

Immunity debt: Hospitals need to be prepared in advance for multiple respiratory diseases that tend to co-occur

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SUMMARY As SARS-CoV-2 transitions from a pandemic to an endemic presence, a significant rise in respiratory diseases such as influenza and *Mycoplasma pneumoniae* is challenging healthcare systems weakened by the impact of COVID-19. This commentary examines the global resurgence of respiratory pathogens, heightened by the post-pandemic "immunity debt", through an analysis of WHO surveillance data and national health reports. Findings reveal a substantial increase in respiratory illnesses, notably among children, compounded by a shortage of pediatricians and growing antimicrobial resistance. This underscores the need to improve hospital preparedness, optimize clinical responses, and enhance public health strategies to effectively navigate the impending peak of concurrent respiratory infections.

Keywords immunity debt, influenza, mycoplasma pneumoniae, respiratory infection, hospital preparedness

As the novel coronavirus SARS-CoV-2 (the cause of COVID-19) gradually transitions from a pandemic-causing pathogen to a common endemic virus, respiratory infectious pathogens such as influenza viruses, respiratory syncytial virus, and *Mycoplasma pneumoniae* have become prevalent again. Healthcare facilities already hit hard by the COVID-19 pandemic are now facing new challenges from the upsurge in respiratory illnesses.

Many countries are repaying their post-COVID-19 "immunity debt", and China is no exception

According to the predictions and assessments of numerous public health experts worldwide, non-pharmaceutical interventions (NPIs) during the COVID-19 pandemic have led to a widespread deficiency in adaptive immunity, which many scholars refer to as "immunity debt" or "immunity gap" (1-3). In other words, a lack of adaptive immunity in the population is very likely to lead to outbreaks of various respiratory diseases. This situation has already occurred in several countries, including the US, France, Australia, and Canada (4). The World Health Organization's (WHO's) surveillance data on global influenza clearly substantiates that contention; In contrast to the low prevalence of influenza during the COVID-19 pandemic(5,6), since the start of 2022, several countries have experienced at least two waves of influenza outbreaks, and the number

of influenza cases is significantly higher than before the outbreak of COVID-19 in 2020 (Figure 1). At the same time, the prevalence of common respiratory viruses has greatly exceeded their baseline levels before the COVID-19 pandemic, leading to a rapid increase in cases in a short period of time (7).

Multiple respiratory diseases that tend to co-occur are the key problem

The seasonal flu epidemic is unquestionably coming in China. Some scholars proposed preparing in advance for the simultaneous epidemic of COVID-19 and influenza in 2022, but China is now facing multiple respiratory virus epidemics (8). Since mid-October of this year, the incidence of influenza-like illnesses in China has increased compared to the same period over the past three years, with a surge in pediatric visits to many hospitals. The daily outpatient volume has doubled, reaching more than 13,000 people at Tianjin Children's Hospital, with pediatric wards at full capacity and lines forming (9). Data obtained from The Third People's Hospital of Shenzhen, China shows that the number of children with a fever has increased by more than 50% in the past month, and more than 90% of children in hospital are infected with *Mycoplasma pneumoniae*. The weekly influenza surveillance report from the Chinese Center for Disease Control and Prevention for week 46 of 2023 shows that positivity according to

