Rapid Communication

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Repeat influenza incidence across two consecutive influenza seasons

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Abstract

Objectives: To characterize the epidemiology of repeat infections and coinfections.

Methods: We systematically analyzed influenza surveillance data from three hospitals in China, focusing on patients with influenza-like illness (ILI) cases (symptom duration≤7 days) and laboratory confirmation (by RAT or RT-PCR) between January 2023 and January 2024. There were 20,270 influenza-positive cases among 19,832 individuals among 40,310 ILI cases. A total of 432 cases exhibited recurrent influenza-positive detections within the study period. Reinfections occurring within 14 days after initial infection were classified as coinfections, while those beyond 14 days were defined as repeat infections.

Results: In this study, 102 cases (23.6 %) were identified as coinfections and 330 cases (76.4 %) as sequential infections. Among all repeat infections, 98.2 % (324/330) involved two infection episodes, while 2.3 % (6/330) exhibited three episodes. Notably, 60.3 % (199/330) occurred within the same influenza season.

Conclusions: Our study revealed that long-lasting flu is possibly due to reinfection by the same or different types of influenza in a very short time.

Keywords: influenza; repeat infection; coinfection

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Introduction

Influenza viruses cause seasonal epidemics, resulting in up to half a million deaths globally each year [1]. Humans can be infected by three kinds of influenza viruses: type A (influenza A virus, IAV), type B (influenza B virus, IBV), and type C (influenza C virus, ICV) [2]. Types A and B are identified as the main causes of significant human disease and seasonal epidemics [3, 4]. While natural infection appears to confer cross-protection against influenza types and subtypes, repeat infections within or across seasons remain surprisingly common [5–8]. Influenza epidemics add an extra dimension to the complexity of understanding repeat influenza [9]. This pattern raises clinical questions about prolonged illness perceptions. Could rapid reinfection create seamless symptom persistence without recovery intervals?

Advances in rapid antigen testing and RT–PCR availability now enable more frequent detection of recurrent influenza cases, allowing differentiation between prolonged illness and rapid reinfection scenarios [10].

China's 2023 post-COVID-19 period witnessed two distinct influenza outbreaks [11, 12]. Most ILI patients undergo antigen/RT–PCR testing in acute care settings (fever clinics, ERs, pediatrics, respiratory units), enabling regional surveillance of sequential infections [13, 14]. During the 2023 winter peak, caregivers frequently reported coinfection with influenza A/B and repeat infections. The analysis of laboratory-confirmed influenza data from three centers was conducted to determine the incidence of repeat infections and coinfections, the time gap between infections, and whether these factors vary by age or gender. These data might increase our understanding of the cross-protection and lasting immunity conferred by influenza infection.

Methods

Population

This retrospective multicenter study analyzed acute care data from three hospitals (the Second Affiliated Hospital of TUTCM and Tianjin 4th Center Hospital in northern China; the Third Affiliated Hospital of CMU in southern China). We enrolled ILI patients with a symptom duration of ≤7 days (January 2023–January 2024) and collected demographic data and laboratory results. All records contained anonymized unique identifiers with age and sex data.

We defined repeat infections as influenza in the same individual caused by distinct influenza types occurring more than 14 days after initial diagnosis. This is due to the likelihood that the virus shedding from the initial infection has ceased [15–17]. Two infections in a row were defined as X-Y, where X is the primary infection type and Y is the secondary infection type.

We defined coinfections as test results for different influenza types with onset dates within 14 days of the original diagnosis [15]. Cases with coinfections occurring on the same day were classified as XY, while those occurring more than 7 days but less than 14 days after the initial diagnosis were classified as X/Y. X is the type of primary infection and Y is the type of secondary infection.

The inclusion criterion was as follows: all-age ILI patients presenting to three acute care centers (January 2023–January 2024) with ≤7 days of symptom duration confirmed by the RAT or RT–PCR. The exclusion criterion was patients whose laboratory data were missing.

