

## RESEARCH ARTICLE

# Epidemiology of influenza under the coronavirus disease 2019 pandemic in Nanjing, China

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## Abstract

**Purpose:** Since the pandemic of coronavirus disease-19 (COVID-19), the incidence of influenza has decreased significantly, but there are still few reports in the short period before and after the pandemic period. This study aimed to explore influenza activity and dynamic changes before and during the pandemic.

**Methods:** A total of 1 324 357 influenza-like illness (ILI) cases were reported under the ILI surveillance network from January 1, 2018, to September 5, 2021, in Nanjing, of which 16 158 cases were detected in a laboratory. Differences in ILI and influenza were conducted with the  $\chi^2$  test.

**Results:** The number of ILI cases accounted for 8.97% of outpatient and emergency department visits. The influenza-positive ratio (IPR) was 7.84% in ILI cases. During the COVID-19 pandemic, ILI% and IPR dropped by 6.03% and 11.83% on average, respectively. Besides this, IPR rose slightly in Week 30–35 of 2021. Not only differences in gender, age, and employment status, but also the circulating strains had changed from type A to B through the COVID-19 pandemic.

**Conclusion:** The level of influenza activity was severely affected by COVID-19, but it seems that it is inevitable to be vigilant against the co-circulation in the future.

## KEYWORDS

COVID-19, epidemiology, etiology, influenza, influenza-like illness

## 1 | INTRODUCTION

Influenza, including seasonal, avian, and zoonic influenza, affects one billion cases of influenza annually, of which 3–5 million are severely ill and the death attributed to seasonal influenza is 290 000–450 000.<sup>1,2</sup> Annually, there are 3 million excess cases of outpatient and emergency department visits caused by influenza and 88 100 influenza-related excess respiratory deaths in China.<sup>3</sup> The overall regional distribution shows that the characteristics of high in Eastern and Southern China.<sup>4</sup> As influenza has no typical clinical features, it relies on syndromic surveillance. It is through influenza-like illness (ILI) in outpatient and emergency department visits and inpatient severe acute respiratory illness (SARI) that the network conducts sentinel surveillance to determine the prevalence of influenza virus in the general population and hospitalized patients.<sup>5</sup>

In addition, due to the rapid variation of influenza viruses, the circulating strains of influenza virus have a certain type of specificity each year. Etiological detection of influenza can determine the activity levels of different strains of influenza virus in real-time, which is helpful for timely recommendation and selection of influenza virus vaccine strains. As shown above, routine monitoring of influenza is conducive to the discovery of variant strains of the influenza virus and provides a scientific basis for preventing large-scale influenza epidemics.<sup>5,6</sup> Under the “intervention” of COVID-19, influenza activity began to decline in a cliff-like manner in 2020, which may cause a regional epidemic of influenza in the future.<sup>7,8</sup> This study explored ILI and influenza activities in Nanjing from 2018 to 2021 and provide a basis for timely adjustment of influenza prevention and control measures in the future period through ILI surveillance after the COVID-19 pandemic.

## 2 | MATERIALS AND METHODS

### 2.1 | Data source

All data came from the Chinese Influenza Surveillance Information System (accessed through Nanjing municipal center for disease control and prevention). The sentinel hospitals were Children's

Hospital of Nanjing Medical University (N MUCH), Nanjing Jiangning Hospital (NJH), Nanjing First Hospital (NFH), Nanjing Drum Tower Hospital (NDTH), and the Second Affiliated Hospital of Nanjing Medical University (NMUSH). Daily ILI consisted of counts of various age groups, outpatient and emergency department visits in monitoring clinics. Detection of ILI specimens were individual case data, including age, gender, employment status, and test results. The time

