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A 14-year influenza reinfection surveillance in Chongqing, China: A retrospective analysis

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ABSTRACT

Influenza poses a significant medical burden and has the potential to cause global pandemics. To better understand the epidemiological characteristics of influenza reinfections and identify factors associated with an increased risk of reinfection, we analyzed influenza data from 2010 to 2023 obtained from the National Notifiable Infectious Disease Reporting Information System in Chongqing, China. The Andersen-Gill model was used to evaluate the association between demographic characteristics and the risk of reinfection. A total of 676,811.47 person-years were observed, with a median time to reinfection of 9.40 months. The log-rank test revealed significant differences in reinfection probability by sex, age, occupation, and residence ($p < .001$). Independent risk factors for influenza reinfection included male sex (adjusted hazard ratio [a*HR*]: 1.026, 95% confidence interval [*CI*]: 1.004–1.049), age ≤ 5 years (a*HR*: 4.645, 95% *CI*: 4.292–5.027), 6–18 years (a*HR*: 3.891, 95% *CI*: 3.574–4.235), age 46–64 years (a*HR*: 1.336, 95% *CI*: 1.158–1.541), and age ≥ 65 years (a*HR*: 2.946, 95% *CI*: 2.533–3.426), urban residency (a*HR*: 1.353, 95% *CI*: 1.315–1.391), and preschool-aged children (a*HR*: 2.103, 95% *CI*: 1.830–2.416). Influenza reinfection in Chongqing is relatively common and significantly associated with several key factors, including male sex, age ≤ 18 or > 45 years, preschool-aged children, and urban residency. These findings underscore the importance of tailored public health strategies, particularly promoting influenza vaccination among at-risk groups, to protect vulnerable populations from reinfection. Future studies are needed to refine influenza prevention measures for at-risk individuals, especially those susceptible to reinfection.

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Introduction

Acute respiratory infections (ARIs) remain a leading cause of acute illness globally, imposing a significant burden on public health systems, especially among vulnerable populations.[1] ARIs are caused by diverse pathogens and range from mild, self-limiting conditions to severe, life-threatening diseases, particularly affecting young children, the elderly, and immunocompromised individuals.[2,3] Among these pathogens, the influenza virus is a major contributor to the global burden of ARIs.[4] Influenza primarily affects the respiratory system and continues to impose a substantial medical burden, with its potential to cause global pandemics remaining a significant concern.[5] Influenza causes over 5 million hospitalizations globally each year, accounting for 14.1% of adult respiratory diseases hospitalizations 4. As a respiratory infectious disease caused by human influenza viruses, it significantly contributes to global mortality and morbidity and incurs considerable economic costs.[6] A five-year analysis of influenza surveillance data from 82 Chinese cities identified a total of 3,735,934 influenza cases, representing 72.71% of all cases, with estimates indicating 300,000–650,000 respiratory deaths annually attributable to seasonal influenza.[7]

Epidemiological studies on influenza reinfections are limited and estimated reinfection rates among humans vary significantly, ranging from 2% to 32%.[8–10] Price et al.[8] reported a cumulative reinfection rate of less than 1% after one year, increasing to 4.6% after five years and 9.6% after a decade, based on a 13-year surveillance dataset from Queensland, Australia. In contrast, Wang et al.[9] observed a cumulative incidence of 2% at six months, 4% at one year, 5% at two years, and 7% after 4.9 years in Guangxi, China, over a seven-year period. Notably, Camacho et al.[10] reported an exceptionally high reinfection rate of 32% on Tristan da Cunha Island within 59 days during a two-wave influenza A/H3N2 epidemic. These heterogeneous estimates highlight the need for updated data in influenza reinfection research. However, epidemiological studies on reinfections remain limited.

Chongqing, a centrally-administered municipality in southwestern China with an area of over 82,400 km^2 and a population of more than 34 million, has a substantial proportion of residents aged 60 years or older (21.87%).[11] Despite

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the initiation of influenza surveillance in 2005, understanding of influenza reinfection rates and characteristics in Chongqing remain limited. This study aims to delineate the epidemiological features of influenza reinfections and identify factors associated with an increased risk of reinfection.

Material and methods

Data source of influenza cases

Data for this study included all influenza cases in Chongqing from 2010 to 2023 recorded in the National Notifiable Infectious Disease Reporting Information System (NIDRIS) database. The database mandates that all newly diagnosed influenza cases be reported within 24 hours after diagnosis, along with demographic data, including patient names, identity card numbers, the names of guardians (for minors under the age of 18), sex, date of birth, age, residential address, diagnosis classification (clinically diagnosed or laboratory-confirmed), dates of illness onset and diagnosis, and virus serotype for laboratory-confirmed cases (if documented by the physician).

