Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editors

The effect of nirmatrelvir plus ritonavir on the long-term risk of epilepsy and seizure following COVID-19: A retrospective cohort study including 91,528 patients

Dear Editor,

We read with interest the recent meta-analysis assessing the clinical efficacy and safety of nirmatrelvir plus ritonavir (NMV-r) in the treatment of patients with COVID-19.[1] Based on the analysis of 13 studies involving 186,306 patients, the authors concluded that NMV-r was effective in reducing the mortality (odds ratio [OR], 0.12; 95% CI, 0.04-0.36) and the risk of hospitalization (OR, 0.32; 95% CI, 0.13-0.75) for patients with COVID-19.[1] These findings indicated that NMV-r could be a useful antiviral treatment for COVID-19. However, it was also noted that a significant proportion of individuals who have recovered from acute COVID-19 may experience long-term complications, a phenomenon referred to as long COVID.[2,3] Moreover, long COVID has been shown to have a negative impact on both physical and mental well-being.[2,3] Therefore, how to prevent the development of long COVID has become a serious concern. In fact, one study showed the promising role of NMV-r in reducing the risks of post-acute COVID-19 sequelae, such as dysrhythmia and ischemic heart disease, deep vein thrombosis, pulmonary embolism, fatigue, liver disease, acute kidney disease, muscle pain, neurocognitive impairment, and shortness of breath.[4] Study from Taquet et al. showed that compared to a matched cohort with influenza, COVID-19 patients had a higher incidence of new seizures or epilepsy diagnoses in the six months following their illness, particularly among those who were not hospitalized.[5] However, the preventive effect of NMV-r on the risk of long-term complications – epilepsy and seizure remained unknown. Therefore, we conducted this retrospective cohort study to evaluate the impact of NMV-r on the long-term risks of epilepsy and seizure.

This study utilized the database from the TriNetX Research Network - a global health-collaborative clinical-research platform, which provided real-time multi-healthcare organization (HCO) and multinational healthcare-associated information.[6] The search and data curation was conducted on January 7, 2023. Initially, we created a cohort of non-hospitalized patients with COVID-19 from 74 HCOs, as previously described.[7] The inclusion criteria were (a) they had at least two times of medical encounters with healthcare organizations from March 1, 2020, to January 1, 2022; (b) people who were older than 18 years old; (c) they had a new diagnosis of COVID-19. Exclusion criteria included (a) the patients who had a prior history of epilepsy or seizure, (b) patients who ever received remdesivir, molnupiravir, monoclonal antibody or convalescent plasma, and (c) COVID-19 patients requiring hospitalization. Thereafter, we divided this population into two cohorts based on the use of NMV-r – a study group receiving NMV-r and a control group without NMV-r. To adjust for the difference in baseline characteristics between the groups, two matched cohorts were created by propensity score with a 1:1 matching method. A standard difference of less than 0.1 indicates good matching. The primary outcome was the one-year incidence of the composite endpoint of epilepsy (ICD-10 code G40) or seizures (ICD-10 code R56). The secondary outcomes included either code separately.[5] The hazard ratio (HR) with 95% confidence interval (95% CI) of incident epilepsy and seizure was calculated for the NMV-r control groups. All statistical analyses were conducted using the built-in function of TriNetX network.

Initially, 45,764 patients receiving NMV-r and 7,167,604 COVID-19 patients without NMV-r were identified (Fig. 1). Through propensity score matching, equal numbers of 45,764 cases were retained in both cohorts (Table 1). Compared to the control cohort. NMV-r cohort had a lower risk of epilepsy and seizure (HR = 0.516; 95% CI = 0.389-0.685) within one year. Specifically, the NMV-r group also had a lower risk of epilepsy (HR, 0.584; 95% CI, 0.362-0.941) and seizure (HR, 0.463; 95% CI, 0.331-0.647) than the control group. Fig. 2 displays the Kaplan-Meier curve of the survival probability of epilepsy and seizure. The curve shows that the NMV-r cohort had a lower risk of epilepsy and seizure during the one-year follow-up period (Log rank $p < 0.001$).

In summary, the results of this large retrospective cohort study suggest that non-hospitalized COVID-19 patients receiving NMV-r may have a lower long-term risk of epilepsy and seizure compared to those who did not receive anti-viral agents. This finding suggests that NMV-r may be effective in reducing the risk of post-acute COVID-19 sequelae, including epilepsy and seizure. Our findings were based on analyzing a large database involving multination, multi-institution, and multi-races. To minimize the potential effects of possible confounding factors, we exclude the patients with prior history of epilepsy or seizure, and the baseline characteristics were well-matched between groups. Therefore, our findings are generalizable, and the level of evidence is robust.

Our findings, in combination with those from a previous observational study,[4] demonstrating the preventive effect of NMV-r on ten post-acute sequelae, suggest a potential role for NMV-r in preventing long COVID. These findings are extremely important because no effective measure can prevent the development of long COVID during this pandemic. If NMV-r can provide clinical benefits for acute COVID-19 and reduce the risk of post-acute sequelae, it may be worth considering changing clinical practice to encourage the use of NMV-r for patients with SARS-CoV-2 infection.

This study had several limitations. First, although we matched the baseline characteristics of NMV-r and control cohorts using the propensity score method, some residual confounding factors, such

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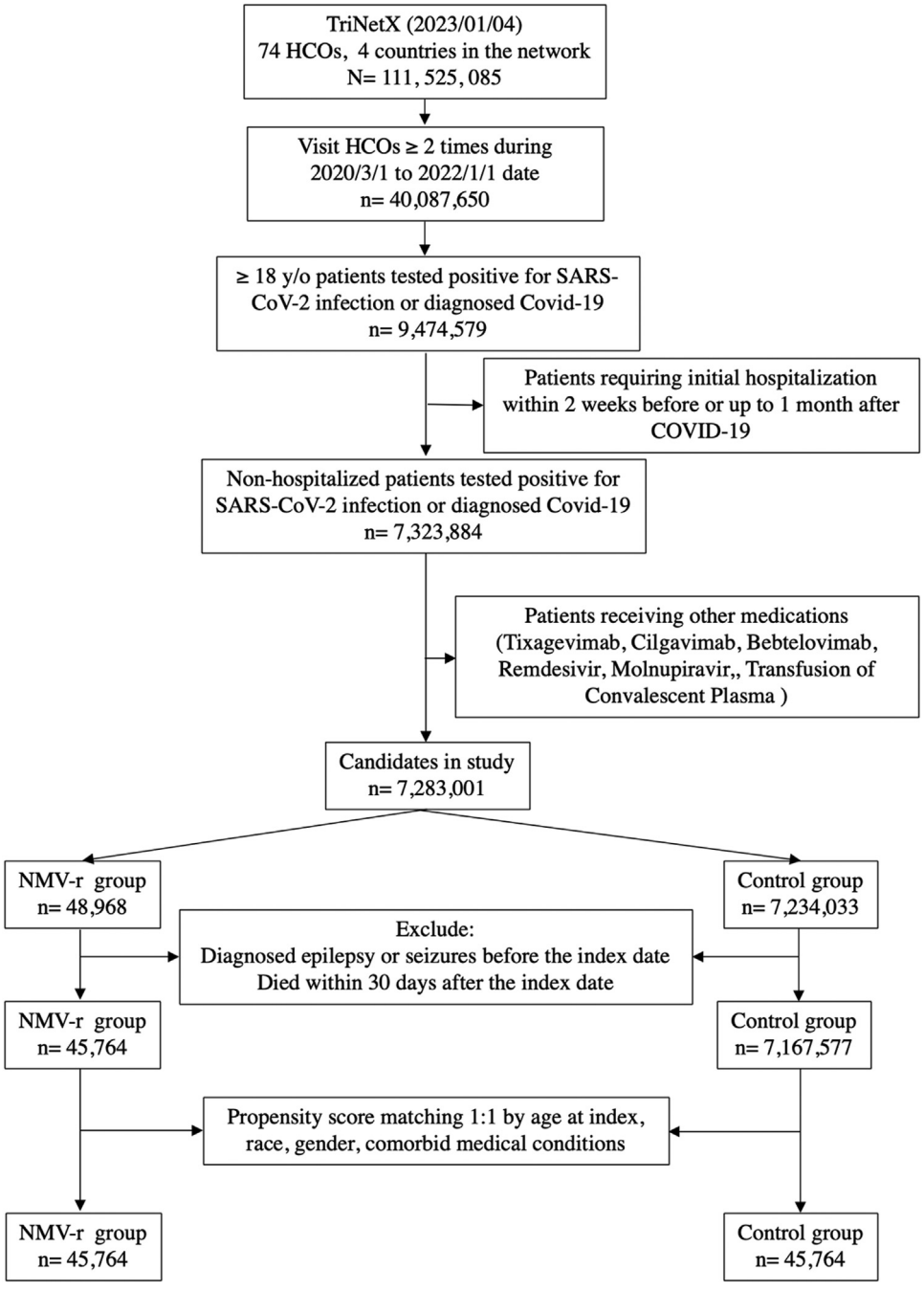

Fig. 1. The algorithm of patient selection and cohort construction.

as the disease severity, SARS-CoV-2 variant, and the vaccine effect, could exist. Second, like other studies using claims databases, the mechanism of NMV-r in preventing long COVID remains unknown. Further study is warranted.

In conclusion, this study demonstrated that COVID-19 patients receiving NMV-r would be associated with a lower risk of epilepsy and seizure and suggested the potential role of NMV-r in preventing long COVID.

Table 1
Comparison of characteristics of patients receiving nirmatrelvir plus ritonavir (NMV-r) and not receiving NMV-r before and after matching.

	Before matching			After matching		
	NMV-r group (n=45,764)	Control group (n=7,167,604)	Std diff	NMV-r group (n=45,764)	Control group (n=45,764)	Std diff
Age at index, Mean ± SD	56.3 ± 16.2	47.2 ±18.5	0.527	56.3 ±16.2	56.3 ±16.2	0.001
Gender						
Female	27,747	4,003,071	0.097	27,747	27,235	0.023
Male	17,742	2,878,324	0.028	17,742	17,737	<0.001
Race, n(%)						
White	37,154	3,926,626	0.590	37,154	37,167	0.001
Black or African American	3,811	977,306	0.170	3,811	4,092	0.022
Asian	897	150,955	0.010	897	581	0.055
Unknown Race	3,767	2,082,102	0.555	3,767	3,799	0.003
Problems related to housing and economic circumstances	380	37,082	0.038	380	335	0.011
Comorbidities						
Hypertensive diseases	18,367	1,316,121	0.493	18,367	18,462	0.004
Ischemic heart diseases	3,992	345,818	0.156	3,992	3,953	0.003
Overweight, obesity and other hyperalimentation	9,606	715,262	0.308	9,606	9,593	0.001
Diabetes mellitus	7,173	570,229	0.241	7,173	6,672	0.031
Neoplasms	13,049	961,176	0.378	13,049	13,065	0.001
Asthma	6,168	421,274	0.259	6,168	6,176	0.001
Chronic obstructive pulmonary disease	1,871	158,466	0.108	1,871	1,887	0.002
Bronchitis, not specified as acute or chronic	2,196	121,842	0.175	2,196	2,139	0.006
Emphysema	850	58,803	0.090	850	730	0.020
Bronchiectasis	252	18,386	0.046	252	233	0.006
Chronic bronchitis	201	12,685	0.047	201	158	0.015
Chronic kidney disease	2,158	247,519	0.064	2,158	2,182	0.002
Alcoholic liver disease	63	13,200	0.012	63	136	0.034
Hepatic failure	39	10,393	0.018	39	88	0.029
Chronic hepatitis	29	3,483	0.006	29	40	0.009
Fibrosis and cirrhosis of liver	305	42,257	0.010	305	454	0.036
Other diseases of liver	3,062	187,974	0.194	3,062	2,375	0.064
Rheumatoid arthritis with rheumatoid factor	413	21,073	0.079	413	264	0.038
Other rheumatoid arthritis	1,023	61,423	0.112	1,023	785	0.037
Nicotine dependence	3,785	432,429	0.087	3,785	3,962	0.014
Mental and behavioral disorders due to psychoactive substance use	4,840	595,588	0.078	4,840	5,345	0.035
Schizophrenia, schizotypal, delusional, psychotic disorders	257	57,479	0.029	257	502	0.059
Cerebral infarction	706	103,535	0.008	706	1,053	0.055
Systemic lupus erythematosus	291	21,633	0.049	291	196	0.029
Psoriasis	930	54,575	0.108	930	667	0.044
Certain disorders involving the immune mechanism	1,181	77,716	0.112	1,181	825	0.053
Renal transplantation procedures	10	1,391	0.002	10	10	<0.001
Liver transplantation procedures	10	496	0.012	10	10	<0.001

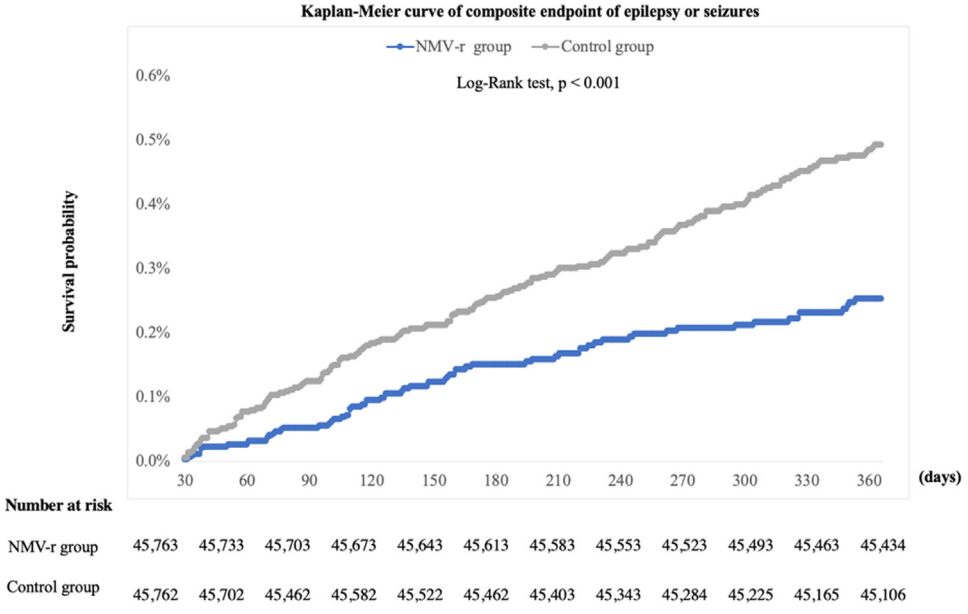

Fig. 2. Kaplan-Meier curves of the primary outcome.

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Nonpharmaceutical intervention is an effective measure to block respiratory virus coinfections with SARS-CoV-2

Dear Editor,

Pengcheng Liu[1] reported that influenza virus activity dropped sharply among children in Shanghai, China, during the COVID-19 pandemic. According to their research, the infection was close to zero in the early stage of the COVID-19 pandemic. At present, the COVID-19 epidemic in China has entered the postpandemic period. Consequently, the Chinese government has announced 10 measures to optimize COVID prevention and control work since 7th December. There is public concern that SARS-CoV-2 will circulate with other respiratory viruses and increase the probability of coinfections. Therefore, we further explored influenza virus coinfections with SARS-CoV-2 during 7th November 2022 and 31st December 2022 before and after the new policy.

COVID-19 poses a great challenge to China's medical and health system, either since the battle of Wuhan and Hubei in 2019 or the battle against Delta and Omicron to date.[2,3] China has a large population. In response to the outbreak, in the past three years, China has organized and mobilized massive human and material resources and adopted strict epidemic prevention measures, such as checking health codes when entering public places, landing inspections for migrants between provinces, checking travel codes, etc. Moreover, standardized good hygiene habits are required in daily life, such as wearing masks in public and washing hands frequently, which have been demonstrated to be very effective in delaying SARS-CoV-2 transmission and remarkably decreasing the incidence and death rate worldwide.[4] However, these anti-epidemic measures have had a great impact on the social economy and daily life. On December 7th, 2022, the Chinese National Health Commission announced ten prevention and control measures to further optimize the COVID-19 response. These new measures include scrapping negative nucleic acid results and health code requirements for entering nonspecial public places and domestic cross-regional travel, changing landing inspection into self-home quarantine in particular asymptomatic carriers and mild COVID-19 patients. The new Ten optimization measures are based on the Omicron variant with weakening "pathogenicity", the popularization of vaccination, and the accumulation of COVID-19 prevention and control experience and have again taken an important step toward precision and science.

To extrapolate the influence of the adjustment, we counted the children who visited the Children's Hospital of Zhejiang University outpatient and inpatient departments (from November 7, 2022 to December 31, 2022) before and after the introduction of the new ten optimization measures. According to the survey, since December 7th, 2022, the number of positive patients with COVID-19 has continued to rise, and on December 22nd, the number of positive patients reached 887, with a positive rate of 68%. After a small peak of infection, the number of infected patients showed a rapid downward trend. This phenomenon is because since December 21, 2022, patients in medical institutions no longer require nucleic acid testing as a mandatory requirement. In line with this policy, the number of people taking part in the test has dropped significantly, and the corresponding number of positive patients has also decreased, but the positive rate has remained above 40%, indicating that the actual number of infected people is still increasing (Fig. 1A, Fig. 2A).

Although the severe disease rate and mortality rate are not as high as the original strain, it still places great pressure on medical institutions. To make matters worse, in the season of high incidence of respiratory viruses such as influenza, respiratory virus coinfections with COVID are more likely to occur. In the past three years, wearing masks and other epidemic prevention measures have rapidly decreased the infection rate of common respiratory viruses such as influenza, but these measures have also reduced people's immunity to those respiratory pathogens. The liberalization of epidemic prevention and control measures may cause a pandemic of these respiratory viruses,[5] which increases the risk of combined common respiratory virus infections, such as influenza in COVID-19. Coinfection is usually considered to lead to more severe symptoms and worsen the clinical outcome of patients with COVID-19. A study from the State Key Laboratory of Virology, Wuhan University[6] found that in COVID-19 receptor hu-

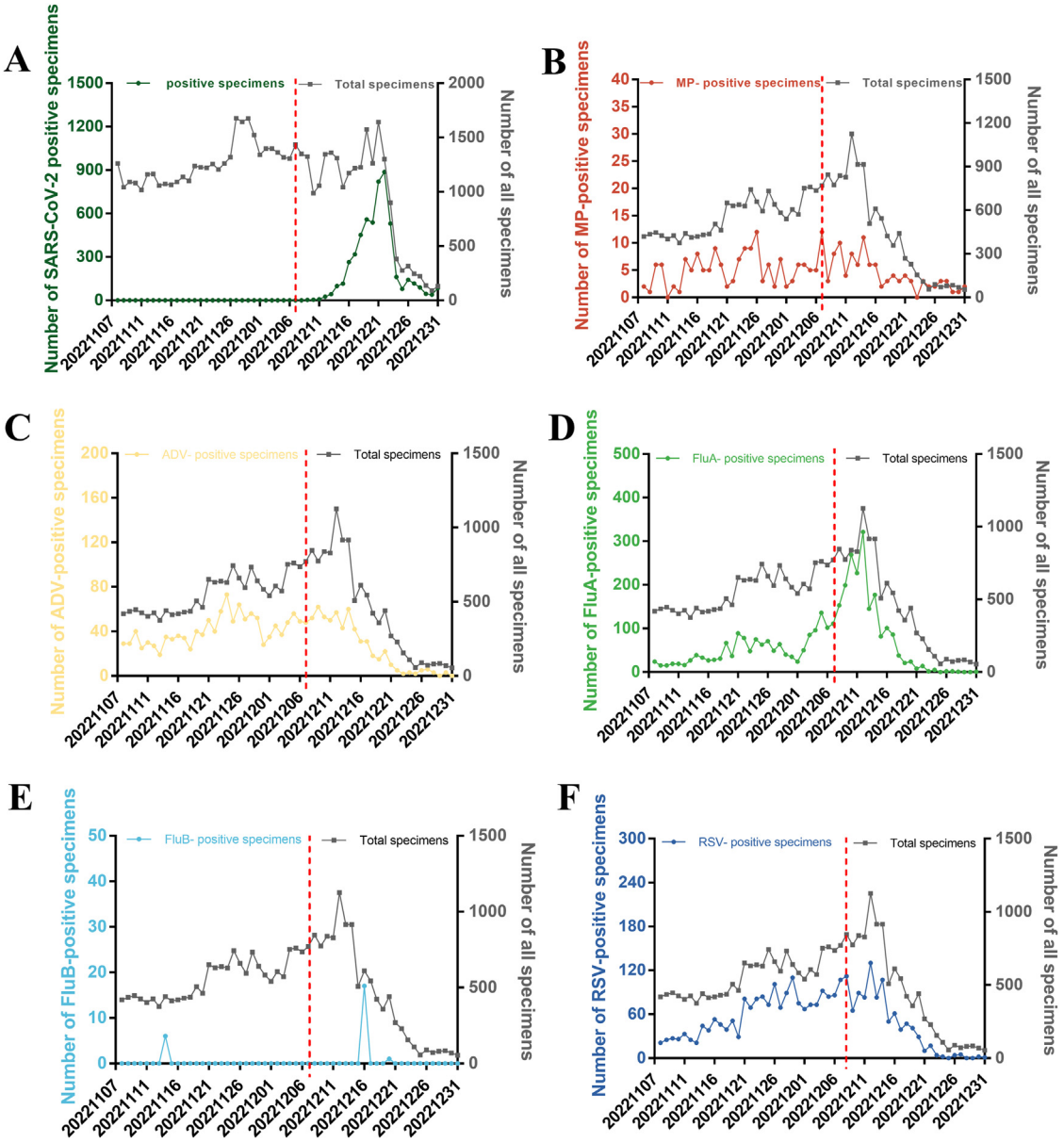

Fig. 1. Number of total and positive specimens of SARS-CoV-2 and respiratory influenza viruses. (A) SARS-CoV-2; (B) Mycoplasma pneumoniae (MP); (C) adenovirus (ADV); (D) influenza A virus (FluA); (E) influenza B virus (FluB); (F) respiratory syncytial virus (RSV). The vertical axis and colored lines on the left show the number of positive specimens for SARS-CoV-2 and respiratory influenza virus. The right vertical axis and the gray line represent the number of total specimens.

man ACE2 transgenic mice, coinfection with influenza and COVID-19 can cause more serious pathological damage to the lung and a higher COVID-19 load, which also means that it may lead to more serious secondary diseases. They found that the expression of ACE2 was slightly upregulated (2∼3 times) by influenza alone but strongly upregulated (approximately 20 times) by influenza coinfection with COVID-19.[6] We inferred from the article that influenza virus infection can increase coronavirus infection by initiating the expression of ACE2 and accelerating the subsequent expression process. At the same time, the study also shows that[7,8] viral infection may worsen the clinical outcome and significantly increase the probability of acute kidney injury, acute heart failure, secondary bacterial infection, multileaf infiltration and ICU admission.

In fact, according to our data, there are few people with coinfection. We selected five kinds of respiratory influenza viruses for research during this period, including Mycoplasma pneumoniae, adenovirus, influenza A virus, influenza B virus and respiratory syncytial virus, which appeared as seasonal epidemics in our hospital in previous years (Fig. 1). However, according to our data, after the rapid increase in SARS-CoV-2 infection, coinfection of SARS-CoV-2 with these viruses is very rare, only 0.23% (Fig. 2). The most important reason should be that although the country has lifted restrictions on the movement of people, the public's awareness of wearing masks has become stronger. Our previous research shows that nonpharmaceutical interventions such as wearing masks and washing hands can be useful to limit the infection of common respiratory viruses, which is an effective measure to block respiratory virus infection in COVID-19.[9,10]

In summary, nonpharmaceutical intervention is an effective measure to block SARS-CoV-2 coinfections with common respiratory virus infections.

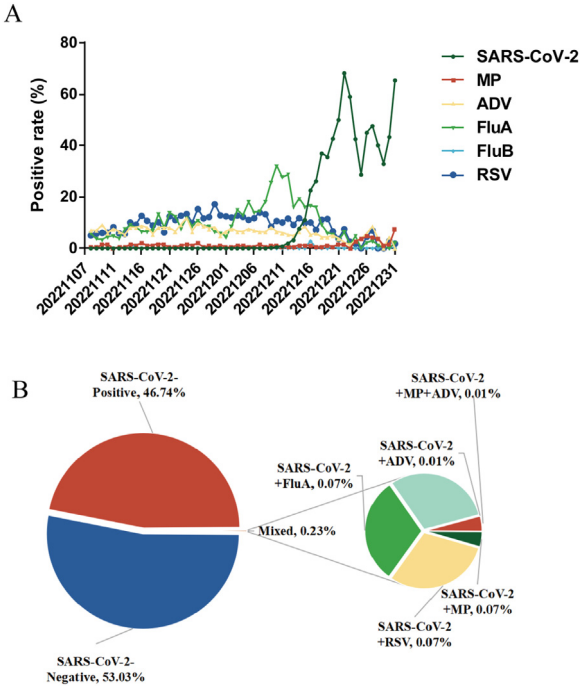

Fig. 2. Proportion of SARS-CoV-2 and respiratory influenza virus positives (A) and proportion of coinfections (B).

Declaration of Competing Interest

The authors report no conflicts of interest.

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Changes of *Mycoplasma pneumoniae* prevalence in children before and after COVID-19 pandemic in Henan, China

Dear Editor,

In this journal, the reports of Li et al.[1] and Zhou et al.[2] attract our attention and interest, which demonstrated that the Coronavirus disease 2019 (COVID-19) pandemic has an impact on the *Haemophilus influenzae* and *Streptococcus pneumoniae* infection in children. However, no data was available regarding the changes of *Mycoplasma pneumoniae* (*M. pneumoniae*) prevalence in children before and after COVID-19 pandemic in Henan, China.

M. pneumoniae is a bacterium that can cause illness by damaging the lining of the respiratory system.[3] *M. pneumoniae* infection is one of the most common causes of community acquired pneumonia (CAP) in children. Up to 10% of *M. pneumoniae*-infected children developed pneumonia.[4] *M. pneumoniae* was mainly transmitted by respiratory droplets formed by people infected with *M. pneumoniae* infection when they coughed or sneezed. COVID-19 is a highly infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that may result in life-threatening complications.[5] To prevent the spread of SARS-CoV-2, strict intervention measures were implemented, such as wearing masks, keeping social distance, limiting crowd gathering and restricting outdoor activities. Theses control measures may also have an impact on the spread of *M. pneumoniae* in children. Analyzing the local data of children with *M. pneumoniae* infection before and after the COVID-19 pandemic can provide evidence-based strategies for the prevention of *M. pneumoniae* infection in children.

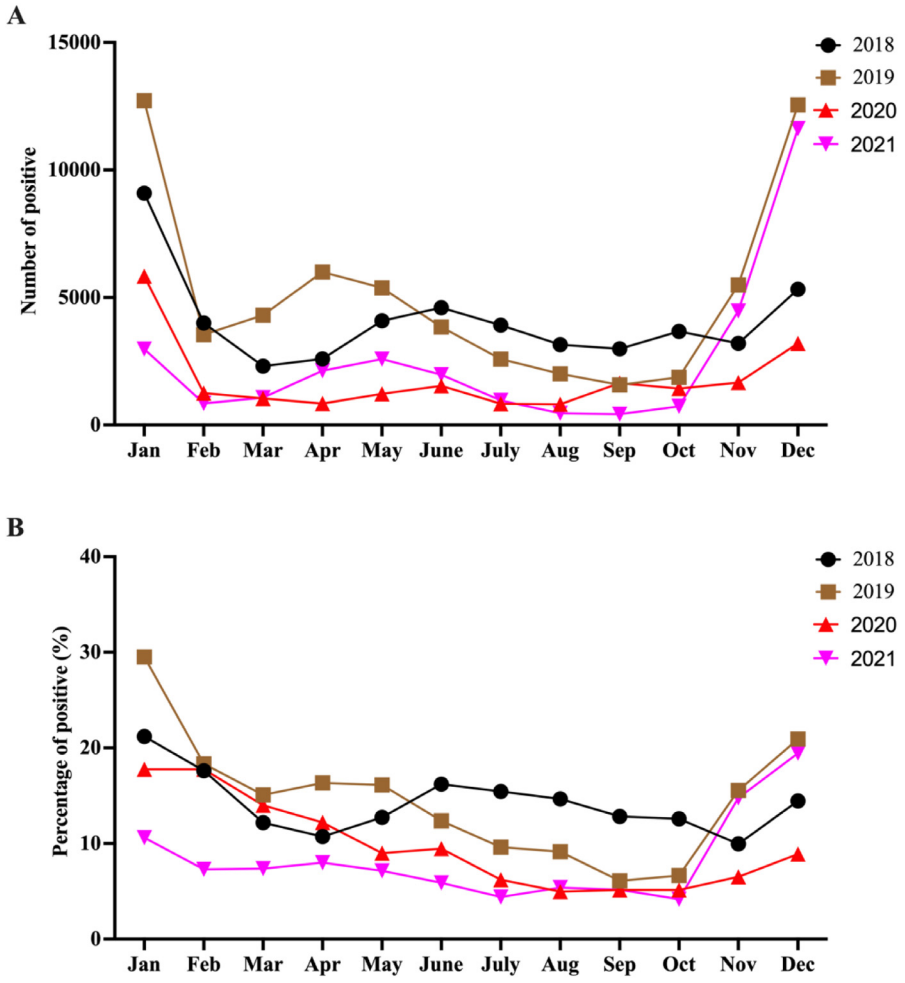

Fig. 1. The positive number and rate of *M. pneumoniae* infection in children from 2018 to 2021.