Sentinel Hospital	Age (years)					Counts	OPD/ED	ILI%
	0–4	5–14	15–24	25–59	≥60			
NMUCH	923 408	227 509	1 020	0	0	1 151 937	9 666 826	11.92
2018	431 712	96 335	357	0	0	528 404	2 746 389	19.24
2019	283 865	79 382	314	0	0	363 561	3 005 430	12.10
2020	136 259	36 843	288	0	0	173 390	2 169 829	7.99
2021	71 572	14 949	61	0	0	86 582	1 745 178	4.96
NJH	43 589	40 212	6 047	16 394	1 652	107 894	1 092 796	9.87
2018	9 127	7 766	1 696	4 433	474	23 496	384 116	6.12
2019	12 381	13 045	2 072	4 952	490	32 940	365 942	9.00
2020	4 183	4 936	481	997	52	10 649	196 475	5.42
2021	17 898	14 465	1 798	6 012	636	40 809	146 263	27.90
NFH	4 746	6 283	2 897	8 377	1 970	24 273	1 006 210	2.41
2018	1 957	2 243	730	2 500	609	8 039	321 197	2.50
2019	2 056	2 603	1 138	3 855	949	10 601	345 298	3.07
2020	525	1 119	752	1 627	195	4 218	204 561	2.06
2021	208	318	277	395	217	1 415	135 154	1.05
NDTH	5	64	3 188	9 885	2 639	15 781	934 113	1.69
2018	3	18	876	2 652	493	4 042	278 148	1.45
2019	1	19	1 023	3 287	661	4 991	268 199	1.86
2020	1	19	699	2 104	680	3 503	231 492	1.51
2021	0	8	590	1 842	805	3 245	156 274	2.08
NMUSH	5 831	4 771	2 690	7 965	3 215	24 472	2 060 542	1.19
2018	2 141	2 307	797	2 583	1 017	8 845	690 405	1.28
2019	316	393	762	2 240	834	4 545	588 790	0.77
2020	1 236	747	814	2 271	1 156	6 224	436 657	1.43
2021	2 138	1 324	317	871	208	4 858	344 690	1.41
Total	977 579	278 839	15 842	42 621	9 476	1 324 357	14 760 487	8.97
2018	444 940	108 669	4 456	12 168	2 593	572 826	4 420 255	12.96
2019	298 619	95 442	5 309	14 334	2 934	416 638	4 573 659	9.11
2020	142 204	43 664	3 034	6 999	2 083	197 984	3 239 014	6.11
2021	91 816	31 064	3 043	9 120	1 866	136 909	2 527 559	5.42

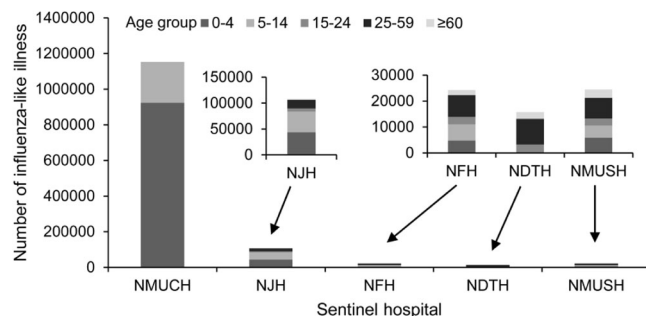
**TABLE 1** Characteristics of influenza-like illness surveillance in Nanjing, January 1, 2018 to September 5, 2021 (192 weeks)

Abbreviations: NDTH, Nanjing Drum Tower Hospital; NFH, Nanjing First Hospital; NJH, Nanjing Jiangning Hospital; N MUCH, Children's Hospital of Nanjing Medical University; NMUSH, the Second Affiliated Hospital of Nanjing Medical University; OPD/ED, number of outpatient and emergency department visits.

of all data was from January 1 (Week 1), 2018, to September 5 (Week 35), 2021. In this study, the initial time of the COVID-19 pandemic was defined as January 23 (Week 4), 2020, from which the first-level response to major public health emergency was activated on the Chinese mainland.<sup>9</sup>