Case definitions

Clinically diagnosed cases and laboratory-confirmed cases were defined according to the influenza diagnosis and treatment protocol established by the National Health Commission of the People's Republic of China.[12] A clinically diagnosed case was defined as a patient exhibiting symptoms such as cough, fever, sore throat, and dry throat, along with a clinician-confirmed influenza-related epidemiological history. A laboratory-confirmed case required not only the manifestation of these clinical symptoms but also a positive result from at least one of the following etiological tests: (a) real-time fluorescence-based quantitative polymerase chain reaction (PCR) or rapid multiplex PCR for influenza virus nucleic acid; (b) a rapid antigen test using either a colloidal gold assay or immunofluorescence; (c) a fourfold or greater increase in influenza virus-specific immunoglobulin G (IgG) antibody titers, or (d) successful isolation of the influenza virus. The study was approved by the Institutional Review Board of the Chongqing Center for Disease Control and Prevention.

Exclusion criteria were as follows: (1) suspected diagnoses; (2) duplicate or misreported medical records; (3) cases lacking essential identification data (including but not limited to patient names and identity cards numbers), which prevented reliable identity verification; and (4) reinfection episodes occurring within 14 days of the preceding event.

Identification criteria for reinfection case

Given the duration of viral shedding following the initial infection,[13] a reinfection case was defined as a subsequent influenza notification for the same patient occurring more than 14 days after a previous notification, consistent with other studies.[8] All cases were reported by doctors, with only a small proportion being confirmed by laboratory detection.

The inclusion criteria for identifying reinfection cases in this study were as follows: (a) matching patient names with identification documents; (b) the presence of at least two consistent data points among the patient's phone number, current address, and the name of a parent or guardian (if available); (c) a diagnosis interval of greater than 14 days between two influenza episodes within the period from 2010 to 2023.

Laboratory-confirmed influenza cases with specified viral typing were categorized as: (1) untyped, (2) influenza A (including all subtypes), (3) influenza B (both Victoria and Yamagata lineages), or (4) A and B coinfection.

Statistical analysis

Baseline characteristics for continuous data were presented as mean ± standard deviation (SD) or median [interquartile range (IQR)] for normally and non-normally distributed continuous data, respectively. Comparisons of primary infection characteristics between individuals with and without reinfection were conducted using the chi-square test or Fisher's exact test for categorical variables and the t-test or Mann-Whitney U test for continuous variables. Patients without a reinfection by December 31, 2023, were right-censored at their last follow-up date. Person-years of follow-up were calculated from the date of the first influenza diagnosis to the date of reinfection or December 31, 2023, whichever occurred first. Kaplan-Meier estimators were used to determine the cumulative incidence of reinfection, and the log-rank test was used to assess the proportion of influenza reinfections over time after the first infection; pairwise comparisons were conducted if necessary.

Our analysis of influenza reinfection was conducted using the Andersen-Gill model, a robust statistical approach specifically designed for recurrent event analysis that accounts for within-subject correlation of multiple events.[14] Hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs) were estimated to explore the characteristics associated with influenza reinfection in both univariate and multivariate analyses.

Classification of influenza reinfection patterns

Patients with consecutive infections involving specific combinations of influenza virus types were included. They were categorized into nine groups based on the virus types of their two consecutive infections:

(a) A – A: reinfection with influenza A after an initial A infection;
(b) A&B – A&B: subsequent coinfection with A and B following an initial A&B coinfection;
(c) B – B: reinfection with influenza B after a prior B infection;
(d) A – A&B: coinfection with A and B following an initial A infection;
(e) A – B: reinfection with B after an A infection;
(f) A&B – A: reinfection with A after an A&B coinfection;
(g) A&B – B: reinfection with B after an A&B coinfection;
(h) B – A: reinfection with A after a B infection;

(i) B – A&B: coinfection with A and B after a B infection.

Patients were classified as either homotypic, involving the same virus type in both infections (groups a, b, and c), or heterotypic, involving different virus types across infections (groups d through i).

Sensitivity analyses

We conducted sensitivity analyses to assess the robustness of our primary findings, consistently adjusting for predefined covariates (age, sex, occupation, residence, and influenza virus type) in all analyses. Four approaches were implemented:

1. Temporal stability assessment through 2023 data exclusion

To account for the atypical influenza activity in 2023 (potentially due to the relaxation of COVID-19 measures and detection bias,[15] we excluded data from 2023 and assessed the consistency of reinfection incidence and risk factors.

2. Diagnostic technology-adapted stratified analysis

We stratified analyses into two diagnostic eras to evaluate potential detection bias resulting from evolving diagnostic technologies:

Era 1 (2010–2015): Dominated by viral culture and immunofluorescence assays.

Era 2 (2016–2023): Characterized by widespread adoption of RT-PCR.

This stratification allowed us to assess whether changes in diagnostic methods affected the reinfection rate estimates.

3. Multidimensional confounder adjustment

In addition to the predefined covariates, we incorporated four factors related to transmission dynamics and healthcare resources – population density, PM2.5 levels, health facility density, and per capita disposable income – into the multivariate model to assess their impact on reinfection risk.