Statistical analysis

Epidemic curves were generated via weekly counts. To determine the cumulative incidence of reinfection, we used Kaplan–Meier analysis (R 4.3.2). Cox regression was used to estimate the hazard ratios for reinfection by gender and age group (SPSS version 25) [18].

Ethical approval

The authors ensure that the work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. The manuscript is in line with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals and aims for the inclusion of representative human populations (sex, age and ethnicity) as per those recommendations. This study received ethnic waiver from the Ethics Committee of the Second Affiliated Hospital of Tianjin University of Traditional Chinese Medicine (Reference number: 2023-025-01-2, Date: 5-23-2023), and informed consent was waived by the ethics committee. The privacy rights of human subjects were observed.

Results

There were 20,270 influenza-positive cases among 19,832 individuals among 40,310 influenza-like illness cases. Among the total cases, 60.8 % (n=12,331) were type A, 39.2 % (n=7,939) were type B, 49.9 % (n=10,117) were female, and 50.1 % (n=10,153) were male. A total of 9.9 % (n=1,997) were aged<5 years, 47.8 % (n=9,690) were aged 5–17 years, 38.9 % (n=7,882) were aged 18–64 years, and 3.5 % (n=701) were aged ≥65 years. A total of 2.2 % (n=432) had more than one influenza infection; 23.6 % (n=102) had coinfections, and 76.4 % (n=330) had repeat infections. The detailed characteristics are shown in Figure 1.

Repeat infections

At least two infections occurring within the same influenza season

A total of 199 (60.3 %) repeat infections were found within the same season (spring or winter). A total of 182 cases were type A-B (91.5 %), 9 cases were B-A (4.5 %), three were type

