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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Letters to the Editor

Childhood immunization services accessibility and utilization during the COVID-19 pandemic in Africa

Dear Editor,

According to the WHO, more than 30 million children under five years of age still suffer from vaccine-preventable diseases (VPDs) every year in Africa.[1] Of these, over half a million die from VPDs annually, representing approximately 58% of global VPD-related deaths.[1] Pre-COVID-19, the immunization programs in most African countries were gaining traction with diseases such as polio and maternal and neonatal tetanus nearing eradication and elimination respectively.[1] As such, the consequences of COVID-19 related disruptions in childhood immunization service delivery will be catastrophic. Granted, most countries in Africa are anticipating an increased risk of a resurgence of VPDs that were controlled or eliminated. To anticipate the consequences related to suboptimal control of VPDs in children following the COVID-19 pandemic, there is a need to assess the extent of these disruptions in the region. In this letter, we present preliminary findings of a review aimed at synthesizing the available evidence on the accessibility and utilization of child immunization services (CIS) in Africa during the COVID-19 pandemic period.

PubMed, Google Scholar, and Africa Journals Online (AJOL) databases were searched for relevant studies. Details on the results of title, abstract and full text screening are presented in Fig. 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart. Ten studies met the inclusion criteria (Table 1). Data were independently extracted from eligible studies.

Out of the 10 studies found eligible for data synthesis, seven studies reported decreased utilization of CIS. One study conducted in Ethiopia reported a 0.3% and 4.7% decrease in pentavalent-1 vaccination and pentavalent-3 vaccination during the first 8 months (March – October 2020) of the pandemic, respectively.[2] This study also reported that there was an overall 0.6% decrease in the number of fully vaccinated during the same period compared to the previous 8 months (July 2019 – February 2020) average performance. A multi-country study conducted in eight sub-Saharan African countries reported that child vaccination had the largest decline in several countries.[3] This study shows that there was a drop in the number of children who received the third dose of the pentavalent vaccination for at least 1 month in all countries except DRC. The reported cumulative reduction in child vaccination from March-July 2020 ranged from 2% in Cameroon to 17% in Mali, with the largest reductions recorded in April and May 2020. In Liberia and Somalia, there were no significant differences in numbers of vaccinated children from pre-COVID levels to June 2020.[3] Other studies conducted in Ethiopia[4] and Rwanda[5] reported a significant decrease in CIS during the COVID-19 pandemic.

Apart from a decrease in the rate of attendance and utilization of child immunization services during the COVID-19 pandemic, delivery of these services was also limited due to the prioritization of COVID-19 patients. Out of the 10 included studies in this review, only three[6–8] reported disruptions on the delivery of CIS from the health care providers' perspectives. Based on the findings of a cross-sectional study in Nigeria, there was a slight decline of three percent in the delivery of CIS.[6] A nearly 10% decline in the number of facilities offering CIS services was observed after the lockdown in Nigeria. About 96.0% to 100% of the selected primary health centers (PHCs) offered CIS before lockdown, while during the lockdown, only 85% were offering the services. During the lockdown, the decline in CIS differed by region. After the lockdown, the level of CIS amongst some facilities remained at lockdown levels while at other PHCs it declined from the lockdown levels. On the other hand, another study in Kinshasa in the DRC[7] reported no significant differences between the pre-COVID and during COVID rates of child vaccinations while vaccination services ceased in lockdown for 4 weeks in Kampala, Uganda.[8]

A study conducted in Nigeria[9] investigated challenges in access and satisfaction with reproductive, maternal, newborn, and child health services during the COVID-19 pandemic. The study reported that about 56% of the participants had no challenge accessing reproductive, maternal, neonatal, and child health (RMNCH) services since the COVID-19 outbreak. However, the remaining 44% of the participants reported a least one challenge with accessing RMNCH services.[9] Close to a third could not access service because they could not leave their houses during the lockdown and about 18% could not access service because there was no transportation during the lockdown. About 3% of the participants mentioned other challenges such as the high cost of transportation, fear of contracting COVID-19 since patients with COVID-19 were also receiving care in the facility, and the mandatory use of facemasks at the facility.

The emergence of the novel severe acute respiratory syndrome coronavirus 2 (COVID-19) resulted in an unprecedented public health crisis. Before the rollout of COVID-19 vaccination programs, measures to mitigate the risks of COVID-19 relied on limiting personal contact, hand hygiene, wearing face masks, and movement restrictions. These measures also disrupted health services such as CIS. This review revealed that there was a decrease in utilization of CIS in most sub-Saharan African countries during the COVID-19 pandemic. The decline in immunization rates differed according to the vaccine and the regions of the countries. This review also revealed that the delivery of CIS was disrupted in some countries, while in some CIS completely ceased during the lockdown, yet in others, there were no significant changes. In some countries, the number of facilities offering CIS decreased. Furthermore, this review revealed that some people in some countries had difficulty accessing CIS due to several reasons. Countries in Africa

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Table 1
Characteristics of included studies.

Author, Year	Study Design	Data Sources	Data Collection Tool	Key findings on child immunization during COVID-19
Kassie et al.[4]	Comparative study	Facility health records for each service component.	Checklist extracted from the Ethiopian Demographic and Health Survey,2016 (EDHS, 2016)	Decrease in overall newborn immunisation service utilisation by 28.5% from the pre-COVID-19 numbers to the COVID-19 period.
Balogun et al.[9]	descriptive Cross-sectional study	Clients: women of reproductive age who had just received RMNCH services at the heatlh facilities.	Structured questionnaire used to conduct exit interviews.	Childhood immunisation was the most frequently received service (42.02%) since the COVID-19 outbreak.
Wanyana et al.[5]	cross-sectional quanitative	Provincial level MCH indicators extracted from the Rwanda Health Management Information System (HMIS).	Not specified but assume the data was exported to a spreadsheet then to SPSS for statistical analysis.	Significant decreases noted in the following vaccinations; BCG, polio zero, polio 1, polio 2, diptheria, tetanus, pertussis, hepatitis B and hemophilus influenza (DTP_HepB_Hib) 1, DTP_HepB_Hib 2, pneumococcus 1, pneumococcus 2, rotavirus 1 and rotavirus 2 BCG and polio zero vaccination services utilization decreased in three out of five provinces. Despite the overall decline in service utilization, the utilisation in the Southern Province of measles and rubella (MR) 1 vaccination services increased with variations probably due to the continuation of community-based interventions in the region.
Adelekan, 2021	cross-sectional study	Health workers (head nurses/midwives) in health facilities.	Semi-structured interviewer-administered questionnaire	Slight decline in childhood immunisation during COVID lockdown by about 3% from pre pandemic levels. Further decline in childhood immunisation by about 10% after the lockdown. The changes in childhood immunisation varied with states.
Gebreegziabher et al.[2]	Cross-sectional	Routine health management information system (HMIS) database form the Addis Ababa Health Bureau	HMIS data entered into Redcap database.	There was a decrease in Pentavalent-1 vaccination (0.3%), Pentavalent-3 vaccination (4.7%) and fully vaccination (0.6%) in the first 8 months of the COVID −19 pandemic (March-October 2020) compared to the previous 8 months (July 2019-February 2020) average perfomance. This could have been due to the deisre to reduce COVID-19 spread in health facilities and the repurposing of health workers may have led to hesitation to continue routine immunisation services in health facilities during the early period of the COVID-19 pandemic.

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Table 1 (*continued*)

Author, Year	Study Design	Data Sources	Data Collection Tool	Key findings on child immunization during COVID-19
Pentavalent-3 vaccination recipients began to decrease during January to March 2020 with accelerated reduction in the period April to June 2020 following the national lockdown. The trend in Measles first dose vaccination across quarters remained above the pre-pandemic baseline level, although a slight positive decrement trend was observed during the periods January–March 2020, July–September 2020 and October–December 2020. Accelerated increment was observed in the period April–June 2020 following lockdown. This may have been due to the nationwide home to home campaign that was conducted in June 2020 in Ethiopia				
Pires, 2021 Qualitative data: interviews with HCWs, traditional birth attendants, clients of MCH services. Qulaitative data: interview guide used for recorded interviews In the non-intervention area, there was a 16% decrease in children completely vaccinated fot the same periods all without statistical significance. In non-intervention area there was a decrease of 16% in the number of children completely vaccinated all without any statistical significance. Clients and TBAs indicated that they continued to attend health services, mostly to get vaccinations for their childern as vaccines were no longer available through community outreach programs.	Mixed-methods research, descriptive, cross-sectional, retrospective Quantitative data: Microsoft Excel There was a 20% decline in childhood vaccinations and an 18% decrease in children completely vaccinated in the intervention area during the three months of COVID-19 pandemic in 2020 when compared to the same period in 2019 all without statistical significance.	Quantitative data: facility monthly official statistics and MCH statistics department.		

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Table 1 (*continued*)

Author, Year	Study Design	Data Sources	Data Collection Tool	Key findings on child immunization during COVID-19
Shapira et al.[3]	interrupted time series design	Panel data from monthly service volumes from health facilities reported into the national HMIS.	Not specified	Child vaccination had the largest declines in several countries as evidenced by the drop for at least 1 month in all countries except DRC in the number of children who received the thrid dose of the pentavalent.
Cumulative reduction in child vaccination in the March-July 2020 period ranged from 2% in cameroon to 17% in Mali with the largest disruptions recorded in April and May. In countries like Liberia and Somalia, there were no significant diffrences in numbers of vaccinated childern from pre-COVID levels byu June 2020. The number of BCG vaccinations adminstered showed a similar pattern but with smaller reductions on average,, with three of seven countries reporting a significant shortfall in gtotal BCG vaccinations delivered. The model does not observe subsequent significant positive increases that would suggecst a catch-up from earlier vaccination reductions in five of the eight countries where the overall 5-month decline is significantly below zero. Vaccination services, relying to a larger extent on outreach campaigns relative to other services, may likely to have been more impacted by activity restrictions introduced to mitigate the virus's spread.				
Shikuku, 2020	cross – sectional	Facility level data extracted from the Kenya Health Information System (KHIS)	Microsoft Excel Spreadsheet	There were no significant changes in the mean total hospital attendance per month for immunization services during a 4-month period (March – June 2019) pre-COVID-19 compared with during the equivalent 4-month period peri–COVID-19 pandemic.
Trends across month showed a reduction in hospital attendance in April 2020 for all the hospital services followed by a sustained increase in May and June 2020 for pentavalent immunization compared with the similar equivalent pre-COVID-19 period				

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Table 1 (*continued*)

Author, Year	Study Design	Data Sources	Data Collection Tool	Key findings on child immunization during COVID-19
Burt, 2021 Since the lifting of the lockdown, there have been a significant reduction (960 fewer) in monthly attendances . There was no change in the rate of children receiving Bacille Calmette-Guerin (BCG) at birth, oral polio, pneumococcal or rotavirus vaccines since the end of lockdown, although fewer children were reported to be attending the immunization clinic. The increase in the rate of measles vaccinations attributable to a catch-up campaign after a long stock out.	Observational study	Facility level electronic medical records (EMR) from Kawempe district, Kampala	Microsoft Excel Spreadsheet	All antenatal and vaccination services ceased in lockdown for 4 weeks.
Hategeka[7] The Gombe health zone had few facilities ($n = 3$) that reported vaccination consistently during the study period, subgroup analyses to undestand the effect of the lockdown policy on vaccinations in the zone. The fact that vaccinations were not affected likely to be explained by the fact that most vaccinations are delivered at health centers which were not affected by lockdowns as comapred to hospitals.	time series	Facility level Health Management Information System (HMIS)	Not specified	Vaccinations were largely not affected by COVID-19 in Kinshasa

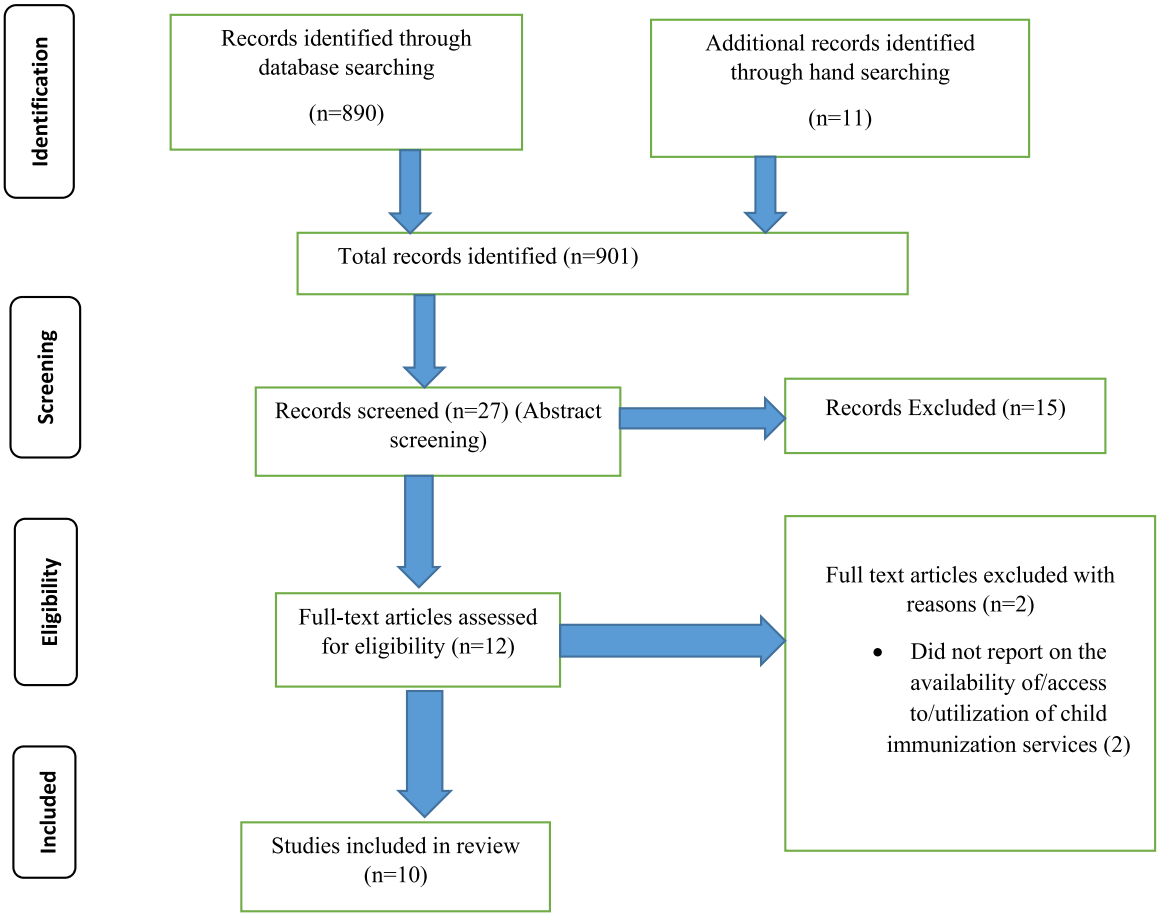

Fig. 1. PRISMA flow diagram.

should therefore monitor childhood immunization trends during the COVID-19 pandemic so that they can implement catch-up vaccination activities for those who would have missed their doses as soon as is practically possible.

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Declaration of Competing Interest

None declared.

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None

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Tafadzwa Dzinamarira*
ICAP at Columbia University, Kigali, Rwanda

Enos Moyo, Perseverance Moyo
Oshakati Medical Centre, Oshakati, Namibia

Gashema Pierre
College of Medicine and Health Sciences, University of Rwanda, Kigali, Rwanda

Etienne Mpabuka
ICAP at Columbia University, Kigali, Rwanda

Morris Kahere, Nigel Tungwarara, Itai Chitungo, Grant Murewanhema
College of Medicine and Health Sciences, University of Zimbabwe, Harare, Zimbabwe

Godfrey Musuka
ICAP at Columbia University, Harare, Zimbabwe

*Corresponding author.
E-mail address: td2581@cumc.columbia.edu (T. Dzinamarira)

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Study on the clinical indications for plasma as an alternative to the bronchoalveolar lavage fluid metagenomic next-generation sequencing test to detect consistent pathogens for septic patients in intensive care units

Dear Editor,

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection,[1] rapid and accurate pathogen diagnosis is essential. A recent paper by Yin and colleagues highlights the rapid and high sensitivity of plasma metagenomic next-generation sequencing (mNGS) for pathogen diagnosis in sepsis.[2] However, how the pathogen detected from plasma mcfDNA represents local infection remains unknown, and whether any clinical metrics can be used for optimal blood sampling time for pathogen diagnosis in septic patients remains unclear.

Here, we performed a prospective study to determine the pathogenic consistency of plasma and local body fluid sample mNGS from septic patients, and to identify clinical indications for plasma mNGS as an alternative to the bronchoalveolar lavage fluid (BALF) mNGS test in sepsis. Severely infected septic patients hospitalized in Shenzhen Second People's Hospital were enrolled from May 2020 to June 2022.

Plasma and local body fluid samples were collected and sent for both conventional microbiology testing (CMT) and mNGS tesing (details in Supplementary Materials). Sepsis diagnoses according to the guidelines of the International Guidelines for Management of Sepsis and Septic Shock (2016) were screened.[3] Discharge diagnosis was used as the gold standard to compare the pathogenic consistency of plasma sample mNGS and local body fluid sample mNGS in septic patients. Clinical indications for plasma mNGS instead of BALF mNGS to detect consistent pathogens in septic patients were determined by constructing a predictive model using LASSO (details in Supplementary Materials). The study schematic workflow was shown in Fig. S1.

Briefly, 278 patients were screened, and 143 patients were enrolled with 458 mNGS tests of plasma, BALF, pleural fluid, ascites, cerebrospinal fluid (CSF) and wound samples. The baseline characteristics of the participants are described in Table S1. mNGS as a new detection method in recent years, offers several advantages that CMT cannot provide. In this study, mNGS performed better than CMT in terms of the agreement rate, specificity and sensitivity (96% vs 52%, 100 vs 92%, 96% vs 52%, Fig. 1A). This result was consistent with several studies in mNGS for sepsis patients.[2,4] Of note, limited by the lack of sampling equipment and sampling professionals, it is difficult to collect suspected local infection samples in early clinical practice.[5] Therefore, it's meaningful to explore the pathogenic consistency of plasma samples and local body fluid samples from septic patients. The consistency rate of septic patient plasma with local body fluid samples was higher than 75%, the rate of plasma with BALF samples was 75.21%, and that with CSF

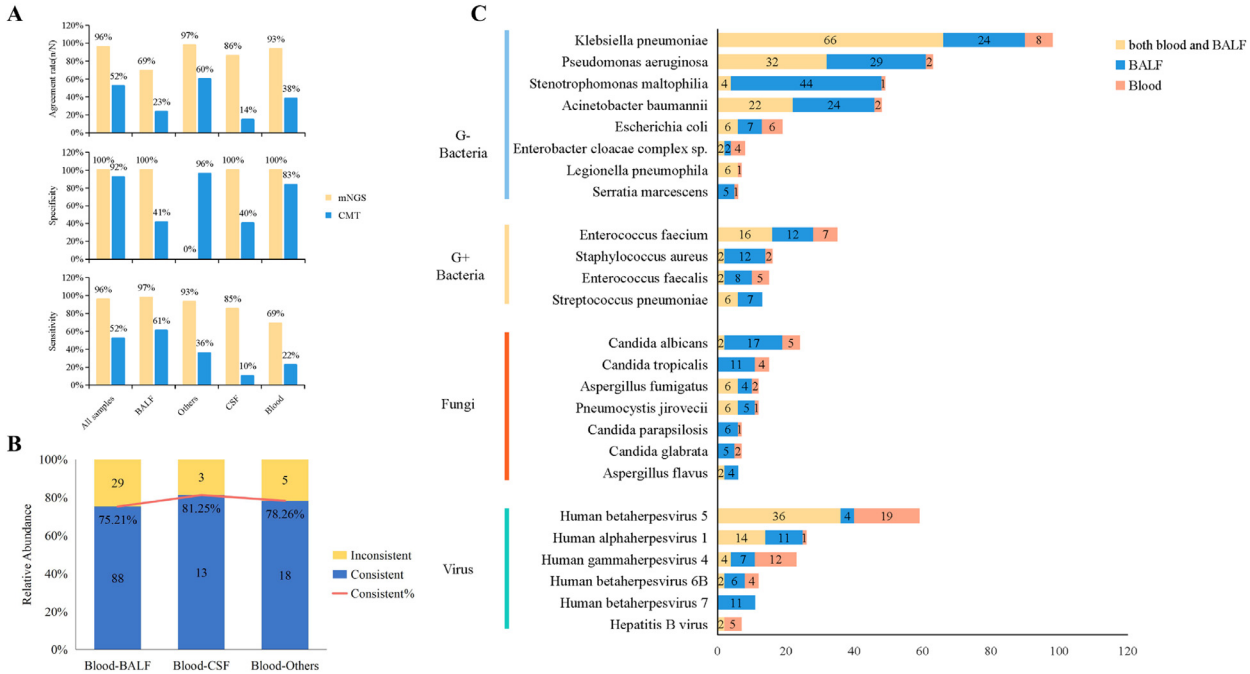

Fig. 1. Analysis of pathogen concordance of plasma and local body fluid samples mNGS. (A) The agreement rate, specificity and sensitivity of mNGS and CMT in all samples, BALF, others, CSF and blood sample types. (B) Pathogen consistency of plasma and local body fluid samples mNGS, including plasma and BALF, plasma and CSF, plasma and other local body fluid samples. (C) The top 25 detected pathogens in plasma and BALF samples.

samples was 81.25% (Fig. 1B). Excluding viruses, the top 3 consistently detected pathogens in plasma and BALF samples were *Klebsiella pneumoniae* (n = 66), *Pseudomonas aeruginosa* (n = 32) and *Acinetobacter baumannii* (n = 22), which are also the most common pathogens in ICU sepsis in mainland China.[6] The results also showed a high consistency in detection in bacteria and viruses (Fig. 1C). Moreover, for fucus on all pathogens detected in septic patients, the details of the detected pathogens among plasma and different local body fluid paired samples were shown in Tables S2-S4. A CDC's report showed that *coagulase-negative staphylococci, Candida* spp., *Staphylococcus aureus, Klebsiella* spp., *Enterococcus faecalis*, *Escherichia coli, Pseudomonas aeruginosa* and *Acinetobacter* spp. are the most frequently reported pathogens in hospital ICUs.[7] In this work, we found that *Candida spp*., *Enterococcus faecium, Pseudomonas* and *Acinetobacter spp*. were most frequently detected, which is consistent with the CDC's report. Furthermore, *Klebsiella pneumoniae, Pseudomonas aeruginosa, Acinetobacter baumannii* and *Stenotrophomonas maltophilia* were also detected frequently. These common pathogens are consistent with the 2021 CHINET report (http://www.chinets.com/).

Due to the high consistency of pathogens detected from plasma and BALF samples, it is critical to find the timing of plasma mNGS as an alternative to BALF mNGS to detect consistent pathogens. We split the paired plasma and BALF samples into two groups according to the mNGS results: plasma-negative BALF-positive group and plasma-positive BALF-positive group (details in Supplementary Materials). Then, we constructed a LASSO model using 56 clinical indicators (Table S5) and screened 7 indicators with weighted contributions including PaO_2/FiO_2, LAC, pH, ALB, RBC, GLB and TBIL (Fig. 2A). In the training cohort (n = 89), the AUC of the model to predict pathogens detected from plasma mNGS as an alternative to BALF mNGS was 0.757, with a specificity, sensitivity, PPV, NPV and accuracy of 50%, 82%, 82%, 50% and 73%, respectively, at a cutoff of 0.914 (Fig. 2B). In the testing cohort (n = 28), the AUC was 0.731, specificity and sensitivity were 71% and 76%, PPV and NPV were 89% and 50%, and the accuracy was 75% (Fig. 2C). A test result may

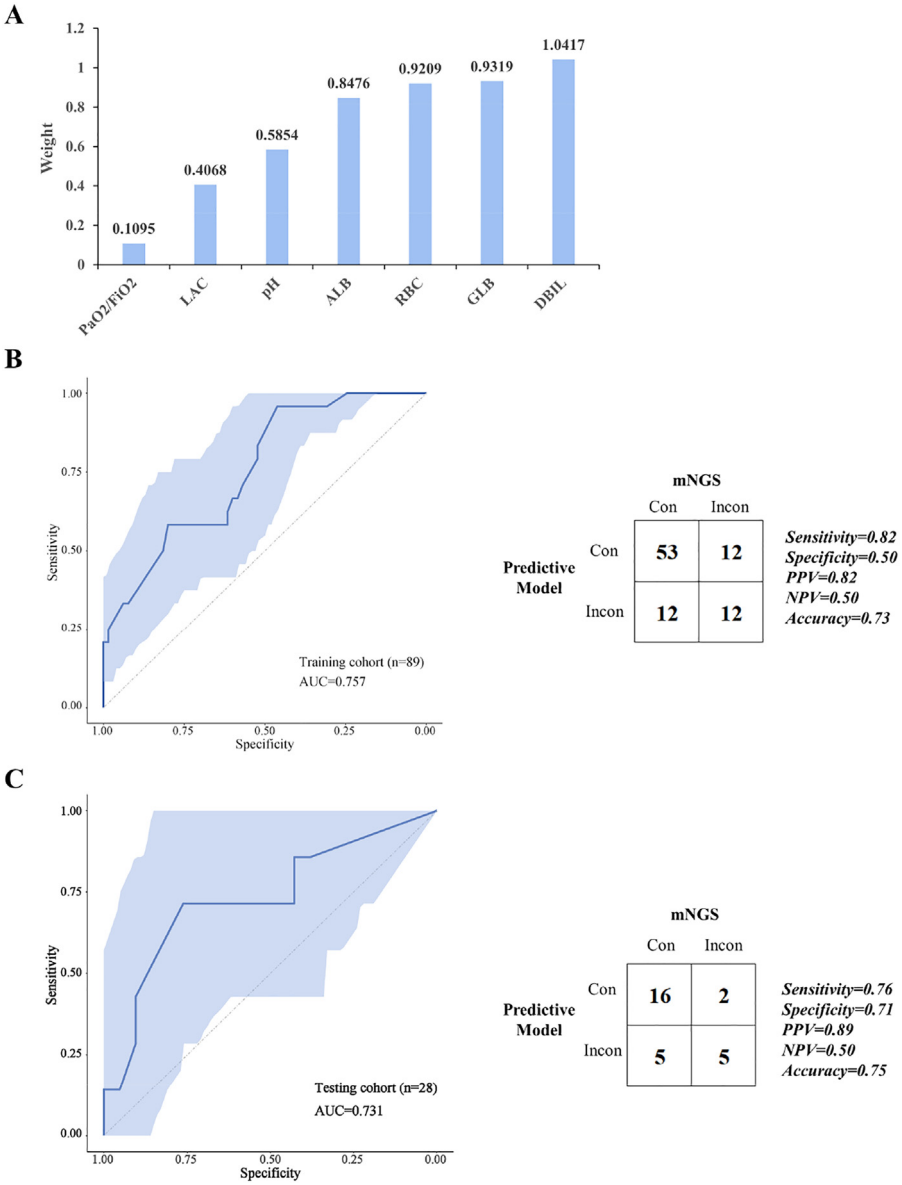

Fig. 2. Clinical indication for plasma mNGS alternative to BALF mNGS. (A) Seven filtered features and their weights that contributed to the predictive model using LASSO. (B) ROC curves and predictive performance of the predictive model for septic patients in the training cohort (n = 89). (C) ROC curves and predictive performance of the predictive model for septic patients in the testing cohort (n = 28).

be considered clinically impactful or clinically relevant if the treating physician makes a management decision based on that result.[8] When the cutoff is ≥ 0.914, the plasma sample is likely to detect pathogens that are consistent with the BALF sample. For example, when it is difficult to collect samples from the primary infection site, plasma samples can be used instead. If cutoff < 0.914, samples from the primary infection site should be collected as much as possible, and the probability of detecting pathogens consistent with the lesion samples in plasma samples is low. If conditions permit, it is better to collect two samples as much as possible. If limited by economic conditions, only one of them can be selected, it is recommended to give priority to samples from local infections.