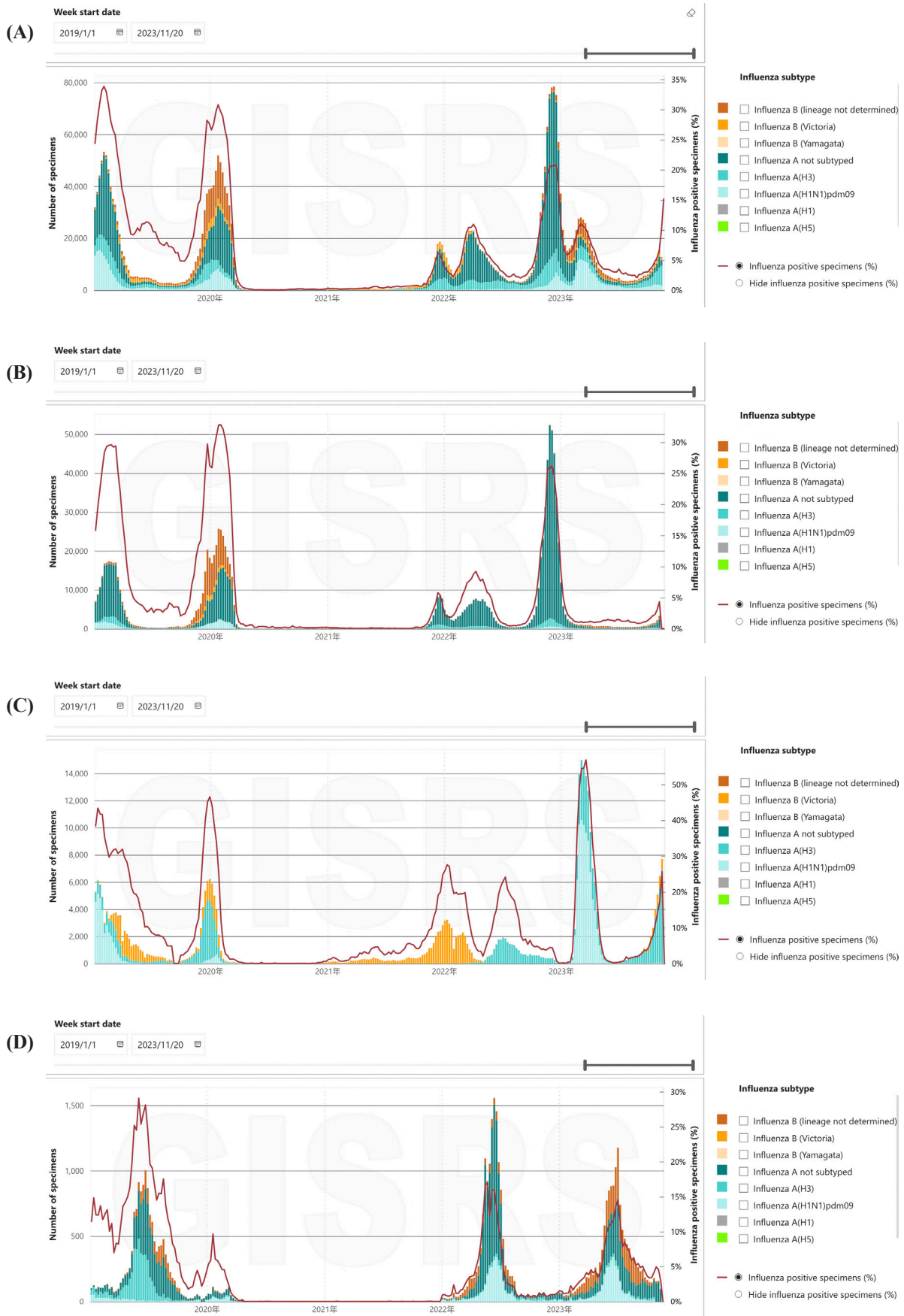


Figure 1. Status of current influenza infections from 01/2019 to 11/2023. (A), Global data on influenza infections from 01/2019 to 11/2023. **(B)** Data on influenza infections in the United States of America from 01/2019 to 11/2023. **(C)** Data on influenza infections in China from 01/2019 to 11/2023. **(D)** Data on influenza infections in Australia from 01/2019 to 11/2023. *Data source: FluNet (<http://www.who.int/tools/fluNet>) (16).*

influenza virus testing continued to rise in November, predominantly involving the A(H3N2) subtype, followed by the B(Victoria) lineage. By November 19th, there were 205 reported outbreaks of influenza-like illnesses (ILI) nationwide. Sentinel hospitals in China's southern provinces reported that the percentage of ILI was 6.4%, which is higher than the previous week's level (5.5%). At the same time, sentinel hospitals in northern provinces reported that the percentage of ILI was 6.2%, which is higher than the previous week's level (5.0%) (10).

