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Epidemiologic trends of hepatitis A in different age groups and regions of China from 1990 to 2018: observational population-based study

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Original Paper

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Abstract

This study characterises changes in the incidence and mortality of hepatitis A in different age groups and provinces of China from 1990 to 2018, and evaluates the effect of the nation-wide expanded programme on immunisation (EPI). A mathematical model was used to estimate the relative change in incidence and mortality in different provinces and age groups. Interrupted time series regression was applied to evaluate the impacts of the inclusion of vaccination in the EPI during 2007–2018. The geographic clustering of hepatitis A incidence was assessed using global Moran's *I* and changing trends over time were estimated using joinpoint regression analysis. Both the incidence (odds ratio (OR) for overall relative change: 0.86; 95% confidence interval (CI): 0.85–0.87; $P < 0.0001$) and the mortality rate (OR for overall relative change: 0.84; 95% CI: 0.83–0.85; $P < 0.0001$) decreased. Most age groups had significant declines in reported incidence over time. The incidence and mortality of hepatitis A significantly reduced after inclusion of hepatitis A vaccine in EPI, showing that the EPI strategy had a continuous effect on the decreasing trend of hepatitis A burden. Increasing the coverage rate of the vaccine and improving hygiene conditions are the key measures for the control of hepatitis A in China.

Introduction

Hepatitis A is a viral hepatitis that is a major challenge to public health worldwide. It is an acute and usually self-limited infection of the liver caused by the hepatitis A virus (HAV) [1]. Transmission is primarily *via* the faecal–oral route and is associated with poor sanitary conditions and person-to-person contact [1]. It can result in serious illness (HAV disease), and the risk for morbidity and mortality is particularly great in susceptible older adults [2]. Global Burden of Disease's estimated global incidence and mortality rates for hepatitis A in 2019 are 2272.1 (95% confidence interval (CI): 2121.8–2421.8) per 100 000 and 0.5 (95% CI: 0.4–0.7) per 100 000, respectively [3]. In developing countries, the prevalence of HAV infection is very high among children, and seroprevalence rates in some populations can reach 100% for children less than 10 years old [4]. In China, the incidence of hepatitis A was greatest among all types of viral hepatitis during the 1990s, and northern China was hyper-endemic for hepatitis A until the middle 1990s [5]. Additionally, clusters of hepatitis A outbreaks occurred during 2005–2007, especially in primary or middle schools in remote rural areas of China [6].

To prevent hepatitis A, the Chinese government approved the first live attenuated hepatitis A vaccine (L-HepA) in 1992. The inactivated hepatitis A vaccine (I-HepA) was licensed in 2002 [7] and was introduced as a free childhood vaccine with funding by the Ministry of Public Health of China in 2008 [8]. Since then, depending on geographic regions, children were given either one dose of L-HepA at the age of 18th month, or one dose of I-HepA at the age of 18th and 24th months, respectively. Between 2008 and 2016, 116 million doses of L-HepA and 30 million doses of I-HepA were administered in China, and the reported coverage increased to 98.8% among target-age children (at the age of 18th months to 24th months who need to be vaccinated in accordance with the expanded programme on immunisation (EPI)) [9]. A recent study of 449 children showed that the immunisation coverage and positivity rate significantly increased with the delay of birth year [10]. Similarly, a large survey in 2014 found significant differences among age groups, in that coverage by the vaccine was 91.73% for children under 5 years old, 81.62% for children 5–9 years old, but less than 30% for individuals more than 15 years old [6].

Although there has been a documented decline of hepatitis A incidence and mortality [11], temporal trends and factors that impact hepatitis A incidence and mortality among different provinces and age groups in China remains unclear, especially after inclusion of hepatitis A in the National Notifiable Disease Reporting System (NNDRS) in 1990 [12]. In this study, we

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describe the changing patterns of hepatitis A incidence and mortality in different provinces and age groups in China from 1990 to 2018, and evaluate the effect of the nationwide EPI. These results will assist evidence-based and region-specific planning and evaluation of the effectiveness of current prevention and control strategies, and help guide the subsequent allocation of limited health care resources.

Methods

Data collection

Data were collected from the Chinese Center for Disease Control and Prevention, and included the number of reported hepatitis A cases and deaths according to age and province. Surveillance cases were defined according to the health industry standard 'Diagnostic Criteria for Viral Hepatitis A (WS298-2008)' issued by the Ministry of Health of the People's Republic of China. According to the requirements of the current Chinese infectious diseases reporting system, the surveillance cases of hepatitis A were defined as clinically diagnosed cases or laboratory diagnosed cases. The notified cases included in this study included clinically diagnosed cases and laboratory diagnosed cases (confirmed cases). The compiled data included the number of reported cases and deaths and the computed incidence and mortality rates for the period of 1990–2018. All incidence data refer to reported incidence (RI). Age-specific data included individuals from age 1 to 85 years old, and were divided into 25 age groups from 2004 to 2016. The geographic data included all 31 provinces of mainland China from 1990 to 2016.

