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Vital Surveillances

Trends of Mortality in End-Stage Liver Disease — China, 2008–2020

Xiaoxiao Wang[1,2,&]; Huixin Liu[3,&]; Jinlei Qi[4]; Fangfang Zeng[5,6,7]; Lijun Wang[4]; Peng Yin[4]; Feng Liu[1,2]; Hongbo Li[8]; Yunning Liu[4]; Jiangmei Liu[4]; Lai Wei[9]; Xiaofeng Liang[5,6,7]; Yu Wang[10]; Huiying Rao[1,2,#]; Maigeng Zhou[4,#]

ABSTRACT

Introduction: Liver cancer and cirrhosis represent the most prevalent forms of end-stage liver diseases (ESLDs). Notably, in China, deaths attributed to ESLDs contribute significantly to the global mortality rate of these disorders. Enhanced comprehension of the mortality profile associated with ESLDs in China could provide crucial insights into intervention prioritization, which could in turn help reduce the overall global burden of these diseases.

Methods: Data were obtained from China's Disease Surveillance Points system. The presentation includes both crude and age-standardized mortality rates, stratified by sex, residential location, and region. Using Joinpoint Regression, trends in annual mortality rates were estimated from the period of 2008 to 2020 and expressed as the average annual percentage change (AAPC).

Results: In 2020, the gross mortality rate of ESLD stood at 30.08 cases per 100,000 individuals. A higher age-standardized ESLD mortality rate was observed in males and rural populations in comparison to their female and urban counterparts, respectively. Noticeably, the highest mortality rates associated with liver cancer and cirrhosis were reported in South and Southwest China, respectively. A positive correlation was noticed between age-specific ESLD mortality rates and advancing age. Interestingly, an annual decrease in the ESLD mortality rate was observed from 2008 to 2020. In urban contexts, the AAPC of cirrhosis was noted to be higher than that of liver cancer.

Conclusions: The mortality rate associated with ESLDs in China decreased between 2008 and 2020. Nevertheless, the death burden attributable to ESLD continues to be alarmingly high. Future initiatives should prioritize the reduction of ESLD mortality in particular populations: males, elderly individuals, and those residing in rural regions of South and Southwest China. The emphasis of future interventions should be placed on antiviral therapy for adults diagnosed with viral hepatitis, and on the prevention of hepatitis B virus (HBV) infection across all demographics.

INTRODUCTION

End-stage liver disease (ESLD), a severe stage of chronic liver disease, represents a significant global public health challenge due to its high mortality rate (*1–2*). Notably, liver cancer and decompensated cirrhosis represent a substantial proportion of ESLD cases. In 2020, liver cancer was the second most common cause of cancer-related deaths in China, accounting for nearly half of liver cancer fatalities worldwide (*3*). Additionally, cirrhosis and other chronic liver disorders constitute approximately 14.9% of global mortality, further emphasizing the severe public health impact of these conditions in China (*4*).

The prevalence and mortality rates of ESLD can significantly differ among various regions in China. Hence, understanding the current state and pattern of ESLD mortality, as well as its temporal trends, within China as a whole and its individual regions is of utmost importance. Such information can guide the formulation of intervention priorities and help reduce the worldwide disease burden of ESLD. In this study, we have gathered data from the Disease Surveillance Points (DSPs) system administered by the Chinese Center for Disease Control and Prevention (CDC) to analyze the mortality profile of ESLD in 2020. Additionally, we have examined the fluctuations in the annual mortality rates from 2008 to 2020, considering factors such as gender, age group, residential location, regional differences, and per capita gross domestic product (GDP).

METHODS

Data Source

Mortality data associated with ESLD, represented by

deaths stemming from liver function decompensation triggered by liver cancer and cirrhosis, were procured from the DSPs system. The DSPs system, initiated by the Chinese government in 1978, has progressively expanded its geographical reach over the past four decades. In 2013, the coverage of the DSPs system broadened from 161 to 605 data points, encapsulating more than 324 million citizens of China (accounting for 24.3% of the national populace). Deaths that transpire within these surveillance points are consistently reported, and the associated cause of death is codified as per the International Classification of Diseases-10th Revision (ICD-10) by professionally trained staff positioned in local hospitals or CDC branches.

This research classifies the root cause of mortality as ESLD, associated with specific ICD-10 codes: C22 signifies liver cancer, as well as K70.2–K70.4 and K74–K74.6, which refer to cirrhosis. This study received approval from the Ethics Committee of the National Center for Chronic and Non-communicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention (No. 202219).

In our analysis, we took into consideration five key sociodemographic factors: year of occurrence, place of residence, gender, age bracket, and geographical location. To categorize age, we used 13 groups: under 30 years, 30–34 years, 35–39 years, 40–44 years, 45–49 years, 50–54 years, 55–59 years, 60–64 years, 65–69 years, 70–74 years, 75–79 years, 80–84 years, and over 85 years. Geographical locations were segmented into seven regions, in line with the divisions provided by the National Statistics Bureau. These divisions include: North China (Beijing Municipality, Tianjin Municipality, Hebei Province, Shanxi Province, and Inner Mongolia Autonomous Region); Northeast China (Heilongjiang Province, Jilin Province, and Liaoning Province); East China (Shanghai Municipality, Jiangsu Province, Zhejiang Province, Anhui Province, Jiangxi Province, Shandong Province, and Fujian Province); Central China (Henan Province, Hubei Province, and Hunan Province); South China (Guangdong Province, Guangxi Autonomous Region, and Hainan Province); Southwest China [Chongqing Municipality, Sichuan Province, Guizhou Province, Yunnan Province, and Xizang Autonomous Region (Tibet)]; and Northwest China (Shaanxi Province, Gansu Province, Qinghai Province, Ningxia Autonomous Region, and Xinjiang Autonomous Region). Data pertaining to per capita GDP was acquired from the National Bureau of Statistics, with the information being accessed on January 8, 2022 (https://data.stats.gov.cn/).

Statistical Analysis

Mortality rates are denoted as a count of deaths per 100,000 individuals. Using data derived from the 2010 Chinese census, the age-standardized mortality rate was computed (ASMRC) and aligned with Segi's world standard population (ASMRW). Using Joinpoint Regression software, the average annual percentage change (AAPC) and its 95% confidence interval (*CI*) were estimated to scrutinize the mortality rate trends from 2008 to 2020. Subsequently, a Gaussian process regression was applied to examine the correlation between ASMRC and per capita GDP.

Statistical analysis was conducted in the Joinpoint Regression Program (version 4.9.0.0, Statistical Research and Applications Branch, National Cancer Institute, Bethesda, MD, USA) and R (version 4.1.1, R Foundation for Statistical Computing, Vienna, Austria), and all testing was two-tailed with statistical significance set at 0.05.

RESULTS

ESLD Mortality in 2020

In 2020, the DSPs system reported a total of 102,067 ESLD-related deaths: 86,692 due to liver cancer and 15,375 attributed to cirrhosis. The average age at death for ESLD was 63.37 years, with liver cancer at 63.57 years and cirrhosis at 62.32 years. The crude mortality rate for ESLD was calculated at 30.08 deaths per 100,000 people, while liver cancer and cirrhosis had rates of 25.57 deaths and 4.51 deaths per 100,000 people, respectively.

Examining the data for each ESLD (liver cancer or cirrhosis), males consistently demonstrated higher age-standardized mortality rates (ASMRC and ASMRW) than females, especially in rural regions. Furthermore, individuals residing in rural locations recorded higher age-standardized mortality rates compared to their urban counterparts.

Upon stratification by region, consistent sex differences in ASMRC and ASMRW persisted due to ESLD, while differences due to residential location experienced slight variations. Specifically, ASMRC and ASMRW were observed to be higher in urban areas compared to rural regions in the North, Northeast, East, and Central regions of China (Supplementary Table S1, available in http://weekly.chinacdc.cn/).

Table 1 displays the geographical distribution of ASMRC of ESLD, inclusive of its individual components (liver cancer and cirrhosis) across China in 2020. While South China recorded the highest ASMRC of liver cancer (26.86 deaths per 100,000 people), the lowest observed ASMRC of liver cancer was in North China (16.44/13.29 deaths per 100,000 people). In contrast, Southwest China experienced the highest ASMRC of cirrhosis (7.14 deaths per 100,000 people). East China had the smallest occurrence, with an ASMRC of merely 2.11 deaths per 100,000 people.

TABLE 1. Geographic distribution of age-standardized mortality rates (ASMR) for end-stage liver disease in 2020 across seven regions in China.

Disease	Area	ASMR (per 100,000)
End-stage liver disease	North China	16.44
	Northeast China	27.43
	East China	20.21
	Central China	25.70
	South China	31.71
	Southwest China	28.34
	Northwest China	20.08
Liver cancer	North China	13.29
	Northeast China	22.80
	East China	18.10
	Central China	23.25
	South China	26.86
	Southwest China	21.20
	Northwest China	16.61
Cirrhosis	North China	3.15
	Northeast China	4.63
	East China	2.11
	Central China	2.45
	South China	4.85
	Southwest China	7.14
	Northwest China	3.46

Note: North China: Beijing Municipality, Tianjin Municipality, Hebei Province, Shanxi Province, and Inner Mongolia Autonomous Region; Northeast China: Heilongjiang Province, Jilin Province, and Liaoning Province; East China: Shanghai Municipality, Jiangsu Province, Zhejiang Province, Anhui Province, Jiangxi Province, Shandong Province, and Fujian Province; Central China: Henan Province, Hubei Province, and Hunan Province; South China: Guangdong Province, Guangxi Zhuang Autonomous Region, and Hainan Province; Southwest China: Chongqing Municipality, Sichuan Province, Guizhou Province, Yunnan Province, and Xizang Autonomous Region (Tibet); and Northwest China: Shaanxi Province, Gansu Province, Qinghai Province, Ningxia Hui Autonomous Region, and Xinjiang Uygur Autonomous Region.

Age-Specific ESLD Mortality in 2008 and 2020

Both in 2008 and 2020, a consistent increase was observed in the age-specific ESLD mortality rates. However, the rate of increase in 2020 was less significant than that in 2008. This trend remained consistent even after accounting for variables such as residential location, sex, and region (Figure 1).

Trends in ESLD Mortality from 2008 to 2020

In 2008, the mortality rate for ESLD in China was significantly high, with a crude rate of 35.92 deaths per 100,000 individuals. From 2008 to 2020, the general ASMRC for ESLD in China exhibited a downward trajectory. This decline remained consistent upon stratification by gender and location (Figure 2, Supplementary Table S2, available in http://weekly.chinacdc.cn/).

From 2008 to 2020, the AAPC in ASMRC of ESLD, stratified by gender or residential location, showed no variability. However, in urban regions, the AAPC in ASMRC of cirrhosis was higher than that linked to liver cancer (AAPC in ASMRC: AAPC=−5.2, 95% *CI*: −5.9, −4.4 versus AAPC=−3.3, 95% *CI*: −4.2, −2.5). This trend continued when data was stratified by gender, for both males and females (Supplementary Table S2).

Upon examining the data by region, there was a consistent decreasing trend in the ASMRC of ESLD from 2008 to 2020 (Figure 2). Throughout this time frame, liver cancer demonstrated a greater AAPC of ASMRC in Northern, Northeastern, Southern, and Southwestern China, while cirrhosis had a higher AAPC of ASMRC in Northeastern and Southwestern China. Additionally, when compared to liver cancer, cirrhosis exhibited a higher AAPC of ASMRC in Northeastern and Eastern China (Figure 2, Supplementary Table S3, available at http://weekly.chinacdc.cn/).

Temporal Trends of Age Standardized ESLD Mortality with per Capita GDP

From 2008 to 2020, there was a noticeable downward trend in the ASMRC of ESLD, which corresponded with an increase in per capita GDP (Figure 3A–C). The lowest ASMRC of cirrhosis was observed when the per capita GDP exceeded 8,000 CNY, after which it appeared to stabilize (Figure 3C).

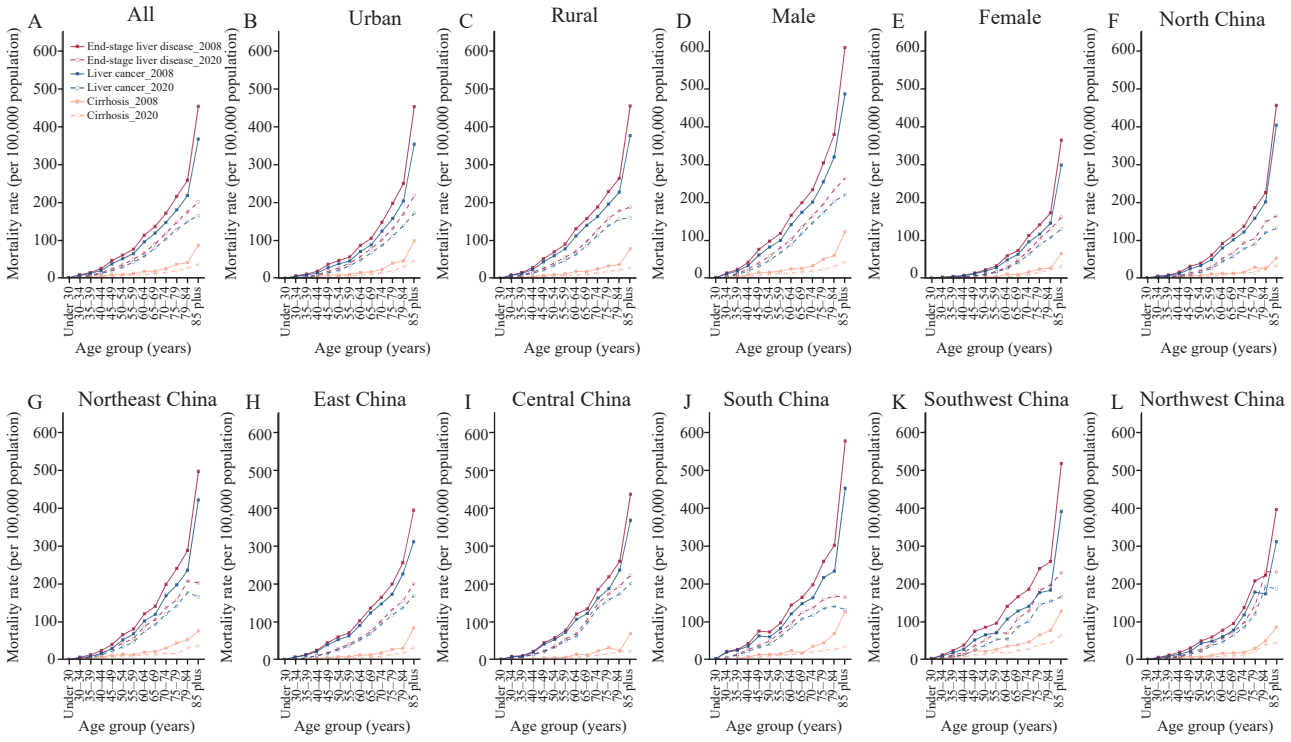

FIGURE 1. Trends in mortality rates for end-stage liver disease, liver cancer, and cirrhosis in 2008 and 2020. Among age groups based on all population (A) residential location (urban or rural, B–C), sex (male or female, D–E), and region (North, Northeast, East, Central, South, Southwest, or Northwest China (F–L).
Abbreviation: ASMRC=age-standardized mortality rates adjusted by the Chinese standard population.

When analyzed on a provincial-level administrative division (PLAD) basis, Guangdong — a province credited with a high per capita GDP — demonstrated the most significant reduction in the ASMRC of liver cancer. Conversely, the greatest decrease in the ASMRC of cirrhosis was recorded in Sichuan Province. Generally, the data insinuates that provinces with higher per capita GDP tend to manifest lower ASMRC of ESLD (Figure 3A–C).