Nevertheless, there are some deficiencies in our study. First, both CMT and mNGS lack unified standards to identify whether detected pathogenic microorganisms are derived from infection, colonization, or contamination. Second, for practical applications of this technique, the subjective judgment of clinicians is still needed, which is highly dependent on clinical experience. Finally, this was a single-center study, multiple regions and larger sample sizes will make the predictive model more accurate. Overall, our results demonstrate the clinical indication to detect consistent pathogens for plasma mNGS alternative to BALF mNGS in ICU septic patients, which will help clinicians use mNGS more flexibly and accurately to diagnose infections in sepsis.

Ethical approval

Ethical approval for this study was obtained from the Committee on the Ethics of Medicine, Shenzhen Second People's Hospital (KS20190521004-FS2019052906-GZ2021).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Declaration of Competing Interest

The authors declare that they have no competing interests.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2022.07.016.

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Ying Li[1], Gui-Yun Li[1]
Department of Critical Care Medicine, The First Affiliated Hospital of Shenzhen University, Shenzhen Second People's Hospital, Shenzhen, China

Dong-Xu Han[1]
Genskey Medical Technology Co., Ltd, Bohui Innovation, No.9, Life Science Park Road, Zhongguancun Life Science Park Changping, Beijing, China

Yong-Wen Feng, Xiao-Min Liang, Di Ren
Department of Critical Care Medicine, The First Affiliated Hospital of Shenzhen University, Shenzhen Second People's Hospital, Shenzhen, China

Li-Juan Yuan
Genskey Medical Technology Co., Ltd, Bohui Innovation, No.9, Life Science Park Road, Zhongguancun Life Science Park Changping, Beijing, China

Lin Zhang, Xin-Ke Meng, Jia-Ze Wang
Department of Critical Care Medicine, The First Affiliated Hospital of Shenzhen University, Shenzhen Second People's Hospital, Shenzhen, China

Yu Ye
Department of Neurosurgery, Shenzhen Long-gang Central Hospital, Shenzhen, China

Jian-Peng Gao
Genskey Medical Technology Co., Ltd, Bohui Innovation, No.9, Life Science Park Road, Zhongguancun Life Science Park Changping, Beijing, China

Sha Wen, Yan-Hong Chen, Xi-Si He, Zhi-Ye Zou
Department of Critical Care Medicine, The First Affiliated Hospital of Shenzhen University, Shenzhen Second People's Hospital, Shenzhen, China

Peng Han
Genskey Medical Technology Co., Ltd, Bohui Innovation, No.9, Life Science Park Road, Zhongguancun Life Science Park Changping, Beijing, China

Xiao-Hong Li
Department of Critical Care Medicine, The First Affiliated Hospital of Shenzhen University, Shenzhen Second People's Hospital, Shenzhen, China

Hao-Bo Tu
Genskey Medical Technology Co., Ltd, Bohui Innovation, No.9, Life Science Park Road, Zhongguancun Life Science Park Changping, Beijing, China

Kai Lai, Mei Yang
Department of Critical Care Medicine, The First Affiliated Hospital of Shenzhen University, Shenzhen Second People's Hospital, Shenzhen, China

Guan-Hua Rao*

Genskey Medical Technology Co., Ltd, Bohui Innovation, No.9, Life Science Park Road, Zhongguancun Life Science Park Changping, Beijing, China

Shui-Qing Gui*
Department of Critical Care Medicine, The First Affiliated Hospital of Shenzhen University, Shenzhen Second People's Hospital, Shenzhen, China

*Corresponding authors.
E-mail addresses: gh.rao@genskey.com (G.-H. Rao), 18782198@qq.com (S.-Q. Gui)

[1] These authors contributed equally to this work.
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Prospective surveillance of human adenovirus in acute respiratory infections reveals epidemiological features and the disappearance of species B during the COVID-19 pandemic in Beijing, China

Dear Editor,

Human adenovirus (HAdV) is an important pathogen in acute respiratory tract infections(ARTIs).[1] In this Journal, both Poole[2] and Lumley[3] reported significant variation in HAdV prevalence during the COVID-19 pandemic. However, the epidemiology of HAdV remains incompletely understood. We conducted a multiple-center prospective surveillance, including ARTI patients of all age categories admitted to 35 sentinel hospitals situated across all 16 districts of Beijing, with the aim of understanding contemporary epidemiological characteristics of HAdV infections in Beijing, China.

A total of 47,338 ARTIs cases were enrolled from 2015 to 2021, including 13,927 children (<18 years old), 32,226 adults (≥18 years old), 1,185 without age information, the median age was 38 years (IQR, 9–68). HAdV was detected in 581 cases, including 337 children, 240 adults, 4 individuals without age information, with a median age of 9 years (IQR, 4–30).

The overall HAdV detection rate was 1.23% (581/47,338). The detection rates varied yearly as follows: 1.40% (93/6,643) in 2015, 1.48% (111/7,522) in 2016, 1.22% (93/7,650) in 2017, 1.49% (117/7,839) in 2018, 1.73% (135/7,806) in 2019, 0.56% (22/3,961) in 2020 and 0.17% (10/5,917) in 2021. The entire HAdV epidemic period could be divided into three stages: epidemic period as period 1 (January 1, 2015–December 31, 2017), high epidemic period as period 2 (January 1, 2018–January 31, 2020), and COVID-19 pandemic period as period 3 (February 1, 2020–December 31, 2021) (Fig. 1). The HAdV-positive rates of period 1, period 2, and period 3 were 1.36% (297/21,815), 1.65% (269/16,333), and 0.16% (15/9,190), respectively, with significantly increasing in period 2 ($p < 0.05$) and dropping in period 3 ($p < 0.001$) (Fig. 1a). It was consistent with the reports that public health measures against COVID-19 had a great impact on the prevention of HAdV and other respiratory pathogens.[2,4,5]

HAdV-positive cases were detected in all age groups. The highest detection rate was observed in the age group of 1–4 years old (2.79%, 177/6,354), followed by the age group of 15–19 years old (2.70%, 36/1,331), 5–9 years old (2.46%, 97/3,941), 10–14 years old (2.17%, 31/1,427), and 20–24 years old (2.02%, 36/1,779). The detection rates decreased dramatically to a low level among the population aged 30 years or older (Fig. 1b). During the COVID-19 pandemic, a total of 15 HAdV-positive cases were detected, including 10 cases aged 1–4 years old. The remaining age groups were almost free of infection. This suggests that HAdV infection in children under 5 years old, except for RSV, is a crucial public health problem that should be taken seriously.

Eleven HAdV types were successfully identified by sequencing the hexon and fiber gene[6] including HAdV-3 (49.74%, 289/581), HAdV-7 (14.29%, 83/581), HAdV-2 (8.78%, 51/581), HAdV-1 (6.71%, 39/581), HAdV-4 (6.54%, 38/581), HAdV-55 (5.51%, 32/581), HAdV-5 (2.58%, 15/581), HAdV-57 (1.03%, 6/581), HAdV-14 (0.86%, 5/581), HAdV-21 (0.69%, 4/581), and HAdV-41 (0.17%, 1/581).

The prevalence of HAdV types varied during three periods. In period 1 and period 2, HAdV-B (3, 7, 14, 21, and 55), HAdV-C (1, 2, 5, and 57), and HAdV-E (4) were all detected. Among them, HAdV-B was the dominant species. In period 3, HAdV-B was undetected, while HAdV-C and HAdV-E remained at a low prevalence (Fig. 2a). This is the first to describe the disappearance of HAdV-B during the COVID-19 pandemic, which had important public health implications. Given that HAdV-B was the most common type of ARTIs in Asia, which had caused outbreaks and severe pneumonia,[7] it was necessary to maintain continuous surveillance in order to keep on alert for the reemergence of HAdV-B in the future.

The prevalence of HAdV-B varied significantly in period 1 and period 2 (0.99% [216/21,815] vs. 1.21% [197/16,333]; $p < 0.05$) (Fig. 2b). HAdV-3 and HAdV-7 were the dominant type. Compared to period 1, HAdV-3 still remained the most dominant type, with no significant variance in period 2 (0.73% [160/21,815] vs. 0.79% [129/16,333]; $p = 0.551$). However, the detection rate of HAdV-7 increased significantly in period 2 (0.14% [31/21,815] vs. 0.32% [52/16,333]; $p < 0.001$). The detection rates of other types of HAdV-B in period 2 remained at a similar level.

The prevalence of HAdV-C did not vary significantly among the three periods (0.26% [56/21,815] vs. 0.25% [41/16,333] vs. 0.15% [14/9,190]; $p = 0.192$) (Fig. 2c). HAdV-C could cause an asymptomatic persistent infection after initial infection.[8] In period 3, the continued prevalence of HAdV-C may be associated with the persistent infection in children. Species E (HAdV-4) increased significantly in period 2(0.07% [15/21,815] vs. 1.21% [197/16,333]; $p < 0.05$) (Fig. 2d). Only one sample of HAdV-4 was detected in period 3. These observations suggested that the rise of HAdV-7 and HAdV-4 led to the high prevalence of HAdV in period 2. HAdV-7 was associated with more severe disease than other HAdV types, and the emergence of HAdV-7 often led to HAdV outbreaks.[9] HAdV-4 has been known to circulate sporadically, while increasing HAdV-4 infections have been found in many countries.[6] The prevalence changes of these HAdV types emphasize the need to closely monitor type in HAdV for early warning and intervention.

The most common clinical manifestation of the HAdV-positive patients was moderate or high fever (≥38 °C, 96.68%), followed by cough (72.93%), sore throat (48.25%), sputum production (44.75%), and rhinorrhoea (24.86%). These clinical characteristics were helpful to differential diagnosis with infections of other respiratory pathogens. We also found HAdV-7 and HAdV-4 had the highest prevalence in severe community-acquired pneumonia (SCAP) in 18–24-year-old patients. Notably, SCAP cases were most commonly observed at children (<1 years old) and the elderly (≥60 years old), which was similar to respiratory syncytical virus.[10] SCAP cases more often experienced respiratory failure, liver damage and kidney failure ($p < 0.05$).

In summary, children were the main population for HAdV infections in Beijing. The elevated prevalence of HAdV in 2018 and 2019 was probably linked to the rise of HAdV-7 and HAdV-

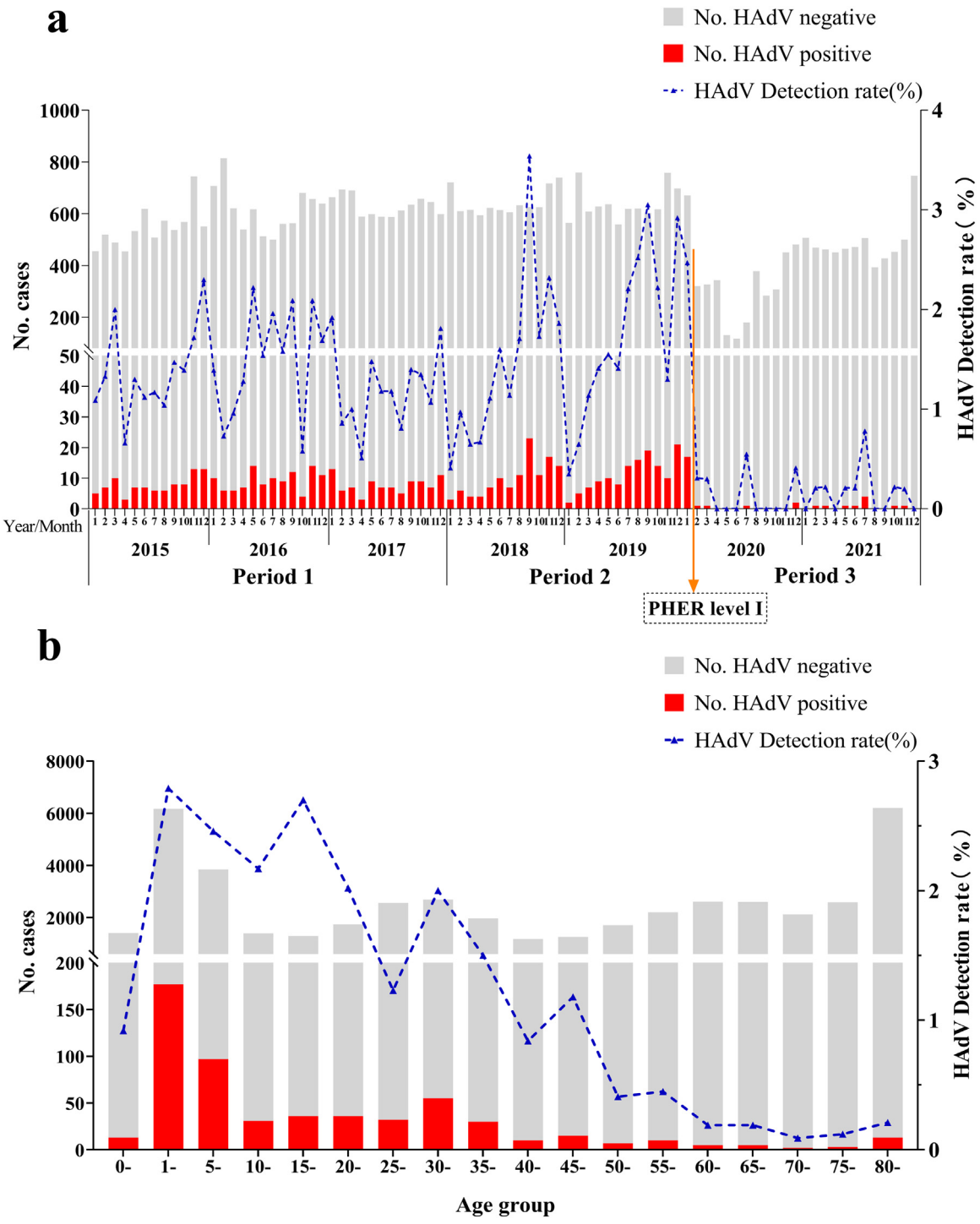

Fig. 1. The prevalence and distribution of HAdV in population, Beijing, 2015–2021. a, the number of HAdV-positive cases and detection rate among patients with ARTIs by month and period, Beijing, 2015–2021. Note: The first COVID-19 case was identified in Beijing on January 19, 2020, and a Level I Public Health Emergency Response (PHER) was implemented on January 24, 2020. Therefore, February 1, 2020, was used as the cutoff point to differentiate the COVID-19 epidemic period. b, the distribution of HAdV infection by age in Beijing, 2015–2021.

4. During the COVID-19 epidemic, the prevalence of HAdV significantly decreased and the long-term dominant HAdV-B disappeared. Continuous, population-wide molecular epidemiological surveillance is essential for the prevention and control of HAdV.

Declaration of Competing Interest

The authors report no conflict of interest.

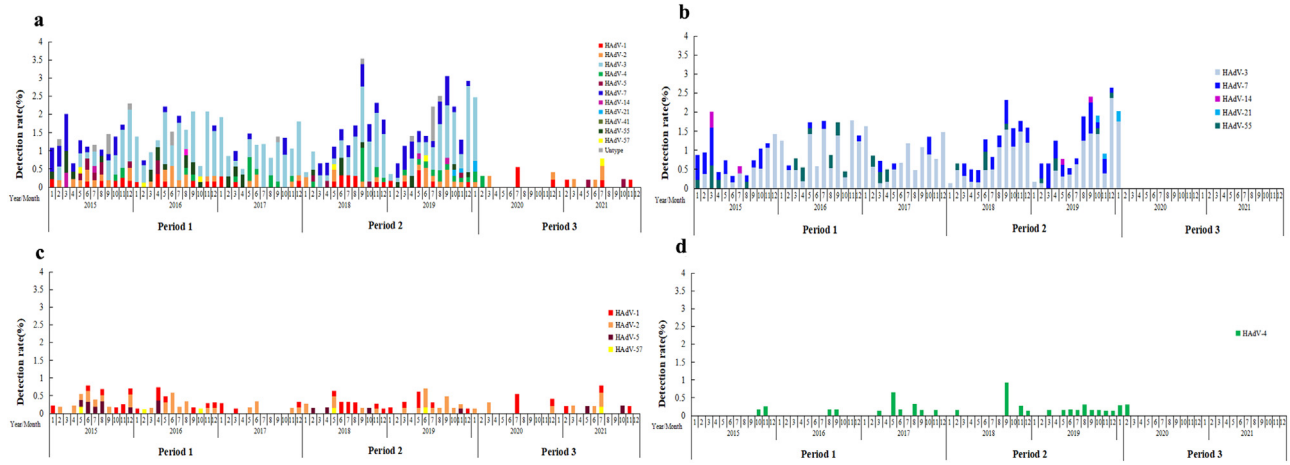

Fig. 2. The prevalence of different HAdV types by month and period, Beijing, 2015–2021. a, The prevalence of HAdV type. b, The prevalence of HAdV-B. c, The prevalence of HAdV-C. d, The prevalence of HAdV-E.

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Maozhong Li
Beijing Center for Disease Control and Prevention/Beijing Academy for Preventive Medicine/Beijing Institute of Tuberculosis Control Research and Prevention, Institute for immunization and prevention, No.16 Hepingli Middle Street, Dongcheng, Beijing 100013, China

Qin Luo
Beijing Center for Disease Control and Prevention/Beijing Academy for Preventive Medicine/Beijing Institute of Tuberculosis Control Research and Prevention, Institute for immunization and prevention, No.16 Hepingli Middle Street, Dongcheng, Beijing 100013, China
College of Public Health, Capital Medical University, Beijing 100069, China

Cheng Gong, Ai Hua Li, Mei Dong, Herun Zhang, Xue Wang, Ming Luo, Yiting Wang, Hui Xie, Lu Kang
Beijing Center for Disease Control and Prevention/Beijing Academy for Preventive Medicine/Beijing Institute of Tuberculosis Control Research and Prevention, Institute for immunization and prevention, No.16 Hepingli Middle Street, Dongcheng, Beijing 100013, China

Qi Huang
Beijing Center for Disease Control and Prevention/Beijing Academy for Preventive Medicine/Beijing Institute of Tuberculosis Control Research and Prevention, Institute for immunization and prevention, No.16 Hepingli Middle Street, Dongcheng, Beijing 100013, China
College of Public Health, Capital Medical University, Beijing 100069, China

Lili Ren**
National Health Commission of the People's Republic of China Key Laboratory of Systems Biology of Pathogens and Christophe Mérieux Laboratory, Institute of Pathogen Biology, Chinese Academy of Medical Sciences & Peking Union Medical College, No.9 Dong Dan San Tiao, Dongcheng, Beijing 100730, China

Key Laboratory of Respiratory Disease Pathogenomics, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, PR China

Fang Huang*
Beijing Center for Disease Control and Prevention/Beijing Academy for Preventive Medicine/Beijing Institute of Tuberculosis Control Research and Prevention, Institute for immunization and prevention, No.16 Hepingli Middle Street, Dongcheng, Beijing 100013, China
College of Public Health, Capital Medical University, Beijing 100069, China

*Correspondence author at: Beijing Center for Disease Control and Prevention/Beijing Academy for Preventive Medicine/Beijing Institute of Tuberculosis Control Research and Prevention, Institute for immunization and prevention, No.16 Hepingli Middle Street, Dongcheng, Beijing 100013, China. **Correspondence author at: National Health Commission of the People's Republic of China Key Laboratory of Systems Biology of Pathogens and Christophe Mérieux Laboratory, Institute of Pathogen Biology, Chinese Academy of Medical Sciences & Peking Union Medical College, No.9 Dong Dan San Tiao, Dongcheng, Beijing 100730, China.
E-mail addresses: renliliipb@163.com (L. Ren), hhffxdd@126.com (F. Huang)

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Poor vaccine responsiveness towards third-dose mRNA vaccine of COVID-19 in Japanese older people

Dear Editor,

The older population is the main victim of the coronavirus disease 2019 (COVID-19) pandemic.[1] Many studies have shown that residents at long-term care facilities (LTCF) have been greatly affected by COVID-19,[2] indicating a requirement of a comprehensive strategy to protect the elderly for normalization of social functions. Here, we aimed to assess the immune response after a third-dose mRNA vaccine booster among older Japanese people. Our results suggest an importance of antibody titter to establish a treatment priority in the vulnerable population.

To investigate the antibody titres against SARS-CoV-2 among older individuals, 23 facilities (12 day-care centres [DCC] and 11 LTCFs) responded to our call to participate. Each participant received either two doses of BNT162b2 or mRNA-1273 vaccines at least six months prior. For comparing the titres with those of younger generations, we collected data from the nursing care staff at the DCCs and LTCFs. Additionally, our previous data of healthcare workers was used.[3] The Mokobio SARS-CoV-2 IgM & IgG Quantum Dot immunoassay (Mokobio Biotechnology R&D centre Inc., MD, USA) was used for the point-of-care fingertip whole blood sampling test. In this study, we defined non-responders as those whose post-booster antibody titres were less than 1000 U/mL at any test time after vaccination (<3 months). This was based on neutralizing activity against the wild-type virus and immune evasion of the Omicron variant as explained in our previous literature.[3] Post-booster antibody titres were analysed by stratifying according to age, sex, living status, and vaccine type. A logistic regression model was used for the multivariate analysis. The institutional review board of Okayama University Hospital approved this study (No. 2112–044), and written informed consent was obtained from all the participants.

Data of 1046 older adults were eligible for the analysis. The median age of the population was 86 years, with a female predominance (66.3%). Among the participants, 67.2% resided at LTCFs. The proportion of receiving vaccine boosters after two doses of BNT162b2 (59.2%) was higher than that of mRNA-1273 (40.2%) vaccine administration. Then, we incorporated data of nursing care staff working at DCCs and LTCFs, and the healthcare workers at hospitals to demonstrate the distribution of post-booster antibody titres by age as compared with COVID-19 survivors at the facility with the cluster.[3] Of the 1771 people, we excluded those examined 1 to 9 days after the booster dose ($N = 415$), and a total of 1356 individuals were analysed.

Antibody titres were widely distributed in each age group (**Fig. 1**). The invalid (too high for measurement) testing rate was over 10% in those aged <60 years. With age, it decreased to 5.4% in septuagenarians, 4.7% in octogenarians, and 3.2% in nonagenarians. Based on the finding, we regarded those with antibody titres less than 250 U/mL as poor responders, which corresponds to twofold the LD50 concentration level *in vitro*. The number and proportion of non-responders increased with age: 2 (0.9%) septuagenarians, 23 (5.4%) octogenarians, and 29 (9.4%) nonagenarians. Moreover, the antibody titers of COVID-19 survivors one month after the cluster event was apparently higher than those after the post third-dose vaccination. Despite the extremely high age of these groups (median ages of those two times-vaccinated and three times-vaccinated were 86.5 years and 88 years, respectively), the invalid testing rates were 39.3% and 47.1%, respectively, and no non-responders were detected.

Further, we investigated the explanatory factors for third-dose vaccine responsiveness among the older population (**Table 1**). To exclude data derived from those shortly after the booster vaccination, we included only data from 10 days after vaccination ($N = 982$). The proportions of responders aged <70 years (81.4%), 70–79 years (septuagenarians, 80.5%), 80–89 years (octogenarians, 72.7%), and ≥90 years (over nonagenarians, 66.3%) decreased with age. Univariate analysis suggested that men, commuters to DCC, and ≥50 days after the booster were significantly associated with the vaccine responsiveness. A result of the multivariate analysis did not show significant differences in age group, sex, and living status; while, the third-dose vaccination with mRNA-1273 was associated with a significantly higher response rate than BNT162b2 (75.8% vs. 70.6%: odds ratio [95% CI]; 1.37 [1.00–1.89]). In comparison with the group of the 10–19 days period, the vaccine response rate in those with a longer period after vaccination (≥50 days) was significantly lower (77.2% vs. 63.0%: odds ratio [95% CI]; 0.55 [0.33–0.92])

Older people are at increased risk of developing severe COVID-19. According to a population-based seroprevalence study in Switzerland, the fatality risk for those aged ≥65 years was approximately 5.6%, significantly higher than that of the younger generation (<0.001%) aged under 50 years.[4] In the United States, the number of deaths among people aged ≥ 65 years is presumably 97 times higher than that among people aged 18–29 years.[5] This can be explained by immunosenescence and multimorbidity of underlying diseases among the elderly.[6,7] People age not only physically but also immunologically, and they lose the capability to respond to foreign antigens.[6] Experts in immune aging indicate that the oldest old (nonagenarians and centenarians) population can be classified into high-performing and low-performing individuals based on genetic variants that advantageously function for healthy aging.[8,9] Notably, there were apparent non-responders to

Table 1
Univariate and multivariate analysis for the third-dose vaccine responsiveness among older population at long-term care facilities and day-care centers.

