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COMMENTARY

Assessing the Lower Incidence of Invasive Pneumococcal Diseases in Japan During the COVOD-19 Pandemic

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Abstract: During the COVID-19 pandemic from 2020 to 2023 in Japan, in our hospital there were seven cases of invasive pneumococcal diseases (IPDs) in this COVID-19 pandemic period although 14 IPD cases were treated in 2019, 2024, and 2025, such as pre-/post- COVID-19 pandemic period. Of these total 21 IPD patients, five (23.8%) died, and they were all treated during pre-/post-pandemic period. Only 2 of the 21 patients (9.5%) children had been vaccinated. Furthermore, compared with survivors, those who died were younger (54.0 vs 69.4 years old, p = 0.0011), had lower white blood cell counts (3672.1 vs 12117.3/μL, p = 0.0011), and had higher C-reactive protein levels (34.5 vs 22.1 mg/dL, p = 0.0010). Two or more bacteria were isolated, and multiple and/or broad antimicrobial agents were used in fatal cases. These data suggested that IPD cases decreased and might have been less pathogenic during the COVID-19 pandemic period than in the pre-/post-COVID-19 pandemic period. In addition, those who died were younger, more septic due to multiple bacterial infections, and received more and broader antimicrobial agents than survivors. No adult patients received pneumococcal vaccination, which suggests that low vaccination rates lead to the high mortality of adult IPD patients.
Keywords: invasive pneumococcal diseases, *Streptococcus pneumoniae*, COVID-19, meropenem, vaccine

Streptococcus pneumoniae (*S. pneumoniae)* is the one of the representative pathogenic bacteria that induces noninvasive diseases such as pneumonia without bacteremia, otitis media, and rhinosinusitis, but it can also cause invasive pneumococcal disease (IPD), including pneumonia with bacteremia and meningitis.[1,2] The morbidity and mortality, especially of IPD in the children and elderly population, are very high, such as 1.4% and 22.8%, respectively in Japan; therefore, vaccination has been recommended for these two populations.

In Japan, a 23-valent pneumococcal polysaccharide vaccine (PPSV23), a 20-valent pneumococcal conjugate vaccine (PCV20), a 15-valent pneumococcal conjugate vaccine (PCV15), and a 21-valent pneumococcal conjugate vaccine (PCV21) are now available as vaccines for elderly persons with or without underlying diseases, and the notification of IPDs is obligatory.[3,4] However, vaccination rates have been very low in Japan, such as 33% in the coverage populations of national immunization program including 65 years old and 60–64 years old patients with severe underlying diseases although the vaccination rates were about 60% in US and UK.[1,5] Therefore, higher mortality rates of IPD patients have been suggested in Japan, compared with the other countries.

On the other hand, from the national report, the number of IPDs reported included 3348 patients in 2019, but it decreased to 1654 patients in 2020.[5] These data suggested that the COVID-19 pandemic period from 2020 to 2023 affected the incidence of severe pneumococcal diseases, such as IPDs. It is unclear that clinical characteristics of IPD during the COVID-19 pandemic period and details in prior COVID-19 related reports in Japan. Therefore, in this study, the number of IPD cases in our hospital was investigated and compared with during and pre-/post-COVID-19 pandemic period, with a focus on fatal cases.

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The period from January 2019 to March 2025 was investigated, and we defined that 2019 was pre-COVID-19 pandemic, 2020–2023 was the COVID-19 pandemic period, and 2024–2025 was the post-COVID-19 period.

IPDs were defined as *S. pneumoniae i*solated from a normally sterile site, such as cerebrospinal fluid, blood, joint fluid, pleural fluid, pericardial fluid, etc.[1,2] The major clinical syndromes of IPDs included pneumonia, bacteremia, and meningitis.

Antimicrobial susceptibility testing was performed using the liquid microdilution method with the MICroFAST Panel Type7J (Beckman Coulter, Brea, CA, USA). The isolates were considered susceptible (S), intermediate (I), or resistant (R) according to Clinical & Laboratory Standards Institute (CLSI) criteria for minimum inhibitory concentration (MIC).[1,2,4]

These cases and the related studies were approved by the Institutional Review Board of Saitama Medical University International Medical Center as #2022-032 on July 06, 2022, and registered as UMIN000047691. The patients whose specimens were used provided written, informed consent to have their case details and any accompanying images published. The parents or the legal guardian of patients under 18 years of age provided informed consent alternatively. This report adhered to the Declaration of Helsinki.

