0002-2286-4593
Yun-Kyung Kim
https://orcid.org/0000-0003-4396-8671
Han Wool Kim
https://orcid.org/0000-0003-3463-3060
Eun Hwa Choi
https://orcid.org/0000-0003-4890-6293

Funding

This study was supported by the Korea Disease Control and Prevention Agency (Grant number 2018E240600) and Pfizer grant (Grant number 69765907).

Disclosure

The authors have no potential conflicts of interest to disclose related to this study. The authors have no conflicts of interest to disclose related to this study. Outside this study, the authors declare that Choi EH has received over the past 36 months, research grants (paid to the Seoul National University Hospital) from Pfizer, Merck, Julius Clinical. Yun KW has received over the past 6 months, research grants (paid to the Seoul National University Hospital) from Pfizer. Lee H has received over the past 36 months, research grants (paid to the Seoul National University Bundang Hospital) from Pfizer, Merck, and GSK. The funders had no role in the decision to submit the paper for publication.

Results: Of the 187 cases with a determined serotype, the most frequent serotypes identified were 10A (21.9%), 15C (11.8%), 15A (9.1%), 15B (8.0%), and 19A (7.5%), and 23B (5.9%). Compared to the pre-COVID-19 period, the proportion of serotype 10A decreased (27.4% vs. 12.9%), while serotypes 23B (0.9% vs. 14.3%) and 6C (0.9% vs. 7.1%) increased. In regard to the vaccine serotype, PCV13 serotypes accounted for 12.3%, PCV15/PCV20 common serotypes for 3.2%, and PCV20 unique serotypes for 35.3% of IPD cases. Serotype 15C, cross protected by the 15B conjugate vaccines, accounted for 11.8%, and non-PCV20 serotypes for 36.4%.
Conclusion: Given the approval of two new PCVs, the study results identified the substantial contribution of non-PCV13 serotypes to pediatric IPD and provide critical insights for optimal vaccination strategies to protect children against pneumococcal diseases.

Keywords: *Streptococcus pneumoniae*; Invasive Pneumococcal Diseases; Pneumococcal Conjugate Vaccines; Serotypes; Children; COVID-19; Korea

INTRODUCTION

Streptococcus pneumoniae is a major pathogen of respiratory infections, and is also a leading cause of invasive diseases, including bacteremia, meningitis, and pneumonia in children.[1,2] More than 100 unique *S. pneumoniae* serotypes have been identified, but only a limited number are responsible for causing severe disease in humans.[3] Both healthy children and those with underlying medical conditions are susceptible to pneumococcal infections, underscoring the importance of comprehensive vaccination programs.[4] In Korea, the 10-valent and 13-valent pneumococcal conjugate vaccines (PCV10 and PCV13, respectively) have been implemented in 2010, and used in the national immunization program (NIP) since 2014. The 15-valent conjugate vaccine (PCV15), which includes additional serotypes 22F and 33F beyond those covered by PCV13, was introduced into the NIP replacing PCV10 and being used alongside PCV13 as of April 2024. Recently, the 20-valent conjugate vaccine (PCV20), which includes additional serotypes 8, 10A, 11A, 12F, and 15B beyond those in PCV15, was approved by Ministry of Food and Drug Safety in October 2024. PCV15 or PCV20 are currently recommended for use in children in about 50 countries worldwide.[5] As of January 2025, the number of countries where both PCV15 and PCV20 are used simultaneously is expanding and the preference for one over the other is an evolving target, as shown in Japan.[6]

As the number of coronavirus disease 2019 (COVID-19) cases began to rise in early 2020 in Korea, non-pharmaceutical interventions (NPIs) such as social distancing, mask wearing, and school closures were implemented. These measures remained in place throughout the pandemic and were lifted gradually since 2022.[7] Studies have reported a significant decline in invasive pneumococcal disease (IPD) cases globally following the onset of the COVID-19 pandemic and the widespread implementation of NPIs.[8,9] As restrictions were lifted and normal activities resumed, a resurgence was observed in several countries, highlighting the influence of public health measures on disease dynamics.[10-13]

According to a previous study in Korea, the IPD case number per in-hospital patients significantly decreased from April 2020 following the onset of the COVID-19 pandemic.[14] Before the COVID-19 pandemic in 2014–2019 period, serotype 10A was the most prevalent in pediatric IPD.[15]

Establishing appropriate vaccination policies for the pediatric population is crucial, not only to prevent pneumococcal disease in children but also to provide indirect effects on

Author Contributions

Conceptualization: Kang D, Choi EH. Data curation: Kang D, Lee H, Song ES, Ahn JG, Park SE, Lee T, Cho HK, Lee J, Kim YJ, Jo DS, Kang HM, Lee JK, Kim CS, Kim DH, Choi JH, Eun BW, Kim NH, Cho EY, Kim YK, Kim HW; Formal analysis: Kang D; Funding acquisition: Choi EH; Investigation: Kang D; Methodology: Choi EH; Software: Kang D, Yun KW; Validation: Choi EH; Visualization: Kang D; Writing - original draft: Kang D; Writing - review & editing: Choi EH.

unvaccinated adults, particularly the elderly. This study aimed to evaluate changes in the number of cases (per in-hospital patients) and the serotype distribution of IPD isolates in children after the COVID-19 pandemic era, to inform the establishment of pneumococcal vaccine policies for Korean children.