Variables	No.	Non-responders ($N = 268$, 27.3%)(FWT <1000 U/mL)		Responders($N = 714$, 72.7%)(FWT >1000 U/mL)	Univariate analysis(vs. Poor responders)p value	Multivariate analysis(vs. Poor responders)	
		Poor responders(<250 U/mL)	Weak responders(250 to <1000 U/mL)			OR [95% CI]	p value
Age							
<70 years	43	0	8 (18.6%)	35 (81.4%)	*Reference*	*Reference*	
70–79 years	205	2 (1.0%)	38 (18.5%)	165 (80.5%)	1	0.95 [0.41–2.22]	0.91
80–89 years	425	23 (5.4%)	93 (21.9%)	309 (72.7%)	0.28	0.63 [0.28–1.42]	0.26
≥90 years	309	29 (9.4%)	75 (24.3%)	205 (66.3%)	0.054	0.52 [0.23–1.20]	0.13
Sex							
Men	320	13 (4.1%)	58 (18.1%)	249 (77.8%)	0.012	*Reference*	
Women	661	41 (6.2%)	156 (23.6%)	464 (70.2%)		0.83 [0.59–1.17]	0.30
Living status							
Commuters	349	13 (3.7%)	68 (19.5%)	268 (76.8%)	0.036	*Reference*	
Residents	633	41 (6.5%)	146 (23.1%)	446 (70.5%)		0.81 [0.57–1.16]	0.25
Vaccine type							
BNT162b2	585	34 (5.8%)	138 (23.6%)	413 (70.6%)	0.079	*Reference*	
mRNA-1273	393	20 (5.1%)	75 (19.1%)	298 (75.8%)		1.37 [1.00–1.89]	0.049
Time after vaccination							
10–19 days	272	11 (4.0%)	51 (18.8%)	210 (77.2%)	*Reference*	*Reference*	
20–29 days	218	12 (5.5%)	42 (19.3%)	164 (75.2%)	0.67	0.77 [0.50–1.18]	0.23
30–39 days	218	14 (6.4%)	49 (22.5%)	155 (71.1%)	0.14	0.68 [0.45–1.04]	0.07
40–49 days	174	9 (5.2%)	43 (24.7%)	122 (70.1%)	0.097	0.69 [0.44–1.06]	0.09
≥50 days	100	8 (8.0%)	29 (29.0%)	63 (63.0%)	0.008	0.55 [0.33–0.92]	0.02

Abbreviation; FWT, fingertip whole blood sampling test: OR, odds ratio.
Antibody data of older population examined 10 days or after the third-dose vaccine booster was applied. Sex information was unavailable in 1 case. Vaccine type was unreported in 4 cases. We performed chi-square test as univariate analysis and logistic regression model as multivariate analysis to compare the statistical difference among the categories. For the multivariate analysis, dummy variables were used.

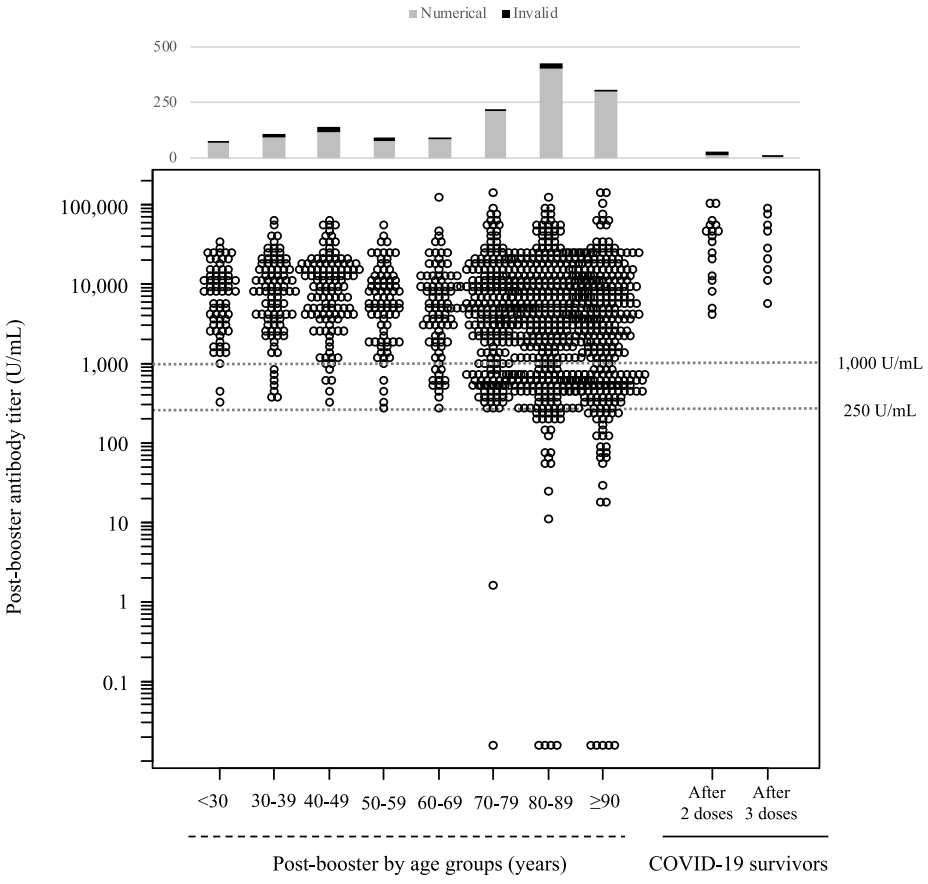

Fig. 1. Distribution of post-third-dose antibody titres of 1356 individuals in comparison with COVID-19 survivors. Antibody data of healthcare workers, nursing care staff, and older people examined 10 days or after the vaccine booster was administered. In addition, the antibody titres of COVID-19 survivors who were infected in a cluster event at a long-term care facility were provided by vaccination doses. The lowest values in each younger age group were 317.9 U/mL in <30 years; 392.3 U/mL, 30–39 years; 320.7 U/mL, 40–49 years; 258.5 U/mL, 50–59 years; and, 284.6 U/mL, 60–69 years.

the third booster, although the multivariate analysis indicated that age was not associated with vaccine response rate. This may be explained by the low-performing properties of these individuals. Our data suggested mRNA-1273 booster was significantly associated with the vaccine responders. Consistently, a randomized control study concluded that, in comparison with BNT123b2, mRNA-1273 booster vaccination can trigger a stronger neutralizing activity against the Omicron variant in older people.[10]

Collectively, to reduce the number of COVID-19 victims among the older people, the establishment of a triage system for non-responders against vaccination is warranted. The fingertip whole blood sampling test as a point-of-care testing was useful to identify the non-responder individuals in LTCF. Henceforward, serological testing protocols and an elderly-oriented booster schedule should be discussed to lessen the clinical burden of the disease and facilitate social normalization.

Data availability statement

Data in detail will be available if requested to the corresponding author.

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Declaration

This manuscript has not been published previously in any language, in whole or in part, and is not currently under consideration elsewhere. We have read and understood your journal's policies and believe that neither the manuscript nor the study violates any of them.

Declaration of Competing Interest

None to report.

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Hideharu Hagiya*
Department of General Medicine, Dentistry and Pharmaceutical Sciences, Okayama University Graduate School of Medicine, Okayama, Japan

Takao Hikita
Office of Innovative Medicine, Organization for Research Strategy and Development, Okayama University, Okayama, Japan
Laboratory for Cell Polarity and Organogenesis, Max Planck Institute for Heart and Lung Research, Bad Nauheim 61231, Germany

Tomohiro Habu
Department of General Thoracic Surgery and Breast and Endocrinological Surgery, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama, Japan

Masaki Asada
Departments of Medical Education, Kurashiki Central Hospital, Japan

Takashi Yorifuji
Department of Epidemiology, Dentistry and Pharmaceutical Sciences, Graduate School of Medicine, Okayama, Japan

Shinichi Toyooka
Department of General Thoracic Surgery and Breast and Endocrinological Surgery, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama, Japan

Fumio Otsuka
Department of General Medicine, Dentistry and Pharmaceutical Sciences, Okayama University Graduate School of Medicine, Okayama, Japan

Masanori Nakayama**
Office of Innovative Medicine, Organization for Research Strategy and Development, Okayama University, Okayama, Japan
Laboratory for Cell Polarity and Organogenesis, Max Planck Institute for Heart and Lung Research, Bad Nauheim 61231, Germany

*Corresponding author. **Corresponding author at: Laboratory for Cell Polarity and Organogenesis, Max Planck Institute for Heart and Lung Research, Bad Nauheim 61231, Germany.
E-mail addresses: hagiya@okayama-u.ac.jp (H. Hagiya), masanori.nakayama@okayama-u.ac.jp (M. Nakayama)

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Fighting Omicron epidemic in China: Real-world big data from Fangcang shelter hospital during the outbreak in Shanghai 2022

Dear Editor,

A recent letter published in your journal by Yuan et al. summarized the measures being taken in China to effectively contain COVID-19 epidemics including the recent Omicron outbreak in Shanghai.[1] Omicron has a reproduction number (R0)>10, and causes relatively mild symptoms, both of which aggravate the rapid spread of the virus in a "stealth mode". Shanghai faces especially severe challenges to control the outbreak at minimal social and economic costs, considering it is a major metropolis with a population of 25 million. As of 30th June 2022, the cumulative diagnosed cases have reached over 600,000 and close to 600 cases have died with or from COVID-19, which poses significant challenges to the city's healthcare system. Fangcang shelter hospital is a type of basic medical facility converted from large public space which offers patients with adequate medical care and provides isolation from their local communities to cut down further spread of the virus, which has been adopted as a central strategy to achieve 'dynamic zero', i.e., to minimize COVID-19 cases as quickly as possible at minimal costs.[2]

In line with the previous letter,[1] this approach has been successfully adopted to rapidly subdue several waves of SARS-CoV-2 in China over the past 2 years. Since the Omicron outbreak in Shanghai, more than one hundred Fangcang shelter hospitals have been rapidly converted from large public spaces including schools, exhibition centers and other public facilities, and have made paramount contributions in providing proper care to patients with mild to moderate symptoms, and preventing further viral spreading in the community.[3] On 1st June 2022, the total reopening of Shanghai marks the end of the city's stringent lockdown since late March and the strategic victory of the implemented public health measures and social services.

Here, we present for the first time, the largest cohort of 165,760 COVID-19 cases during the Omicron outbreak in Shanghai. This dataset was acquired at one of the largest Fangcang shelter hospitals in China that was converted from the Shanghai National Exhibition and Convention Center, the world's third-largest exhibition center with an indoor space of 400,000 m.[2] To suppress this extremely contagious Omicron outbreak, Shanghai has employed a series of effective measures to have the majority of its 25 million residents screened by SARS-CoV-2 PCR tests on a very frequent basis. With efficient referral and transfer mechanisms in local communities, the majority of patients were admitted to Fangcang shelter hospitals within 1–2 days after they tested positive. All patients admitted to the Fangcang shelter hospitals were screened daily by PCR tests, and were discharged only when two consecutive PCR tests returned negative. Accordingly, the average length of hospital stay corresponds to approximate the negative conversion time for the infection. The data from this cohort showed an average length of hospital stay of 7.18 ± 3.05 days, as compared to the 16.08 ± 5.13 days for those who were treated at Fangcang shelter hospitals during the outbreak of the original alpha strain in Wuhan, in early March 2020.[4] Additional analysis of the cumulative discharge incidence revealed that about 50% of patients were discharged on day 6 and 90% were discharged on day 10 (Fig. A), indicating a much faster hospital bed turnover rate and a generally milder spectrum of symptoms for this wave of Omicron infection compared to that of alpha strain infection in Wuhan.[4] The data is

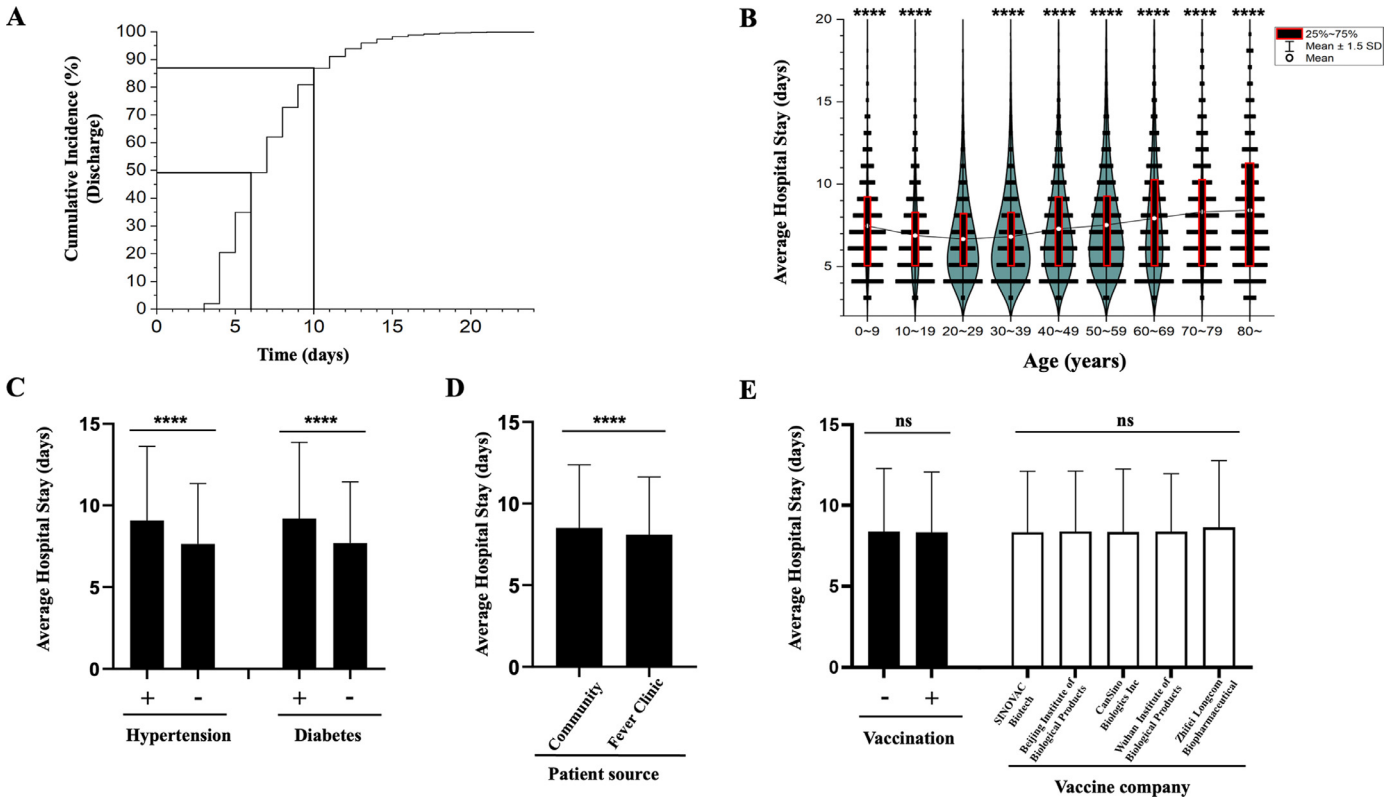

Figure A. A. **The cumulative incidence functions for the time it took for patient discharge.** The 50% and 90% cumulative incidence of discharge were labeled in the graph (n=165,760). B. **Average length of hospital stay for different age groups.** Results were presented as violin plots. One-way ANOVA with Dunnett's multiple comparison tests were performed for any age group compared to the age group 20-29 (control), **** P<0.0001 (n=165,760). C. **Average length of hospital stay for patients with or without chronic diseases.** Results of patients with (+) or without (-) hypertension or diabetes were analyzed. Unpaired t-tests, **** P<0.0001 (Hypertension n=2,707, Diabetes n=1,096, Total n=37,825). D. **Impact of patient source on the average length of hospital stays.** Results of patients discovered at their local community or in the fever clinic were shown. Unpaired t-tests, **** P<0.0001 (Community n=24,479, Fever Clinic n=13,346, Total n=37,825). E. **Impact of vaccination status and vaccine production company on the average length of hospital stays.** Left: results of unvaccinated (-) or vaccinated (+) patients of different doses were shown. Right: results of different vaccine companies including SINOVAC BIOTECH, Beijing Institute of Biological products, CanSino Biologics Inc, Wuhan Institute of Biological Products, Zhifei Longcom Biopharmaceutical. Unpaired t-tests (left) and one-way ANOVA (right), (ns= not significant). (Unvaccinated n=10,984, Vaccinated n=26,841; SINOVAC BIOTECH n = 17,878, Beijing Institute of Biological products n=6,531, CanSino Biologics Inc n=601, Wuhan Institute of Biological Products n=1,405, Zhifei Longcom Biopharmaceutical n=426).

further supported by a recent study in Southern California by Lewnard et al., that symptomatic hospital admission due to Delta variant is roughly 2.5 times more than that of Omicron infection.[5]

A detailed examination of the age cohorts revealed young adults (age 20–29) were the fastest to recover (6.67 ± 2.75 days), while children (age <10) and the elderly population (age >80) needed the longest length of stay to turn negative, with an average of 7.47 ± 3.01 days and 8.42 ± 3.99 days, respectively. There was also a clear trend that as adults age they gradually recover slower from the infections (Fig. B). Out of the total 165,760 cases admitted at the Fangcang shelter hospital, 37,825 cases had detailed information about the origin of the patients, their accompanying medical conditions, and vaccination history and enabled further analysis. Notably, patients with chronic illnesses such as diabetes and hypertension took remarkably longer to recover compared to the unaffected population (Fig. C). This emphasized the importance to protect the chronically ill populations, as reported before.[6] Interestingly, the patients who were discovered at the fever clinic were discharged much quicker than patients who were screened from the community (Fig. D). This may be explained by a theory that the latter was often asymptomatic and therefore at the preliminary stage of infection, while the former was frequently symptomatic and therefore at a later stage of disease of the natural history of COVID-19 infection.[7] Furthermore, we examined the impact of vaccination on hospital stay, yet found out that neither vaccination nor types of vaccine made remarkable differences (Fig. E). The little difference could be partially explained by the relatively mild nature of Omicron infection as the majority (~90%) of patients recovered within 10 days. The immune evasion due to epitope drifting is another possible explanation as the Omicron variant has mutated significantly compared to the original strain used for the generation of the approved vaccines in China. The impact of vaccination to reduce the incidence of severe cases or death rates was not examined in this cohort as Fangcang shelter hospitals only handle asymptomatic cases or patients with mild to moderate symptoms.

To conclude, we have provided the largest dataset of COVID-19 naturally recovered cases at the Fangcang shelter hospital which may serve as an excellent reference for public sectors, policymakers and healthcare professionals to assess the pandemic control strategies and better understand the disease characteristics of mild or asymptomatic COVID-19 patients. The Fangcang shelter hospital model in Shanghai has once again demonstrated its significance as a critical measure for patient care and pandemic control and has fulfilled the goal of China's "Dynamic Zero" policy. All in all, while the dawn of victory lies ahead for this wave of the Omicron epidemic in Shanghai, the tug of war between mankind and COVID-19 or other types of infectious disease continues. The Shanghai experience shared here may advance people's understanding of the SARS-CoV-2 Omicron variant as well as the use of Fangcang shelter hospitals. This may help prepare society for the epidemics to come.

Author contributions

L.Y performed data curation, formal analysis, and wrote the manuscript. W.F.L performed data validation and wrote the manuscript. J.S performed data curation and analysis. Both Z.X and J.J helped in data retrieval and project administration. H.X conceptualized and supervised the study as well as edited the manuscript. All authors contributed to the manuscript revision and read and approved the submitted version.

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Declaration of Competing Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Lingying Ye[1]
Department of Rheumatology and Immunology, Changzheng Hospital, Naval Medical University, Shanghai, China

Wing Fai Li[1]
School of Medicine, Tsinghua University, Beijing, China

Jinsong Shao
Department of Rheumatology and Immunology, Changzheng Hospital, Naval Medical University, Shanghai, China

Zhengmei Xu
Changzheng Hospital, Naval Medical University, Shanghai, China

Jintao Ju
Naval Medical University, Shanghai, China

Huji Xu*
Department of Rheumatology and Immunology, Changzheng Hospital, Naval Medical University, Shanghai, China
School of Medicine, Tsinghua University, Beijing, China

*Corresponding author at: Department of Rheumatology and Immunology, Changzheng Hospital, Naval Medical University, Shanghai, China.
E-mail address: xuhuji@smmu.edu.cn (H. Xu)

[1] These authors contributed equally.

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Staff and patient surveillance in hospitals: Good sentinels for the emergence of new SARS-CoV-2 variants

Dear Editor,

Wang et al. highlighted the importance of enhanced surveillance amongst healthcare workers (HCWs) to prevent nosocomial transmission of Coronavirus disease 2019 (COVID-19) as lifting of lockdowns and safe management measures occurred after the initial COVID-19 wave in 2020.[1] The arrival of the Delta variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Singapore led to increased community cases and a cluster at Tan Tock Seng Hospital (TTSH), a 1600-bed acute general hospital co-located with the national COVID-19 referral center (National center of Infectious Diseases) in April 2021.[2] Subsequently, TTSH enhanced its measures against COVID-19. These included personal protective equipment (PPE) upgrade for staff, rostered routine testing (RRT) for staff and inpatients, contact tracing and quarantine of exposed contacts – all of which effectively prevented further nosocomial transmission in the hospital.[2]

On October 11, 2021, the national strategy pivoted from containment to controlled mitigation of COVID-19. Hospital protocols for management of COVID-19 exposures consequently shifted to align with national policies. Unlike the prior protocol, exposed staff contacts were no longer subjected to 14-day quarantines. Instead, they were placed on enhanced surveillance and issued health risk warnings which required a negative antigen rapid test (ART) daily for seven days prior to coming to work.[3] Inpatient close contacts of COVID-19 cases were also closely monitored by undergoing daily polymerase chain reaction (PCR) testing for seven days. However, the gradual shift towards living with COVID-19 and relaxing of measures was expected to inevitably bring about a surge in community cases, especially with the arrival of new variants.

The Omicron (B.1.1.529) variant, which has a higher transmission rate and shorter incubation period than previous strains, was first discovered in Botswana in November 2021 and soon after was named a variant of concern by the World Health Organization.[4,5] Studies have estimated Omicron to have an infectivity rate that is ten-fold higher than that of the wild type and approximately twice as high as that of the Delta variant.[6] Omicron quickly became the dominant strain after it first emerged in Singapore in early December 2021. The high infectivity rate of Omicron, coupled with the discontinuation of containment measures, led to a jump in community cases – reaching a record high of more than 25,000 cases a day at its peak in February 2022.[7]

Despite the revised hospital changes catering to a controlled mitigation approach, numerous safe management measures were still kept in place to prevent nosocomial transmission and hospital clusters. For instance, staff and inpatients continued to undergo RRT, and previously established enhanced sickness surveillance systems remained in place to screen staff with acute respiratory illness (ARI) symptoms.[8,9] Furthermore, staff continued to don enhanced PPE, maintain 1-meter safe distancing, have meals alone, and suspend social gatherings at work. Hence, staff infected with SARS-CoV-2 were more likely to have acquired the infection in the

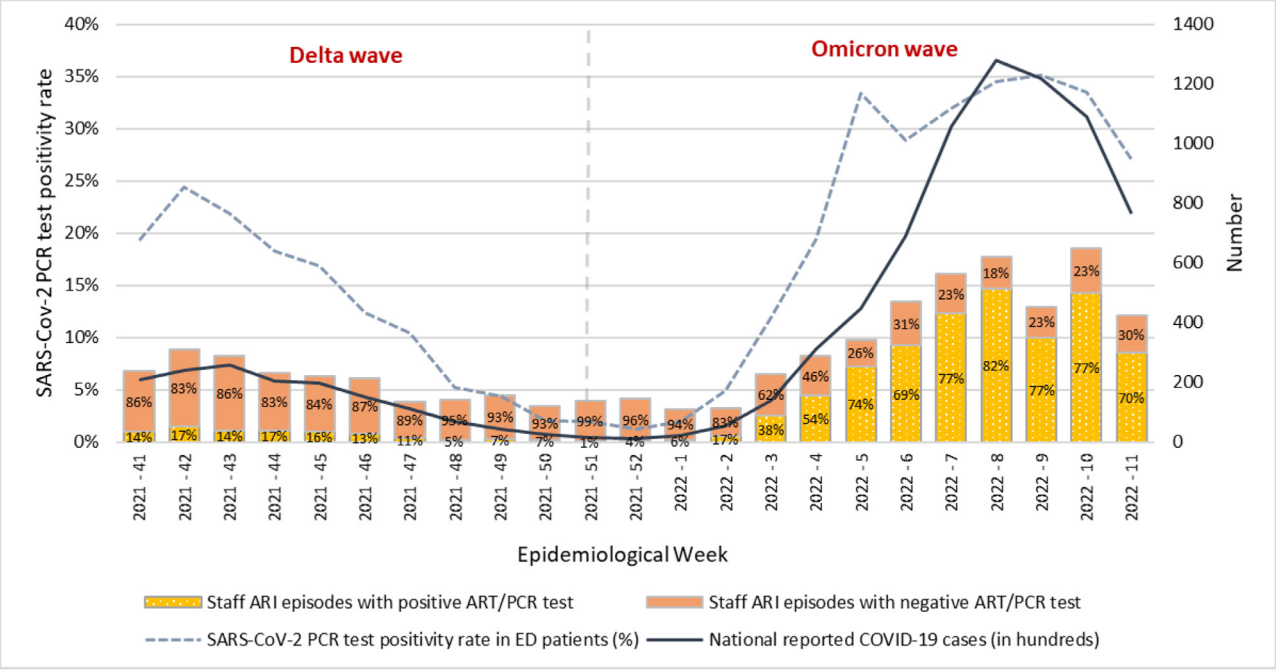

Fig 1. Weekly SARS-Cov-2 PCR test positivity rate among patients who attended at the emergency department with ARI symptoms, number of COVID-19 cases in the community, and numbers of staff ARI episodes with a positive and negative SARS-CoV-2 antigen rapid or PCR test, from October 10, 2021 through March 19, 2022.

community than in the hospital. Therefore, we posit that HCWs might serve as good sentinels for emerging COVID-19 trends in the community, as picked up by our comprehensive surveillance systems.