Data analyses

Temporal changes in incidence and mortality

To analyse temporal changes in the incidence and mortality of hepatitis A, a mathematical model that allows comparisons among regions and age groups was used [13]. The original data were processed using a logit transformation, and secular changes were then assessed using a linear regression model [13]. To visualise the results, the original 26 age groups were merged into nine groups (<1, 1–5, 6–9, 10–19, 20–29, 30–39, 40–49, 50–59 and ≥60 years old). Relative changes in the RI and mortality of hepatitis A during the study period were presented as odds ratios (ORs) relative to the first year of data collection, which refers to 1990 in general and 2004 when discussing age-specific data. Moran's I is a widely used spatial statistic for detecting global spatial patterns such as an east-west trend or an unusually large cluster [14]. It was used to describe the regional clustering (spatial autocorrelation) of hepatitis A incidence [15].

Incidence and mortality trend decomposition

Joinpoint regression, a common method used for analysis of time trends in epidemiological data [16], was used to analyse local temporal trends in hepatitis A incidence and mortality. Joinpoint regression establishes a piecewise regression according to the time characteristics of disease distribution, divides the time into different intervals using several joinpoints and each interval is then trend-fitted and optimised. Furthermore, the changes in specific disease characteristics during different intervals were evaluated in more detail. The RIs and mortality rates from hepatitis A were processed using joinpoint, and the results depict RIs and mortality rates in a piecewise manner.

Impact of the EPI on hepatitis A burden

An interrupted time series (ITS) regression was used to evaluate the effectiveness of the EPI [17]. To alleviate the heavy burden of liver diseases caused by HAV, the hepatitis A vaccine was incorporated into the EPI during 2007 [18]. A multiple linear regression model (time variable X1, intervention variable X2 and observation variable X3) was constructed. The Durbin–Watson test was used to detect autocorrelation and the t-test was used to verify the regression coefficient.

Statistical software

R software version 4.0.3 was used for all statistical analyses, including calculations of ORs, RIs and mortality rates from hepatitis A in different provinces and age groups. A P-value below 0.05 was deemed significant. Spatial pattern analyses were conducted to identify clusters of hepatitis A using ArcGIS version 10.2 (ESRI, Redlands, CA, USA); this software was also used to compute the annual Moran's I at the national level [19].

Results

Analysis of the distribution of surveillance data

Surveillance data for hepatitis A in China from 1990 to 2018 are provided in the Appendix (Table S1). Time trends were plotted by regions and by age groups (Figs S1 and S2). In the case of different regions, we could see that the incidence of hepatitis A in the northwest of China fluctuated greatly, whereas other provinces have a relatively obvious trend of decline. The incidence was highest in the eastern region between 1990 and 1993 which declined rapidly since then. At the same time, both the incidence and mortality of hepatitis A are poorly controlled in Southwest China. In general, the incidence was high in the western region and low in the eastern region. The mortality was higher in the south and lower in the north. In the case of different age groups, the incidence showed a significant downward trend in all age groups. However, because of the really low mortality in China, the mortality was heavily influenced by random events. There was only an overall downward trend observed. In addition, the proportion of different age groups has changed. The proportion of reported cases of 6–9-year-old and 10–19-year-old age groups decreased significantly. However, the proportion of reported cases in the age groups over 40 years old gradually increased. A similar trend was observed in the number of deaths. After 2009, there were almost no deaths in the age group below 30. The proportion of death cases in middle-aged and elderly population increased gradually.

Temporal trends in RI and mortality

The total number of newly reported cases of hepatitis A decreased rapidly during recent decades, from 584 353 in 1990 to 16 196 in 2018. Thus, the incidence declined from 52.58 per 100 000 in 1990 to 1.16 per 100 000 in 2018, corresponding to a decline of 97.8% over this time period (Fig. 1a). During the same period, the total number of hepatitis A deaths decreased from 416 (1990) to 3 (2018). The mortality rate thus decreased from 0.0374 per 100 000 to 0.000215 per 100 000, corresponding to a decline of 99.4% over this time period (Fig. 1b). From 1990 to 2016, there were significant nation-wide overall relative declines in hepatitis A incidence (OR = 0.86; 95% CI: 0.85–0.87; $P <$ 0.0001) and mortality (OR = 0.84; 95% CI: 0.83–0.85; $P <$