METHODS

Study design

A multicenter surveillance network for IPD was launched in 1996 at 18 sites and has since been expanded to 20–29 sites, with participation of the specialists in pediatric infectious diseases. Due to changes in the staff members over time, 20 hospitals participated during our study period; 13 hospitals located in the national capital and suburban region (Seoul St. Mary's Hospital, Seoul National University Children's Hospital, Severance Children's Hospital, Samsung Medical Center, Seoul Asan Medical Center, Nowon Eulji Medical Center, Ewha Womans University Hospital, Inha University Hospital, Inje University Ilsan Paik Hospital, Korea University Ansan Hospital, Seoul National University Bundang Hospital, CHA Bundang Medical Center, and Hallym University Medical Center), and 7 hospitals located in the regional central cities of provinces (Chungcheongbuk-do: Chungbuk National University Hospital, Chungcheongnam-do: Chungnam National University Hospital, Jeollabuk-do: Jeonbuk National Univeristy Hospital, Gwangju/Jeollanam-do: Chonnam National University Hospital, Daegu/Gyeongsangbuk-do: Keimyung University Dongsan Medical Center, Busan/Gyeongsangnam-do: Pusan National University Yangsan Hospital, and Jeju-do: Jeju National University Hospital). Data were collected from children and adolescents under 19 years of age who were diagnosed with IPD from January 2016 to December 2023. IPD was defined as disease caused by *S. pneumoniae* isolated from normally sterile body fluids, such as blood, cerebrospinal fluid (CSF), pleural fluid, joint fluid, ascites, or a deep-seated abscess. We selected only the first isolate to avoid duplication from multiple sources (e.g., blood and CSF) during a single infection episode or repeated isolation in follow-up cultures. Initial identification of the isolates was performed at the respective study site, with subsequent confirmation at the central research laboratory at Seoul National University Children's Hospital. Investigators reviewed hospital medical records to extract data of demographic characteristics and clinical manifestations.

The study period was divided into two phases based on the onset of the COVID-19 pandemic. Pre-COVID-19 period was defined as a period from January 2016 to December 2019, and during/post-COVID-19 period was defined as a period from January 2020 to December 2023.

Definition

S. pneumoniae was confirmed by culture, antigen detection and polymerase chain reaction (PCR). Serotypes were determined by the Quellung reaction using antisera from Statens Serum Institut, Copenhagen, Denmark. PCV13 serotypes were defined as the group of serotypes included in PCV13 vaccine (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F). PCV15/PCV20 common serotypes referred to the serotypes that are not included in the PCV13 vaccine but are commonly included in the PCV15 and PCV20 vaccine (22F and 33F), while PCV20 unique serotypes referred to the serotypes that are not included in the PCV15 vaccine but are included in the PCV20 vaccine (8, 10A, 11A, 12F, and 15B). Non-PCV20 serotypes were defined as all other serotypes. Serotype 15C was considered PCV20-related, as capsular polysaccharides of serotypes 15B and 15C show similar chemical structures and serotype

https://doi.org/10.3346/jkms.2025.40.e250

15B polysaccharide conjugate containing vaccine elicits a partial cross-functional immune response to 15C.[16-18]

To infer the trend of annual prevalence, we assessed the monthly and yearly number of IPD cases in individuals under 19 years old from the participating hospitals, as well as the yearly number of in-hospital pediatric patients from these hospitals. The annual number of IPD cases per 100,000 in-hospital pediatric patients were estimated.

Statistical analysis

Mean, median, and proportion were used for the statistics. Statistical analyses were performed using SPSS software version 29.0 (IBM SPSS, Chicago, IL, USA). Rates and proportions were compared using either the chi-square test or Fisher's exact test, as appropriate. A *P* value of less than 0.05 was considered statistically significant.

Ethics statement

This study protocol was approved by the Institutional Review Board (IRB) of Seoul National University Hospital (IRB No. 2109-105-1255) and each participating hospital. Informed consent was exempted because the pneumococcal isolates were obtained as a standard part of routine patient care.

RESULTS

Subject characteristics

A total of 188 IPD isolates were identified from normally sterile body fluids, including blood, CSF, pleural fluid, joint fluid, ascites, or deep-seated abscesses, in Korean children during the study period; 117 cases in the pre-COVID-19 period and 71 cases in the during/post-COVID-19 period. The clinical characteristics were presented in **Table 1**. Among the total IPD cases, 56.9% (n = 107) were male and 43.1% (n = 81) were female. The median age was 32 (range, 2–223) months old, with 39.4% (n = 74) patients under 2 years old, 30.3% (n = 57) patients between 2–5 years old, and 29.3% (n = 55) patients over 5 years old. Clinical diagnoses were bacteremia without focus in 52.7% (n = 99), meningitis in 14.4% (n = 27), and bacteremic pneumonia and/or empyema in 16.5% (n = 31). Regarding risk factors, 62.8% (n = 118) patients had no known risk factors for IPD, 26.1% (n = 49) were immunocompromised, 10.1% (n = 19) had underlying medical conditions, and 1.1% (n = 2) had asplenia. There was no statistically significant difference in sex, age, diagnosis, and underlying disease among patients with IPD between the pre-COVID-19 period and the during/post-COVID-19 period.

Annual IPD case number per in-hospital patients

The annual cumulative IPD cases are shown in **Fig. 1**. The average yearly case number in pre-COVID-19 period was 22.2 per 100,000 in-hospital patients, whereas the yearly cumulative case number during and after the COVID-19 pandemic was 10.0 per 100,000 in 2020, 22.1 per 100,000 in 2021, 24.7 per 100,000 in 2022, and 26.3 per 100,000 in 2023, respectively, showing a trend of significant reduction in 2020 followed by recovering pattern from then end of 2021. From January 2020, the IPD case number was generally lower than the average number observed during the pre-COVID-19 period. However, by early 2022, the monthly case number began to exceed those of the pre-COVID-19 period. Additionally, in 2020, the usual seasonal pattern of a sharp rise in late autumn and winter was not seen. This seasonal trend began to re-emerge in 2021, resembling the pattern observed before the COVID-19 pandemic.