As for the statistical analysis, sample numbers were not huge and might not be exclude the confounders. In addition, the samples did not show normal data distributions; therefore, non-parametric analysis was mainly performed, and no additional analysis such as regression modeling, multivariable or adjusted analysis were performed. A p-value less than 0.05 was defined as significant difference. All analyses were performed using StatMate Version VI software (Nihon 3B Scientific, Niigata, Japan), which is the same as Easy R software (Saitama, Japan) and SPSS (IBM, Chicago, IL, USA) and available in Japan.

There were 4 IPD cases in 2019, 7 IPD cases in 2020–2023, and 10 IPD cases in 2024–2025 (Total 21 IPD cases) (Figure 1). In 2020–2023, during the COVID-19 pandemic period, the number of IPD cases (7 cases) was half that of the pre- and post- COVID-19 periods (14 cases). In addition, there were 5 fatal IPD cases among the total 21 IPD cases in this study (mortality rate: 5/21 = 23.8%), and all 5 fatal cases occurred in the pre- and post-COVID-19 periods (2 cases in 2019 and 3 cases in 2024) (Table 1). Most of all IPD cases were pneumonia with bacteremia. The others were meningitis, and no arthritis, spondylitis, abscesses were observed. Underlying diseases were heart diseases, malignancies, and diabetes mellitus, etc. In addition, all 21 IPD cases were shock status and managed in the intensive care units (ICUs) with vasopressor and respirators (data not shown). These data also suggested that the COVID-19 pandemic might have

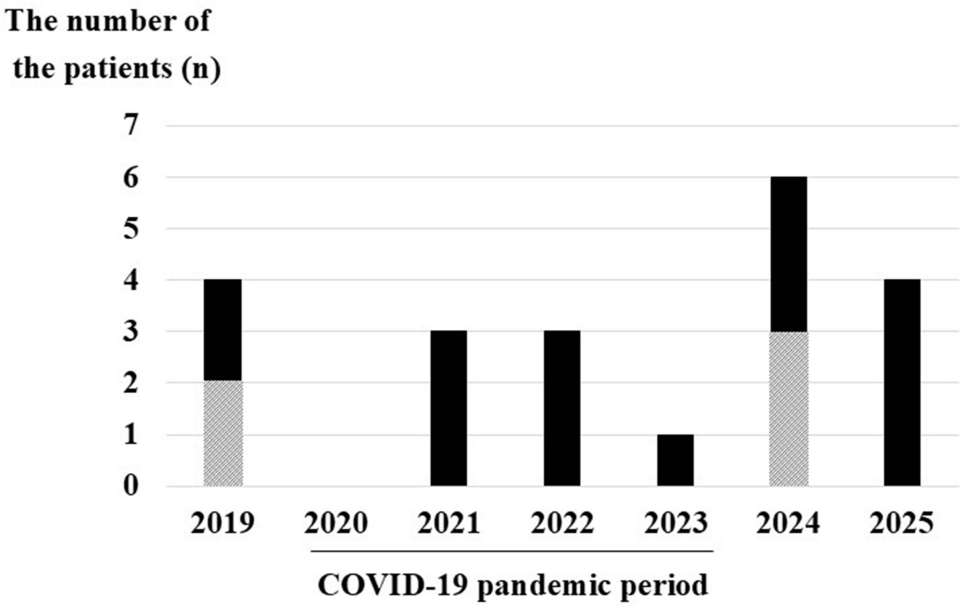

Figure 1 The number of invasive pneumococcal disease (IPD) cases in each year during the COVID-19 pandemic period and the pre-/post-COVID-19 pandemic periods. Striped bars: fatal cases, and black bars: non-fatal cases.