We present weekly data on the SARS-CoV-2 PCR test positivity rate in patients attending at the hospital's emergency department (ED) for ARI, number of staff ARI episodes and SARS-CoV-2 antigen/PCR test positive rate, and national reported COVID-19 cases from October 10, 2021 to March 19, 2022 (i.e., epidemiological week (e-week) 41, 2021 to e-week 11, 2022) (Fig. 1). After the change in strategy from containment to controlled mitigation on e-week 41, the SARS-CoV-2 test positivity rate among ED ARI patients rose slightly in e-week 42, 2021. Notably, the uptick was observed a week before the increase in national COVID-19 cases reported by Singapore's Ministry of Health. Subsequently, SARS-CoV-2 test positivity rate in ED patients decreased steadily till the end of the year. During the trough weeks (e-week 50, 2021 to e-week 1, 2022), the mean (standard deviation) of SARS-CoV-2 test positivity rate among ED ARI patients, proportion of staff ARI with positive antigen/PCR test, and national reported COVID-19 cases were 1.8% (0.4%), 4.7% (2.4%), and 1862 (648.6) respectively. On e-week 2, 2022, there was a jump in SARS-CoV-2 test positivity rate among ED ARI patients and symptomatic staff to 4.9% and 17% respectively, beyond two standard deviations above the mean weekly rates of the trough weeks. The national reported COVID-19 cases also surged to 5260 that week, indicating the emergence of the Omicron variant. The following weeks showed continued uptrending of COVID-19 in ED patients, staff, and the community, as Omicron swept through Singapore. As the national reported COVID-19 cases crested on e-week 8, 2022, the SARS-CoV-2 test positivity rate among ED patients and staff also peaked. Following which, a decline was observed.

Throughout the study period, safe management measures such as bi-weekly RRT, enhanced PPE, having meals alone, and suspension of social activities remained in place, which enabled the surveillance of staff ARI incidence and SARS-CoV-2 positivity to serve as good sentinel surveillance of COVID-19 in the community. Furthermore, surveillance on the SARS-Cov-2 test positivity rate of ED ARI patients provided a one-week lead time in detecting the national uptick of COVID-19 cases after the discontinuation of containment strategies in October 2021. All ARI patients attending at the ED were screened with the PCR test, which is 30–40% more sensitive than the ART more frequently adopted in the community.[10] With the emergence of the Omicron variant, whose infections have higher viral loads occurring earlier in the course of illness, and a shorter incubation period, surveillance of SARS-CoV-2 test positivity in ED patients did not provide a time advantage, but showed an increase at the same time as national reported COVID-19 cases.

In conclusion, we have demonstrated that staff and patients undergoing surveillance in an acute hospital can serve as good sentinels for the national surveillance of COVID-19. With the relentless waves of new variants of SARS-CoV-2, such surveillance systems can serve as good and sensitive complements to the national reporting system.

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Rhea Khanna, Htet Lin Htun, Anthony Lianjie Li, Win Mar Kyaw, Hou Ang, Brenda Ang, Angela Chow*
Tan Tock Seng Hospital, Singapore

*Corresponding author.
E-mail address: Angela_Chow@ttsh.com.sg (A. Chow)

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Equity in recruitment to Combined Infection Training, 2021: Diversity & Inclusion considerations

Dear Editor,

Lawrence et al. recently described the state of the infection workforce in the United Kingdom.[1] The authors reported a disparity in specialist infection expertise across the country, and high consultant vacancy rates. Together with increasing pressures from the threat of emerging infections, rising antimicrobial resistance and more complex clinical care for patients, there is a need to strengthen infection services across the country.[1,2] Attracting specialist trainee applicants is a key element in this endeavour, but it is important that recruitment decisions and processes are fair and inclusive.

Equitable opportunities for employment regardless of personal identity and characteristics are a necessity. For medicine, it is crucial that the workforce reflects the diversity of the society it serves. Infectious diseases disproportionately affect Minority Ethnic groups and having a diverse workforce serves to better understand patient needs. Furthermore, workplaces that are diverse and inclusive result in a more productive, innovative, and engaged workforce.[3] Infection specialities are well placed to lead on equality and diversity. Prospects of remote working, a varied training (e.g. laboratory and ward-based), participation in global health initiatives, and academic career opportunities, amongst other factors, mean infection specialities have the potential to attract a diverse pool of applicants. Monitoring recruitment data is crucial in identifying whether there are significant disparities in recruitment decisions between demographic groups but not routinely done. Where disparities are identified, these should be investigated and action taken where necessary. We shed light on these important considerations for the 2021 infection speciality recruitment cycle.

Data on the gender, ethnicity, disability status, and country of qualification of applicants to Combined Infection Training (CIT) for the 2021 recruitment cycle was made available through a Freedom of Information request to Health Education England (HEE). HEE follows the Information Commissioner's Office code of practice relating to data anonymisation; release of small numbers (<5 in a geographical area/demographic) has therefore been suppressed. Analysis was performed in Excel 2016 and R version 4.02. Figures were generated in R version 4.02. Pairwise comparisons of successful recruitment between categories were evaluated using chi-squared tests. To compare success of applications by ethnicity, and maximally utilise data, minority groups with fewer than five successful applicants were grouped. We used a multivariate logistical regression model to compare the odds ratio of successful application between White-British and other Minority Ethnic groups.

We found 121/255 (47.5%) of applicants to CIT were female in 2021. 6/255 (2.4%) individuals preferred not to state their gender. There was no significant difference seen between the success rates of male (30/128, 23.4%) and female (36/121, 29.8%) applicants ($\chi 2(1)=0.97$, $p = 0.32$) (Fig. 1). Less than 5 applicants reported a disability and no disabled applicants were successful in their application. Applications for CIT by Ethnicity are shown in Fig. 2a. There was a significant difference seen between the success rates of White-British applicants (28/59, 47.5%) compared to other Minority Ethnic group applicants (38/196, 19.4%) ($\chi 2(1)=17.2$, $p=<0.001$). We found all Minority Ethnic groups had a significantly lower odds ratio of successful application to CIT when compared to the White-British group other than 'Any Other Asian Background' (Fig. 2b).

To further evaluate the underlying reasons for the discrepancy shown in applicant success by ethnicity, we examined the impact of applicants' country of qualification (UK vs Non-UK graduate). 156/255 (61.2%) of applicants to CIT were Non-UK medical graduates in 2021 (Fig. 2c). There was a significant difference seen between the success rates of Non-UK graduates (19/156, 12.2%) compared to UK graduates (47/99, 47.5%) ($\chi 2(1)=37.5$, $p=<0.001$). Due to a lack of individual-level data it is difficult to assess the impact of country of qualification on the low success rate by Minority Ethnic groups. However, if we assume all White-British applicants are UK graduates (see **Supplementary Methods**), there is no difference observed in success by White-British applicants (28/59, 47.5%) compared to Minority Ethnic groups (19/40, 47.5%) amongst the UK graduate cohort ($\chi 2(1)=0$, $p = 1$).

We provide the most complete assessment of diversity data relating to specialist trainee recruitment to infection specialities to our knowledge, which should serve as a framework for other medical and surgical specialities to adopt. Reassuringly, we demonstrate applications and success rates for CIT in 2021 were gender balanced. However, we note a category allowing individuals to self-describe their gender identity (e.g. non-binary) is not available; we encourage this to be included in future data monitoring exercises as a step towards inclusivity. The data suggests that White-British applicants are disproportionately successful in the CIT recruitment process compared to all other ethnicities and a significant explanatory factor for this may be a high rejection rate amongst Non-UK qualified applicants. We propose stakeholders investigate underlying reasons for lower success rates amongst Non-UK graduates and consider how this may be addressed including mitigating for possible unconscious bias. Approximately 20% of the working population has a disability in the UK, while 1.5% of the UK medical workforce report a disability – thought to significantly under-estimate true figures.[4,5] Efforts should be taken to encourage applications to CIT by disabled applicants; as previously suggested by the GMC, these doctors are uniquely placed to relate to their patients and are an invaluable source of experience.[6] The hospital working environment should be accessible to all and the possibility of work-

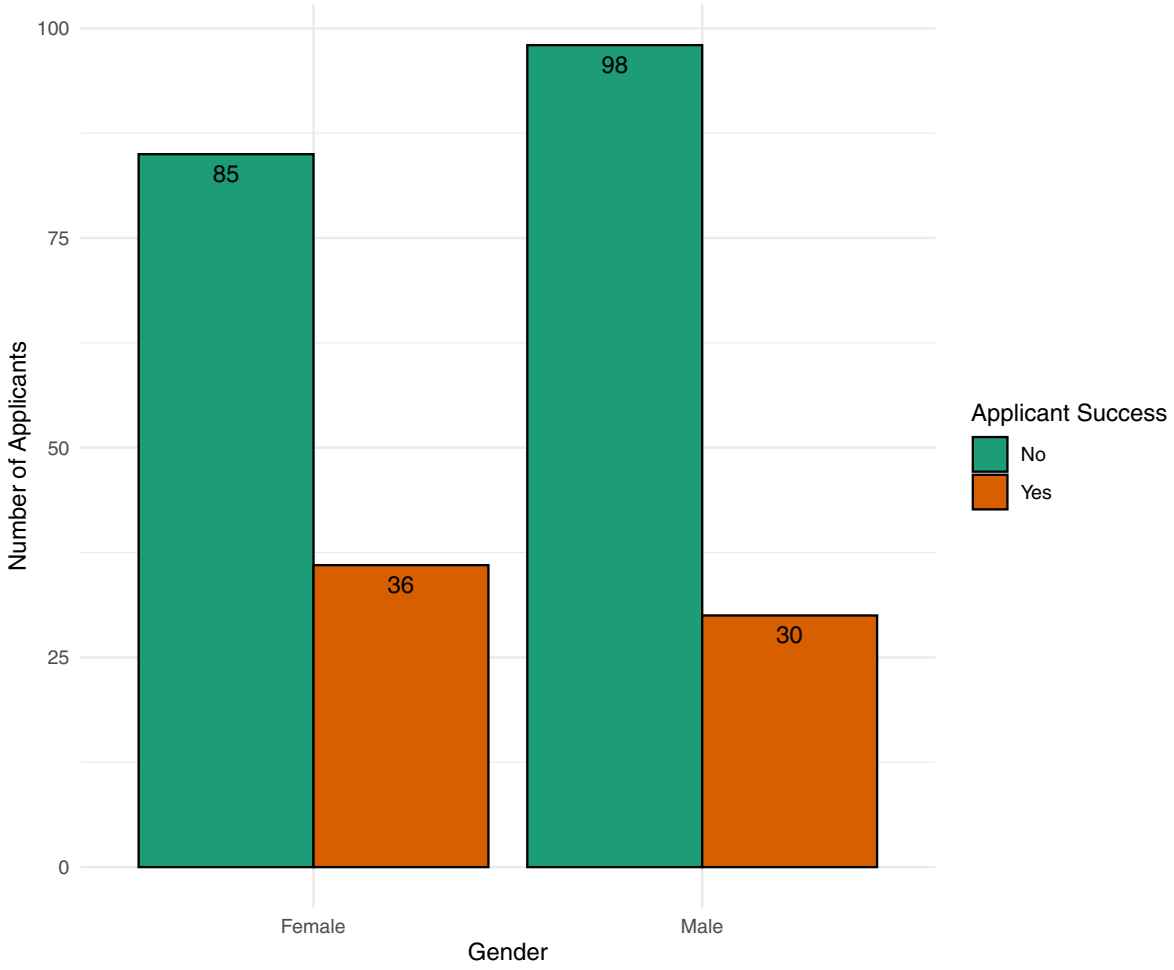

Fig. 1. Applications and outcomes for Combined Infection Training in the 2021 recruitment year by Gender. Bar chart demonstrating applications and outcomes of trainees to Combined Infection Training by Gender. There was no significant difference in successful applications by Gender ($\chi 2(1) = 0.97$, $p = 0.32$).

ing less than full-time and working from home should make infection specialities an attractive prospect for doctors living with disabilities.

This analysis is representative of one year of recruitment; ongoing systematic data monitoring is necessary to evaluate trends in applications and successful recruitment by demographic characteristics over time. Future work should also include examination of disparities in the demographic make-up between applicants to CIT and all other specialities. We report an analysis of recruitment to CIT which is only one aspect of assessing the diversity and inclusiveness of a profession; disparities in pay by gender and race, for example, are well-documented at a national level within the NHS.[7] We encourage the assessment of pay gaps, progression and retention of the workforce by Gender, Ethnicity, and other protected characteristics within infection specialities. In conclusion, collecting and analysing this data is the first step towards shining a light on fair recruitment processes within infection specialities, however significant work remains to address the issues highlighted and implementation of wider data monitoring exercises to shift the dial towards a truly inclusive speciality.

Declaration of Competing Interest

None.

Data statement

The datasets analysed and reported during the current study and further details on gaining access are available from the corresponding author (DA; dinesh.aggarwal@nhs.net) on reasonable request.

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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.2022.06.031.

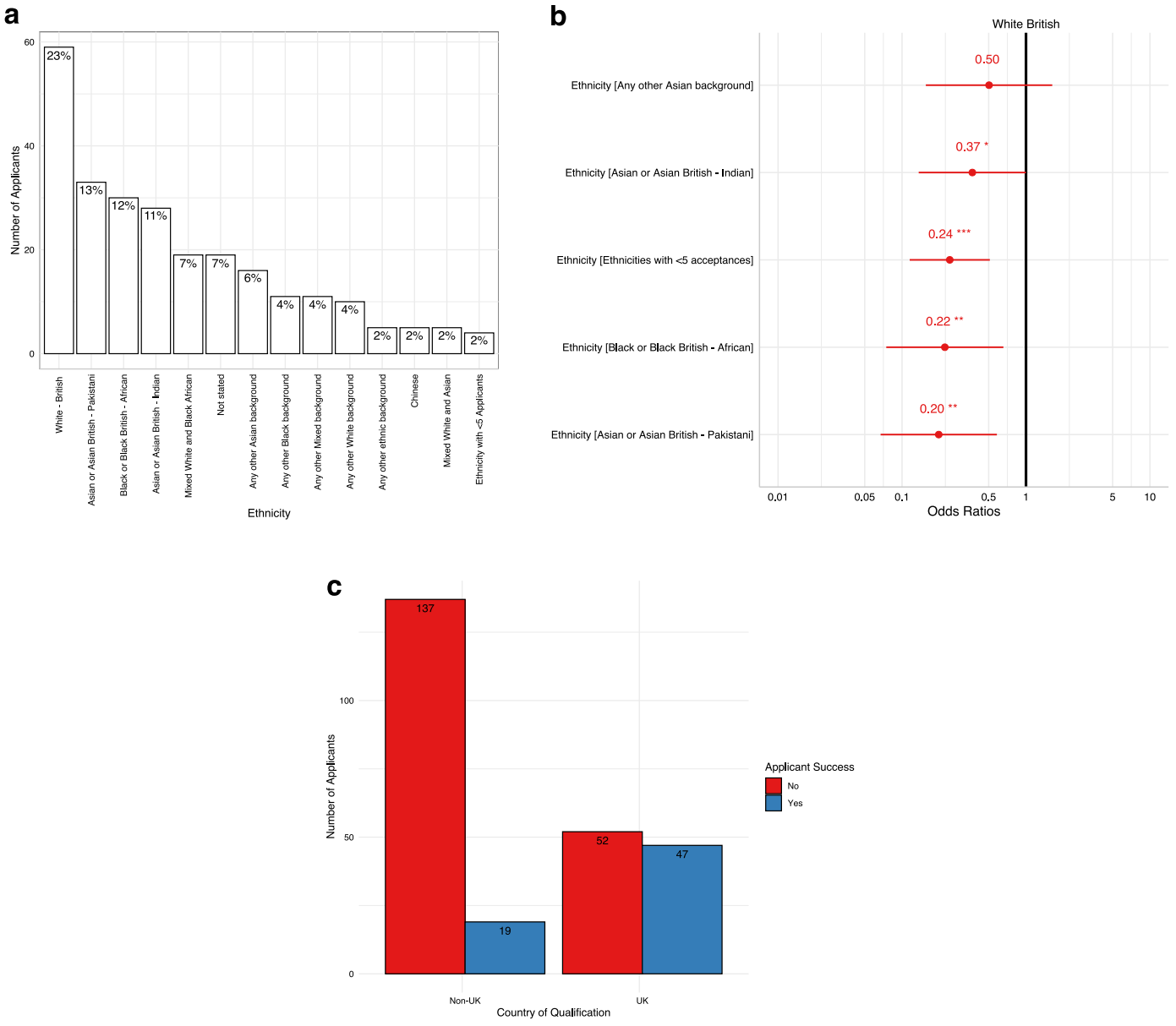

Fig. 2. Applications and outcomes for Combined Infection Training in the 2021 recruitment year by ethnicity. (**a**) Applications to Combined Infection Training by ethnicity. (**b**) Multivariate logistic regression model comparing success of application to Combined Infection Training by minority ethnic groups to the White British demographic. Minority Ethnic groups including fewer than 5 successful applicants include Chinese, Any other Black background, Mixed White and Asian, Mixed White and Black African, Any other Mixed background, Any other White background, Not stated, Any other ethnic background, Asian or Asian British – Bangladeshi, White – Irish, Mixed White and Black Caribbean, and Black or Black British – Caribbean. (**c**) Applications and outcomes by country of qualification (UK vs Non-UK).

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Dinesh Aggarwal*
Department of Medicine, University of Cambridge, Hills Rd, Cambridge CB2 0QQ, United Kingdom
Cambridge University Hospital NHS Foundation Trust, Hills Rd, Cambridge CB2 0QQ, United Kingdom
Wellcome Sanger Institute, Hinxton, Saffron Walden CB10 1RQ, United Kingdom

Meera Roy-Chowdhury
Bar Standards Board, High Holborn, London WC1V 7HZ, United Kingdom

Nicola Xiang
St Mary's Hospital, Imperial College Healthcare NHS Trust, Praed St, London W2 1NY, United Kingdom

Sharon J. Peacock
Department of Medicine, University of Cambridge, Hills Rd, Cambridge CB2 0QQ, United Kingdom
Cambridge University Hospital NHS Foundation Trust, Hills Rd, Cambridge CB2 0QQ, United Kingdom

*Corresponding authors at: Department of Medicine, University of Cambridge, Hills Rd, Cambridge CB2 0QQ, United Kingdom
E-mail address: dinesh.aggarwal@nhs.net (D. Aggarwal)

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Monkeypox and pan-resistant *Campylobacter spp* infection in *Entamoeba histolytica* and *Chlamydia trachomatis* re-infection in a man who have sex with men

Dear Editor,

In this journal Heskin et al. recently presented the cases of two men who have sex with men (MSM) who acquired monkeypox (MPX) infection suggesting that sexual intercourse is becoming the predominant transmission route of the new MPX outbreak [1]. Multiple cases of MPX infection have also been reported in Italy, predominantly among MSM [2]. Co-infection with other sexually transmitted infections (STIs) has also been documented, corroborating the hypothesis of sexual transmission [2].

We present the case of a 42-years-old MSM who was receiving HIV pre-exposure prophylaxis (PrEP) since 2017 at the Infectious Diseases Department of San Raffaele Hospital, Milan, Italy. He was diagnosed with MPX infection in June 2022, together with a pan-resistant *Campylobacter spp* infection and an *Entamoeba histolytica* and *Chlamydia trachomatis* proctitis re-infection.

Over the last 2 years, he has been diagnosed with multiple STIs and sexually transmitted enteric infections (STEI), including chlamydia and *Entamoeba histolytica* (Table 1).

Table 1
Previous STIs over 5 years of follow-up.

Year	STIs / STEIs
Month 0	Chlamydia proctitis
Month 2	Chlamydia pharyngitis
Month 13	Gonorrhea proctitis
Month 19	Gonorrhea urethritis
Month 24	Chlamydia proctitis
Month 28	*Entamoeba histolytica*
Month 29	Chlamydia proctitis
Month 35	Gonorrhea proctitis
Month 36	Giardiasis
Month 37	Genital Herpes Simplex
Month 41	Gonorrhea proctitis
Month 44	Chlamydia proctitis

Abbreviations: STI: sexually transmitted infection; STEI: sexually transmitted enteric infection

No travel history to MPX endemic areas or previous smallpox vaccination was reported.

He went to Gran Canaria, Spain 30 days before symptoms onset, where a huge MPX outbreak is thought to have occurred [3]. He reported engaging in multiple condomless receptive and insertive intercourse with >20 partners in the month preceding symptoms onset. Moreover, a non-sexual close contact with a confirmed MPX case occurred 5 days prior to symptoms onset, although the individual had a negative oropharyngeal swab for MPX and only rectal lesions, in the absence of cutaneous involvement, suggesting that the infection was not acquired by the contact with the confirmed MPX case. Furthermore, we believe that MPX infection was locally acquired in Italy, given the long delay in symptoms onset following return from Gran Canaria, although we cannot exclude a prolonged incubation period [4].

He presented to our clinic complaining diarrhea, tenesmus and two single atypical small (2 × 2 mm) non-vesicular erythematous cutaneous and perianal lesions, which were non-tender. No other systemic symptoms or cutaneous involvement were documented. Upon high-resolution anoscopy examination several rectal ulcers were documented, suggesting that this was the primary infection site (Fig. 1). Real-time PCR (RealStar® Orthopoxvirus PCR Kit 1.0 – altona DIAGNOTICS) targeting *variola virus* and *non-variola* Orthopoxvirus species (*cowpox, monkeypox, raccoonpox, camelpox, vaccinia virus*) showed the presence of *non-variola* DNA on serum, rectal and cutaneous swabs (cycle thresholds: 37, 35 and 27, respectively). A specific Real-Time PCR targeting Monkeypox virus DNA (Liferiver - SHANGHAI ZJ BIO-TECH CO., LTD) subsequently confirmed the MPX virus infection. Plasma, urines, seminal fluid and an oropharyngeal swab tested negative for MPX. A full STIs and STEIs screening was performed to rule out differential diagnoses: this revealed concurrent *Chlamydia trachomatis* proctitis, 1st line therapy pan-resistant *Campylobacter spp* (azithromycin, ciprofloxacin, clarithromycin and doxycycline resistant) and *Entamoeba histolytica* infection. Abdominal ultrasound ruled out hepatic involvement. *Entamoeba histolytica* re-infection was treated with tinidazole, *Chlamydia trachomatis* proctitis with doxycycline and stool cultures were repeated, documenting spontaneous clearance of *Campylobacter spp* infection, with resolution of diarrhea in 7 days. Lastly, serum, plasma, seminal fluid, urines and cutaneous, oropharyngeal and rectal swabs were collected after 10 days from MPX diagnosis, without further evidence of presence of *non-variola* Orthopoxvirus DNA.

We observed the case of MPX diagnosis in an MSM with concurrent STI and STEIs diagnoses.

This case corroborates the idea that sexual intercourse could be the predominant way of transmission of MPX. Firstly, the individuals reported multiple condomless intercourse with different partners and a broad clinical history of previous STIs. Moreover, MPX involvement was mostly at the rectal site, as documented by anoscopy, without systemic symptoms. Presence of a concurrent STI which might explain the observed lesions or symptoms should not rule out MPX infection among suspected cases, given the risk of co-infection. Anoscopy examination might be helpful in revealing unnoticed lesion among individuals reporting receptive intercourse. We believe that physicians should be aware of MPX among individuals with a previous history of STIs, who report high-risk sexual behaviors. Moreover, given a MPX diagnosis we suggest performing among all individuals a full STI screening, considering also STEIs if diarrhea is present. We detected a *Campylobacter spp* infections which was resistant to all 1st line therapies, which highlights how antimicrobial resistance is a major concern referring to both STIs and STEIs.

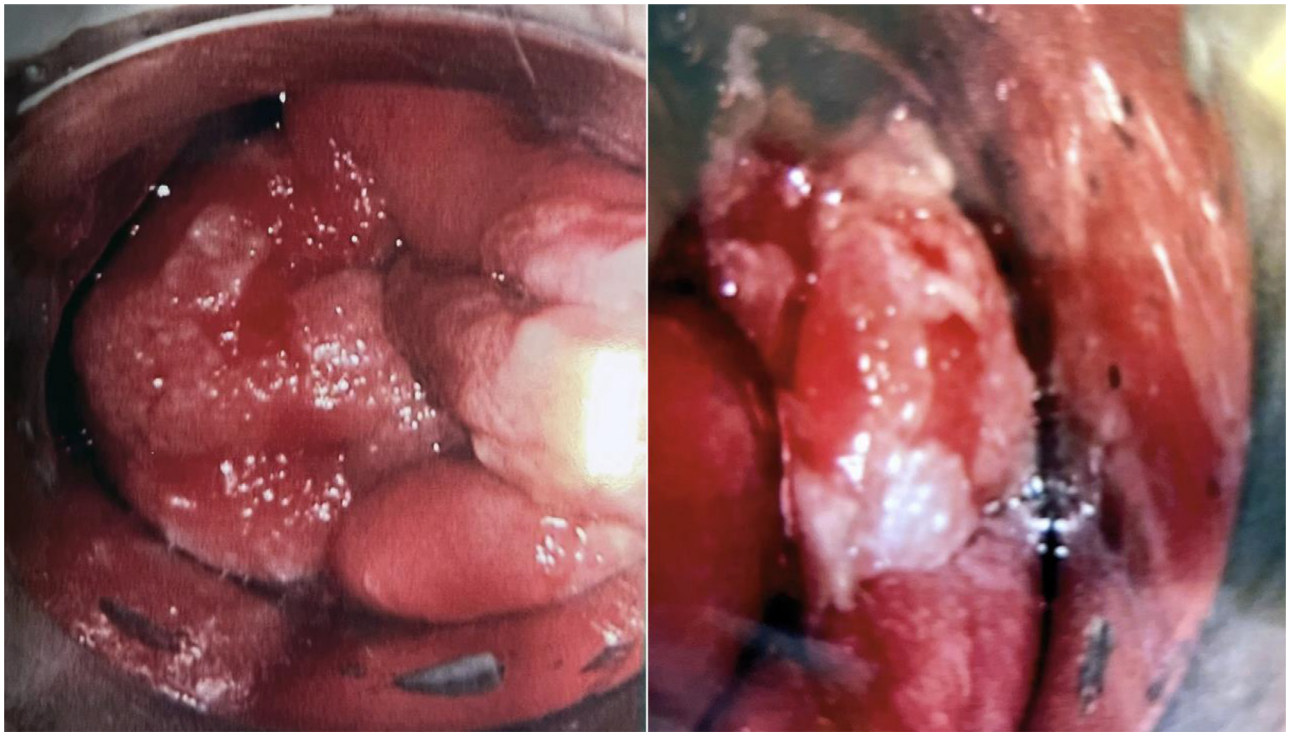

Fig. 1. Monkeypox rectal ulcers upon high-resolution anoscopy.

Contributorship statement

S.N. visited the individual and contributed to writing the article. A.R.R. contributed to writing the article. E.B., D.C. and A.C. contributed to the reviewing of the article. D.M. and A.R. coordinated virologic activities and performed PCR tests for MPX. A.M.T. performed anoscopy examination.