DISCUSSION

This study reveals a significant decrease in the mortality rates associated with liver cancer and cirrhosis between 2008 and 2020, likely due to the effective management of chronic viral hepatitis, inclusive of both hepatitis B and C. Since 1992, China has instituted a policy mandating neonatal hepatitis B vaccinations (*5*). Furthermore, in 2009, a nationwide "catch-up" hepatitis B vaccination initiative for children aged between 8 and 15 was commenced (*6*). These collective strategies resulted in a substantial decrease in the rate of hepatitis B surface antigen (HBsAg) positivity. Moreover, national guidelines endorsed the use of first-line antiviral medicines, including pegylated interferon, entecavir, and tenofovir (*7*). Consequently, the proportion of chronic hepatitis B (CHB) patients receiving antiviral therapy increased from 13.5% in 2003 to 79.7% in 2016 (*8*). Concerning chronic hepatitis C (CHC), the implementation of direct-acting antiviral agents (DAAs) drastically lessened the burden of hepatitis C virus (HCV) infection in China. Specifically, the population with viremic HCV in China declined by around 536,000 from 2015 to 2020 (*9*). Collectively, these initiatives have reduced the mortality rates of liver cancer and cirrhosis associated with chronic viral hepatitis. A smaller decrease in mortality due to ESLD was observed in rural areas compared to urban areas — a correlation to the easier access in urban areas to timely treatment for chronic viral hepatitis, cirrhosis, and liver cancer (*10*).

From 2008 to 2020, decreases were observed in the mortality rates of ESLD, liver cancer, and cirrhosis concurrent with increases in per capita GDP. This trend aligns with prior research, which demonstrated a negative correlation between the Sociodemographic Index (SDI) values and the age-standardized mortality rates of cirrhosis and other chronic liver diseases (*11*).

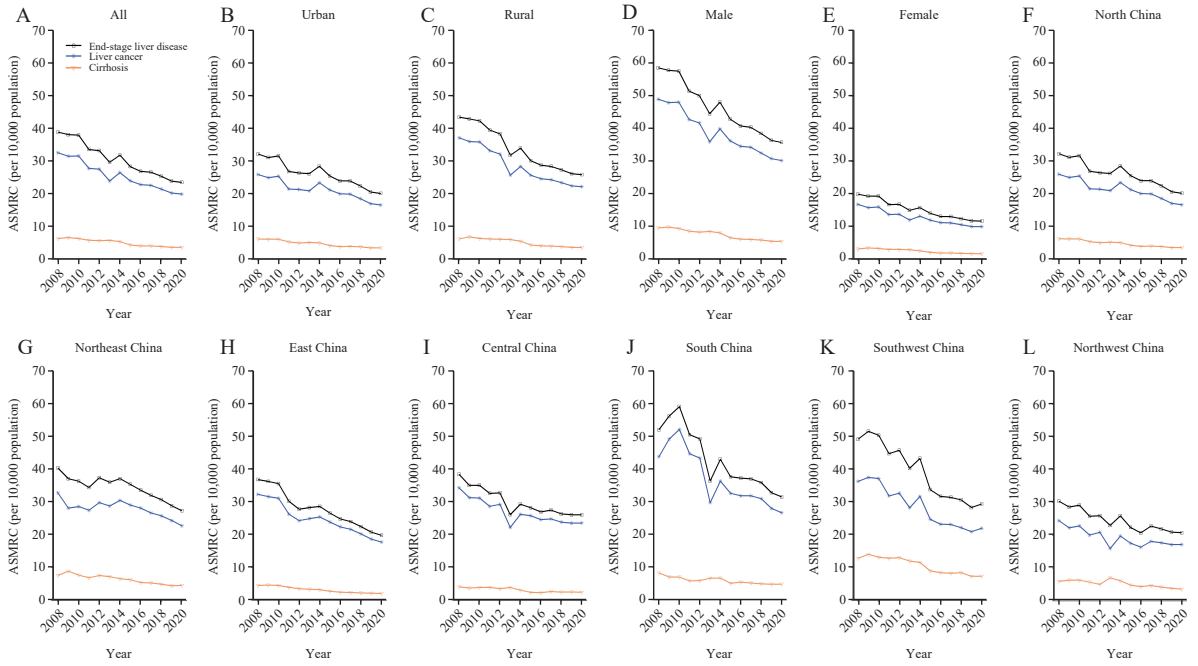

FIGURE 2. Trends in the ASMRC for end-stage liver disease, liver cancer, and cirrhosis from 2008 to 2020, broken down by all population (A), residential location (urban or rural, B–C), sex (male or female, D–E), and region (North, Northeast, East, Central, South, Southwest, or Northwest China, F–L).
ASMRC: age-standardized mortality rates, adjusted in accordance with the Chinese standard population

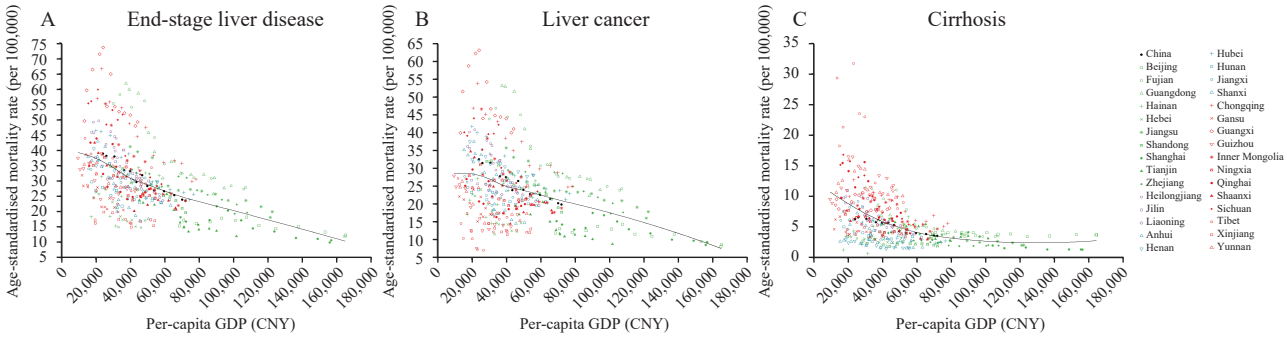

FIGURE 3. Age-standardized mortality rates for end-stage liver diseases stratified by per capita GDP in China from 2008 to 2020. (A) End-stage liver disease, (B) Liver cancer and (C) Cirrhosis.
Abbreviation: GDP=gross domestic product; CNY=Chinese Yuan.

It's possible that the decline in mortality rates could be attributed to improvements in sanitation, healthcare conditions, and the increased public awareness of medical treatment, all potentially facilitated by the rise in per capita GDP.

Hepatitis B virus (HBV) and HCV continue to be predominant contributors to cirrhosis and liver cancer mortality rates in China (*12–13*). As indicated by the GBD data of 2017, liver-related deaths (including liver cancer and cirrhosis) totalled 0.61 million in East Asia, 0.34 million in South Asia, 0.25 million in Southeast Asia, 0.12 million in Western Europe, and 0.1 million in the Middle East and North Africa (MENA) (*14*). In 2020, the death toll related to ESLD remained significantly high in China. This was consistent with the results from a data study on the burden of all cancers (*15*). First, despite the implementation of the neonatal hepatitis B vaccination program leading to a noticeable decline in HBV incidence and transmission, the prevalence of hepatitis B in China remains high due to an extensive population, approximately 84 million, living with CHB (*8*). Particularly in women of reproductive age, the prevalence of HBsAg persists between 5%–6% with the continuing risk being mother-to-child transmission. This poses a substantial challenge in advancing diagnostic coverage, eradicating

HBV infection, and lessening ESLD mortality resulting from CHB. Second, while DAA treatment has proven to achieve a higher curative rate in patients suffering from CHC (*16*), the actual diagnostic rate of Hepatitis C in China stands only at 2.1% (*17*). Owing to this low diagnostic rate, fewer CHC patients avail antiviral therapy, leading to higher incidences of HCV-related ESLD.

Our study faced several limitations. First, due to data unavailability in the DSPs system, we were unable to analyze morbidity and mortality data concerning specific etiologies of ESLD. Second, our study did not investigate fatalities resulting from other potential causes such as type 2 diabetes mellitus, which may have contributed to incompleteness in the report. Third, a significant challenge associated with the DSP data is the under-reporting of deaths, with higher rates observed in the west compared to the east and central regions, and rural areas more so than urban ones. This could potentially result in an underestimation of the overall mortality burden of ESLD, given that higher death rates were seen in rural areas and the west region. Despite these caveats, our study offers important insights into the mortality burden and shifting trends of ESLD, as well as disparities in mortality between liver cancer and cirrhosis. These findings enable the identification of high-risk populations and the development of preventive strategies, guiding future etiological studies on ESLD in China.

In sum, the last decade has witnessed a substantial decline in ESLD mortality rates in China, which can be largely attributed to the implementation of the HBV vaccine and treatment for chronic viral hepatitis. Nevertheless, the mortality burden of ESLD remains substantial. As such, future research efforts and healthcare initiatives should prioritize the exploration of antiviral therapy for adults diagnosed with viral hepatitis and preventative measures against HBV infection across all demographics, with the goal of further reducing ESLD mortality.

Conflicts of interest: Prof. Rao HY has received speaking fees from Bristol-Myers Squibb, Gilead, and AbbVie. The other authors declared no conflicts of interest.

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[#] Corresponding authors: Huiying Rao, rao.huiying@163.com; Maigeng Zhou, zhoumaigeng@ncncd.chinacdc.cn.

[1] Peking University People's Hospital, Peking University Hepatology Institute, Beijing, China; [2] Beijing Key Laboratory of Hepatitis C and Immunotherapy for Liver Diseases, Beijing International Cooperation Base for Science and Technology on NAFLD Diagnosis, Beijing, China; [3] Peking University People's Hospital, Department of Clinical Epidemiology and Biostatistics, Beijing, China; [4] National Center for Chronic and Non-communicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, China; [5] Department of Public Health and Preventive Medicine, School of Medicine, Jinan University, Guangzhou City, Guangdong Province, China; [6] Disease Control and Prevention Institute of Jinan University, Guangzhou City, Guangdong Province, China; [7] Jinan University-BioKangtai Vaccine Institute, Jinan University, Guangzhou City, Guangdong Province, China; [8] China Center for Economic Research, National School of Development, Peking University, Beijing, China; [9] Beijing Tsinghua Changgung Hospital, Tsinghua University, Beijing, China; [10] Chinese Foundation for Hepatitis Prevention and Control, Beijing, China.

[&] Joint first authors.

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SUPPLEMENTARY TABLE S1. Mortality rates of end-stage liver disease in 2020, China

Region	location	Sex	ESLD				Liver cancer				Cirrhosis				LC/C ratio
			Death numbers	Crude rate ($1/10^5$)	ASMRC ($1/10^5$)	ASMRW ($1/10^5$)	Death numbers	Crude rate ($1/10^5$)	ASMRC ($1/10^5$)	ASMRW ($1/10^5$)	Death numbers	Crude rate ($1/10^5$)	ASMRC ($1/10^5$)	ASMRW ($1/10^5$)	
All	All	Both	102,067	30.08	23.50	17.89	86,692	25.57	19.92	15.18	15,375	4.51	3.59	2.71	5.55
		Male	74,688	43.18	35.65	27.22	63,347	36.66	30.16	23.05	11,341	6.52	5.49	4.17	5.50
		Female	27,365	16.45	11.69	8.79	23,335	14.03	9.99	7.53	4,031	2.42	1.70	1.27	5.87
	Urban	Both	36,620	25.89	20.21	15.38	30,256	21.41	16.69	12.72	6,365	4.48	3.52	2.66	4.74
		Male	26,455	36.57	30.25	23.17	21,990	30.43	25.13	19.26	4,465	6.14	5.12	3.91	4.91
		Female	10,161	14.70	10.41	7.77	8,262	11.96	8.51	6.36	1,898	2.74	1.90	1.41	4.47
	Rural	Both	65,447	33.08	25.91	19.71	56,437	28.55	22.26	16.96	9,011	4.53	3.65	2.76	6.10
		Male	48,232	47.94	39.66	30.21	41,357	41.15	33.88	25.84	6,876	6.79	5.78	4.37	5.86
		Female	17,205	17.69	12.60	9.52	15,072	15.51	11.04	8.35	2,132	2.18	1.56	1.17	7.07
North China	All	Both	9,102	21.29	16.44	12.56	7,406	17.32	13.29	10.17	1,696	3.97	3.15	2.39	4.22
		Male	6,369	29.07	23.69	18.20	5,189	23.69	19.22	14.76	1,180	5.39	4.47	3.44	4.30
		Female	2,733	13.11	9.35	7.04	2,217	10.63	7.58	5.74	516	2.48	1.76	1.30	4.30
	Urban	Both	3,557	17.90	13.71	10.50	2,635	13.25	10.10	7.74	922	4.65	3.61	2.75	2.80
		Male	2,457	23.98	19.46	15.09	1,857	18.13	14.72	11.38	599	5.86	4.74	3.72	3.10
		Female	1,100	11.43	8.02	5.96	778	8.07	5.67	4.25	323	3.36	2.35	1.71	2.41
	Rural	Both	5,545	24.26	18.89	14.41	4,772	20.89	16.13	12.32	773	3.38	2.76	2.09	5.84
		Male	3,912	33.58	27.56	21.03	3,332	28.62	23.28	17.80	581	4.97	4.28	3.23	5.44
		Female	1,632	14.56	10.51	7.99	1,440	12.85	9.27	7.05	193	1.72	1.24	0.94	7.48
Northeast China	All	Both	11,280	41.56	27.43	21.00	9,446	34.80	22.80	17.47	1,834	6.75	4.63	3.53	4.93
		Male	8,146	59.83	40.99	31.56	6,768	49.71	33.83	26.05	1,378	10.12	7.16	5.51	4.72
		Female	3,134	23.16	14.31	10.80	2,678	19.79	12.20	9.23	456	3.37	2.11	1.57	5.78
	Urban	Both	3,565	36.20	23.20	17.87	2,843	28.86	18.41	14.12	723	7.34	4.79	3.74	3.85
		Male	2,548	51.73	34.82	26.87	2,023	41.07	27.55	21.13	525	10.66	7.28	5.74	3.79
		Female	1,017	20.68	12.15	9.30	819	16.65	9.81	7.52	198	4.03	2.34	1.78	4.20
	Rural	Both	7,715	44.60	29.96	22.84	6,603	38.18	25.42	19.43	1,112	6.42	4.53	3.41	5.61
		Male	5,598	64.40	44.56	34.23	4,744	54.59	37.47	28.85	853	9.81	7.09	5.38	5.28
		Female	2,117	24.58	15.72	11.76	1,859	21.58	13.73	10.31	258	2.99	1.98	1.46	6.93