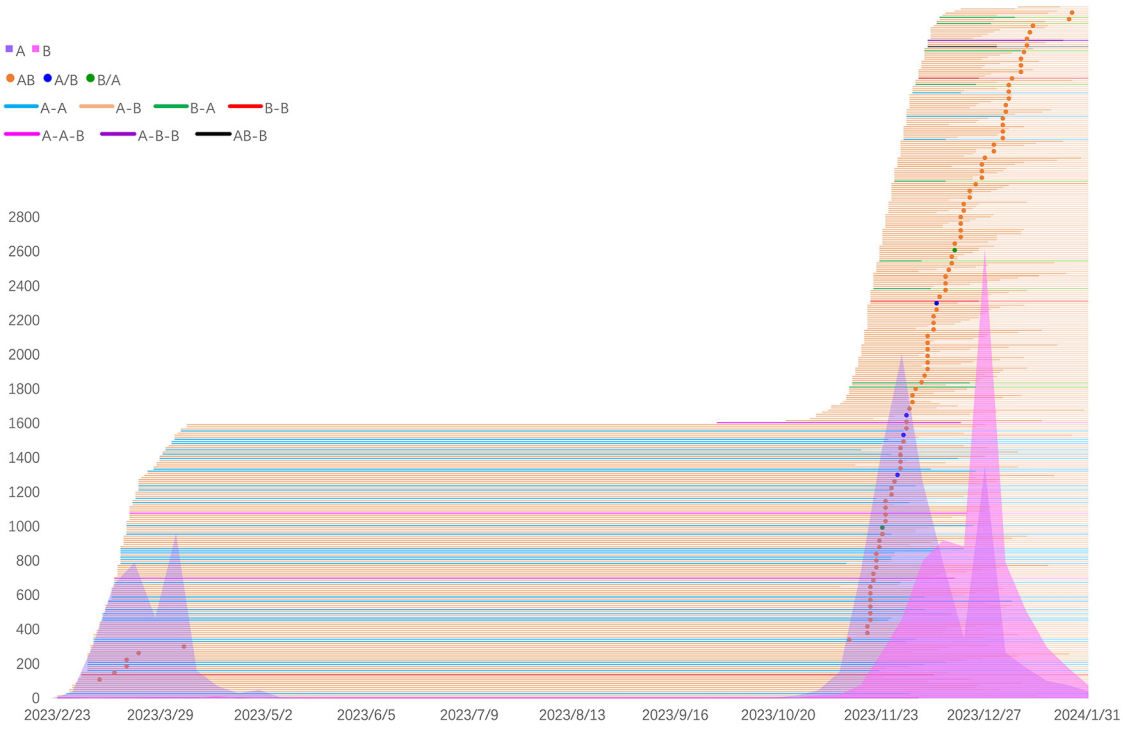

Figure 1: Influenza cases in two consecutive influenza seasons. Notes: X-axis: time. Y-axis: number of influenza A or B cases. Area chart: Distribution of influenza A and influenza B. Dots: Distribution of coinfections. Horizontal lines: Distribution of repeat infections.

A-A (1.5 %), two were type B-B (1.0 %), one was type A-B (0.5 %), A-B-B (0.5 %), and AB-B (0.5 %) accounted for 1 case.

Repeat infections over two influenza seasons

Most individuals (98.4 %, n=19,194) had one positive result. The detection of multiple positive results among individuals became more common with the increase in total influenza cases and the duration of the epidemic. A total of 131 individuals had more than one influenza infection in 2023; among them, 128 individuals had two infections, and three individuals had three infections. Among 93 consecutive type A-B infections, 71 % were the most common, followed by A-A (26.0 %, n=34), A-A-B (2.3 %, n=3), and B-B (0.8 %, n=1) infections.

Cumulative incidence of repeat infections

Figure 2 presents the Kaplan-Meier curve for the cumulative incidence of repeat infections. The incidence rates of reinfection 5 weeks after a previous infection for the whole sample were 0.8 %, 1.3 % after 10 weeks, 3.7 % after 40 weeks, and 4.9 % after 45 weeks (Figure 2A).

The cumulative incidence did not differ significantly by gender (p=0.366); after 5 weeks, it was 0.9 and 0.6 %, 1.5 and 1.0 % after 10 weeks, 3.6 and 3.8 % after 40 weeks, and 5.2 and 4.7 % after 45 weeks for males and females, respectively (Figure 2B).

The cumulative incidence was highest among those aged under 18 years and differed by age (p<0.001). For children aged under 5 years, the cumulative incidence rates were 0.9 , 1.3, 5.2 and 7.6 % after five, ten, forty and forty–five weeks, respectively. For 5–17 years, it was 1.3 , 2.1, 5.2 and 6.8 %; for 18–64 years, it was 0.1 , 0.2, 0.6 and 0.6 %; and for≥65 years, it was 0.3 , 0.3, 0.3 and 0.3 %. The risk was tenfold higher in individuals under 18 compared to adults (hazard ratio (HR) 9.92, 95 % confidence interval (CI) 6.16–15.97) (Figure 2C).

The distribution of consecutive infections after initial infection is described in Table 1.

Coinfections

Among all coinfections (n=102, 0.5 % of all cases), the majority were detected in the same test samples (n=96, 94.1 %),