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Declaration of Interest

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Angelo Roberto Raccagni*
Vita-Salute San Raffele University, Via Stamira D'Ancona 20, Milan 20127, Italy

Davide Mileto
Laboratory of Clinical Microbiology, Virology and Bioemergencies, Ospedale Sacco, Milan, Italy

Diana Canetti
Infectious Diseases Unit, San Raffaele Scientific Institute, Milan, Italy

Andrea Marco Tamburini
Vita-Salute San Raffele University, Via Stamira D'Ancona 20, Milan 20127, Italy
Gastrointestinal Surgery Unit, San Raffaele Scientific Institute, Milan, Italy

Alberto Rizzo
Laboratory of Clinical Microbiology, Virology and Bioemergencies, Ospedale Sacco, Milan, Italy
University of Milan, Milan, Italy

Elena Bruzzesi
Vita-Salute San Raffele University, Via Stamira D'Ancona 20, Milan 20127, Italy

Antonella Castagna
Vita-Salute San Raffele University, Via Stamira D'Ancona 20, Milan 20127, Italy
Infectious Diseases Unit, San Raffaele Scientific Institute, Milan, Italy

Silvia Nozza
Infectious Diseases Unit, San Raffaele Scientific Institute, Milan, Italy

*Corresponding author.
E-mail address: raccagni.angelo@hsr.it (A.R. Raccagni)

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Monoclonal antibody therapy improves severity and mortality of COVID-19 in organ transplant recipients: A meta-analysis

Dear Editor,

We read with great interest the article in this journal by Tang et al. regarding an impaired immunologic response in solid organ transplant patients after COVID-19 mRNA vaccination.[1] Organ transplant patients are vulnerable to COVID-19 infection, progression to severe disease, and mortality given their need for immunosuppressive therapy to prevent transplant rejection. As such, a significantly lower seroconversion rate following vaccination compared to healthy controls prompts the need for effective treatment modalities in this high-risk patient population.[1]

Organ transplant patients have a markedly low seroconversion rate after 2 doses of COVID-19 mRNA vaccine compared with healthy controls.[1] Although COVID-19 vaccines have been effective in mounting an immune response in immunocompetent patients, a more effective alternative is needed for organ transplant recipients. Monoclonal antibodies (mAbs) have been highly studied in the literature as immunotherapy that target specific SARS-CoV-2 domains. As a therapeutic option that does not rely on the body's own immune response, mAbs have value in immunosuppressed patients and considerable potential as a treatment modality for organ transplant patients with COVID-19.[2,3]

To the best of our knowledge, there exists no meta-analysis describing the effect of mAbs on organ transplant recipients with COVID-19. We perform this meta-analysis to evaluate the association between monoclonal antibody therapy and outcomes of organ transplant patient following COVID-19 infection.

An exhaustive electronic search was conducted using PubMed, Embase, Cochrane Library databases, Web of Science, Scopus and medRxiv from December 1st 2019 to May 20th, 2022 without any restrictions on language. The search was performed using the following keywords: "2019-nCoV", "coronavirus disease 2019″, "COVID-19″, "SARS-CoV-2″, "novel coronavirus", "transplant recipients", "transplantation", "organ-transplant recipients", "monoclonal antibody", "neutralizing antibody", "casirivimab", "imdevimab", "sotrovimab", "bamlanivimab", "LY-Cov555". The inclusion criteria were as follows: (1) organ transplant recipients with COVID-19; (2) reports containing original data with available risk estimates and/or with data on the number of clinical outcomes in mAbs and control groups; (3) comparative studies with a control group with no mAbs. The following studies were excluded (1) conference abstracts, editorials, reviews, and case reports; (2) duplicated publications.

Data analysis was conducted using Review Manager, version 5.2 (Cochrane Collaboration, Oxford). Odds ratio (OR) and 95% confidence interval (CI) were calculated. Heterogeneity was assessed with Cochrane's Q-test and quantified with I^2 values. A P value of <0.05 was considered statistically significant. This meta-analysis is registered with PROSPERO (International Prospective Register of Systematic Reviews, number CRD42022337101).

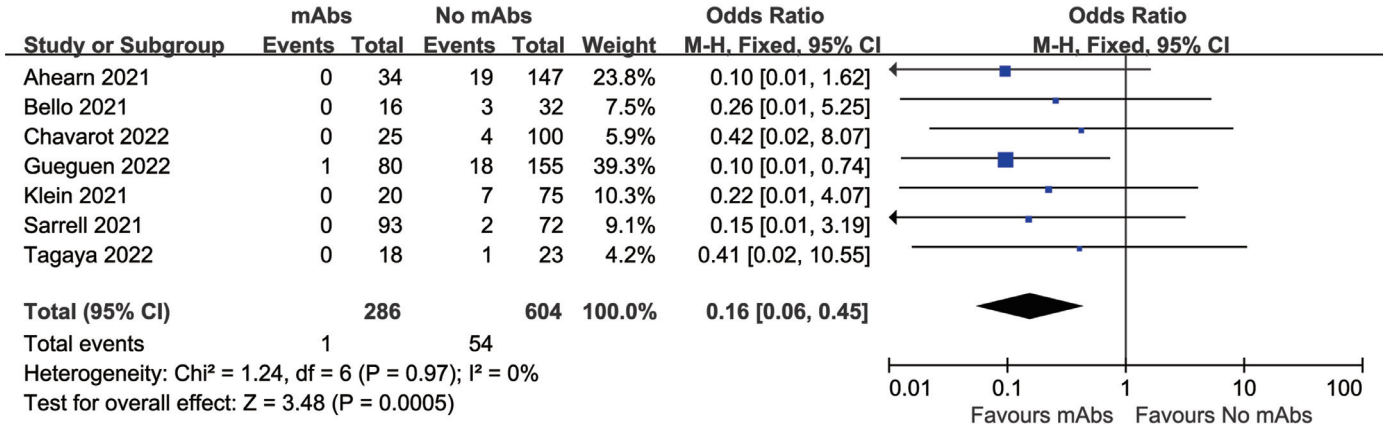
A total of 8 studies[2–9] were identified. All studies were retrospective in design. This meta-analysis included 313 patients in the mAbs group and 617 patients in the control group. Demographics and disease characteristics of the 930 patients included in the pooled analysis are summarized in Table 1. The eight studies were published between 2021 and 2022 with different sample patient sizes that ranged from 40 to 235 patients with COVID-19. Four studies were from USA, three from France and one from Japan. Patients received bamlanivimab or casirivimab-imdevimab or bamlanivimab-etesevimab or sotrovimab. Progression to severe COVID-19 disease included ICU admission and the need for high oxygen support.

Table 1
Characteristics of included studies.

Study	Region	Study design	Sample size	mAbs		No mAbs		Patients included	Transplant recipients	Usage of mAbs
				Age[a]	Male (%)	Age[a]	Male (%)			
Ahearn[2] 2021	USA	Retrospective	181	49.3 ± 14.3	22(65)	54 ± 14.5	83(56)	Outpatients	94 kidney, 87 liver	Bamlanivimab or Casirivimab-imdevimab
Bello[3] 2021	France	Retrospective	48	54 ± 14	10	59 ± 13	20	Hospitalized, having symptoms for <6 d, and not requiring oxygen	37 kidney, 2 liver, 5 heart, 2 kidney-pancreas, 1 kidney-liver	Bamlanivimab, bamlanivimab-etesevimab, casirivimab-imdevimab
Chavarot[4] 2022	France	Retrospective	125	54 (46–62)	21 (84.0)	53 (37.8–52)	54 (54.0)	Outpatient mild-to-moderate Omicron COVID-19	125 kidney	Sotrovimab
Gueguen[5] 2022	France	Retrospective	235	57 (46–64.5)	45 (56.3)	57 (44–65)	90 (58)	Recent symptoms (<5 days) and no need of oxygen	155 kidney	Bamlanivimab, bamlanivimab-etesevimab, casirivimab-imdevimab
Klein[6] 2021	USA	Retrospective	95	55.0 (31–79)	15 (75.0)	58 (38–78)	45 (60.0)	(1) were not hospitalized due to COVID-19, (2) did not require oxygen therapy due to COVID-19, and (3) had symptoms for <10 days	75 kidney	Bamlanivimab, bamlanivimab-etesevimab, casirivimab-imdevimab
Sarrell[7] 2021	USA	Retrospective	165	55.1 (42.8–63.5)	56 (60.2)	52.0 (41.7–66.3)	39 (54.2)	Outpatient mild to moderate COVID-19	50 kidney, 17 liver, 11 lung, 9 heart, 6 dual-organ	Bamlanivimab, casirivimab-imdevimab
Tagaya[8] 2022	Japan	Retrospective	41	53.72 (26–73)	13(72)	48.04 (20–80)	19 (82.6)	Hospitalized mild-to-moderate COVID-19	36 kidney, 3 liver, 2 bone marrow	Casirivimab-imdevimab
Wang[9] 2022	USA	Retrospective	40	52 (37–61)	15(56)	44 (32–54)	4(31)	Outpatient mild to moderate COVID-19	40 kidney	Bamlanivimab, casirivimab-imdevimab

[a] Age data presented as median (IQR) or mean (SD).

A



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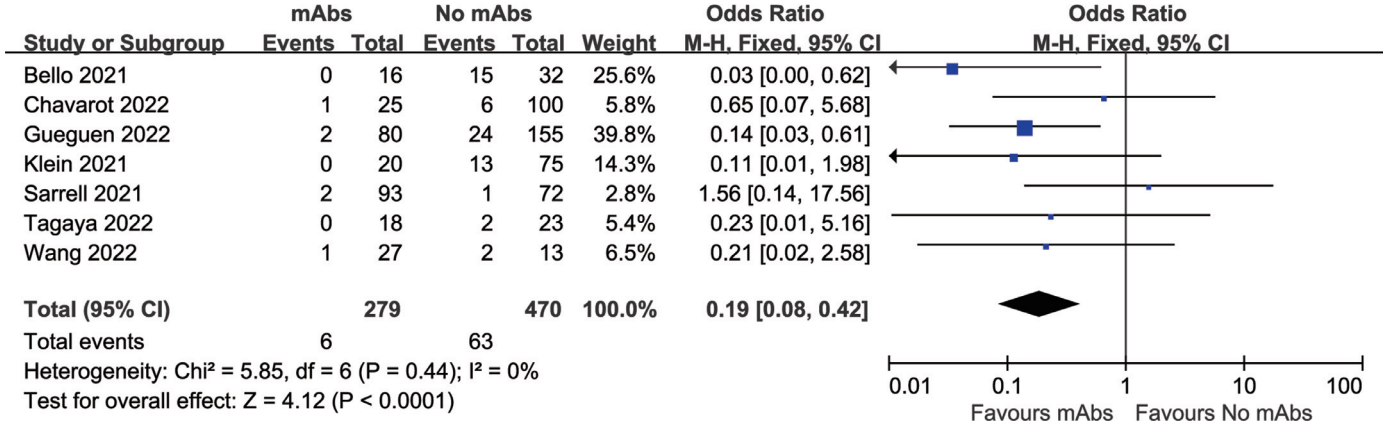

Fig. 1. (A) Association between mAbs treatment and mortality (B) Association between mAbs treatment and developing severe COVID-19.

The meta-analysis indicated that the mAbs group had lower mortality compared with the control group (OR=0.16, 95%CI: 0.06 to 0.45, $P = 0.0005$; I^2=0%) (Fig. 1A). Moreover, mAbs treatment was associated with a reduced risk of developing severe COVID-19 disease as compared to the control group (OR=0.19, 95%CI: 0.08 to 0.42, $P < 0.0001$; I^2=0%) (Fig. 1B).

In this study, we find that mAb therapy in organ transplant recipients with COVID-19 is associated with a significant improvement in disease severity as well as overall mortality.

The reduced morbidity and mortality of organ transplant recipients with COVID-19 following mAb treatment is likely related to a decreased progression to severe disease. Neutralizing mAbs target specific domains of the SARS-CoV-2 spike protein, inhibiting viral internalization and reducing viral load and virulence.[10] With organ transplant patients having increased baseline risks for disease severity and mortality given pre-existing comorbidities and anti-rejection immunosuppressive therapy, mAbs serve as a protective factor through a lower propensity to progress to severe disease. This reduces the need to discontinue anti-rejection immunosuppressive therapy in patients admitted for severe disease thus reducing risk of transplant rejection. Increased transplant organ survival rates further benefit health, social, and financial factors.

While mAbs have considerable potential as a novel therapeutic option, SARS-CoV-2 continues to mutate as increasing variants of concern emerge. Recent studies have shown that newer COVID-19 variants may have developed resistance against neutralizing mAbs developed specifically against SARS-CoV-2 thus decreasing treatment efficacy.[10] As such, there is considerable value in having ongoing research and development of mAbs which target the dominant variant strains of COVID-19 in order to keep up with global epidemiological needs.

There are several limitations to our study that should be noted. There was a small sample size of eight included articles for use in the meta-analysis. In addition, all included articles were retrospective in study design, leaving the results vulnerable to selection bias and confounding bias. Furthermore, each study looked at a different number and combination of mAbs without providing individual therapeutic data and as such subgroup analysis restricted to any single mAb was not able to be conducted. Despite these limitations, our study is the first meta-analysis to explore the effect of mAb therapy on organ transplant recipients with COVID-19.

Further research is needed to investigate the impact of mAbs as treatment for organ transplant patients with COVID-19 to provide additional insight into the efficacy of individual mAbs as well as combination therapy on morbidity and mortality. Future studies should aim to provide a large sample size through study designs that are prospective and more robust.

In conclusion, treatment with mAbs in organ transplant patients with COVID-19 is associated with a significant improvement in both severity and mortality. Additional exploration is needed to

evaluate the impact of individual mAbs and validate these findings in prospective studies.

Declaration of Competing Interest

The authors declare that they have no competing interest.

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Mingyang Yang[1]
West China Fourth Hospital/West China School of Public Health, Sichuan University, Chengdu, Sichuan, China
Health Emergency Management Research Center, China-PUMC C.C. Chen Institute of Health, Sichuan University, Chengdu, Sichuan, China

Anthony Li[1]
School of Medicine, Queen's University, Kingston, Canada

Yushu Wang[1]
Chengdu West China Clinical Research Center, Chengdu, Sichuan, China

Carolyn Tran
Schulich School of Medicine and Dentistry, Western University, London, Canada

Siyi Zhao
Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, Chengdu, Sichuan, China

Guangyu Ao *
Department of Nephrology, Chengdu First People's Hospital, Chengdu, Sichuan, China

*Corresponding author.
E-mail address: agy1990418@163.com (Guangy. Ao)

[1] These authors contributed equally to this work.

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Risk of Intensive Care Unit admission or mortality in patients hospitalised for COVID-19 during the first two waves: An Italian cohort study

Dear Editor,

in the article "First and second COVID-19 waves in Japan: A comparison of disease severity and characteristics", Saito et al. [1] presented a study on severity and characteristics of the first and second waves in Japan. Several countries have faced a two to three-wave pattern of COVID-19 during 2020–2021, previous reports suggesting that the subsequent waves of COVID-19 differ from the first one by the characteristics of both the virus [2] and the patients affected [1,3–5]. In order to compare the changes over time of COVID-19 patients and clinical outcomes in Italy, we assessed whether 28-day Intensive Care Unit admission (ICU) or mortality in a cohort of COVID-19 symptomatic hospitalised patients were changed over time, considering the roles of patients' characteristics and severity of COVID-19 at hospital admission.

We analysed a prospective cohort of all symptomatic patients who were consecutively diagnosed with COVID-19 in the Città della Salute e della Scienza (CSS) – Molinette Hospital of Turin, from March 2020 to June 2021. The CSS Molinette is a large teaching hospital of about 1000 available beds for general inpatients. Patients data were collected using a standardized data collection form by a team of data managers and registered in the web EPICLIN platform.

According to the weekly frequency of Covid-19 admissions, two different waves were defined: a first wave from March to September 2020, and a second wave from October 2020 to June 2021 (supplementary figure 1). The primary outcome was 28-day intensive care unit (ICU) admission or mortality, and the secondary outcome was 28-day mortality only.

In the first wave period 311 symptomatic patients were admitted to the emergency department and hospitalized at the CSS Molinette hospital and 1270 in the second one (supplementary figure 2). Overall, the distribution of gender, hypertension and Charlson's comorbidity index was similar in the two waves (Table 1). During the first wave, there was a higher prevalence of patients with 85+ years and more severe COVID-19 disease. Median length of hospital stay was 2 days shorter in the first wave (10 days vs 12, $p < 0.01$) for all patients (13.5 days vs 12 days, p-value: 0.259, for patients discharged alive only). In the first wave ICU admission/death occurred in 107/311 (34.41%) patients and death in 91/311 patients (29.26%), whereas in the second wave the same figures were 301/1270 (23.70%) and 254/1279 (20.00%). Estimates for effects of waves and patients' characteristics on outcomes are reported in Table 2. Considering the combined outcome (28-days ICU admission/death) there was a risk reduction in the second wave with respect to the first wave (OR=0.69, 95%CI 0.50–0.95). In the adjusted model, older age, male gender, higher Charlson's index, NEWS2 score, WBC and creatinine levels were associated with

Table 1
Demographic and clinical characteristics at ED admission of symptomatic patients hospitalized for COVID19 at "Città della Salute e della Scienza di Torino hospital" by wave (March 2020–June2021).

	Total ($N = 1581$)	First wave (March 2020-Sept 2020) ($N = 311$)	Second wave (Oct 2020-June 2021) ($N = 1270$)	P-value[a]
Age: median (IQR)	72 (60–81)	73 (57–82)	72 (60–80)	0.832
Age group: N (%)				
0–59	391 (24.73)	90 (28.94)	301 (23.70)	
60–75	577 (36.50)	91 (29.26)	486 (38.27)	0.002
76–85	410 (25.93)	76 (24.44)	334 (26.30)	
≥86	203 (12.84)	54 (17.36)	149 (11.73)	
Gender: N (%)				
Male	983 (62.18)	188 (60.45)	795 (62.60)	0.484
Female	598 (37.82)	123 (39.55)	475 (37.40)	
Body mass index (BMI): N (%)				
Underweight/Normal weight	1277 (80.77)	263 (84.57)	1014 (79.84)	0.058
Overweight/Obese	304 (19.23)	48 (15.43)	256 (20.16)	
Hypertension: N (%)				
No	760 (48.07)	142 (45.66)	618 (48.66)	0.392
Yes	821 (51.93)	169 (54.34)	652 (51.34)	
Charlson comorbidity index: N (%)				
0	676 (42.76)	129 (41.48)	547 (43.07)	
1	342 (21.63)	70 (22.51)	272 (21.63)	0.499
2	233 (14.74)	39 (12.54)	194 (15.28)	
3	134 (8.48)	27 (8.68)	107 (8.43)	
4+	196 (12.40)	46 (14.79)	150 (11.81)	
Creatinine (mg/dL): N (%)				
≤1.30	1169 (73.94)	223 (71.70)	946 (74.49)	0.314
>1.30	412 (26.06)	88 (28.30)	324 (25.51)	
National Early Warning Score 2 risk: N (%)				
Low	835 (52.81)	152 (48.55)	684 (53.86)	
Low-medium	202 (12.78)	31 (9.97)	171 (13.46)	0.008
Medium	268 (16.85)	51 (16.40)	217 (17.09)	
High	276 (17.46)	78 (25.08)	198 (15.59)	
White blood cell count (WBC): N (%)				
<10	1229 (77.74)	232 (74.60)	997 (78.50)	0.346
≥10	352 (22.26)	79 (25.40)	273 (21.50)	
C-reactive protein (CRP) (mg/L): N (%)				
<5.0	167 (10.56)	24 (7.72)	143 (11.26)	0.069
≥5.0	1414 (89.44)	287 (92.28)	1127 (88.74)	
Length of hospital stay: median (IQR)	12 (8–21)	10 (6–21)	12 (8–21)	0.003

[a] chi-square test for discrete variables, Kruskal-Wallis test for continuous variables.

Table 2
Unadjusted and Adjusted effects on 28-days ICU admission or death and on 28-days mortality in symptomatic patients admitted for COVID19 at "Città della Salute e della Scienza di Torino hospital".

Outcome	28-days ICU admission or death		28-days mortality	
	Unadjusted OR (95% CI)	Adjusted model OR (95% CI)	Unadjusted OR (95% CI)	Adjusted model OR (95% CI)
Period				
First (March 2020-Sept 2020)	1	1	1	1
Second (Oct 2020-June 2021)	0.59 (0.45–0.78)	0.69 (0.50–0.95)	0.60 (0.45–0.79)	0.76 (0.53–1.08)
Period (unit: month)	0.96 (0.94–0.98)		0.95 (0.93–0.98)	
Age group				
0–59	1	1	1	1
60–75	2.34 (1.60–3.41)	2.17 (1.43–3.29)	3.29 (1.99–5.45)	2.87 (1.68–4.93)
76–85	4.62 (3.15–6.77)	3.73 (2.42–5.76)	9.51 (5.80–15.60)	7.50 (4.37–12.86)
≥86	8.12 (5.31–12.42)	6.12 (3.71–10.10)	17.66 (10.42–29.92)	13.26 (7.28–24.13)
Gender				
Male	1	1	1	1
Female	0.76 (0.60–0.96)	0.59 (0.44–0.78)	0.81 (0.63–1.04)	0.58 (0.42–0.80)
Body mass index (BMI) (N,%)				

(*continued on next page*)

Table 2 (*continued*)

Outcome	28-days ICU admission or death		28-days mortality	
	Unadjusted OR (95% CI)	Adjusted model OR (95% CI)	Unadjusted OR (95% CI)	Adjusted model OR (95% CI)
Underweight/Normal weight	1	1	1	1
Overweight/Obese	0.85 (0.63–1.14)	1.07 (0.75–1.51)	0.73 (0.53–1.01)	1.01 (0.68–1.50)
Hypertension				
No	1	1	1	1
Yes	1.46 (1.16–1.83)	0.99 (0.75–1.31)	1.52 (1.19–1.94)	0.93 (0.69–1.26)
Charlson comorbidity index				
0	1	1	1	1
1	1.84 (1.35–2.50)	1.35 (0.95–1.94)	2.39 (1.70–3.35)	1.66 (1.11–2.46)
2	1.81 (1.28–2.57)	1.38 (0.93–2.06)	2.41 (1.65–3.53)	1.73 (1.12–2.68)
3	2.34 (1.55–3.53)	1.44 (0.90–2.31)	3.06 (1.97–4.75)	1.78 (1.07–2.97)
4+	3.89 (2.76–5.50)	2.36 (1.58–3.53)	5.82 (4.04–8.40)	3.48 (2.26–5.35)
Creatinine (mg/dL)				
≤1.30	1	1	1	1
>1.30	3.62 (2.84–4.62)	1.84 (1.37–2.46)	4.49 (3.48–5.79)	2.12 (1.56–2.88)
National Early Warning Score 2 risk				
Low	1	1	1	1
Low-medium	1.91 (1.31–2.79)	1.62 (1.09–2.42)	1.63 (1.08–2.46)	1.33 (0.85–2.09)
Medium	2.85 (2.06–3.94)	2.79 (1.97–3.96)	2.52 (1.79–3.55)	2.51 (1.70–3.70)
High	8.22 (6.04–11.18)	6.40 (4.52–9.06)	7.27 (5.31–9.95)	5.70 (3.91–8.29)
White blood cell count (WBC) (N,%)				
<10	1	1	1	1
≥10	2.49 (1.93–3.20)	1.50 (1.11–2.03)	2.44 (1.87–3.17)	1.40 (1.01–1.94)
C-reactive protein (CRP) (mg/L)				
<5.0	1	1	1	1
≥5.0	1.30(0.88–1.91)	0.91 (0.59–1.42)	1.37 (0.90–2.08)	0.97 (0.60–1.59)

higher 28-day mortality. Considering 28-day mortality, the associations between variables and outcomes were similar to the main analysis, but the reduction of risk of death in the second wave was less evident (OR=0.76, 95%CI 0.53–1.08).

In the present study, a reduction of 28-day ICU admission or death in patients with symptomatic COVID-19 of an Italy Hospital was showed (from 29.3% in the period to March-September 2020 to 20.0% in the period October 2020-June 2021). Patients admitted to the ED of our hospital in the first period were older, reflecting also the frequent outbreaks in nursing-home residents. In Italy access for visitors of nursing-homes was forbidden in April 2020 and isolation protocols for staff and patients were implemented. Furthermore, patients in the first period were more hypertensive, had a higher co-morbidity burden and presented at the ED with more severe symptoms and a worse inflammatory profile. However, adjustment for all these factors did not explain the period effect on mortality.

Consistently with Saito's Japanese cohort, the severity of Italian patients at ED presentation (measured with NEWS 2 score and two markers related to mortality [6]) was reduced in the second wave. Furthermore, as expected, higher level and lower levels of WBC counts, higher levels of CRP and more severe clinical conditions (NEWS2 score >=7) were associated with higher mortality in COVID-19 patients. Low severity at admission has been associated to a reduction of death risk in the second wave coherently with other previous studies [1,4]. Anyway, in our experience also patients with very severe presentation at the ED had an improved prognosis in the second wave, probably due to better organization and experience gained along the whole care pathway of more critical patients.

The excess mortality observed in the first period of pandemics could be due, at least in part, to distinct factors not related to the characteristics of the patients. I) Knowledge about the clinical course of the disease and evidence on effective and ineffective treatments rapidly accumulated during the first pandemic wave. In the peak of the first phase, emergency rooms, hospitals and intensive care units were challenged by the need of simultaneously providing care to a high number of critically ill patients. In the second wave, hospitals were better organized to receive COVID-19 patients with dedicated pathways, wards, beds, respiratory supports and protective devices. [7]. II) The treatment approach changed over the two periods, i.e., those admitted to hospital in the second phase were less likely to receive antivirals and more likely to be treated with steroids and antithrombotic prophylaxis or therapy [8]. Furthermore, in the second wave, a more timely and non-invasive ventilation support was employed [9]. The second wave captured a predominance of patients affected by the alpha variant of SARS-COV-2. The alpha variant was described as more contagious than wild type SARS-COV-2 and probably a cause of a more severe disease [10]. This is in contrast with our findings because, in the second wave, when a higher prevalence of alpha variant of SARS-COV-2 was expected, we noticed a lower mortality rate. However, it must be noticed that the genomic determination of SARS-COV-2 subfamilies was not performed routinely in Italy, so that we can only speculate on the genomic family of SARS-COV-2 among infected patients.