Continued

Region	location	Sex	ESLD				Liver cancer				Cirrhosis				LC/C ratio
			Death numbers	Crude rate (1/10^5)	ASMRC (1/10^5)	ASMRW (1/10^5)	Death numbers	Crude rate (1/10^5)	ASMRC (1/10^5)	ASMRW (1/10^5)	Death numbers	Crude rate (1/10^5)	ASMRC (1/10^5)	ASMRW (1/10^5)	
East China	All	Both	28,287	27.63	20.21	15.37	25,337	24.74	18.10	13.78	2,950	2.89	2.11	1.59	8.59
		Male	20,457	39.29	30.66	23.39	18,424	35.38	27.57	21.04	2,034	3.91	3.09	2.35	8.91
		Female	7,832	15.57	10.16	7.62	6,915	13.74	9.02	6.78	917	1.83	1.14	0.84	7.90
	Urban	Both	10,630	24.33	17.80	13.55	9,323	21.33	15.64	11.92	1,307	3.00	2.16	1.63	7.23
		Male	7,491	33.36	26.20	20.03	6,652	29.62	23.24	17.78	838	3.74	2.96	2.25	7.86
		Female	3,140	14.79	9.55	7.14	2,671	12.58	8.20	6.15	469	2.21	1.35	0.99	6.08
	Rural	Both	17,657	30.09	21.99	16.71	16,014	27.28	19.92	15.15	1,643	2.80	2.07	1.56	9.64
		Male	12,967	43.78	34.04	25.93	11,772	39.74	30.84	23.51	1,195	4.04	3.20	2.42	9.63
		Female	4,693	16.13	10.59	7.95	4,244	14.59	9.60	7.22	448	1.54	0.99	0.73	9.69
Central China	All	Both	17,017	32.26	25.70	19.55	15,421	29.24	23.25	17.71	1,595	3.02	2.45	1.84	9.49
		Male	12,137	45.32	38.32	29.13	10,959	40.92	34.53	26.27	1,179	4.40	3.79	2.87	9.12
		Female	4,876	18.77	13.67	10.38	4,460	17.17	12.50	9.52	416	1.60	1.17	0.86	10.64
	Urban	Both	4,016	26.84	21.57	16.32	3,416	22.84	18.31	13.87	600	4.01	3.26	2.45	5.61
		Male	2,867	38.24	32.37	24.57	2,439	32.53	27.48	20.86	428	5.71	4.89	3.71	5.62
		Female	1,148	15.38	11.44	8.56	976	13.08	9.73	7.31	172	2.30	1.71	1.25	5.70
	Rural	Both	13,001	34.41	27.38	20.86	12,005	31.77	25.25	19.25	996	2.63	2.13	1.60	11.85
		Male	9,270	48.08	40.75	30.98	8,519	44.18	37.40	28.45	751	3.89	3.35	2.54	11.16
		Female	3,728	20.14	14.58	11.10	3,483	18.82	13.61	10.39	245	1.32	0.97	0.71	14.01
South China	All	Both	13,405	33.25	31.71	24.34	11,335	28.13	26.86	20.64	2,069	5.12	4.85	3.69	5.54
		Male	10,788	51.22	51.74	39.74	9,141	43.43	43.91	33.77	1,647	7.80	7.83	5.97	5.61
		Female	2,615	13.60	11.72	8.87	2,193	11.40	9.87	7.48	422	2.20	1.84	1.39	5.35
	Urban	Both	5,375	26.22	26.62	20.45	4,626	22.58	23.00	17.71	749	3.64	3.63	2.74	6.34
		Male	4,308	39.99	43.32	33.51	3,708	34.45	37.48	29.09	600	5.54	5.84	4.43	6.42
		Female	1,067	10.97	10.29	7.64	918	9.43	8.89	6.60	149	1.54	1.40	1.03	6.34
	Rural	Both	8,030	40.66	37.95	29.02	6,710	33.97	31.75	24.29	1,320	6.69	6.20	4.72	5.12
		Male	6,480	63.21	62.71	47.78	5,433	53.00	52.59	40.07	1,047	10.21	10.12	7.70	5.20
		Female	1,548	16.33	13.29	10.18	1,275	13.45	11.01	8.45	273	2.88	2.28	1.73	4.83

Continued

Region	location	Sex	ESLD				Liver cancer				Cirrhosis				LC/C ratio
			Death numbers	Crude rate ($1/10^5$)	ASMRC ($1/10^5$)	ASMRW ($1/10^5$)	Death numbers	Crude rate ($1/10^5$)	ASMRC ($1/10^5$)	ASMRW ($1/10^5$)	Death numbers	Crude rate ($1/10^5$)	ASMRC ($1/10^5$)	ASMRW ($1/10^5$)	
Southwest China	All	Both	17,500	35.87	28.34	21.47	13,201	27.06	21.20	16.09	4,298	8.81	7.14	5.38	2.97
		Male	13,168	53.21	43.97	33.40	9,833	39.73	32.53	24.80	3,335	13.48	11.44	8.61	2.84
		Female	4,322	17.97	12.95	9.68	3,362	13.97	10.09	7.53	960	3.99	2.86	2.16	3.53
	Urban	Both	6,607	33.26	25.18	19.07	5,009	25.21	19.00	14.42	1,598	8.04	6.18	4.65	3.07
		Male	4,908	49.09	38.71	29.49	3,716	37.17	29.08	22.27	1,192	11.92	9.63	7.22	3.02
		Female	1,695	17.17	11.97	8.88	1,290	13.07	9.17	6.76	405	4.10	2.80	2.11	3.28
	Rural	Both	10,893	37.66	30.62	23.20	8,192	28.32	22.80	17.30	2,700	9.34	7.82	5.90	2.92
		Male	8,260	56.00	47.75	36.22	6,117	41.47	35.03	26.63	2,143	14.53	12.73	9.59	2.75
		Female	2,627	18.52	13.64	10.25	2,071	14.61	10.75	8.07	555	3.91	2.90	2.18	3.71
Northwest China	All	Both	5,477	22.13	20.08	15.05	4,545	18.36	16.61	12.45	932	3.76	3.46	2.59	4.80
		Male	3,622	28.81	26.86	20.37	3,035	24.14	22.48	17.05	588	4.67	4.38	3.32	5.13
		Female	1,853	15.21	13.38	9.81	1,509	12.39	10.88	7.97	344	2.82	2.51	1.84	4.34
	Urban	Both	2,871	23.20	19.51	14.58	2,405	19.44	16.29	12.21	466	3.77	3.23	2.38	5.05
		Male	1,877	29.93	26.18	19.84	1,595	25.43	22.20	16.85	282	4.50	3.98	2.99	5.58
		Female	993	16.27	13.07	9.51	810	13.26	10.63	7.77	184	3.01	2.44	1.74	4.35
	Rural	Both	2,606	21.06	20.61	15.49	2,141	17.29	16.91	12.68	466	3.76	3.70	2.81	4.57
		Male	1,745	27.70	27.46	20.81	1,440	22.85	22.65	17.16	305	4.84	4.80	3.65	4.72
		Female	860	14.15	13.68	10.12	700	11.51	11.14	8.19	161	2.64	2.55	1.93	4.37

Abbreviation: ESLD=End-stage liver disease; ASMRC=age-standardized mortality rate adjusted by the Chinese standard population; ASMRW=age-standardized mortality rate adjusted by the world standard population; LC=liver cancer; C=cirrhosis.

SUPPLEMENTARY TABLE S2. Crude rates, ASMRC, ASMRW and AAPC of ESLD and by residence and sex in China, 2008–2020.

		Year	All			Urban			Rural		
			Crude rate ($1/10^5$)	ASMRC ($1/10^5$)	ASMRW ($1/10^5$)	Crude rate ($1/10^5$)	ASMRC ($1/10^5$)	ASMRW ($1/10^5$)	Crude rate ($1/10^5$)	ASMRC ($1/10^5$)	ASMRW ($1/10^5$)
ESLD	Total	2008	35.92	38.89	29.79	32.44	32.28	24.55	38.03	43.56	33.49
		2020	30.11	23.53	17.91	25.86	20.19	15.36	33.15	25.97	19.76
		AAPC (95% *CI*) 2008–2020	−1.9 (−2.5, −1.4)	−4.4 (−4.9, −3.8)	−4.1 (−4.8, −3.8)	−2.1 (−2.9, −1.3)	−3.7 (−4.4, −2.9)	−3.6 (−4.4, −2.7)	−1.7 (−2.5, −1.0)	−4.8 (−5.5, −4.1)	−4.8 (−5.4, −4.1)
		P-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	Male	2008	52.17	58.43	44.67	47.06	48.18	36.64	55.21	65.59	50.25
		2020	43.19	35.67	27.23	36.51	30.2	23.13	48.01	39.73	30.26
		AAPC (95% *CI*) 2008–2020	−2.0 (−2.5, −1.5)	−4.3 (−4.9, −3.8)	−4.2 (−4.8, −3.7)	−2.3 (−3.1, −1.5)	−3.7 (−4.5, −2.9)	−3.5 (−4.4, −2.6)	−1.7 (−2.5, −1.0)	−4.7 (−5.4, −4.0)	−4.6 (−5.3, −3.9)
		P-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	Female	2008	18.98	19.96	15.29	17.46	16.96	12.86	19.91	22.13	17.04
		2020	16.48	11.72	8.81	14.69	10.41	7.92	17.75	12.64	9.55
		AAPC (95% *CI*) 2008–2020	−1.7 (−2.3, −1.1)	−4.7 (−5.2, −4.1)	−4.7 (−5.3, −4.2)	−1.7 (−2.5, −0.9)	−4.0 (−4.6, −3.3)	−4.0 (−4.6, −3.3)	−1.6 (−2.3, −0.8)	−5.2 (−5.8, −4.5)	−5.2 (−5.8, −4.5)
		P-value	<0.001	<0.001	<0.001	0.001	<0.001	<0.001	0.001	<0.001	<0.001
Liver cancer	Total	2008	30.15	32.59	24.94	26.23	26.01	19.84	32.53	37.4	28.75
		2020	25.57	19.92	15.15	21.37	16.66	12.69	27.41	21.21	16.39
		AAPC (95% *CI*) 2008–2020	−1.7 (−2.3, −1.1)	−4.1 (−4.8, −3.5)	−4.1 (−4.7, −3.4)	−1.8 (−2.6, −1.0)	−3.3 (−4.2, −2.5)	−3.2 (−4.1, −2.3)	−1.5 (−2.3, −0.7)	−4.6 (−5.4, −3.8)	−4.6 (−5.4, −3.8)
		P-value	<0.001	<0.001	<0.001	0.001	<0.001	<0.001	0.001	<0.001	<0.001
	Male	2008	43.7	48.84	37.41	38.22	39.04	29.78	46.97	56.46	43.26
		2020	36.63	30.15	23.04	30.35	25.07	19.21	39.71	32.19	24.92
		AAPC (95% *CI*) 2008–2020	−1.8 (−2.4, −1.2)	−4.1 (−4.8, −3.5)	−4 (−4.7, −3.4)	−2.0 (−2.8, −1.2)	−3.4 (−4.2, −2.5)	−3.2 (−4.1, −2.3)	−1.6 (−2.3, −0.7)	−4.6 (−5.5, −3.7)	−4.5 (−5.3, −3.6)
		P-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.001	<0.001	<0.001
	Female	2008	16.02	16.83	12.89	13.94	13.5	10.25	17.3	19.22	14.8
		2020	14.05	10.01	7.54	11.95	8.5	6.35	15.55	11.07	8.37
		AAPC (95% *CI*) 2008–2020	−1.4 (−2.0, −0.7)	−4.3 (−5.0, −3.7)	−4.3 (−5.0, −3.7)	−1.3 (−2.2, −0.5)	−3.5 (−4.3, −2.7)	−3.5 (−4.4, −2.7)	−1.3 (−2.1, −0.5)	−4.9 (−5.6, −4.1)	−4.9 (−5.7, −4.1)
		P–Value	0.001	<0.001	<0.001	0.001	<0.001	<0.001	0.004	<0.001	<0.001

TABLE S2. (Continued)

		Year	All			Urban			Rural		
			Crude rate ($1/10^5$)	ASMRC ($1/10^5$)	ASMRW ($1/10^5$)	Crude rate ($1/10^5$)	ASMRC ($1/10^5$)	ASMRW ($1/10^5$)	Crude rate ($1/10^5$)	ASMRC ($1/10^5$)	ASMRW ($1/10^5$)
Cirrhosis	Total	2008	5.77	6.3	4.79	6.21	6.26	4.71	5.50	6.33	4.83
		2020	4.54	3.61	2.73	4.49	3.53	2.67	4.56	3.68	2.78
		AAPC (95% *CI*) 2008–2020	−3.2 (−4.3, −2.1)	−5.5 (−6.4, −4.6)	−5.5 (−6.4, −4.6)	−3.6 (−4.6, −2.6)	−5.2 (−5.9, −4.4)	−5.1 (−5.9, −4.3)	−2.5 (−4.9, 0.1)	−5.7 (−6.9, −4.5)	−5.7 (−6.9, −4.6)
		P-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.055	<0.001	<0.001
	Male	2008	8.47	9.59	7.26	8.84	9.14	6.86	8.25	9.9	7.53
		2020	6.56	5.52	4.19	6.16	5.14	3.92	6.84	5.82	4.41
		AAPC (95% *CI*) 2008–2020	−3.1 (−4.1, −2.1)	−5.3 (−6.1, −4.5)	−5.2 (−6.0, −4.4)	−3.7 (−4.7, −2.8)	−5.1 (−5.9, −4.2)	−4.9 (−5.8, −4.1)	−2.3 (−4.6, 0.1)	−5.4 (−6.5, −4.4)	−5.4 (−6.4, −4.4)
		P-Value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.064	<0.001	<0.001
	Female	2008	2.96	3.13	2.39	3.52	3.46	2.62	2.62	2.9	2.24
		2020	2.43	1.71	1.27	2.75	1.9	1.41	2.2	1.57	1.18
		AAPC (95% *CI*) 2008–2020	−3.4 (−4.7, −1.9)	−6.4 (−7.7, −5.2)	−6.5 (−7.7, −5.3)	−3.4 (−4.6, −2.2)	−5.8 (−6.6, −4.9)	−5.9 (−6.7, −5.0)	−2.8 (−5.8, 0.3)	−6.9 (−8.5, −5.3)	−7.0 (−8.6, −5.4)
		P-Value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.072	<0.001	<0.001

Abbreviation: ESLD=end-stage liver disease; ASMRC=age-standardized mortality rate adjusted by the Chinese standard population; ASMRW=age-standardized mortality rate adjusted by the world standard population; AAPC=average annual percentage change.

SUPPLEMENTARY TABLE S3. Crude rates, ASMRC, ASMRW and AAPC of ESLD by region in China, 2008–2020.