Therefore, we conducted a retrospective study to investigate the changes of *M. pneumoniae* prevalence in children before and after COVID-19 pandemic in Henan, China. A total of 1,259,697 children aged 1days to 18 years who came to Henan Children's Hospital (Zhengzhou, China) for *M. pneumoniae* IgM testing from 2018 to 2021 were enrolled in this study. As shown in Fig. 1, the positive number and rate of children with *M. pneumoniae* infection decreased in 2020 and 2021, compared with the same period in 2018 and 2019 (Except that in November and December 2020). Our data also showed that the peak of *M. pneumoniae* infection occurred in January and December. Meanwhile, we further divided the children into four groups according to age (0-1years, 1-3years, 3-6 years and $>$ 6 years). As shown in Fig. 2, the positive number and rate of children infected with *M. pneumoniae* in all age groups decreased in 2020 and 2021, compared with that in 2018 and 2019. The number of children aged 3-6 years with *M. pneumoniae* infection is the largest. Of note, the positive rate of children infected with *M. pneumoniae* infection increased with age.

In conclusion, our data showed that COVID-19, as well as well as its prevention and control measures, decreased the positive number and rate of children with *M. pneumoniae* infection in 2020 and 2021. Maintaining effective and continuous surveillance is very important for the prevention of *M. pneumoniae* infection in children aged $>$ 3 years, especially in December and January.

This study had several strengths. First, it is a large study with more than 1 million children undergoing *M. pneumoniae* IgM testing, reporting 162,338 children with *M. pneumoniae* infection. Sec-

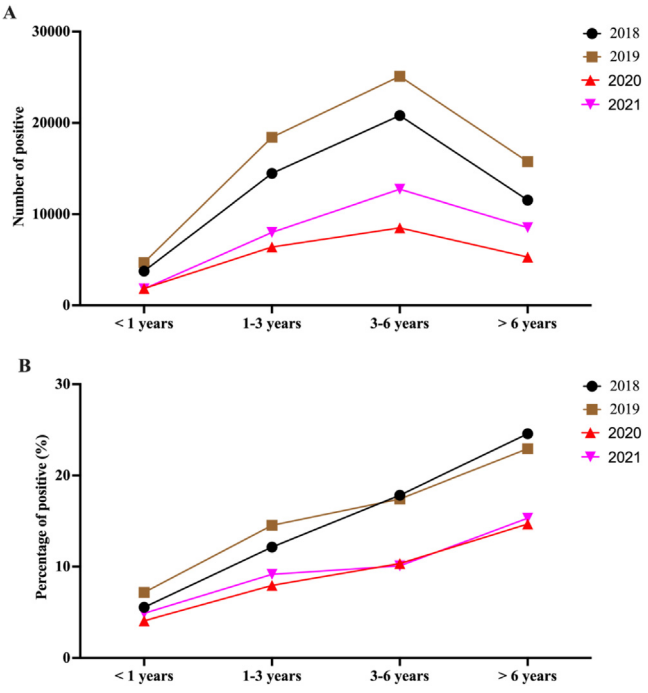

Fig. 2. The number of positive and positive rates of *M. pneumoniae* infection in children by age group from 2018 to 2021.

ond, children aged 1 day to 18 years old were enrolled in this study. This study also has a few limitations. First, this was a cross-sectional study, and we did not track the future clinical outcomes. Second, this was a single-center study conducted in Henan, China. The results may differ in other regions.

Declaration of Competing Interest

The authors declare no conflict of interests.

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Impact of non-pharmaceutical interventions during COVID-19 pandemic on measles and mumps in Mainland China☆,☆☆,☆☆☆,☆☆☆☆

Dear Editor,

We read with great interest a recent paper in the Journal of Infection by Fricke et al.[1], which suggested that non-pharmaceutical interventions (NPI) implemented during the COVID-19 pandemic influenced the incidence of other respiratory diseases transmitted through respiratory droplets and aerosols. There were also several other reports indicating that the COVID-19 pandemic affected the incidence of influenza and other human respiratory infections such as pertussis, scarlet fever and hand-foot-mouth disease.[2–4] However, there is a lack of data on seasonal trends of other common respiratory infections such as measles and mumps impacted by NPI strategy during the COVID-19 pandemic.

Measles is an acute respiratory infection whose basic reproduction number is currently the highest (R0 = 18).[5] Pandemics occur every 2 to 3 years. Mumps is a common childhood infection caused by the mumps virus (R0 = 10).[6] It can occur round the year and is prevalent in the winter and spring. Although the above-mentioned infectious diseases can be prevented by vaccination, the World Health Organization (WHO) reported that the epidemiological trends of the infectious diseases have changed globally due to the impact of the COVID-19 pandemic.[7] Considering the public health risks posed by these infectious diseases and taking into account the COVID-19 prevention and control strategies in mainland China, we conducted a comparative analysis to explore the impact of COVID-19 pandemic on measles and mumps infections in mainland China. It will facilitate the design of more effective key interventions and preventive measures to combat these resurgent infectious diseases.

Surveillance data for infectious diseases collected from January 2017 to August 2022 were extracted from the National Health Commission of the People's Republic of China (http://www.nhc.gov.cn/wjw/yqbb/list.shtml). Given that seasonal fluctuating trends in respiratory infectious diseases might bias the true variability, we removed seasonality by averaging over the same month each year from the data to focus on fluctuations in the data trends. As shown in the following functions, it is a function of month and is independent of year.

$$N(\mathrm{m}) = \frac{1}{\#\ \text{of years}} \sum_{\mathrm{y}} \mathrm{N}(\mathrm{y}, \mathrm{m})$$

In this function, the N (y, m) is the number of new cases in the year (y) and the month (m). The adjusted series will be $N(y, m) - S(m)$. Following seasonal adjustment, we conducted *t*-test or rank-sum test to investigate differences in the adjusted number of new cases before and after the COVID-19 outbreak. Otherwise, the absolute growth rate was also calculated to eliminate misinformation caused by flaws in the annual report. Data analysis and visualization were performed with Python software.

The shape of the curve showed that the overall trends for measles and mumps were broadly similar. Compared to previous years, the curve flattened out after sharply declining from 2020 onwards. The number of reported cases of measles increased significantly between March and June, while mumps increased significantly between May and June and between November and December each year. No change in the peak measles and mumps period was observed before and after the emergence of SARS-CoV-2. Measles cases were reported on average 409 cases per month from 2017 to 2019, whereas average 96 cases per month were reported from 2020 to 2022. Given the non-normality of the data, we used the Mann-Whitney U test to compare the seasonally-adjusted data. Results from the analysis of the number of positive measles infections revealed a significant difference in the number of measles infections before and after the COVID-19 outbreak in mainland China (Fig. 1A and 1B; Mann-Whitney U test: $P < 0.0001$). As for mumps, positive cases were reported on average 22,761 cases per month from 2017 to 2019, while average 11,161 cases per month were reported from 2020 to 2022. Compared to the number of monthly cases from 2017 to 2019, there was a statistically significant differ-

☆ **Author contributions:** Haiyan Yang, Fang Liu and Guangcai Duan designed the study. Jie Xu and Yujia Wang conducted data collection. Jie Xu conducted statistical analyses. Jie Xu wrote the manuscript. All the authors approved the final version of the manuscript.

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☆☆☆ **Conflicts of interest statement:** The authors declare that they have no any potential conflict of interest regarding this submitted manuscript.

☆☆☆☆ **Data availability statement:** The data that support the findings of this study are included in this article and available from the corresponding author upon reasonable requests.

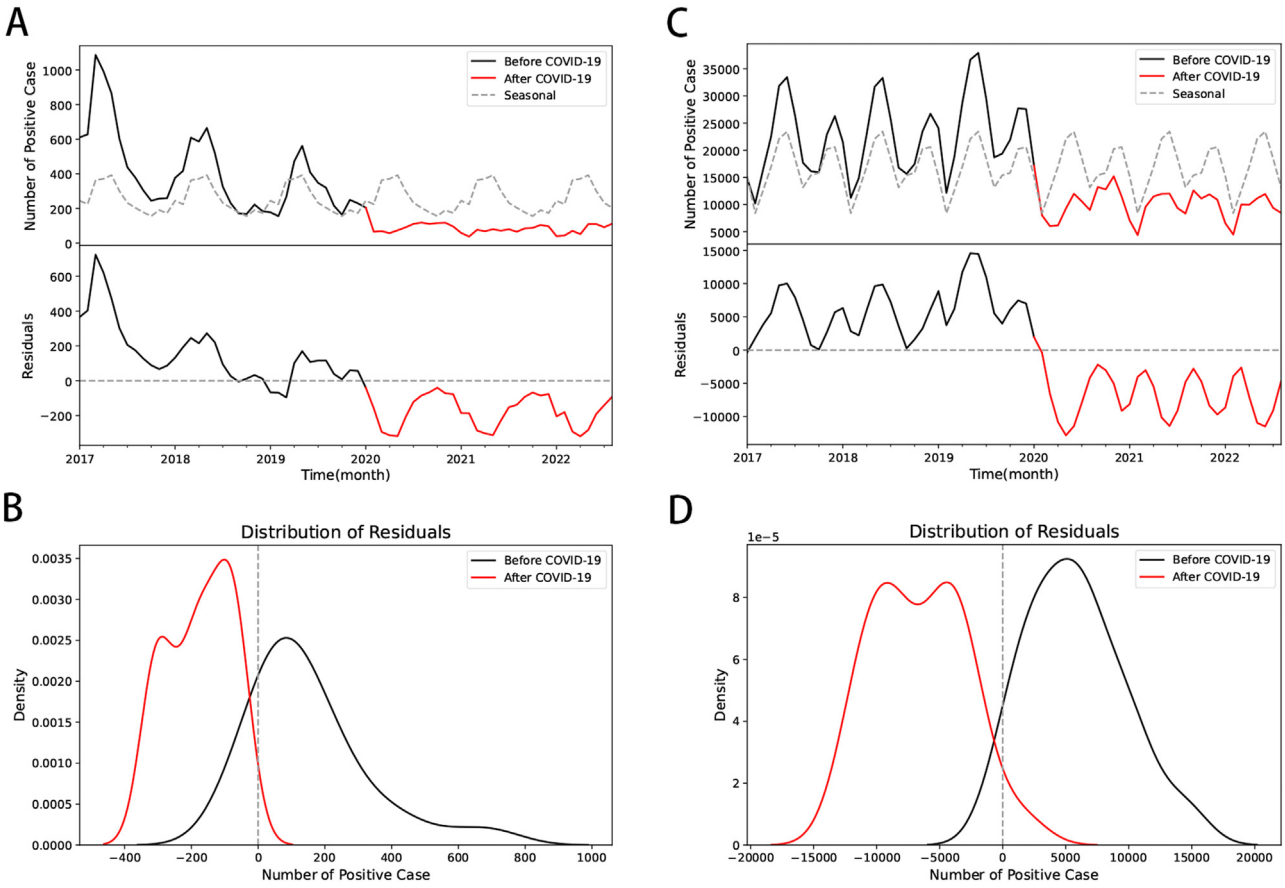

Fig. 1. The monthly new cases of measles and mumps before and after the COVID-19 pandemic. A) the raw monthly new cases of measles (solid line) and the seasonal component (dash line) in the upper panel, and the residual after removing the seasonal component in the lower panel. B) the residual distributions of measles before (black) and after (red) the COVID-19 pandemic. They illustrated that the COVID-19 pandemic decreased the number of new cases significantly ($P < 10^{-5}$ from the Mann-Whitney U test on the two distributions in Fig. 1B). C) the raw monthly new cases of mumps (solid line) and the seasonal component (dash line) in the upper panel, and the residual after removing the seasonal component in the lower panel. D) the residual distributions of mumps before (black) and after (red) the COVID-19 pandemic. They illustrated that the COVID-19 pandemic decreased the number of new cases significantly ($P < 10^{-5}$ from the student's *t*-test on the two distributions in Fig. 1D).

Table 1
The absolute growth rate of measles and mumps diseases in Mainland China from 2017 to 2021.

Year	Measles		Mumps	
	Reported cases	The absolute growth rate	Reported cases	The absolute growth rate
2017 vs 2018	6670 vs 4483	-32.7%	254796 vs 261493	2.6%
2018 vs 2019	4483 vs 3573	-20.2%	261493 vs 303105	15.9%
2019 vs 2020	3573 vs 1234	-65.4%	303105 vs 130911	-56.8%
2020 vs 2021	1234 vs 916	-25.7%	130911 vs 120776	-7.7%
2018-2019 vs 2020-2021	8056 vs 2150	-73.3%	564598 vs 251687	-55.4%

ence in the decrease in cases from 2020 to 2022 (Fig. 1C and 1D; *t*-test: $P < 0.0001$).

Interestingly, the monthly average of mumps infections went from 21,233 to 25,259 between 2017 and 2020 compared to the previous two years (Table 1), and peaked in June 2019. However, the number of cases decreased following the implementation of the COVID-19 restrictions in January 2020. Moreover, compared to the previous year, the number of measles and mumps infections both indicated the most decrease in the absolute growth rate in 2020 (Table 1). Measles cases reported in 2020 decreased by 65.4%, while mumps decreased by 56.8%. The decrease in 2021 was not as obvious as in 2020, which might be related to the relaxation of the full intervention policy in mainland China in 2021. Anyway, in comparison to 2018 to 2019, measles was reported 77.3% lower and mumps 55.4% lower in 2020 to 2021. The fluctuation of the absolute growth rate was more pronounced for measles than that for mumps, which might be due to the fact that the effectiveness of NPI in lowering the reproductive rate of infection depended heavily on the underlying pre-intervention reproductive rate.

Overall, the present study based on seasonality-adjusted values showed that the number of measles and mumps infections decreased during the COVID-19 pandemic compared to the previous period, which was consistent with recently published studies about other human respiratory infections.[2,4,8–10] In the mainland China, interventions taken by the government to control the COVID-19 pandemic, including temporary lockdowns, wearing of masks, social distancing, enhanced personal hygiene and reduced travel, can be effective in preventing the infection of other respiratory infectious diseases which share the same transmission route. In addition, according to this policy, all patients presenting with fever and respiratory symptoms are advised to attend hospital for screening if there are no contraindications. It might lead to a significant increase in the proportion of patients newly diagnosed with measles and mumps. Therefore, we suggest that this reduction could be

explained by the NPI implemented in mainland China during the COVID-19 pandemic.

In short, our present findings demonstrate that the number of reported cases of measles and mumps is related to the intervention strategy. NPI plays a positive role in the prevention and control of the prevalence of these common respiratory infectious agents.

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Changes of Klebsiella pneumoniae infection and carbapenem resistance in ICU elderly infected patients before and after the COVID-19 pandemic in Zhengzhou, China

Dear Editor,

Recent articles suggested that Streptococcus pneumonia (S. pneumoniae), Haemophilus influenzae (H. influenzae) and Moraxella catarrhalis (M. catarrhalis) infections among children in Zhengzhou, China showed a decreasing trend during the COVID-19 pandemic.[1–3] Previous studies also reported changes in carbapenemase-producing Enterobacteriaceae and extended-spectrum beta-lactamase (ESBL) E. coli infections during the COVID-19 pandemic.[4,5] However, Klebsiella pneumoniae (*K. pneumoniae*), especially carbapenem-resistance *K. pneumonia* (CRKP) infection, is the main cause of mortality among elderly in the ICU, and its' impact during the COVID-19 pandemic has not been reported.

K. pneumoniae is a Gram-negative pathogen associated with pneumonia, urinary tract infection, sepsis, wound infection, and meningitis.[6] K. pneumoniae naturally colonizes the nasopharyngeal and gastrointestinal tracts after infection. However, nasopharyngeal colonization was relatively low (maximum of 15%) compared with that of the gut (approximately 20%).[7] *K. pneumoniae* is usually susceptible to carbapenems, but more than 40% of clinical *K. pneumoniae* isolates collected from 30 medical centers in China were identified as CRKP in 2017. CRKP has emerged as a major worldwide human health threat, as CRKP infections are associated with high mortality and morbidity.[8] Moreover, the morbidity and mortality rates for CRKP-infected patients in the ICU are much higher than the non-ICU patients. A previous study showed that nearly half of all K. pneumonia (45.7%) infections occurred in the elderly, and suggested that age is also an independent risk factor for CRKP, which may result from the decreased immune function of elderly patients.[9] Therefore, the prevention and control of *K. pneumonia* and CRKP infections in elderly ICU patients is a major public health concern worldwide.

In this study, we assessed the positive rate, age, basic information and epidemic trend of *K. pneumonia* and CRKP infections in ICU elderly infected patients before and after the COVID-19 pandemic to provide a reference for hospital infection control and treatment of CRKP. The number of positive cases of *K. pneumonia* and CRKP infections among elderly (defined as more than 60 years old), in the stratified age groups of 60–70 years, 70–80 years and more than 80 years, were examined between January 1, 2018, and December 31, 2021, at the First Affiliated hospital of Zhengzhou University according to laboratory surveillance. The number of elderly with *K. pneumonia* and CRKP infections increased from 2018 to 2019, but showed a steady decline after the outbreak of COVID-19 in Zhengzhou, China. Additionally, *K. pneumonia* and CRKP infections showed an obvious seasonality from 2018 to 2019 before the COVID-19 pandemic, with the number of positive cases increasing in winter, but no seasonality was observed in 2020–2021 after the COVID-19 pandemic (Fig. 1A and 1C). Furthermore, the percentage of positive cases (positive cases/total cases) with *K. pneumonia* and CRKP infections showed an obvious seasonality from 2018 to 2019 before the pandemic, in which the percentage of positive cases was higher in winter, but the seasonality was inconspicuous from 2020 to 2021 after the COVID-19 pandemic (Fig. 1B and 1D). Interestingly, the number of positive cases of *K. pneumonia* and CRKP infections in 2021 was slightly lower than in 2020, which may be associated with the preventive and control measures of COVID-19 that resulted in a significant reduction in the number of elderly going to the hospital. Furthermore, both the number of

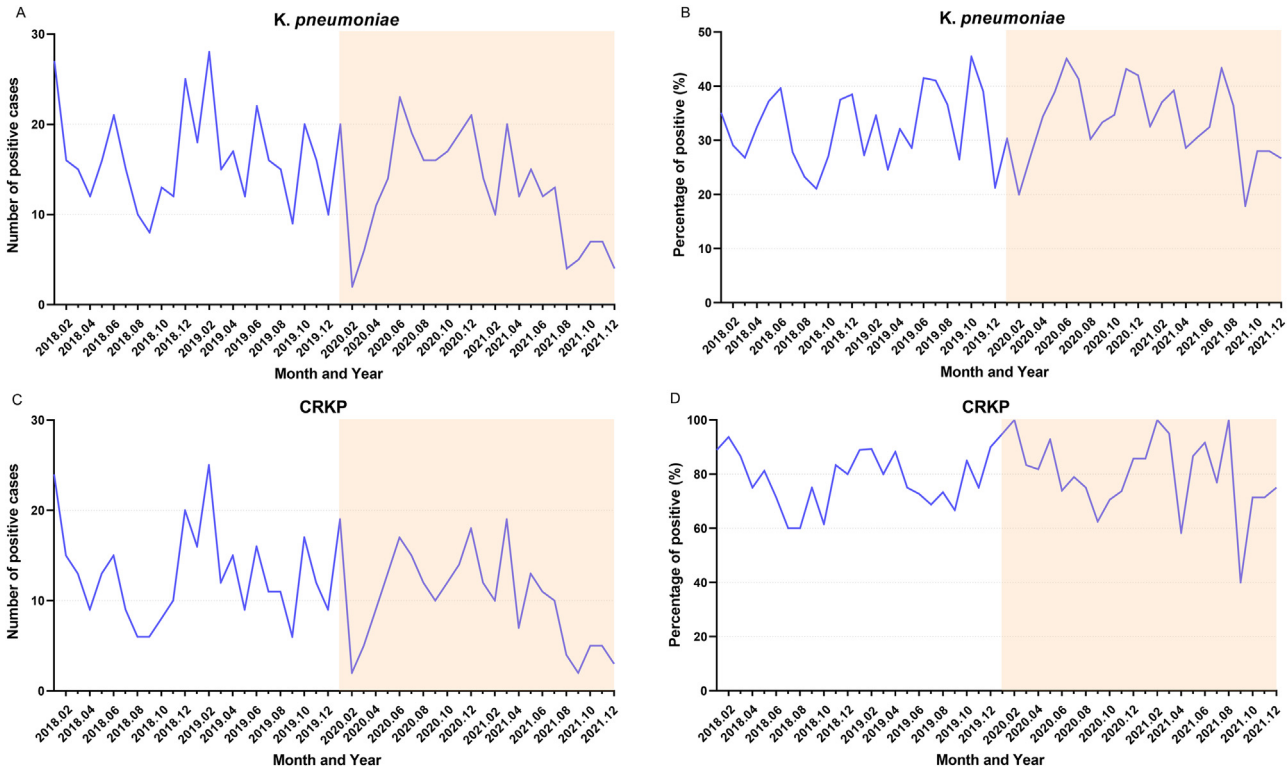

Fig. 1. **(A)** The number of positive infections of K. *pneumoniae* from January 2018 to December 2021. **(B)** The percentage of positive infections of K. *pneumoniae* from January 2018 to December 2021. **(C)** The number of positive infections of CRKP from January 2018 to December 2021. **(D)** The percentage of positive infections of CRKP from January 2018 to December 2021.

positive cases of *K. pneumonia* and CRKP infections, as well as the percentage of positive cases of *K. pneumonia* infections rapidly increased owing to the COVID-19 outbreak in Zhengzhou from February to June 2021 (Fig. 1A–C). The percentage of positive cases of *CRKP* infections rapidly increased due to the COVID-19 outbreak in Zhengzhou between July and August 2021,and the large population mobility and increased transmissibility of COVID-19 may cause it's increased during the Chinese Spring Festival (Fig. 1D). Taken together, these results suggested that the COVID-19 pandemic could influence the infection status of *K. pneumonia* and CRKP infections.

Additionally, the number of elderly infected with *K. pneumonia* and CRKP in the ICU was the lowest in the >80 years age group, who only accounted for 23.3% and 24.5% of the total number of infected elderly ICU patients from 2018 to 2021, and was similar between the 60–70 years age group and the 70–80 years age group (Fig. 2A and 2C). However, among all age groups, the highest proportion of *K. pneumonia* and CRKP infections in the >80 years age group was 35.3% and 84%, respectively. Importantly, the number of infections showed a decreasing trend before and after the COVID-19 pandemic, particularly in the >80 years age group, but the percentage of positive cases showed an increasing trend in the elderly, especially, in the >80 years age group. This may like a report showed that although the number of positive cases with infections (i.e., the numerator) decreased, the extent of the decrease in the total number of tested patients (i.e., the denominator) was larger.[10] Specifically, the decrease in the total number of tested patients would be because the increase in the number of new polymerase chain reaction-positive COVID-19 patients and hospitalized COVID-19 patients caused a decrease in the number of hospital admissions due to other diseases and increased the testing threshold due to the risk of transmission of COVID-19. Although the COVID-19 pandemic restrictions are completely lifted in some Chinese cities, the global pandemic continues and its prevention and control remains inadequate. Therefore, the long-term prevalence of *K. pneumonia* and CRKP infections in elderly ICU patients should be closely monitored. Moreover, ICU elderly infected patients, especially those >80 years old, should be aware of the risk of K. *pneumoniae* and CRKP infections.

In summary, this study suggested that K. *pneumoniae* and CRKP infections in ICU elderly infected patients had decreased during the COVID-19 pandemic. Monitoring epidemiological trends is important for preventing K. *pneumoniae* and CRKP infections in ICU elderly infected patients who are more than 80 years old.

Declaration of Competing Interest

None.

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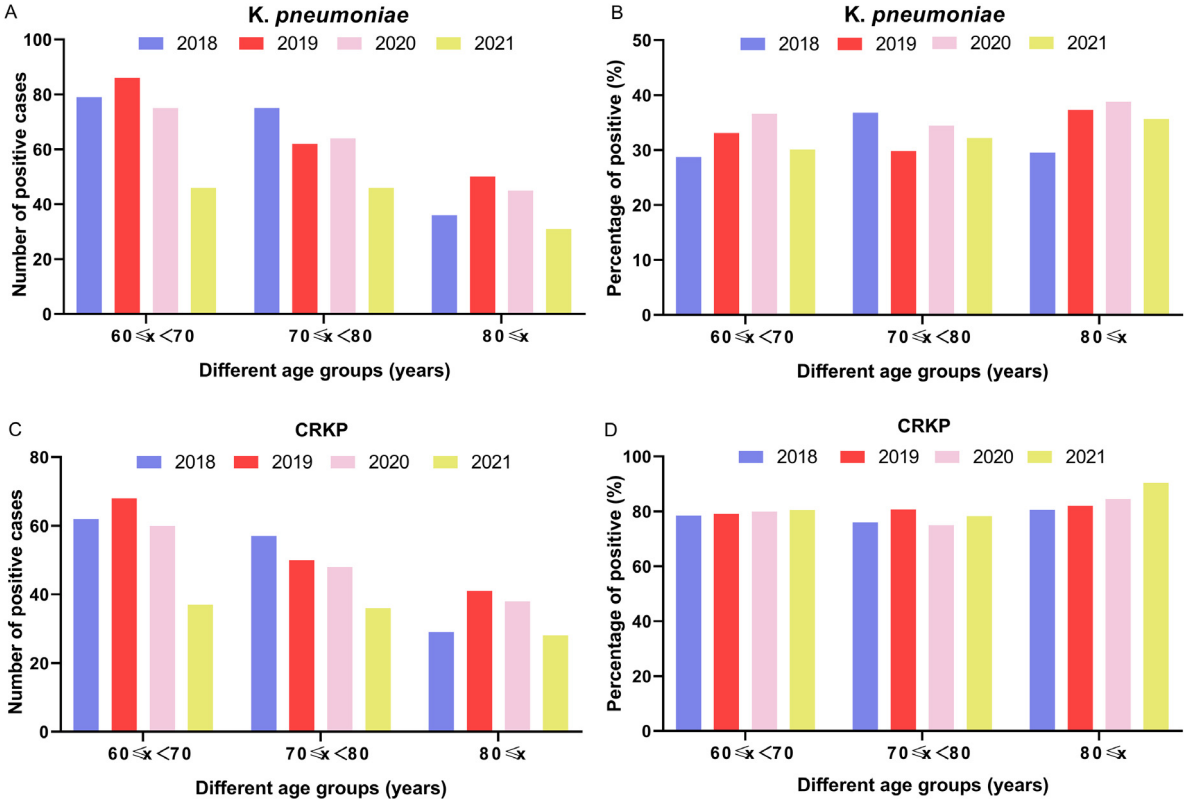

Fig. 2. **(A)** The number of positive infections of K. *pneumoniae* in different age groups from January 2018 to December 2021. **(B)** The percentage of positive infections of K. *pneumoniae* in different age groups from January 2018 to December 2021. **(C)** The number of positive infections of CRKP in different age groups from January 2018 to December 2021. **(D)** The percentage of positive infections of CRKP in different age groups from January 2018 to December 2021.

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Feasibility of emulating Singapore's experience during the Omicron wave in China

Dear Editor,

The world has undergone five waves of COVID-19 pandemics, with a sixth wave likely to be led by China as policies in China begin to relax.[1] In this journal, Ming Zheng stated that the emergence of Omicron variants of SARS-CoV-2 will present China with unprecedented challenges, especially following the announcement of optimized anti-COVID-19 policies.[2] Regions across the nation will swiftly encounter the first wave of an epidemic since the Chinese government announced the "Ten New Measures" on December 7, 2022, with adjusted standards for managing risk areas, nucleic acid testing, and quarantine.[3] With only 9 million hospital beds and 120,000 ICU beds in reserve, China could face severe strain on its healthcare system if it continues to adopt further reopening during a spike in infections.[4] The healthcare system in Hong Kong, China, had been under tremendous pressure in response to its fifth wave of Omicron (as of May 1, 2022, the death toll was 9100).[5] In contrast, Singapore responded to the wave of Omicron with much less of a strain on the healthcare system. Drawing lessons from Singapore's experience is worthwhile.