4. Modeling framework robustness verification

We compared results obtained from the Andersen-Gill model with those from a standard Cox proportional hazards model to evaluate the impact of model selection on risk estimates. A two-tailed P-value <.05 was considered statistically significant for all analyses. All analyses were conducted using R software, version 4.0.2 (The R Foundation, Boston, MA). The main model fitting was conducted using the 'survival' packages.[16]

Results

Patient demographic characteristics

From January 2010 to December 2023, our study identified 696,343 influenza cases. After screening, 521,818 cases from 489,526 individuals were included (Figure 1). The age at first episode ranged from 17 to 90 years, with a median of 8.00 years (IQR: 6.00–13.00). Of the study population, 87.56% were

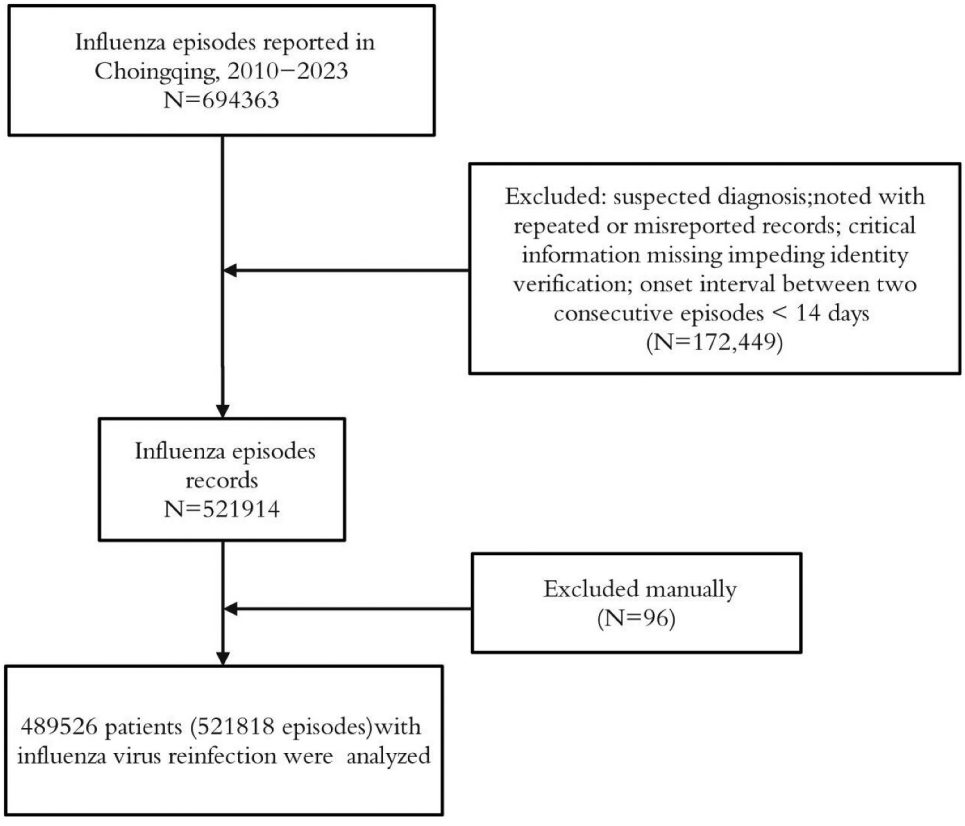

Figure 1. Flow diagram of selection process for patients.