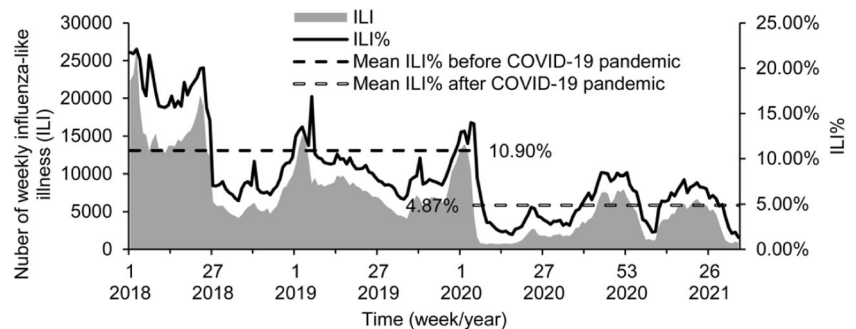
## 2.2 | Statistical analysis

The number of ILI and the percentage of ILI in outpatient and emergency department visits (ILI%) were used to reflect the activity of ILI in sentinel hospitals. The activity of influenza in ILI was indicated through the influenza-positive detection ratio of specimens. The distribution of influenza virus types showed the activity of a specific type. The above indicators were conducted to describe the distribution of time and population. Data processing and analysis were performed in Excel version 2108 (Microsoft) and SPSS version 26.0 (IBM). Spearman rank correlation was tested between ILI and ILI%. The  $\chi^2$  test or Fisher's exact test was used for the distribution of qualitative data (Fisher-Freeman-Halton test for the contingency table) with the statistical level  $\alpha = 0.05$ .



**FIGURE 1** Age groups of influenza-like illness in five sentinel hospitals in Nanjing, January 1, 2018 to September 5, 2021 (192 weeks). Abbreviations: NDTH, Nanjing Drum Tower Hospital; NFH, Nanjing First Hospital; NJH, Nanjing Jiangning Hospital; NMUCH, Children's Hospital of Nanjing Medical University; NMUSH, the Second Affiliated Hospital of Nanjing Medical University

**FIGURE 2** Time series chart of influenza-like illness (ILI) and ILI% and influenza-positive ratio in Nanjing, January 1, 2018 to September 5, 2021 (192 weeks). There are 52 weeks in 2018, 2019, 2021, and 53 weeks in 2020. The horizontal ordinate label interval is 13 weeks



## 3 | RESULTS

### 3.1 | Overview of ILI surveillance

From January 1, 2018 (Week 1 of 2018) to September 5, 2021 (Week 35 of 2021), a total of 1 324 357 ILI cases were reported in Nanjing. As shown in Table 1, the total number of outpatient and emergency department visits in the monitoring clinics was 14 760 487 and the ILI% was 8.97%. The annual ILI% of sentinel hospitals was 0.77%–27.90% (incomplete surveillance data in 2021). In the observing period, the Children's Hospital of Nanjing Medical University (NMUCH) reported the most ILI cases, with 1 151 937 cases, accounting for 86.98% of all ILI. The rest were Nanjing Jiangning Hospital (NJH) (8.15%), the Second Affiliated Hospital of Nanjing Medical University (NMUSH) (1.85%), Nanjing First Hospital (NFH) (1.83%), and Nanjing Drum Tower Hospital (NDTH) (1.19%). The range of age was 0–24 years in NMUCH, while other sentinel hospitals existed for whole age groups (Table 1 and Figure 1). Overall, the number of ILI and ILI% dropped sharply (6.03% on weekly mean ILI%) after the COVID-19 pandemic, especially in the early period (Figure 2). Besides this, the trends of ILI and ILI% were the same, and the Spearman rank correlation existed between them ( $r_s = 0.964$ ,  $p$ -value < 0.001). Despite the COVID-19 pandemic, the peak period of ILI (ILI%) was concentrated in Winter-Spring and Summer of the year (December to February and June to July).