Announcements from Beijing, Tianjin, Changchun, and some southern cities in China have indicated that there has been a significant increase in the incidence of respiratory infectious diseases. The proportion of cases of *Mycoplasma pneumoniae* in children with pneumonia has markedly increased, with many patients presenting with co-infections of multiple pathogens.

Respiratory diseases that overlap in prevalence put tremendous pressure on the administration of many hospitals

On November 22, the WHO requested that China provide detailed information regarding the increase in respiratory diseases and the cluster of pediatric pneumonia mentioned in related reports. The next day, the WHO stated that data from the Chinese Center for Disease Control and Prevention indicated that the current peak of pediatric pneumonia is attributed to known pathogens, including influenza viruses, *Mycoplasma pneumoniae*, and respiratory syncytial viruses (11,12). The National Health Commission of China released information predicting that influenza will peak nationwide during the winter and spring, and *Mycoplasma pneumoniae* infections will continue to occur at high rates in certain regions for some time. This winter and coming spring, China may face a situation where COVID-19, influenza, *Mycoplasma pneumoniae* infections, and other respiratory diseases overlap in prevalence (13).

Given the current pressure pediatric patients are placing on many Chinese hospitals, the shortage of pediatricians is a problem that needs to be urgently addressed. In addition, there is a widespread epidemic of *Mycoplasma pneumoniae* in children, and clinicians have warned that azithromycin resistance among children with mycoplasma pneumonia could be as high as 90%. This has once again made the public aware that incidence of macrolide-resistant *Mycoplasma pneumoniae* (MRMP) is so high that azithromycin has gradually been relegated to a second-line clinical drug. Even research published in JAMA in 2022 warned of a high incidence of MRMP globally (13). This was particularly true in the Western Pacific, where that incidence was 53.4%, but China had the highest rate of MRMP at 79.5%.

Prioritization of hospital preparedness for respiratory infections

The cooccurrence of multiple respiratory diseases due to several pathogens, the shortage of pediatricians, and increased drug resistance represent complex challenges to healthcare administration. According to our predictions, the peak period of overlapping multiple respiratory infections has not yet been reached, so preparations and responses by hospitals are the priorities.

Adaptability in clinical protocols: Clinical treatment regimens need to be tailored to the diverse etiologies of respiratory infections. Given that acute respiratory infections represent a significant cause of pediatric and geriatric morbidity and mortality worldwide, preemptive clinical intervention is imperative to forestall the progression to critical illness within these vulnerable cohorts.

Pharmacological sensitivity and efficacy: Emphasis must be placed on the judicious selection of antimicrobials in therapeutic management. Notwithstanding the prevalent use of azithromycin for pediatric co-infections with *Mycoplasma pneumoniae*, increasing resistance underscores the need for vigilant monitoring of drug efficacy.

Nosocomial infection control: Enhancing infection control protocols is essential to minimizing the incidence of iatrogenic infections, particularly during patient influxes. Upholding fundamental prophylactic standards and implementing strict contact isolation practices are critical to mitigating nosocomial transmission.

Resource allocation in response to the pathogen burden: The cooccurrence of multiple respiratory pathogens necessitates the pre-emptive allocation of medical personnel and the stockpiling of medicinal supplies and facilities to accommodate patients. Hospitals should formulate preemptive logistics and communication strategies to effectively manage the anticipated patient surge.

Future strategies for hospitals to manage respiratory infectious diseases

A robust mechanism for an effective response: Research on and improvements in emergency preparedness and response frameworks are required, and this includes vaccines and novel pharmacological treatments (14). The expeditious improvement of clinical infrastructure and the of comprehensive expansion of clinical treatment capacity are also of paramount importance.

Enhanced pathogen surveillance: Prior to the appearance of novel pathogenic entities, surveillance systems need to be continually improved, ensuring prompt pathogen identification. This involves continuous improvement of monitoring methodologies and the enhancement of early detection and warning capabilities.

Improved health education: Prioritizing health education is quintessential to alleviating public trepidation and the consequent overtaxing of healthcare systems (15). This initiative should incorporate the

provision of timely, accurate, and impartial information, along with interpretations of relevant policies, to facilitate communication with the general population.

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