Table 1. Clinical characteristics of invasive pneumococcal isolates

Variables	No. (%) of isolates		
	Pre-COVID-19 (2016–2019) (n = 117)	During/post-COVID-19 (2020–2023) (n = 71)	Total (N = 188)
Sex			
Male	69 (59.0)	38 (53.5)	107 (56.9)
Female	48 (41.0)	33 (46.5)	81 (43.1)
Age, yr			
Median age, mon	33 (2–223)	32 (2–199)	32 (2–223)
< 2	48 (41.0)	26 (36.6)	74 (39.4)
2–5	34 (29.1)	23 (32.4)	57 (30.3)
≥ 5	35 (29.9)	20 (28.2)	55 (29.3)
Diagnosis			
Bacteremia without focus	59 (50.4)	40 (56.3)	99 (52.7)
Meningitis	21 (18.0)	6 (8.5)	27 (14.4)
Bacteremic pneumonia or empyema	18 (15.4)	13 (18.3)	31 (16.5)
Septic arthritis or osteomyelitis	8 (6.8)	1 (1.4)	9 (4.8)
Peritonitis	3 (2.6)	1 (1.4)	4 (2.1)
Endocarditis	1 (0.9)	1 (1.4)	2 (1.1)
Others	7 (6.0)	5 (7.0)	12 (6.4)
Underlying conditions			
No known risk factor	69 (59.0)	49 (69.0)	118 (62.8)
Immunocompromised	34 (29.1)	15 (21.1)	49 (26.1)
Immunosuppressive drug	24 (20.5)	12 (16.9)	36 (19.1)
Congenital immunodeficiency	7 (6.0)	3 (4.2)	10 (5.3)
Chronic renal failure or nephrotic syndrome	3 (2.6)	0 (0.0)	3 (1.6)
Underlying medical condition	13 (11.1)	6 (8.5)	19 (10.1)
Chronic heart disease	6 (5.1)	2 (2.8)	8 (4.3)
Chronic respiratory disease	4 (3.4)	2 (2.8)	6 (3.2)
Cochlear implant	3 (2.6)	1 (1.4)	4 (2.1)
CSF leak	0 (0.0)	1 (1.4)	1 (0.5)
Asplenia	1 (0.9)	1 (1.4)	2 (1.1)

Values are presented as number (%) or median (range).
COVID-19 = coronavirus disease 2019, CSF = cerebrospinal fluid.

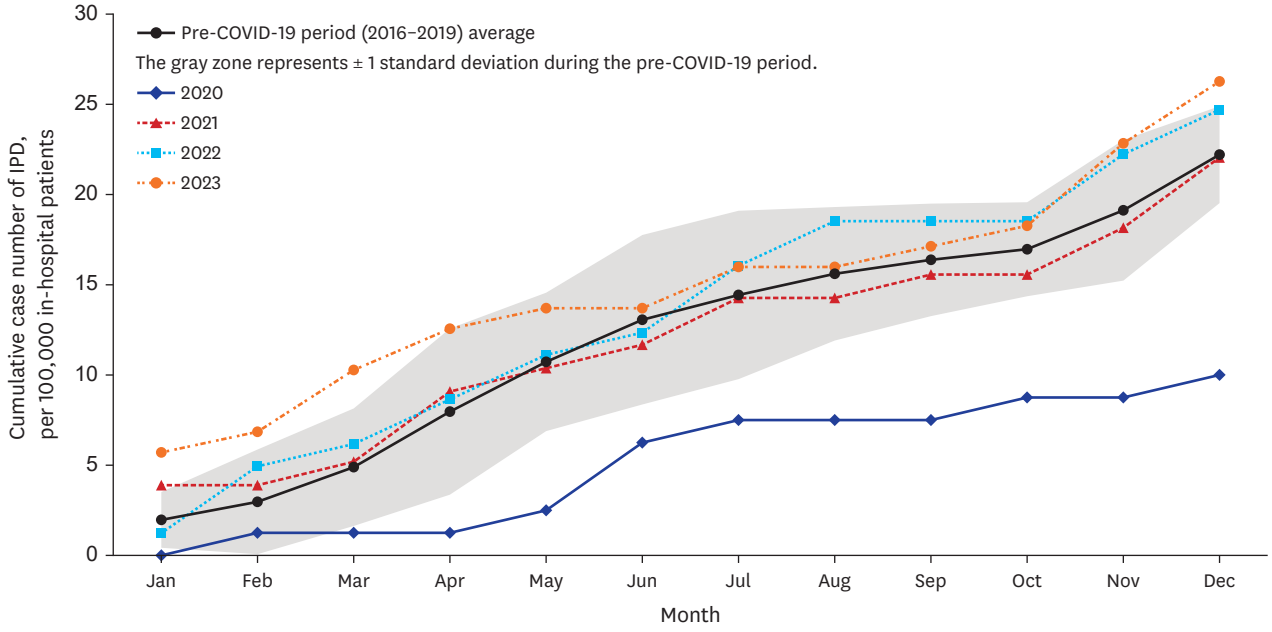

Fig. 1. Annual case number of IPD per 100,000 in-hospital patients, from 2020 to 2023. The black bold line represents average annual incidence of IPD in pre-COVID-19 period (2016–2019). The gray zone represents ± 1 standard deviation of the cumulative case number of IPD in pre-COVID-19 period.
COVID-19 = coronavirus disease 2019, IPD = invasive pneumococcal disease.