In conclusion, in a cohort of COVID-19 patients admitted to an Italian hospital a decreased risk of ICU admission or mortality was documented after the first wave that was only marginally attenuated by adjustment for patients' characteristics and severity of COVID-19 at hospital admission.

Declaration of Competing Interest

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2022.06.023.

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Carlotta Sacerdote, Lorenzo Milani
Unit of Cancer Epidemiology, Città della Salute e della Scienza Hospital, University of Turin and CPO Piemonte, Turin, Italy

Anna Castiglione, Eva Pagano, Enrica Migliore
Unit of Clinical Epidemiology, Città della Salute e della Scienza Hospital, University of Turin and CPO Piemonte, Turin, Italy

Carlo Albera
Department of Medical Sciences, Unit of Pneumology. University of Turin and Città della Salute e della Scienza Hospital, Turin, Italy

Mario Bo
Department of Medical Sciences, Section of Geriatrics, University of Turin and Città della Salute e della Scienza Hospital, Turin, Italy

Luca Brazzi
Department of Surgical Sciences, University of Turin, Turin, Italy
Department of Anesthesia, Intensive Care and Emergency, Città della Salute e della Scienza Hospital, Turin, Italy

Francesco Giuseppe De Rosa
Department of Medical Sciences, Infectious Diseases, University of Turin and Città della Salute e della Scienza Hospital, Turin, Italy

Marilena Durazzo
Department of Medical Sciences, Unit of Medicine 3, University of Turin and Città della Salute e della Scienza Hospital, Turin, Italy

Enrico Lupia, Giuseppe Montrucchio
Department of Medical Sciences, University of Turin and Città della Salute e della Scienza Hospital, Turin, Italy

Emanuele Pivetta
Department of General and Specialized Medicine, Division of Emergency Medicine and High Dependency Unit. Città della Salute e della Scienza Hospital, Turin, Italy

Massimo Porta
Department of Medical Sciences, Unit of Medicine 1, University of Turin and Città della Salute e della Scienza Hospital, Turin, Italy

Luca Scaglione
Internal Medicine Unit, Città della Salute e della Scienza Hospital, Turin, Italy

Franco Veglio
Department of Medical Sciences, Internal Medicine and Hypertension Division. University of Turin and Città della Salute e della Scienza Hospital, Turin, Italy

Marinella Zanierato
Department of Surgical Sciences, University of Turin, Turin, Italy

Fulvio Ricceri
Centre for Biostatistics, Epidemiology and Public Health, Department of Clinical and Biological Sciences, University of Turin, Orbassano and Unit of Epidemiology, Regional Health Service ASL TO3, Grugliasco, Italy

Valeria Caramello
Emergency Department and High Dependency Unit, San Luigi Gonzaga University Hospital, Orbassano, Italy

Gitana Scozzari, Antonio Scarmozzino
Hospital Medical Direction, Ospedale Molinette, University Hospital Città Della Salute e Della Scienza di Torino, Turin, Italy

*Corresponding author.
E-mail address: Carlotta.sacerdote@cpo.it (C. Sacerdote)

[1] COVID-EASY NET working group: Grazia Maria Auzzas, Cristina Balestro, Carol Brentisci, Francesco Brunetti, Umberto Fiandra, Claudia Galassi, Manuela Gangemi, Lisa Giacometti, Marco Gilardetti, Fulvio Lazzarato, Vitor Hugo Martins, Matteo Papurello, Francesca Ponti di Sant'Angelo, Stefano Roggero, Fabio Saccona, Carlo Silvestre, Antonella Stura, Danila Turco, Federico Vischia, Susanna Zozzoli. (SSD Epidemiologia clinica e valutativa, SC Epidemiologia dei tumori, AOU Città della salute e della scienza di Torino – CPO Piemonte, Torino).

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No durable impact of COVID-19 measures on the hospital burden of respiratory syncytial virus (France, 2018–2022)

Dear Editor,

Lumley *et al.* recently reported that, at the beginning of the COVID-19 pandemic, the usual winter 2020/2021 Respiratory Syncytial Virus (RSV) peak did not occur in Oxfordshire, UK, with an inter-seasonal rise several months later,[1] as described worldwide.[2-6] We previously described, in our French tertiary hospital, that the delayed RSV 2020/2021 outbreak involved less adults and was associated with more hospitalization, higher age of pediatric inpatients and milder median clinical phenotype than observed before the COVID-19 pandemic.[2] In France, severe public restrictions (national lockdown, curfew) ended in May-June 2021, but some measures have been maintained (universal masking policy in adults and children ≥6 years in healthcare settings, schools, public transportations and most indoor spaces, educational interventions for prevention of community and healthcare-associated respiratory infections). Our study aims to evaluate (i) if these measures had an impact on the hospital burden of RSV in the 2021/2022 season when compared to the prepandemic outbreaks and (ii) if the epidemiological changes observed in 2020/2021 were also seen in 2021/2022.

All subjects admitted to Necker Hospital (Paris, France) between August 1, 2018 and February 28, 2022, with a diagnosis of RSV acute lung respiratory infection (ALRI) were included. The ALRIs was designated as nosocomial when the patient had been hospitalized ≥2 days before the onset of symptoms. The medical record of each inpatient with a positive RSV testing was examined to collect clinical and microbiological data (Supplementary data).

Overall, 1062 RSV ALRIs were diagnosed during the study period, including 1015 community-acquired infections (Table). The 2021/2022 outbreak had similar seasonality pattern than the pre-COVID-19 outbreaks: contrary to 2020/2021 where 93.5% of cases occurred between January and March, nearly 90% of RSV ALRIs occurred between mid-October and mid-February in 2018/2020 and in 2021/2022. In pediatric units, the incidence density of community-acquired RSV ALRIs among inpatients significantly increased between 2018/2020 and 2020/2021 (8.9 versus 12.1/1000 inpatients, $p = 0.0001$), between 2018/2020 and 2021/2022 (8.9 versus 22/1000 inpatients, $p<0.0001$) and between 2020/2021 and 2021/2022 ($p<0.0001$). The proportion of the number of hospitalization days due to pediatric inpatients infected with community-acquired RSV among all subjects admitted during the study period was stable between 2018/2020 and 2020/2021 but increased between 2018/2020 and 2021/2022 (1.13/100 versus 2.83/100 hospitalization days, $p<0.0001$) and between 2020/2021 and 2021/2022 (1.56/100 versus 2.83/100 hospitalization days, $p<0.0001$). In adults units, the incidence density of community-acquired infections among inpatients was stable over time. After a transient decrease in 2020/2021, the proportion of hospitalization days due to adults infected with community-acquired RSV reached a similar rate in 2021/2022 than observed before the COVID-19 pandemic (data not shown). Compared to 2018/2020, the 2021/2022 outbreak had similar distribution of age categories but involved less subjects with underlying complex chronic conditions (CCC) (29.4% versus 38.8%, $p = 0.008$) and/or severe diseases (median length of hospital stay = 6 [4–8] versus 7 [5–9] days ($p = 0.0005$), admission to intensive care unit (ICU) = 32.5% versus 42.2% ($p = 0.008$), use of non-invasive ventilation and/or high-flow nasal oxygen = 23.6% versus 31.8%, ($p<0.02$)).

Nosocomial RSV ALRIs were diagnosed in 47 subjects (Supplementary Table). The incidence density of nosocomial RSV ALRIs increased in pediatric units between 2018/2020 and 2021/2022 (0.31 versus 0.84/100 inpatients, $p = 0.02$) but was stable in adults units between study periods. Compared to community-acquired RSV, nosocomial infections were diagnosed less frequently in infants aged <6 months (17.0% versus 51.2%, $p<0.0001$), but more frequently in adults (21.3% versus 1.5%, $p<0.0001$), subjects with underlying CCC (87.2% versus 34.9%, $p<0.0001$) and subjects requiring ICU admission (87.2% versus 35.4%, $p<0.001$). The death rate (whatever the cause of death) was higher in subjects with nosocomial RSV ALRIs than in those admitted with community-acquired infections (4.3 versus 0.6%, $p = 0.045$).

Despite the maintain of some public health measures in France and the repeated educational interventions for prevention of respiratory infections in the community, the RSV 2021/2022 outbreak occurred with a higher proportion of hospitalization days due to community-acquired ALRIs compared to what observed during the pre-COVID-19 era. Our study highlights the great fragility of RSV control in the population and the fact that, except in case of extreme measures such as national lockdown, primary prevention measures are not sufficient to significantly decrease the hospital burden of community RSV ALRIs.

In 2021/2022, the distribution of age categories returned to similar values as observed during pre-COVID-19 outbreaks. However, the proportion of subjects with underlying CCC was significantly lower in 2021/2022 than in 2018/2020, which could, at less partly, explain the lower median severity of RSV infections during the recent outbreak. Two hypotheses could explain this finding. First, the cohort of RSV-naïve individuals was probably still larger in 2021/2022 than during the pre-COVID-19 era, leading to a higher incidence of RSV ALRIs in the general pediatric population (even in children without CCC). Second, individuals with CCC could be more sensitive to prevention messages about infection control, diffused repeatedly since the emergence of SARS-CoV-2, compared to the general population. Further studies are needed during future RSV outbreaks in order to evaluate if an impact of hygiene measures can be seen durably in individuals with CCC.

Compared to the pre-COVID-19 era, the recent RSV outbreak was characterized by a higher density incidence of nosocomial ALRIs in pediatric units. However the percentage of nosocomial infections among all diagnosed RSV ALRIs remained lower in our center than in previous pediatric studies (3.7% versus 5–6%).[7,8] Thus, no clear impact of reinforced hygiene measures taken during the COVID-19 pandemic was seen in our center, in the context of a pre-existing low rate of nosocomial RSV infections due to our multifaceted infection control strategy. Despite these encouraging findings, sustained efforts are required to prevent nosocomial RSV infections in adult units. Indeed, the proportion of adults with nosocomial infections was disproportionately higher than that of adults admitted with community-acquired ALRIs. Finally, the higher death rate observed in subjects with nosocomial ALRIs than in those with community-acquired infections was in line with studies suggesting a higher severity of nosocomial RSV infections.[8,9]

Because RSV may not have been screened in all patients with ALRI, this study may underestimate the real burden of RSV infection in our center. This underestimation may be more pronounced in patients with milder symptoms, where RSV may have been less frequently screened than in case of severe infection.

To conclude, current public health measures, although intensified compared to the pre-COVID-19 era, did not mitigate the hospital burden of RSV in 2021/2022. The identification of new preventive strategies targeted to the RSV reservoir in the population is urgently needed.

Funding

This study was carried out as part of our routine work.

Table
Comparison between characteristics and follow-up of patients admitted at Necker Hospital (Paris, France) with community-acquired RSV-associated ALRI between August 2018 and July 2020 (2018/2019 and 2019/2020 RSV outbreaks) and those of subjects admitted between August 2020 and April 2021 (2020/2021 RSV outbreak).

	2018/2019 and 2019/2020 outbreaks("pre-COVID-19" outbreaks)						2020/2021 outbreak		p*	2021–2022 outbreak		p§
	August 2018 – July 2019 (n = 229)		August 2019 – July 2020 (n = 183)		Total(n = 412)		August 2020 – July 2021(n = 277)			August 2021 – February 2022 (n = 326)		
Rate of patients admitted with RSV ALRIs (/1000 inpatients)												
In pediatric units	9.3		8.5		8.9		12.1		**<0.0001**	22		**<0.0001**
In adult units	0.8		0.7		0.8		0.1		0.12	0.7		1
Rate of total hospitalization days due to subjects with RSV ALRIs (/100 days)												
In pediatric units	1.81		1.26		1.55		1.56		0.8	2.83		**<0.0001**
In adults units	0.1		0.14		0.12		0.02		**<0.0001**	0.08		0.54
Male sex (n,%)	107	(46.7)	94	(51.4)	201	(48.8)	145	(52.3)	0.39	178	(54.6)	0.12
Age (n,%)												
0–5 months	138	(60.3)	95	(51.9)	233	(56.6)	112	(40.4)	**<0.0001**	175	(53.7)	0.46
Including children born between 32 and 36 WOG	23		10		33		8			20		
Including children born <32 WOG	3		1		4		0			1		
6–11 months	27	(11.8)	27	(14.8)	54	(13.1)	68	(24.5)	**0.0001**	52	(16.0)	0.29
12–23 months	23	(10.0)	29	(15.8)	52	(12.6)	52	(18.8)	**0.03**	43	(13.2)	0.83
2–17 years	35	(15.3)	27	(14.8)	62	(15.0)	44	(15.9)	0.83	53	(16.3)	0.22
≥ 18 years	6	(2.6)	5	(2.7)	11	(2.7)	1	(0.4)	**0.03**	3	(0.9)	0.11
Underlying medical conditions (n,%)												
At least one	94	(41.0)	66	(36.1)	160	(38.8)	98	(35.4)	0.38	96	(29.4)	**0.008**
Neuromuscular CCC	13	(5.7)	12	(6.6)	25	(6.1)	15	(5.4)		23	(7.1)	
Cardiovascular CCC	21	(9.2)	19	(10.4)	40	(9.7)	10	(3.6)		9	(2.7)	
Respiratory CCC	48	(21.0)	47	(25.7)	95	(23.1)	63	(22.7)		57	(17.5)	
Renal CCC	7	(3.1)	8	(4.4)	15	(3.6)	1	(0.4)		7	(2.1)	
Gastrointestinal CCC	6	(2.6)	6	(3.3)	12	(2.9)	6	(2.2)		13	(4.0)	
Hematological CCC and/or immune deficiency	18	(7.9)	11	(6.0)	29	(7.0)	19	(6.9)		19	(5.8)	
Metabolic CCC	2	(0.9)	10	(5.5)	12	(2.9)	5	(1.8)		9	(2.8)	
Other congenital or genetic defect	21	(9.2)	15	(8.2)	36	(8.7)	16	(5.8)		23	(7.1)	
Antiviral prophylaxis (n,%)									0.06			**0.049**
Palivizumab	6	(2.6)	0	(0.0)	6	(1.5)	0	(0.0)		1	(0.3)	
i.v. or s.c. polyvalent immunoglobulin	3	(1.3)	0	(0.0)	3	(0.7)	1	(0.4)		0	(0.0)	
Bacterial lower respiratory tract co-/super-infection												
Microbiologically proven infection	13	(5.7)	5	(2.7)	18	(4.4)	9	(3.2)	0.55	7	(2.1)	0.11
Suspected infection	64	(27.9)	78	(42.6)	142	(34.5)	92	(33.2)	0.74	121	(37.1)	0.49
Clinical follow-up												
LOS (days) (median, IQR)	7	[5–9]	7	[5–10]	7	[5–9]	6	[4–8]	**0.0002**	6	[4–8]	**0.0005**
ICU admission (n,%)	94	(41.0)	80	(43.7)	174	(42.2)	79	(28.5)	**0.0003**	106	(32.5)	**0.008**
Oxygen requirement (n,%)	182	(79.5)	151	(82.5)	333	(80.8)	217	(78.3)	0.44	246	(75.5)	0.09
Mechanical ventilation requirement (n,%)	8	(3.5)	9	(4.9)	17	(4.1)	8	(2.9)	0.53	10	(3.1)	0.55
Non-invasive ventilation and/or high-flow nasal oxygen requirement (n,%)	72	(31.4)	59	(32.2)	131	(31.8)	49	(17.7)	**<0.0001**	77	(23.6)	**0.02**
Antibiotic treatment (n,%)	137	(59.8)	95	(51.9)	232	(56.3)	136	(49.1)	0.07	167	(51.2)	0.18
Death (n,%)	3	(1.3)	1	(0.5)	4	(1.0)	0	(0.0)	0.15	2	(0.6)	0.70

RSV = respiratory syncytial virus; ALRI = acute lower respiratory tract infection; WOG = weeks of gestation; CCC = chronic complex conditions; i.v. = intraveinous; s.c. = subcutaneous; LOS = length of stay; ICU = intensive care unit.

* Comparison of patients admitted during the 2020/2021 outbreak versus those admitted during the "pre-COVID-19 outbreaks".

§ comparison of patients admitted during the 2021/2022 outbreak versus those admitted during the "pre-COVID-19 outbreaks".

Ethics

Participants provided informed consent for the anonymous use of their clinical and biological data for biomedical research and publication (for pediatric patients, informed consent was provided by parents/guardians). This study was reviewed and approved by the Necker Hospital Institutional Review Board (registration number in the registry of the Assistance Publique – Hôpitaux de Paris: 20190729122906).

Authors' contribution

JF and PF conceived the study and drafted the manuscript; JT, HC, CD, FM, PP, AS, HA and MLV provided contribution to the analysis of the data and the revision of the manuscript. All authors approved the final version to be published and agreed to be accountable for all aspects of the work.

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.2022.06.019.

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Jacques Fourgeaud
Laboratoire de microbiologie clinique, Hopital Necker – Enfants malades, Groupe hospitalier Assistance Publique – Hôpitaux de Paris (AP-HP).Centre – Université Paris Cité, 149 rue de Sèvres, Paris 75015, France
EHU 7327, Institut Imagine, Université de Paris, Paris, France
CNR Cytomegalovirus, Laboratoire associé, Hôpital Necker-Enfants malades, Paris, France

Julie Toubiana
Service de Pédiatrie générale et Maladies infectieuses, Hôpital Necker – Enfants malades, Groupe hospitalier AP-HP.Centre – Université Paris Cité, Paris, France
CNR de la Coqueluche et autres Bordetelloses, Unité « Biodiversité et épidémiologie des bactéries pathogènes », Institut Pasteur, Paris, France

Hélène Chappuy
Service d'Urgences pédiatriques, Hôpital Necker – Enfants malades, Groupe hospitalier AP-HP.Centre – Université Paris Cité, Paris, France
EA7323, Université Paris Cité, Paris, France

Christophe Delacourt
Service de pneumologie et allergologie pédiatriques, Hôpital Necker – Enfants malades, Groupe hospitalier AP-HP.Centre – Université Paris Cité, Paris, France

Florence Moulin
Service de Réanimation et surveillance continue médico-chirurgicale pédiatrique, Hôpital Necker Enfants-Malades, Groupe hospitalier AP-HP.Centre –Université Paris Cité, Paris, France

Perrine Parize
Service de Maladies infectieuses et tropicales, Hôpital Necker – Enfants malades, Groupe hospitalier AP-HP.Centre –Université Paris Cité, Paris. France

Anne Scemla
Service de Néphrologie – Transplantation, Hôpital Necker-Enfants malades, Groupe hospitalier AP-HP.Centre – Université Paris Cité, Paris, France
RTRS Centaure, Labex Transplantex, Université Paris Cité, France

Hanene Abid
Laboratoire de microbiologie clinique, Hopital Necker – Enfants malades, Groupe hospitalier Assistance Publique – Hôpitaux de Paris (AP-HP).Centre – Université Paris Cité, 149 rue de Sèvres, Paris 75015, France

Marianne Leruez-Ville
Laboratoire de microbiologie clinique, Hopital Necker – Enfants malades, Groupe hospitalier Assistance Publique – Hôpitaux de Paris (AP-HP).Centre – Université Paris Cité, 149 rue de Sèvres, Paris 75015, France
EHU 7327, Institut Imagine, Université de Paris, Paris, France
CNR Cytomegalovirus, Laboratoire associé, Hôpital Necker-Enfants malades, Paris, France

Pierre Frange*
Laboratoire de microbiologie clinique, Hopital Necker – Enfants malades, Groupe hospitalier Assistance Publique – Hôpitaux de Paris (AP-HP).Centre – Université Paris Cité, 149 rue de Sèvres, Paris 75015, France
EHU 7327, Institut Imagine, Université de Paris, Paris, France

*Corresponding author.
E-mail address: pierre.frange@aphp.fr (P. Frange)

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Faecal calprotectin as a potential biomarker of disease severity in SARS-CoV-2 infection☆☆☆

Dear Editor,

We read with interest the article by Ijaz et al. regarding the mapping of SARS-CoV-2 IgM and IgG in gingival crevicular fluid (GCF), and its linkage to disease severity in hospitalised COVID-19 patients. The authors report some evidence that higher levels of antibody in GCF in the first 14 days post symptom onset were associated with severe disease and poor outcome.[1] The utility of less invasive, non-venous analytes has been increasingly recognised during the global pandemic. These may be used for both disease detection and prediction of severity. The identification of biomarkers of disease severity in COVID-19 would be of considerable clinical value, particularly with the current limited availability of novel antiviral therapy, which are known to exert a maximal efficacy when given early in the disease course.

While predominantly recognised as an infection of the respiratory tract, gastrointestinal symptoms are frequently reported, with the incidence of diarrhoea and abdominal pain ranging from 2 to 49%.[2] Both the SARS-CoV-2 receptor, angiotensin-converting enzyme 2 (ACE-2), as well as the SARS-CoV-2 nucleocapsid protein have been detected in gastrointestinal epithelial cells (enterocytes), suggesting a role for direct viral infection resulting in cytokine release and neutrophil activation.[3] Furthermore, SARS-CoV-2 RNA has been detected in stool samples and colonic biopsies, implicating the gut as a site of viral replication.[4]

The hypothesised effects of SARS-CoV-2 infection on enterocytes include a direct viral insult resulting in gastrointestinal inflammation and disruption to intestinal barrier function, with subsequent release and up regulation of inflammatory cytokines causing an exaggerated inflammatory response.[5] Indeed, alterations in intestinal barrier function, supporting this hypothesis, have been demonstrated in patients with COVID-19.[6] Whether inflammation and disruption of the intestinal barrier by COVID-19 results in up-regulation of the host immune response and a resultant increased severity of disease remains unknown.

Faecal calprotectin (FCP), a measure of neutrophil activation, is a recognised correlate of intestinal injury which rises in response to both acute and chronic inflammatory conditions. This non-invasive measurement of intestinal inflammation is frequently employed in the assessment of inflammatory bowel conditions. Elevated levels of FCP have been demonstrated in patients with symptomatic COVID-19, with the presence of both acute and resolved diarrhoea,[7] and in the absence of gastrointestinal symptoms,[8] regardless of whether SARS-CoV-2 RNA is detected in stool samples. Elevated levels of serum calprotectin (SCP) have previously been demonstrated in patients with severe complications of SARS-CoV-2 infection,[9] however in a large ambulatory cohort of individuals with COVID-19, SCP was not predictive of developing severe disease.[10]

We performed an analysis within a prospective observational study to assess the presence and significance of intestinal inflammation in a cohort of individuals with mild-moderate, PCR-confirmed SARS-CoV-2 infection (classified as per the World Health Organisation classification of severity), with and without gastrointestinal symptoms. We compared these findings with an age and sex-matched control group with a respiratory infection but who were confirmed SARS-CoV-2 PCR negative. We sought to determine whether intestinal inflammation was more prevalent in those with COVID-19, and what association, if any, this had with disease severity and clinical outcome.

Patients admitted to hospital due to complications of COVID-19 during the first wave of the SARS-CoV-2 pandemic (March–November 2020) were recruited to a prospective, multicentre cohort study (the All-Ireland Infectious Disease Cohort (AIID) Study). Patients with mild to moderate disease severity as per WHO severity index (WHO 1–2) were included and asked to provide a stool sample for analysis. Demographic and biochemical data were collected, as well as details of clinical course and use of steroid and antibiotic therapy. Systemic serum markers of inflammation (C-reactive protein, ferritin, platelets) were recorded. Requirement for non-invasive ventilation, escalation to intensive care and death were recorded and combined as a composite outcome of severity. Length of stay was also recorded as a surrogate marker of severity. Stool samples were tested for the presence of faecal calprotectin using a qualitative immunochromatographic assay (output as elevated or negative) and a quantitative enzyme-linked im-

☆ This study has been approved by the Research Ethical Committee of St. Vincent's University Hospital

☆☆ PM and GD contributed to the conception and design of the study. NOM, MT and AGL contributed to the acquisition, analysis, and interpretation of data. NOM drafted the article. JD and RS contributed to critically revising the article. PM and GD contributed to revising the article and gave final approval of the version to be submitted.

Table 1
Demographics, patient characteristics, biochemical data of patients with COVID-19.

COVID +ve (n = 22)	FCP +ve (n = 13)	FCP –ve (n = 9)	P value
Age (median) [IQR]	70 [63 – 82]	54 [48 – 56]	0.17
Gender (female)	38% (n = 5)	67% (n = 6)	0.19
BMI (kg/m2)	24	28	0.18
Co-Morbidities	92% (n = 12)	89% (n = 8)	
- Hypertension	62% (n = 8)	33% (n = 3)	
- GI Disease	0%	44% (n = 4)	
Respiratory Symptoms	62% (n = 8)	66% (n = 6)	0.58
Viral Symptoms	33% (n = 5)	89% (n = 8)	0.25
Nausea	0	0	
Abdominal Pain	13% (n = 2)	0	
Diarrhoea	13% (n = 2)	33% (n = 3)	
Time to stool sample (days) [IQR]	11 [4-35]	7 [3-19]	
Faecal Calprotectin	119 [84-532]	26 [12-29]	<0.01
Quantitative (+ve) (median) [IQR]			
CRP (median)	15	6	0.12
Ferritin	638	240	0.053
Leukocytes	5.95	5.3	0.95
PPI use	20% (n = 3)	22% (n = 2)	0.68
Length of Stay (days) [IQR]	54 [13-71]	9 [3-11]	*0.017*

munosorbent assay (ELISA) (reported in ug/g). Use of proton-pump inhibitors (PPI), known to cause an elevation in FCP, was recorded as a potential confounder.

During the study period, we collected stool samples from 37 subjects, of whom 22 (59%) had SARS-CoV-2 detected on PCR from nasopharyngeal swab, with 15 (41%) SARS-CoV-2 negative controls. The median ages (62 vs. 67, $p = 0.5$), gender (female 50% vs. 53%, $p = 0.5$) and median BMI (25.1 vs. 26.3 kg/m^2) were similar between the two groups. While GI symptoms were more common in the COVID-19 group (32% vs 0%, p=<0.05), there was no significant difference in qualitative FCP (45% vs. 40%, $p = 0.5$) with similar median quantitative FCP (73ug/g vs. 95ug/g, $p = 0.7$). There was also no between-group difference in PPI use (23% vs. 25%, $p = 0.5$), co-morbidities (92% vs. 89%), LOS (16.5 days vs. 6, $p = 0.4$) or markers of systemic inflammation (data not shown).