#### 3.1.1 | Detection for influenza virus from ILI

Five sentinel hospitals sent 16 158 throat swab specimens from ILI cases, with a total influenza-positive ratio of 7.84% (1 267/16 158). All the characteristics (gender, age, employment, and sentinel hospital) showed statistically significant differences in the influenza-positive ratio ( $p$ -value < 0.05) (Table 2), while there was various performance before and after the COVID-19 pandemic (Figure 3). A significant difference in gender was observed in 2018–2019 and not in 2020–2021, but employment status was contrary to the former. The population employed had a lower influenza-positive ratio than the unknown and unemployed. For age groups and sentinel

**TABLE 2** Detection for influenza virus from influenza-like illness (ILI)

	ILI	Influenza-positive (n/ratio%)	$\chi^2$	p-value
Total	16 158	1 267/7.84		
Gender			11.414	0.001
Male	8 489	608/7.16		
Female	7 669	659/8.59		
Age (years)			193.066	<0.001
0–4	2 888	237/8.21		
5–14	2 014	298/14.80		
15–24	2 021	152/7.52		
25–59	6 883	490/7.12		
≥60	2 352	90/3.83		
Employment			21.072	<0.001
Employed	5 503	363/6.60		
Unknown	2 034	192/9.44		
Unemployed	8 621	712/8.26		
Sentinel hospital			181.64	<0.001
NMUCH	3 801	436/11.47		
NJH	961	88/9.16		
NFH	3 849	316/8.21		
NDTH	3 816	306/8.02		
NMUSH	3 731	121/3.24		

Abbreviations: NDTH, Nanjing Drum Tower Hospital; NFH, Nanjing First Hospital; NJH, Nanjing Jiangning Hospital; NMUCH, Children's Hospital of Nanjing Medical University; NMUSH, the Second Affiliated Hospital of Nanjing Medical University.

hospitals, the influenza-positive ratio from NMUCH (at the age of 0–14 years) was much higher than other hospitals (other age groups) in 2018–2021.

During the COVID-19 pandemic (Week 5 of 2020 to Week 35 of 2021), only 31 ILI cases were reported for influenza (influenza-positive ratio at 0.44%), and there were no influenza-positive cases until Week 4 of 2021 (Figure 4). Before the COVID-19 pandemic, the peak period of ILI% was Weeks 1–7 (January–February) of the year, whereas no peak appeared in 2021 (as of Week 35).

### 3.1.2 | Etiology of influenza virus from ILI cases

In the observing period, influenza A virus (IAV) was the main type, accounting for 52.01% (659/1 276), 46.72% (592/1 276) for IBV, and 1.26% (16/1 276) for mixed infection with IAV and IBV