https://doi.org/10.3346/jkms.2025.40.e250

Serotype distribution

Serotypes were determined for 187 cases except one isolate that failed to grow (**Table 2**). Throughout the study period, the serotypes with more than 5 isolates were identified in the following order: 10A (n = 41, 21.9%), 15C (n = 22, 11.8%), 15A (n = 17, 9.1%), 15B (n = 15, 8.0%), 19A (n = 14, 7.5%), 23B (n = 11, 5.9%), 23A (n = 8, 4.3%), 19F (n = 7, 3.7%), 34 (n = 7, 3.7%), 35B (n = 7, 3.7%), 6C (n = 6, 3.2%), and 11A (n = 6, 3.2%). Overall, PCV13 serotypes accounted for 12.3% (n = 23), PCV15/PCV20 common serotypes accounted for 3.2% (n = 6), PCV20 unique serotypes accounted for 35.3% (n = 66), PCV20 related serotypes accounted for 11.8% (n = 22), and non-PCV20 serotypes accounted for 36.4% (n = 68). **Fig. 2** shows the annual serotype distribution of IPD cases during the study period.

Before the COVID-19 pandemic, PCV13 serotypes accounted for 12.8% (n = 15), PCV15/PCV20 common serotypes accounted for additional 4.3% (n = 5), PCV20 unique serotypes accounted for additional 50% (n = 42.7), PCV20 related serotype accounted for 9.4% (n = 11), and non-PCV20 serotypes accounted for 29.1% (n = 34) (**Supplementary Table 1**). During this period, serotype 10A was the most prevalent (n = 32, 27.4%), followed by serotype 15C (n = 11, 9.4%), 19A (n = 11, 9.4%), 15B (n = 9, 7.7%), and 15A (n = 9, 7.7%). During and after the COVID-19 pandemic, PCV13 serotypes accounted for 11.4% (n = 8), PCV15/PCV20 common serotypes accounted for 1.4% (n = 1), PCV20 unique serotypes accounted for 22.9% (n = 16), PCV20 related serotype accounted for 15.7% (n = 11), and non-PCV20 serotypes accounted for 48.6% (n = 34). In this phase, serotypes 15C (n = 11, 15.7%), and 23B (n = 10, 14.3%) were prevalent, followed by 10A (n = 9, 12.9%), and 15A (n = 8, 11.4%), and 15B (n = 6, 8.6%).

Table 2. Annual serotype distribution of invasive pneumococcal isolates, from 2016 to 2023

Serotype	No. (%) of isolates by year								
	2016	2017	2018	2019	2020	2021	2022	2023	Total
PCV13	2 (6.5)	6 (18.2)	2 (8.0)	5 (17.9)	-	3 (15.8)	2 (10.5)	3 (13.0)	23 (12.3)
19A	2 (6.5)	5 (15.2)	1 (4.0)	3 (10.7)	-	-	1 (5.3)	2 (8.7)	14 (7.5)
19F	-	-	-	2 (7.1)	-	3 (15.8)	1 (5.3)	1 (4.3)	7 (3.7)
6A	-	1 (3.0)	1 (4.0)	-	-	-	-	-	2 (1.1)
PCV15/PCV20 common	2 (6.5)	1 (3.0)	2 (8.0)	-	1 (11.1)	-	-	-	6 (3.2)
22F	2 (6.5)	1 (3.0)	1 (4.0)	-	1 (11.1)	-	-	-	5 (2.7)
33F	-	-	1 (4.0)	-	-	-	-	-	1 (0.5)
PCV20 unique	14 (45.2)	11 (33.3)	12 (48.0)	13 (46.4)	3 (33.3)	5 (26.3)	4 (21.1)	4 (17.4)	66 (35.3)
10A	7 (22.6)	9 (27.3)	7 (28.0)	9 (32.1)	2 (22.2)	4 (21.1)	3 (15.8)	-	41 (21.9)
15B	3 (9.7)	1 (3.0)	3 (12.0)	2 (7.1)	1 (11.1)	1 (5.3)	1 (5.3)	3 (13.0)	15 (8.0)
11A	1 (3.2)	1 (3.0)	1 (4.0)	2 (7.1)	-	-	-	1 (4.3)	6 (3.2)
12F	3 (9.7)	-	1 (4.0)	-	-	-	-	-	4 (2.1)
PCV20 related	3 (9.7)	5 (15.2)	1 (4.0)	2 (7.1)	-	-	4 (21.1)	7 (30.4)	22 (11.8)
15C	3 (9.7)	5 (15.2)	1 (4.0)	2 (7.1)	-	-	4 (21.1)	7 (30.4)	22 (11.8)
Non-PCV20	10 (32.3)	9 (27.3)	8 (32.0)	7 (25.0)	5 (55.6)	11 (57.9)	9 (47.4)	9 (39.1)	68 (36.4)
15A	4 (12.9)	-	4 (16.0)	1 (3.6)	2 (22.2)	4 (21.1)	1 (5.3)	1 (4.3)	17 (9.1)
23B	-	1 (3.0)	-	-	1 (11.1)	3 (15.8)	2 (10.5)	4 (17.4)	11 (5.9)
23A	1 (3.2)	-	2 (8.0)	2 (7.1)	-	-	1 (5.3)	2 (8.7)	8 (4.3)
34	-	2 (6.1)	-	1 (3.6)	1 (11.1)	2 (10.5)	-	1 (4.3)	7 (3.7)
35B	1 (3.2)	2 (6.1)	-	1 (3.6)	1 (11.1)	1 (5.3)	1 (5.3)	-	7 (3.7)
6C	1 (3.2)	-	-	-	-	-	4 (21.1)	1 (4.3)	6 (3.2)
13	3 (9.7)	-	-	2 (7.1)	-	-	-	-	5 (2.7)
24F	-	2 (6.1)	-	-	-	1 (5.3)	-	-	3 (1.6)
20	-	1 (3.0)	1 (4.0)	-	-	-	-	-	2 (1.1)
16F	-	-	1 (4.0)	-	-	-	-	-	1 (0.5)
38	-	1 (3.0)	-	-	-	-	-	-	1 (0.5)
Nontypeable	-	1 (3.0)	-	1 (3.6)	-	-	-	-	2 (1.1)
Total	31 (100.0)	33 (100.0)	25 (100.0)	28 (100.0)	9 (100.0)	19 (100.0)	19 (100.0)	23 (100.0)	187 (100.0)