Table 1 Clinical Characteristics of 21 Invasive Pneumococcal Disease Cases

No	Year	Age	Male/ Female	Underlying Diseases	Vaccine	Types of IPDs	WBC (/μL)	CRP (mg/dL)	Isolated Bacteria	Antibiotics	Survive/ Death
1	2019	73	M	Breast cancer	None	Pneumonia, bacteremia	15650	7.412	PSSP	MEPM	Survive
2	2019	64	F	DM	None	Pneumonia, bacteremia	5420	46.487	PSSP, *E. coli*	MEPM	Death
3	2019	55	M	None	None	Meningitis	9490	19.976	PSSP	MEPM, VCM	Survive
4	2019	72	M	Lung cancer	None	Pneumonia, bacteremia	6680	37.155	PSSP	MAPM, AZM	Death
5	2021	71	M	Heart failure, Nephrosis	None	Pneumonia, bacteremia	15940	19.437	PSSP, MSSA	TAZ/PIPC	Survive
6	2021	77	F	SSS	None	Pneumonia, bacteremia	2397	23.347	PSSP	CTRX	Survive
7	2021	75	M	DM	None	Pneumonia, bacteremia	1517	31.911	PSSP	MEPM	Survive
8	2022	79	M	DM, Brain infarction	None	Pneumonia, bacteremia	2960	10.381	PSSP	CTRX, LVFX	Survive
9	2022	54	M	COVID-19	None	Pneumonia, bacteremia	1740	69.239	PSSP	TAZ/PIPC	Survive
10	2022	47	M	None	None	Pneumonia, bacteremia	19650	22.197	PSSP	VCM, CLDM	Survive
11	2023	4	F	TGA	Yes	Pneumonia, bacteremia	6880	6.171	PSSP, MSSA	SBT/ABPC	Survive
12	2024	52	F	Colon cancer	None	Pneumonia, bacteremia	3550	28.987	PSSP, *K. pneumoniae*	MEPM	Death
13	2024	73	M	Lung cancer	None	Pneumonia, bacteremia	28000	13.128	PSSP	LVFX	Survive
14	2024	81	M	COVID-19, Candemia	None	Pneumonia, bacteremia	1990	54.407	PSSP	RDV, CTRX, FLCZ	Death
15	2024	1	F	TAPVR	Yes	Pneumonia, bacteremia	720	5.66	PSSP, *K. pneumoniae*	MEPM, VCM	Death
16	2024	62	M	Esophagus cancer	None	Pneumonia, bacteremia	18830	10.849	PSSP, MRSA	TAZ/PIPC	Survive
17	2024	50	M	DM, Parkinson sx	None	Pneumonia, bacteremia	10252	52.242	PISP	SBT/ABPC	Survive
18	2025	68	F	Influenza	None	Meningitis	21000	17.116	PSSP, *K. pneumoniae*	Peramivir, CTRX	Survive
19	2025	84	M	None	None	Meningitis	15600	18.484	PSSP	VCM, MEPM	Survive
20	2025	91	M	Colon cancer	None	Pneumonia, bacteremia	13480	9.152	PSSP	CTRX	Survive
21	2025	78	M	Aortic aneurysm	None	Pneumonia, bacteremia	10490	23.303	PSSP	TAZ/PIPC	Survive

decreased the incidence of severe pneumococcal diseases, such as IPDs and fatal cases, and these IPDs increased again after the COVID-19 pandemic period.

Of the total 21 cases, the 5 fatal cases were younger (54.0 vs 69.4 years old, p = 0.0011), but the male/female ratio was similar, compared with the 16 survivors (Table 2). Underlying diseases, including Charlson Comorbidity Index (mean: 4.71 vs 4.6) and vaccination histories, were also identical. Only two of 21 patients (9.5%) had been vaccinated. However, white blood cell counts were lower (3672.1 vs 12117.3/μL, p = 0.0011), and C-reactive protein (34.5 vs 22.1 mg/dL, p = 0.0010) was higher in the fatal cases than in the survivors. Two or more bacteria, including *Escherichia coli* and *Klebsiella pneumoniae*, were isolated, and multiple antimicrobial agents, including azithromycin, remdesivir, and fluconazole were used in fatal cases. Penicillin resistant type *S. pneumoniae* (PRSP) were not isolated from both survivors and non-survivors.