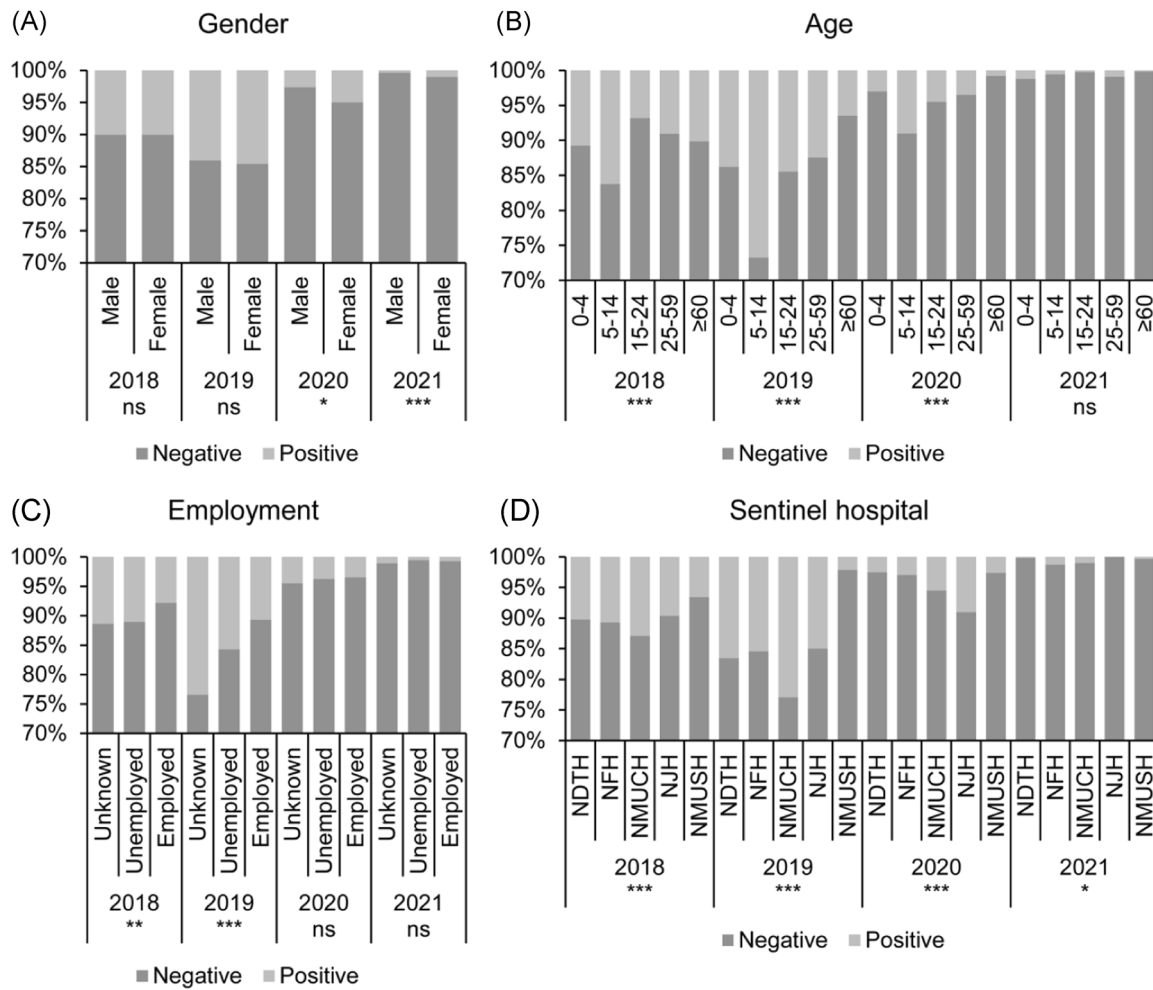
(Table 3). The mainstreaming type had changed IAV to IBV after the COVID-19 pandemic (Figure 5). A significant difference was not observed in 2018–2021 but found in 2019, in which the IAV ratio of 0–4 and ≥60 years was significantly higher than the others.

## 4 | DISCUSSION

ILI surveillance was a respiratory infections surveillance carried out by including patients with nonspecific symptoms to adapt influenza activity and epidemical trends timely and provide preparations for potential epidemics. In total, 1 324 357 ILI cases were reported with ILI% of 8.97% in five sentinel hospitals in 2018–2021, which was much higher than the level of ILI activity in 2006–2015.<sup>10</sup> After the COVID-19 pandemic, ILI and influenza activity was decreasing with a 6.15% drop on average weekly ILI% and nearly zero influenza laboratory-confirmed cases. In 2018–2019, ILI activity in Nanjing was similar to that in Huai'an<sup>11</sup> and higher than in Liaoning,<sup>12</sup> Zhejiang,<sup>13</sup> and Beijing,<sup>14</sup> suggesting that the level of ILI surveillance may be related to the geographical environment and the setting of sentinel hospitals in different regions. In addition, measures in response to the COVID-19 pandemic may affect ILI and influenza surveillance or activity.<sup>13</sup> Significantly, the influenza-positive ratio has rebounded slightly in Week 30–35 of 2021.