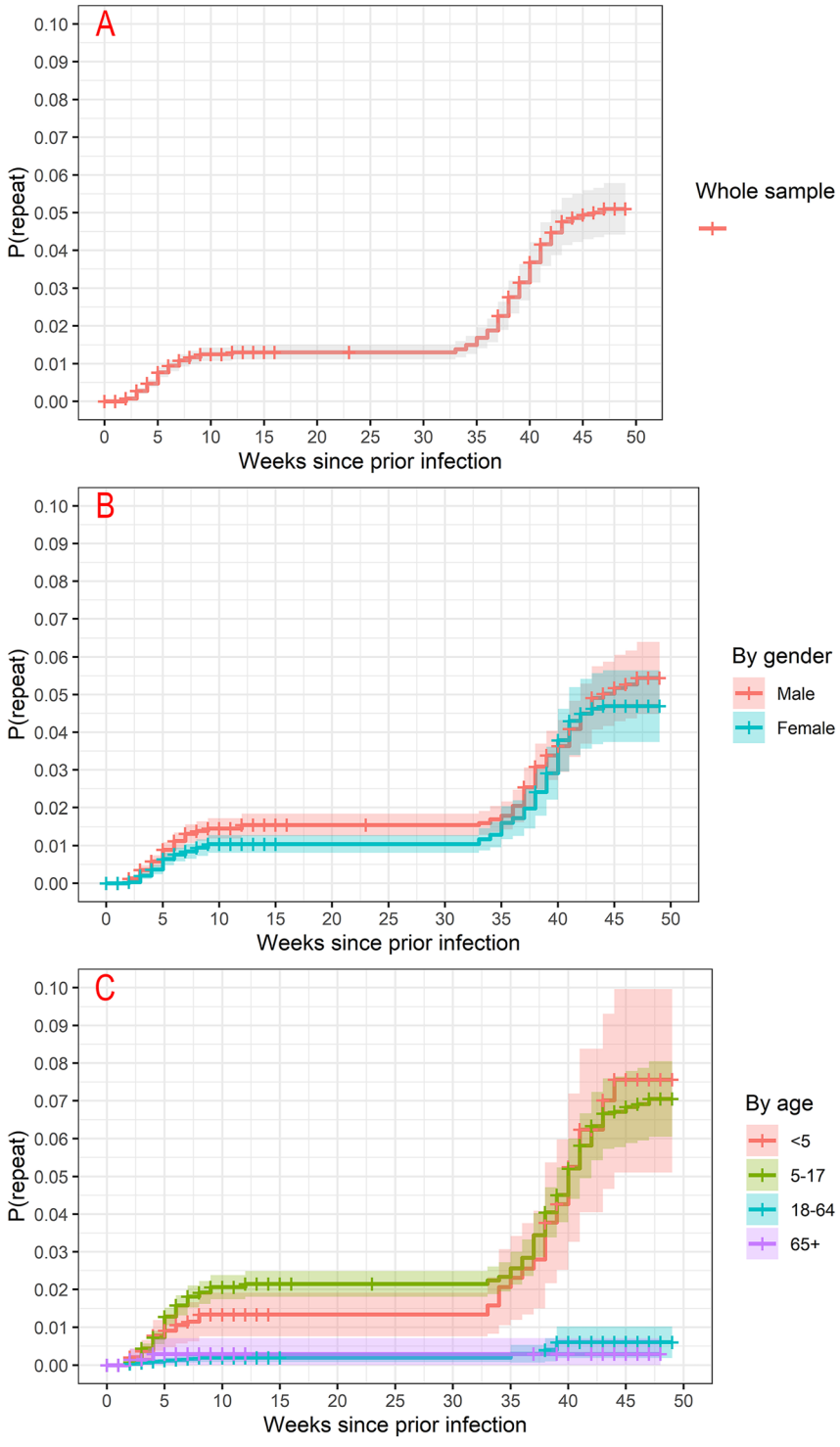

Figure 2: Kaplan-Meier plots displaying cumulative incidence of repeat infections. Notes: 2A: Cumulative incidence of repeat infections in the whole sample. 2B: Cumulative incidence of repeat infections by gender. 2C: Cumulative incidence of repeat infections by age. P (repeat): probability (cumulative incidence) of repeat infections. Shading indicates the 95 % confidence interval.

and the remainder were detected at different visits (Table 2). The majority of coinfections were type AB (n=96, 94.1 % of total coinfections), type A/B (n=4, 3.9 % of total coinfections), and type B/A (n=2, 2.0 % of total coinfections) coinfections.

Table 1: Distribution of repeat infections.