It is urgently needed to make efforts to alert the healthcare system before it becomes overwhelmed, and smooth the epidemic curve after China reopens. Here we propose tightening and relaxing public health and social measures (PHSMs) according to hospital and ICU bed occupancy thresholds. The real-time hospital and ICU bed occupancy data is accessible, notwithstanding the surveillance system's inadequacy to detect all the infections in the forthcoming wave. PHSMs are tightened when either the real-time hospital or ICU bed occupancy rises to the "red line" (assuming 10% of the region's hospital beds are available for COVID-19 treatment), relaxed if both are reduced to the "green line" (assuming 10% of red line bed counts).

We reproduced the multiple Omicron waves in Singapore using a multi-dimensional model[6] developed earlier that activates dynamic PHSMs based on medical bed count. Between January 1, 2022, and December 8, 2022, the cumulative symptomatic cases were 1.9 million, and the death toll is 879 in Singapore, according to publicly reported data.[5] Our model shows that the cumulative symptomatic cases in Singapore will reach 2.26 million, and the death toll will be 865 in the 365 days simulation. Our model shows that the simulated epidemic curve matches the publicly reported data (Fig. 1). To extend Singapore's experience to China, we used the model to predict the epidemic wave in Xiamen, a city with a population size and age structure similar to Singapore. The results demonstrate that Xiamen will experience two epidemic peaks after reopening if tightening and relaxing PHSMs at time points in Supplementary Table 4, with a cumulative symptomatic of 2.6 million cases, a peak symptom onset of 29,800, a peak hospital bed occupancy of 1769 and a death toll of 1209. The healthcare system in Xiamen might not be overwhelmed, assuming 10% of the city's hospital beds are available for COVID-19 treatment. The results show the feasibility and existence of successful control in Xiamen, China (Fig. 1).

Therefore, we advocate that cities in China emulate Singapore's response to the Omicron wave through dynamic PHSMs adjustment, thereby reducing the disease and healthcare system burden. The model simulation needs to be further refined based on regional vaccination status and medical resources due to the heterogeneities across over 300 cities in China.

Author contributions

YCG, ZYZ, GXH, and TMC conceived and designed the study. YCG, XHG, and STY standardized the data and performed the statistical analysis. ZYZ and TMC guided the research. YCG, ZYZ, XHG, and STY interpreted the results and drafted the manuscript. All authors revised and approved the final manuscript.

Declaration of Competing Interest

The authors declare no competing interests.

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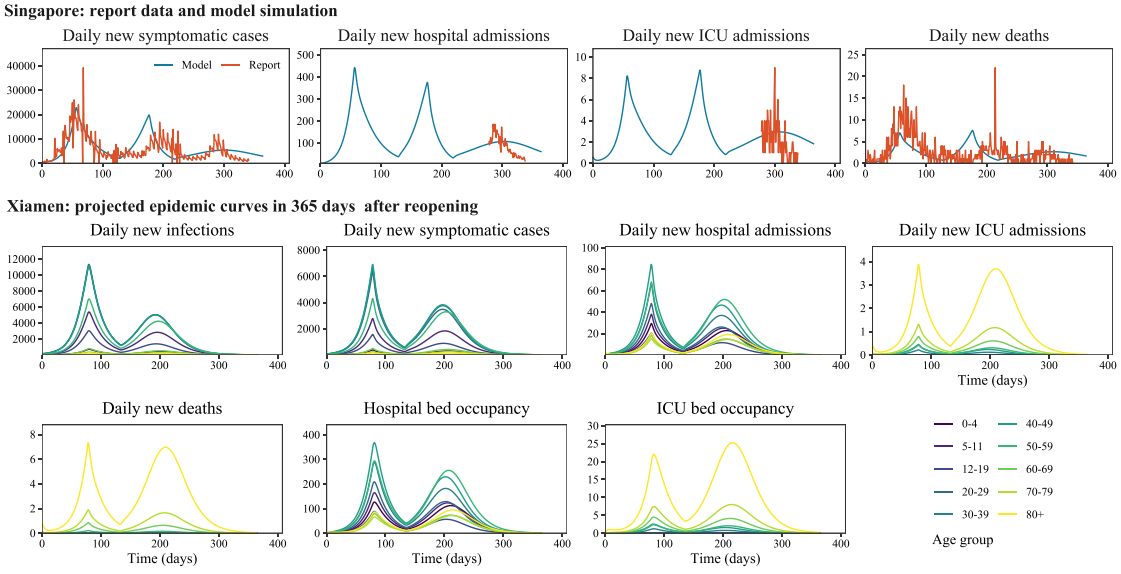

Fig. 1. Report data and model simulation in Singapore and projected epidemic curves after reopening in Xiamen City, China.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2023.01.007.

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The risk of methicillin-resistant *Staphylococcus aureus* infection following COVID-19 and influenza: A retrospective cohort study from the TriNetX network

Dear Editor,

We read with great interest that several studies reported the co- and secondary bacterial infections following severe acute respiratory syndrome coronavirus 2 (SARS–CoV–2) infection, especially for patients with severe-to-critical coronavirus disease 2019 (COVID-19).[1–3] However, the reported incidences of secondary infection post COVID-19 were inconsistent in different studies.[4,5] Therefore, continuing surveillance investigation of the pathogens, especially multidrug-resistant organisms causing secondary infections following COVID-19 is needed to provide the epidemiologic information and further guide the appropriate use of antimicrobials for the patients with SARS-CoV-2 infection.[6] Although it is well known that *Streptococcus pneumoniae* and *Staphylococcus aureus*, including methicillin-resistant *S. aureus* (MRSA) could be the common pathogens causing secondary infection following influenza,[7] it is unclear whether the incidence of MRSA secondary infection in patients with COVID-19 could be as high as that in patients with influenza. We, therefore, examined a large dataset of global healthcare records to determine the incidence of MRSA infection within one month after COVID-19 infection, and compare these risks with the matched patients following infection with influenza.

This retrospective cohort study was conducted using the TriNetX health records network with 73 healthcare organizations worldwide. COVID-19 was defined by the ICD-10 codes (U07.1-U07.2, B97.29, B34.2, J12.81) or positive laboratory results (TNX:LAB:9008-SARS coronavirus 2 and related RNA), and influenza was defined by ICD-10 codes (J09-J11). Cases who were 18 or older were included between March 1, 2020 and September 30, 2022. To avoid contamination between cohorts, the control influenza cohort excluded cases who had COVID-19 within 3 months, and the influenza cases were excluded in the COVID-19 cohort at any point in time. Primary outcome was the risk of secondary MRSA infection (B95.62, A49.02, J15.212) after the 48 h of the index event. Secondary outcome was the risk of MRSA bacteremia (R78.81).

Propensity score with 1:1 matching method was used to identify matched cohorts. Any characteristic with a standardized mean difference between cohorts lower than 0.1 was considered well matched. Hazard ratios (HRs) with 95% confidence intervals were calculated using the Cox model and the null hypothesis of no difference between cohorts was tested using log-rank tests. The Kaplan-Meier estimator was used to estimate the incidence of the outcomes.

Initial, 3,004,268 patients with COVID-19 and 128,393 patients with influenza were identified and then, each 128,392 cases remained in the both cohorts after propensity score matching (Table 1). Compared with the influenza cohort, the COVID-19 cohort was associated with the higher risk of secondary MRSA infection (HR, 1.52; 95% CI, 1.19-1.94) within one month. The higher risk of MRSA infection following SARS-CoV-2 infection than influenza cohort remained unchanged in different time frames (2-5 days: HR, 1.78; 95% CI, 1.20-2.64; 2-10 days: HR, 1.63; 95% CI, 1.90-2.24; 2-15 days: HR, 1.65; 95% CI, 1.24-2.20; 2-20 days: HR, 1.56; 95% CI, 1.20-2.04 and 2-30 days: HR, 1.52; 95% CI, 1.19-1.94). In addition, COVID-19 patients also had higher risk of MRSA bacteremia than patients with influenza in one month (HR, 1.43; 95% CI, 1.16-1.75). The higher risk of MRSA bacteremia remained consistent across different time periods (2-5 days: HR, 1.30; 95% CI, 0.94-1.79; 2-10 days: HR, 1.46; 95% CI, 1.12-1.91; 2-15 days: HR, 1.49; 95% CI, 1.18-1.90; 2-20 days: HR, 1.55; 95% CI, 1.24-1.93 and 2-30 days: HR, 1.43; 95% CI, 1.16-1.75). Further Kaplan-Meier estimation showed a similar finding that the incidence of MRSA infection for COVID-19 patients was higher than those with influenza (Log rank $p < 0.05$) (Fig. 1).

In summary, this retrospective cohort study demonstrated that COVID-19 patients would carry a significantly higher risk of MRSA infections, including MRSA bacteremia, than patients with influenza. The causes of higher risk of MRSA infection and bacteremia in COVID-19 patients than patients with influenza could be multifactorial. In contrast to influenza, systematic corticosteroid and interleukin-6 blockade are recommended for hospitalized patients with severe COVID-19. However, the use of these anti-inflammatory agents may increase the risk of secondary infection. In addition, infection prevention and control measures may not be strictly executed during COVID-19 pandemic. Thus, the incidence of nosocomial infections including MRSA infection could be higher than usual. Finally, the immune status following SARS-CoV-2 infection could be different from those after influenza. However, further investigation is warranted to clarify these mechanisms and validate our findings. Overall, the finding of the present study is consistent with several observational studies which reported that MRSA could be a frequent pathogen causing superinfection following SARS-CoV-2 infections.[8,9] In one review on the epidemiol-

Table 1
Baseline characteristics for COVID-19 and influenza cohorts before and after matching.

	Before matching			After matching		
	COVID-19	Influenza	SMD	COVID-19	Influenza	SMD
Number	3,004,268	128,393		128,392	128,392	
Age; mean ± SD, year	47.3±17.7	47.5±19.3	0.781	47.4±19.2	47.5±19.3	0.004
Sex; n (%)						
Female	1,678,280 (55.9)	75,617 (58.9)	0.061	75,641 (58.9%)	75,616 (58.9%)	<0.001
Male	1,288,549 (42.9)	51,780 (40.3)	0.052	51,763 (40.3%)	51,780 (40.3%)	<0.001
Race; n (%)						
White	1,603,957 (53.3)	488,603 (60.3)	0.141	84,667 (65.9%)	83,796 (65.3%)	0.014
Black or African American	402,873 (13.4)	17,012 (13.2)	0.005	17,005 (13.2)	17,012 (13.2)	<0.001
Hispanic or Latino	234,190 (7.8)	9,562 (7.4)	0.013	9,280 (7.2)	9,562 (7.4)	0.008
Comorbidities; n (%)						
Disease of respiratory system	852,444 (28.4)	66,991 (52.2)	0.500	66,952 (52.1)	66,990 (52.2)	0.001
Disease of circulatory system	829,730 (27.6)	59,017 (46.0)	0.388	58,991 (45.9)	59,016 (46.0)	<0.001
Hypertensive disease	623,360 (20.7)	44,753 (34.9)	0.319	44,906 (35.0)	44,752 (34.9)	0.003
Neoplasms	409,135 (13.6)	35,981 (28.0)	0.361	35,558 (27.7)	35,980 (28.0)	0.007
Chronic lower respiratory disease	313,002 (10.4)	26,912 (21.0)	0.251	26,470 (20.6)	26,912 (21.0)	0.008
Diabetes mellitus	301,326 (10.0)	24,521 (19.1)	0.259	24,308 (18.9)	24,520 (19.1)	0.004
Asthma	194,640 (6.5)	16,751 (13.0)	0.223	16,425 (12.8)	16,751 (13.0)	0.008
Chronic kidney disease	150,798 (5.0)	16,864 (13.1)	0.285	16,659 (13.0)	16,863 (13.1)	0.005
Overweight, obesity and other hyperalimentation	358,122 (11.9)	23,370 (18.2)	0.176	23,096 (18.0)	23,370 (18.2)	0.006

SD, standard deviation; SMD, Standardized mean difference

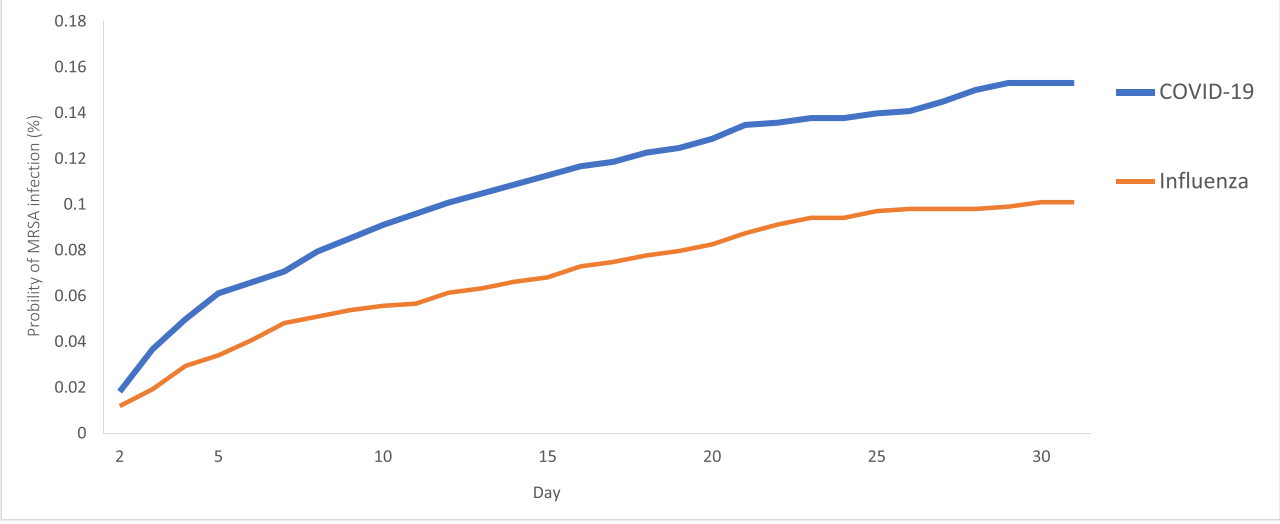

Fig. 1. The incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) infection in COVID-19 and influenza cohorts.

ogy of MRSA lung infection in patients with COVID-19,[10] the relative prevalence among all identified bacteria could range from 2% to 29%. All these findings indicated the critical role of MRSA among patients with COVID-19 and suggestd that clinicians keep alert the possible MRSA secondary infection following SARS-CoV-2 infections. Because inappropriate empirical antibiotic would be associated with poor outcome of patient with sepsis, empirical use of anti-MRSA agents for COVID-19 patients with secondary infection should be considered, especially for those with risk of MRSA infection.

This study had several limitations. First, although we matched the baseline characteristics of COVID-19 and influenza cohorts using propensity score method, some residual confounding factors, such as the disease severity, the use of anti-inflammatory agents, and the vaccine effect still existed. Second, SARS-CoV-2 infection could present as asymptomatic, so the influenza cohort might include patients without identified COVID-19. To avoid this confounding, the cases in the influenza cohort in this study was identified before 2020, when there was no COVID-19.

In conclusion, patients with COVID-19 would be associated with a higher risk of secondary MRSA infection than those with influenza. During this pandemic, clinicians should consider MRSA as potential pathogens causing secondary infection following SARS-CoV-2 infection.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Facial nerve palsy as a possible adverse drug reaction of the modified vaccinia ankara-bavarian nordic (MVA-BN) smallpox vaccine: A pharmacovigilance analysis

Dear Editor,

Facial nerve palsy; Bell's palsy; Monkeypox; Adverse drug reaction; Pharmacovigilance

Monkeypox (MKP) virus is a re-emerging pathogen first evidenced in Sub-saharian Africa and responsible for an ongoing global outbreak, mainly among men having sex with men in western countries. In this context, immunization has been urgently implemented since June 2022 and recommended by national authorities for populations at risk of exposure.[1] It relies on a third-generation live, attenuated, non-replicating orthopoxvirus-based vaccine obtained from the Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN) strain (Jynneos® or Imvanex®). Here, we report the first national case series of facial nerve palsy following MVA-BN vaccination.

Case #1

A 29-year-old man without significant medical history except depression with an ongoing paroxetine treatment was admitted in the emergency ward for numbness of the left face and left facial hemiparesis that appeared the day before. He did not report any other complaint. He had received 8 days before a first shot of MVA-BN vaccine (Imvanex®). The day after he was treated with a single dose of ceftriaxone for oral gonorrhea. He was afebrile, and did not report any pain, headache, walking or balance disorder. Blood pressure was 134/80 mmHg, heart rate was 76 bpm. Glasgow coma scale was normal (15/15). Physical evaluation did not evidence other neurological defect, nor otitis or skin rash. Work-up included cerebral MRI that ruled out recent or old ischemic injuries or neoplastic process; serological testing for HIV infection and Lyme borreliosis were negative. The patient was discharged with prednisone 1 mg/kg/d for seven days, and fully recovered over the next three weeks. He did not receive the second vaccine shot.

Case #2

A 41-year-old man without significant medical history was admitted in the emergency ward for mouth anesthesia extending to the whole right face. He had received 8 days before a first shot of MVA-BN vaccine (Jynneos®). He was afebrile, did not report any pain, headache, walking or balance disorder. Besides hypoesthesia of the right face associated with a light right eyelid ptosis, physical examination was otherwise normal, without otitis, rash or other neurological disorder, including no objective deficit of cranial nerves. Blood pressure was 126/89 mmHg, heart rate was 82 bpm. Glasgow coma scale was normal (15/15). The patient was discharged with prednisone 1 mg/kg/d for seven days and valaciclovir 1g tid. Four days later (12 days after vaccination), medical examination found a typical frank left Bell's palsy, without other neurological signs. Brain magnetic resonance imaging revealed isolated enhanced contrast on the left facial nerve, without any other defect. He fully recovered under physical therapy over the next four weeks. He received the second MVA-BN vaccine shot about 6 weeks after the first shot, without any facial palsy relapse.

Case #3

A 43-year-old man without significant past medical history except a left eye cataract and no usual treatment presented a right facial nerve palsy 7 days after a first shot of MVA-BN vaccine (Jynneos®). Physical evaluation did not evidence fever, otitis, rash, hearing or any additional neurological disorder. Serological testing for hepatitis B and C, HIV infection and Lyme borreliosis were negative. Brain magnetic resonance imaging was normal. He was prescribed prednisone 1 mg/kg/d and valaciclovir 1g tid for ten days. However, no significant improvement could be noted days after treatment at the time of reporting, and the patient was still classified with grade VI facial nerve palsy according to the classification

Abbreviations: vaccine, vaccine.

of House and Brackmann was diagnosed. He did not receive the second vaccine shot.

To date, preventive immunization and educational measures are the most effective prevention tools against the current MKP outbreak. Immunization is based on a third-generation live, attenuated, non-replicating vaccine, MVA-BN vaccine approved for both smallpox and monkeypox in the USA, Canada, and Europe.[2,3] Previous live replication-competent variola virus vaccines have been associated with encephalitis, and myo-/pericarditis, and especially, in immunocompromised patients, with progressive vaccinia or eczema vaccinatum.[4] Third-generation MVA-BN vaccine, given its live but non replicative nature, induce immune response that is comparable to those obtained with conventional vaccinia virus-based vaccines, but can be safely used in the immunocompromised population. During clinical trials and early post-marketing period, about 10,700 people have been exposed to the MVA-BN vaccine, usually in an immunization scheme of two doses administered four weeks apart.[3] Most common adverse drug reactions (ADRs) include local reactogenicity such as mild to moderate erythema or local pain (40% of cases), or mild systemic symptoms such as myalgia or headache (20%). Unsolicited adverse events in clinical trials mainly consisted in pruritus, increased troponin I and nasopharyngitis. Interestingly, the only reported neurological adverse event that was considered as probably related to MVA-BN vaccine consisted in a single observation of grade 3 intensity extraocular muscle paresis that developed 8 days after the second shot, in an otherwise healthy and vaccinia-naïve individual (POX-MVA-008 study: estimated incidence of one over 10,700, i.e. about 0.1/1000). Detailed analysis of our cases could rule out the possibility for any neurological/infectious origin, providing reasonable grounds for vaccine causality.

To further analyzes the possible causality between facial palsy and MVA-BN vaccine we took advantage of VigiBase (https://who-umc.org/vigibase/), the World Health Organization (WHO) global individual case safety report database, which contains anonymized reports of suspected ADRs from more than 150 countries and represents the world's largest pharmacovigilance database. We analyzed all "Smallpox vaccine live (MVA-BN)" reports using the preferred terms "facial paralysis" or "Bell's palsy" from the Medical Dictionary for Regulatory Activities (MedDRA). Beyond our three observations, three additional cases were reported worldwide up to November 1st, 2022 (**Table S1**). All involved men who developed peripheral facial palsy within 21 days after vaccination, with a median time interval from vaccination to reaction onset of 11 days and no alternate drug suspected.

How frequent is this suspected adverse drug reaction with regard to MVA-BN vaccine? As of 1st November 2022, 134,698 doses of vaccine have been administered in France, suggesting a reporting rate of about 2.2 per 100,000 administered doses.[5]

Facial palsy have been longstanding reported with almost all viral vaccines, including COVID-19 mRNA vaccines.[6-8] Although mechanisms at play are not elucidated, reactivation of a herpesvirus latent infection or a type I interferon disturbance are currently considered the most reasonable scenario.[7,9] Noteworthy, facial palsy is also mentioned as a possible ADR in the European labels of COVID-19 mRNA vaccines. Rare cases of facial palsy temporally associated with smallpox vaccination have also been reported in the US,[10] with median time interval between vaccination and symptoms onset of 7 days (range, 3-8 days), and reporting rate of 1.7 per 100,000 doses administered, similarly to the range we report here. Although the authors stated that this reporting rate is lower than expected incidence in general population (15 to 40 cases per 10,000 individuals per year), owing to longstanding known large underreporting in pharmacovigilance systems and to a striking temporal association with a narrow timing after vaccination, one can reasonably hypothesize a possible causal role of vaccine.

Altogether, this national case series of facial palsy within the first days following MVA-BN vaccination, combined with supportive worldwide database and literature analyses, provide converging grounds for a safety signal.

It should be emphasized that given (i) its transient and mild nature (ii) the non-systematic recurrence after reexposure (iii) the potential severity and (iv) epidemiological concerns associated with monkeypox infection, benefits of vaccination still largely overweight this possible rare risk that requires further evaluation. Meanwhile, physicians should be aware of this possible reaction and patients should seek medical assistance in case of sudden weakness of the face in days following MVA-BN vaccination.

Note

These cases have been reported to the French Pharmacovigilance System under the numbers FR-AFSSAPS-PV20221376, FR-AFSSAPS-PS20221774 and FR-AFSSAPS-PP20220858.

VigiBase is a fully deidentified database maintained by the Uppsala Monitoring Center (UMC). The authors are indebted to the National Pharmacovigilance centres that contributed data. Information from VigiBase comes from a variety of sources, and the probability that the suspected adverse effect is drug-related is not the same in all cases. The information does not represent the opinion of the Uppsala Monitoring Center (UMC) or the World Health Organization and only reflects the authors' opinion. According to VigiBase access rules, no specific ethical approval is needed. VigiBase access is granted to national and regional pharmacovigilance centers such our teams.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2023.01.005.

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Oseltamivir is protective for in-patient mortality in PCR confirmed influenza B and influenza A(H3N2) infections in an historic cohort of 1,048 patients hospitalised during the 2016-17 and 2017-18 influenza seasons

Dear Editor,

As predicted by Poole et al., a return to normal levels of activity of seasonal influenza and other respiratory viruses alongside SARS-CoV-2 has followed the end of pandemic social controls in the U.K.[1,2] Hospitals will therefore need to assure their compliance with current national guidelines on molecular testing of patients admitted to hospital with respiratory illness and prompt treatment of confirmed seasonal influenza A and B infections with oseltamivir 75mg twice daily for five days.[3]

Because gold standard evidence from placebo-controlled randomised clinical trials of oseltamivir treatment of seasonal influenza A and influenza B and in patient mortality are lacking, evidence for guidelines in this area depends on observational studies.[4]

We previously reported an 85 per cent reduction in odds of in-patient mortality associated with standard course oseltamivir treatment compared to no treatment in a retrospective cohort study of PCR confirmed influenza A (H3N2) infected patients admitted during the 2016-17 influenza season, undertaken as a service improvement audit.[5]

Activity of influenza B was also high in the 2016 -17 and 2017-18 seasons affording an opportunity to extend our cohort to see if the protective association between standard course oseltamivir and in patient mortality differed between influenza B and influenza A (H3N2), influenza A (H1N1pdm09) or between the 2016-17 and 2017-18 influenza seasons. We extended our cohort to include all PCR confirmed cases of seasonal influenza B and influenza A (H1N1 pdm09) admitted in the 2016-17 and 2017-18 seasons; and all PCR confirmed influenza A (H3N2) patients admitted in the 2017-18 season.

Single variable and multivariable stepwise logistic regression of the odds of in- patient death was done as described before,[5] except adding interactions of variables with season and variables for influenza strain (Influenza B, influenza A (H3N2), influenza A (H1N1pdm09) and influenza A generic)); influenza season of admission (2016-17 or 2017-18); and placing into a single category non-standard oseltamivir courses. all of which were less than the standard course of 75mg twice daily for five days. (Table 1)

In patient mortality for influenza B was 30/371 (8.1%), influenza A (H3N2) 51/610 (8.4%), influenza A(H1N1pdm09) 0/48 (0%); and influenza A generic 2/19 (10.5%). Standard course oseltamivir 75mg two times daily for five days was associated with an 82% reduction of odds of in-patient death (OR 0.18 (0.07,0.51)) compared to a less than standard course (OR 0.39 (0.14,1.14)) and to no treatment OR (1.0 (Reference) ($p = 0.003$)) in our final multivariable logistic regression model.(Table 2) No difference in protection associated with standard course oseltamivir treatment 75mg twice daily for five days was detected between seasonal influenza B and influenza A (H3N2) infections in the final multivariable model. This model adjusted for age, attribution of acquisition of infection to hospital versus community setting, admission to critical care, radiological evidence of pneumonia, non-invasive respiratory support, heavy alcohol use, tobacco use, serum haemoglobin, serum urea and total white cell count. Substituting oseltamivir course in our final multivariable model with delay between onset of symptoms and starting oseltamivir treatment, the odds ratio for in patient mortality increased by five per cent per day of delay in starting oseltamivir, Odds Ratio 1.05 (0.97, 1.14) per day. $p = 0.01$.