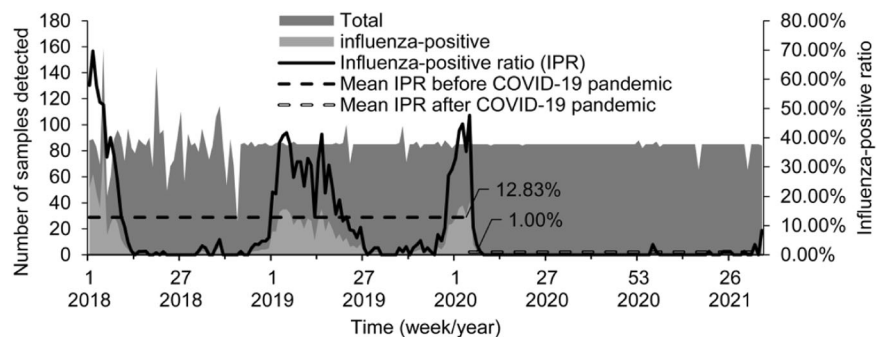
The difference in gender, age, and employment status existed before and after the COVID-19 pandemic. There was no significant gender difference in 2018–2019, whereas it was opposite to that in 2020–2021. For gender, endocrine regulation may alter the response to influenza and other infections in individuals,<sup>15,16</sup> but similar results were not performed with the population-based data. In this study, the population with a high influenza-positive ratio was that aged 0–14 years, unemployed or employment-unknown. In general, employment status was associated with C-reactive protein (CRP) and fibrinogen, which are inflammatory indicators, and unemployment was related to poorer physical health for individuals.<sup>17,18</sup> For the population level, the higher employment rate may increase influenza-related rates.<sup>19</sup> Moreover, the influenza-positive ratio of children aged 5–14 years was much higher than that of 0–4 years, which might be related to the more complicated social activities and a greater chance of infection of the former than the latter. Children, students, and the elderly tended to be unemployed or employment-unknown, and the overall risks of infections were higher than that of the young and middle-aged population. However, it may be due to social distancing measures lowering influenza activity that differences in age and employment status have changed during the COVID-19 pandemic.<sup>20</sup>

The circulating influenza virus strains will show large or small changes yearly due to variations of the genome (antigen drift and shift).<sup>21</sup> The dominant types of influenza virus in 2018–2019 and



**FIGURE 3** The influenza-positive ratio for gender (A), age (B), employment (C), and sentinel hospital (D) in 2018–2021. Abbreviations: NDTH, Nanjing Drum Tower Hospital; NFH, Nanjing First Hospital; NJH, Nanjing Jiangning Hospital; NMUCH, Children's Hospital of Nanjing Medical University; NMUSH, the Second Affiliated Hospital of Nanjing Medical University. ns refers to  $p$ -value > 0.05; \* refers to  $0.05 \geq p$ -value > 0.01; \*\* refers to  $0.01 \geq p$ -value > 0.001; \*\*\* refers to  $p$ -value  $\leq 0.001$

**FIGURE 4** The number of specimens detected for influenza and influenza-positive ratio in Nanjing, January 1, 2018 to September 5, 2021 (192 weeks). There are 52 weeks in 2018, 2019, 2021, and 53 weeks in 2020. The horizontal ordinate label interval is 13 weeks