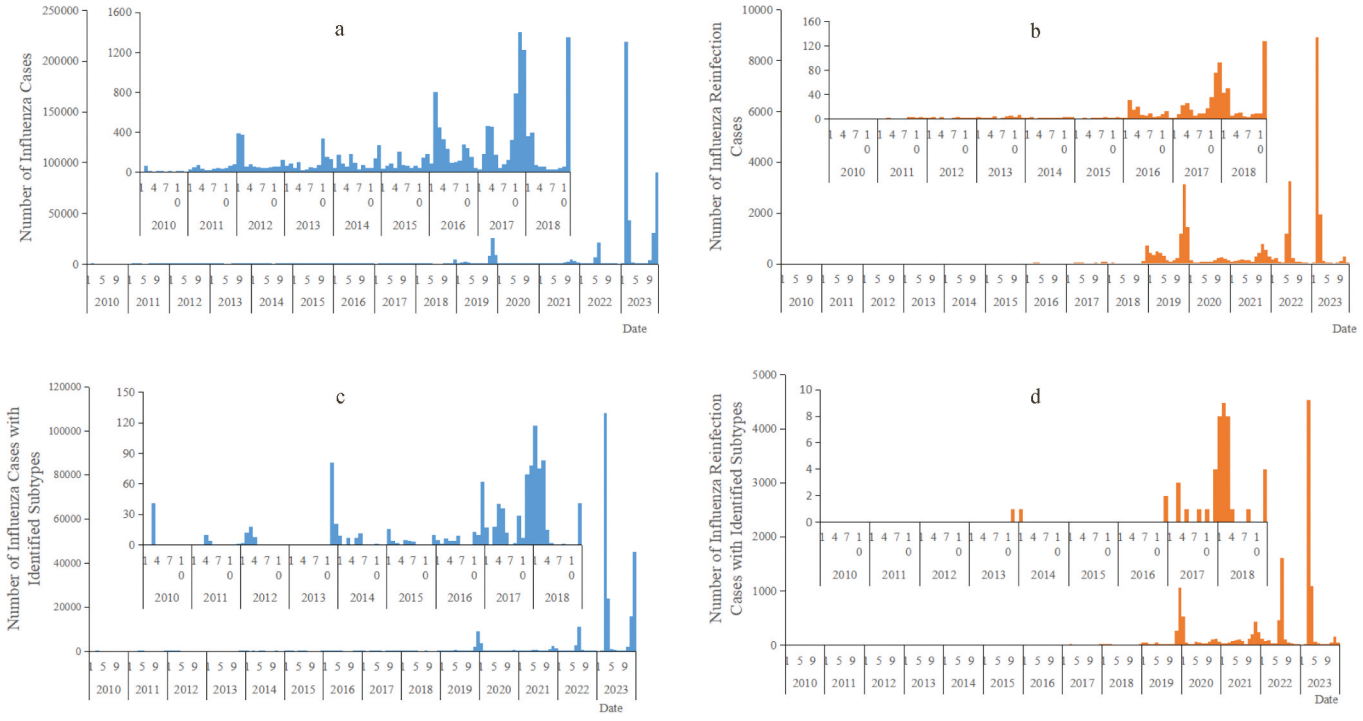

Figure 2. Temporal patterns of influenza virus activity and reinfection in Chongqing, China, 2010–2023. a. Total influenza cases (clinical and laboratory-confirmed). b. Influenza reinfection cases (clinical and laboratory-confirmed). c. Laboratory-confirmed influenza cases with identified subtypes. d. Laboratory-confirmed reinfection cases with identified subtypes.

minors. Of the 489,526 individuals, 260,318 (53.18%) were male, and 229,208 (46.82%) were female; 297,954 (60.87%) were students, and 404,991 (82.73%) lived in urban areas. Overall, 380,755 (77.78%) cases were laboratory-confirmed cases, while 108,771 (22.22%) were clinically diagnosed. Among the laboratory-confirmed cases, influenza A was the most prevalent (38.15%), followed by untyped influenza (32.04%), influenza B (5.88%), and coinfection with influenza A/B (1.71%). Figure 2 displays the seasonal patterns of influenza virus activity in Chongqing from 2010 to 2023. Although influenza viruses circulate year-round, peak activity is generally observed during fall and winter, sometimes extending into spring. A marked increase in influenza incidence was observed after 2018, with a particularly sharp rise in 2023, likely influenced by policy adjustments in the post-COVID-19 era. These temporal patterns were consistently observed across total influenza cases (including both clinically diagnosed and laboratory-confirmed cases) and laboratory-confirmed cases with identified subtypes.

Table 1 compares the demographic characteristics between patients with and without reinfection. Those with reinfection tended to be younger, predominantly male, and more likely to have laboratory-confirmed diagnoses ($p < .001$).

Characteristics of reinfection patients

Over the 14-year observation period, the study population accumulated 676,811.47 person-years of data. The vast majority (93.89%) experienced only a single influenza episode, while a small proportion (6.11%; 29923 individuals) had multiple reinfections, ranging from 1 to 8 episodes. Among the reinfection group, 93.56% (27,997 individuals) experienced one reinfection, 5.43% (1,626 individuals) experienced two, and 1.00% (300 individuals) experienced three or more.

The intervals between infections varied widely, ranging from 0.50 to 149.13 months, with a median interval of 9.40 months and a mean of 18.61 months. The median time between the first and subsequent reinfections decreased progressively: 19.04 months (first to second reinfection), 13.68 months (second to third), 11.83 months (third to fourth), 9.02 months (fourth to fifth), 9.25 months (fifth to sixth), 7.06 months (sixth to seventh), 9.01 months (seventh to eighth), and 9.08 months (eighth to ninth).

In the population experiencing reinfection, statistically significant differences were observed in sex, age, occupation, and the distribution of influenza virus subtypes across varying reinfection counts, as detailed in Table 2.

Incidence of influenza reinfection

From 2010 to 2023, the cumulative incidence of influenza reinfection increased progressively: 0.70% at 6 months, 5.40% at 12 months, 9.30% at 24 months, 11.70% at 36 months, 17.40% at 48 months, 21.50% at 60 months, and peaked at 23.90% after 120 months (Figure 3a). Females consistently exhibited higher reinfection probabilities than males at each time point: 0.80% vs. 0.70% at 6 months, 5.30% vs. 5.50% at 12 months, 9.00% vs. 9.50% at 24 months, 11.40% vs. 12.00% at 36 months, 16.90% vs. 17.80% at 48 months, 20.80% vs. 22.10% at 60 months, and 23.20% vs. 24.50% at 120 months

Table 1. Sociodemographic characteristics of individuals with and without influenza reinfection in Chongqing, China, 2010–2023.