	Overall (n=330)	Same season (n=199)	Consecutive seasons (n=131)
Type, no. (%)			
A-A	37 (11.2)	3 (1.5)	34 (71.0)
A-B	275 (83.3)	182 (91.5)	93 (26.0)
B-A	9 (2.7)	9 (4.5)	None
B-B	3 (0.9)	2 (1.0)	1 (0.8)
A-A-B	4 (1.0)	1 (0.5)	3 (2.3)
A-B-B	1 (0.3)	1 (0.5)	None
AB-B	1 (0.3)	1 (0.5)	None
Gender, no. (%)			
Male	192 (58.2)	119 (59.8)	73 (55.7)
Female	138 (41.8)	80 (40.2)	58 (44.3)
Age, no. (%)			
<5	46 (13.9)	21 (10.6)	25 (19.1)
5–17	266 (80.6)	164 (82.4)	102 (77.9)
18–64	16 (4.8)	12 (6.0)	4 (3.1)
65+	2 (0.6)	2 (1.0)	None

Same season: Repeat infections occurring within the same influenza season (spring or winter), with an interval of less than 90 days. Consecutive seasons: Repeat infections occurring across two influenza seasons (from spring to winter), with an interval of more than 180 days.

Table 2: Distribution of coinfections.

	Overall (n=102)
Type, no. (%)	
AB	96 (94.1)
A/B	4 (3.9)
B/A	2 (2.0)
Gender, no. (%)	
Male	50 (49.0)
Female	52 (51.0)
Age, no. (%)	
<5	10 (9.8)
5–17	53 (52.0)
18–64	33 (32.4)
65+	6 (5.9)

Discussion

Our analysis revealed 0.5 % coinfection and 1.6 % reinfection rates among influenza patients. Pediatric patients (<18 years) are at increased risk of consecutive infection. Our study revealed that long-lasting flu is possibly due to reinfection by the same or different types of influenza in a very short time. This finding aligns with previous research conducted in Queensland, Australia, further supporting our conclusions and enhancing the accuracy and reliability of these results [15]. However, it should be noted that systematic research on repeated influenza infections remains relatively limited.

During the study period, influenza types A-B were the most prevalent. The predominant subtypes shifted from influenza A (H1N1) in spring, followed by influenza A (H3N2) and influenza B (Victoria) consecutively during the winter season. In most cases, it seems to be the same type, and even different types of protection exist. Type B influenza infections are associated with less severe disease in adults [19], which may reduce their likelihood of seeking medical care and thus being included in adult case counts. In contrast, prolonged illness in children prompted frequent ER visits, leading to a high number of confirmed cases documented in this study.

Type A-B or B-A infections within the same season were frequently observed. Among the 330 cases of reinfection documented within one year, 199 occurred within 3 months of the initial infection. Notably, cases of three consecutive influenza infections in the same season were identified, with affected patients reporting persistent symptoms resembling unrelenting influenza illness. A small clinical study in healthy adults demonstrated that reinfection did not elicit overt clinical symptoms [20]. However, the true burden of reinfection is likely underestimated, as patients with nonspecific or mild symptoms are less inclined to seek hospital care, and clinicians often refrain from ordering diagnostic testing for individuals without a recent history of influenza.

Consecutive infections were most prevalent across all pediatric age groups (under five and under 18 years), contradicting previous findings [15]. Despite multiple prior influenza exposures, children under 18 years of age maintained significantly higher incidence rates than adults did. This may correlate with immature immune development in children, resulting in diminished durability of protective immunity compared with that in adults [21]. Notably, even adults over 65 years of age presented low repeat infection rates during the 2023 season – another deviation from historical patterns.

Coinfections were rare in spring but more prevalent during winter, likely because of the threefold longer duration of the season and the viral shift from influenza A (H3N2) to B (Victoria) (comparable case numbers). Pediatric cases were not associated with cardiopathy or mortality.