PCV = pneumococcal conjugate vaccine.

https://doi.org/10.3346/jkms.2025.40.e250

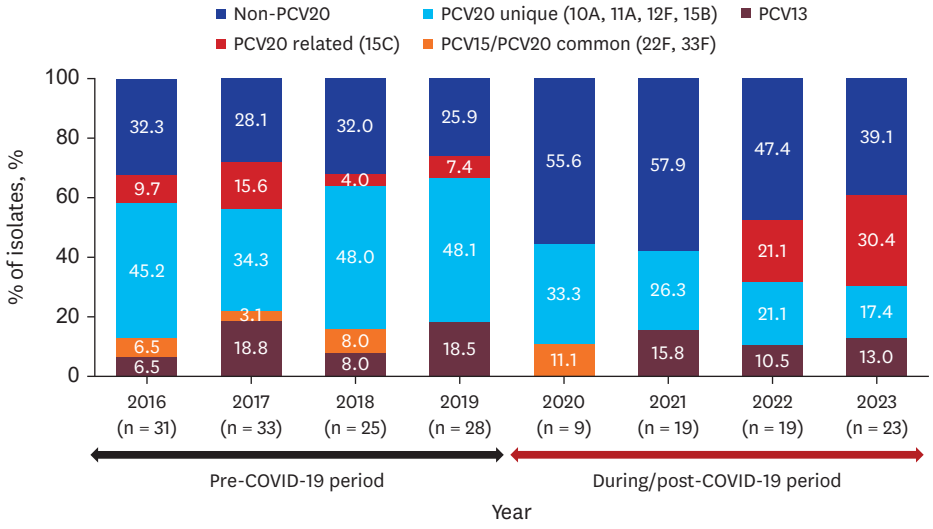

Fig. 2. Changes in the annual serotype distribution of invasive pneumococcal isolates by vaccine type, from 2016 to 2023.
PCV = pneumococcal conjugate vaccine, COVID-19 = coronavirus disease 2019.

Fig. 3 shows the changes in serotype prevalence for each serotype between the pre-COVID-19 period and the during/post-COVID-19 period. Serotype 10A decreased significantly from 27.4% (n = 32) in the pre-COVID-19 period to 12.9% (n = 9) in the during/post-COVID-19 period ($P = 0.020$). Serotype 23B increased significantly from 0.9% (n = 1) to 14.3% (n = 10) ($P < 0.001$). Serotype 6C also showed a significant rise from 0.9% (n = 1) to 7.1% (n = 5) ($P = 0.028$).

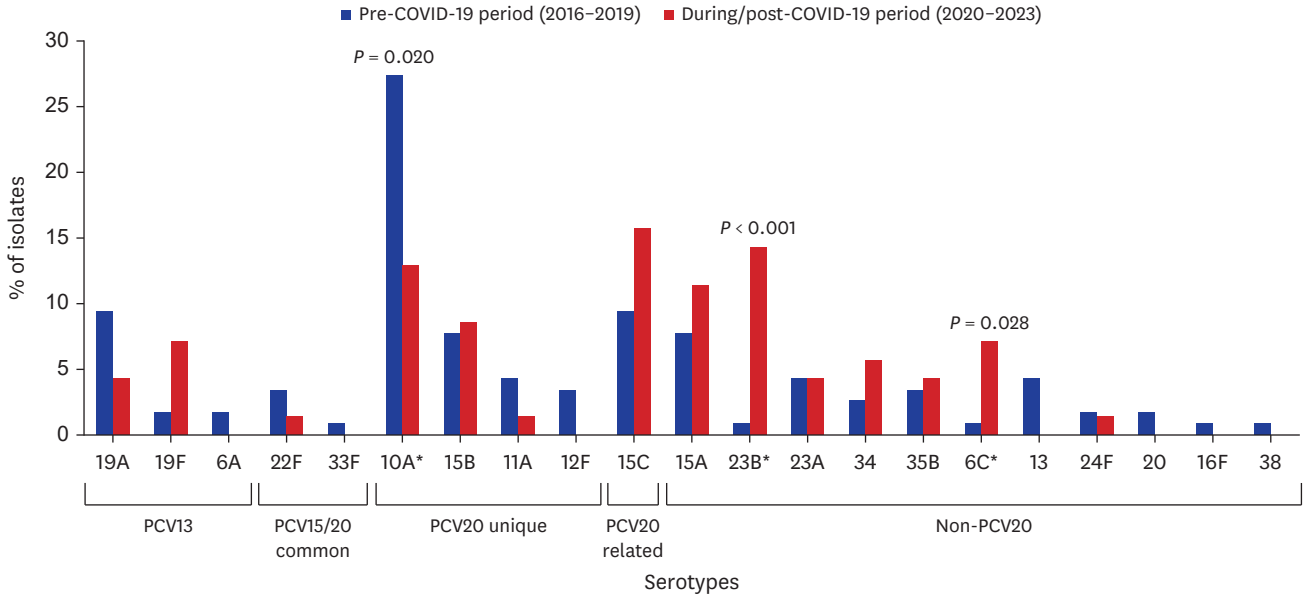

Fig. 3. Comparison of serotype distribution of invasive pneumococcal isolates between pre- and during/after-COVID-19 pandemic period.
PCV = pneumococcal conjugate vaccine, COVID-19 = coronavirus disease 2019.
*Statistically significant *P* values < 0.05 by χ^2 test or Fisher's exact test are shown.