Characteristic	Total	Patients with 1 episode, N (%)	Patients with ≥2 pisodes(reinfection), N (%)	Statistics	*P*-value
Total	489,526	459,603	29,923	–	–
Sex					
Male	260318	243967 (93.72)	16351 (6.28)	27.445	<.001
Female	229208	215636 (94.08)	13572 (5.92)		
Age at first episode (years)					
0–5	121267	104889 (86.49)	16378 (13.51)	15957.618	<.001
6–18	307365	295145 (96.02)	12220 (3.98)		
19–45	48589	47866 (98.51)	723 (1.49)		
46– 64	8253	7986 (96.76)	267 (3.24)		
≥65	4052	3717 (91.73)	335 (8.27)		
Median (IQR*)	8.00 (6.00–13.00)	9.00 (6.00–14.00)	5.00 (3.00–7.00)	80.545	<.001
Occupation					
Farmers	3075	2662 (86.57)	413 (13.43)	77777.602	<.001
Other	174968	163092 (93.21)	11876 (6.79)		
Preschool-aged children	9542	2599 (27.24)	6943 (72.76)		
Students	297954	287350 (96.44)	10604 (3.56)		
Medical staff	3987	3900 (97.82)	87 (2.18)		
Residence					
Urban	404991	381080 (94.09)	23911 (5.91)	177.760	<.001
Rural	84535	78523 (92.89)	6012 (7.11)		
Primary infection with influenza virus type					
Clinically diagnosed cases	108771	99691 (91.65)	9080 (8.35)	1393.189	<.001
Laboratory-confirmed cases					
Untyped influenza virus	156827	147993 (94.37)	8834 (5.63)		
Influenza A	186778	177300 (94.93)	9478 (5.07)		
Influenza B	28763	26785 (93.12)	1978 (6.88)		
Coinfection of influenza A and B	8387	7834 (93.41)	553 (6.59)		

*Interquartile Range, IQR; No, Number.

Table 2. Characteristics of influenza reinfection in Chongqing, China, 2010–2023.

Characteristic	Total	Frequency of reinfection episode, N (%)				Statistics	P-value
		0	1	2	≥3		
Total	489526	459603 (93.89)	27997 (5.72)	1626 (0.33)	300 (0.06)	–	–
Sex							
Male	260318	243967 (93.72)	15313 (5.88)	885 (0.34)	153 (0.06)	29.171	<.001
Female	229208	215636 (94.08)	12684 (5.53)	741 (0.32)	147 (0.06)		
Age groups (years)							
0–5	121267	104889 (86.49)	14862 (12.26)	1245 (1.03)	271 (0.22)	–	0.005*
6–18	307365	295145 (96.02)	11856 (3.86)	341 (0.11)	23 (0.01)		
19–45	48589	47866 (98.51)	708 (1.46)	13 (0.03)	2 (0.00)		
46 –64	8253	7986 (96.77)	256 (3.10)	10 (0.12)	1 (0.01)		
≥65	4052	3717 (91.73)	315 (7.77)	17 (0.42)	3 (0.07)		
Mean (SD)	11.67 ± 11.00	11.96 ± 11.00	7.30 ± 10.03	5.01 ± 8.88	3.72 ± 8.86	5445.213	<.001
Occupation							
Farmers	3075	2662 (86.57)	390 (12.68)	19 (0.62)	4 (0.13)	–	0.005*
Other	174968	163092 (93.21)	11064 (6.32)	701 (0.40)	111 (0.06)		
Preschool-aged children	9542	2599 (27.24)	6141 (64.36)	635 (6.66)	167 (1.75)		
Students	297954	287350 (96.44)	10318 (3.46)	269 (0.09)	17 (0.01)		
Medical staff	3987	3900 (97.82)	84 (2.11)	2 (0.05)	1 (0.03)		
Residence							
Urban	404991	381080 (94.10)	22430 (5.54)	1242 (0.31)	239 (0.06)	192.754	<.001
Rural	84535	78523 (92.89)	5567 (6.59)	384 (0.45)	61 (0.07)		
Primary infection with influenza virus type							
Clinically diagnosed cases	108771	99691 (91.65)	8212 (7.55)	692 (0.64)	176 (0.16)	1768.618	<.001
Laboratory-confirmed cases							
Untyped influenza virus	156827	147993 (94.37)	8398 (5.36)	403 (0.26)	33 (0.02)		
Influenza A	186778	177300 (94.93)	9080 (4.86)	338 (0.18)	60 (0.03)		
Influenza B	28763	26785 (93.12)	1798 (6.25)	159 (0.55)	21 (0.07)		
Coinfection of influenza A and B	8387	7834 (93.41)	509 (6.07)	34 (0.41)	10 (0.12)		

*Fisher's exact test was used for statistical analysis; No., Number.

(Figure 3b). Children under the age of 5 showed the highest reinfection probabilities, reaching 44.00% after 120 months (Figure 3c). Reinfection probabilities in urban areas were consistently higher than those in rural areas at all measured time points: 0.70% vs. 0.80% at 6 months and 25.90% vs. 19.70% at 120 months (Figure 3d). Children in home care had significantly higher reinfection probabilities, with aprobability of 90.22% at 120 months, compared to 8.60% among medical staff (Figure 3e). Laboratory-confirmed cases with mixed A and B infections exhibited the highest reinfection