Region	Disease	Year	All			Urban			Rural		
			Crude rate ($1/10^5$)	ASMRC ($1/10^5$)	ASMRW ($1/10^5$)	Crude rate ($1/10^5$)	ASMRC ($1/10^5$)	ASMRW ($1/10^5$)	Crude rate ($1/10^5$)	ASMRC ($1/10^5$)	ASMRW ($1/10^5$)
North China	ESLD	2008	28.06	30.19	23.13	26.07	24.99	18.91	29.88	36.08	27.89
		2020	20.99	16.21	12.38	17.54	13.45	10.29	24.01	18.69	14.26
		AAPC (95% *CI*) 2008–2020	−3.1 (−5.1, −1.0)	−5.7 (−6.7, −4.7)	−5.6 (−6.6, −4.6)	−4.2 (−5.6, −2.8)	−5.4 (−6.4, −4.5)	−5.2 (−6.2, −4.3)	−1.8 (−4.8, 1.2)	−6.2 (−7.5, −4.9)	−6.2 (−7.5, −5.0)
		P-value	0.004	<0.001	<0.001	<0.001	<0.001	<0.001	0.238	<0.001	<0.001
	Liver cancer	2008	23.78	25.67	19.73	20.87	20.17	15.30	26.46	31.99	24.79
		2020	17.08	13.10	10.03	13.00	9.91	7.59	20.66	15.95	12.19
		AAPC (95% *CI*) 2008–2020	−3.2 (−5.7, −0.7)	−5.9 (−7.1, −4.7)	−5.8 (−7.1, −4.6)	−4.6 (−6.1, −3.1)	−5.9 (−7.0, −4.8)	−5.7 (−6.8, −4.6)	−2.9 (−4.9, −0.9)	−6.7 (−8.5, −4.8)	−6.7 (−8.4, −4.9)
		P-value	0.012	<0.001	<0.001	<0.001	<0.001	<0.001	0.005	<0.001	<0.001
	Cirrhosis	2008	4.27	4.52	3.40	5.20	4.82	3.61	3.43	4.09	3.10
		2020	3.91	3.10	2.36	4.55	3.53	2.70	3.35	2.74	2.00
		AAPC (95% *CI*) 2008–2020	−2.4 (−3.7, −1.1)	−4.5 (−5.8, −3.3)	−4.5 (−5.7,-3.2)	−2.3 (−4.9, 0.3)	−3.8 (−5.0, −2.7)	−3.7 (−4.8, −2.5)	−1.2 (−4.4, 2.1)	−3.7 (−7.8, 0.6)	−3.6 (−7.7, 0.7)
		P-value	0.002	<0.001	<0.001	0.087	<0.001	<0.001	0.48	0.093	0.099
Northeast China	ESLD	2008	39.44	40.39	30.88	35.93	34.59	26.37	42.41	45.95	35.19
		2020	41.41	27.34	20.93	36.14	23.17	17.84	44.40	29.83	22.75
		AAPC (95% *CI*) 2008–2020	1.0 (−0.3, 2.3)	−2.7 (−3.9, −1.4)	−2.8 (−4.0, −1.5)	0.6 (−0.1, 1.3)	−2.8 (−4.2, −1.4)	−2.7 (−4.1, −1.2)	0.8 (−0.5, 2.1)	−3.2 (−4.2, −2.2)	−3.2 (−4.2, −2.2)
		P-value	0.126	<0.001	<0.001	0.092	<0.001	<0.001	0.236	<0.001	<0.001
	Liver cancer	2008	31.86	32.76	25.15	27.90	26.92	20.62	35.20	38.33	29.45
		2020	34.68	22.73	17.41	28.81	18.39	14.11	38.00	25.31	19.35
		AAPC (95% *CI*) 2008–2020	1.8 (0.7, 2.8)	−2.2 (−4.0, −0.4)	−2.1 (−3.9, −0.4)	1.1 (0.4, 1.9)	−2.2 (−2.9, −1.4)	−2.0 (−2.9, −1.1)	1.6 (−0.2, 3.5)	−2.6 (−4.2, −1.0)	−2.7 (−4.3, −1.1)
		P-value	0.003	0.015	0.019	0.006	<0.001	0.001	0.089	<0.001	0.001
	Cirrhosis	2008	7.58	7.62	5.73	8.03	7.67	5.75	7.21	7.62	5.74
		2020	6.73	4.61	3.52	7.33	4.78	3.74	6.40	4.52	3.40
		AAPC (95% *CI*) 2008–2020	−2.3 (−3.5, −1.1)	−5.2 (−6.3, −4.2)	−5.2 (−6.3, −4.1)	−1.4 (−3.2, 0.4)	−4.2 (−5.3, −3.0)	−4.0 (−5.2, −2.8)	−2.9 (−4.6, −1.2)	−6.1 (−7.6, −4.5)	−6.1 (−7.7, −4.5)
		P-value	0.003	<0.001	0.001	0.003	<0.001	0.001	0.003	<0.001	0.001

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Region	Disease	Year	All			Urban			Rural		
			Crude rate ($1/10^5$)	ASMRC ($1/10^5$)	ASMRW ($1/10^5$)	Crude rate ($1/10^5$)	ASMRC ($1/10^5$)	ASMRW ($1/10^5$)	Crude rate ($1/10^5$)	ASMRC ($1/10^5$)	ASMRW ($1/10^5$)
East China	ESLD	2008	36.31	36.74	28.12	32.69	31.52	24.06	39.09	41.23	31.62
		2020	26.99	19.75	15.02	23.76	17.39	13.23	29.41	21.49	16.34
		AAPC (95% *CI*) 2008–2020	−2.6 (−3.1, −2.2)	−5.0 (−5.6, −4.4)	−4.9 (−5.6, −4.2)	−2.8 (−3.7, −1.8)	−4.7 (−5.5, −3.9)	−4.6 (−5.4, −3.7)	−2.7 (−3.1, −2.2)	−5.4 (−5.9, −4.9)	−5.4 (−5.9, −4.8)
		P-value	<0.001	<0.001	0.001	<0.001	<0.001	0.001	<0.001	<0.001	0.001
	Liver cancer	2008	31.96	32.26	24.7	27.85	26.72	20.41	35.13	37.01	28.40
		2020	24.18	17.7	13.47	20.84	15.28	11.64	26.67	19.48	14.82
		AAPC (95% *CI*) 2008–2020	−2.3 (−2.8, −1.8)	−4.7 (−5.4, −4.0)	−4.6 (−5.4, −3.8)	−2.4 (−3.4, −1.3)	−4.3 (−5.2, −3.4)	−4.2 (−5.1, −3.2)	−2.5 (−2.8, −2.1)	−5.2 (−5.7, −4.7)	−5.2 (−5.7, −4.6)
		P-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	Cirrhosis	2008	4.35	4.49	3.42	4.85	4.81	3.65	3.97	4.22	3.22
		2020	2.82	2.05	1.55	2.92	2.11	1.59	2.74	2.02	1.52
		AAPC (95% *CI*) 2008–2020	−4.9 (−5.8, −3.9)	−7.3 (−8.1, −6.6)	−7.3 (−8.0, −6.6)	−5.2 (−6.5, −3.9)	−7.4 (−8.2, −6.5)	−7.3 (−8.2, −6.5)	−4.6 (−5.8, −3.3)	−7.3 (−8.2, −6.4)	−7.2 (−8.1, −6.4)
		P-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Central China	ESLD	2008	34.25	38.47	29.53	29.02	30.10	22.98	36.10	41.68	32.03
		2020	32.75	26.09	19.85	27.25	21.90	16.57	34.93	27.80	21.17
		AAPC (95% *CI*) 2008–2020	−0.4 (−1.3, 0.6)	−3.1 (−4.1, −2.2)	−3.1 (−4.0, −2.1)	−0.4 (−1.2, 0.5)	−2.1 (−2.9, −1.2)	−2.1 (−3.0, −1.2)	−0.4 (−1.4, 0.7)	−3.6 (−4.6, −2.7)	−3.4 (−4.6, −2.2)
		P-value	0.402	<0.001	<0.001	0.360	<0.001	<0.001	0.487	<0.001	<0.001
	Liver cancer	2008	30.66	34.35	26.35	23.74	24.33	18.64	33.11	38.20	29.30
		2020	29.68	23.60	17.98	23.18	18.59	14.08	32.26	25.63	19.55
		AAPC (95% *CI*) 2008–2020	−0.2 (−1.3, 1.0)	−2.9 (−4.1, −1.8)	−2.9 (−4.0, −1.7)	0 (−0.9, 0.9)	−1.7 (−2.6, −0.7)	−1.7 (−2.7, −0.7)	−0.2 (−1.5, 1.2)	−3.3 (−4.7, −1.8)	−3.2 (−4.6, −1.8)
		P–Value	0.762	<0.001	<0.001	0.974	0.003	0.004	0.774	<0.001	<0.001
	Cirrhosis	2008	3.58	4.12	3.18	5.28	5.78	4.33	2.98	3.48	2.73
		2020	3.07	2.49	1.87	4.07	3.31	2.49	2.68	2.16	1.63
		AAPC (95% *CI*) 2008–2020	−2.2 (−3.9, −0.4)	−4.9 (−6.5, −3.2)	−5.0 (−6.6, −3.4)	−2.1 (−3.2, −0.9)	−3.9 (−5.1, −2.8)	−4.0 (−5.0, −2.9)	−2.3 (−4.9, 0.4)	−5.2 (−7.7, −2.7)	−5.4 (−7.8, −3.0)
		P-value	0.021	<0.001	<0.001	0.003	<0.001	<0.001	0.084	0.001	0.001

Continued

Region	Disease	Year	All			Urban			Rural		
			Crude rate (1/10^5)	ASMRC (1/10^5)	ASMRW (1/10^5)	Crude rate (1/10^5)	ASMRC (1/10^5)	ASMRW (1/10^5)	Crude rate (1/10^5)	ASMRC (1/10^5)	ASMRW (1/10^5)
South China	ESLD	2008	44.96	51.91	39.77	38.52	41.22	31.53	48.11	58.71	45.04
		2020	32.93	31.42	24.11	25.74	26.13	20.07	40.51	37.84	28.93
		AAPC (95% *CI*) 2008–2020	−3.9 (−5.5, −2.3)	−4.9 (−6.2, −3.6)	−4.8 (−6.1, −3.5)	−3.5 (−5.2, −1.9)	−2.9 (−4.8, −1.0)	−2.7 (−4.8, −0.6)	−3.2 (−5.4, −0.9)	−5.2 (−7.4, −3.0)	−5.2 (−7.3, −2.9)
		P-value	<0.001	<0.001	<0.001	0.001	0.007	0.016	0.011	<0.001	<0.001
	Liver cancer	2008	37.91	43.67	33.56	30.71	32.76	25.19	41.42	50.53	38.84
		2020	27.85	26.60	20.44	22.15	22.56	17.37	33.85	31.66	24.22
		AAPC (95% *CI*) 2008–2020	−4.1 (−6.0, −2.2)	−5.0 (−6.6, −3.4)	−4.9 (−6.5, −3.3)	−3.2 (−4.9, −1.5)	−2.5 (−4.4, −0.6)	−2.4 (−4.4, −0.3)	−3.5 (−6.0, −0.9)	−5.6 (−8.1, −3.0)	−5.5 (−8.0, −2.9)
		P-value	0.001	<0.001	<0.001	0.002	0.014	0.030	0.013	0.001	0.001
	Cirrhosis	2008	7.05	8.24	6.21	7.81	8.46	6.34	6.68	8.18	6.20
		2020	5.08	4.82	3.67	3.59	3.57	2.70	6.66	6.18	4.71
		AAPC (95% *CI*) 2008–2020	−2.8 (−4.1, −1.6)	−3.9 (−5.2, −2.7)	−3.8 (−5.0, −2.5)	−5.1 (−7.2, −3.0)	−4.8 (−7.4, −2.1)	−4.6 (−7.2, −1.9)	−0.8 (−2.4, 0.9)	−2.9 (−4.3, −1.6)	−2.8 (−4.1, −1.6)
		P-value	<0.001	<0.001	<0.001	<0.001	0.002	0.003	0.319	0.001	<0.001
Southwest China	ESLD	2008	43.79	49.08	37.75	39.93	41.75	31.61	45.58	53.01	41.03
		2020	37.18	29.38	22.25	34.47	26.10	19.77	39.04	31.74	24.05
		AAPC (95% *CI*) 2008–2020	−2.7 (−4.0, −1.5)	−5.4 (−6.4, −4.3)	−5.3 (−6.3, −4.4)	−2.3 (−3.8, −0.7)	−4.5 (−5.9, −3.1)	−4.4 (−5.8, −3.0)	−2.8 (−4.2, −1.4)	−5.6 (−6.9, −4.4)	−5.6 (−6.7, −4.5)
		P–Value	0.001	<0.001	<0.001	0.008	<0.001	<0.001	0.001	<0.001	<0.001
	Liver cancer	2008	32.49	36.26	28.02	29.71	31.04	23.59	33.78	39.08	30.41
		2020	28.05	21.98	16.68	26.13	19.69	14.95	29.36	23.63	17.93
		AAPC (95% *CI*) 2008–2020	−2.6 (−3.8, −1.3)	−5.2 (−6.2, −4.2)	−5.2 (−6.1, −4.2)	−1.7 (−3.5, 0.1)	−3.9 (−5.6, −2.2)	−3.8 (−5.5, −2.1)	−2.9 (−4.4, −1.3)	−5.7 (−7.2, −4.3)	−5.7 (−7.1, −4.3)
		P-value	0.001	<0.001	<0.001	0.064	<0.001	0.001	0.002	<0.001	<0.001
	Cirrhosis	2008	11.30	12.82	9.73	10.23	10.70	8.02	11.80	13.93	10.62
		2020	9.13	7.40	5.57	8.34	6.41	4.82	9.63	8.11	6.11
		AAPC (95% *CI*) 2008–2020	−2.8 (−5.4, −0.1)	−5.8 (−7.0, −4.5)	−5.7 (−7.0, −4.5)	−4.0 (−6.0, −2.1)	−6.3 (−8.0, −4.5)	−6.2 (−7.9, −4.4)	−2.0 (−4.0, 0.1)	−4.8 (−6.7, −3.0)	−4.9 (−6.6, −3.1)
		P–Value	0.042	<0.001	<0.001	0.001	<0.001	<0.001	0.067	<0.001	<0.001

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Region	Disease	Year	All			Urban			Rural		
			Crude rate ($1/10^5$)	ASMRC ($1/10^5$)	ASMRW ($1/10^5$)	Crude rate ($1/10^5$)	ASMRC ($1/10^5$)	ASMRW ($1/10^5$)	Crude rate ($1/10^5$)	ASMRC ($1/10^5$)	ASMRW ($1/10^5$)
Northwest China	ESLD	2008	23.46	30.46	23.02	27.20	30.93	23.10	21.78	30.25	23.06
		2020	22.94	20.81	15.60	24.05	20.22	15.12	21.83	21.36	16.06
		AAPC (95% *CI*) 2008–2020	−0.3 (−1.3, 0.6)	−3.1 (−4.0, −2.3)	−3.2 (−4.0, −2.4)	−1.3 (−4.2, 1.7)	−2.8 (−4.2, −1.4)	−2.8 (−4.2, −1.4)	−0.4 (−1.4, 0.5)	−3.0 (−4.5, −1.5)	−3.1 (−4.5, −1.7)
		P-value	0.485	<0.001	<0.001	0.383	0.001	0.001	0.344	<0.001	<0.001
	Liver cancer	2008	18.87	24.48	18.51	22.58	25.49	19.04	17.20	23.94	18.27
		2020	19.04	17.22	12.91	20.15	16.88	12.66	12.92	17.53	13.14
		AAPC (95% *CI*) 2008–2020	0.1 (−1.3, 1.5)	−2.8 (−4.1, −1.4)	−2.8 (−4.1, −1.5)	−1.3 (−4.2, 1.8)	−3.0 (−4.4, −1.6)	−2.9 (−4.3, −1.5)	0.2 (−1.4, 1.9)	−2.6 (−4.3, −0.9)	−2.7 (−4.4, −1.0)
		P–Value	0.889	0.001	0.001	0.406	0.001	0.001	0.748	0.006	0.005
	Cirrhosis	2008	4.59	5.97	4.51	4.62	5.44	4.06	4.57	6.31	4.79
		2020	3.90	3.59	2.69	3.90	3.34	2.46	3.90	3.84	2.92
		AAPC (95% *CI*) 2008–2020	−1.9 (−3.9, 0.2)	−4.5 (−6.4, −2.7)	−4.6 (−6.5, −2.7)	0.2 (−2.5, 2.9)	−2.2 (−4.9, 0.6)	−2.3 (−5.1, 0.7)	−2.4 (−5.8, 1.2)	−5.5 (−8.0, −2.9)	−5.1 (−8.0, −2.1)
		P-value	0.07	<0.001	<0.001	0.889	0.113	0.115	0.191	0.001	0.001

Abbreviation: ESLD=end-stage liver disease; ASMRC=age-standardized mortality rate adjusted by the Chinese standard population; ASMRW=age-standardized mortality rate adjusted by the world standard population; AAPC=average annual percentage change.

Vital Surveillances

Changes in HIV-1 Subtypes/Sub-Subtypes, and Transmitted Drug Resistance Among ART-Naïve HIV-Infected Individuals — China, 2004–2022

Xiu Liu[1]; Dong Wang[1]; Jing Hu[1]; Chang Song[1]; Lingjie Liao[1]; Yi Feng[1]; Dan Li[1]; Hui Xing[1]; Yuhua Ruan[1,#]

ABSTRACT

Introduction: The efficacy of treatment and clinical outcomes may be jeopardized by factors such as transmitted drug resistance (TDR) and the genetic diversity of the human immunodeficiency virus type 1 (HIV-1). This comprehensive study aims to examine the alterations in HIV-1 subtypes or sub-subtypes and TDR among Chinese individuals, who have been diagnosed with HIV infection and are previously untreated with antiretroviral therapy (ART), across the span of 2004 to 2022.