https://doi.org/10.3346/jkms.2025.40.e250

DISCUSSION

In this study, we analyzed trends in the number of IPD cases per in-hospital patient and changes in the serotype distribution of IPD isolates detected in Korean children between 2016 and 2023. Throughout the study period from 2016 to 2023, the most frequent serotypes identified were 10A (21.9%), 15C (11.8%), 15A (9.1%), 15B (8.0%), 19A (7.5%), and 23B (5.9%). In regard to the vaccine type, PCV13 serotypes accounted for 12.3%, PCV15/PCV20 common serotypes for 3.2%, PCV20 unique serotypes for 35.3% of IPD cases. Additionally, PCV20 related serotype 15C for 11.8%, and non-PCV20 serotypes for 36.4%.

PCV15 was first approved for use in adults by the U.S. Food and Drug Administration and the European Medicines Agency in 2021. Subsequently, in 2022, both agencies extended approval for its use in infants. PCV20 was approved for use in adults in the U.S. and Europe in 2021 and 2022, respectively, with approvals for use in infants granted in June 2023 in the U.S. and January 2024 in Europe. Both PCV15 and PCV20 are currently included in the NIP for infants in selected countries including the U.S., some European countries, and Japan.[16,17] In Korea, both PCV13 and PCV15 are included in the current NIP, and PCV20, recently licensed, is expected to be available in early 2025.

Throughout the study period from 2016 to 2023, only 12.3% of IPD cases among children were attributable to the serotypes included in PCV13. Compared to the period before the introduction of PCV13,[19] the proportion of PCV13 type has decreased from 67.9% in 2010 to 12.3% in our study period. Instead, the proportion of non-PCV13 serotypes increased from 32.1% to 87.7%. Though PCVs have significantly reduced the burden of pneumococcal diseases, serotype replacement, in which non-vaccine serotypes become more prevalent after vaccination, could increase in prevalence and reduce the benefits of vaccination. With the availability of two new PCVs, PCV15 and PCV20, evaluating the optimal immunization program is crucial to address the remaining disease burden not covered by PCV13.

The capsular polysaccharides of serotypes 15B and 15C show similar chemical structures and can interconvert in vivo[16,17] The serotype 15B polysaccharide conjugate containing vaccine, PCV20, elicits a cross-functional immune response to 15C.[18] In PCV20-vaccinated adults, robust opsonophagocytic activity antibody titers were detected against both serotypes 15B and 15C.[18] Therefore, many reports do not differentiate between them and categorize them as 15B/C.[8,17] By including 15B/C in the PCV20 serotypes, PCV13 serotypes (6A, 19A, 19F) were responsible for 12.3%, the two additional serotypes included in PCV15 (22F, 33F) serotypes caused 3.2%, and the five additional serotypes included in PCV20 (10A, 11A, 12F, 15B/C) caused additional 47.1% of IPD cases between 2016 and 2023. The proportion of serotypes covered by PCV15 accounted for 15.5%, and those covered by PCV20 including 15B/C accounted for 62.6% of all the IPD cases.

Development of an optimal immunization program requires a complex decision-making process, considering expansion of protection for disease burden, immunogenicity, cost for the implementation, and serotype replacement.

For the expansion of protection, PCV20 takes advantage over PCV13 and PCV15 as our study results revealed that PCV20 can protect additional 47.1% of remaining IPD burden, highlighting its broader coverage and potential public health impact. Higher-valency PCVs tend to elicit lower serotype-specific antibody levels. Except for serotype 3,

the immunogenicity of PCV15 and PCV20 for the common serotypes was lower compared to PCV13, though the non-inferiority met the criteria and was sufficient to provide protection against IPD.[20,21] PCV15 demonstrated a significantly stronger immune response against serotype 3 compared to PCV13.[20] Since serotype 3 pneumococci release a higher amount of capsular polysaccharide than other serotypes, this reduces the ability of anticapsular antibodies to bind to the bacterial surface to induce killing.[22] The scientific evidence of higher immunogenicity to serotype 3 must be confirmed through vaccine efficacy studies. Interestingly, during the 8-year study period, serotype 3 was not identified in any of the IPD cases in Korea. A possible reason for this low prevalence of serotype 3 in IPD could be its low prevalence in carriage rate among children or its high susceptibility to antimicrobial agents in Korea. Two carriage studies conducted on children attending daycare centers in 2014 and 2019[23,24] along with a single-center study analyzing carriage status in children from 2010 to 2015[25] reported serotype 3 carriage rates ranging from 0.8% to 1.8%. Moreover, all serotype 3 isolates were found to be susceptible to penicillin and cefotaxime, which are frequently prescribed for acute infectious disease in children in Korea.[25]