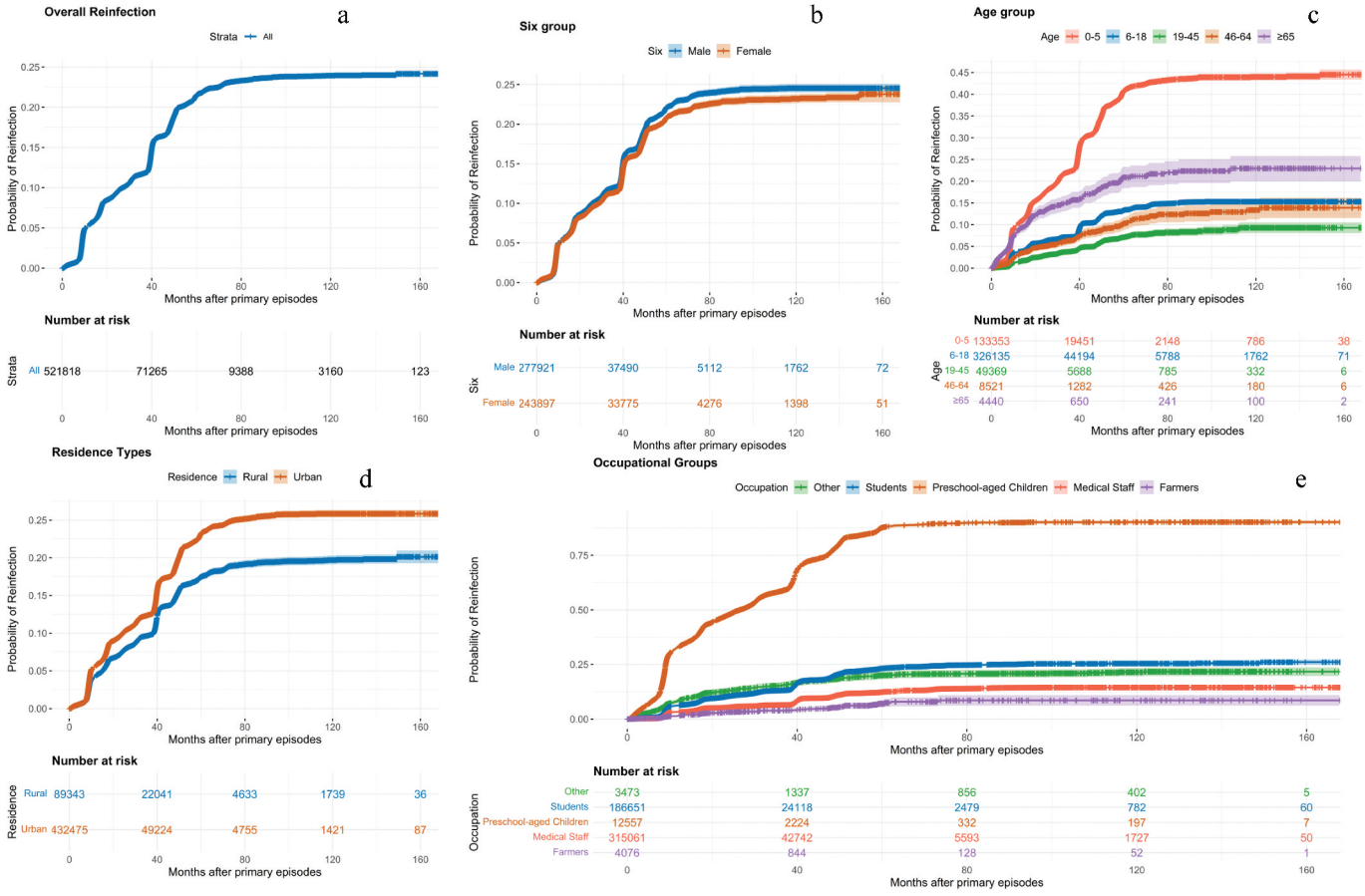

Figure 3. Kaplan-Meier survival analysis of influenza reinfection following primary infection episodes in Chongqing, China, 2010–2023. a. Cumulative probability of reinfection for all patients. b. Cumulative probability of reinfection by sex. c. Cumulative probability of reinfection by age group. d. Cumulative probability of reinfection by residence type. e. Cumulative probability of reinfection by occupational group.

probability, escalating to 43.10% by 60 months. Notably, the log-rank test revealed significant differences in reinfection probabilities by sex, age groups, occupation, and residence ($p < .001$).

Predictors of influenza reinfection

The univariate Cox regression analysis revealed significant associations between influenza reinfection and several factors, including age group, occupation, place of residence, and the type of influenza virus in the initial infection. Multivariate Cox regression analysis further identified independent risk factors for reinfection, including male sex (adjusted hazard ratio [a*HR*]: 1.026, 95% CI: 1.004–1.049) and specific age groups: ≤ 5 years (a*HR*: 4.645, 95% CI: 4.292–5.027), 6–18 years (a*HR*: 3.891, 95% *CI*: 3.574–4.235), 46–64 years (a*HR*: 1.336, 95% CI: 1.158–1.541), and ≥65 years (a*HR*: 2.946, 95% CI: 2.533–3.426).

Additionally, residing in an urban area (a*HR*: 1.353, 95% *CI*: 1.315–1.391) and being a preschool-aged child (a*HR*: 2.103, 95% *CI*: 1.830–2.416) were associated with an increased risk of reinfection. In contrast, students (a*HR*: 0.185, 95% *CI*: 0.160–0.211) and medical staff (a*HR*: 0.363, 95% *CI*: 0.282–0.467) exhibited a significantly reduced risk. Primary infections with influenza A (a*HR*: 1.619, 95% *CI*: 1.571–1.667), coinfection with influenza A and B (a*HR*: 1.878, 95% *CI*: 1.733–2.035), and influenza B (a*HR*: 1.540, 95% *CI*: 1.472–1.612) were identified as significant independent risk factors for reinfection. Table 3 summarizes the univariate and multivariate analyses of influenza reinfection.