Methods: Sequences of the HIV-1 *pol* gene region were obtained from ART-naïve HIV-positive individuals across 31 provincial-level administrative divisions between 2004 and 2022. To predict susceptibility to 12 antiretroviral drugs, the research utilized the Stanford HIV Drug Resistance Database. The Cochran-Armitage trend test facilitated the analysis of changes in HIV-1 subtype/sub-subtype prevalence and TDR. This analysis was conducted in alignment with the progression of the National Free Antiretroviral Treatment Program's stages between 2004 and 2022.

Results: Among the 57,902 ART-naïve individuals infected with HIV, there was a notable decline in the prevalence of CRF01_AE, B, and C from 37.3%, 24.1%, and 1.3% respectively in 2004–2007 to 29.4%, 7.3%, and 0.2% respectively in 2020–2022. Simultaneously, a significant increase was observed in the proportions of CRF07_BC, CRF08_BC, CRF55_01B, other CRFs, and URFs, from 24.1%, 11.5%, 0.1%, 0.4%, and 0.9% respectively in 2004–2007 to 40.8%, 11.5%, 3.8%, 3.7%, and 2.8% respectively in 2020–2022 (all $P<0.001$ for trend). The prevalence of TDR to overall, non-nucleoside reverse transcriptase inhibitor (NNRTI), efavirenz, and nevirapine also significantly increased from 2.6%, 1.8%, 1.6%, and 1.8% respectively in 2004–2007 to 7.8%, 6.7%, 6.3%, and 6.7% respectively in 2020–2022 (all $P<0.001$ for trend). However, there were no meaningful changes in the TDR prevalence of nucleoside reverse transcriptase inhibitor and protease inhibitor. Notably, in 2020–2022, the overall TDR prevalence exceeded 15% in Xinjiang.

Conclusions: The total prevalence of TDR in China has achieved a moderate level (7.8%) from 2020 to 2022, with NNRTI resistance standing prominently at 6.7%. Consequently, measures to curb TDR are urgently required, particularly among ART-naïve HIV-infected individuals in China.

In 2022, there were approximately 39 million people living with human immunodeficiency virus (HIV), 1.3 million newly infected people, and 29.8 million people who were accessing antiretroviral therapy (ART) globally (*1*). The prevalent use of ART is designed to suppress replication of human immunodeficiency virus type 1 (HIV-1), yet the development of drug resistance correlates with a higher likelihood of virological failure. This resistance potentially compromises the effectiveness of first-line ART regimens (*2*). The issue of transmitted drug resistance (TDR) is troublesome because it can escalate in prevalence, thus critically restricting treatment options available to ART-naïve individuals living with HIV. While the United States (*3*) and Europe (*4*) routinely conduct baseline testing for TDR, this is not standard practice in many countries with limited resources. Additionally, HIV drug resistance (HIVDR) testing is not a routine part of clinical management in most low- and middle-income nations, despite these countries bearing the largest global HIV-1 infection burden.

As a highly populated nation, China is making strenuous efforts in the prevention and control of HIV/AIDS, significantly contributing to the universal objective of eradicating the AIDS epidemic as a public health threat by 2030. In 2004, the Chinese National

Free Antiretroviral Treatment Program (NFATP) was fully implemented. By 2008, the NFATP had been further expanded and standardized, mandating ART initiation for those individuals having a CD4 count less than 200 cells/mm^3. Post 2012, this threshold was raised to less than 350 cells/mm^3. In 2016, all individuals living with HIV were made eligible for ART, regardless of their CD4 counts (*5*). The emergence of TDR owing to the expansion of ART is a serious public health concern, as TDR can negatively impact prognosis and potentially affect treatment efficacy. Consequently, evaluating the levels and trends of TDR in China is of vital importance in relation to the global response to HIV/AIDS. The primary aim of this broad-scale study was to examine the alterations in HIV-1 subtypes/sub-subtypes and TDR among ART-naïve HIV-infected individuals in China spanning the period 2004 to 2022.

METHODS

A total of 67,739 sequences were extracted from the HIV-1 *pol* gene region (HXB2 (*6*) positions 2,253–3,312) of ART naïve HIV-infected individuals between the period of 2004 and 2022. These sequences were procured from both the National Center for AIDS/STD Control and Prevention, China CDC and the HIV sequence databases of the Los Alamos National Laboratory (https://www.hiv.lanl.gov/, retrieved December 30, 2022).

Data verification steps were undertaken; the records from China CDC were scrutinized to ensure participants were indeed ART-naïve and HIV-infected. Furthermore, GenBank annotations and corresponding published articles were scrutinized to isolate those fulfilling the set criteria: the documentation of an ART-naïve HIV-1-infected population; the sampling year; and the recruitment site.

The reference sequence for the study was HXB2. HIV-Trace was utilized for sequence alignment, while the HIV-1 subtypes/sub-subtypes were determined via the construction of phylogenetic trees using the maximum-likelihood method of IQ-Tree v 2.0.6 (*7*).

Individuals were included in the study based on the following criteria: age of 18 years and above, availability of the sampling year and provincial-level administrative division (PLAD), protease and at least the initial 238 amino acids of the reverse transcriptase (HXB2 positions 2,280–3,263) were available, and, if multiple sequences were available for a person, the earliest one was chosen.

A total of 57,902 HIV-1 *pol* gene region sequences that covered 31 PLADs made up the final dataset (Supplementary Figure S1, available in https://weekly.chinacdc.cn/). This study received approval from the Ethics Committee of the National Center for AIDS/STD Control and Prevention, China CDC (approval number X140617334).

The Stanford HIV Drug Resistance Database (HIVdb) was leveraged to extrapolate susceptibility to 12 antiretroviral drugs, using the World Health Organization (WHO)'s 2014 HIVDR guidelines as a reference (*8*). Viruses interpreted as possessing low, intermediate, or high-level resistance were classified as resistant with a penalty score equal to or greater than 15 (*9*). The assessment of drug resistance was accomplished using Stanford University's HIVDR Database's online sequence analysis tool (https://hivdb.stanford.edu/hivdb/by-sequences/).

Statistical evaluations were conducted using SAS (version 9.4, SAS Institute Inc., Cary, NC, USA). The collected data from 2004 to 2022 was stratified into five distinct sampling periods that aligned with the NFATP developmental stages in China. The Chi-square test was utilized to scrutinize the sociodemographic characteristics relative to these five sampling periods. For evaluating trends in subtypes, sub-subtypes, and TDR prevalence within these periods, the Cochran-Armitage trend test was employed. A two-tailed *P*-value less than 0.05 established statistical significance.

RESULTS

The study population consisted of 57,902 ART-naïve HIV-infected individuals, which were categorized according to the development stages of the NFATP. The distribution of the subjects over the years was as follows: 1,251 (2.2%) were enrolled between 2004 and 2007, 8,794 (15.2%) between 2008 and 2011, 21,467 (37.1%) between 2012 and 2015, 21,391 (36.9%) between 2016 and 2019, and 4,999 (8.6%) between 2020 and 2022 (Table 1). A Pearson's Chi-squared test revealed significant variations in sociodemographic variables across these five periods (P<0.001).

The data indicated significant decreases in the proportions of ART-naïve HIV-infected individuals over time for circulating recombinant form (CRF)01_AE, B, and C. Specifically, they fell from 37.3%, 24.1%, and 1.3% in 2004–2007 to 29.4%, 7.3%, and 0.2% in 2020–2022, respectively (all P<0.001 for trend) (Table 2). For ART-naïve HIV-

TABLE 1. Characteristics of Chinese individuals with ART-naïve HIV infection, categorized by stages of NFATP development, 2004–2022.

Characteristic	2004–2007		2008–2011		2012–2015		2016–2019		2020–2022		*P**	Total	
	N†	%§	*N*	%	*N*	%	*N*	%	*N*	%		*N*	%
Total	1,251	100.0	8,794	100.0	21,467	100.0	21,391	100.0	4,999	100.0		57,902	100.0
Age (years)											<0.001		
18–29	82	6.6	1,663	18.9	3,158	14.7	3,236	15.1	896	17.9		9,035	15.6
30–49	96	7.7	448	5.1	1,717	8.0	4,706	22.0	1,331	26.6		8,298	14.3
≥50	19	1.5	80	0.9	907	4.2	3,373	15.8	1,424	28.5		5,803	10.0
Unknown	1,054	84.3	6,603	75.1	15,685	73.1	10,076	47.1	1,348	27.0		34,766	60.0
Sex											<0.001		
Male	375	30.0	3,171	36.1	6,218	29.0	9,115	42.6	2,989	59.8		21,868	37.8
Female	98	7.8	694	7.9	1,290	6.0	2,763	12.9	663	13.3		5,508	9.5
Unknown	778	62.2	4,929	56.0	13,959	65.0	9,513	44.5	1,347	26.9		30,526	52.7
Ethnicity											<0.001		
Han	0	0.0	1,348	15.3	4,319	20.1	8,303	38.8	3,134	62.7		17,104	29.5
Others	1,105	88.3	6,330	72.0	10,702	49.9	4,727	22.1	393	7.9		23,257	40.2
Unknown	146	11.7	1,116	12.7	6,446	30.0	8,361	39.1	1,472	29.4		17,541	30.3
Education											<0.001		
Primary school or below	0	0.0	314	3.6	1,176	5.5	4,855	22.7	1,098	22.0		7,443	12.9
Junior high school	0	0.0	586	6.7	1,420	6.6	3,075	14.4	1,082	21.6		6,163	10.6
Senior high school and above	0	0.0	554	6.3	1,913	8.9	3,044	14.2	1,450	29.0		6,961	12.0
Unknown	1,251	100.0	7,340	83.5	16,958	79.0	10,417	48.7	1,369	27.4		37,335	64.5
Marital status											<0.001		
Single, or never married	0	0.0	1,048	11.9	2,266	10.6	3,624	16.9	1,382	27.6		8,320	14.4
Married	0	0.0	688	7.8	1,743	8.1	5,575	26.1	1,540	30.8		9,546	16.5
Divorced/widowed	0	0.0	166	1.9	498	2.3	1,825	8.5	712	14.2		3,201	5.5
Unknown	1,251	100.0	6,892	78.4	16,960	79.0	10,367	48.5	1,365	27.3		36,835	63.6
Risk groups											<0.001		
MSM	121	9.7	2,266	25.8	3,801	17.7	3,432	16.0	1,475	29.5		11,095	19.2
HET	164	13.1	1,153	13.1	3,126	14.6	7,197	33.6	1,982	39.6		13,622	23.5
IDU	188	15.0	651	7.4	351	1.6	1,008	4.7	31	0.6		2,229	3.8
Unknown	778	62.2	4,724	53.7	14,189	66.1	9,754	45.6	1,511	30.2		30,956	53.5
ART-naïve CD4 count (cells/mm^3)											<0.001		
<200	63	5.0	247	2.8	701	3.3	2,583	12.1	1,166	23.3		4,760	8.2
200–499	138	11.0	948	10.8	2,607	12.1	4,479	20.9	1,681	33.6		9,853	17.0
≥500	49	3.9	477	5.4	1,124	5.2	1,565	7.3	383	7.7		3,598	6.2
Unknown	1,001	80.0	7,122	81.0	17,035	79.4	12,764	59.7	1,769	35.4		39,691	68.5

Abbreviation: ART=antiretroviral therapy; HIV=human immunodeficiency virus; NFATP=National Free Antiretroviral Treatment Program; MSM=men who have sex with men; HET=heterosexual; IDU=injection drug use.

* *P* values were calculated using Pearson's Chi-squared test. *P* values <0.05 is statistically significant.

† Number of ART-naïve individuals infected with HIV surveyed.

§ Prevalences of ART-naïve individuals infected with HIV.

infected individuals, the proportions of CRF01_AE within cluster 1, cluster 2, cluster 3, cluster 6, cluster 7, and CRF01_AE-other also significantly decreased from 13.3%, 2.5%, 1.0%, 0.5%, 0.5%, and 6.4% in 2004–2007 to 4.2%, 2.2%, 0.7%, 0.1%, 0.0%, and 2.0% in 2020–2022, respectively (all $P<0.001$ for trend). In contrast, the proportions of ART-naïve HIV-infected individuals for CRF01_AE-cluster 4,

TABLE 2. Changes in HIV-1 subtypes/sub-subtypes among Chinese individuals naïve to ART across various stages of the NFATP from 2004 to 2022.

HIV-1 subtype/sub-subtype	2004–2007		2008–2011		2012–2015		2016–2019		2020–2022		*P**	Total	
	N[†]	%[§]	*N*	%	*N*	%	*N*	%	*N*	%		*N*	%
Total	1,251	100.0	8,794	100.0	21,467	100.0	21,391	100.0	4,999	100.0		57,902	100.0
CRF01_AE	467	37.3	3,911	44.5	9,049	42.2	7,906	37.0	1,472	29.4	<0.001	22,805	39.4
CRF01_AE-cluster 1	166	13.3	763	8.7	1,155	5.4	1,276	6.0	210	4.2	<0.001	3,570	6.2
CRF01_AE-cluster 2	31	2.5	389	4.4	388	1.8	1,424	6.7	108	2.2	<0.001	2,340	4.0
CRF01_AE-cluster 3	13	1.0	40	0.5	97	0.5	193	0.9	34	0.7	<0.001	377	0.7
CRF01_AE-cluster 4	101	8.1	1,740	19.8	5,397	25.1	2,960	13.8	681	13.6	<0.001	10,879	18.8
CRF01_AE-cluster 5	64	5.1	589	6.7	1,469	6.8	1,485	6.9	335	6.7	0.205	3,942	6.8
CRF01_AE-cluster 6	6	0.5	14	0.2	23	0.1	9	0.0	3	0.1	<0.001	55	0.1
CRF01_AE-cluster 7	6	0.5	31	0.4	40	0.2	17	0.1	1	0.0	<0.001	95	0.2
CRF01_AE-other	80	6.4	345	3.9	480	2.2	542	2.5	100	2.0	<0.001	1,547	2.7
CRF07_BC	301	24.1	2,540	28.9	7,397	34.5	8,194	38.3	2,038	40.8	<0.001	20,470	35.4
CRF07_BC-MSM	68	5.4	1,261	14.3	5,353	24.9	4,412	20.6	1,217	24.3	<0.001	12,311	21.3
CRF07_BC-other	233	18.6	1,279	14.5	2,044	9.5	3,782	17.7	821	16.4	<0.001	8,159	14.1
CRF08_BC	144	11.5	390	4.4	1,191	5.5	2,097	9.8	577	11.5	<0.001	4,399	7.6
CRF55_01B	1	0.1	221	2.5	1,170	5.5	1,125	5.3	189	3.8	<0.001	2,706	4.7
B	301	24.1	1,223	13.9	1,652	7.7	967	4.5	364	7.3	<0.001	4,507	7.8
C	16	1.3	128	1.5	113	0.5	105	0.5	12	0.2	<0.001	374	0.6
Other subtypes	5	0.4	52	0.6	80	0.4	78	0.4	24	0.5	0.179	239	0.4
Other CRFs	5	0.4	197	2.2	398	1.9	489	2.3	183	3.7	<0.001	1,272	2.2
URFs	11	0.9	132	1.5	417	1.9	430	2.0	140	2.8	<0.001	1,130	2.0

Abbreviation: ART=antiretroviral therapy; HIV=human immunodeficiency virus; NFATP=National Free Antiretroviral Treatment Program; CRF=circulating recombinant form; URFs=unique recombinant forms.