In this study, IPD cases decreased during the COVID-19 pandemic period. These data suggested that SARS-CoV-2 might affect *S. pneumoniae*, and several studies have shown that, in 2020, during the first months of the COVID-19 pandemic, the incidence of IPDs was significantly decreased, particularly in children <5 years of age.[6] This finding was

Table 2 Differences Between Fatal and Non-Fatal Cases with Invasive Pneumococcal Diseases

		Survived (n = 16)	Non-Survived (n = 5)	p value
Age		69.2 (4–91)	54.0 (1–81)	0.0011**
Male/Female		3/13	2/3	0.33
Underlying diseases				
	Malignancy	4 (25.0%)	2 (40.0%)	0.52
	Heart Diseases	4 (25.0%)	1 (20.0%)	0.82
	Diabetes Mellitus	3 (18.8%)	1 (20.0%)	0.95
	Brain diseases	2 (12.5%)	0	0.41
	Infectious Diseases	2 (12.5%)	1 (20.0%)	0.68
	Kidney diseases	1 (6.3%)	0	0.57
	None	3 (18.8%)	0	0.95
	Two or more diseases	3 (18.8%)	1 (20.0%)	0.95
Vaccine (+/−)		1/15	1/4	0.36
Source of infection	Bacteremia, Pneumonia	13 (86.7%)	5 (100%)	0.3
	Meningitis	3 (18.8%)	0	0.3
Bacteria	PSSP	15 (93.8%)	5 (100%)	0.57
	PISP	1 (6.3%)	0	0.57
	PRSP	0	0	N/A
	+MSSA	2 (12.5%)	0	0.41
	+MRSA	1 (6.3%)	0	0.57
	+*E. coli*	0	1 (20.0%)	0.067*
	+*K. pneumoniae*	1 (6.3%)	2 (40.0%)	0.07*
	Two or more bacteria	3 (18.8%)	3 (60.0%)	0.075*
WBC		12117.3 (1517–28000)	3672.1 (720–6680)	0.0011**
CRP		22.1 (6.2–69.2)	34.5 (5.7–54.4)	0.0010**
Antibiotics	MEM	4 (25.0%)	4 (80.0%)	0.027*
	TZP	4 (25.0%)	0	0.21
	CRO	4 (25.0%)	1 (20.0%)	0.82
	VCM	3 (18.8%)	1 (20.0%)	0.95
	LFX	2 (12.5%)	0	0.41
	SAM	2 (12.5%)	0	0.41
	+Azithromycin	0	1 (20.0%)	0.067*
	+Clindamycin	1 (6.3%)	0	0.57
	+Peramivir	1 (6.3%)	0	0.57
	+Remdesivir	0	1 (20.0%)	0.067*
	+Fluconazole	0	1 (20.0%)	0.067*
	Two or more antibiotics	5 (31.3%)	4 (80%)	0.055*

Notes: *p < 0.05, and **p < 0.01, respectively.

Abbreviations: PSSP, penicillin susceptible *Streptococcus pneumoniae*; PISP, penicillin intermediate *Streptococcus pneumoniae*; PRSP, penicillin resistant *Streptococcus pneumoniae*; MRSA, methicillin resistant *Staphylococcus aureus*; MSSA, methicillin susceptible *Staphylococcus aureus*; MEM, meropenem; TZP, tazobactam/piperacillin; CRO, ceftriaxone; VCM, vancomycin; LFX, levofloxacin; SAM, subactam/ampicillin; respectively.

generally attributed to the impact of non-pharmaceutical interventions, such as mask-wearing, hand hygiene, social distancing, travel restrictions, and school closures, although it was not definitively clarified whether the greater role was played by the reduction of interpersonal transmission of the pathogen or by the suppression of the activity of several seasonal respiratory viruses, such as influenza viruses, RSV, and hMPV, that favor pneumococcal colonization and are frequently complicated by *S. pneumoniae* superinfection.[7,8] However, the monthly rates of supposed or documented bacterial and viral community acquired pneumonia (CAP) cases, nasopharyngeal pneumococcal carriage, nasopharyngeal respiratory virus evidence, and nationwide IPDs in children <5 years during the COVID-19 pandemic and in the several years before were reported, and it was found that the incidences of both pneumococcal CAP and viral CAP were strongly reduced concomitantly with a full suppression of RSV, influenza viruses, and hMPV circulation, although carriage