Our observations are consistent with standard course oseltamivir 75mg twice daily for five days being effective in reducing the risk of in-patient mortality in PCR confirmed seasonal influenza B and influenza A (H3N2), with no evidence of a difference in protection between these strains or between the 2016-17 and 2017-18 influenza seasons. The significant dose response relationship for oseltamivir and reduced odds of in-patient death and the increasing odds of in-patient death with increasing delay in commencing treatment are also consistent with standard course oseltamivir being effective in protecting against in-patient mortality. The increased odds of in-patient mortality with longer time to starting treatment also emphasises the importance of starting os-

Table 1
Single variable analysis.
N = 1048

Variable	Category or measure	Expired	Not expired	OR (95% CI)	*p*-value
Season	2016/17	31	287	1.00	**0.16**
	2017/18	52	678	0.71 (0.45, 1.13)	
Age at positive specimen (years)	Minimum	17	0	1.04 (1.02, 1.06)	**<0.001**
	25th centile	73	53		
	Median	84	74		
	75th centile	87	84		
	Maximum	102	101		
Gender	Female	37	523	1.00	**0.09**
	Male	46	442	1.47 (0.94, 2.31)	
Pregnancy	Pregnant	0	15	0.00 (n.e.)	0.09
	Not pregnant	37	508	1.00	
	Male	46	442	1.43 (0.91, 2.24)	
Oseltamivir course completed	Not given	8	96	1.00	**<0.001**
	Non-standard course	27	140	2.31 (1.01, 5.31)	
	Standard course	48	729	0.79 (0.36, 1.72)	
Days between admission and first dose of oseltamivir	Minimum	-3	-3	1.04 (0.94, 1.07)	**0.99**
	25th centile	2	2		
	Median	2	3		
	75th centile	5	5		
	Maximum	36	36		
Receipt of influenza vaccination	Yes	34	391	1.53 (0.87, 2.72)	**0.14**
	No	20	353	1.00	
Current smoker	Yes	7	101	0.79 (0.35, 1.78)	0.6
	No	64	734	1.00	
Long term oxygen therapy	Yes	5	14	4.35 (1.53, 12.4)	**0.01**
	No	78	951	1.00	
Hypertension	Yes	39	324	1.75 (1.12, 2.75)	**0.02**
	No	44	641	1.00	
Trauma	Yes	3	14	2.55 (0.72, 9.05)	**0.19**
	No	80	951	1.00	
Excessive alcohol use	Yes	4	12	4.02 (1.27, 12.8)	**0.04**
	No	79	953	1.00	
Surgery	Yes	3	16	2.22 (0.63, 7.79)	0.3
	No	80	949	1.00	
Immune suppressed	Yes	11	182	0.66 (0.34, 1.26)	0.19
	No	72	782	1.00	
Admitted to intensive care	Yes	17	68	3.40 (1.89, 6.12)	**<0.001**
	No	65	884	1.00	
Influenza subtypes	A (H3N2)	51	559	1.00	**0.04**
	A generic	2	17	1.29 (0.29, 5.74)	
	B	30	341	0.96 (0.60, 1.54)	
	A (H1N1pdm09)	0	48	0.00 (n.e.)	
Radiological evidence of pneumonia	Yes	40	200	3.56 (2.25, 5.62)	**<0.001**
	No	43	765	1.00	
Chemotherapy	Yes	1	61	0.18 (0.02, 1.32)	0.02
	No	82	904	1.00	
Radiotherapy	Yes	1	3	3.91 (0.40, 30.0)	0.3
	No	82	962	1.00	
Organ transplant	Yes	1	14	0.83 (0.11, 6.38)	0.9
	No	82	951	1.00	
Bone marrow transplant	Yes	0	15	0.00 (n.e.)	0.11
	No	83	950	1.00	
Bone marrow transplant 2016/17	Yes	0	4	0.00 (n.e.)	0.4
	No	83	961	1.00	
Bone marrow transplant 2017/18	Yes	0	13	0.00 (n.e.)	0.14
	No	83	952	1.00	
Cycle Threshold (CT) value	Minimum	16	14		**0.048**
	25th centile	24	25	CF [a]	
	Median	28	29		
	75th centile	32	32		
	Maximum	38	41		
Temperature degrees Celsius	Minimum	35.4	35.3	0.89 (0.69, 1.16)	0.4
	25th centile	37.7	37.7		
	Median	38.3	38.3		
	75th centile	38.7	38.8		
	Maximum	40.2	41.1		
Haemoglobin g/L	Minimum	61	45	CF[b]	**0.004**
	25th centile	106	110		
	Median	117	126		
	75th centile	130	139		
	Maximum	224	184		
Total white cell counts 10^9/L	Minimum	1.3	0.0		**<0.001**
	25th centile	6.2	4.9	QF [c]	
	Median	9.4	6.8		
	75th centile	13.2	9.4		
	Maximum	84.5	122		

(*continued on next page*)

Table 1 (*continued*)

Variable	Category or measure	Expired	Not expired	OR (95% CI)	*p*-value
Lymphocyte count	Minimum	0.2	0.0	0.99 (0.88, 1.11)	0.9
10^9/L	25th centile	0.5	0.5		
	Median	0.8	0.8		
	75th centile	1.3	1.2		
	Maximum	5.1	46.7		
C-reactive protein mg/L	Minimum	3.3	1.0	1.01 (1.00, 1.01)	**<0.001**
	25th centile	27.1	16.4		
	Median	68.0	37.2		
	75th centile	134	76.0		
	Maximum	599	479		
Creatinine mmol/L	2016/2017				**<0.001***
	Minimum	53	7.6	QF[d]	
	25th centile	84.5	65.8		
	Median	106	84.9		
	75th centile	141	114.1		
	Maximum	178	928		
	2017/2018	45	18		
	Minimum	74.8	61		
	25th centile	117	78		
	Median	146	102		
	75th centile	460	622		
	Maximum				
Urea mmol/L	2016/2017				**<0.001***
	Minimum	3.7	1.6	QF[e]	
	25th centile	7.8	4.8		
	Median	9.3	6.4		
	75th centile	11.4	8.8		
	Maximum	18.5	39.2		
	2017/2018	3.0	1.3		
	Minimum	6.9	4.0		
	25th centile	9.8	5.6		
	Median	14.1	7.7		
	75th centile	41.1	47.3		
	Maximum				
Glucose mmol/L	Minimum	3.8	3.3	1.04 (0.98, 1.11)	0.2
	25th centile	6.5	6.0		
	Median	7.8	6.9		
	75th centile	8.8	8.4		
	Maximum	24.0	36.2		
Continuous Positive Airways Pressure	Yes	4	13	3.71 (1.18, 11.6)	**0.046**
	No	79	952	1.00	
Non-invasive ventilation	Yes	7	13	6.74 (2.61, 17.4)	**<0.001**
	No	76	952	1.00	
Invasive ventilation	Yes	9	35	3.23 (1.50, 6.98)	**0.007**
	No	74	930	1.00	
Myocardial infarct	Yes	17	87	2.60 (1.46, 4.63)	0.003
	No	66	878		
Congestive heart failure	Yes	14	78	2.31 (1.24, 4.29)	0.01
	No	69	887	1.00	
Peripheral vascular disease	Yes	5	28	2.15 (0.81, 5.71)	0.16
	No	78	937	1.00	
Cerebro vascular disease	Yes	18	97	2.48 (1.41, 4.35)	0.003
	No	65	868	1.00	
Dementia	Yes	27	113	3.64 (2.21, 5.99)	<0.001
	No	56	852	1.00	
Chronic lung disease	Yes	35	278	1.80 (1.14, 2.85)	0.01
	No	48	687	1.00	
Connective tissue disease	Yes	4	43	1.09 (0.38, 3.10)	0.9
	No	79	922	1.00	
Peptic ulcer	Yes	3	16	2.22 (0.63, 7.79)	0.3
	No	80	949	1.00	
Mild liver disease	Yes	1	6	1.95 (0.23, 16.4)	0.6
	No	82	959	1.00	
Moderate or severe liver disease	Yes	4	18	2.66 (0.88, 8.06)	0.12
	No	79	947	1.00	
Diabetes without end organ damage	Yes	9	103	1.02 (0.49, 2.09)	0.96
	No	74	862	1.00	
Diabetes with end organ damage	Yes	5	47	1.25 (0.48, 3.24)	0.99
	No	78	918	1.00	
Hemiplegic	16/17				0.03*
	Yes	1	13	0.70 (0.90, 5.56)	
	No	30	274	1.00	
	17/18	3	4	6.85 (1.46, 32.1)	
	Yes	49	674	0.66 (0.41, 1.07)	
	No				

(*continued on next page*)

Table 1 (*continued*)

Variable	Category or measure	Expired	Not expired	OR (95% CI)	*p*-value
Moderate or severe kidney disease	Yes	14	86	2.07 (1.12, 3.84)	0.03
	No	69	879	1.00	
Tumour without metastasis	Yes	9	79	1.36 (0.66, 2.83)	0.4
	No	74	886	1.00	
Tumour with metastasis	Yes	2	36	0.64 (0.15, 2.69)	0.5
	No	81	929	1.00	
Leukaemia	Yes	2	50	0.45 (0.11, 1.89)	0.22
	No	81	915	1.00	
Lymphoma	Yes	1	33	0.34 (0.05, 2.55)	0.22
	No	82	932	1.00	
Obesity	Yes	1	20	0.58 (0.08, 4.35)	0.6
	No	82	945	1.00	
Non- age adjusted Charlson co-morbidity index units	Minimum	0	0	QF[f]	**0.001**
	25th centile	1	0		
	Median	2	1		
	75th centile	4	3		
	Maximum	8	10		
Apportionment	Community	50	761	1.00	**0.003**
	Hospital	32	196	2.48 (1.55, 3.98)	
Admitted from	Own home	57	825	1.00	**<0.001**
	Residential care	18	69	3.78 (2.11, 6.77)	
	Another hospital	7	36	2.81 (1.20, 6.60)	
	Other	1	31	0.47 (0.06, 3.48)	

n.e. = not estimable.
*p-value for interaction.
Bold p value - variable met criteria for inclusion in multivariable modelling or part of study hypothesis.
QF Quadratic function, CF Cubic function.
CF[a] CT Cycle Threshold counts. At least cubic: Linear: OR 7.82 (0.56, 108).
Quadratic: OR 0.92 (0.83, 1.01); Cubic: OR 1.00 (1.00, 1.00).
CF[b] Serum haemoglobin g/L At least cubic: Linear: OR 1.38 (0.95, 2.01) Quadratic: OR 1.00 (0.99, 1.00) Cubic: OR 1.00 (1.00, 1.00)
QF[c] Total white cell count 10^9 / L· Linear: OR 1.15 (1.09, 1.21) Quadratic: OR 1.00 (1.00, 1.00).
QF[d] Serum creatinine mmol/L. Quadratic 2016/17:- Linear: 1.06 (1.02, 1.11), Quadratic: OR 1.00 (1.00, 1.00). 2017/18:- Linear: OR 1.02 (1.01, 1.04), Quadratic: OR 1.00 (1.00, 1.00).
QF[e] Serum urea mmol/L. Quadratic 2016/17- Linear: OR 2.76 (1.59, 4.80) Quadratic: OR 0.96 (0.94, 0.99); 017/18:- Linear: OR 1.37 (1.21, 1.55), Quadratic: OR1.00 (1.00, 1.00).
QF[f] Non age adjusted Charlson Co-morbidity Index. Units. Linear: OR 2.03 (1.43, 2.89) Quadratic: OR 0.93 (0.89, 0.98).

Table 2
Multivariable analysis (n = 954).

Variable	Category	OR	95% CI	*p*-value
Age		1.05	1.02-1.07	<0.001
Apportionment	Community	1.00		0.02
	Hospital	2.08	1.12-3.87	
Admitted from	2016/17			0.01*
	Own home	1.00	0.10-1.85	
	Residential care	0.44	0.07-2.67	
	Another hospital	0.42	n.e.	
	Other	0.00	1.85-11.7	
	2017/18	1.00	0.59-14.0	
	Own home	4.65	0.49-46.5	
	Residential care	2.87		
	Another hospital	4.79		
	Other			
Non-invasive ventilation	Yes	6.83	1.91-24.5	0.004
	No	1.00		
Admitted to critical care	Yes	3.16	1.23-8.13	0.02
	No	1.00		
Radiological evidence of pneumonia	Yes	2.08	1.13-3.83	0.02
	No	1.00		
Excessive alcohol use	Yes	22.7	4.67-110	<0.001
	No	1.00		
Oseltamivir course completed	Not given	1.00		0.003
	Non-standard course	0.39	0.14-1.14	
	Standard course	0.18	0.07-0.51	
Haemoglobin g/L		QF[a]		0.009*
Total white cell count		1.08	1.03-1.13	0.002
Urea		QF[b]		<0.001*
Cycle Threshold (CT) value		CF[c]		0.03

*p-value for interaction n.e.= not estimable.
QF Quadratic function, CF Cubic function.
QF[a] Haemoglobin g/L 2016/17:- Linear: OR 1.03 (0.82, 1.30) Quadratic: 1.00 (1.00, 1.00).
2017/18:- Linear: OR 0.85 (0.75, 0.96) OR Quadratic: 1.00 (1.00, 1.00).
QF[b] Urea mmol/L 2016/17:-Linear: OR 2.44 (1.22, 4.91), Quadratic: OR 0.96 (0.93, 0.99).
2017/18:- Linear: OR 1.34 (1.15, 1.56) Quadratic: OR 0.99 (0.99, 1.00).
CF[c] CT value Linear: OR 22.7 (0.97, 525) Quadratic: OR 0.88 (0.79, 0.99) Cubic: OR 1.00 (1.00, 1.00).

eltamivir treatment as soon as possible, but not for withholding oseltamivir because of delay.

Our descriptive observations support and may reduce inhibition to compliance with current guidelines for treatment of seasonal influenza B and influenza A infections in hospitalised patients with oseltamivir 75mg twice daily for five days to protect against in patient mortality. Our results also showed incomplete compliance with the national guidelines and the need for clinicians and hospitals to strive to correct this.

Work done at Addenbrooke's Hospital, Hills Road, Cambridge CB2 0QQ, UK.

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Klebsiella pneumoniae infection in the paediatric population before and after the COVID-19 pandemic in Shenzhen, China

Dear Editor,

Healthcare professionals epically infectious diseases are under high pressure during the COVID-19 pandemic or even after the pandemic due to co-infection such as influenza and bacterial pneumonia (11–35% of cases) in hospitalized patients caused mostly by *Streptococcus pneumoniae* and *Staphylococcus aureus*.[1] The recent data published in this journal by Li et al., Zhu et al., and Ying et al. has reported reduced *Streptococcus pneumoniae* and *Haemophilus influenzae* and *Mycoplasma pneumoniae* infections, respectively in the paediatric population during and after the COVID-19 pandemic.[2–4] In addition, data from France revealed that ultra-broad-spectrum β-lactamases in *Escherichia coli* infections have declined and the number of infections decreased after the lockdown.[5] However, best of our knowledge no data is available regarding ESBL-producing *Klebsiella pneumoniae* (*K. pneumoniae*) infection during the COVID-19 pandemic amongst paediatric clinical cases. Here, we report the changes in *K. pneumoniae*

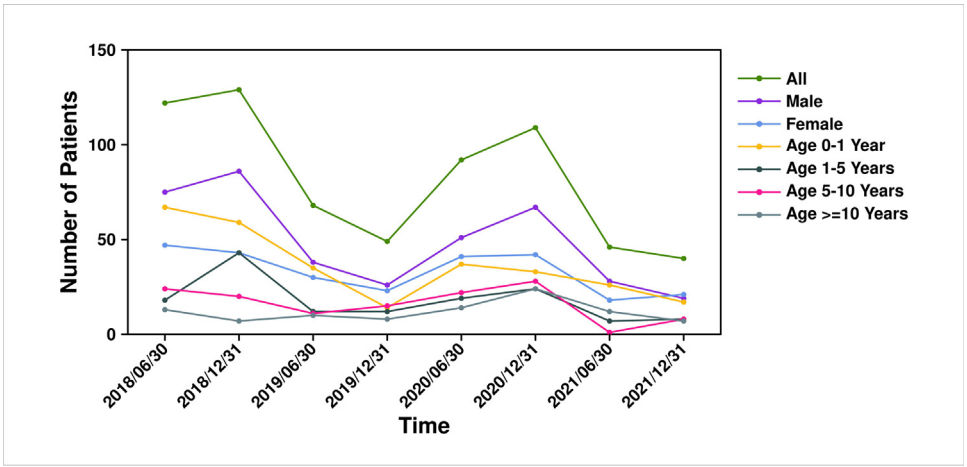

Fig. 1. The changes of *Klebsiella pneumoniae* infection in children from 2018–2021.

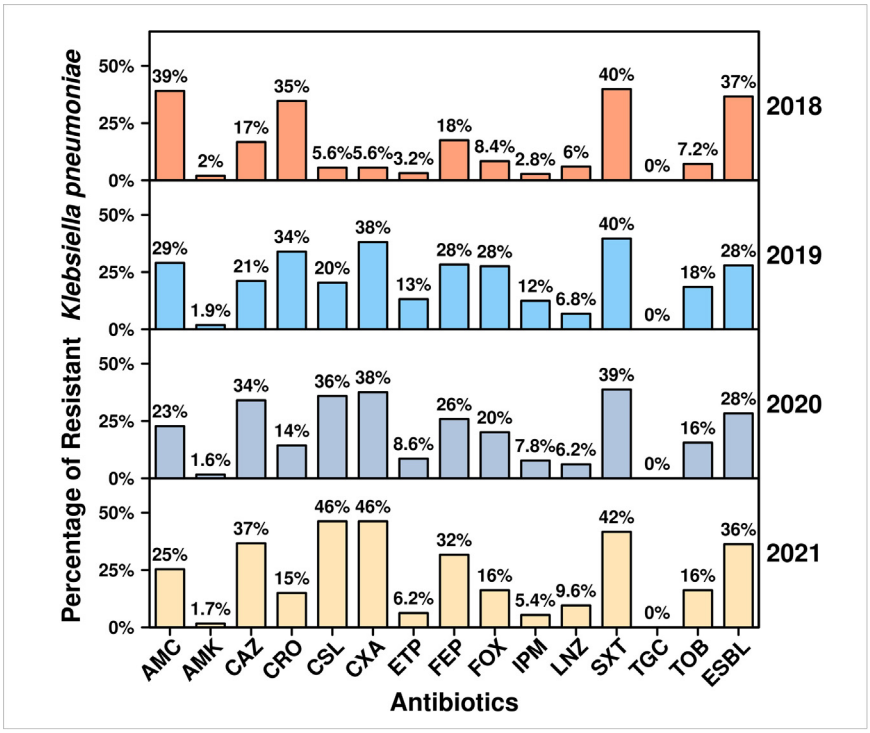

Fig. 2. The changes of antimicrobial resistance in *Klebsiella pneumoniae* from 2018–2021.
Source: Note: AMC:Amoxicillin+clavulanic acid; AMK:Amikacin; CAZ:Ceftazidime; CRO:Ceftriaxone; CSL: Cefoperazone/sulbactam; CXA: Ceftolozane; ETP:Ertapenem; FEP:Cefepime; FOX:Cefoxitin; IMP:Imipenem; LNZ:Linezolid ; SXT:Trimethoprim / sulfamethoxazole; TCG: Tigecycline; TOB:Tobramycin; ESBL:Extended-β-lactamse

infection before and after the COVID-19 pandemic in Shenzhen, China.

K. pneumoniae is a gram-negative, encapsulated, non-motile bacterium found in the environment and humans and has been associated with pneumonia, bloodstream infection, wound or surgical site infections, and meningitis resulting in mortality of about 20% in particular children.[6] It can show high virulence and antimicrobial resistance carbapenems after entering the host. It's a major concern in sick patients who are receiving treatment for other conditions such as SARS-COVID-19 infection. So far, *K. pneumoniae* pneumonia is considered the most common cause of nosocomial pneumonia and accounts for 3 to 8% of all nosocomial bacterial infections. With changing the epidemiology of other infectious agents, particularly in paediatric patients. It is important to conduct a surveillance study of *K. pneumoniae* infection and antimicrobial resistance change during the COVID-19 pandemic in Children. In the present study, we inlight on the changes in *K. pneumoniae* infection and antimicrobial resistance in children before and after the COVID-19 pandemic, which may help to get data to use in management and prevention strategies in the health care settings. Shenzhen Children's Hospital is one of the major paediatric hospitals in south China. In the present study, *K. pneumoniae* infection was monitored in the hospital and isolates were collected from January 1, 2018, to December 31, 2021. All isolates were identified by the Vitek-2 system with 395hhhhhh further confirmed by using the API-20 strip. In addition, the antimicrobial susceptibility test (AST) was performed by the Vitek-2 system.

A total of 1243 isolates were recovered for paediatric patients, $n = 518$ from females while $n = 725$ from males which were

from different departments of the hospital. The data revealed that male patients get more infected than females. The present study revealed the year 2018 has a high rate of infection but a decline in 2019. Although, in 2020 it increased slightly in the covid-19 pandemic but did not reach up to 2018. The present study supports the previous studies regarding the decline of *Streptococcus pneumoniae* and *Haemophilus influenzae* and *Mycoplasma pneumoniae* infections in children in China. We report the age group 0–1year shows the highest changes as a decline in infection, but the age group 5–10 does not have many changes During the COVID-19 pandemic. >10 age children group has lower infection during the COVID-19 and after the pandemic. This lower rate may be mainly related to increased awareness of wearing masks and paying attention to hand hygiene during the COVID-19 pandemic. All details are shown in Fig. 1. AST results suggested that *K. pneumoniae* increased the development of resistance against Ceftazidime, cefoperazone/sulbactam, Ceftolozane, and cefepime but the resistance trend declined in the case of Amoxicillin+clavulanic acid, Ceftriaxone, and Cefoxitin. The increased resistance against the cephalosporin group may result from the overuse of antibiotics during the pandemic. To support this, a recent study has reported *K. pneumoniae* shows high resistance to cephalosporin antibiotics because the high capacity for clonal expansion and exchange of mobile genetic elements carries resistance determinants.[7] ESBLs producing isolates analysis showed a decline in the COVID-19 pandemic but again increased in 2021. AST data are shown in Fig. 2 and it indicates *K. pneumoniae* MDR phenotype which is worrisome in the management of clinical conditions. *K. pneumoniae* infection declined in paediatric patients compared to the year 2018 but constant surveillance is needed not for this but also for various pathogens. We all face the COVID −19 pandemic and found it an enemy to humans. The scientific community must come together to help each other, jointly address risks and challenges and jointly safeguard the world. In conclusion, *K. pneumoniae* infection in children of all ages has declined during and after the COVID-19 pandemic but resistance development has increased. Close monitoring of epidemiological trends helps to prevent K. pneumonia infection in children.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Neutralizing antibodies against Omicron BA.4/5 after COVID-19 vaccination in SARS-CoV-2 experienced versus naïve individuals in the general population

Dear Editor,

We read with interest the study published by Dimeglio *et al.* in the *Journal of Infection* showing that SARS-CoV-2 Omicron BA.1

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breakthrough infection following receipt of two or three COVID-19 vaccine doses elicits a stronger homotypic (BA.1) neutralizing antibody (NtAb) response than vaccination alone in the general population.[1] In this study most recruited individuals were young (median age, 39 years) and NtAb measurements (using a live SARS-CoV-2 Omicron BA.1 isolate) were performed soon after receipt of the last vaccine dose (between 3 and 6 weeks). Omicron BA.1 has been long displaced worldwide by several Omicron sublineages, including Omicron BA.4/5 which display an increased ability to evade NtAb responses elicited by Wuhan-Hu-1 vaccine platforms compared to BA.1.[2-4] Here, we extend the observations of Dimeglio et al.[1] to show that long after full or booster vaccination (median, 287 days; IQR, 260–332), SARS-CoV-2 experienced individuals exhibit more robust NtAb responses against Omicron BA.4/5 than their vaccinated SARS-CoV-2 naïve counterparts, regardless of whether infection was due to Wuhan-Hu-1, Omicron BA.1 or Omicron BA.2 variants.

Sera from a total of 130 individuals (62 males/68 females; median age, 56 years; IQR, 34–72) were analyzed as described below. Individuals were randomly selected from a total of 787 participants in a SARS-CoV-2 seroprevalence cross-sectional, region-wide, population-based study that was conducted in the primary care zones of the Valencian Community (VC) in (Spain) during October of 2022 (unpublished results), as described in an analogous study conducted in April 2022.[5] The requirement for informed consent was waived by the Research Ethics Committee of Public Health (ref. 20,220,408/02) since the project was developed under the epidemiological surveillance competencies of the VC Ministry of Health (Law 10/2014 of the Valencian Community on Public Health).

Out of the 130 participants, 91 were categorized as SARS-CoV-2 experienced (VAC-ex) upon detection of anti-SARS-CoV-2 nucleocapsid protein IgG antibodies (Elecsys® Anti-SARS-CoV-2 N assays; Roche Diagnostics, Pleasanton, CA, USA). Twenty-two out of the 91 had a record of a positive RT-PCR assay in nasopharyngeal specimens [VC microbiology registry (RedMiVa)]. The remaining 39 participants were deemed as SARS-CoV-2 naïve (VAC-n), as they lacked anti-N IgGs and had no record of prior infection. As shown in Table 1, VAC-ex and VAC-n participants were matched by sex, vaccine platform employed, receipt of a booster dose, type of booster (homologous vs. heterologous), and the time elapsed since the last vaccine dose. Nevertheless, participants in the VAC-n group were significantly younger ($P<0.007$). NtAbs were measured using a GFP-expressing vesicular stomatitis virus pseudotyped with the Wuhan-Hu-1 or Omicron BA.4/5 spike (S) protein, as previously described.[5,6] The BA.4/5 spike was cloned into a pCG1 vector using a codon-optimized Omicron BA.4/5 S expression plasmid obtained from Addgene (Catalog number 186,031) as the template. Both constructs used lacked the terminal 19 amino acid residues to improve pseudotyping efficiency. Neutralization assays were performed as previously described,[6] except VeroE6/TMPRSS2 cells (JCRB Cell bank catalog code: JCRB1819) were used. Sera testing negative (undetectable) were arbitrarily ascribed a titer of 1/20. Most VAC-ex (100%) and VAC-n (94.7%) participants exhibited detectable NtAb responses against the Wuhan-Hu-1 variant ($P = 0.30$). In contrast, the percentage of VAC-n individuals displaying detectable NtAb against Omicron BA.4/5 was significantly lower than that for VAC-ex (52.6% vs. 98.9%; $P<0.001$). Overall, as shown in Fig. 1A, NtAb titers against Omicron BA.4/5 were significantly lower than that against Wuhan-Hu-1 in both VAC-ex (median inverse reciprocal titer for BA.4/5 and Wuhan-Hu-1, respectively of 1462; IQR,536–4803 vs. 11,398; IQR, 4652–62,500; $P<0.001$) and VAC-n (median, 24 IQR,10–204, vs. 1504; IQR, 565–6883; $P<0.001$). Nevertheless, compared to VAC-n, VAC-ex exhibited significantly higher NtAb titers against both Wuhan-Hu-1 (7-fold; $P<0.001$) and Omicron BA.4/5 (61-fold; $P<0.001$), irrespective of whether participants receiving a regular vaccine schedule or boostered with an additional vaccine dose were analyzed separately (not shown).

Table 1
Participant characteristics.

Parameter	Vaccinated/ SARS-CoV-2 experienced ($n = 91$)	Vaccinated/ SARS-CoV-2 naïve ($n = 39$)	*P* value[a]
Sex: no. male/female (%)	42/49 (46/54)	20/19 (51/49)	0.99
Age (median years, IQR)	70 (31–67)	51 (48–82)	0.007
0–9	3 (3.3%)	2 (5.1%)	
10–19	8 (8.8%)	1 (2.6%)	
20–34	19 (20.9%)	2 (5.1%)	
35–49	14 (15.4%)	7 (18%)	
50–64	21 (23%)	5 (12.8%)	
65–79	20 (22%)	9 (23%)	
≥80	6 (6.6%)	13 (33.3%)	
Vaccine platform: no. (%)			0.91
mRNA Comirnaty® (BioNTech /Pfizer)	54 (59)	29 (74)	
mRNA Spikevax® (Moderna / Lonza)	16 (17.6%)	5 (12.8)	
Viral Vector Vaxzevria® (Oxford / AstraZeneca)	15 (16.5)	2 (5)	
Viral Vector Jcovden® (JandJ / Janssen)	5 (5)	3 (7.7)	
Inactivated CoronaVac® (Sinovac Biotech)	1 (1)	0	
Number of vaccine doses: no. (%)			0.99
One	2 (2.20)	1 (2.6)	
Two	25 (27.5)	10 (25.6)	
Three	62 (68)	28 (71.8)	
Four	2 (2.2)	0	
Receipt of a booster vaccine dose (Yes,%/No,%)	68 (75) /23 (25)	30 (77) /9 (23)	0.99
Type of booster: no. (%)			0.96
Homologous	28 (41)	15 (50)	
Heterologous	40 (59)	14 (50)	
Days elapsed since last vaccine dose (median, IQR)	283 (260–322)	307 (267–336)	0.09

[a] Fisher's exact test or Mann-Whitney U test, as appropriate. Two-sided exact *P*-values are reported. A *P*-value <0.05 was considered statistically significant. The analyses were performed using SPSS version 20.0 (SPSS, Chicago, IL, USA) and STATA 17.0 (StataCorp, College Station, Texas, USA).