* *P* values were calculated using Cochran-Armitage trend test. *P* values <0.05 is statistically significant.

[†] Number of ART-naïve individuals infected with HIV surveyed.

[§] Proportions of ART-naïve individuals infected with HIV.

CRF07_BC, CRF07_BC-MSM, CRF07_BC-other, CRF08_BC, CRF55_01B, other CRFs, and unique recombinant forms (URFs) showed a significant increase from 8.1%, 24.1%, 5.4%, 18.6%, 11.5%, 0.1%, 0.4%, and 0.9% in 2004–2007 to 13.6%, 40.8%, 24.3%, 16.4%, 11.5%, 3.8%, 3.7%, and 2.8% in 2020–2022, respectively (all $P<0.001$ for trend). However, there were no significant changes observed over time in the proportions of CRF01_AE-cluster 5 and other subtypes.

The reported prevalence of TDR progressively increased from 2004–2007 to 2020–2022 (Table 3). A significant prevalence of 23.4% was recorded in Xinjiang within the 2020–2022 timeframe. The prevalence of TDR, both overall and in connection with the non-nucleoside reverse transcriptase inhibitor (NNRTI), increased gradually from 2004–2007 to 2020–2022. Over the same series of intervals, the TDR prevalence for efavirenz (EFV) and nevirapine (NVP) escalated from 2004–2007 to 2020–2022 (Supplementary Figure S2, available in https://weekly.chinacdc.cn/).

We observed an almost threefold increase in the prevalence of TDR during 2020–2022 (7.8% and 6.7%) in comparison to the period from 2004–2007 (2.6% and 1.8%), for both overall and NNRTI rates ($P<0.001$ for trend). Notably, the prevalence of transmitted NNRTI resistance specific to EFV and NVP marked a significant increase from 1.6% and 1.8% in 2004–2007 to 6.3% and 6.7% in 2020–2022, respectively ($P<0.001$ for trend). Yet, the prevalence of TDR associated with nucleoside reverse transcriptase inhibitor (NRTI) and protease inhibitor (PI) demonstrated no significant variation over time. The overall TDR prevalence findings remained consistent with the trends of missing and non-missing values for each sociodemographic factor (Supplementary Table S1, available in https://weekly.chinacdc.cn/). The

TABLE 3. Changes in transmitted drug resistance among Chinese individuals with HIV, naïve to ART, according to the stages of the NFATP development, from 2004 to 2022.

Antiretroviral drug	2004–2007 (*n*=1,251)		2008–2011 (*n*=8,794)		2012–2015 (*n*=21,467)		2016–2019 (*n*=21,391)		2020–2022 (*n*=4,999)		*P**	Total (*n*=57,902)	
	N[†]	%[§]	*N*	%	*N*	%	*N*	%	*N*	%		*N*	%
Total	32	2.6	283	3.2	740	3.4	953	4.5	392	7.8	<0.001	2,400	4.1
NNRTI	23	1.8	177	2.0	479	2.2	708	3.3	336	6.7	<0.001	1,723	3.0
EFV	20	1.6	144	1.6	407	1.9	640	3.0	315	6.3	<0.001	1,526	2.6
NVP	23	1.8	177	2.0	479	2.2	708	3.3	336	6.7	<0.001	1,723	3.0
NRTI	13	1.0	117	1.3	276	1.3	293	1.4	76	1.5	0.190	775	1.3
ABC	9	0.7	57	0.6	126	0.6	148	0.7	45	0.9	0.100	385	0.7
AZT	5	0.4	47	0.5	112	0.5	102	0.5	25	0.5	0.700	291	0.5
D4T	10	0.8	90	1.0	193	0.9	221	1.0	42	0.8	0.923	556	1.0
DDI	12	1.0	57	0.6	99	0.5	136	0.6	27	0.5	0.723	331	0.6
FTC	7	0.6	45	0.5	99	0.5	112	0.5	38	0.8	0.120	301	0.5
3TC	7	0.6	45	0.5	99	0.5	112	0.5	38	0.8	0.120	301	0.5
TDF	7	0.6	34	0.4	55	0.3	87	0.4	16	0.3	0.880	199	0.3
PI	2	0.2	25	0.3	56	0.3	39	0.2	9	0.2	0.094	131	0.2
ATV/r	2	0.2	20	0.2	45	0.2	28	0.1	7	0.1	0.059	102	0.2
DRV/r	0	0.0	5	0.1	25	0.1	18	0.1	1	0.0	0.754	49	0.1
LPV/r	1	0.1	25	0.3	48	0.2	34	0.2	8	0.2	0.079	116	0.2

Abbreviation: ART=antiretroviral therapy; HIV=human immunodeficiency virus; NFATP=National Free Antiretroviral Treatment Program; NNRTI=non-nucleoside reverse transcriptase inhibitor; EFV=efavirenz; NVP=nevirapine; NRTI=nucleoside reverse transcriptase inhibitor; ABC=abacavir; AZT=azidothymidine; D4T=stavudine; DDI=didanosine; FTC=emtricitabine; 3TC=lamivudine; TDF=tenofovir; PI=protease inhibitor; ATV/r=atazanavir/ritonavir; DRV/r=darunavir/ritonavir; LPV/r=lopinavir/ritonavir.

* *P* values were calculated using Cochran-Armitage trend test. *P* values <0.05 is statistically significant.

[†] Number of drug resistance amongst ART-naïve individuals infected with HIV.

[§] The prevalence of ART-naïve individuals with HIV who exhibit drug resistance.

Cochran-Armitage trend test results revealed an increasing trend over time in NNRTI resistance mutations for A98, E138, G190, K101, K103, K238, P225, V106 and V179, as well as in NRTI resistance mutations for L74 and M184 (all $P<0.05$ for trend). Conversely, there were no significant developments discernible over time in the PI resistance mutations (Supplementary Table S2, available in https://weekly.chinacdc.cn/).

CONCLUSIONS

To the best of our knowledge, this study represents the largest survey conducted thus far regarding the national distribution and trends of HIV-1 subtypes/sub-subtypes and TDR. With a sample size of 57,902, it spans from 2004 to 2022, encompassing the entire period during which dependable estimates were available for ART-naïve HIV-infected individuals in China.

Between 2004 and 2015, an increasing trend was noted in CRF01_AE, while subtypes B and C displayed a decreasing trend. These findings align with the results of a systematic review of Chinese HIV-1 subtypes from 1990 to 2015 (*10*). The review indicated that CRF01_AE raised from 27.2% to 47.2% between 2005–2009 and 2010–2015, whereas subtypes B and C decreased from 38.7% and 1.7% to 17.8% and 1.6% in the same periods, respectively.

The 2006 Chinese National Molecular Epidemiologic Survey reported that the primary HIV-1 subtypes were largely recombinant, including CRF01_AE, CRF07_BC and CRF08_BC which made up to 80% of the cases, whereas subtype B and remaining subtypes constituted nearly 20%. A retrospective review of HIV/AIDS prevention and control over 30 years in China revealed the prevalence of injection drug use-linked HIV epidemic until 2008, increasing incidence in heterosexuals, and the complexity of HIV-1 subtypes as the proportion of CRFs surpassed other subtypes (*11*).

Our study corroborates the findings of the 2006 Chinese National Molecular Epidemiologic Survey that CRF01_AE, CRF07_BC and CRF08_BC

increasingly predominated in China from 2004 to 2008 (*12*). The data reveal increases in CRF01_AE-cluster 4, CRF07_BC-MSM, CRF07_BC-Other, CRF08_BC, CRF55_01B, Other CRFs, and URFs. In contrast, CRF01_AE-cluster 5 and other subtypes remained consistent, whereas instances of CRF01_AE, cluster 1, cluster 2, cluster 3, cluster 6, and cluster 7, and subtypes B and C showed a deduction.

These shifting patterns have contributed significantly to the complexity and diversity of HIV-1 subtypes and CRFs. A noteworthy observation was the varied distributions of HIV-1 subtypes and recombinant forms and alterations among ART-naïve HIV-infected individuals in different years. The genetic diversity of HIV-1 subtypes/sub-subtypes is driven by a multitude of causes, including potential biological differences between subtypes/sub-subtypes that may impact transmission and disease progression. However, other contributing NVP factors could include aspects like transportation connectivity, migration, urbanization, and population growth.

Incomplete treatment or unequal prevention coverage, and disparities in effectiveness across different geographical regions or risk groups can potentially skew control of the HIV epidemic. Such disparities might contribute to varying regional distributions of HIV-1 subtypes and recombinant forms, with particular regions or risk groups more affected by certain HIV variants.

The 2017 WHO HIV Drug Resistance Guidelines defined the prevalence of transmitted HIVDR as low (<5%), moderate (5%–15%), and high (>15%) (*13*). This study witnessed a significant increase in overall TDR prevalence, even climbing to moderate levels between the years 2020 and 2022. However, in the Xinjiang region, it exceeded 15%, indicating a high level. A comprehensive analysis of HIV-1 TDR in China from 2001 to 2017 indicated an upward trend in overall TDR prevalence, consistent with this study's findings (*14*). A review of HIV-1 TDR studies spanning 2009 to 2019 (*15*) showed that the overall TDR prevalence in Sub-Saharan Africa and North America significantly expanded from 3.6% and 12.1% respectively, in 2009–2013, to 6.0% and 14.2%, respectively, in 2014–2019, as per the WHO 2009 surveillance drug resistance definitions (*16*). There were, however, no observable changes in the overall TDR prevalence in South/Southeast Asia, Latin America/Caribbean, Europe, and Upper-Income Asian Countries in the same periods (*15*). A comprehensive U.S. study from 2004 to 2016 displayed considerable increase in overall TDR prevalence from 9.8% to 17.9% (*17*). Conversely, another large U.S. study from 2014 to 2018 found no statistically significant changes in overall TDR prevalence, which stood at 18.9% (*18*). In our study, overall TDR prevalence was 3.2%, 4.4%, and 4.5% for 2008–2011, 2012–2015, and 2016–2019, respectively. These findings are similar to those from a South/Southeast Asia study (*16*), where the majority of data originated from China. Given the size of this dataset, the study is representative and likely to credibly mirror TDR rates among ART-naïve, HIV-infected individuals in China from 2004 to 2022. Of significant concern is the sharp increase in overall TDR prevalence to 7.8% in the years 2020–2022 — a moderate level — with Xinjiang seeing overall TDR prevalence reach 23.4%, a high level. As TDR becomes a critical issue in China, the country must prioritize resistance monitoring, and reevaluate first-line antiviral treatment regimens at a regional level.

In this investigation, a marked upward trend in the prevalence of TDR specifically regarding NNRTI was identified, reaching moderate levels from 2020–2022. Yet, no significant changes were detected in the TDR prevalence for NRTI and PI. This is aligned with a comprehensive review of HIV-1 TDR in China from 2001 to 2017, underlining NNRTI resistance as the primary driver (*14*). A large-scale study in the United States from 2014 to 2018 found the prevalence of TDR for NNRTI, NRTI, and PI to be 12.0% (5,662/47,215), 6.9% (3,258/47,215), and 4.2% (1,983/47,215), respectively (*18*). These findings, particularly the elevated prevalence of transmitted NNRTI resistance (12.0%), correspond with those of the present study.

EFV and NVP-based ART regimens were most commonly initiated in countries that reported data to the WHO between 2014 and 2020 (*8*). In China, Xinjiang exhibited an overall TDR prevalence exceeding 10%, primarily due to NNRTI resistance. This suggests countries displaying a prevalence of transmitted HIVDR to NNRTI equal to or above 10% should urgently consider non-NNRTI first-line ART regimens (*13*).

From 2020–2022, moderate TDR levels were observed in the application of EFV and NVP regimens, which are the primary drug regimens recommended by China's NFATP. The detection of EFV and NVP-specific HIVDR is of paramount importance due to these drugs' widespread use. Notably, resistance mutations for NNRTI, specifically K103, E138, and V179, have seen an increase from 0.4%, 0.1%, and

0.3% in 2004–2007 to 3.4%, 0.8%, and 1.7% in 2020–2022, respectively; while resistance mutations for NRTI, particularly M184, have risen from 0.2% in 2004–2007 to 0.7% in 2020–2022.

CRFs represent the foremost subtype of HIV-1 in China, meriting further exploration of their specific mutations or polymorphisms in relation to drug resistance, using phenotypic drug resistance methods (*19*). Such surveillance is crucial for future TDR planning in the context of HIV infection. Finally, it is noteworthy to mention that in late 2019, public health services shifted their focus toward the coronavirus disease 2019 (COVID-19) pandemic (*20*), necessitating further investigation of any potential links between COVID-19 and HIV drug resistance.

This study presents several limitations. The sociodemographic indicators utilized in the research revealed certain data gaps. The comparison created between non-absent and absent values for each sociodemographic variable showed no significant shift in the overall TDR prevalence as demonstrated in Supplementary Table S1. Second, we failed to gather pertinent clinical information such as the stage of HIV, the time of HIV diagnosis, and the number of sexual partners. In future studies, incorporating this data could augment the accuracy of the results and further enable analysis of variant effects. Finally, potential sampling bias entailed by regional variation necessitates attention; future endeavors will incorporate a thorough evaluation of shifts in the spatio-temporal distribution of drug resistance amongst ART-naïve HIV-positive patients.

Our research findings suggest that the overall prevalence of TDR among ART-naïve individuals infected with HIV in China during 2020–2022 reached a moderate level, with Xinjiang exhibiting a high level. Individuals with HIV who present with drug resistance carry these resistant strains for life, consequently lowering the efficacy of antiretroviral drugs, thereby increasing new HIV infections and associated morbidity and mortality rates. As a result, these individuals should be given precedence for prevention strategies and optimal treatment. It is imperative to carry out field investigations to determine the reasons for TDR among ART-naïve individuals infected with HIV; this would enable the development of targeted interventions to reduce the occurrence and transmission of HIV drug-resistant strains. Regular monitoring and surveillance of drug resistance at national and provincial levels among ART-naïve individuals infected with HIV, along with escalating efforts to prevent TDR development, are vital to achieving the global objective of eradicating AIDS as a public health threat by 2030.

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[#] Corresponding author: Yuhua Ruan, ruanyuhua92@163.com.

[1] State Key Laboratory of Infectious Disease Prevention and Control (SKLID), National Center for AIDS/STD Control and Prevention, Chinese Center for Disease Control and Prevention (China CDC), Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, Beijing, China.

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SUPPLEMENTARY MATERIAL

SUPPLEMENTARY TABLE S1. Changes in the prevalence of overall transmitted drug resistance between missing and non-missing values across each sociodemographic variable by stages of NFATP development, from 2004 to 2022.