Within the COVID-19 group, a positive FCP qualitative assay ($n = 13$) corresponded to a median FCP of 119 ug/g (IQR 84–532). Interestingly, an elevated FCP was associated with a statistically significantly higher ferritin (638 ug/L vs. 240 ug/L, $p = 0.05$) and a longer hospital length of stay (54 vs. 9 days, $p = 0.02$). Although an elevated FCP was not linked to reported GI symptoms (16% in those with elevated FCP vs. 33% in those with a negative FCP, $p = 0.4$), need for supplemental oxygen (median Fi02 28%) or need for steroid therapy (dexamethasone 6 mg), there was a trend towards a more severe clinical disease course for those with evidence of intestinal inflammation. In the group with elevated FCP, 2 were referred to intensive care, both of whom died. All patients with a negative FCP were discharged home and did not reach the composite outcome of severity.

Our study suggests that while GI symptoms are commonly reported in patients with SARS-CoV-2 infection, these correlate poorly with non-invasive markers of intestinal inflammation. Faecal calprotectin, in our study, was not a sensitive marker of SARS-CoV-2 related intestinal injury, with similar levels detected in both COVID-19 subjects and control groups. Nonetheless, elevated FCP levels in those with mild to moderate SARS-CoV-2 did demonstrate an association with elevated systemic inflammation as measured by serum ferritin levels, a significantly longer length of hospital stay, and a more severe clinical course. This suggests its utility may lie as a biomarker of disease severity in those with confirmed SARS-CoV-2 infection. Further larger prospective cohort studies are required to confirm this association.

The All Ireland Infectious Diseases (AIID) Study Group members:

Prof Patrick Mallon	Prof of Microbial Disease	St Vincent's University Hospital/ University College Dublin
Dr Aoife Cotter	Infectious Disease Consultant	Mater Misericordiae University Hospital/ University College Dublin
Dr Eoghan de Barra	Infectious Disease Consultant	Beaumont Hospital/ Royal College of Surgeons in Ireland
Dr Eoin Feeney	Infectious Disease Consultant	St Vincent's University Hospital/ University College Dublin
Prof Mary Horgan	Professor School of Medicine	Cork University Hospital/ University College Cork

(*continued on next page*)

Prof Jack Lambert	Infectious Disease Consultant	Mater Misericordiae University Hospital/ University College Dublin
Dr Corinna Sadlier	Infectious Disease Consultant	Cork University Hospital/ University College Cork
Dr Obada Yousif	Consultant in General Medicine (Endocrine and Diabetes)	Wexford General Hospital/ University College Dublin

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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N O'Moráin, R Stack, J Doherty
on behalf of the *Centre for Colorectal Disease, St. Vincent's University Hospital, Elm Park, Dublin 4, Ireland*
School of Medicine, University College Dublin, Dublin, 4, Ireland

M Tosetto
Centre for Colorectal Disease, St. Vincent's University Hospital, Elm Park, Dublin 4, Ireland

A Garcia Leon
Centre for Experimental Pathogen Host Research, University College Dublin, Dublin, 4, Ireland

P Mallon
Centre for Experimental Pathogen Host Research, University College Dublin, Dublin, 4, Ireland
Department of Infectious Disease, St. Vincent's University Hospital, Dublin, 4, Ireland

G Doherty
Centre for Colorectal Disease, St. Vincent's University Hospital, Elm Park, Dublin 4, Ireland
School of Medicine, University College Dublin, Dublin, 4, Ireland

*Corresponding author at: Centre for Colorectal Disease, St. Vincent's University Hospital, Elm Park, Dublin 4, Ireland.
E-mail address: neilomorain@svhg.ie (N. O'Moráin)

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Immunogenicity of a single dose of BNT162b2, ChAdOx1 nCoV-19, or CoronaVac against SARS-CoV-2 delta and omicron variants among previously infected adults: A randomized trial

Dear Editor,

In this journal, Westrop *et al.* (2022) reported that heterologous COVID-19 vaccine schedules involving adenoviral-vector and mRNA vaccines were highly immunogenic, and that the immune responses were higher among previously infected adults compared to infection-naïve adults.[1] These findings were consistent with a number of studies that demonstrated that two-dose mRNA COVID-19 vaccine regimens in individuals previously infected with SARS-CoV-2 were more immunogenic compared to natural infection or vaccination alone.[2-4] However, this evidence was largely based on mRNA vaccine regimens and was conducted before the introduction and global spread of the omicron variant.

Prior to the emergence of omicron, a retrospective study in Israel suggested that a single dose of BNT162b2 after natural infection provided high vaccine effectiveness (82%) against SARS-CoV-2 reinfection compared to participants who were infected but unvaccinated; this was the same for two doses.[5] However, it remained unclear whether natural immunity against previous SARS-CoV-2 variants (*i.e.,* Wuhan or alpha), followed by a single dose of COVID-19 vaccine, was sufficient to protect individuals from omicron. As the immunogenicity of inactivated and adenoviral vectored vaccines among individuals previously infected with SARS-CoV-2 had not been described, we investigated the immunogenicity of a single dose of BNT162b2, ChAdOx1 nCoV-19 (ChAdOx1), or CoronaVac against SARS-CoV-2 delta and omicron variants in individuals who recovered from COVID-19.

Enrolled participants provided written informed consent, were ≥18 years old, and diagnosed with COVID-19 between 6-24 weeks prior to study recruitment. Exclusion criteria included individuals: with RT-PCR confirmed SARS-CoV-2 reinfection, that received two doses of any registered COVID-19 vaccine before diagnosis of COVID-19, that received prophylactic treatment or investigational agents against COVID-19, that had a history of vaccine hypersensitivity, that were immunocompromised or received immunosuppressive agents, or that had unstable underlying diseases. This randomized study was performed between May and August 2021, when D614G ancestral and alpha SARS-CoV-2 variants were circulating in Thailand. Participants were randomly assigned to receive a single dose of CoronaVac (Sinovac Life Science), ChAdOx1 (Oxford-AstraZeneca), or BNT162b2 (Pfizer-BioNTech), with blood samples collected before and 14 days after vaccination. SARS-CoV-2 specific anti-receptor binding domain IgG (Abbott SARS-CoV-2 IgG II Quant assay), pseudovirus-based neutralizing antibodies against delta and omicron variants, as well as SARS-CoV-2-specific memory T-Cell responses against spike and nucleoprotein-membrane protein-open reading frame (NMO) proteins of the ancestral strain (IFN-γ ELISpot, Mabtech, Sweden) were measured. This study was approved by the Siriraj Institutional Review Board (COA no. Si 546/2021), and its protocol registered at the Thai Clinical Trial Registry (TCTR20210720005).

Anti-RBD IgG and neutralizing antibodies were reported as geometric mean concentration (GMC) and geometric mean titers (GMT) with 95% confidence intervals (CI), respectively. For multiple comparisons, the analysis of variance (ANOVA) for parametric data and Wilcoxon Rank Sum test for non-parametric data were used to assess the differences among groups. Paired and unpaired *t* tests were used to compare GMC and GMT within group and between groups, respectively, using GraphPad Prism 9 version 9.2.0 (283) (GraphPad Software, CA, USA), respectively. Correlation analysis was performed using the Spearman correlation analysis. Other statistical analyses were conducted using STATA version 17 (Stata Corp, LP, College Station, TX, USA). Adverse events (AEs) and secondary outcome measures were descriptively analyzed.

Of the 166 participants screened, 23 were excluded from the study per aforementioned criteria, and 29 were excluded from the analysis due to receiving doses of COVID-19 vaccines prior to SARS-CoV-2 infection (Supplementary Fig. 1). A total of 114 adults were included in the final analysis , 52 (45.2%) participants were male, and the median age (IQR) was 38.5 (29-45) years (Table 1). There was no statistical difference in baseline characteristics and intervals between COVID-19 diagnosis and vaccination across the three vaccination groups (Table 1).

A single dose of either study vaccine significantly increased the SARS-CoV-2 IgG concentration (Supplementary Fig. 2) and neutralizing antibody titers ($PVNT_{50}$) against delta and omicron variants (Fig. 1A-B) from pre-vaccination. Both BNT162b2 and ChAdOx1 groups induced significantly higher antibody responses than the CoronaVac group: the geometric mean $PVNT_{50}$ (95% CI) for BNT162b2, ChAdOx1, and CoronaVac groups for delta were 2,503 (1865, 3359), 1,093 (808,1480), and 340 (228,507); and for omicron were 372 (193,717), 176 (84.8, 364), and 6.9 (2.2, 22.1), respectively (Fig. 1A-B). Importantly, a single dose of BNT162b2 or ChAdOx1 but not CoronaVac induced similar $PVNT_{50}$ against delta and omicron as to those induced by three doses of COVID-19 vaccines (two primary doses of ChAdOx1 plus a BNT162b2b booster) previously reported in healthy Thai adults who never had SARS-CoV-2 infection (5) (Fig. 1A-B). A single dose of CoronaVac in previously infected individuals produced similar $PVNT_{50}$ as those who received two doses of BNT162b2 primary series (7) (Fig. 1B).

Similarly, all three vaccines significantly increased T-Cell responses to spike protein (Fig. 1C), while only CoronaVac significantly increased T-Cell responses to NMO proteins (Fig. 1D). Both BNT162b2 and ChAdOx1 induced significantly higher T-Cell responses than CoronaVac. There was a strong correlation between SARS-CoV-2 IgG and spike-specific T-Cell responses (Supplementary Fig. 3).

Our results suggested that among individuals who were previously infected with SARS-CoV-2 (ancestral strain, with D614G mutation, and alpha strain), a single dose of BNT162b2 or ChAdOx1, but not CoronaVac, may provide similar protection against delta and omicron variants as individuals vaccinated with three doses of COVID-19 vaccines. These findings are particularly relevant for countries where there have been with limited access to vaccines such as BNT162b2 and ChAdOx1 but have a high level of natural immunity to SARS-CoV-2. Limitations of the study include the small sample size, and generalization of our findings to other COVID-19 vaccines and previous infection with other SARS-CoV-2 variants.

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Declaration of Competing Interests

The authors declare no competing interests.

Table 1
Baseline characteristics of vaccine-naïve participants enrolled by type of vaccines.

Baseline characteristics	Type of vaccinations following SARS-CoV-2 detection				
	Total	BNT162b2	ChAdOx1	CoronaVac	*P* value
Number of participants, n (%)	114	31 (27.2)	45 (39.5)	38 (33.3)	
Male, n (%)	52	14 (45.2)	19 (42.2)	19 (50.0)	0.78
Age, median (IQR)	38.5 (29, 45)	37 (28, 44)	39 (29, 48)	39 (29, 45)	0.90
Body mass index, median (IQR)	24.40 (21.0, 27.4)	23.3 (20.3, 26.4)	24.5 (21.8, 27.4)	25.4 (21.1, 28.6)	0.17
Days from diagnosis to enrollment, median (IQR)	85 (61, 119)	67 (54, 126)	111(61, 120)	88 (62, 114)	0.20

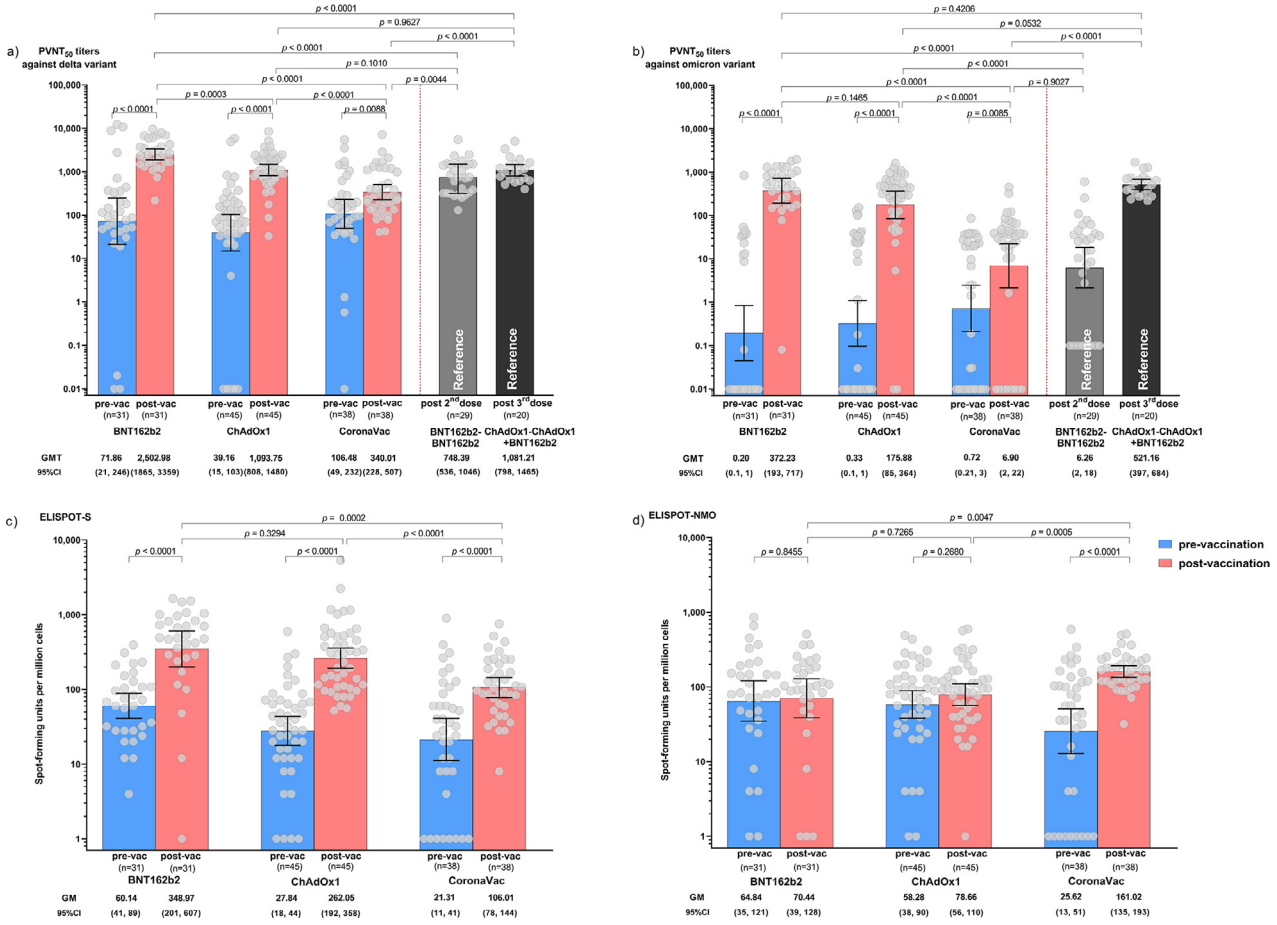

Fig. 1. A) Neutralization titers against delta variant determined using the pseudovirus neutralization assay. B) Neutralization titers against omicron variant determined using the pseudovirus neutralization assay. C) IFN-γ T-Cell responses against spike protein of ancestral strain determined using ELISpot assay. D) IFN-γ T-Cell responses against NMO protein of ancestral strain determined using ELISpot assay. ELISpot indicates enzyme-linked immunospot; $PVNT_{50}$, 50% reduction of infectivity; IFN, interferon; SFU, spot-forming unit; pre-vac, pre-vaccination; post-vac, post-vaccination. In panel A and B, data were presented as geometric mean titers with 95% confidence interval. Paired pre- and post-vaccination $PVNT_{50}$ titers were log-transformed and compared using paired Student's t-test. $PVNT_{50}$ titers between vaccine groups were log-transformed and compared using unpaired Student's t-test. In panel C and D, data were presented as geometric mean SFU with 95% confidential interval. Paired pre- and post-vaccination SFU were log-transformed and compared using paired Student's t-test. SFU between vaccine groups were log-transformed and compared using unpaired Student's t-test. The reference bar in panel A and B were the results from studies conducted in the same setting as this study (6,7).

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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.2022.06.014.

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Suvimol Niyomnaitham
Department of Pharmacology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700 Thailand
Siriraj Institute of Clinical Research (SICRES), Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand

Zheng Quan Toh, Paul Vincent Licciardi
Infection and Immunity, Murdoch Children's Research Institute, Parkville, Victoria 3052 Australia
Department of Pediatrics, The University of Melbourne, Parkville, Victoria 3010 Australia

Patimaporn Wongprompitak
Department of Immunology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700 Thailand

Kanjana Srisutthisamphan
National Center for Genetic Engineering and Biotechnology (BIOTEC), National Science Development Agency (NSTDA), Pathum Thani 12120 Thailand

Katherine Kradangna Copeland
Mahidol University International College, Mahidol University, Salaya, Nakhon Pathom 73170 Thailand

Kulkanya Chokephaibulkit*
Siriraj Institute of Clinical Research (SICRES), Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand
Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700 Thailand

*Corresponding author at: Kulkanya Chokephaibulkit, MD. Professor of Paediatrics, Department of Paediatrics and Siriraj Institute of Clinical Research (SICRES), Faculty of Medicine Siriraj Hospital, 2 Wanglang Road, Bangkoknoi, Bangkok 10700, Thailand.
E-mail address: kulkanya.cho@mahidol.ac.th (K. Chokephaibulkit)

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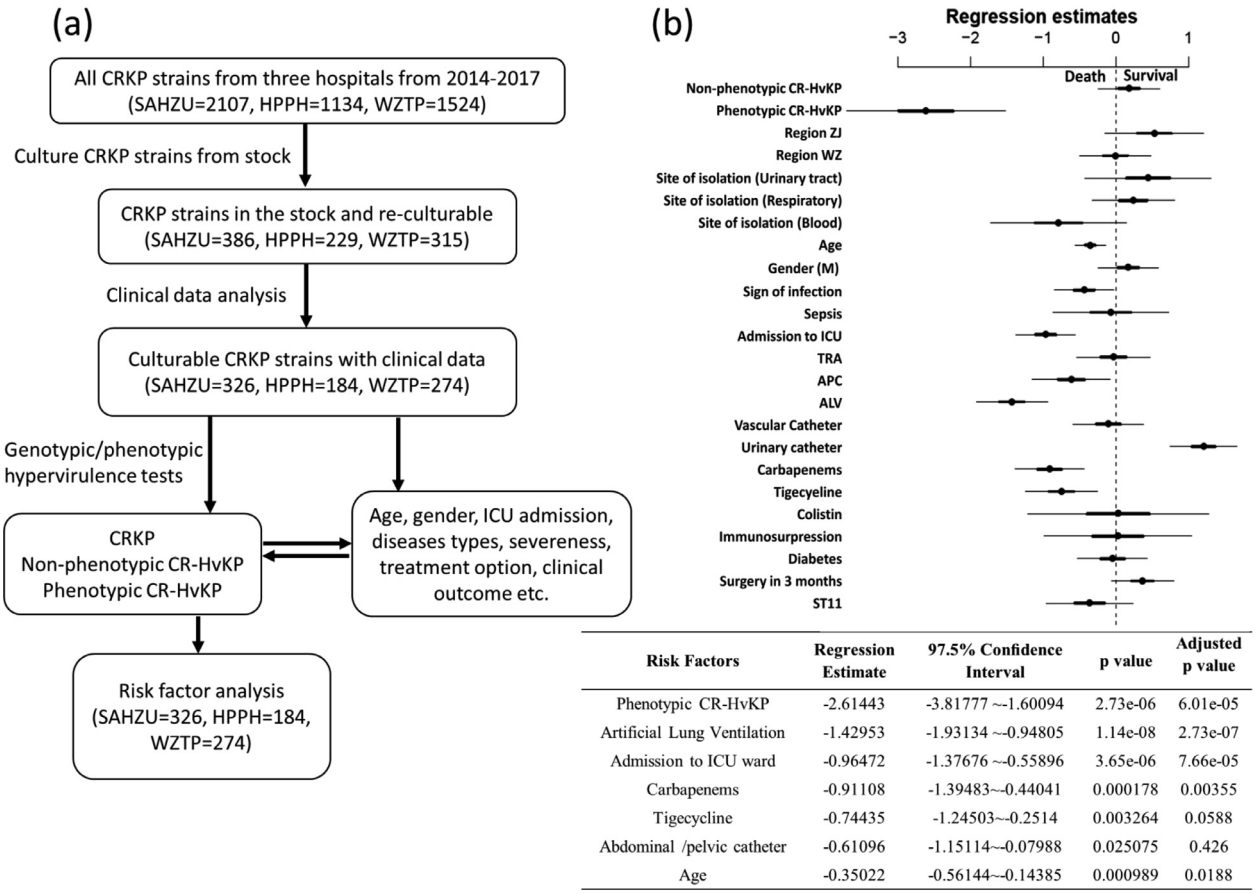
Risk factors and clinical impact associated with infections caused by different types of carbapenem-resistant *Klebsiella pneumoniae* in China: A clinical study from 2014 to 2017

Dear Editor,

We read with great interest on a recent study by Tao Lou and colleagues entitled "Risk factors for infection and mortality caused by carbapenem-resistant *Klebsiella pneumoniae*: A large multicentre case-control and cohort study" in this journal.[1] Data from this study showed a very high clinical mortality rate caused by carbapenem-resistant *K. pneumoniae* (CRKP) infections, reaching 24.2% for the 28-day crude mortality and over 45% for bloodstream infections. We believe that CRKP strains in this study included the newly discovered carbapenem-resistant and hypervirulent *K. pneumoniae* (CR-HvKP).[2] It is interesting and important to compare the clinical mortality caused by CRKP and CR-HvKP strains. We have conducted a study to compare the clinical risk factors involved in clinical infections caused by CRKP and CR-HvKP strains, which will provide additional insights into current study.

A total of 784 CRKP strains collected during the period 2014–2017 from three hospitals, Second Affiliated Hospital of Zhejiang University (SAHZU) and Wenzhou Tertiary Hospital (WZTH), located in different cities of the same province, Zhejiang Province, China and Henan Provincial People's Hospital (HPPH), located in a city in Henan Province, which is geographically distant from Zhejiang Province. These three hospitals have a total of around 10,000 beds and serve for over 27 million populations. The workflow of the current study is outlined in Fig. 1**a**. The rate of CRKP infection increased stably from 20% in 2014 to 36.3% in 2017 in SAHZU, from 8.7% in 2014 to 61.4% in 2017 in HPPH, and from 6.4% in 2014 to 18% in 2017 in WZTH. To assess the prevalence of CR-HvKP among these strains, we performed screening of the conservative, plasmid-borne virulence genes *rmpA, rmpA2* and *iutA* by PCR assays[3,4] and found that carriage of the virulence plasmid among clinical CRKP strains was a common event, with 457/784 (58%) of the CRKP strains tested carrying at least two of these three genes. The overall carriage rate of the virulence plasmid in CRKP strains collected from these three hospitals increased dramatically from 2014 to 2016, dropping slightly in SAHZU and HPPH in 2017, whereas the carriage rate in WZTH declined gradually over the years. String test was also performed on all 784 strains regardless of their status of carriage of virulence plasmid.[4] Surprisingly, we found that carriage of the virulence plasmid did not correlate with the string test results. Among the 457 clinical CRKP strains that harbored the virulence plasmid, only 64 (14%) were positive for string test; 60 of these 64 strains exhibited high survival rate (>70%) in neutrophils. We define these 60 strains that carried *rmpA2* and *iutA*, and exhibited hypermucovisity phenotype and >70% survival rate in neutrophil assay as phenotypically hypervirulent (phenotypic CR-HvKP). It should be noted that in one hospital (SAHZU), the recovery rate of phenotypic CR-HvKP increased from none in 2014 and 2015 to 6% and 18% in 2016 and 2017 respectively.

Analysis of clinical record of patients from whom these 784 CRKP strains were recovered showed that CRKP were most commonly among ICU patients (54%). CRKP strains were recoverable from a variety of specimens, with respiratory (58%) and blood (17%) samples being the most common. Invasive procedures were commonly associated with CRKP infections, with 96% of the patients being treated with at least one type of invasive procedures, among which mechanical lung ventilation (67%), vascular catheter (58%) and urinary catheter (58%) were the most common (Table 1). Most of the patients had been treated with a range of antibiotics, with carbapenems being the most commonly prescribed drug (75%), followed by tigecycline (30%). The overall mortality rate for these CRKP was very high reaching 41% (322/784). There are 329 out of 784 patients were confirmed to be recovered, while 133 patients lacked of confirmative outcome due to being transferred to other hospitals. We performed comparative analysis of clinical data from patients with clinical outcome of dead (n = 322) or survival (n = 329) to identify risk factors that contributed to clinical morality of CRKP infections using multivariate logistic regression analysis. Holm correction was



Risk Factors	Regression Estimate	97.5% Confidence Interval	p value	Adjusted p value
Phenotypic CR-HvKP	-2.61443	-3.81777 ~-1.60094	2.73e-06	6.01e-05
Artificial Lung Ventilation	-1.42953	-1.93134 ~-0.94805	1.14e-08	2.73e-07
Admission to ICU ward	-0.96472	-1.37676 ~-0.55896	3.65e-06	7.66e-05
Carbapenems	-0.91108	-1.39483~-0.44041	0.000178	0.00355
Tigecycline	-0.74435	-1.24503~-0.2514	0.003264	0.0588
Abdominal /pelvic catheter	-0.61096	-1.15114~-0.07988	0.025075	0.426
Age	-0.35022	-0.56144~-0.14385	0.000989	0.0188

Fig. 1. Study design and risk factor analysis. (a) Enrollment and randomization of patients and CRKP strains. SAHZU, Second Affiliated Hospital of Zhejiang University; HPPH, Henan Provincial People's Hospital; WZTH, Wenzhou Tertiary Hospital. CRKP, carbapenem-resistant *K. pneumoniae*; Non-phenotypic CR-HvKP, CRKP strains carrying virulence plasmid without exhibiting the hypervirulence phenotype; Phenotypic CR-HvKP, CRKP strains with hypervirulence phenotype. (b) Risk factors of clinical mortality of CRKP infections as depicted by Cox regression analysis. TRA, Tracheal intubation / tracheotomy; ALV, Artificial lung ventilation; APC, Abdominal /pelvic catheter. Regression estimate approaching to negative number represents higher association with clinical mortality and that approaching to positive number represents high survival.

used to adjust the P value. We separated all CRKP strains into three groups, namely, virulence plasmid-negative CRKP (vpnCRKP), virulence plasmid-positive but non-phenotypic hypervirulent CR-HvKP (nphCR-HvKP) and virulence plasmid-positive and phenotypic hypervirulent CR-HvKP (phCR-HvKP) to analyze their potential contribution to mortality. Ethical approval for this study has been obtained for this study with approval number of 2,017,084. Our analysis has identified factors that were strongly associated with clinical mortality of CRKP infections including (1) infection by phenotypic CR-HvKP (harzard ratio, −2.61; 95% CI, −3.81∼ −1.60; p = 6.01e-05), (2) use of artificial lung ventilation (harzard ratio, −1.43; 95% CI, −1.93 ∼ −0.94; p = 2.73e-07) and (3) admission to ICU (harzard ratio, −0.96; 95% CI, −1.37 ∼ −0.55; p = 7.66e-05), (4) use of carbapenems (harzard ratio, −0.91108; 95% CI, −1.39∼−0.44; p = 0.00356) and (5) ages (harzard ratio, −0.35022; 95% CI, −0.56∼−0.14; p = 0.0188). Interestingly, clinical use of tigecycline was also marginally associated with high clinical morality (harzard ratio, −0.74435; 95% CI, −1.24∼−0.25; p = 0.0588). Regression estimate analysis using Boost Regression Tree method showed that the level of risks of these factors, with the order of high to low, was as follows: infection by phenotypic CR-HvKP, artificial lung ventilation, admission to ICU ward, use of carbapenems, use of tigecycline, abdominal /pelvic catheter and old age (Fig. 1**b**). Importantly, our data were consistent with the current study in several aspects with the most interesting finding was that the use of antibiotics such as carbapenems and tigecycline was the risk factor associated with high mortality. This is important since carbapenems and tigecycline are commonly used clinically to treat CRKP infections in China. More researches are needed to confirm these risk factors. Furthermore, our data showed that phenotypic CR-HvKP strains are strongly associated with clinical mortality, which need further attention since CR-HvKP are increasingly prevalent in China.