The occurrence of repeat infections may be associated with the rapid evolution of influenza virus through antigenic shift and antigenic variation. The biophysical consequences resulting from amino acid changes introduced by antigenic drift vary across different subtypes and among different antigenic sites [22]. Waning immunity may also lead to a considerable portion of the population becoming susceptible again [23]. Furthermore, high community transmission rates in both consecutive seasons could have increased the probability of repeat infections. The increased likelihood of repeat infections underscores the necessity for repeated influenza vaccination. Current evidence indicates that revaccinated individuals achieve clinical protection levels comparable to those of first-time vaccinated individuals [24]. However, supporting studies remain limited. Consequently, future research should prioritize investigating the underlying mechanisms of repeat infections and their relationship with vaccination efficacy.

This study was medical center-based, and influenza was tested in most ILI patients; therefore, our data reflect field conditions. A substantial number of cases were observed over a relatively short period. However, the retrospective analysis of laboratory data in this study is subject to several limitations. First, the 14-day cutoff used to define reinfection may not be universally applicable across all individuals. Second, repeat influenza infections often lead to less severe symptoms [15]. This reduction in symptom severity can lower the probability of individuals seeking medical care. Third, physicians are less likely to order influenza testing for patients who have been recently diagnosed with the illness. Fourth, during the study period, outpatient and emergency departments in some participating centers were restricted to testing for COVID-19 and influenza viruses only. Consequently, data on the incidence of coinfections with other respiratory pathogens could not be acquired. Fifth, there are issues with patient identification across different centers. Unique patient identifiers lack consistency. Some individuals may have multiple identifiers within the same center, and different centers may use different identification systems. These factors may lead to an underestimation of the rates of repeat infection and coinfection. Moreover, this study did not assess influenza subtypes or clinical severity. This prevented the analysis of strain-specific mechanisms and whether repeat infections exacerbate disease manifestations, which remains an essential area for further investigation.

Our study demonstrated that consecutive influenza infections can occur. Moreover, repeated infections within the same influenza season are not only possible but also relatively common, particularly during extended influenza seasons. Prolonged influenza illness may be attributed to repeated influenza infections. Patients who have recently recovered from influenza within the same influenza season present with ILI symptoms in a manner indistinguishable from those without a recent influenza history. Therefore, relevant diagnostic tests should be ordered for such patients.

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Conflict of interest: Authors state no conflict of interest.

Data availability statement: All data generated or analysed during this study are included in this published article and its supplementary information files.

References

1. Paget J, Spreeuwenberg P, Charu V, Taylor RJ, Iuliano AD, Bresee J, et al. Global mortality associated with seasonal influenza epidemics: new burden estimates and predictors from the GLaMOR project. J Glob Health 2019;9:020421.
2. Cho HM, Doan TP, Ha TKQ, Kim HW, Lee BW, Pham HTT, et al. Dereplication by high-performance liquid chromatography (HPLC) with quadrupole-time-of-flight mass spectroscopy (qTOF-MS) and antiviral activities of phlorotannins from ecklonia cava. Mar Drugs 2019;17:149.
3. Brody H. Influenza. Nature 2019;573:S49.