Characteristics of influenza reinfection based on identifiable virus types

We conducted a subgroup analysis of influenza reinfections in 29,923 patients, identifying 8,588 cases with identifiable virus types in both primary and subsequent infections. Homotypic reinfection occurred in 4,579 cases (53.32%), with a mean interval of 14.55 months, while heterotypic reinfection was observed in 4,009 cases (46.68%), a mean interval of 16.26 months between episodes. The interval between reinfections significantly varied across groups ($p < .001$), ranging from 0.50 to 80.90 months. Patients with homotypic reinfections had an mean age of 7.17 years, significantly lower than the 7.55 years for those with heterotypic reinfections ($p < .001$).

Homotypic reinfections were significantly more frequent in children under 5 years of age, accounting for 65.85% of these cases, and were most commonly observed during the winter season, constituting 45.79% of total reinfections. In contrast, heterotypic reinfections peaked among individuals aged 6 to 18 years, with winter also being the predominant season for

Table 3. Univariate and multivariate analyses of factors associated with influenza reinfection in Chongqing, China, 2010–2023.

	Univariate analysis			Multiple analysis		
Factors	*HR*	95%*CI*	*P*-value	a*HR*	95%*CI*	*P*-value
Sex(ref: female)						
Male	1.043	(1.019,1.067)	<.001	1.026	(1.004,1.049)	0.021
Age group(ref: 19–45 year)						
0–5	6.970	(6.472,7.505)	<.001	4.645	(4.292,5.027)	<.001
6–18	2.255	(2.093,2.429)	<.001	3.891	(3.574,4.235)	<.001
46–64	1.725	(1.501,1.982)	<.001	1.336	(1.158,1.541)	<.001
≥65	4.436	(3.897,5.048)	<.001	2.946	(2.533,3.426)	<.001
Occupation(ref: farmers)						
Other	1.099	(0.994,1.215)	0.065	0.348	(0.303,0.399)	<.001
Preschool-aged children	7.262	(6.568,8.029)	<.001	2.103	(1.830,2.416)	<.001
Students	0.563	(0.510,0.623)	<.001	0.185	(0.160,0.211)	<.001
Medical Staff	0.292	(0.231,0.369)	<.001	0.363	(0.282,0.467)	<.001
Residence types(ref:rural)						
Urban	1.332	(1.295,1.371)	<.001	1.353	(1.315,1.391)	<.001
Primary infection with influenza virus type(ref: clinically diagnosed cases)						
Untyped influenza virus	1.320	(1.281,1.360)	<.001	1.461	(1.419,1.504)	<.001
Influenza A	1.460	(1.417,1.505)	<.001	1.619	(1.571,1.667)	<.001
Influenza B	1.466	(1.398,1.537)	<.001	1.540	(1.472,1.612)	<.001
Coinfection of influenza A and B	1.698	(1.565,1.841)	<.001	1.878	(1.733,2.035)	<.001

HR: adjusted hazard ratio; *CI*: confidence interval.

these cases, and were especially common among students and urban residents ($p < .001$). A detailed summary of these findings is provided in Supplementary Table S1.

Sensitivity analyses

We analyzed data from 2010 to 2023 using a standard Cox proportional hazards model. The results aligned with those presented in Table 3 and are detailed in Supplementary Table S2. After excluding 2023 data, the cumulative probability of influenza reinfection increased steadily over time, from 1.49% at 6 months to 23.88% at 120 months. The 6-month reinfection probability was lower when excluding 2023 data (0.73%) compared to the complete 2010–2023 dataset (1.49%), but cumulative probabilities at other time points remained stable (Supplementary Table S4; see Supplementary Table S2 for multivariate analysis results). Stratified analyses by time period (pre-2016 [2010–2015] and post-2016 [2016–2023]) revealed that the cumulative probability of reinfection was lower in the pre-2016 period compared to the full 2010–2023 dataset, while post-2016 probabilities were similar to those of the full dataset (Supplementary Table S3). Including socioeconomic and environmental factors – such as population density, PM2.5 levels, healthcare facility density, and per capita disposable income – had minimal impact on the results, further supporting the robustness of our findings (Supplementary Table S5).