Variable		2004–2007 (*n*=1,251)			2008–2011 (*n*=8,794)			2012–2015 (*n*=21,467)			2016–2019 (*n*=21,391)			2020–2022 (*n*=4,999)			*P**	Total (*n*=57,902)		
		N†	*n*§	%**	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%		*N*	*n*	%
Total	Missing or not	1,251	32	2.6	8,794	283	3.2	21,467	740	3.4	21,391	953	4.5	4,999	392	7.8	<0.001	57,902	2,400	4.1
Age	Yes	1,054	22	2.1	6,603	208	3.2	15,685	506	3.2	10,076	383	3.8	1,348	106	7.9	<0.001	34,766	1,225	3.5
	No	197	10	5.1	2,191	75	3.4	5,782	234	4.0	11,315	570	5.0	3,651	286	7.8	<0.001	23,136	1,175	5.1
Sex	Yes	778	16	2.1	4,929	164	3.3	13,959	469	3.4	9,513	362	3.8	1,347	106	7.9	<0.001	30,526	1,117	3.7
	No	473	16	3.4	3,865	119	3.1	7,508	271	3.6	11,878	591	5.0	3,652	286	7.8	<0.001	27,376	1,283	4.7
Ethnicity	Yes	146	32	4.1	1,116	242	6.1	6,446	576	4.2	8,361	404	3.9	1,472	106	7.7	<0.001	17,541	1,360	4.5
	No	1,105	0	2.4	7,678	41	2.8	15,021	164	3.1	13,030	549	4.8	3,527	286	7.9	<0.001	40,361	1,040	4.0
Education	Yes	1,251	32	2.6	7,340	242	3.3	16,958	576	3.4	10,417	404	3.9	1,369	106	7.7	<0.001	37,335	1,360	3.6
	No	0	0		1,454	41	2.8	4,509	164	3.6	10,974	549	5.0	3,630	286	7.9	<0.001	20,567	1,040	5.1
Marital status	Yes	1,251	32	2.6	6,892	229	3.3	16,960	560	3.3	10,367	401	3.9	1,365	106	7.8	<0.001	36,835	1,328	3.6
	No	0	0		1,902	54	2.8	4,507	180	4.0	11,024	552	5.0	3,634	286	7.9	<0.001	21,067	1,072	5.1
Risk groups	Yes	754	16	2.1	4,525	147	3.2	14,014	455	3.2	9,733	377	3.9	1,507	134	8.9	<0.001	30,533	1,129	3.7
	No	497	16	3.2	4,269	136	3.2	7,453	285	3.8	11,658	576	4.9	3,492	258	7.4	<0.001	27,369	1,271	4.6
CD4 count	Yes	1,001	19	1.9	7,122	221	3.1	17,035	553	3.2	12,764	517	4.1	1,769	123	7.0	<0.001	39,691	1,433	3.6
	No	250	13	5.2	1,672	62	3.7	4,432	187	4.2	8,627	436	5.1	3,230	269	8.3	<0.001	18,211	967	5.3

Abbreviation: ART=antiretroviral therapy; HIV=human immunodeficiency virus; NFATP=National Free Antiretroviral Treatment Program.
* *P* values were calculated using Cochran-Armitage trend test. *P* values <0.05 is statistically significant.
† Total number of individuals infected with HIV who have not yet received ART surveyed.
§ The number of drug resistance amongst ART-naïve individuals infected with HIV.
¶ Proportion of ART-naïve individuals infected with human immunodeficiency virus who showcase drug resistance.

SUPPLEMENTARY TABLE S2. Evolution of drug resistance mutations in Chinese individuals with HIV who are naïve to antiretroviral therapy, categorized by stages of NFATP development, from 2004 to 2022.

Drug resistance mutation	2004–2007 (*n*=1,251)		2008–2011 (*n*=8,794)		2012–2015 (*n*=21,467)		2016–2019 (*n*=21,391)		2020–2022 (*n*=4,999)		*P**	Total (*n*=57,902)	
	N†	%§	*N*	%	*N*	%	*N*	%	*N*	%		*N*	%
Total	32	2.6	283	3.2	740	3.4	953	4.5	392	7.8	**<0.001**	2,400	4.1
NNRTI (EFV, NVP)	23	1.8	177	2	479	2.2	708	3.3	336	6.7	**<0.001**	1,723	3.0
A98G	2	0.2	17	0.2	16	0.1	30	0.1	22	0.4	**0.007**	87	0.2
L100I	1	0.1	2	0	5	0	7	0	4	0.1	0.268	19	0
K101E/P/H	1	0.1	17	0.2	41	0.2	45	0.2	22	0.4	**0.010**	126	0.2
K103S/T/N	5	0.4	41	0.5	119	0.6	216	1	172	3.4	**<0.001**	553	1.0
V106I/M/A	4	0.3	24	0.3	66	0.3	97	0.5	32	0.6	**<0.001**	223	0.4
V108I	5	0.4	26	0.3	52	0.2	37	0.2	14	0.3	0.097	134	0.2
E138A/G/K/Q	1	0.1	11	0.1	96	0.4	141	0.7	39	0.8	**<0.001**	288	0.5
V179D/E/L/T	4	0.3	35	0.4	165	0.8	243	1.1	84	1.7	**<0.001**	531	0.9
Y181C/I	7	0.6	27	0.3	56	0.3	60	0.3	21	0.4	0.889	171	0.3
Y188C/F/L	0	0	14	0.2	13	0.1	22	0.1	9	0.2	0.398	58	0.1
G190A/C/E/S	3	0.2	22	0.3	52	0.2	69	0.3	25	0.5	**0.008**	171	0.3
H221Y	1	0.1	10	0.1	23	0.1	39	0.2	7	0.1	0.105	80	0.1
P225H	1	0.1	2	0	7	0	13	0.1	16	0.3	**<0.001**	39	0.1
F227C/I/L	2	0.2	4	0	14	0.1	15	0.1	1	0	0.523	36	0.1
M230I/L	2	0.2	4	0	7	0	22	0.1	2	0	0.352	37	0.1

Continued

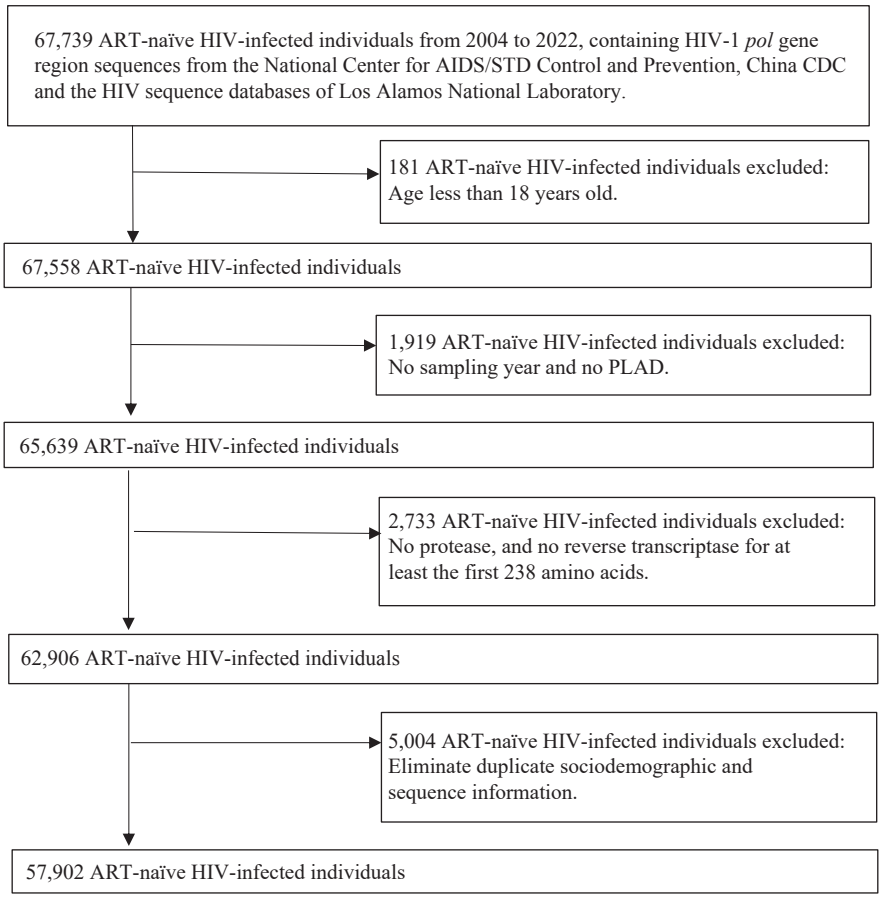
Drug resistance mutation	2004–2007 (*n*=1,251)		2008–2011 (*n*=8,794)		2012–2015 (*n*=21,467)		2016–2019 (*n*=21,391)		2020–2022 (*n*=4,999)		*P**	Total (*n*=57,902)	
	N†	%§	*N*	%	*N*	%	*N*	%	*N*	%		*N*	%
L234I	0	0	0	0	1	0	1	0	0	0	0.813	2	0
K238N/T	0	0	2	0	7	0	13	0.1	7	0.1	**0.002**	29	0.1
NRTI (any)	13	1	117	1.3	276	1.3	293	1.4	76	1.5	0.190	775	1.3
M41L	2	0.2	13	0.1	32	0.1	22	0.1	5	0.1	0.173	74	0.1
E44A/D	0	0	3	0	1	0	0	0	0	0	**0.016**	4	0
A62V	2	0.2	4	0	9	0	4	0	2	0	0.081	21	0
K65R	2	0.2	14	0.2	19	0.1	44	0.2	8	0.2	0.165	87	0.2
D67N	2	0.2	15	0.2	34	0.2	41	0.2	11	0.2	0.372	103	0.2
S68G	1	0.1	10	0.1	23	0.1	29	0.1	1	0	0.660	64	0.1
T69D/N	4	0.3	7	0.1	16	0.1	12	0.1	6	0.1	0.280	45	0.1
K70E/T/R/	2	0.2	14	0.2	35	0.2	48	0.2	7	0.1	0.442	106	0.2
L74F/I	0	0	2	0	14	0.1	19	0.1	5	0.1	**0.023**	40	0.1
V75A/M/I	1	0.1	14	0.2	13	0.1	19	0.1	2	0	0.117	49	0.1
F77L	1	0.1	1	0	0	0	1	0	1	0	0.447	4	0
Y115F	0	0	1	0	3	0	8	0	1	0	0.172	13	0
F116Y	1	0.1	2	0	0	0	0	0	0	0	**0.001**	3	0
Q151M/L	1	0.1	5	0.1	1	0	1	0	0	0	**0.001**	8	0
M184I/V	3	0.2	29	0.3	85	0.4	82	0.4	33	0.7	**0.019**	232	0.4
L210W	1	0.1	15	0.2	41	0.2	23	0.1	4	0.1	0.070	84	0.1
T215F/Y	2	0.2	36	0.4	67	0.3	61	0.3	15	0.3	0.335	181	0.3
K219E/N	3	0.2	11	0.1	6	0	15	0.1	3	0.1	0.102	38	0.1
PI (ATV/r, DRV/r, LPV/r)	2	0.2	25	0.3	56	0.3	39	0.2	9	0.2	0.094	131	0.2
L10F	0	0	1	0	1	0	1	0	1	0	0.737	4	0
K20T	0	0	0	0	1	0	2	0	0	0	0.544	3	0
L24I	0	0	0	0	0	0	0	0	1	0	0.070	1	0
V32I	0	0	1	0	6	0	1	0	0	0	0.282	8	0
L33F	0	0	0	0	1	0	3	0	1	0	0.110	5	0
K43T	0	0	1	0	0	0	0	0	1	0	0.813	2	0
M46I/L	0	0	3	0	10	0	4	0	0	0	0.193	17	0
I47V	0	0	3	0	10	0	5	0	0	0	0.273	18	0
G48R	0	0	0	0	4	0	1	0	0	0	0.719	5	0
I50V/L	1	0.1	3	0	4	0	4	0	1	0	0.286	13	0
F53L	0	0	0	0	4	0	1	0	0	0	0.719	5	0
I54M/V	0	0	3	0	9	0	5	0	2	0	0.881	19	0
Q58E	0	0	0	0	1	0	3	0	0	0	0.377	4	0
G73R/V	0	0	0	0	2	0	3	0	0	0	0.535	5	0
L76V	0	0	0	0	3	0	5	0	0	0	0.389	8	0
V82A/F	1	0.1	5	0.1	14	0.1	8	0	2	0	0.279	30	0.1
I84L/V	0	0	2	0	4	0	4	0	0	0	0.610	10	0
N88S/T	0	0	0	0	5	0	4	0	1	0	0.381	10	0
L89T	0	0	1	0	0	0	0	0	0	0	0.140	1	0
L90M	0	0	10	0.1	9	0	5	0	4	0.1	0.164	28	0

Abbreviation: ART=antiretroviral therapy; HIV=human immunodeficiency virus; NFATP=National Free Antiretroviral Treatment Program; NNRTI=non-nucleoside reverse transcriptase inhibitor; EFV=efavirenz; NVP=nevirapine; NRTI=nucleoside reverse transcriptase inhibitor; (any: ABC=abacavir; AZT=azidothymidine; d4T=stavudine; DDI=didanosine; FTC=emtricitabine; 3TC=lamivudine; TDF=tenofovir); PI=protease inhibitor; ATV/r=atazanavir/ritonavir; DRV/r=darunavir/ritonavir; LPV/r=lopinavir/ritonavir.

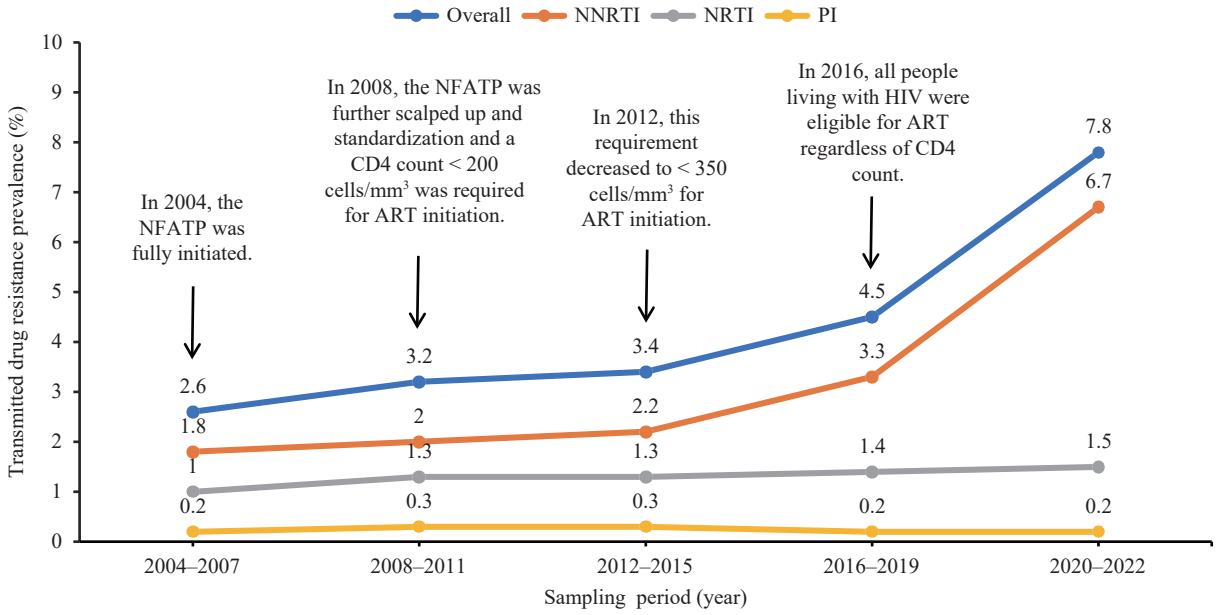
* *P* values were calculated using Cochran-Armitage trend test. *P* values <0.05 is statistically significant.

† Number of drug resistance amongst ART-naïve individuals infected with HIV surveyed.

§ Prevalence of ART-naïve individuals infected with HIV that exhibit drug resistance.



SUPPLEMENTARY FIGURE S1. Flow chart showing the derivation of study sets meeting the inclusion criteria.
Abbreviation: ART=antiretroviral therapy; HIV=human immunodeficiency virus; PLAD=provincial-level administrative division.



SUPPLEMENTARY FIGURE S2. Changes in transmitted drug resistance among Chinese ART-naïve HIV-infected individuals by the NFATP development stages, 2004−2022.
Abbreviation: ART=antiretroviral therapy; HIV=human immunodeficiency virus; NFATP=National Free Antiretroviral Treatment Program; NNRTI=non-nucleoside reverse transcriptase inhibitor; NRTI=nucleoside reverse transcriptase inhibitor; PI=protease inhibitor.