Out of the 22 VAC-ex individuals with a record of a positive SARS-CoV-2 RT-PCR assay, in 13 infection was documented during 2022 within waves dominated (≥95% of cases) by BA.1 ($n = 6$) and BA.2 ($n = 7$), and before the emergence of BA.4/5 in the VC; the remaining 9 individuals had contracted SARS-CoV-2 infection during 2020/2021, prior to the surge of the Omicron variant in the VC. Following the matching of individuals in both comparison groups according to the time elapsed from the receipt of the last vaccine dose, NtAb titers against Omicron BA.4/5, but not against Wuhan-Hu-1 (Fig. 1B), were significantly lower ($P<0.001$) in individuals that contracted SARS-CoV-2 infection prior to 2022. Importantly, VAC-n individuals displayed lower NtAb titers against both Wuhan-Hu-1 ($P<0.01$) and Omicron BA.4/5 ($P<0.001$) than VAC-ex, irrespective of when SARS-CoV-2 infection was documented. The current study has several limitations. First, the date of SARS-CoV-2 infection could only be documented in a small percentage of VAC-ex participants. Second, the SARS-CoV-2 lineages could not be confirmed by sequencing in cases with positive RT-PCR results. Third, whether participants that experienced COVID-19 due to Wuhan-Hu-1 were reinfected by Omicron BA.1 or BA.2 could not be ascertained. Fourth, due to the possibility of N-seroreversion some participants could have been miscategorized as being SARS-CoV-2 naïve. In summary, the main observation of our study was that long (median 287 days) after COVID-19 vaccination with full or booster regimens, VAC-ex individuals display a more robust NtAb response against Omicron BA.4/5 compared to VAC-n. Interestingly,

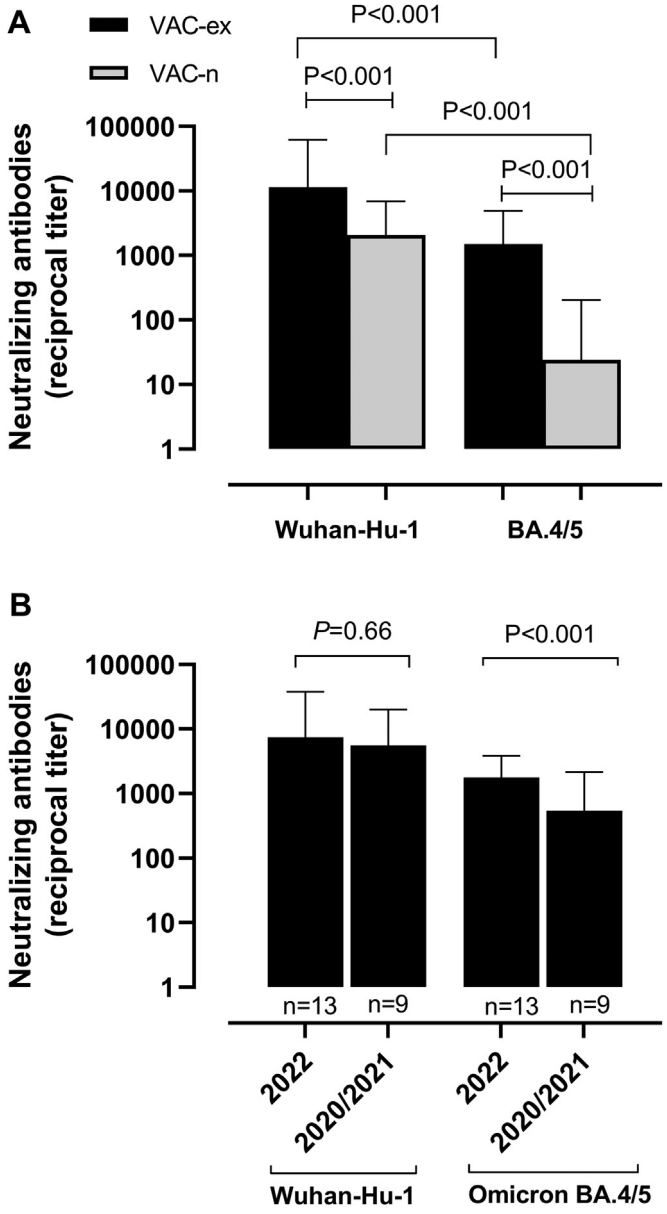

Fig. 1. Neutralizing antibody (NtAb) responses against Wuhan-Hu-1 and Omicron BA.4/5 as measured using a pseudotyped vesicular stomatitis virus system. (A) Reciprocal NtAb titers against Wuhan-Hu-1 and Omicron BA.4/5 in vaccinated/SARS-CoV-2 experienced (VAC-ex) and vaccinated/SARS-CoV-2 naïve participants (VAC-n). (B) Reciprocal NtAb titers against Wuhan-Hu-1 and Omicron BA.4/5 in vaccinated/SARS-CoV-2 experienced (VAC-ex) participants with SARS-CoV-2 infection documented by RT-PCR. *P* values for comparisons across groups (Mann-Whitney U test) are shown. A *P* value <0.05 was deemed as significant. The analyses were performed using SPSS version 20.0 (SPSS, Chicago, IL, USA) and STATA 17.0 (StataCorp, College Station, Texas, USA).

although the difference across groups was more marked when participants contracting Omicron BA.1 or BA.2 infection were considered separately, it was also maintained for those that were infected with the ancestral SARS-CoV-2 Wuhan-Hu-1 variant or pre-Omicron variants of concern. Our observation agrees with data reported in several series comprising individuals vaccinated (either boostered or not) with mRNA or inactivated SARS-CoV-2-based COVID-19 vaccine platforms[2-4,7,8] and may help inform public health decision-making regarding COVID-19 vaccination policies for the near future.

Declaration of Competing Interest

The authors declare no conflicts of interest.

Author contributions

JC, JZ, EG, LR, S V-A and EA, methodology and data validation. HV and RL participated in the implementation of the vaccine roll-out program in the Valencian Community. SP, RG and DN, conceptualization and data analysis. RG and DN wrote the manuscript.

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Data availability statement

The data presented in the manuscript have not been made available, but can be shared upon request.

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Remdesivir and survival outcomes in critically ill patients with COVID-19: A multicentre observational cohort study

Dear Editor,

The role of remdesivir (RDV) in the treatment of critically ill COVID-19 patients remains ill-defined.[1] The impact of the systemic inflammation and other aspects adding to the potential severity of patients in the SARS-CoV-2 viral dynamics are not well elucidated, particularly in critically ill patients.[2–4] Thus, we aimed to evaluate the effect of RDV on the outcomes of critically ill patients with severe COVID-19 and analyze such outcomes in certain subsets of patients to investigate whether RDV proved particularly beneficial in a particular group of critically ill patients.

Multicentre, observational cohort study including consecutive COVID-19 patients admitted to 55 Spanish ICUs between 5 February 2020 and 21 December 2021. We compared two main groups: patients receiving RDV versus those who did not receive RDV at any moment. The primary outcome was all-cause 90-day mortality. We examined outcomes according to the following categories: (1) overall population; (2) several patient subgroups based on baseline data at ICU admission: age, illness severity and organ damage (Acute Physiology and Chronic Health Evaluation [APACHE] -II and Sequential Organ Failure Assessment [SOFA] score, respectively), laboratory findings (lymphocyte count and C-reactive protein [C-RP]), respiratory support; (3) by corticosteroids therapy; (4) by SARS-CoV-2 viral load (viral RNAemia, viral antigenemia and viral RNA load [N1 region]); and (5) by RDV administration timing. To evaluate the effect of remdesivir on 90-day mortality, we used a Cox regression model stratified on the center variable, tested in univariable and propensity-adjusted multivariable analyses. A further analysis using the propensity score matching method was performed to confirm the results obtained with the propensity-adjusted multivariable model. On the other hand, effect modification by factors potentially associate with patient outcomes and remdesivir use were assessed by an interaction term. We also analysed the association between remdesivir therapy and the following variables: in-hospital and 30-day mortality (by means of a Fine-Gray competing risks model stratified on the center variable and a Cox regression model stratified on the center variable, respectively); and nosocomial bacterial pneumonia (by means of generalised estimating equations, considering a binomial distribution and accounting for the effect raised by the clustering of patients from the same center).

Among the 6225 COVID-19 patients that were admitted to 55 ICUs. We included 5004 patients in this analysis, of whom 4209 (84%) did not receive RDV and 795 (16%) received RDV during hospitalization (Fig. 1).

Ninety-day mortality rate was lower in patients who received RDV than in those who did not receive RDV (34 % vs. 29%, $p = 0.012$). Also, in-hospital (31 % vs. 27%, $p = 0.025$) and 30-day mortality (25 % vs. 18%, $p<0.001$) were lower in the RDV group (Supplementary Table 1). In the propensity-adjusted multivariable analysis, RDV use was not significantly associated with 90-day mortality (HR 1.00, 95% CI 0.85 to 1.17; $p = 0.970$), nor with in-hospital (sHR 0.94, 95% CI 0.81 to 1.09, $p = 0.41$) and 30-day mortality (HR 0.86, 95% CI 0.71 to 1.05, $p = 0.145$) (Table 1). In the analysis using the propensity score matching (777 patients received RDV and 777 did not receive RDV), the Kaplan-Meier curves showed that there was no statistical difference between both groups for 90-day mortality ($p = 0.280$) (Supplementary Figure 1). Furthermore, Cox regression showed that RDV use was not associated with the risk of 90-day mortality (HR 0.95, 95% CI 0.79 to 1.16; $p = 0.636$), nor with in-hospital mortality (sHR 0.92, 95% CI 0.76 to 1.11; $p = 0.36$) and 30-day mortality (HR 0.81, 95% CI 0.65 to 1.02; $p = 0.075$).

To examine mortality risk for particular types of patients, we explored modification effects by age, APACHE-II score, SOFA score, lymphocyte count, C-RP, respiratory support, corticosteroids, viral RNAemia, viral antigenemia and viral RNA load in plasma. No significant effect modification was found after adjustment for covariates using propensity score (Table 1).

Among the overall population receiving RDV, there was significant association observed between early administration (<5 days since symptoms' onset) and the propensity-adjusted risk of 90-day mortality (HR 1.53, 95% CI 1.02 to 2.31, $p = 0.042$) (Table 1). In contrast, there were no significant association between <7 days since symptoms' onset and the risk of 90-day mortality (HR 1.21, 95% CI 0.85 to 1.72, $p = 0.285$).

When compared to the non-RDV group, patients in the RDV group less frequently presented myocarditis, cardiac ischemia, delirium, coagulation disorder, anemia, acute renal failure and

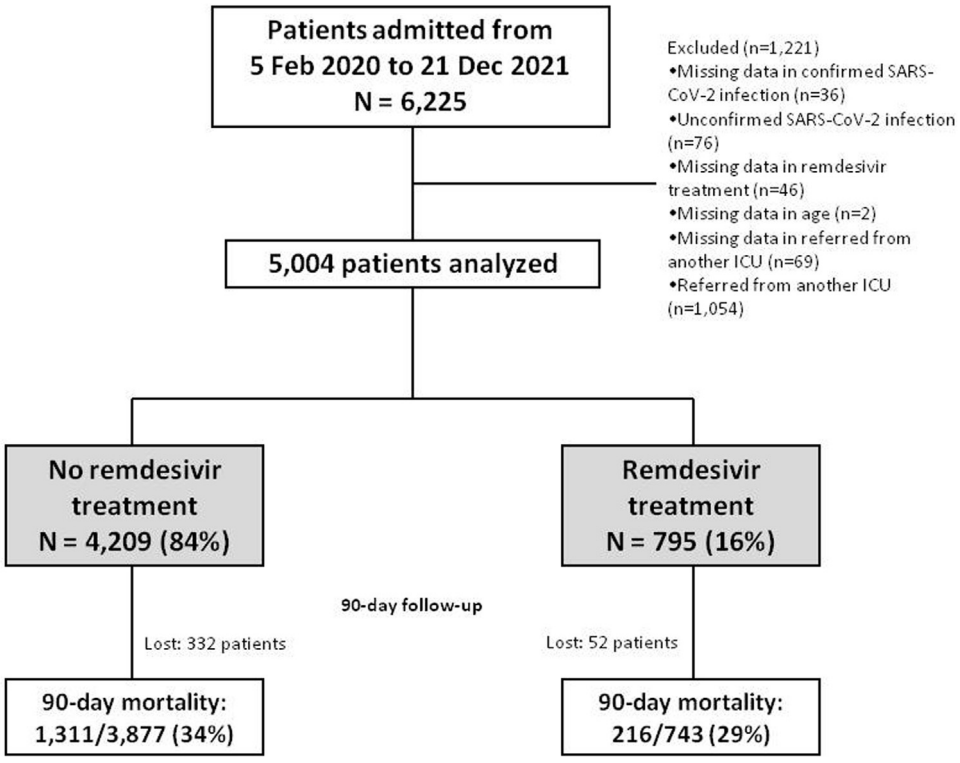

Fig. 1. Flowchart of the study population.

liver dysfunction (Supplementary Table 2). The propensity-adjusted analysis showed no association between RDV treatment and nosocomial bacterial pneumonia (OR 1.06, 95 CI 0.84 to 1.33, $p = 0.640$). In the analysis using the propensity score matching, RDV use was not associated with nosocomial bacterial pneumonia (OR 1.22, 95 CI 0.98 to 1.52, $p = 0.068$) (Supplementary Table 3).

In this large, multicentre study involving over five thousand critically ill patients with COVID-19 admitted to 55 Spanish ICUs, we observed that the use of RDV was not associated with an overall reduced risk of 90-day mortality, nor when analyzing by subgroup populations; patients treated with RDV overall presented longer lengths of ICU stay, which seems to be due to longer length of mechanical ventilation; early administration of RDV from symptoms' onset was associated with a higher risk of 90-day mortality in the overall population; and patients treated with RDV showed lower significant rates of organic damage associated with severe COVID-19 such as cardiac, neurological, coagulation, renal and liver complications.

The underlying pathophysiological mechanisms associated with severe COVID-19 are not fully elucidated,[5,6] nor are therefore the tools to identify early phenotypes with high risk of developing more severe cases of COVID-19 that might potentially benefit more of early and intensive antiviral treatment.[7] This has become a major challenge for the scientific community, as patients developing severe COVID-19, and in particular those requiring ICU admission have poor prognosis.[8] Our hypothesis that certain subsets of patients with either pro-inflammatory phenotypes or presenting with high viral loads[9] might particularly benefit from RDV treatment seems to be refuted by our findings. The lack of influence of RDV on mortality independently of the viral load in plasma and the inflammatory status could reflect an inability of RDV to mediate a significant inhibitory activity of viral replication and/or clinical benefit in patients already exhibiting a large burden viral replication (both groups, RDV treated and non-treated presented to the ICU with high median levels of viral load in plasma), which in turn is associated to a strong stimulation of the innate immunity leading to exacerbated inflammation. Whether new, more specific/potent antivirals could mediate a beneficial effect in this context remains to be elucidated. Our results are in accordance of the recent published update of a living review about remdesivir in adults hospitalized with COVID-19 that confirm that remdesivir probably results in little to no difference in mortality.[10]

A possible limitation of the propensity score methods is their inability to control for unmeasured confounding. Another limitation is the different waves of the pandemic, which could have influenced our results. We have however adjusted all of our analyses for this confounder.

In summary, treatment with RDV was not associated with improved outcomes in critically ill patients with severe COVID-19, neither overall nor when stratifying by clinically relevant variables such as age, illness severity, organ damage, laboratory findings, respiratory support or SARS-CoV-2 viral load in plasma. Moreover, RDV treatment was associated with longer lengths of ICU admission. Early administration since symptoms onset may prove harmful. Our study adds to the mounting evidence suggesting that RDV is not efficacious in treating severe COVID-19, although further studies are warranted to elucidate whether certain subsets of patients might benefit from it.

Authors' contributions

Conceptualization: CC, AM, AT; Data Curation: CC, AM, TC, Formal analysis: AG; Methodology: all authors; Investigation: CC, AM, TC, FB, AT; Project administration: CC, AM, AT; critical revision of the manuscript for important intellectual content: CC, AM, FB, and AT; and Funding acquisition: AT; Resources: CC, AM, AT; Sofware: AG; Supervision: AT; Validation:all authors; Visualization: all the authors, Writing-original draft: all authors; Writing-review and editing: CC, AM, FB, TC, AT. AThad full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved

Table 1
Association of remdesivir therapy and 90-day mortality (Panel A) and early administration of remdesivir treatment from first symptoms and 90-day mortality (Panel B).

	Univariable analysis		Adjusted analysis[a]	
	HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
Panel A - Remdesivir therapy				
All patients (N = 5004)	0.78 (0.67 to 0.91)	0.001	1.00 (0.85 to 1.17)	0.970
Subgroup analyses[b]				
Age group				0.284[c]
Age <40 years (n = 281)	0.13 (0.02 to 1.05)	0.055	-	-[d]
Age ≥40 - <65 years (n = 2419)	0.75 (0.58 to 0.98)	0.033	1.02 (0.77 to 1.36)	0.885
Age ≥65 years (n = 2304)	0.89 (0.74 to 1.08)	0.238	0.96 (0.78 to 1.17)	0.681
Severity of illness at ICU admission group				0.368[c]
APACHE-II score <12 (n = 1411)	0.57 (0.37 to 0.89)	0.012	0.97 (0.60 to 1.57)	0.893
APACHE-II score ≥12 (n = 1476)	0.86 (0.65 to 1.12)	0.260	0.96 (0.72 to 1.29)	0.793
Organ dysfunction and failure at ICU admission group				0.465[c]
SOFA score <5 (n = 1667)	0.76 (0.55 to 1.05)	0.095	0.88 (0.62 to 1.26)	0.494
SOFA score ≥5 (n = 1803)	0.89 (0.70 to 1.13)	0.333	1.01 (0.79 to 1.31)	0.922
Laboratory findings at ICU admission				
Lymphocyte count group				0.694[c]
Lymphocyte count <0.724 × 10^9/L (n = 2613)	0.84 (0.69 to 1.03)	0.087	0.97 (0.78 to 1.20)	0.768
Lymphocyte count ≥0.724 × 10^9/L (n = 2221)	0.73 (0.57 to 0.93)	0.010	1.04 (0.80 to 1.36)	0.753
C-reactive protein group				0.333[c]
C-reactive protein <150 mg/L (n = 2627)	0.84 (0.68 to 1.03)	0.099	1.00 (0.80 to 1.26)	0.974
C-reactive protein ≥150 mg/L (n = 2048)	0.71 (0.56 to 0.91)	0.006	0.93 (0.72 to 1.21)	0.614
Respiratory support at ICU admission group				0.133[c]
Conventional oxygen therapy (n = 371)	0.85 (0.45 to 1.63)	0.633	0.69 (0.28 to 1.74)	0.436
High-flow nasal cannula / Non-invasive mechanical ventilation (n = 2046)	0.99 (0.78 to 1.24)	0.902	1.25 (0.97 to 1.62)	0.088
Invasive mechanical ventilation (n = 2571)	0.77 (0.62 to 0.96)	0.020	0.90 (0.72 to 1.14)	0.397
Corticosteroid therapy during ICU admission group				0.225[c]
No (n = 684)	0.71 (0.38 to 1.33)	0.285	0.73 (0.36 to 1.46)	0.370
Yes (n = 4271)	0.81 (0.69 to 0.95)	0.008	1.05 (0.89 to 1.24)	0.561
SARS-CoV-2 viral load				
Viral RNAemia in plasma group				0.367[c]
No (n = 167)	0.70 (0.20 to 2.51)	0.588	3.32 (0.14 to 80.96)	0.462
Yes (n = 584)	0.88 (0.60 to 1.29)	0.507	0.83 (0.55 to 1.26)	0.384
Viral antigenemia in plasma group				0.238[c]
No (n = 400)	1.08 (0.62 to 1.87)	0.791	1.51 (0.81 to 2.84)	0.195
Yes (n = 335)	0.77 (0.47 to 1.27)	0.310	0.74 (0.41 to 1.34)	0.320
Viral RNA load in plasma (N1 region) group[e]				0.753[c]
0 copies/mL (n = 130)	1.33 (0.27 to 6.53)	0.723	0.97 (0.04 to 26.90)	0.987
>0 - <3255 copies/mL (n = 376)	0.89 (0.50 to 1.59)	0.692	1.08 (0.55 to 2.13)	0.824
≥3255 copies/mL (n = 245)	0.90 (0.53 to 1.54)	0.702	1.25 (0.68 to 2.28)	0.469
Panel B - Early administration of remdesivir treatment from first symptoms				
All patients receiving remdesivir (N = 733)[f]				
<5 days	1.65 (1.13 to 2.40)	0.009	1.53 (1.02 to 2.31)	0.042
<7 days	1.19 (0.88 to 1.60)	0.253	1.21 (0.85 to 1.72)	0.285

Abbreviations: HR indicates hazard ratio; CI, confidence interval; APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment; RNA, ribonucleic acid.

[a] Adjusted for variables (age, sex, body mass index, diabetes mellitus, chronic liver disease, chronic heart disease, chronic lung disease, chronic renal failure, immunosuppression, APACHE-II score at ICU admission, lymphocyte count at ICU admission, C-reactive protein at ICU admission, respiratory support at ICU admission, septic shock at ICU admission, lopinavir/ritonavir administration, tocilizumab administration, other antiviral administration, corticosteroids, COVID-19 wave and the propensity score).

[b] APACHE-II score was assessed in 2887 patients; SOFA score in 3470 patients; lymphocyte count in 4834 patients; C-reactive protein in 4675 patients; respiratory support in 4988 patients; corticosteroids in 4956 patients; viral RNAemia in plasma in 751 patients; viral antigenemia in plasma in 735 patients; and viral RNA load in plasma (N1 region) in 751 patients.

[c] Interaction effect for the subgroup and treatment group.

[d] Estimation failed due to numerical problem. Because the coefficients did not converge, no further models were fitted.

[e] Cut-off value obtained from ROC curve for 90-day mortality.

[f] The time of administration of remdesivir treatment from first symptoms was not available for 62 patients.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethics approval and consent to participate

The study received approval by the Hospital Clínic de Barcelona Institutional Review Board (Comité Ètic d'Investigació Clínica, registry number HCB/2020/0370), and either patients or their relatives

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2022.12.027.

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Air detection of monkeypox virus in a dedicated outpatient clinic room for monkeypox infection diagnosis

Dear Editor,

We read with interest the article by Raccagni et *al.* reporting, in the context of the recent worldwide outbreak,[1,2,3] monkeypox virus (MPXV) infection occurred among individuals who got the smallpox shot. Healthcare workers (HCWs) are eligible for smallpox vaccination to prevent infection.[4] In addition, to protect them from an occupational disease, Personal Protective Equipment (PPE) is required, mainly to avoid MPXV infection. MPXV is transmitted by direct contact with wounded skin or mucous membranes of a person with a monkeypox infection. The virus might also spread through large respiratory droplets, from mucus or saliva, during close face-to-face contact. Previous studies of monkeypox outbreaks show that spreading MPXV through respiratory secretions is unlikely.[5]

However, a MPXV transmission from a patient to a healthcare worker in the United Kingdom has been reported; authors

Fig. 1. Outpatient clinic with the AerosolSense™ sampler.

Table 1
Patients' characteristics, clinical and virological Monkeypox virus status. Air samples were taken during a four-hour period that the patients were in the examination room.

Date	Patient number	Sex	Age	MPXV infection	Type of diagnosis	Type of samples tested	MPXV PCR Result	MPXV PCR Ct value	Air sampler result	Air PCR MPXV Ct value
July	1	M	32	no	-	oropharyngeal	negative		**positive**	35
26th	2	M	54	no	-	-	-			
	3	M	36	**yes**	clinical	-	-			
	4	M	39	**yes**	clinical	-	-			
	5	M	44	no	-	-	-			
	6	M	31	no	-	skin lesion	negative			
	7	M	36	no	-	-	-			
	8	M	35	**yes**	clinical	-	-			
July	9	M	35	**yes**	virological	oropharyngeal	positive	35	**positive**	35
27th	10	M	29	no	-	skin lesion	negative			
	11	M	30	no	-	skin lesion	negative			
	12	M	34	no	-	skin lesion	negative			
	13	M	34	**yes**	clinical	-	-			
	14	M	34	**yes**	clinical	-	-			
	15	M	49	no		skin lesion	negative			
July	16	M	34	**yes**	clinical	-	-		**positive**	38
29th	17	M	41	**yes**	clinical	-	-			
	18	M	45	no	-	skin lesion	negative			
	19	M	37	no	-	-	-			
	20	F	45	no	-	skin lesion	negative			
August	21	M	33	**yes**	clinical	-	-		**positive**	32
1st	22	M	38	no	-	skin lesion	negative			
	23	F	19	no	-	vulva lesion	negative			
	24	M	40	no	-	skin lesion	negative			
	25	M	25	**yes**	clinical	-	-			
	26	M	22	**yes**	clinical	-	-			
	27	M	54	**yes**	virological	penis lesion	positive	18		
	28	M	29	**yes**	virological	skin lesion	positive	21		
August	29	M	28	**yes**	virological	oropharyngeal	positive	20	**positive**	37
3rd	29	M	28	**yes**	virological	anal lesion	positive	22		
	30	M	35	**yes**	clinical	-	-			
	31	M	51	no	-	skin lesion	negative			
	32	M	41	no	-	skin lesion	negative			
August	33	F	25	no	-	skin lesion	negative		**positive**	37
4th	34	M	44	**yes**	clinical	-	-			
	35	M	24	**yes**	clinical	-	-			
	36	M	32	-	-	-	-			
	37	M	28	no	-	skin lesion	negative			
August	38	F	33	no	-	-	-		negative	-
5th	39	M	37	no	-	-	-			
	40	M	34	no	-	-	-			

hypothesized that transmission probably occurred through contact with contaminated bedding of a monkeypox-confirmed patient who presented active skin lesions.[6]

In this study, we investigated whether the MPXV could be detected from air sampling in the consultation room of the monkeypox diagnostic center set up within the Infectious Diseases department of Saint-Louis Hospital, Paris, France.

The investigation was carried out in a 130 ft^2 consultation room. This space benefits from one large window that can be opened, allowing fresh air to come in. In addition, a ventilation system ensures air renewal through several vents allowing air to pass in/out for blowing and aspiration. Bio cleaning was performed between each consultation.

One AerosolSense™ sampler (ThermoFisher Scientific™) was set in the room and settled 100 cm above the floor on a dedicated surface, as depicted in Fig 1. The sampler collects air thanks to an omnidirectional sampling head at a rate of 200 L/minute. A collection substrate is in a sample cartridge inside the sampler. The air sample is sent to the collection substrate through an accelerated slot impactor. Air is drawn through the sampler and particles are trapped on the collection substrate. After the sampling cycle, the sample cartridge was removed and sent to the Virology laboratory for PCR testing. Particles were eluted by squeezing the sample cartridge sponge in a tube containing 2 ml of phosphate buffer saline. After a heat inactivation step of clinical and air samples (12 minutes at 70°C), nucleic acids were extracted using MagNA Pure LC 2.0 Instrument (Roche, Meylan, France). MPXV-specific real-time polymerase chain reaction (PCR) assay was performed on an ABI 7500 Real-Time PCR System (Thermo Fisher Scientific™, Waltham, MA) as described previously.[7] Results of MPXV detection were reported with cycle threshold (Ct) values. Results with Ct values higher than 40 were considered negative.

We performed air and patients sampling during seven days, from July 26th to August 5th, 2022. The air sampling took place continuously, during sessions of four hours each day. Patient samples (oropharyngeal, skin, or genital) were collected during the consultation if the clinical diagnosis of monkeypox was not obvious clinically.

HCWs wore PPE composed of N95 Filtering Facepiece Respirators while consulting patients in the MPXV dedicated room. In addition, patients were required to wear surgical masks, except during oropharyngeal sampling. Finally, patients and HCWs had to perform hand hygiene before and after each consultation.

Patients' characteristics and results are presented in Table 1. Seven bioaerosol samples were taken during the study period. Throughout the sampling periods, 40 patients visited the clinic for suspected MPXV infection, and five different HCWs took care of these patients as medical assistants, nurses, and physicians.

Over the seven sampled sessions, six samples were positive with a median Ct value of 36 (min-max: 32.0 – 38.0). Of the forty patients examined; 17 (43%) were diagnosed monkeypox-positive; 13 clinically and four virologically with a median Ct of 21 (min-max: 18.0 – 35.0). One session sampled did not show the presence of MPXV in the bioaerosol, corresponding to the only session during which no patients were diagnosed with monkeypox.

Neither HCWs nor monkeypox-negative consulting patients reported MPXV symptoms during the study period or within the following 21 days.

Thus, we report the presence of viral DNA in the air, although patients wore surgical masks, reinforcing the importance of the HCWs being suitably protected, and wearing N95-type masks.

MPXV can spread in the immediate environment of infected people.[8] Medical literature reports a case of human-to-human transmission of MPXV through contact with contaminated bedding[6] questioning the possibility of MPXV airborne transmission, even though no such transmission route has been reported during the current outbreak. A recent publication reported evidence of MPXV infectious particles in hospitalized patients' rooms on surfaces and one air sample in the PPE doffing area.[9]

Even though we identified the presence of MPXV particles among air samples, we cannot confirm if they were infectious or not. However, no HCWs in contact with these patients declared monkeypox symptoms during the 21 days following exposure. Of note, HCWs all wore PPE, including N95 Filtering Facepiece Respirators, gloves, and protective glasses and performed hand hygiene before and after care. In addition, we noticed that no monkeypox-negative patients, examined on the days during positive air samples, were found to have contracted MPXV infection although they only wore surgical masks. Additional studies could be performed with cultures of MPXV from air samples with high viral loads to determine its ability to be infectious.

To our knowledge, we report the first air sampling taking place in an outpatient consultation room in a quaternary healthcare facility receiving patients with suspected monkeypox infection. The viral particles detected could have been spread through the air from the skin, genital or oropharyngeal lesions, or respiratory secretions.

The presence of viral fragments identified in bioaerosols suggests that greater attention should be paid to the possibility of a respiratory human-to-human transmission, to avoid HCWs infection or hospital-acquired infection, especially for immunocompromised patients who are numerous in a quaternary healthcare facility.