4. Portnoff AD, Patel N, Massare MJ, Zhou H, Tian JH, Zhou B, et al. Influenza hemagglutinin nanoparticle vaccine elicits broadly neutralizing antibodies against structurally distinct domains of H3N2 HA. Vaccines 2020;8:99.
5. Koutsakos M, Illing PT, Nguyen THO, Mifsud NA, Crawford JC, Rizzetto S, et al. Human CD8(+) T cell cross-reactivity across influenza A, B and C viruses. Nat Immunol 2019;20:613–25.
6. Kreijtz JH, Fouchier RA, Rimmelzwaan GF. Immune responses to influenza virus infection. Virus Res 2011;162:19–30.
7. Möst J, Redlberger-Fritz M, Weiss G. Multiple influenza virus infections in 4 consecutive epidemiological seasons: a retrospective study in children and adolescents. Open Forum Infect Dis 2019;6:ofz195.
8. Möst J, Weiss G. Consecutive infections with influenza A and B virus in children during the 2014-2015 seasonal influenza epidemic. J Infect Dis 2016;214:1139–41.
9. Servadio JL, Thai PQ, Choisy M, Boni MF. Repeatability and timing of tropical influenza epidemics. PLoS Comput Biol 2023;19:e1011317.
10. Lu M, Joung Y, Jeon CS, Kim S, Yong D, Jang H, et al. Dual-mode SERS-based lateral flow assay strips for simultaneous diagnosis of SARS-CoV-2 and influenza a virus. Nano convergence 2022;9:39.
11. Becker M, Dulovic A, Junker D, Ruetalo N, Kaiser PD, Pinilla YT, et al. Immune response to SARS-CoV-2 variants of concern in vaccinated individuals. Nat Commun 2021;12:3109.
12. Zhao Q, Zhao R, Geng Z, Bao L, Guo S, Wang Y, et al. Xuanfei baidu granule alleviates coronavirus-induced pneumonia in low-temperature and high-humidity environments. Acupunct Herb Med 2023;3:200–6.
13. Zhang T, Du Y, Ren Y, Chen H, Wen X, Gao X. Difference between real world practice and clinical research: a comparison of oropharyngeal and nasopharyngeal sampling data in influenza. J Infect Pub health. 2024;17:102581.
14. Zhang T, Du J, Cao Y, Han H, Du Y, Hou Y, et al. Comparative study of rapid influenza antigen tests versus PCR in an influenza-like illness population: a real-world multicenter study in China. Infection, genetics and evolution. J Mol Epidemiol Evol Gene Infect Dis 2025;133:105794.
15. Price O, Birrell FA, Mifsud EJ, Sullivan SG. Epidemiology of repeat influenza infection in Queensland, Australia, 2005-2017. Epidemiol Infect 2022;150:e144.
16. Fielding JE, Kelly HA, Mercer GN, Glass K. Systematic review of influenza A(H1N1)pdm09 virus shedding: duration is affected by severity, but not age. Influ Other Respir Virus 2014;8:142–50.
17. Carrat F, Vergu E, Ferguson NM, Lemaitre M, Cauchemez S, Leach S, et al. Time lines of infection and disease in human influenza: a review of volunteer challenge studies. Am J Epidemiol 2008;167:775–85.
18. Amorim LD, Cai J. Modelling recurrent events: a tutorial for analysis in epidemiology. Int J Epidemiol 2015;44:324–33.
19. Koutsakos M, Nguyen TH, Barclay WS, Kedzierska K. Knowns and unknowns of influenza B viruses. Future Microbiol 2016;11:119–35.
20. Memoli MJ, Han A, Walters KA, Czajkowski L, Reed S, Athota R, et al. Influenza A reinfection in sequential human challenge: implications for protective immunity and “Universal” vaccine development. Clin Infect Dis Off Publ Infect Dis Soc Am 2020;70:748–53.
21. Ranjeva S, Subramanian R, Fang VJ, Leung GM, Ip DKM, Perera R, et al. Age-specific differences in the dynamics of protective immunity to influenza. Nat Commun 2019;10:1660.
22. Stray SJ, Pittman LB. Subtype- and antigenic site-specific differences in biophysical influences on evolution of influenza virus hemagglutinin. Virol J 2012;9:91.
23. Moriyama M, Hugentobler WJ, Iwasaki A. Seasonality of respiratory viral infections. Annu Rev Virology 2020;7:83–101.
24. Cowling BJ, Wong SS, Santos JJS, Touyon L, Ort JT, Ye N, et al. Preliminary findings from the dynamics of the immune responses to repeat influenza vaccination exposures (DRIVE I) study: a randomized controlled trial. Clin Infect Dis Off Publ Infect Dis Soc Am 2024; 79:901–9.