**TABLE 3** Types of influenza virus from influenza-like illness

	Influenza virus (n/ratio%)			$\chi^2$	p-value
	IAV	IBV	IAV + IBV		
Total	659/52.01	592/46.72	16/1.26		
Year				57.78	<0.001
2018	259/58.73	177/40.14	5/1.13		
2019	348/54.29	284/44.31	9/1.40		
2020	51/30.72	113/68.07	2/1.20		
2021	1/5.26	18/94.74	0/0		
Gender				0.521	0.771
Male	318/52.30	281/46.22	9/1.48		
Female	341/51.75	311/47.19	7/1.06		
Age (years)				18.38	0.012
0–4	145/61.18	89/37.55	3/1.27		
5–14	131/43.96	162/54.36	5/1.68		
15–24	78/51.32	72/47.37	2/1.32		
25–59	252/51.43	233/47.55	5/1.02		
≥60	53/58.89	36/40.00	1/1.11		
Employment				12.97	0.011
Employed	170/46.83	190/52.34	3/0.83		
Unknown	119/61.98	71/36.98	2/1.04		
Unemployed	370/51.97	331/46.49	11/1.54		
Sentinel hospital				12.13	0.118
NMUCH	230/52.75	198/45.41	8/1.83		
NJH	53/60.23	35/39.77	0/0.00		
NFH	167/52.85	142/44.94	7/2.22		
NDTH	146/47.71	159/51.96	1/0.33		
NMUSH	63/52.07	58/47.93	0/0.00		

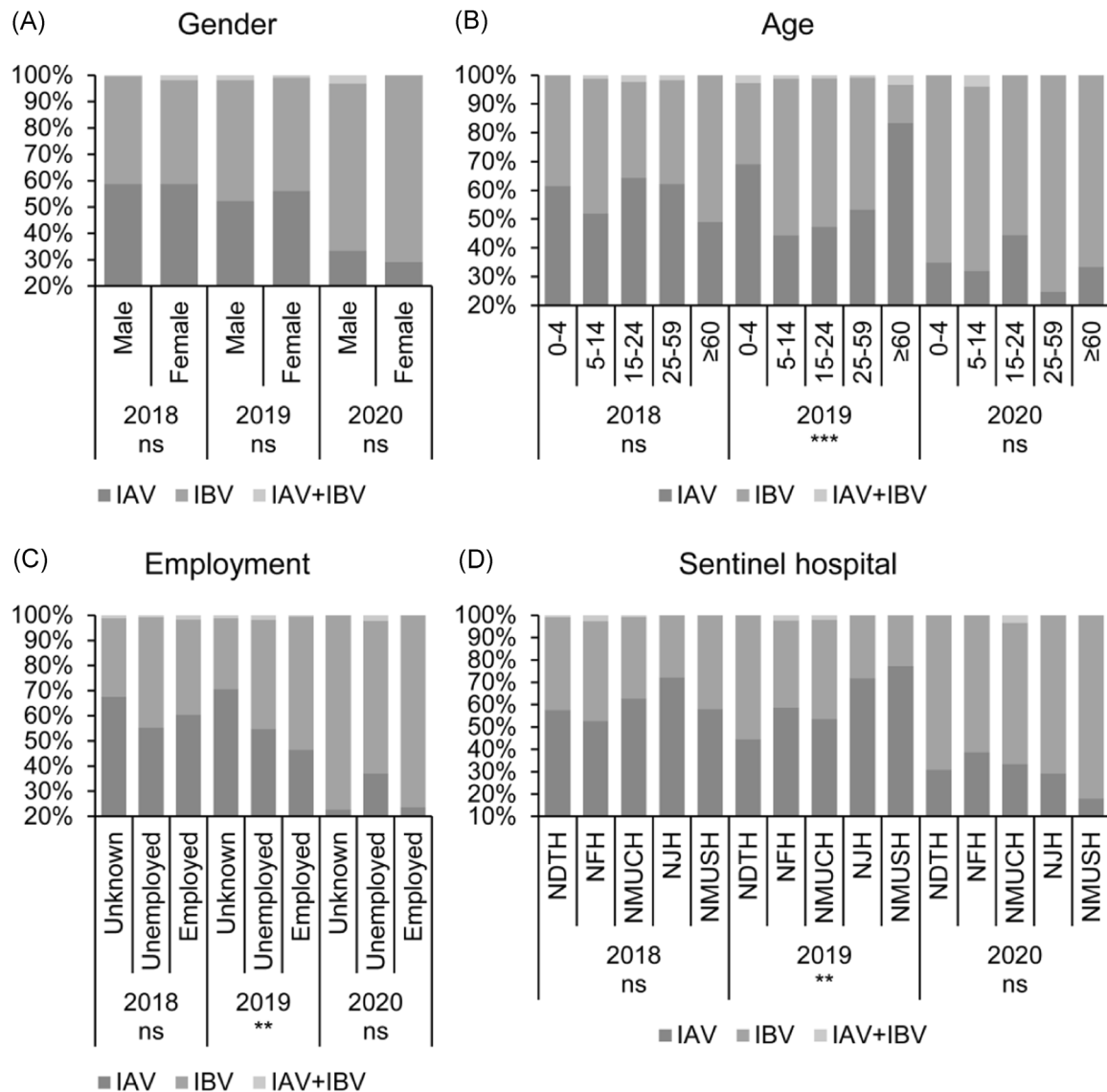
Abbreviations: NDTH, Nanjing Drum Tower Hospital; NFH, Nanjing First Hospital; NJH, Nanjing Jiangning Hospital; NMUCH, Children's Hospital of Nanjing Medical University; NMUSH, the Second Affiliated Hospital of Nanjing Medical University.