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Predicting monkeypox incidence: Fear is not over!

Dear Editor,

In a recent article, we highlighted the challenges and suggested the way forward for the emerging monkeypox (mpox) infection.[1] However, following the methodology and prediction tool based on the article "A quick prediction tool for unfavorable outcome in COVID-19 inpatients: Development and internal validation" by Salto-Alejandre et al.,[2] we performed prediction of mpox based on previously reported cases.

Early in May of 2022, the first cases of mpox outside of endemic regions were recorded, and new cases are continually being detected in various endemic regions. Often these patients with a travel history visited Europe and North America, not West or Central Africa, where mpox is widespread.[3] It's the first time an epidemic has coincided across some nations, most of which have no apparent epidemiological ties to the endemic regions.[4] In light of the current mpox outbreak, the Director-General of the World Health Organization (WHO) has declared a Public Health Emergency of International Concern (PHEIC).

Two forecasting models were implemented to get significant outcomes. The one is a widely used time-series model, autoregressive integrated moving average (ARIMA). The second is that artificial neural networks (ANNs) have developed a potent tool for machine learning (ML) and artificial intelligence (AI). ARIMA is a generalized form of autoregressive moving average (ARMA). ARIMA is a linear model for forecasting the upcoming trend based on historical data.[5] ANNs are prediction techniques that permit complex, nonlinear relationships between the predictor factors and the response. They are based on basic mathematical models of the brain. A neural network resembles a network of "neurons" controlled in layers. The lower layer is made up of the predictors (or inputs), and the upper layer is made up of the forecasts (or outputs). The lag values can be utilized as inputs to the neural network in the instance of time series data; this model is referred to as neural network autoregression (NNAR). This paper considers the feed-forward neural network with one hidden layer, designated by NNAR (p, k) and consisting of p delayed inputs and k hidden nodes.[6]

This study predicts the mpox outbreak worldwide for the next month (31st January 2023). The dataset was obtained from the worldwide website (https://ourworldindata.org/mpox), which covers the period from 1st May 2022 to 29th November 2022 and is considered for the prediction. In addition to offering insight into the transmission patterns of the outbreaks, the purpose of this study is to furnish accurate predictions of the outbreak to the authorities and severity by applying fundamentally significant models. These tools can assist in predicting future medical requirements and timely planning to curb the disease.

The comparison between the two models indicates that the ARIMA (5,2,3) for mpox cases and ARIMA (0,2,1) for mpox deaths are more effective in explaining the estimates of mpox trends. The predicted number of daily infected cases and deaths for the next two months upto (31st January 2023) estimates might reach 87,276 (CI 95%: 66,224- 108,328) for cases, and the estimate might reach 94 (CI 95%: 69–118) for deaths. Figs. 1 and 2 depict both models' predicted performance, showing that the lines increase for the confirmed cases and deaths. We checked the models' accuracy through mean absolute error (MAE), root mean square error (RMSE), and akaike information criterion (AIC). ARIMA (5,2,3) daily confirmed cases model with AIC: 2955, MAE: 306.12 and RMSE: 391.39 was significantly predicted. Significant predictions were made using the ARIMA (0,2,1) daily deaths model, which had an AIC of 477, MAE of 0.35, and RMSE:0.73.

Mpox can be transmitted from animals to people by direct contact with diseased body parts or fluids, clawing or scratching, eating infectious meat, and handling contaminated objects.[7] However, the person-to-person transmission of mpox is reported via intimate contact with an infected person's respiratory secretions, skin sores or genitals, face-to-face contact, bedding, and clothes.[8] In addition, cases have primarily, though not solely, involved males who have intercourse with other men, and the vast majority have been detected to be infected with the mpox virus.[9]

The rise in mpox cases is most likely attributable to natural and man-made factors. On the other side, human–wildlife interactions have increased owing to, among many other things, climate change, forest fires, and the Ukrainian–Russian conflict.[10] Following the designation of mpox as a public health emergency, global health communities should strengthen their awareness campaigns, animal screening camps, immunization programs, quarantine facilities, and diagnostic capabilities for the mpox outbreak in order to stop the virus's spread. Public health workers, in particular, need to be better educated on mpox and its clinical care and more adept at infection prevention and control. At the same time, efforts should be made to address stigma and prejudice within the MSM community adequately, and fair access to treatment and immunizations should be assured; otherwise, mpox free world would be a dream.

Ethics committee approval

Not applicable.

Role of funding source

There is no role of any funding source for this manuscript.

Declaration of Competing Interest

We declare no competing interest.

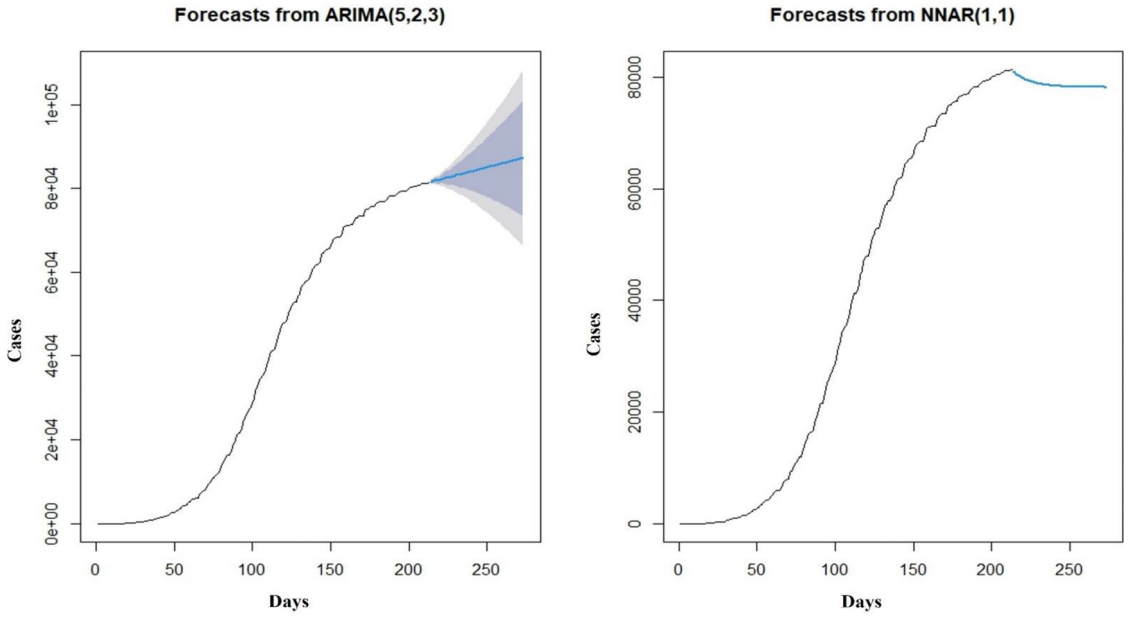

Fig. 1. ARIMA (5,2,3) more effectively explains the estimation of mpox cases trend with an AIC: 2955, MAE: 306.12, and RMSE: 391.39. The predicted line shows a significant increase for the upcoming month (up to January 31, 2023).

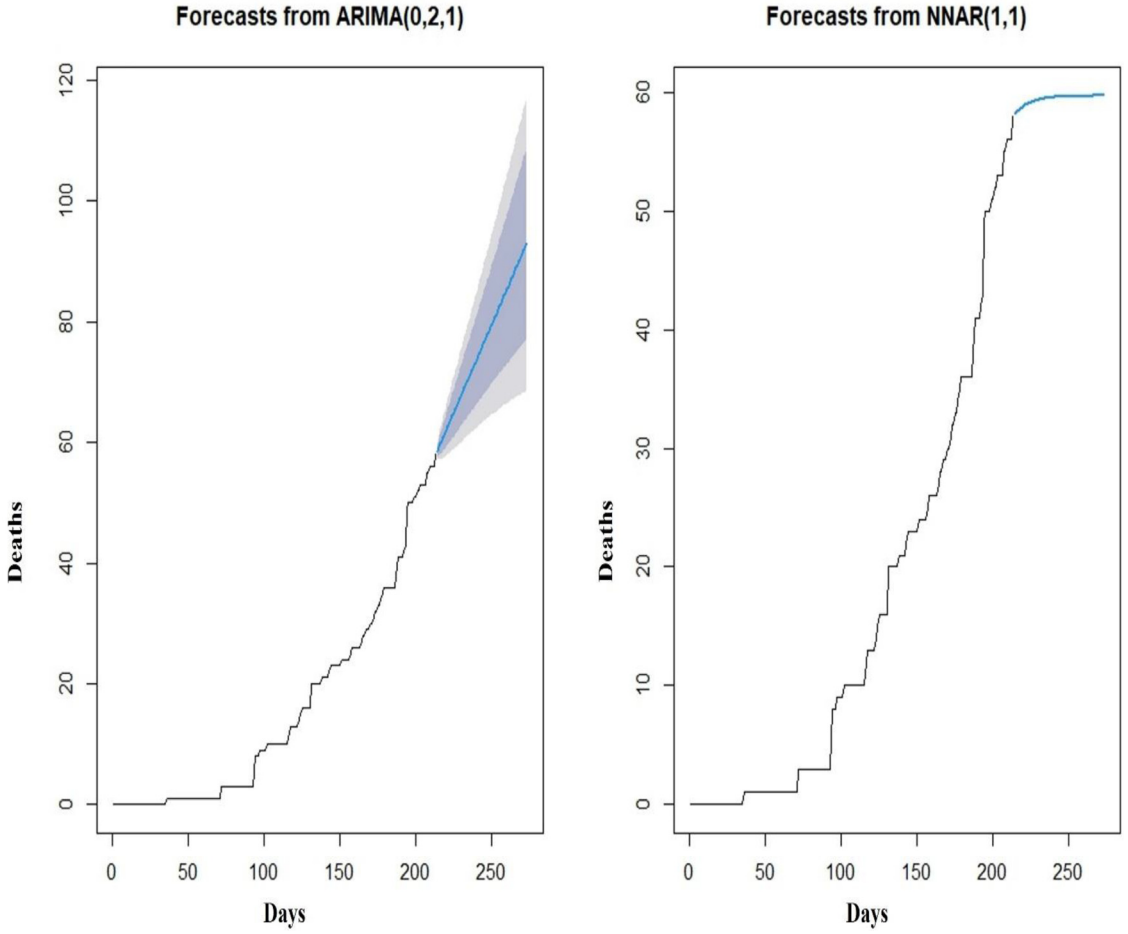

Fig. 2. ARIMA (0,2,1) more effectively explains the estimation of mpox deaths trend with an AIC of 477, MAE of 0.35, and RMSE:0.73. The predicted line shows a significant increase for the upcoming month (up to January 31, 2023).

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Influence of the COVID-19 pandemic on *Staphylococcus aureus* bloodstream infection in children, Henan, China

Dear Editor,

We read with interest the article by Kouijzer and colleagues,[1] which proposes a new approach to define the extent of infection in patients with Staphylococcus aureus (*S. aureus*) bacteremia. Zhou et al.[2] found a reduction in Haemophilus influenzae infection in children during the COVID-19 pandemic; In addition, Duverger et al.[3] reported a reduction in the incidence of carbapenem-producing Enterobacteriaceae after the COVID-19 pandemic. However, few studies have examined the impact of the COVID-19 pandemic on *S. aureus* bloodstream infection in children. We hope to provide additional information to support these conclusions by sharing the results of one of our studies, which analyzed changes in *S. aureus* bloodstream infection in children before and after the COVID-19 pandemic in Henan, China.

S. aureus is one of the major pathogens responsible for bloodstream infections or bacteremia, and it is the most commonly isolated single pathogen associated with nosocomial infections.[4,5] It has high rates of morbidity and mortality. According to the sensitivity to methicillin, *S. aureus* can be divided into methicillin-resistant Staphylococcus aureus (MRSA) and methicillin-susceptible Staphylococcus aureus (MSSA). Compared with MSSA bacteremia patients, the mortality of MRSA bacteremia patients increased by 40%.[6] *S. aureus* bloodstream infections, particularly MRSA bloodstream infections, seriously threaten the health and lives of children.[7,8] During the COVID-19 pandemic, the government has adopted relatively strict control measures and non-pharmaceutical interventions(NPI), which have changed the original epidemic trend of many pathogens.[2,3,9] Therefore, analysis of the trend of *S. aureus* bloodstream infection in children before and after the COVID-19 pandemic can provide a reference for the development of relevant prevention and treatment measures for children.

This study was a multicenter retrospective study. To evaluate the impact of COVID-19 on the epidemiological characteristics of *S. aureus* bloodstream infection in children, we compared and analyzed the laboratory data of children with blood culture records from three large hospitals in Henan Province from 2017 to October 2022. They were all younger than 18 years of age and included 306,404 children (n=45,939 in 2017, n=52,917 in 2018, n=57,755 in 2019, n=40,233 in 2020, n=53,652 in 2021, 2022 n=55,908). When we analyzed the total number of positive blood cultures, the number of *S. aureus* positive blood cultures, and the number of MRSA positive blood cultures (Fig. 1a), as well as the *S. aureus* positive rate and the MRSA positive rate (Fig. 1b), according to year, we found that the total number of positive blood cultures, the number of *S. aureus* positive blood cultures, and the number of MRSA positive blood cultures all decreased significantly in 2020 after the outbreak of the COVID-19 pandemic. In addition, the positive rate of MRSA in *S. aureus* bloodstream infections in children was higher (55.7% in 2017, 72.0% in 2018, 58.3% in 2019, 49.1% in 2020, 53.1% in 2021 and 55.9% in 2022). The prevalence of *S. aureus* and MRSA decreased after the COVID-19 pandemic, indicating that the epidemiological characteristics of *S. aureus* bloodstream infection in children were significantly affected by the COVID-19 pandemic. However, the total number of positive blood cultures, the positive number and positive rate of *S. aureus* and the positive number and positive rate of MRSA have increased in 2021, and the number of positive *S. aureus* and MRSA in 2022 has approached the level before the COVID-19 pandemic, so we need to be alert to the risk of recurrence.

The rise of antibiotic resistance remains a global crisis. With the widespread use of highly effective antimicrobials in clinical practice, MRSA resistance has increased, and the picture for multi-drug resistance is grim. We analyzed the resistance of MRSA strains to common antimicrobial agents before and after the COVID-19 pandemic (Table 1).In addition, our analysis of children with *S. aureus* bloodstream infection according to different age groups found that the number of *S. aureus* positive (Fig. 2a) and the positive rate (Fig. 2b), the number of MRSA positive (Fig. 2c) and the positive rate (Fig. 2d) decreased in children under 3 years old after the COVID-19 pandemic, and the downward trend was more signifi-

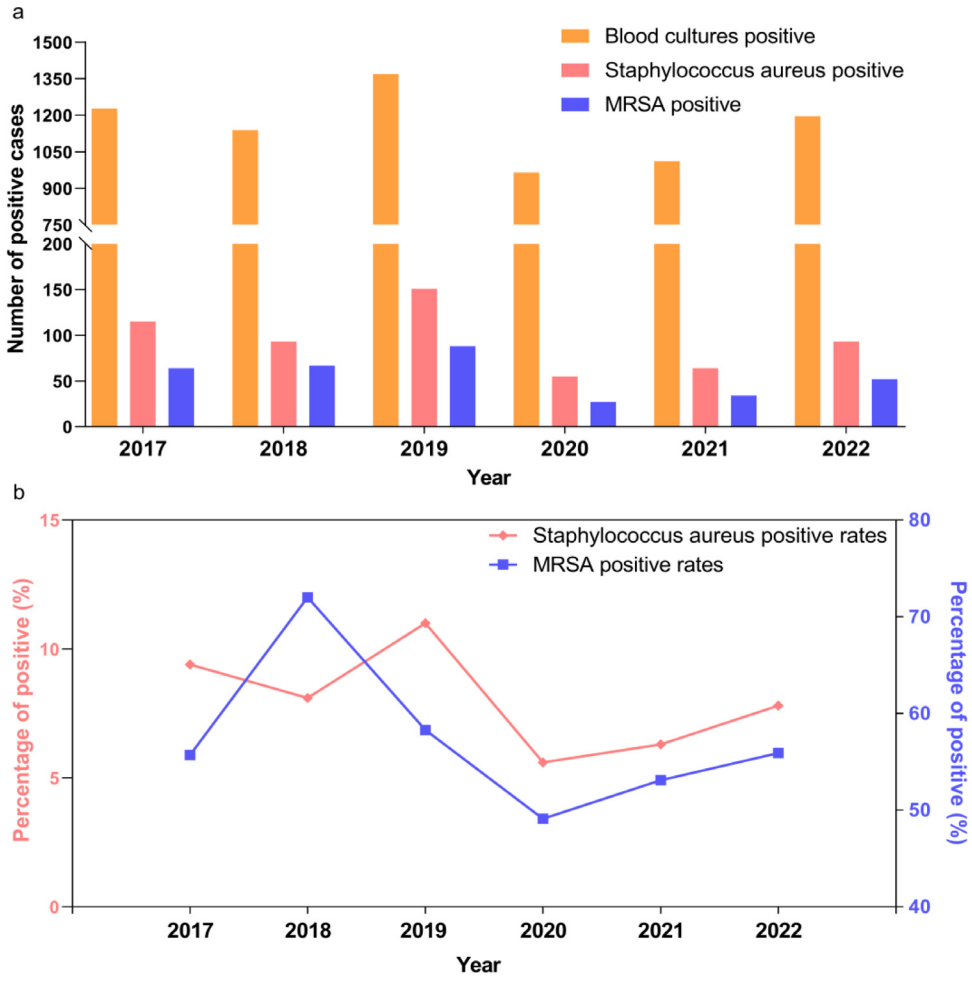

Fig. 1. The total number of positive cases, the number of *S. aureus* positive cases, and the number of MRSA positive cases (a), the *S. aureus* positive rate and the MRSA positive rate (b)in children with blood cultures from 2017-2022.

Table 1
Analysis of drug resistance of MRSA strains to common drugs from 2017 to 2022.

Drugs	2017(n=64)	2018(n=67)	2019(n=88)	2020(n=27)	2021(n=34)	2022(n=52)
Penicillin	64(100)	67(100)	88(100)	27(100)	34(100)	52(100)
Ampicillin	64(100)	67(100)	88(100)	27(100)	34(100)	52(100)
Erythromycin	60(93.7)	59(88.1)	80(90.1)	23(85.2)	29(85.3)	46(88.5)
Clindamycin	58(90.6)	58(86.6)	78(88.6)	22(81.5)	28(82.4)	45(86.5)
Tetracycline	17(26.6)	13(19.4)	16(18.2)	6(22.2)	6(17.7)	11(21.2)
Cotrimoxazole	6(9.4)	5(7.5)	7(7.9)	2(7.4)	2(5.9)	4(7.7)
Gentamicin	4(6.3)	3(4.5)	4(4.5)	1(3.7)	2(5.9)	3(5.8)
Rifampicin	3(4.7)	4(5.9)	3(3.4)	2(7.4)	2(5.9)	4(7.7)
Ciprofloxacin	3(4.7)	2(2.9)	2(2.3)	1(3.7)	1(2.9)	3(5.8)
Teicoplanin	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
Vancomycin	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
Linezolid	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)

cant in infants under 1 years old. Interestingly, before and after the COVID-19 pandemic, *S. aureus* as well as the number of MRSA infections accounted for the highest proportion of infants younger than 1 year, indicating that *S. aureus* and MRSA infections were predominantly in infants younger than 1 year, a feature that does not seem to be related to the COVID-19 pandemic.

In summary, the ongoing COVID-19 pandemic and associated public health measures have altered the epidemic trend of *S. aureus* bloodstream infection in children in Henan, China. During the COVID-19 pandemic, the number of positive cases and positive rates of *S. aureus* and MRSA showed a downward trend. However, with the easing of the COVID-19 pandemic and the relaxation of relevant policies, the number of *S. aureus* bloodstream infections in children has shown signs of recovery, which should cause us to remain vigilant and closely monitor their trends.

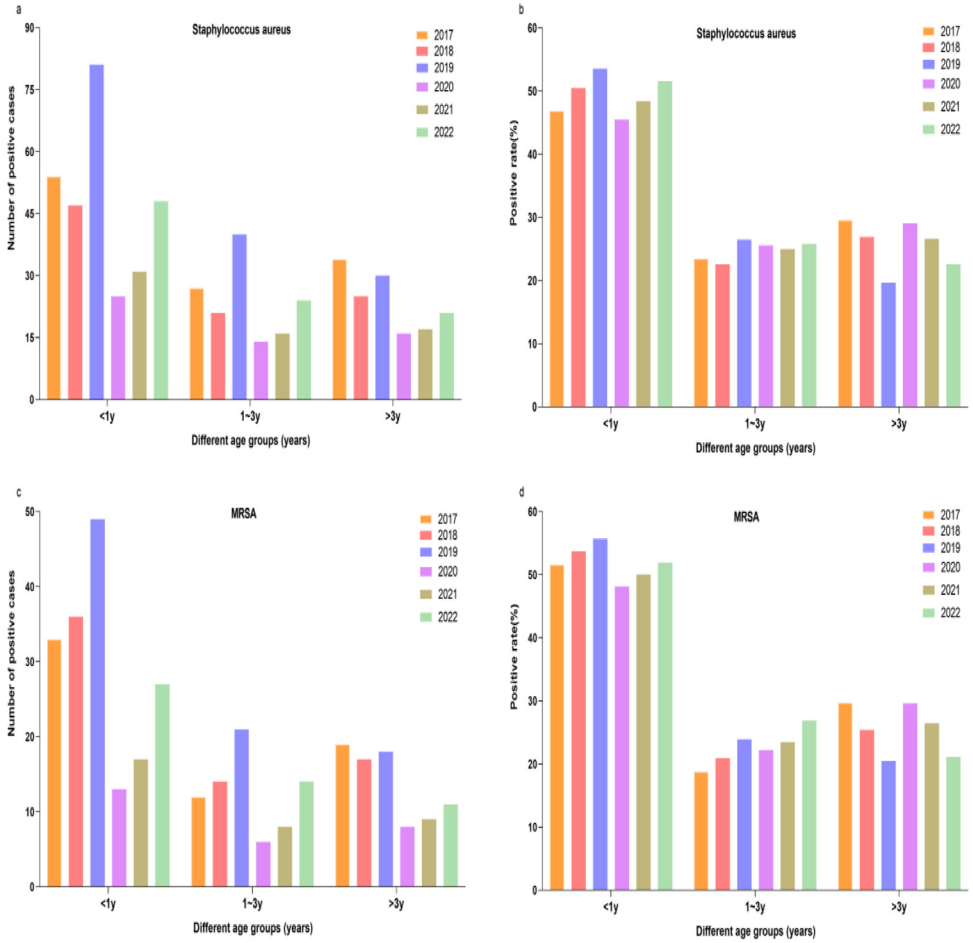

Fig. 2. The number of *S. aureus* positive (a) and the positive rate (b), the number of MRSA positive (c) and the positive rate (d) in different age groups from 2017-2022.

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Recommendation for broad use of Covid-19 mRNA vaccine boosters due to waning vaccine effectiveness is taking the easy way out

Dear Editor,

Most recently, Hannawi and co-workers presented data on the efficiency of a bivalent recombinant SARS-CoV-2 protein based vaccine that appears to induce consistent neutralizing antibodies while showing a promising safety profile.[1] The authors conclude that this vaccine type could be a new tool for vaccination against emerging variants. Taking into account these data, protein based vaccination strategies should not yet drift out of focus.

An update of the CDC's VISION network analyses confirmed the decreasing effectiveness of Covid-19 mRNA vaccines within a few months independent of the vaccine shot number.[2] Based on their test negative case-control study Ferdinandis et al. concluded that their findings support recommendations for broad use of Covid-19 mRNA vaccine booster doses. In principle, this statement is correct but oversimplified, as various issues remain disregarded.

During the last decades, nanotechnology attracted increasing attention including drug delivery systems based on nanoparticles. In response to the Covid-19 pandemic lipid nanoparticles (LNPs) as mRNA carrier receive particular attention as they are used for vaccination against SARS-CoV-2. Randomized trials of Comirnaty® (Pfizer-BionTech, clinical trial: NCT04368728) and Spikevax® (Moderna, clinical trial: NCT04405076) showed protection against Covid-19 of about 95% using physiological saline in the control groups. While this is a commonly applied approach, it bears the risk of a systematic bias regarding unspecific immune-effects as it has already been reported that ionizable lipids may stimulate the secretion of pro-inflammatory cytokines and reactive oxygen species.[3] Although the immunogenicity of these lipids has to be further determined, they may induce alterations of the innate and adaptive immune response and activation.[3,4] For this reason, the usage of empty or non-sense RNA containing lipid nanoparticles would have been the proper study control for NCT04368728 and NCT04405076 to exclude undirected protection-effects only based on various LNP components. Considering that protection against serious clinical courses of COVID-19 may be just influenced to some extent by innate immunity effects triggered by unspecific components of the LNP sheath (ZITAT 3), this may explain the limited duration of mRNA vaccine effectiveness.

Beside the issue of an undirected immune system activation bias, concerns regarding potential side effects remain. Although development of biomaterials for drug delivery improved it has recently been shown that mRNA-based Covid-19 vaccines due to their structural components still have the potential to induce antibodies against PEG (polyethylene glycol) leading to various side effects[5]). In this context a recent re-analyses of serious adverse effects of mRNA SARS-CoV-2 vaccinations suggests that these occur more frequently than initially assumed.[6] For this reason more attention has to be paid to cases of unexpected deaths after close temporal connection to SARS-CoV-2 mRNA vaccination as shown at the University Hospital Heidelberg by the Institute of Pathology together with the DZIF (German Centre for Infection Research), which identified acute myocarditis due to vaccine-induced inflammation as the likely cause of death in patients with otherwise unobtrusive health constellation.[7]

In most studies vaccine and booster effectiveness is defined by a reduction of hospital admitted Covid-19 cases. On the one hand, as this measurand is highly dependant on risk factors like age and comorbidities.[8,9] it is important to identify and define risk groups that derive a substantial health benefit from SARS-CoV-2 mRNA vaccination, On the other hand, an objective assessment of vaccine effectiveness is hardly possible due to unavailable control groups as a result of legal and moral immunization requirements.

Taking into account that safety profiles of LNPs depend on dosage and composition and that long-term adverse effects, especially after multiple dose application, cannot be seriously predicted as information on long-term health outcome is obviously not available yet. Further investigations should re-evaluate the harm-benefit ratio before a continuous broad use of mRNA vaccines in low risk groups regarding life threatening courses is considered. However, it needs more transparency regarding the documentation of adverse side effects, also taking subjective perception into account. More detailed data on long-term immunogenic properties and intracellular signalling effects is required even on structural components of the delivery vesicles, especially because mRNA vaccines become more important due to the economic factors „time and costs" as shown by the example of influenza.[10]

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Clinical accuracy of SARS-CoV-2 rapid antigen testing in screening children and adolescents

Dear Editor,

Recently in this journal Shamez Ladhani presented the need of verified, objective evidence of significant benefit without potential or proven harms for the implementation of COVID-19 mitigation strategies among children.[1] Besides face masking, regular use of SARS-CoV-2 rapid antigen detection tests (RDT) has been established as infection control strategy in nurseries and schools.(2) Despite this, a large-scale, real-life analysis of RDT performance among children and adolescents considering COVID-19 vaccination status and SARS-CoV-2 virus variants of concern (VOC) is still missing.[3–7]

From the 12th of November 2020 to the 30th of September 2022, the RDT performance was evaluated prospectively in comparison to quantitative reverse transcription polymerase chain reaction (RT-qPCR) with oropharyngeal sampling as screening test strategy for all hospitalised children and adolescents under the age of 18 in a tertiary care hospital in Bavaria/Germany. 9760 RDT/RT-qPCR tandems on 7472 individuals (median age: 5 years) with equal gender composition were enrolled. Three different RDT were used (NADAL®, PANBIO™, and MEDsan®; Fig. 1). As this study follows two former RDT performance assessments as paediatric follow-up, details on the study protocol, VOC assessment, and RT-qPCR are described earlier.[7,8] A logistic lasso regression analysis identified factors being associated with the RDT result. Using a ten-fold cross-validation procedure for model parameters estimation, the model with the lowest mean squared error (MSE) of ~0.89 was chosen.

351 of 9760 enrolled samples tested RT-qPCR positive, the overall RDT sensitivity was 44.7% (157/351, 95%CI: 39.6–50.0%), specificity 99.8% (9392/9409, 95%CI: 99.7–99.9%).

In the logistic lasso regression analysis, the factors viral load, and Omicron VOC infection showed associations influencing the RDT result. The viral load level significantly increased the odds of having a positive RDT ($p < 0.0001$) while the independent negative influence of Omicron VOC on the RDT result was not significant ($p = 0.12$).