To decide on the inclusion of a new higher-valency PCV into NIP in Korea, an economic analysis that assesses both the costs and benefits is crucial. Currently, PCV15 is provided free of charge through the NIP at the same price as PCV13 when purchased by the government. Therefore, switching from PCV13 to PCV15 is considered cost-saving option for the routine pediatric PCV program. One study demonstrated that PCV20 prevented more pneumococcal diseases and deaths, while the PCV20 vaccination strategy incurred lower total medical costs compared to the PCV13 vaccination strategy in Korean children.[26] Another study in Germany showed that the PCV20 3+1 schedule was more effective in preventing pneumococcal disease and resulted in lower costs compared to both the PCV13 2+1 and PCV15 2+1 schedules.[27]

In the present study, we found serotypes 23B and 6C were in an increasing trend among the non-PCV20 serotypes. We do not know whether the COVID-19 pandemic itself led to the rise and fall of the specific serotype. The secular trend of pneumococcal serotypes has tended to influence changes in the ecological epidemiology of serotype distribution and has been occurring over the years. Considering the relatively small increase in serotypes 23B and 6C after the pandemic, this change resembles the secular trend in serotype distribution that we observed before the COVID-19 pandemic. Using a high-valency PCV in children can decrease the transmission of the vaccine-contained serotypes in the population level as young children are the main source of carriage and transmission. Surveillance for the nasopharyngeal carriage in children and IPD burdens in all age groups are mandatory for the decision of immunization program.

This study has several limitations. IPD isolates were collected from children diagnosed at 20 hospitals, which does not represent all hospitals nationwide and includes a small case number only. Moreover, the yearly number of in-hospital pediatric patients may have been influenced by other factors such as NPIs during the COVID-19 pandemic, recent changes in hospital operations and personnel shortages, particularly in pediatric patient care. Since this study is not population based, an accurate incidence and the reduction in disease burden achieved by vaccination program cannot be determined. Secondly, due to changes in the population structure of South Korea, age standardization is necessary, but this was not performed in our study. Despite these limitations, this study is the largest multicenter-based analysis in Korea to date, providing valuable insights into the incidence and serotype distribution of pediatric IPD isolates.

This hospital-based surveillance study reveals a significant reduction in the number of IPD cases during the COVID-19 pandemic, with a subsequent return to pre-pandemic levels. More importantly, the study identified a notable shift in serotype distributions of pediatric IPD isolates. These findings on serotype distribution provide critical insights for planning optimal vaccination strategies to protect children against pneumococcal diseases. In addition to evaluating the effectiveness of vaccination, further research on the cost-effectiveness and economic impact of vaccination programs is needed.

SUPPLEMENTARY MATERIAL

Supplementary Table 1

Serotype distribution of invasive pneumococcal isolates before and after COVID-19 pandemic

REFERENCES

1. Troeger C, Blacker B, Khalil IA, Rao PC, Cao J, Zimsen SRM, et al. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory infections in 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Infect Dis* 2018;18(11):1191-210. PUBMED | CROSSREF
2. Weiser JN, Ferreira DM, Paton JC. *Streptococcus pneumoniae*: transmission, colonization and invasion. *Nat Rev Microbiol* 2018;16(6):355-67. PUBMED | CROSSREF
3. Geno KA, Gilbert GL, Song JY, Skovsted IC, Klugman KP, Jones C, et al. Pneumococcal capsules and their types: past, present, and future. *Clin Microbiol Rev* 2015;28(3):871-99. PUBMED | CROSSREF
4. Backhaus E, Berg S, Andersson R, Ockborn G, Malmström P, Dahl M, et al. Epidemiology of invasive pneumococcal infections: manifestations, incidence and case fatality rate correlated to age, gender and risk factors. *BMC Infect Dis* 2016;16(1):367. PUBMED | CROSSREF
5. Wodi AP, Murthy N, McNally VV, Daley MF, Cineas S. Advisory committee on immunization practices recommended immunization schedule for children and adolescents aged 18 years or younger - United States, 2024. *MMWR Morb Mortal Wkly Rep* 2024;73(1):6-10. PUBMED | CROSSREF
6. Ministry of Health, Labour and Welfare (JP). Pneumococcal vaccine for children. https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/kenkou/kekkaku-kansenshou/yobou-sesshu/vaccine/pneumococcus-child/index.html. Updated 2024. Accessed December 2, 2024.
7. Cho HJ, Rhee JE, Kang D, Choi EH, Lee NJ, Woo S, et al. Epidemiology of respiratory viruses in Korean children before and after the COVID-19 pandemic: a prospective study from national surveillance system. *J Korean Med Sci* 2024;39(19):e171. PUBMED | CROSSREF
8. Yildirim I, Lapidot R, Shaik-Dasthagirisaheb YB, Hinderstein S, Lee H, Klevens M, et al. Invasive pneumococcal disease after 2 decades of pneumococcal conjugate vaccine use. *Pediatrics* 2024;153(1):e2023063039. PUBMED | CROSSREF
9. Brueggemann AB, Jansen van Rensburg MJ, Shaw D, McCarthy ND, Jolley KA, Maiden MCJ, et al. Changes in the incidence of invasive disease due to *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis* during the COVID-19 pandemic in 26 countries and territories in the invasive respiratory infection surveillance initiative: a prospective analysis of surveillance data. *Lancet Digit Health* 2021;3(6):e360-70. PUBMED | CROSSREF
10. Shaw D, Abad R, Amin-Chowdhury Z, Bautista A, Bennett D, Broughton K, et al. Trends in invasive bacterial diseases during the first 2 years of the COVID-19 pandemic: analyses of prospective surveillance data from 30 countries and territories in the IRIS Consortium. *Lancet Digit Health* 2023;5(9):e582-93. PUBMED | CROSSREF
11. Bertran M, Amin-Chowdhury Z, Sheppard CL, Eletu S, Zamarreño DV, Ramsay ME, et al. Increased incidence of invasive pneumococcal disease among children after COVID-19 pandemic, England. *Emerg Infect Dis* 2022;28(8):1669-72. PUBMED | CROSSREF
12. Perniciaro S, van der Linden M, Weinberger DM. Reemergence of invasive pneumococcal disease in Germany during the spring and summer of 2021. *Clin Infect Dis* 2022;75(7):1149-53. PUBMED | CROSSREF