2020–2021 were IAV and IBV respectively, which was consistent with national and global surveillance.<sup>22,23</sup>

In summary, vaccination is always one of the most effective means to reduce the morbidity and mortality of influenza and COVID-19.<sup>24</sup> As of September 18, 2021, 76.22% of the Chinese population has received at least one dose of a COVID-19 vaccine,<sup>25</sup> while the overall coverage of influenza vaccination was about 23.2% in China,<sup>26</sup> which was much lower than that of developed countries such as Europe and the United States,<sup>27,28</sup> and there were still large poorly immunized populations. Although influenza caused mild symptoms (e.g., fever, cough, and headache), it could easily cause plenty of complications in the population with low immune levels or sub-health, and the direct or indirect economic burden is very

huge.<sup>3,29,30</sup> The spread of the influenza virus and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are both greatly affected by nonpharmacological interventions.<sup>31</sup> A series of measures during the COVID-19 pandemic, such as wearing masks and vaccination, have not only prevented the spread of SARS-CoV-2 to a large extent but also affected influenza. However, the continuing low level of influenza virus immunity for the entire population may cause influenza epidemics in the future.

In conclusion, the level of influenza activity during the COVID-19 pandemic was much lower than that in previous years, but the activity rebounded slightly. In the context of the COVID-19 pandemic, more prevention and surveillance of infectious diseases still required greater attention.



**FIGURE 5** Influenza types for gender (A), age (B), employment (C), and sentinel hospital (D) in 2018–2020. Abbreviations: NDTH, Nanjing Drum Tower Hospital; NFH, Nanjing First Hospital; NJH, Nanjing Jiangning Hospital; NMUCH, Children's Hospital of Nanjing Medical University; NMUSH, the Second Affiliated Hospital of Nanjing Medical University. ns refers to  $p$ -value  $> 0.05$ ; \* refers to  $0.05 \geq p$ -value  $> 0.01$ ; \*\* refers to  $0.01 \geq p$ -value  $> 0.001$ ; \*\*\* refers to  $p$ -value  $\leq 0.001$ . In 2021, 19 influenza cases were laboratory-confirmed, which led to no statistically significant difference

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#### CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

#### AUTHOR CONTRIBUTIONS

Kangjun Wu and Lei Hong designed this study. Xiaoqing Wu and Weixiang Wang gathered and verified the data. Kangjun Wu and Xiaoqing Wu carried out analysis and interpretation of data. Kangjun Wu and Weixiang Wang drafted the manuscript. Lei Hong revised the

manuscript for intellectual content. All authors read and approved the final manuscript.

#### DATA AVAILABILITY STATEMENT

All the data used and analyzed in this study are available from the corresponding author on reasonable request.

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