RT-qPCR detected a median viral load of 1.8×10^6 (IQR: 2.7×10^4–3.8×10^7) RNA copies per ml in SARS-CoV-2 positive children and adolescents. Significantly higher median viral loads were obtained for RDT positive samples (median: 4.0×10^7) than for RDT negative samples (median: 4.6×10^4, $p < 0.0001$, Mann-Whitney U test). RDT sensitivity increased significantly by viral load. Considering the viral load threshold of 10^6 SARS-CoV-2 RNA

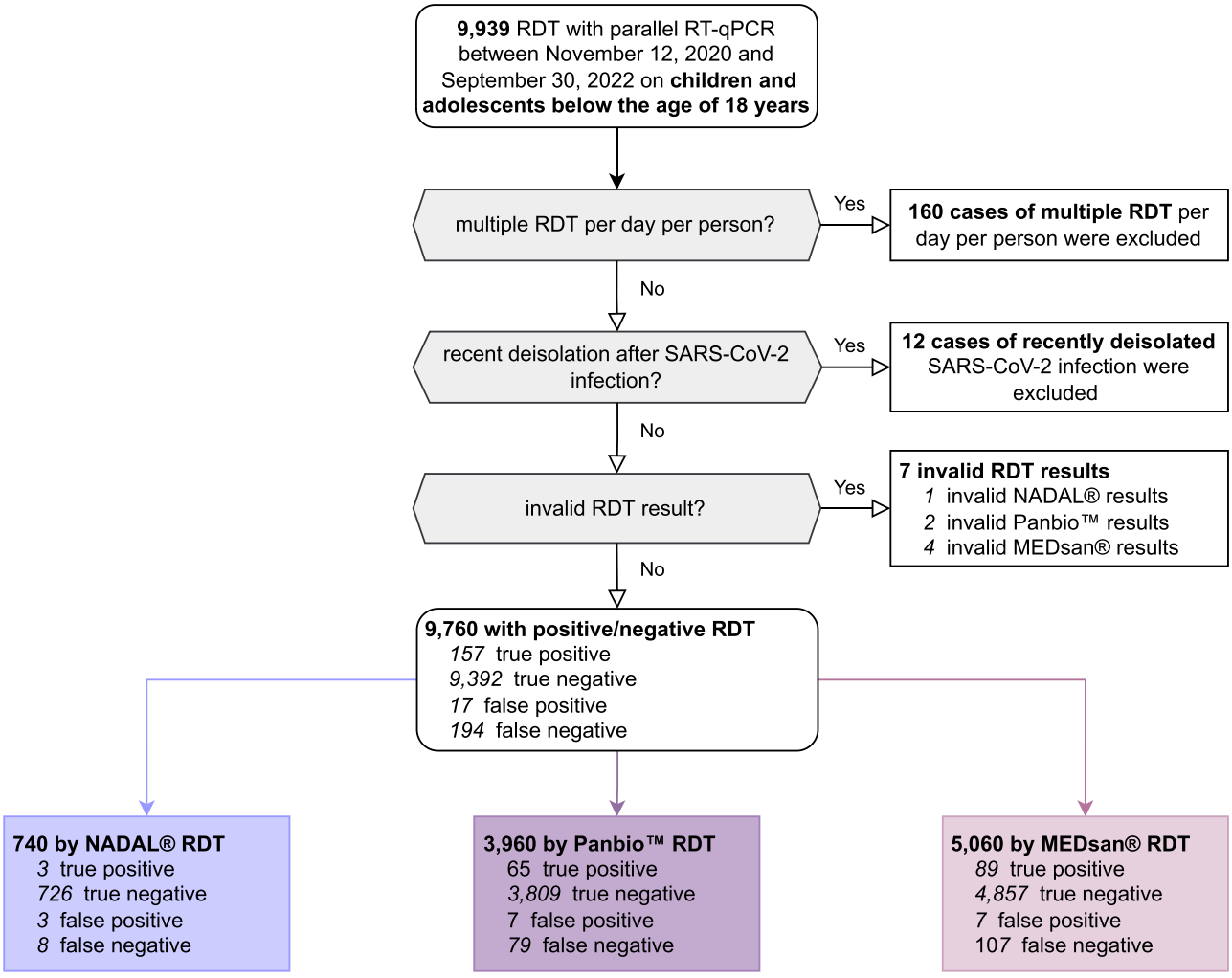

Fig. 1. Enrolment of antigen rapid diagnostic test (RDT) results.
RDT: Antigen rapid diagnostic test.
RT-qPCR: Quantitative reverse transcription polymerase chain reaction.

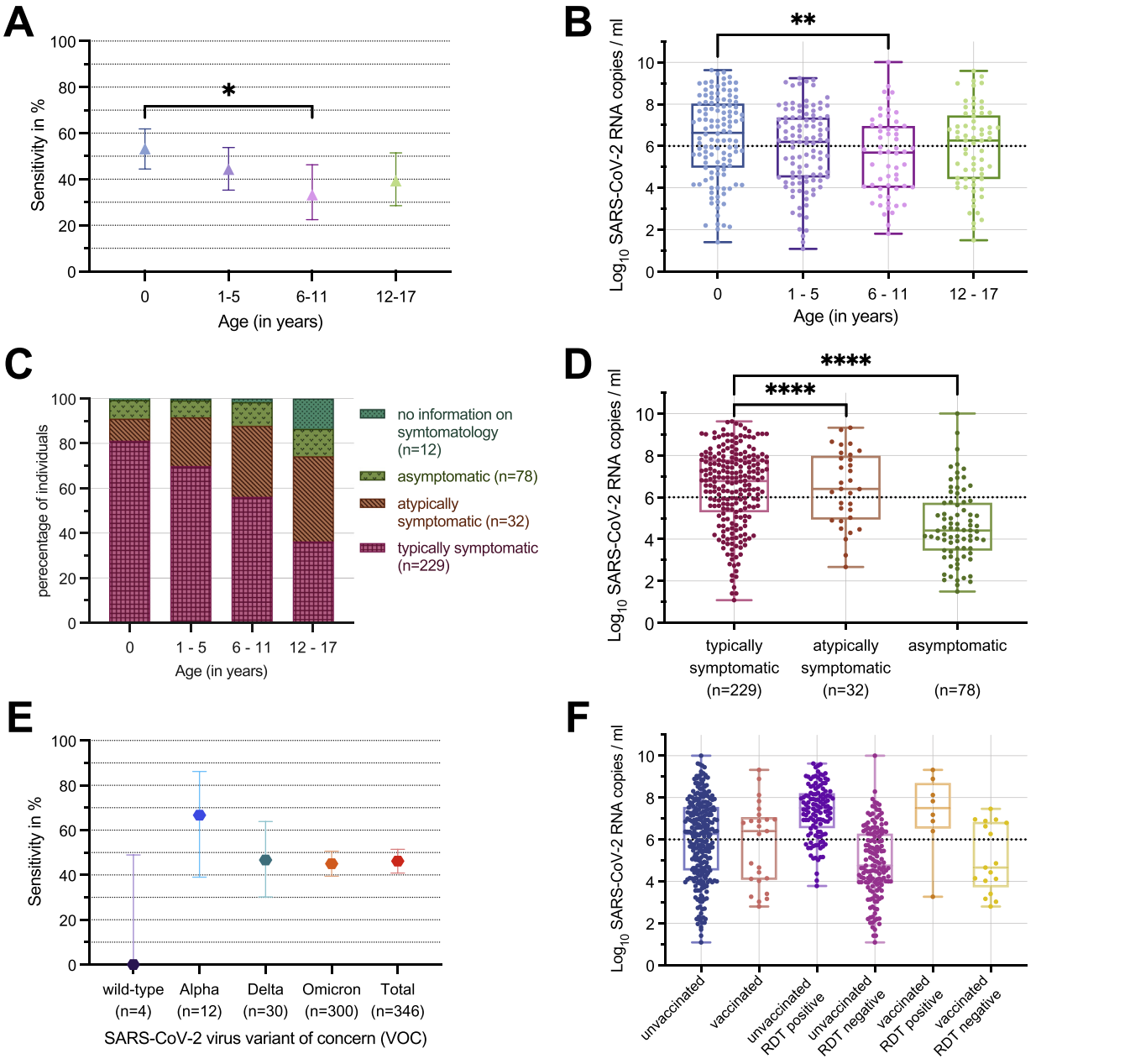

Fig. 2. RDT performance in comparison to RT-qPCR stratified by age categories, VOC, and COVID-19 symptomatology.
Fig. 2 A–C: RDT sensitivity (n = 351), logarithmised viral load (n = 348), and symptomatology (n = 351) in SARS-CoV-2 RNA copies/ml stratified by age categories (first year of life, 1 to 5 years, 6 to 11 years, 12 to 17 years). D portrays the logarithmised viral load in SARS-CoV-2 RNA copies/ml, separated by RDT and COVID-19 symptomatology, n = 339. The viral load of specimen of typically COVID-19 symptomatic children and adolescents exceeded statistically significant the viral load of atypically symptomatic or asymptomatic individuals. E included 346 specimens with either molecularly confirmed or epidemiologically assigned VOC (in case of no molecular VOC diagnostics or, if available, known VOC of the infection source, VOC was assigned based on the VOC corresponding to at least 90% of the German COVID-19 cases at RDT performance).F: Viral load in 306 specimens with known COVID-19 vaccination status stratified by vaccination status only and by vaccination status and RDT result.
The viral load threshold of 10^6 SARS-CoV-2 RNA copies/ml, suggested as infectivity threshold, is added as horizontal dotted line to B,D,F.[9]
n: Number of enrolled RDT per group.
RDT: Antigen rapid diagnostic test.
RT-qPCR: Quantitative reverse transcription polymerase chain reaction.
*$p < 0.05$.
**$p < 0.01$.
****$p < 0.0001$.

copies per ml, suggested as SARS-CoV-2 infectivity threshold,[9] RDT sensitivity was estimated 71.0% (95%CI: 64.1–77.1%).

The median viral load was 2.6×10^4 (IQR: 2.8×10^3–5.5×10^5) SARS-CoV-2 RNA copies per ml among 78 asymptomatic, 2.5×10^6 (IQR: 8.6×10^4–9.7×10^7) among 32 atypically symptomatic (e.g. seizures, diarrhoea), and 6.1×10^6 (IQR: 1.9×10^5–6.4×10^7) among 229 typically COVID-19 symptomatic children. RDT sensitivity was significantly reduced in asymptomatic (20.5%) compared to the symptomatic children (52.9%; $p = 0.0022$, Fisher's exact test, Fig. 2D).

RDT sensitivity ranged from 52.3% (65/122, 95%CI: 44.5–61.9%) for children in the first year of life, to 44.3% (47/106, 95%CI: 35.3–54.0%) for children aged 1 to 5 years, 33.3% (19/57, 95%CI: 22.49–46.28%) aged 6 to 11 years and 39.4% (26/66, 95%CI: 28.5–51.5%) aged 12 to 17 years (Fig. 2A)in line with differing median viral loads (Fig. 2B). Children between 6 and 11 years showed a significantly reduced RDT sensitivity ($p = 0.016$, Fisher's exact test, Fig. 2A) and viral load ($p = 0.0033$, Mann-Whitney U test, Fig. 2B) compared to children in the first year of life going in line with a lower rate of typically symptomatic children (Fig. 2C).

Sensitivity decreased from the Alpha VOC (66.7%, 8/12, 95%CI: 39.1–86.2%) over the Delta VOC (46.7%, 14/30, 95%CI: 30.2–63.9%), to the Omicron VOC (45.0%, 135/300, 95%CI: 39.5–50.7%). Differences in VOC specific sensitivity were not significant (pairwise comparisons using Fisher's exact test, all $p > 0.08$, Fig. 2E).

In 7990 of 9760 (81.9%) enrolled RDT, information on COVID-19 vaccination status was available: 6977 RDT (87.3%) were performed on unvaccinated, 1013 (12.7%) on children and adolescents with at least one dose of COVID-19 vaccine. Among unvaccinated, RDT sensitivity was 44.8% (126/281, 95%CI: 39.1–50.7%), specificity 99.8% (6681/6696, 95%CI: 99.6–99.9%). Among vaccinated, sensitivity was 32.0% (8/25, 95%CI: 17.2–51.6%), specificity 100.00% (988/988, 95%CI: 99.6–100.0%). Differences in sensitivity ($p = 0.29$) and specificity ($p = 0.24$, both Fisher's exact test) were not significant. Viral load did not significantly differ comparing COVID-19 unvaccinated with vaccinated ($p = 0.20$, Mann-Whitney U test, Fig. 2F).

Compared to previous data, the presented sensitivtiy scores are at the lower end. However, they were obtained in a study which resulted in more case numbers in a real-life point-of-care setting.[3–5] Reliability of RDT performance clearly depended on specimens' viral load which is influenced by age and days since symptom onset. The differences in the age-stratified viral load levels may be explained by the different proportions of COVID-19 symptomatology. As typically symptomatic infants in the first year of life may enlist the hospitals' medical care early and large-scale, the school children aged 6 to 11 years may be detected coincidentally in the COVID-19 screening having differing non-infectious reasons for medical consultation. No significantly reduced viral load was observed in Omicron VOC(7) being potentially explained by the dominating proportion of Omicron VOC in this study. RDT sensitivity did not correlate with immunisation status which has been reported in a preprint analysis as factor impairing RDT sensitivity.[6]

The study is limited in several aspects: Data collection in the real-life and point-of-care setting led to differing distributions and proportional use of the three RDT across the pediatric departments and over the study period. The direct comparability between the manufacturers' is limited. The potential influence and inhomogeneity in sampling, especially considering the preanalytical challenges in children, in test execution, and in interpretation is probable. Molecularly based VOC determination was only performed from January 2021 to January 2022.[10]

For children and adolescents, the indication, as well as advantages and disadvantages for RDT usage is comparable to the one for adults.[7,8] Due to the low sensitivity in asymptomatic individuals, the usefulness of RDT seems limited in large-scale SARS-CoV-2 screening programs. This intrahospital assessed data on RDT reliability should also be considered in terms of RDT screening usage, including its self-testing option for children and adolescents as COVID-19 management strategy in the context of schools and nurseries.

Data access, responsibility, and analysis

Dr Krone and Ms Wagenhäuser had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Data sharing statement

Individual participant data that underlie the results reported in this article after deidentification is available on request immediately following publication ending 5 years following article publication to researchers who provide a methodological sound proposal to achieve aims in the approved proposal. Proposals should be directed to krone_m@ukw.de.

Information on previous presentation of the information

1034 RDT results on children and adolescents have already been included in an age independent RDT performance assessment in a cohort of 5068 RDT with data collection from the 12th of November 2020 to the 28th of February 2021 8 as wells as the sequel up to the 30th of January 2022 including 35479 specimen within 5623 on children and adolescents.[7]

Ethics committee approval

The Ethics committee of the University of Wuerzburg considered the study protocol and waived the need to formally apply for ethical clearance due to the study design (File 20221018 01).

Declaration of Competing Interest

Manuel Krone receives honoraria from Abbott outside the submitted work. None of the other authors has any conflicts of interests to declare.

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Role of the funding source

This study was initiated by the investigators. The sponsoring institutions had no function in study design, data collection, analysis, and interpretation of data as well as in writing of the manuscript. All authors had unlimited access to all data. Dr Krone, Ms Wagenhäuser, Prof Liese, and Dr Andres had the final responsibility for the decision to submit for publication.

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Tuberculosis following two-dose SARS-CoV-2 vaccination with messenger RNA vaccine (BNT162b2) and inactivated virus vaccine (CoronaVac)[††]

Dear Editor,

Although the waning of antibodies is anticipated after two-dose SARS-CoV-2 vaccination, the cellular response, especially the Th1 cell response that promotes T-cell immunity, has been reported recently.[1] Development of the T-cell and cellular immune response triggers long-term memory with potential cross-pathogen protection – known as trained immunity.[2,3] Animal and epidemiological studies[4–6] showed a cross-protection effect from Bacille Calmette-Guerin (BCG) vaccination on COVID-19 by inducing trained immunity. We hypothesize that SARS-CoV-2 vaccination could also trigger trained immunity and offer protection against tuberculosis (TB) through a similar mechanism.

In this population-based real-world outcome study in Hong Kong, we linked territory-wide electronic health records (EHRs) with SARS-CoV-2 vaccination records and applied two epidemiological study designs, case-control study and retrospective cohort study, to investigate the effect of two-dose SARS-CoV-2 vaccination on the occurrence of TB. Matching between EHR and vaccination records was based on anonymized personal identification document numbers. The record-linked EHR database has been used for several population-based pharmacovigilance studies for the SARS-CoV-2 vaccine with proven population representativeness and data accuracy.[7,8]

We identified the interest of outcome as newly diagnosed TB from the inpatient setting between February 23, 2021, and January 31, 2022, using ICD-9-CM diagnostic codes (010–018). To ensure the TB cases were incident events during the period, patients with a recorded TB diagnosis or TB-related antibiotics prescription (isoniazid or rifampin) were excluded. Cases were further verified by prescription records of isoniazid, rifampin, pyrazinamide and ethambutol or streptomycin within 14 days after hospital admission. In the cohort study, we included all the patients' records in the linked database and categorized the cohort into two-dose vaccinated or unvaccinated group according to the vaccination status by September 30, 2021. We matched vaccine recipients with unvaccinated individuals by age and sex using maximum ratio matching and followed them up until the occurrence of outcome, death or study end date. Patients with metastatic cancer, age<18 years, with clinical history of TB or TB-related treatment, or with single-dose or heterologous vaccines were excluded. Multi-group Inverse Probability of Treatment Weighting (IPTW) was adopted to ascertain the balance of patient characteristics across groups. Cox Proportional-Hazards model was applied to estimate the hazard ratio (HR). In the nested case-control study, TB cases were 1:10 matched with controls admitted to hospital during the same period but without a diagnosis of TB, using the incidence density sampling with replacement by age, sex, and hospital admission date (±1 day). Multivariable conditional logistic regression was applied to evaluate odds ratio (OR). HR and OR were estimated separately for BNT162b2 and CoronaVac. Subgroup analysis (by age, sex) and a series of sensitivity analyses were conducted. The detailed study design and statistical analysis are shown in Supplementary Methods.

The study cohort included 1662,879 unvaccinated individuals, 1320,654 two-dose BNT162b2 vaccine recipients, and 944,331 two-dose CoronaVac vaccine recipients (Supplementary Fig. 1). After IPTW with 1% extreme values trimmed, we obtained a well-balanced cohort with all standard mean difference (SMD) <0.1 except for age (Supplementary Table 1), which was adjusted by Cox regression. During a median follow-up of 178–199 days, incidence of TB in the BNT162b2 group [(1.35 (95% CI: 1.1–1.63) per 10,000-person year] and the CoronaVac group [1.53 (95% CI: 1.23–1.89) per 10,000-person year] were lower than the unvaccinated group [3.47 (95% CI: 3.09–3.88) per 10,000-person year] (Supplementary Table 2). Cox regression showed the adjusted HR was 0.42 (95% CI: 0.31–0.57) for BNT162b2 and 0.51 (95% CI: 0.39- 0.69) for CoronaVac when compared to the unvaccinated group. Age- and sex-stratified Cox regression showed similar associations for both vaccines (Fig. 1). Sensitivity analyses using the recorded diagnosis of TB regardless of TB-related prescription as the outcome definition, considering 30 days washout period for TB occurrence, Fine-Gray regression considering death as a competing risk for TB, or using appendicitis as the negative outcome control, all showed similar findings with the main analysis (Table 1). The case-control study (Supplementary Fig. 2 for cases and controls selection and Supplementary Table 3 for baseline demographics) yielded similar, but a more conservative risk estimate [adjusted OR 0.76 (95% CI: 0.57–1.01) for BNT162b2; 0.74 (95% CI: 0.56–0.99) for CoronaVac] (Fig. 1).

Hong Kong is among the few jurisdictions that implemented two types of SARS-CoV-2 vaccines with established territory-wide vaccine safety surveillance. From both mRNA and inactivated virus vaccine technology platforms, we observed a significantly lower risk of incident TB among people who received two-dose vaccines. The overall estimated relative risk reduction was 49–58% in the cohort analysis and 24–26% in the case-control analysis. Consistent findings from sensitivity analyses further supports the trained immunity theory, and it is likely that the cross-pathogen protection could be sustained for at least 6 months, according to the median follow-up period of the cohort study.

Long-term boosting of innate immune responses by live vaccines, such as BCG, could potentially induce heterologous protection against infections through epigenetic, transcriptional, and functional reprogramming of innate immune cells.[9] Therefore, it was proposed that the induction of trained immunity might represent an important tool for reducing susceptibility to and severity of SARS-CoV-2,[9] which was recently proved in an animal study with SARS-CoV-2 challenge.[6] Our results, consistent with the trained immunity theory, warrants further pathogenesis and epigenetic investigation. Notably, our observation relating to the cross-pathogen protection is not specific to mRNA or inactivated virus vaccine platform. This indicates that the trained immunity might involve sev-

[††] **Short summary:** Both the mRNA and the inactivated virus SARS-CoV-2 vaccine potentially offer a protective effect on TB

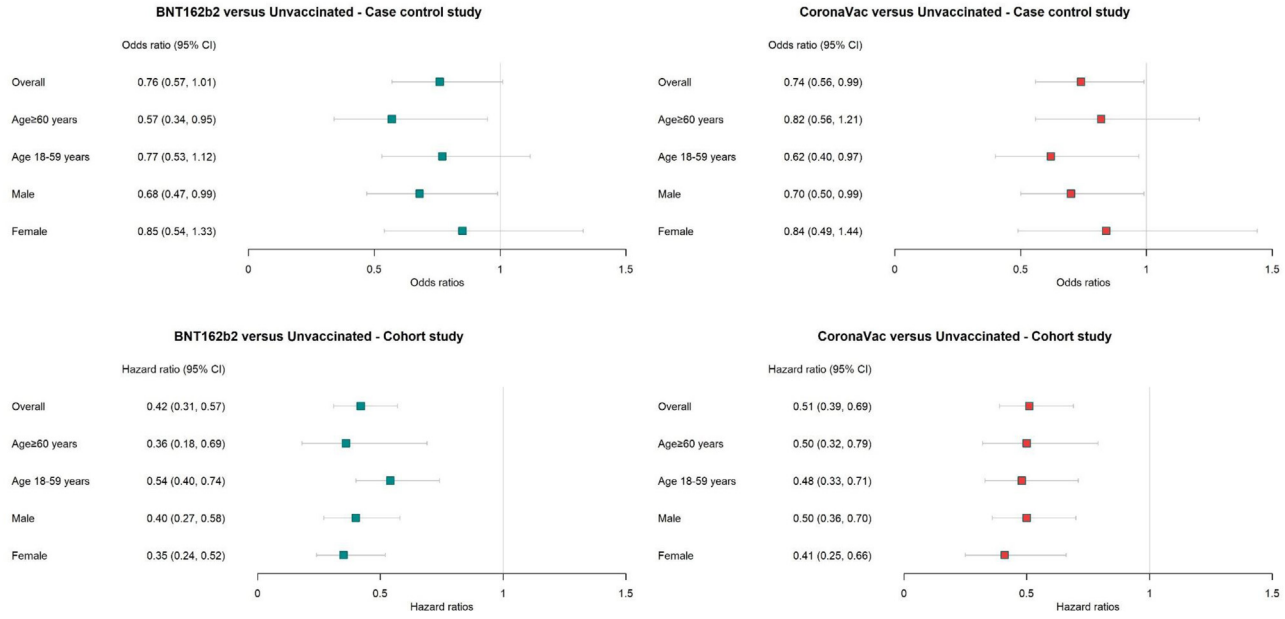

Fig. 1. Risk estimation from cohort and case-control study.

Table 1
Sensitivity analyses for cohort study.

	Events (N)	Cohorts (N)	Time-to-event [days, median (IQR)]	Follow-up time (person-years)	Incidence (10,000 person-years, 95% CI)	Adjusted HR (95% CI)	*P*-value
Hospitalized TB regardless of TB-related prescription within 14 days							
None	554	1,662,879	178 (144, 226)	849,496	6.52(5.99, 7.08)	Ref	
BNT162b2	131	1,320,654	188 (158, 230)	712,629.8	1.84(1.54, 2.17)	0.36 (0.27, 0.47)	<0.001
CoronaVac	130	944,331	199 (164, 255)	541,118	2.4(2.01, 2.84)	0.45 (0.36, 0.57)	<0.001
30-day wash out period for TB definition							
None	250	1,662,879	178 (144, 226)	849,587.4	2.94(2.59, 3.32)	Ref	
BNT162b2	88	1,320,654	188 (158, 230)	712,641.8	1.23(0.99, 1.51)	0.44 (0.32, 0.6)	<0.001
CoronaVac	76	944,331	199 (164, 255)	541,134.3	1.4(1.11, 1.74)	0.54 (0.4, 0.74)	<0.001
Fine-Gray competing risk of death analysis							
None	295	1,662,879	178 (144, 226)	849,565.4	3.47(3.09, 3.88)	Ref	
BNT162b2	96	1,320,654	188 (158, 230)	712,638.1	1.35(1.1, 1.63)	0.49 (0.38, 0.62)	<0.001
CoronaVac	83	944,331	199 (164, 255)	541,130.4	1.53(1.23, 1.89)	0.51 (0.4, 0.66)	<0.001
Negative outcome control (appendicitis)							
None	468	1,662,879	178 (144, 226)	849,519.7	5.51(5.02, 6.02)	Ref	
BNT162b2	495	1,320,654	188 (158, 230)	712,514.6	6.95(6.35, 7.58)	1.10 (0.94, 1.29)	0.222
CoronaVac	328	944,331	199 (164, 255)	541,041.6	6.06(5.43, 6.74)	1.01 (0.87, 1.18)	0.859

eral cell-pathogenesis cross-talks and regulations, and the potential of whole-microorganism vaccines as an important tool for reducing the susceptibility of SARS-CoV-2.

Despite several limitations inherently associated with EHR-based real-world outcome studies, our study has significant public health implications, particularly for low-and low-middle-income economies with dual threats from high prevalent TB and uncontrolled COVID-19 due to low uptake of SARS-CoV-2 vaccines.[10] Potential additional benefits of SARS-CoV-2 vaccination should be made known to the public to overcome vaccine hesitancy; and to policymakers, to facilitate feasible and cost-effective vaccination programs for COVID-19 and TB control.

Ethics approval

This study was approved by the Institutional Review Board of the University of Hong Kong / Hospital Authority Hong Kong West (UW 21–149 and UW 21–138) and the Department of Health Ethics Committee (LM 21/2021).

Data availability

Data are not available as the data custodians (the Hospital Authority and the Department of Health of Hong Kong SAR) have not given permission for sharing due to patient confidentiality and privacy concerns. Local academic institutions, government departments, or non-governmental organizations may apply for access to data through the Hospital Authority's data sharing portal (https://www3.ha.org.hk/data).

Author's contribution

Professor Wong had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: XL, KP, ICKW
Drafting of the manuscript: XL, KP
Data acquisition and management: CSLC, FTTL, EYFW, XL, CKW, EWC, ICKW
Statistical analysis: KP, FC, XL
Clinical investigators: DCLL, MSMI, CSL
Interpretation of data: all authors
Critical revision of the manuscript for important intellectual content: all authors
Administrative, technical, or material support: ICKW, EWC
Supervision: XL, ICKW

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Declaration of Competing Interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2022.12.016.

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Changes of *Mycoplasma pneumoniae* infection in children before and after the COVID - 19 pandemic, Henan, China

Dear Editor,

In this journal, Li et al., and Zhou et al., successively reported the decline of *Streptococcus pneumoniae* and *Haemophilus influenzae* infections in children under the impact of the COVID - 19 pandemic[1,2]. Li et al. compared the effect of COVID - 19 on the incidence of Escherichia coli infections in respiratory system and digestive system in children, the results indicated indicate that the COVID - 19 may mainly affect the incidence of respiratory system infection, and has little impact on the incidence of digestive system infection[3]. Up to now, there was no data on *Mycoplasma pneumoniae* (*M. pneumoniae*) infections during the COVID - 19 pandemic.

M. pneumoniae is a prokaryotic microorganism without cell wall, insensitive to cell wall antimicrobial agents such as lactam, and transmitted through air droplets, coughing, sneezing and close contact[4]. *M. pneumoniae* causes up to 40% of community-acquired pneumonia in children and can develop into serious life-threatening diseases such as refractory mycoplasma pneumoniae pneumonia, necrotizing pneumonia, fulminant pneumoniae and *M. pneumoniae* encephalitis[5-7]. In China, macrolide-resistant *M. pneumoniae* is very common and the prevalence ranges from 83% to 95%, which makes it difficult to treat mycoplasma infection[6]. Therefore, it is important to dynamically monitor children's *M. pneumoniae* infection and understand its epidemiological changes so as to formulate preventive strategies. Here we evaluated the changes in *M. pneumoniae* infection in children before and after the COVID - 19 pandemic, which may help to inform the implementation of clinical prevention strategies.