13. Rybak A, Assad Z, Levy C, Bonarcorsi S, Béchet S, Werner A, et al. Age-specific resurgence in invasive pneumococcal disease incidence in the COVID-19 pandemic era and its association with respiratory virus and pneumococcal carriage dynamics: a time-series analysis. *Clin Infect Dis* 2024;78(4):855-9. PUBMED | CROSSREF

14. Kim YK, Choi YY, Lee H, Song ES, Ahn JG, Park SE, et al. Differential impact of nonpharmaceutical interventions on the epidemiology of invasive bacterial infections in children during the coronavirus disease 2019 pandemic. *Pediatr Infect Dis J* 2022;41(2):91-6. PUBMED | CROSSREF

15. Yun KW, Rhie K, Kang JH, Kim KH, Ahn JG, Kim YJ, et al. Emergence of serotype 10A-ST11189 among pediatric invasive pneumococcal diseases, South Korea, 2014-2019. *Vaccine* 2021;39(40):5787-93. PUBMED | CROSSREF

16. van Selm S, van Cann LM, Kolkman MA, van der Zeijst BA, van Putten JP. Genetic basis for the structural difference between *Streptococcus pneumoniae* serotype 15B and 15C capsular polysaccharides. *Infect Immun* 2003;71(11):6192-8. PUBMED | CROSSREF

17. Andam CP, Mitchell PK, Callendrello A, Chang Q, Corander J, Chaguza C, et al. Genomic epidemiology of penicillin-nonsusceptible pneumococci with nonvaccine serotypes causing invasive disease in the United States. *J Clin Microbiol* 2017;55(4):1104-15. PUBMED | CROSSREF

18. Hao L, Kuttel MM, Ravenscroft N, Thompson A, Prasad AK, Gangolli S, et al. *Streptococcus pneumoniae* serotype 15B polysaccharide conjugate elicits a cross-functional immune response against serotype 15C but not 15A. *Vaccine* 2022;40(33):4872-80. PUBMED | CROSSREF

19. Cho EY, Lee H, Choi EH, Kim YJ, Eun BW, Cho YK, et al. Serotype distribution and antibiotic resistance of *Streptococcus pneumoniae* isolated from invasive infections after optional use of the 7-valent conjugate vaccine in Korea, 2006-2010. *Diagn Microbiol Infect Dis* 2014;78(4):481-6. PUBMED | CROSSREF

20. Lupinacci R, Rupp R, Wittawatmongkol O, Jones J, Quinones J, Ulukol B, et al. A phase 3, multicenter, randomized, double-blind, active-comparator-controlled study to evaluate the safety, tolerability, and immunogenicity of a 4-dose regimen of V114, a 15-valent pneumococcal conjugate vaccine, in healthy infants (PNEU-PED). *Vaccine* 2023;41(5):1142-52. PUBMED | CROSSREF

21. Senders S, Klein NP, Tamimi N, Thompson A, Baugher G, Trammel J, et al. A phase three study of the safety and immunogenicity of a four-dose series of 20-valent pneumococcal conjugate vaccine in healthy infants. *Pediatr Infect Dis J* 2024;43(6):596-603. PUBMED | CROSSREF

22. Choi EH, Zhang F, Lu YJ, Malley R. Capsular polysaccharide (CPS) release by serotype 3 pneumococcal strains reduces the protective effect of anti-type 3 CPS antibodies. *Clin Vaccine Immunol* 2016;23(2):162-7. PUBMED | CROSSREF

23. Choe YJ, Lee HJ, Lee H, Oh CE, Cho EY, Choi JH, et al. Emergence of antibiotic-resistant non-vaccine serotype pneumococci in nasopharyngeal carriage in children after the use of extended-valency pneumococcal conjugate vaccines in Korea. *Vaccine* 2016;34(40):4771-6. PUBMED | CROSSREF

24. Choe YJ, Han MS, Choi YY, Sohn YJ, Kim YK, Kim KM, et al. Trend change of nasopharyngeal colonization with *Streptococcus pneumoniae* and non-typeable *Haemophilus influenzae* in children attending daycare centres: nationwide population-based study, South Korea 2014 and 2019. *Int J Infect Dis* 2021;111:328-32. PUBMED | CROSSREF

25. Lee JK, Yun KW, Choi EH, Kim SJ, Lee SY, Lee HJ. Changes in the serotype distribution among antibiotic resistant carriage *Streptococcus pneumoniae* isolates in children after the introduction of the extended-valency pneumococcal conjugate vaccine. *J Korean Med Sci* 2017;32(9):1431-9. PUBMED | CROSSREF

26. Kang DW, June Choe Y, Lee JY, Suk IA, Kim YS, Kim HY, et al. Cost-effectiveness analysis of the 20-valent pneumococcal conjugate vaccine for the pediatric population in South Korea. *Vaccine* 2024;42(22):126000. PUBMED | CROSSREF

27. Ta A, Kühne F, Laurenz M, von Eiff C, Warren S, Perdrizet J. Cost-effectiveness of PCV20 to prevent pneumococcal disease in the pediatric population: a German societal perspective analysis. *Infect Dis Ther* 2024;13(6):1333-58. PUBMED | CROSSREF