prevalence of *S. pneumoniae* was only marginally reduced.[7,8] These data suggested that reduction of IPDs during the COVID-19 pandemic was mainly due to the suppression of viral infections, rather than increased bacterial transmission. We did not find any cases of co-infected with respiratory virus, including influenza, RSV and hMPV, and *S. pneumoniae* in this study, however, a change of viral prevalence other than SARS-CoV-2 was observed in Japan during the COVID-19 pandemic period in fact.[9–11]

Furthermore, fatal cases were younger but received more multiple antimicrobial agents and broader spectrum antibiotics, including meropenem, due to the other microorganisms that were isolated, compared with survivors. Underlying diseases and vaccination history were not different, and penicillin-resistant *Streptococcus pneumoniae* (PRSP) was not isolated in both fatal cases and survivors. On the other hand, we find one IPD patient who had the penicillin-intermediate susceptible *S. pneumoniae*. This patient survived and these data suggested that drug susceptibility might not be related with the mortality.

Recently, *S. pneumoniae* serotype 35B, a non-vaccine type, has been a major contributor to the increase in pneumococcal infection post-vaccination, and its serotype showed high rates with the genes of Type 1 pilus (T1P), an adhesion factor that may play a role in the establishment and virulence of *S. pneumoniae*.[12] Furthermore, the penicillin-non-susceptible rate of 35B was 87.5%, and the meropenem-resistant 35B rate was 35.0%, which increased from 14.5% in 2014–2017 ($p = 0.009$) in Japan.[4] These data were also consistent with the present results that fatal cases showed lower WBC counts, but higher CRP levels, suggested a more severe and septic status in fatal cases than in survivors. Increased non-vaccinated serotype *S. pneumoniae* might also have contributed to the increase of severe cases resistant to antibiotics such as meropenem. In this study, we did not find both penicillin and meropenem resistant *S. pneumoniae* (data not shown). From the data of JANIS (Japan Antimicrobial Resistance Surveillance System), meropenem -resistant *S. pneumoniae* isolated from the non-meningitis patients including pneumonia patients were not so high, about 8.5%.[13] Although we did not examine the serotypes of isolated *S. pneumoniae* from each IPD patient in this study, some more high virulent serotypes other than serotype 35B, might be included. More detailed microbiological analysis, especially serotype, which might be one of the most important key factors that contribute the mortality, will be needed near future.

However, only 2 of 21 IPD patients had been vaccinated; all 19 adult IPD patients had not been vaccinated, including all 4 fatal adult cases.

This study, which is retrospective, single-center design, has the limitation because sample size is not huge and may lead the generalizability limitation of the results and data. The patients were divided into two cases, such as in the COVID-19 cases and pre-/post-COVID-19 period cases although we had three periods, such as pre-COVID-19, pandemic, post-COVID-19. The comparison of non-pandemic cases as a single group (pre- and post-COVID-19) might introduce a slight selection bias. In addition, we could not examine the serotypes of isolated *S. pneumoniae* from each IPD patient. However, this study provides real-world comparative data on survivors and non-survivors of severe IPD patients in hospitalized around COVID-19 pandemic period.

In conclusion, the incidence of IPDs during the COVID-19 pandemic period and the pre-/post-COVID-19 period was investigated, and the clinical features of fatal cases were reviewed. IPD cases were significantly decreased during the COVID-19 pandemic period, which suggested the effects of the other pneumococcal-favorable viruses, such as influenza, RSV, and hMPV. Vaccination rates were very low, and none of the adult IPD patients had received the pneumococcal vaccine. Fatal IPD cases were younger, but showed multiple infections other than *S. pneumoniae*, and they were more septic than survivors. More pathogenic and antibiotic-resistant serotypes, including 35B, might recently be circulating in Japan. More detailed investigations about meropenem susceptibility and the mechanism of increased inflammation in IPD cases are needed.

Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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