The Henan Children's Hospital was approved as the National Children's Regional Medical Center, Henan Children's Medical Center, and Henan Pediatric Disease Clinical Medical Research Center. In this study, *M. pneumoniae* infection was monitored in the Henan Children's Hospital from January 1, 2017 to October 31, 2022. From 2017 to 2019, the positive number and positive rate of *M. pneumoniae* RNA and *M. pneumoniae* serological tests fluctuated seasonally, while during the two COVID-19 pandemics, the positive number and positive rate of *M. pneumoniae* RNA and *M. pneumoniae* serological tests decreased significantly twice (Figs. 1A and 2A). In particular, after the end of the two COVID - 19 pandemics, the positive number and positive rate of *M. pneumoniae* RNA and *M. pneumoniae* serological tests continued to decrease for several months, which may inhibit the seasonal upward trend of *M. pneumoniae* infection. Although the positive number and positive rate of *M. pneumoniae* RNA and *M. pneumoniae* serological test in children increased slightly during the recovery period after two COVID - 19 pandemics, it was still lower than that in the same period before COVID - 19 pandemic. Therefore, the epidemic trend of *M. pneumoniae* infection in children in Henan Province changed before and after the epidemic of COVID - 19.

Furthermore, the total number of *M. pneumoniae* RNA positive patients over 5 years old accounted for 49% of the total number of *M. pneumoniae* RNA positive between 0 - 18 y old from 2017 to 2021 (Fig. 1B), but this proportion was not significant in *M. pneumoniae* serological tests (Fig. 2B). In addition, after COVID - 19 pandemic, the positive number and positive rate of *M. pneumoniae* RNA and *M. pneumoniae* serological test decreased in < 1y, 1 - 3y, 3 - 5y and 5 - 18y age groups (Figs. 1C, 1D, 2C and 2D), especially in children over 5 years old, indicating that the COVID-

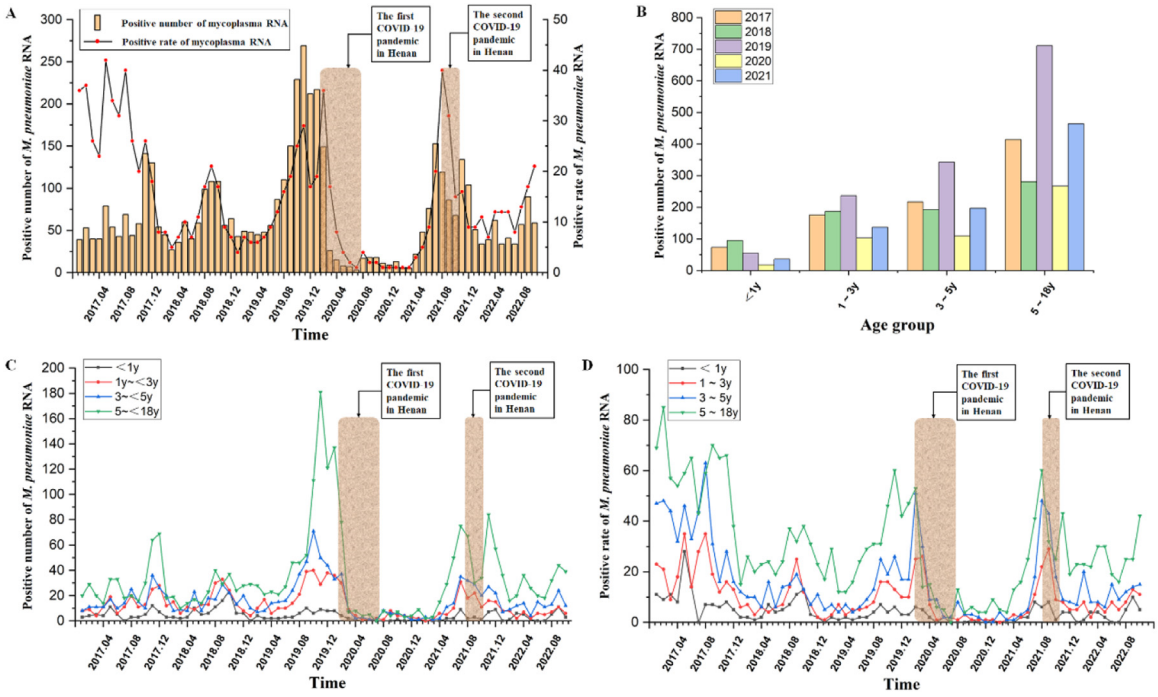

Fig. 1. **(A)** The positive number of *M. pneumoniae* RNA and the positive rate of *M. pneumoniae* RNA from January 2017, to October 2022. **(B)** The number of positive infection of *M. pneumoniae* RNA form 2017 to 2021. **(C)** The number of *M. pneumoniae* RNA positive in different ages from January 2017 to October 2022. **(D)** The positive rate of *M. pneumoniae* RNA in different ages from January 2017 to October 2022.

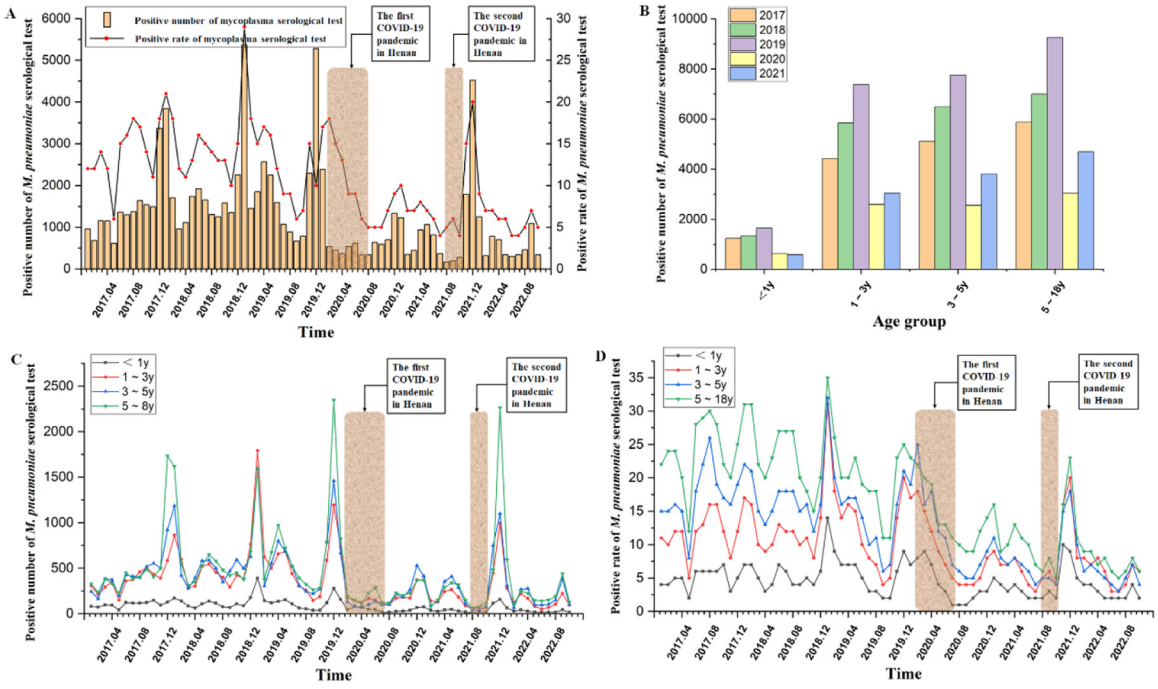

Fig. 2. **(A)** The positive number of *M. pneumoniae* serological test and the positive rate of *M. pneumoniae* serological test from January 2017, to October 2022. **(B)** The number of positive infection of *M. pneumoniae* serological test form 2017 to 2021. **(C)** The number of *M. pneumoniae* serological test positive in different ages from January 2017 to October 2022. **(D)** The positive rate of *M. pneumoniae* serological test in different ages from January 2017 to October 2022.

19 pandemic reduced the infection of *M. pneumoniae* in school-age children. This change may be mainly related to a series of strict measures taken during the COVID-19 pandemic, such as suspension of classes (reduced contact between children), increased awareness of wearing masks and paying attention to hand hygiene.

M. pneumoniae infection decreased in children of 0 - 18y during the COVID - 19 pandemic. It also shows that the COVID - 19 pandemic is something we must all face. The epidemic knows no borders, and the virus is the common enemy of mankind. The international community must foster the vision of a community with a shared future for mankind, help each other, jointly address risks and challenges, and jointly safeguard the well-being of people around the world. Therefore, we need to closely observe the epidemic changes of various pathogens affecting the respiratory system before and after the epidemic of COVID - 19.

In short, *M. pneumoniae* infections in children of all ages have declined during the COVID - 19 pandemic. Close monitoring of epidemiological trends helps to prevent *M. pneumoniae* infection in children, especially in children over 5 years of age.

Declaration of Competing Interest

The authors declare no conflict of interests.

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Following the Omicron wave, the majority of children in England have evidence of previous COVID infection

Dear Editor,

We previously reported large increases in SARS-CoV-2 seropositivity in children in England due to the Delta wave since April 2021 and roll out of paediatric vaccination to 16–17 year-olds since August 2021 and 12–15 year-olds since September 2021.[1] The emergence of the Omicron variant in November 2021 along with multiple subvariant waves thereafter has resulted in high rates of infection across all age groups, particularly in young children.[2] Additionally, the UK recommended non-urgent COVID-19 vaccination for 5–11 year-olds from April 2022.[3] Here, we describe the changes in SARS-CoV-2 seroprevalence rates in children during September 2021 to September 2022 in England.

Our serosurveillance methodology has been described previously.[1] Briefly, the UKHSA Sero-epidemiology Unit (SEU) coordinates the collection of residual samples from children aged 1–17 years having a blood test as part of their clinical management in 44 hospital trusts across seven National Health Service (NHS) regions (~400 residual samples/month). Samples were processed using two serological assays; the Roche Elecsys assays for i) antibodies to the nucleocapsid (N) protein, informing on previous exposure to SARS-C0V-2 and ii) antibodies to the spike (S) protein receptor binding domain, detecting previous infection as well as vaccine-induced immune response.[4] Statistical methods were described previously.[1]

From September 01 2021, to September 30 2022, 4873 paediatric sera (age groups 1–4 years $n = 551$; 5–11 years $n = 1331$; 12–15 years $n = 2364$; 16–17 years $n = 627$) were tested. The overall national prevalence estimate of seropositivity, weighted by age group and NHS region, based on results from the Roche S assay, increased from 48.5% (95% CrI 40.8%–55.1%) during September-October 2021 to 97.2% (95% CrI 93.7%–98.9%) by September 2022 (see Figs. 1 and 2). For N-antibody positivity, the respective rates were 34% (27.5%–41.2%) and 86.7% (81.1%–91.6%).

During November-December 2021, S-antibody seropositivity was highest in 16–17 year-olds at 86.5% (78.7%–91.7%) and 12–15 year-olds at 78% (69.8%–83.5%), however a considerable proportion (46.6% and 24.3% respectively) tested S positive and N negative, largely indicating immune response to vaccination alone (a small proportion being due to faster waning and decreased sensitivity of the N antibody response). This is consistent with a vaccine uptake of at least 1 dose of 16.7% in 16–17 and < 1% in 12–15 year-olds, respectively, by September 2021.[5]

Seropositivity decreased with age and was 36.9% (25.5%–49.7%) in 1–4 year olds with the majority of those testing S positive also testing N positive. With the emergence of the highly transmissible Omicron variant which was able to evade both natural and vaccine-induced immunity in November 2021, large increases in N-antibody seropositivity were observed in early 2022, consistent with widespread infection. N-antibody seropositivity increased across all childhood age-groups throughout 2022, reaching 93.3% (80.4%–98.6%) in children aged one to four years, to 98.6% (95.1%–99.8%) in those aged 16–17 years by September 2022. The difference in S and N seropositivity decreased to 7.3% in the oldest age group, close to that seen in the younger age groups (1–11 years). From April 2022, whilst acknowledging that most 5–11 year-olds had already been exposed to SARS-CoV-2, the UK Joint Committee for Vaccination and Immunisation (JCVI) recommended two doses of COVID-19 vaccine to this age group to 'increase the immunity of vaccinated individuals against severe COVID-19 in advance of a potential future wave'.[3] Consistent with the low proportion of 5–11 year-olds who were only S-antibody positive (representing mostly vaccinated but uninfected children) by September 2022, national uptake of at least one dose of a COVID-19 vaccine in this age group was 10.7% compared to 50.1% in 12–15 year-olds and 64.1% in 16–17 year-olds.[5]

Overall, our findings show large increases of SARS-CoV-2 antibody seropositivity in children following the emergence of the Omicron variant, resulting in high rates of primary infection in

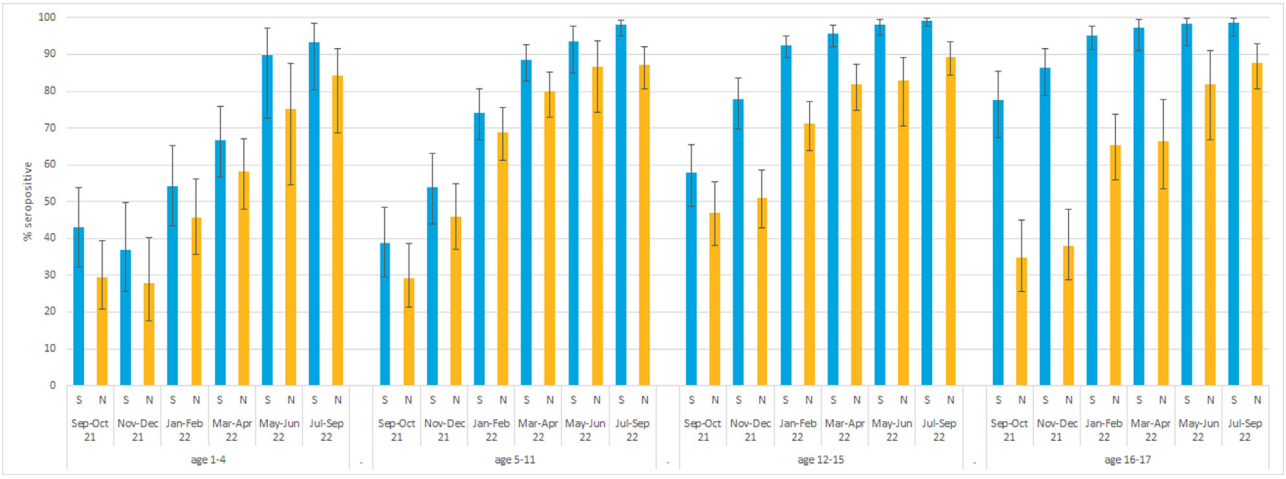

Fig. 1. Population weighted seropositivity estimates of residual paediatric samples by period and age group collected from 1st September 2021 to 30th September 2022, using the Roche N and S assays.

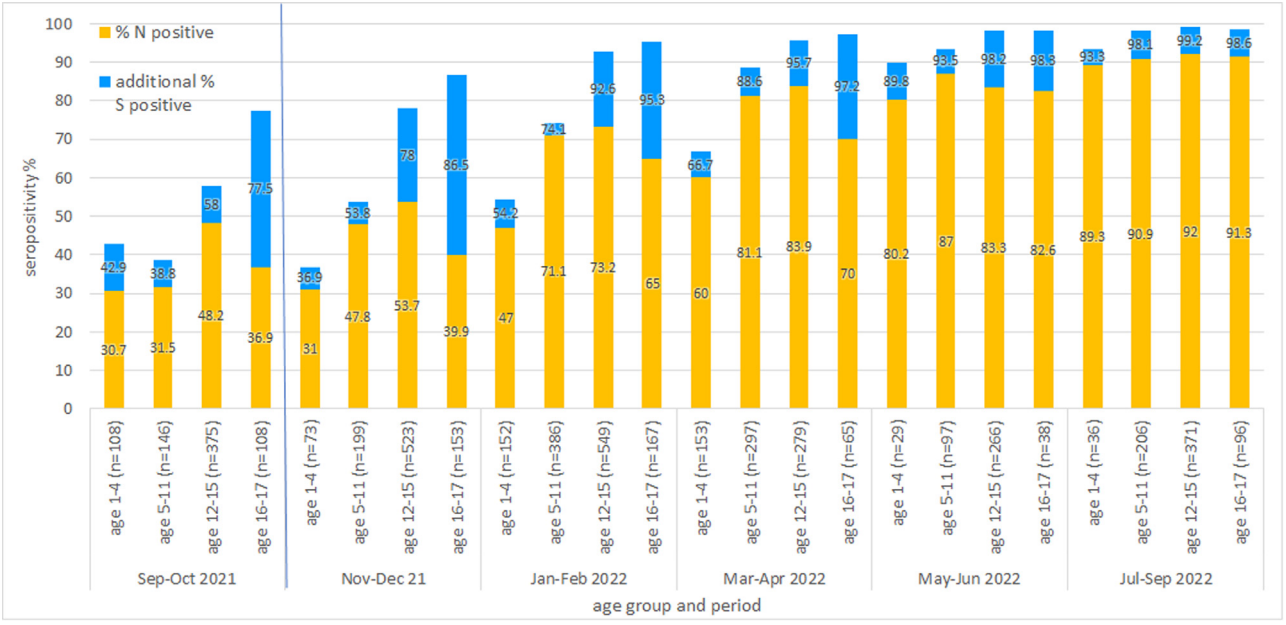

Fig. 2. Population weighted seropositivity estimates of residual paediatric samples by period and age group collected from 1st September 2021 to 30th September 2022, using the Roche N and S assays, stacked columns represent the proportion of samples testing positive with both assays (yellow) and the proportion testing positive with Roche S only (blue).

unvaccinated children and breakthrough infection in previously-vaccinated, mainly older children.

Consistent with these findings, a large nationally representative study using oral fluids in schools in England, estimated that 82.0% (95% CI: 80.3% to 83.5%) of 4–10 year-olds and 99.3% (95% CI: 98.9% to 99.6%) of 11–17 year-olds were sero-positive by March 2022 through a combination of infection and vaccination.[6]

A national household survey by the Office of National Statistics (ONS)[7] measures seroprevalence using two different S-antibody thresholds to distinguish between response to natural infection (179 ng/ml, equivalent to 100 BAU/ ml) and vaccination (800 ng/ml, equivalent to 447 BAU/ml).[8] By the end of September 2022, this survey estimated that 74.2% of 8–11 year-olds and 93.0% of 12–15 year-olds had antibody levels $\geq$ 179 ng/ml.[7]

When applying the same threshold of $\geq$100 BAU to our samples for the period July to September 2022, seropositivity rates in our cohort were similar; 69.9% (60.4% - 79.8%) of 5–11 year-olds and 92% (87.7% - 95.1%) of 12–15 year-olds (see Table 1).

Limitations of our study include the small sample size and the use of residual sera taken from children attending healthcare settings, potentially limiting the representativeness of our cohort,[1] however similar findings from the ONS household survey show that sero-surveillance using SEU samples is a valid, cost-effective and important source to monitor seroprevalence in children.

A growing number of post-implementation studies have reported significant albeit short-term protection against SARS-CoV-2 infection as well as protection against hospitalisation for COVID-19 in vaccinated compared to unvaccinated, previously uninfected children.[9] More recent studies have shown significant protection after primary SARS-CoV-2 infection against reinfection as well as hospitalisation for severe COVID-19, especially after primary omicron infection, with potentially longer protection in previously-infected, vaccinated children.[10] Such data are critical for making decisions on COVID-19 vaccination and boosting in countries where nearly all children have been exposed to SARS-CoV-2 at least once.[9]

Table 1
Population weighted seropositivity estimates of residual paediatric samples using the Roche S assays by age group collected July-September 2022 applying manufacturer recommended threshold of ≥ 1BAU/ml and ≥100 BAU, equivalent to 179 ng/ml used in the ONS survey.

	pos	total	modelled population weighted% positive (95% CrI) ≥ 1BAU/ml	≥100	total	modelled population weighted% ≥ 100 BAU/ml (95% CrI)
Overall	658	669	97.2% (93.7% - 98.9%)	553	669	74.6% (67.6% - 82.3%)
age 1–4	30	34	93.3% (80.4% - 98.6%)	18	34	56.5% (38.5% - 73.7%)
age 5–11	192	196	98.1% (95.1% - 99.4%)	130	196	69.9% (60.4% - 79.8%)
age 12–15	349	351	99.2% (97.8% - 99.8%)	321	351	92% (87.7% - 95.1%)
age 16–17	87	88	98.6% (95.1% - 99.8%)	84	88	95.6% (90% - 98.5%)

In conclusion, in currently the most up-to-date seroprevalence study following multiple omicron waves in England, we estimate that nearly all children aged 1–17 years have been exposed to SARS-CoV-2 irrespective of vaccination status. Our findings have implications for future recommendations for childhood COVID-19 vaccination.

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Changes of pathogen distribution in children with bacterial meningitis before and after the COVID-19 pandemic in Zhengzhou, China

Dear Editor,

In the Journal of infection, Li et al.[1] and Zhou et al.[2] reported the changes in *Streptococcus pneumoniae* and *Haemophilus influenzae* infections in children before and after the Coronavirus disease 2019 (COVID-19) pandemic, which attracted our intense attention and interest. However, no data is available regarding pathogen dis-

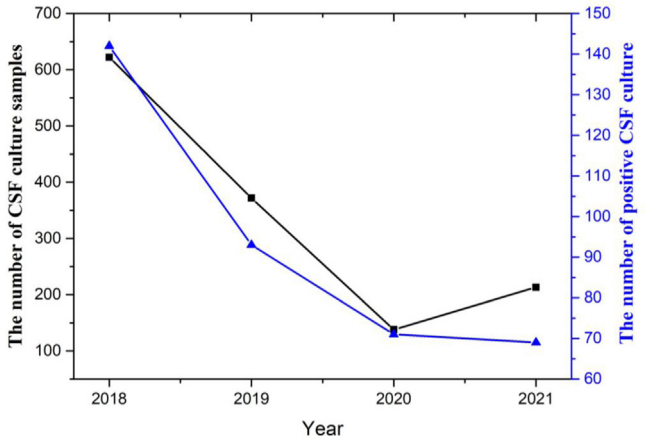

Fig. 1. The number of cerebrospinal fluid (CSF) culture samples, positive CSF culture from 2018 to 2021.

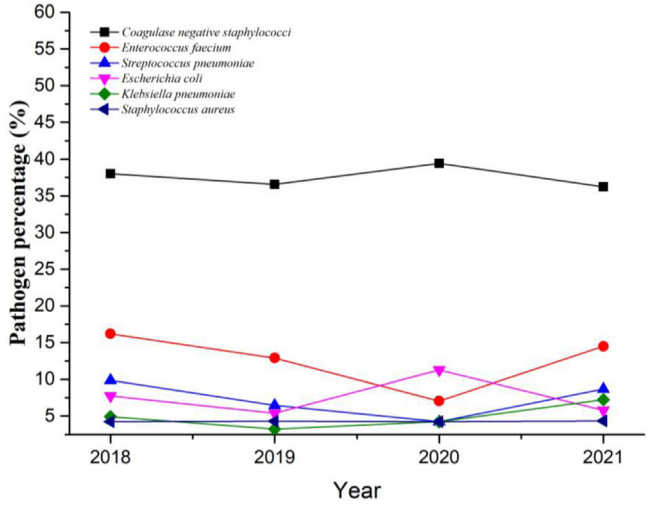

Fig. 2. Percentages of common pathogens in cerebrospinal fluid from 2018 to 2021.

tribution of bacterial meningitis. Here, we present the pathogen distribution of children with bacterial meningitis before and after the COVID-19 pandemic in Zhengzhou, China.

Bacterial meningitis is a common infectious disease of the central nervous system in children. In China, the incidences varies between 20 and 80 cases per 100 000 population[3]. The mortality rate is high, and some survivors have permanent neurological sequelae[4,5]. Bacterial meningitis could be caused by pathogen infection acquired through birth contact, inhalation, nasopharyngeal colonization and blood flow invasion[6]. Common pathogens include *Streptococcus pneumoniae*, Group B *hemolytic streptococcus, Escherichia coli, Enterococcus, Haemophilus influenzae, Staphylococcus aureus*, coagulase negative *staphylococcus, Acinetobacter baumannii, Klebsiella pneumoniae* and *Neisseria meningitidis*[7]. The distribution of pathogens may be different in different regions. Since the outbreak of COVID-19 pandemic in 2019, many countries have implemented strict intervention measures, such as wearing masks, keeping hands clean and keeping social distance, limiting outdoor activities, etc. COVID-19 and related measures have seriously affected people's lifestyle, and may also affect the epidemiology of pathogens. Hence, we assessed the number of children's bacterial meningitis cases and the distribution of pathogens before and after the COVID-19 pandemic, providing a basis for hospital infection prevention and clinical management strategies.

In this study, we compared the number of child cases with bacterial meningitis and the proportion of different pathogens before and after the COVID-19 pandemic in Zhengzhou Children's Hospital to explore the impact of the COVID-19 pandemic on the pathogen distribution of bacterial meningitis in children. The results showed that (Fig. 1) the number of bacterial meningitis in children declined significantly in 2020 (n = 622 in 2018, n = 372 in 2019, n = 138 in 2020 and n = 213 in 2021). However, the number decline could be restriction of movement to the city from town or village. The total positive numbers with reported pathogen were 375 (n = 142 in 2018, n = 93 in 2019, n = 71 in 2020 and n = 69 in 2021). The number of positive cerebrospinal fluid cultures decreased in 2020, the first year of COVID-19 pandemic. However, the total positive rates were not following the decreasing trend.

In addition, we analyzed the distribution of pathogens in cerebrospinal fluid cultures of children with bacterial meningitis before and after the COVID-19 pandemic (Table 1, Fig. 2). The results showed that before and after the COVID-19 pandemic, the pathogenic bacteria in cerebrospinal fluid culture of children with bacterial meningitis were mainly coagulase negative *staphylococcus, Enterococcus faecium, Streptococcus pneumoniae, E. coli, Klebsiella pneumoniae,* and *Staphylococcus aureus*, accounting for more than 65% of the pathogenic microorganisms. Among these pathogens, the percentage of *Enterococcus faecium* and *Streptococcus pneumoniae* decreased from 2018 to 2020, and then increased slightly in 2021. The percentage of *Acinetobacter baumannii* gradually decreased in 2020. However, the percentage of *E. coli* gradually increased in 2020. In addition, *Haemophilus influenzae* and *Stenotrophomonas maltophilia* were detected in 2018 and 2019, but were not detected in 2020 and 2021. Other pathogens kept a relatively stable state.

Our data indicated that the COVID-19 pandemic reduced the number of cases of bacterial meningitis in children and changed the distribution of pathogens in cerebrospinal fluid cultures. With the COVID-19 pandemic under control gradually, people's life return to normal, and the distribution of pathogens also changes. For example, the proportion of *Enterococcus faecium* and *Streptococcus pneumoniae* decreased during the period of strict control of COVID-19 (2020), while *S. maltophilia* and *H. influenzae* were not detected. Therefore, it is necessary to pay attention to the changes of pathogen distribution in children's bacterial meningitis before and after the COVID-19 pandemic.

In conclusion, since the outbreak of COVID-19, the number of children with bacterial meningitis has decreased significantly, and the distribution of pathogens has also changed. Effective and continuous monitoring is of great significance for the prevention and control of bacterial meningitis in children.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Table 1
The pathogen distribution of cerebrospinal fluid cultures in children.

Pathogens	2018 (n = 142)	2019 (n = 93)	2020 (n = 71)	2021 (n = 69)
Coagulase negative *staphylococci*	54(38.03%)	34(36.56%)	28(39.44%)	25(36.23%)
Enterococcus faecium	23(16.20%)	12(12.90%)	5(7.04%)	10(14.49%)
Streptococcus pneumoniae	14(9.86%)	6(6.45%)	3(4.23%)	6(8.70%)
E. coli	11(7.75%)	5(5.38%)	8(11.27%)	4(5.80%)
Klebsiella pneumoniae	7(4.93%)	3(3.23%)	3(4.23%)	5(7.25%)
Staphylococcus aureus	6(4.23%)	4(4.30%)	3(4.23%)	3(4.35%)
Haemophilus influenzae	3(2.11%)	4(4.30%)	0(0.00%)	0(0.00%)
Acinetobacter baumannii	2(1.41%)	6(6.45%)	2(2.82%)	1(1.45%)
Stenotrophomonas maltophilia	1(0.70%)	2(2.15%)	0(0.00%)	0(0.00%)
Pseudomonas aeruginosa	2(1.41%)	2(2.15%)	1(1.41%)	1(1.45%)
Other pathogens	19(13.38%)	15(16.13%)	18(25.35%)	14(20.29%)

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