Contributors

QLS, YLH, YL and JPL collected the strains, performed strain characterization and collected clinical data; XMY helped with strain characterization and clinical data analysis; HDH and CCL helped with data analysis; RZ and SC designed and supervised the study, and interpreted the data; SC wrote the manuscript.

Declaration of Competing Interest

We declare that we have no conflicts of interest.

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Table 1
Analysis of risk factors that significantly contribute to clinical mortality of CRKP infections.

Factors	Death n = 322 (%)	Recovered n = 329 (%)	P value	Adjusted P+
Region				
Hangzhou	129	110		
Zhengzhou	83	87	0.1248	1
Wenzhou	110	132	0.9877	1
Age (years)			0.0009887	0.01879 *
<18	1 (0.3)	5 (1.5)		
18–60	137 (41.3)	170 (51.7)		
>60	184 (55.4)	154 (46.8)		
Sex (male)	215 (64.8)	230 (69.9)	0.4246	1
Site of isolation				
Respiratory	163 (49.1)	199 (60.5)	0.4013	1
Blood stream	93 (28.0)	40 (12.2)	0.09649	1
Urinary tract	20 (6.0)	35 (10.6)	0.3148	1
Others	46 (10.8)	55 (16.7)		
Admission to ICU	221 (66.7)	125 (38.0)	3.647e-06	7.660e-05 *
Comorbidities				
Immunosuppression	18 (5.4)	13 (4.0)	0.9519	1
Diabetes	102 (30.7)	74 (22.5)	0.8571	1
Surgery in 3 months	147 (44.3)	189 (57.4)	0.09326	1
TRA	159 (47.9)	131 (39.8)	0.9063	1
ALV	245 (73.8)	175 (53.2)	1.139e-08	2.734e-07 *
Vascular catheter	197 (59.3)	168 (51.1)	0.6786	1
APC	197 (59.3)	168 (51.1)	0.0251	0.4263
Urinary catheter	166 (50.0)	204 (62.0)	2.617e-07	6.019e-06 *
Sepsis	114 (35.4)	129 (39.2)	0.8655	1
Sign of infections	186 (57.8)	57 (17.3)	0.03851	0.6162
Type of antibiotic used (within one month since the detection of *K. pneumoniae*)				
Carbapenems	276 (83.1)	224 (68.1)	1.777e-04	0.003555 *
Tigecycline	118 (35.5)	67 (20.4)	0.003264	0.05875
Colistin	12 (3.6)	6 (1.8)	0.9570	1
Type of CRKP strains				
CRKP	131 (39.5)	134 (40.7)		
Non-phen CR-HvKP	144 (43.4)	190 (57.8)	0.3988	1
Pheno CR-HvKP	47 (14.3)	5 (1.5)	2.732e-06	6.009e-05 *
ST type				
11	282 (87.6)	281 (85.4)	0.2370	1
others	40 (12.4)	48 (14.6)		

TRA, Tracheal intubation / tracheotomy; ALV, Artificial lung ventilation; APC, Abdominal /pelvic catheter.
+, P-value was determined by multivariate logistics regression. Adjusted P was determined by Holm corrections.
*statistically significant.

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Qiaoling Sun[1]
Department of Clinical Laboratory Medicine, Second Affiliated Hospital of Zhejiang University, Hangzhou, China
Department of Laboratory Medicine, School of Medicine, The First Affiliated Hospital, Zhejiang University, Hangzhou, China

Xuemei Yang[1]
Department of Infectious Diseases and Public Health, City University of Hong Kong, Kowloon, Hong Kong, China

Yonglu Huang
Department of Clinical Laboratory Medicine, Second Affiliated Hospital of Zhejiang University, Hangzhou, China

Yi Li
Department of Clinical Laboratory Medicine, Henan Provincial People's Hospital, Zhengzhou, China

Jianping Lin
Department of Clinical Laboratory Medicine, Wenzhou People's Hospital, Wenzhou, Zhejiang, China

Daihai He
Department of Applied Mathematics, The Hong Kong Polytechnic University, Hong Kong, China

Congcong Liu
Department of Clinical Laboratory Medicine, Second Affiliated Hospital of Zhejiang University, Hangzhou, China

Sheng Chen*
Department of Infectious Diseases and Public Health, City University of Hong Kong, Kowloon, Hong Kong, China

Rong Zhang*
Department of Clinical Laboratory Medicine, Second Affiliated Hospital of Zhejiang University, Hangzhou, China

*Corresponding authors.
E-mail addresses: shechen@cityu.edu.hk (S. Chen), zhang-rong@zju.edu.cn (R. Zhang)

[1] These authors contributed equally to the work.

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COVID-19 "Rebound" associated with nirmatrelvir/ritonavir pre-hospital therapy

Dear Editor,

The efficacy of nirmatrelvir/ritonavir, an orally active chymotrypsin-like cysteine protease inhibitor in combination with a CYP3A4 inhibitor, in reducing hospitalisation or death from COVID-19 infection has been demonstrated in a high-risk adult population.[1] Treatment within five days of COVID-19 symptoms was associated with a progressive reduction in viral load compared to the placebo arm; the duration of COVID-symptoms and changes in symptom severity were not reported.[1]

The effectiveness of nirmatrelvir/ritonavir in vaccinated individuals or against novel SARS-CoV-2 variants remains uncertain. Case reports are emerging of a recurrence ("rebound") of COVID-19 symptoms during or shortly after nirmatrelvir/ritonavir therapy without evidence of infection with an alternative variant in vaccinated, immunocompetent individuals.[3–5] No universally agreed definition of "rebound" COVID-19 associated with antiviral treatment currently exists, however, the United States Centres for Disease Control and Prevention describes rebound as a recurrence of COVID-19 symptoms or a new positive viral test after negative testing within two to eight days of initial recovery.[5]

Nirmatrelvir/ritonavir has conditional marketing authorisation in the UK for the treatment of COVID-19 in adults not requiring oxygen therapy and who are considered at risk of hospitalisation and/or death from COVID-19.[6] In December 2021, the Cardiff and Vale University Health Board was commissioned to provide a National Antiviral Service (NAVS) with responsibility for the clinical assessment of and supply of oral antiviral medicines to clinically extremely vulnerable patients in Wales who test positive for COVID-19. The first patients began receiving nirmatrelvir/ritonavir from NAVS in February 2022 in accordance with a UK wide clinical access policy.[7] As of 5 June 2022, the National Antiviral Service (NAVS) has recommended treatment with nirmatrelavir/ritonavir, molnupiravir and neutralising monoclonal antibodies (Casirivimab/Imdevimab or Sotrovimab) for 939, 647 and 1498 patients respectively. To date, NAVS has received three spontaneous reports from service users of apparent recurrence of COVID symptoms associated with new positive antigen lateral flow tests, Table 1.

Two cases were female and one male. Ages ranged from 44 to 59 years. All three cases had underlying active immune-mediated inflammatory disease, for which they were receiving treatment, and had received a full course of COVID-19 vaccination. Nirmatrelvir/ritonavir was started within one to three days of the onset of typical COVID-19 symptoms and a positive lateral flow test. All three cases reported taking nirmatrelvir/ritonavir, as prescribed, for five days.

Symptomatic improvement was reported from three to five days after initial onset and persisted for two to six days until symptoms were reported to reoccur. Lateral flow tests were newly positive eight to 19 days from initial onset. Two out of three cases did not require hospitalisation but the third was referred to her local Medical assessment Unit to exclude a complication of COVID,

Table 1
Cases describing relapse of COVID-19 symptoms during out of hospital Paxlovid treatment.

Case number	Age (years)	Sex	Comorbidities	Medications	Symptom onset	LFT +ve	Paxlovid duration	Symptoms improved	LFT -ve	Symptoms reoccurred	LFT +ve	Hospitalised
1	55	Male	Rheumatoid arthritis, vasculitis	Rituximab Prednisolone	Day 1	Day 1	Day 2 to Day 6	Day 5 to Day 7	Day 6	Day 8	Day 8	No
2	44	Female	Crohn's disease	Ustekinumab	Day 1	Day 1 Day 2 Day 3	Day 4 to Day 9	Day 5 to Day 11	Day 5 to Day 11	Day 14	Day 14 (x3) Day 15	No
3	59	Female	Vasculitis	Rituximab Mycofenolate Prednisolone Hydroxychloroquine	Day 1	Day 1	Day 2 to Day 7	Day 3 to Day 5	Day 6	Day 19	Day 19	Assessed but not admitted

such as venothromboemobolism or secondary infection, and received sotrovimab for on-going symptoms associated with positive lateral flow tests.

It is unclear if COVID-19 "rebound" associated with nirmatrelvir/ritonavir is a distinct clinical phenomenon. The number needed to treat in the pivotal nirmatrelvir/ritonavir was approximately 18,[1] suggesting that failure to respond to nirmatrelvir/ritonavir therapy may be an explanation. Alternatively, "rebound" may reflect the natural history of certain SARS-CoV-2 variants.[8] Investigators have reported second peaks in viral load in "rebound" cases,[2,3] however, these do not correlate well with either symptoms or antigen test positivity. The inclusion of untreated controls and other COVID-19 therapies in future, formal, observational studies would address both alternative hypotheses.

In summary, we describe three cases of apparent recurrence of COVID symptoms associated with new positive lateral flow tests in immunosuppressed adults at high risk of severe COVID-19 treated with nirmatrelvir/ritonavir. The number of reported cases represents a small proportion of all those treated (<1%) although we cannot account for unreported cases. The strengths of our conclusions are limited by the strong risk of reporting bias and a lack of viral load or viral genomic data to exclude early re-infection with an alternative or mutant SARS-CoV-2 subvariant. Our adverse reaction information for patients letter has been amended to encourage patients to report recurrence of COVID symptoms during or following treatment.

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J.M. Coulson*
Cardiff University, Cardiff, United Kingdom
All Wales Therapeutics and Toxicology Centre, Cardiff and Vale University Health Board, Llandough, Penlan Road, Cardiff CF64 2XX, United Kingdom

A. Adams
National Antiviral Service, Cardiff and Vale University Health Board, United Kingdom

L.A. Gray
All Wales Therapeutics and Toxicology Centre, Cardiff and Vale University Health Board, Llandough, Penlan Road, Cardiff CF64 2XX, United Kingdom

A. Evans
Chief Pharmaceutical Officer for Wales, Health and Social Services Group, Welsh Government, United Kingdom

*Corresponding author at: All Wales Therapeutics and Toxicology Centre, Cardiff and Vale University Health Board, Llandough, Penlan Road, Cardiff CF64 2XX, United Kingdom.
E-mail address: coulsonjm@cardiff.ac.uk (J.M. Coulson)

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Significantly lower 30 day/inpatient mortality observed in people who inject drugs (PWID) compared to non-PWID with Staphylococcus aureus bacteraemia

Dear Editor,

We note with interest the retrospective 5-year study[1] by Wilekens showing sustained raised 30-day mortality in staphylococcus aureus bacteraemia (SAB) despite good adherence to quality indicators in a. People who inject drugs (PWID) are known to have increased rates of bloodstream infections including SAB.[2] Anecdotally, PWID have reduced mortality from SAB than non-PWID however there has been minimal direct comparison published in the literature. We set out to test this hypothesis by performing a retrospective case note review of all SAB cases detected at Hull University Teaching Hospitals NHS trust in 2017 (the most recent year with published time to culture data).

Patients were classified into PWID and non PWID categories based on documented drug use behaviours. Outcomes including biochemical and physiological parameters at time of blood culture and mortality outcomes at 30 days, 1 year and 4 years were collected from combination of paper and electronic note review. Ethical approval was granted by Wales Research Ethics Committee 1 (IRAS 305642).

Statistical comparison was performed using SPSS IBM statistics. Students T-test and Mann-Whitney-U tests were performed as appropriate for linear parametric and non-parametric comparisons, respectively. Chi-squared testing was performed for categorical variables with Fisher's exact testing performed when expected values were <5. The Haldane-Anscombe correction was performed when producing odds ratios where a value of 0 was observed in either group. Due to small total population numbers and small events rate in the PWID group, multivariate analysis was not performed.

Results are summarised in Table 1 / supplementary table 1 and Fig. 1. Mortality was significantly lower in PWID (n = 26) compared to non-PWID (n = 95) at 30 days/inpatient, 1 year and 4 years (p = 0.013, 0.004 and <0.001, respectively; Table 1a). PWID associated cases were younger, had less comorbidity, more complicated infection, less metabolic derangement and were more likely to be cared for on the infectious diseases unit.

Table 1
a Comparing biochemical/physiological parameters between PWID and non-PWID.

	PWID (n = 26)	Non-PWID (n = 95)	p-value
Male %(n)	65.4 (17)	70.5 (67)	0.614
Age (median, range)	38.5 (22–59)	68.0 (34–96)	**<0.001∼***
Time to blood culture positive (hours)	14.25 +/- 8.4	14.67 +/- 7.7	0.570∼
MRSA %(n)	0 (0)	4.2 (4)	0.576
Previous Staphylococcus Aureus isolated (any site) %(n)	38.5 (10)	46.3 (44)	0.475
Infectious disease inpatient stay %(n)	52.8 (14)	10.6 (10	**0.001***
Complex infection %(n)	88.5 (23)	58.8 (50)	**0.005**
PMH Cardiovascular disease %(n)	0 (0)	41.1 (39)	**<0.001***
PMH Chronic kidney disease %(n)	3.8 (1)	22.1 (21)	**0.042***
PMH Diabetes %(n)	3.8 (1)	22.1 (21)	**0.004**
PMH Chronic obstructive pulmonary disease %(n)	0 (0)	15.8 (15)	**0.029***
PMH Active malignancy %(n)	0 (0)	31.6 (30)	**<0.001***
PMH Alcohol excess %(n)	11.5 (3)	1.1 (1)	**0.031***
PMH Hepatitis B %(n)	0 (0)	0 (0)	n/a
PMH Hepatitis C %(n)	65.4 (17)	0 (0)	**<0.001***
PMH HIV %(n)	0 (0)	0 (0)	n/a
Charlson comorbidity index	0.9 (0.8)	5.2 (3.2)	**<0.001***
Sodium mmol/L	131.9 (3.9)	134.7 (6.9) (n = 94)	0.052
Urea mmol/L	8.9 (10.8)	12.4 (10.8) (n = 93)	**0.006∼**
Creatinine μmol/L	128.2 (192.3)	147.2 (164.6) (n = 93)	**0.013∼***
Albumin g/L	28.3 (4.9) (n = 25)	28.0 (7.7) (n = 94)	0.879
Alanine aminotransferase IU/L	77.7 (226.7) (n = 25)	44.5 (40.7) (n = 92)	0.209∼
C reactive protein mg/L	211.9 (139.0) (n = 23)	164.7 (117.6) (n = 72)	0.113
Lactate mmol/L	1.4 (0.6) (n = 15)	2.4 (1.9) (n = 49)	**0.013∼***
Bicarbonate mmol/L	24.4 (3.8) (n = 17)	24.0 (5.0) (n = 70)	0.724
Haemoglobin g/L	113.6 (22.0) (n = 25)	113.0 (26.3) (n = 94)	0.917
White cell count x10^9/L	12.9 (5.8) (n = 25)	13.5 (6.8) (n = 94)	0.644
Neutrophils x10^9/L	10.4 (5.3) (n = 24)	11.6 (6.4) (n = 94)	0.408
Lymphocytes x10^9/L	1.3 (0.8) (n = 24)	1.0 (0.8) (n = 94)	**0.045***
Platelets x10^9/L	260.2 (178.3) (n = 24)	241.2 (136.3) (n = 93)	0.387
Pulse beats/minute	92.8 (18.3) (n = 21)	97.0 (22.5) (n = 77)	0.425
Systolic blood pressure mmHg	115.9 (20.5) (n = 21)	122.5 (28.0) (n = 75)	0.319
Diastolic blood pressure mmHg	67.1 (12.4) (n = 21)	66.8 (17.0) (n = 76)	0.939
Respiratory rate breaths/minute	18.3 (2.3) (n = 20)	20.5 (5.8) (n = 69)	0.205∼
Oxygen saturations %	97.1 (2.3) (n = 20)	95.9 (3.4) (n = 66)	0.147
Temperature °C	37.5 (1.3) (n = 21)	37.5 (1.4) (n = 79)	0.881
Altered mental status %(n)	5.0 (1)	11.0 (8)	0.678
Length of stay post positive blood culture (days)	28.1 (18.2)	24.7 (22.1)	0.153∼
Inpatient/30-day mortality %(n)	3.8 (1)	26.3 (25)	**0.013***
One year mortality %(n)	7.7 (2)	36.8 (35)	**0.004**
Four year mortality %(n)	11.5 (3)	58.9 (56)	p < **0.001****
Re-admission within 90 days %(n)	44.0 (11)	39.7 (29)	0.707

All values are presented as mean (standard deviation) unless otherwise stated.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.∼ Mann-Whitney U analysis for non-parametric variables.MRSA = methicillin resistant Staphylococcus Aureus, PMH = past medical history.

When comparing those who died within 30 days (n = 26) versus those that survived beyond 30 days (n = 95) (Table 1b) multiple factors were significantly different. Age was significantly lower in the surviving group (median 68 and 38 for non-PWID and PWID respectively, $p < 0.001$). Of the 26 PWID, 25 were in the surviving group (Odds ratio [OR] 0.11, 95%CI 0.01–0.87, $p = 0.013$). Of those cared as an inpatient by infectious diseases there was no deaths (OR 0.06, 95% CI 0.00–0.94, $p = 0.004$). Fig. 1a and b show Kaplan-Meier survival curves by PWID status and by infectious diseases inpatient stay (Log-Rank $p < 0.001$ for both).

These data suggest that despite more complex disease and similar physiological response to SAB, PWID patients have lower mortality up to the 4 year time point. Due to the inability to perform statistically sound multivariate analysis the impact of confounding is unknown. Age and comorbidities are significant drivers of the influence of PWID status and infectious diseases inpatient care on mortality. Although a higher proportion of PWID versus non-PWID were cared for within Infectious Diseases as inpatients, day-to-day care of SAB patients by experts may have been important. A larger prospective study may allow clarification of some of these potential confounders.

Previous studies have identified this link between PWID status and reduced mortality.[3,4] Studies have also demonstrated difference in Staphylococcus Aureus (SA) strain isolation between PWID and non PWID with FIN-4 strains and strains with haemolytic properties being found more commonly in PWID ($p = 0.03$ and $p = 0.007$ respectively).[4] Higher teichoic acid antibodies titres were also seen in PWID than non PWID.[4] It is unclear whether PWID may have acquired immunity due to increased rates of SA infection and recurrent SA infection compared to the general population or whether physiological response is different due to other factors.[2,3] There is recent evidence that community acquired SAB in PWID spreads amongst this group and may have altered expression of some virulence factors.[5]

Complex disease was defined as per published guidance.[6] Despite complex disease being present more commonly in PWID, their outcomes are better and this doesn't appear to be due to an impaired inflammatory response (with no significant difference in

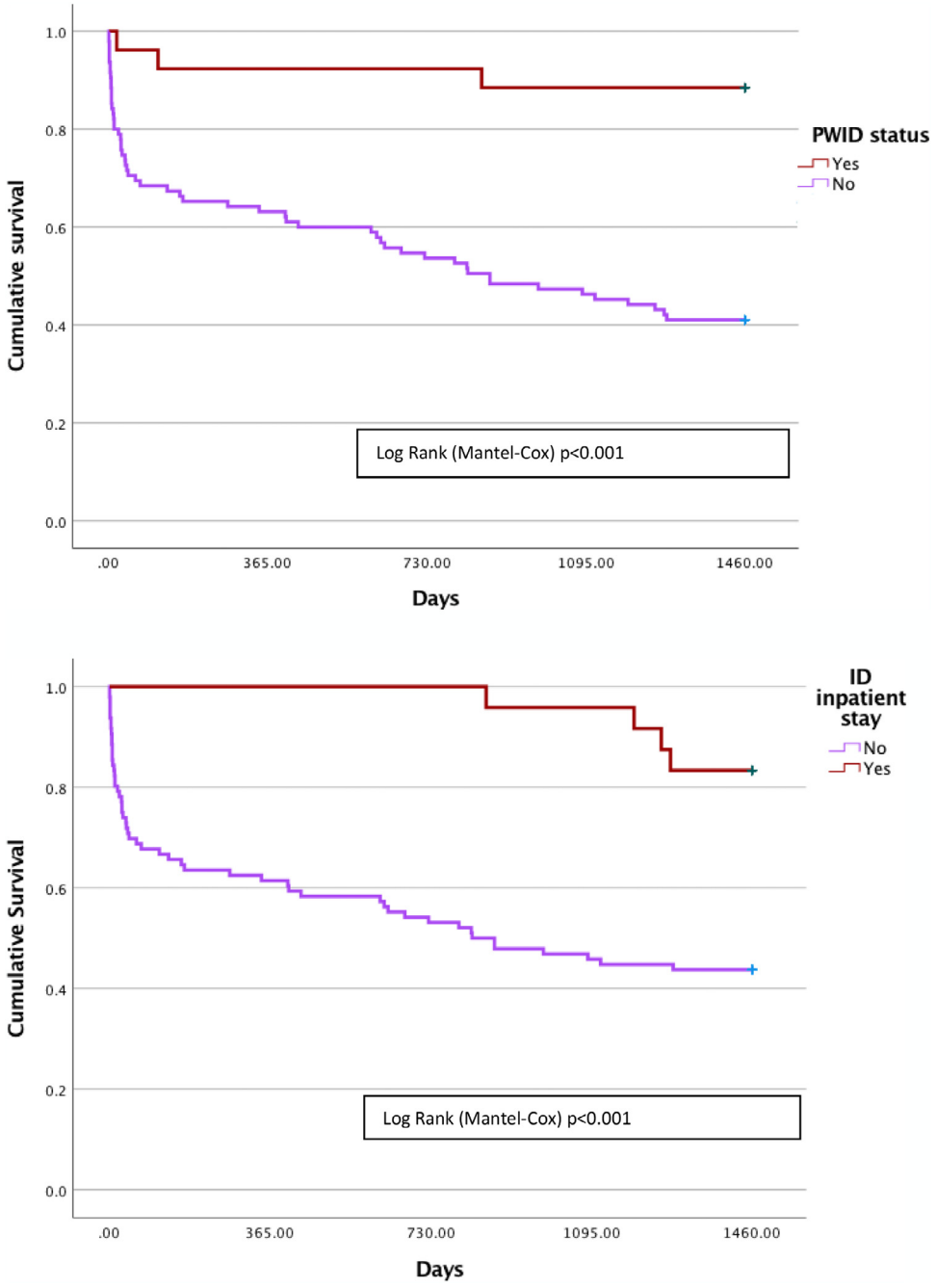

Fig. 1. (a). Kaplan-Meier survival curve showing time to death stratified by PWID status. (b). Kaplan-Meier survival curve showing time to death stratified by ID inpatient stay status.

CRP or white blood cell counts) or the magnitude of the pathogen burden as measured indirectly by time to blood culture positivity (indeed with PWID patients having difficult phlebotomy their result may be longer due to lower volumes inoculated into blood culture bottles). Readmission rates were higher than previously noted but comparable between PWID and non PWID groups.[3] The long term mortality was marked in non PWID and comparable to our previous data for all cause blood stream infection.[7] The association between multimorbidity, age and infection death over the longer term[8] may be part of the explanation of the marked difference between PWID and non PWID groups in the 4 year mortality.

Inpatient infectious disease stay was shown to be a significant reducer of mortality. This has been previously shown in literature with regard to infection consultation[9] but our data may indicate that ongoing infection specialist care could be important in further reducing mortality. At our hospital, a high proportion of SAB patients managed out-with the infection ward are still reviewed at least once by members of the infection team at the bedside.

There are several limitations to this study. Firstly, total study numbers and event outcome numbers are small which has prevented a meaningful multivariate analysis. Furthermore, given the retrospective nature of the study missing data may contribute to some confounding and there is potential for misclassification bias due to reliance on prior documented PWID status.

SAB in PWID presents with a different spectrum of disease to non PWID and its investigation and management should be tailored accordingly.[3,5] With a high readmission rate, identifying fac-

tors associated with this would allow for both improved outcomes and reduced costs. With further investigation into attributable factors of reduced PWID mortality it may be possible that novel preventative or therapeutic tools could be identified in the treatment of SAB. In the future a larger prospective cohort study is required to clarify the role of pathogen, age and injection drug use in SAB outcome.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2022.06.010.

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Isabel Mortimer, Katie Drury, Shakeel Lowe
Hull Teaching Hospitals NHS Trust, Hull, UK

Marium Akhtar
Hull York Medical School, UK

Gavin D Barlow
Hull Teaching Hospitals NHS Trust, Hull, UK
Hull York Medical School, UK
Experimental Medicine & Biomedicine, York Biomedical Research Institute, University of York, UK
Infection Research Group, Hull Teaching Hospitals NHS Trust, UK

Nicholas Easom, Patrick J Lillie*
Hull Teaching Hospitals NHS Trust, Hull, UK
Infection Research Group, Hull Teaching Hospitals NHS Trust, UK

*Corresponding author.
E-mail address: p.lillie1@nhs.net (P.J. Lillie)

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