Discussion

Influenza reinfections are common throughout the lifespan.[17–19] In our study, over 6% of patients experienced reinfection, with the risk increasing as the interval since the previous episode lengthened, consistent with previous findings.[8,9] Compared to a study from Guangxi, China,[9] our research reported a higher overall reinfection rate, except during the first six months. This discrepancy likely arises from differences in reinfection criteria: we defined reinfections as episodes separated by at least 14 days, while Wang et al.[9] used a 35-day interval. Our 14-day threshold aligns with the documented duration of viral shedding[13,20] and is supported by other studies.[8]

Reinfection episodes in our study began to rise significantly from 2018, with minor peaks in 2019 and 2022 and a record high peak in 2023, mirroring the patterns of initial influenza cases. The consistent trend between initial infections and reinfections suggests that an increase in infections is likely to drive a corresponding rise in reinfections. The surge in influenza cases observed in 2019 and 2023 aligns with reports from other countries and regions within China.[9,21,22] One possible explanation is the emergence of a variant with a three-amino-acid deletion, which was antigenically distinct from the vaccine strain used during the 2018–2019 season. Additionally, the sharp rise in influenza cases in 2023 may be linked to the relaxation of national control measures following the COVID-19 pandemic.[23] In sensitivity analyses excluding 2023 data, the cumulative reinfection rates remained largely consistent, except for a notable difference at 6 months (0.73% vs. 1.49%), further underscoring the robustness of our findings.

Furthermore, our analysis indicated that individuals aged 19–45 years were less likely to experience influenza reinfection compared to other age groups. Reinfection rates were highest among children ≤5 years, followed by those aged 6–18 years and individuals ≥65 years. This age-related susceptibility pattern aligns with the established understanding that children's developing immune systems and older adults' waning immunity make them more prone to recurrent infections, as supported by previous studies.[8,9,24] Specifically, children's immature immune systems increase their susceptibility to infections.[25] Adults' immunological responses, as indicated by modeling studies, provide longer-lasting protection following exposure to the same influenza strain.[26] Similarly, adults over 45 years of age exhibit a higher likelihood of reinfection compared to those aged 18–45 years, consistent with the well-documented effects of immunosenescence on influenza immunity.[27,28] However, this population is the least likely to seek medical care for symptoms related to acute respiratory infections.[29] Future studies should collect region-specific data on healthcare-seeking behavior and

testing rates to better distinguish true epidemiological differences from potential detection bias.

Our study further revealed that residing in urban areas was significantly associated with an increased risk of influenza reinfection. The availability of advanced medical facilities in urban areas may lead to more frequent influenza testing, potentially increasing reinfection detection rates due to detection bias.[30,31] Healthcare-seeking behavior may also influence reinfection risk. For example, Dai et al.[29] reported that only 50.92% of patients with acute respiratory infections sought treatment at healthcare facilities in rural areas.

Our study also found that the mean interval to influenza reinfection was 18.61 months after the initial infection, which decreased to 15.51 months when both reinfections involved identified virus types, a finding consistent with other studies in China.[9] More than half of the reinfections were caused by the same virus type, with shorter intervals typically observed in consecutive homotypic infections, suggesting waning immunity.[8] The marked increase in genetic diversity and antigenic drift likely contributed to the observed reinfections and the shortening of intervals.[32]

This study has several strengths and limitations that should be acknowledged. A key strength is the extensive observation period and large sample size, which enabled detailed documentation of infection cases. Our in-depth analysis of reinfection characteristics in both the general influenza population and specific subtypes provides valuable insights into these patterns. The use of the Andersen-Gill model, which is more suitable than the standard Cox model for analyzing recurrent influenza infections, ensures that within-individual correlations are appropriately addressed.[14] To address potential biases, we conducted sensitivity analyses by excluding 2023 data, stratifying by diagnostic era (pre-2016 and post-2016), adjusting for socioeconomic and environmental factors, and comparing model results. The minimal variation observed supports the robustness of our findings. However, the post-pandemic period may reflect a distinct immunological context that warrants further investigation.

However, this study has limitations inherent to record-based data. The lack of individual-level vaccination history limits our ability to assess vaccine-induced immunity's role in modifying age- and occupation-related reinfection risks, potentially overestimating risks in unvaccinated populations and underestimation vaccination's protective effects.[33] Vaccination significantly reduces influenza-related hospitalizations in high-risk groups, particularly among the elderly and children.[34] Future studies should incorporate vaccination data to improve reinfection risk assessments. Changes in China's healthcare system, such as expanded universal healthcare coverage, increased healthcare-seeking behavior, and improved infectious disease reporting, may have enhanced case detection and reporting over time. These factors could potentially influence the observed temporal trends in reinfection rates.[35] Furthermore, our findings may underestimate the true incidence of influenza reinfection, as reinfections often present with milder symptoms, reducing the likelihood of individuals seeking medical attention or testing.[8,36,37] The definition of reinfections relied on a 14-day threshold between positive tests, which, although aligned with typical viral shedding periods, may not fully distinguish true reinfections and prolonged viral shedding or reactivation.[38] Future studies should establish a more accurate threshold by integrating clinical symptom profiles, serological testing, and time-based criteria. Finally, data limitations prevented competing risk analyses accounting for mortality and other censoring events, which could be addressed in future studies through linkage with mortality registries.

Conclusions

In conclusion, our 14-year study highlights a significant burden of influenza reinfection in Chongqing, particularly among males and individuals aged ≤ 18 or >45 years. These findings underscore the importance of tailored public health strategies, including promoting influenza vaccination among at-risk groups, to protect vulnerable populations from reinfection. Future studies are needed to refine influenza prevention measures for at-risk individuals, especially those susceptible to reinfection.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical approval

Ethical approval for this study was obtained from the institutional review board of the Chongqing Center for Disease Control and Prevention (Record number: 2021026).

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