Notes from the Field

No Novel Prevalent Mutations Detected in the Circulating Strains of BF.7, BA.5.2, DY, and XBB — China, November 2022 to June 2023

Liang Wang[1,#]; George F. Gao[1,2]

Ongoing surveillance of severe acute respiratory syndrome virus 2 (SARS-CoV-2)'s genetic variations remains crucial for effective epidemic prevention and control. Our prior research demonstrates the co-circulation of two pre-existing Omicron subvariants, BA.5.2 and BF.7, which were responsible for the coronavirus disease 2019 (COVID-19) surge in Beijing following modifications to prevention and control policies in mid-November 2022 — a snapshot of China's situation at the time (*1*). Following a period of relatively low COVID-19 case count after February 2023, a noticeable increase was observed from late April 2023 (*2*). Post-analysis of SARS-CoV-2 genomic data gathered in China post November 11, 2022, [sourced from Global Initiative of Sharing All Influenza Data (GISAID) as of July 6, 2023], revealed that the Omicron subvariants most detected were BA.5.2, BF.7, DY (descendants of BA.5.2.48), and XBB — along with their corresponding descendants denoted as BA.5.2*, BF.7*, DY*, and XBB*, respectively (Figure 1A). Interestingly, detection of BA.5.2*, BF.7*, and DY* plateaued by May 2023, while that of XBB*, previously without local transmission, showed notable growth post-April 2023 (Figure 1B). Further, key nonsynonymous mutations were identified, with high-frequency mutations (≥10%) being 4 in BA.5.2*, 4 in BF.7*, 6 in DY*, and 7 in XBB*, excluding the defining mutations present in ≥ 80% of the genomes in each lineage (Figure 1C). Six of these mutations showed high prevalence in China (frequency ≥80%). However, these 21 mutations were not exclusive to China, having been first identified outside the country prior to 2023 (Figure 1D). Collectively, despite the co-circulation of BA.5.2*, BF.7*, and DY* in China for over six months, prevalently novel nonsynonymous mutations have not been discovered in them. Notably, XBB* has displayed significant immune-evasion capabilities (*3*) and has effectively evaded responses induced by several types of vaccines widely used in China (*4*). Moreover, it has been approximately six months since the first large-scale infections wave at the end of 2022, with patient antibody levels gradually declining, implying the dominance of XBB* over BA.5.2*, BF.7*, and DY* and triggering a second wave of infections. Given China's dense population, ongoing local transmissions — both local and imported — of various SARS-CoV-2 variants have the potential to generate innovative variants in humans or animals. Consequently, continuous, comprehensive surveillance remains vital and should be conducted under the "One Health" framework.

Conflicts of interest: George F. Gao is the Founding Editor-in-Chief of *China CDC Weekly*. He was not involved in the peer review or handling of the manuscript. The authors have no other competing interests to disclose.

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[#] Corresponding author: Liang Wang, wangliang@im.ac.cn.

[1] CAS Key Laboratory of Pathogen Microbiology and Immunology, Institute of Microbiology, Center for Influenza Research and Early-warning (CASCIRE), CAS-TWAS Center of Excellence for Emerging Infectious Diseases (CEEID), Chinese Academy of Sciences, Beijing, China; [2] University of Chinese Academy of Sciences, Beijing, China.

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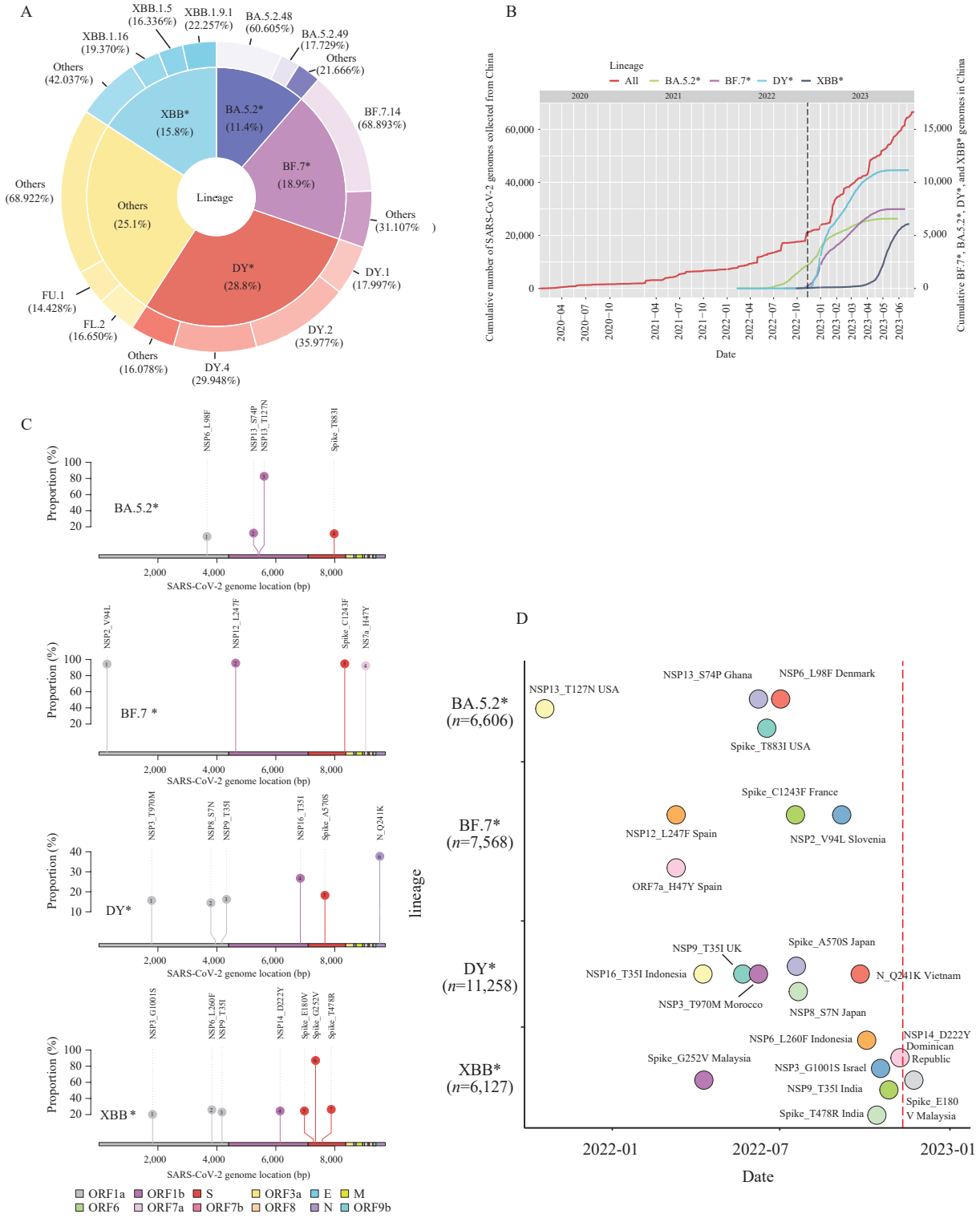

FIGURE 1. Trends and statistics of BA.5.2*, BF.7*, DY*, and XBB* variants of severe acute respiratory syndrome virus 2 (SARS-CoV-2) genomes in China. (A) The composition of SARS-CoV-2 variants circulating from November 11, 2022, to June 30, 2023. (B) The cumulative number of SARS-CoV-2 genomes derived from China. (C) Mutations categorized as BA.5.2*, BF.7*, DY*, and XBB* have been identified with high frequency in China. (D) The initial detection date and location of each high-frequency mutation within their respective lineages.

Note: Different lineages are demonstrated through color-coding. The red dashed line represents the timing of preventive and control policy adjustments. The number of genomes gathered from China for each lineage is also depicted. The implementation of changes to prevention and control policies is represented by a dashed line in panel B. Genes encoded by SARS-CoV-2 genomes were demonstrated through color-coding in panel C.

Notifiable Infectious Diseases Reports

Reported Cases and Deaths of National Notifiable Infectious Diseases — China, January 2023*

Diseases	Cases	Deaths
Plague	0	0
Cholera	0	0
SARS-CoV	0	0
Acquired immune deficiency syndrome†	1,815	1,777
Hepatitis	89,719	32
Hepatitis A	523	0
Hepatitis B	74,790	18
Hepatitis C	12,785	13
Hepatitis D	17	0
Hepatitis E	1,144	1
Other hepatitis	460	0
Poliomyelitis	0	0
Human infection with H5N1 virus	0	0
Measles	18	0
Epidemic hemorrhagic fever	217	2
Rabies	5	15
Japanese encephalitis	4	0
Dengue	1	0
Anthrax	19	0
Dysentery	1,924	0
Tuberculosis	53,730	327
Typhoid fever and paratyphoid fever	184	0
Meningococcal meningitis	6	0
Pertussis	883	0
Diphtheria	0	0
Neonatal tetanus	6	0
Scarlet fever	276	0
Brucellosis	2,318	0
Gonorrhea	4,762	0
Syphilis	28,708	3
Leptospirosis	6	0
Schistosomiasis	0	0
Malaria	149	2
Human infection with H7N9 virus	0	0
Influenza	15,270	0
Mumps	2,370	0
Rubella	40	0

Continued

Diseases	Cases	Deaths
Acute hemorrhagic conjunctivitis	1,156	0
Leprosy	14	0
Typhus	33	0
Kala azar	17	0
Echinococcosis	240	0
Filariasis	0	0
Infectious diarrhea[§]	42,950	0
Hand, foot and mouth disease	2,484	0
Total	249,324	2,158

* According to the National Bureau of Disease Control and Prevention, not included coronavirus disease 2019 (COVID-19).
† The number of deaths of acquired immune deficiency syndrome (AIDS) is the number of all-cause deaths reported in the month by cumulative reported AIDS patients.
§ Infectious diarrhea excludes cholera, dysentery, typhoid fever and paratyphoid fever. The numbers of cases and cause-specific deaths refer to data recorded in National Notifiable Disease Reporting System in China, which includes both clinically-diagnosed cases and laboratory-confirmed cases. Only reported cases of the 31 provincial-level administrative divisions in Chinese mainland are included in the table, whereas data of Hong Kong Special Administrative Region, Macau Special Administrative Region, and Taiwan, China are not included. Monthly statistics are calculated without annual verification which is usually conducted in February of the next year for de-duplication and verification of reported cases in annual statistics. Therefore, 12-month cases could not be added together directly to calculate the cumulative cases because the individual information might be verified via National Notifiable Disease Reporting System according to information verification or field investigations by local CDCs.

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Notifiable Infectious Diseases Reports

Reported Cases and Deaths of National Notifiable Infectious Diseases — China, February 2023*

Diseases	Cases	Deaths
Plague	0	0
Cholera	0	0
SARS-CoV	0	0
Acquired immune deficiency syndrome†	4,516	1,937
Hepatitis	140,383	59
Hepatitis A	850	0
Hepatitis B	116,063	18
Hepatitis C	20,580	41
Hepatitis D	20	0
Hepatitis E	2,207	0
Other hepatitis	663	0
Poliomyelitis	0	0
Human infection with H5N1 virus	1	0
Measles	53	0
Epidemic hemorrhagic fever	270	0
Rabies	15	4
Japanese encephalitis	1	0
Dengue	11	0
Anthrax	12	0
Dysentery	2,346	1
Tuberculosis	71,841	324
Typhoid fever and paratyphoid fever	341	0
Meningococcal meningitis	4	0
Pertussis	538	0
Diphtheria	0	0
Neonatal tetanus	3	0
Scarlet fever	470	0
Brucellosis	5,662	0
Gonorrhea	6,589	0
Syphilis	43,574	2
Leptospirosis	7	0
Schistosomiasis	3	0
Malaria	117	0
Human infection with H7N9 virus	0	0
Influenza	240,687	1
Mumps	4,548	0
Rubella	67	0

Continued

Diseases	Cases	Deaths
Acute hemorrhagic conjunctivitis	1,958	0
Leprosy	40	0
Typhus	50	0
Kala azar	27	1
Echinococcosis	324	0
Filariasis	0	0
Infectious diarrhea[§]	96,292	0
Hand, foot and mouth disease	3,935	0
Total	624,685	2,329

* According to the National Bureau of Disease Control and Prevention, not included coronavirus disease 2019 (COVID-19).
† The number of deaths of acquired immune deficiency syndrome (AIDS) is the number of all-cause deaths reported in the month by cumulative reported AIDS patients.
§ Infectious diarrhea excludes cholera, dysentery, typhoid fever and paratyphoid fever.
The numbers of cases and cause-specific deaths refer to data recorded in National Notifiable Disease Reporting System in China, which includes both clinically-diagnosed cases and laboratory-confirmed cases. Only reported cases of the 31 provincial-level administrative divisions in Chinese mainland are included in the table, whereas data of Hong Kong Special Administrative Region, Macau Special Administrative Region, and Taiwan, China are not included. Monthly statistics are calculated without annual verification which is usually conducted in February of the next year for de-duplication and verification of reported cases in annual statistics. Therefore, 12-month cases could not be added together directly to calculate the cumulative cases because the individual information might be verified via National Notifiable Disease Reporting System according to information verification or field investigations by local CDCs.

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Notifiable Infectious Diseases Reports

Reported Cases and Deaths of National Notifiable Infectious Diseases — China, March 2023*

Diseases	Cases	Deaths
Plague	0	0
Cholera	0	0
SARS-CoV	0	0
Acquired immune deficiency syndrome†	5,785	1,992
Hepatitis	155,705	57
Hepatitis A	1,289	0
Hepatitis B	126,932	27
Hepatitis C	23,625	30
Hepatitis D	20	0
Hepatitis E	3,117	0
Other hepatitis	722	0
Poliomyelitis	0	0
Human infection with H5N1 virus	0	0
Measles	81	0
Epidemic hemorrhagic fever	330	0
Rabies	9	13
Japanese encephalitis	3	0
Dengue	7	0
Anthrax	20	0
Dysentery	2,530	0
Tuberculosis	76,331	289
Typhoid fever and paratyphoid fever	452	0
Meningococcal meningitis	15	1
Pertussis	821	0
Diphtheria	0	0
Neonatal tetanus	0	0
Scarlet fever	858	0
Brucellosis	6,543	0
Gonorrhea	8,029	0
Syphilis	49,855	1
Leptospirosis	5	0
Schistosomiasis	3	0
Malaria	138	1
Human infection with H7N9 virus	0	0
Influenza	3,721,370	38
Mumps	7,299	0
Rubella	90	0

Continued

Diseases	Cases	Deaths
Acute hemorrhagic conjunctivitis	2,208	0
Leprosy	43	0
Typhus	77	0
Kala azar	37	0
Echinococcosis	374	0
Filariasis	0	0
Infectious diarrhea[§]	122,646	0
Hand, foot and mouth disease	9,631	1
Total	4,171,295	2,393

* According to the National Bureau of Disease Control and Prevention, not included coronavirus disease 2019 (COVID-19).
† The number of deaths of acquired immune deficiency syndrome (AIDS) is the number of all-cause deaths reported in the month by cumulative reported AIDS patients.
§ Infectious diarrhea excludes cholera, dysentery, typhoid fever and paratyphoid fever.
The numbers of cases and cause-specific deaths refer to data recorded in National Notifiable Disease Reporting System in China, which includes both clinically-diagnosed cases and laboratory-confirmed cases. Only reported cases of the 31 provincial-level administrative divisions in Chinese Mainland are included in the table, whereas data of Hong Kong Special Administrative Region, Macau Special Administrative Region, and Taiwan, China are not included. Monthly statistics are calculated without annual verification which is usually conducted in February of the next year for de-duplication and verification of reported cases in annual statistics. Therefore, 12-month cases could not be added together directly to calculate the cumulative cases because the individual information might be verified via National Notifiable Disease Reporting System according to information verification or field investigations by local CDCs.

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