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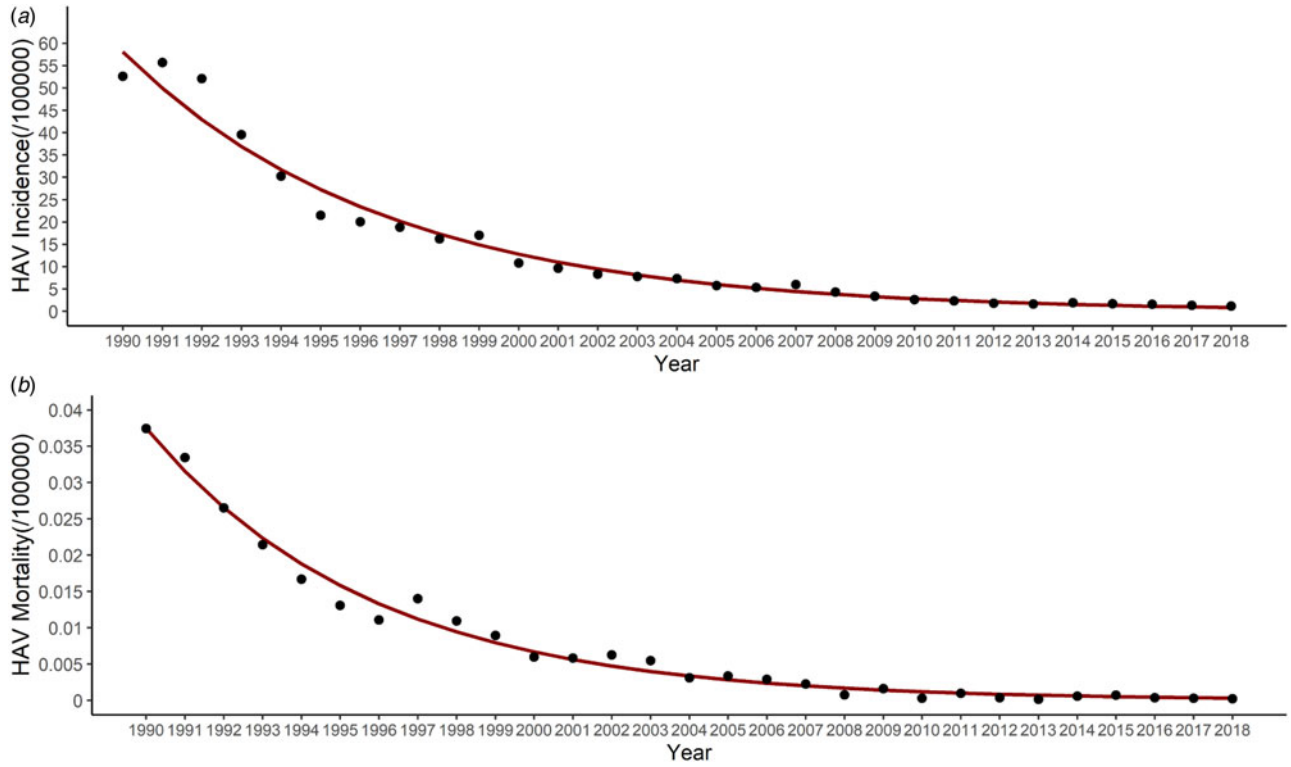

Fig. 1. Annual RI (a) and mortality (b) of hepatitis A in China from 1990 to 2018. The lines are fits to logistic regression equations.

0.0001). Thus, there was a significant amelioration of the hepatitis A epidemic in China during recent decades.

Distribution by geographic region and age

Since 2010, the RIs of hepatitis A in northern, northeastern, eastern and south-central China were below 2 per 100 000 per year, but the northwestern and southwestern regions only reached this level in 2016. Declines in hepatitis A were lowest in the northwestern region (Fig. 2 and Table 1).

The incidence in East China was the greatest during the earlier years, and there were peaks in Jiangsu (RI = 123.17 per 100 000) and Anhui (RI = 106.27 per 100 000) around 1992. Compared with other regions, Northwest and Southwest China had large fluctuations during these 29 years, although there were trends of gradual declines in Northwest and Southwest China. Especially in Northwest China, Gansu peaked during 1991 (RI = 56.20 per 100 000) and 1998 (RI = 60.82 per 100 000), and its highest incidence was 60.81 per 100 000 in 2008; Ningxia reached peaks during 1991 (RI = 54.33 per 100 000) and 2007 (RI = 38.92 per 100 000); and Xinjiang had a peak during 2007 (RI = 39.83 per 100 000). Xinjiang is the only province that had no significant upward or downward trends in incidence from 1990 to 2016 (OR = 1.00; 95% CI: 0.98–1.02; $P = 0.964$).

Analysis of mortality indicated a small amount of fluctuation. Most provinces had gradual downward trends, but the mortality rates in Tibet and Guizhou fluctuated during this time. The control of hepatitis A-related deaths in Tibet was poor before 1994, and its highest mortality rate (0.224 per 100 000) was in 1991. Qinghai had an unusually high mortality rate (0.855 per 100 000) in 1997, nearly eight times higher than that reported in 1990 (0.116 per 100 000). Jilin and Hainan had mortality rates close to 0, and Ningxia had no reports of hepatitis A deaths after 2006. At the provincial level, the mortality from hepatitis A in some provinces (JL, NX, QH and HN) had no general trends, in contrast to the trends of decreasing incidence.

We identified remarkable age-specific patterns in the incidence and mortality of hepatitis A from 2004 to 2016 (Fig. 3). The logistic regression fitting indicated obvious downward trends of RI and mortality in all age groups. The incidence of regular vaccinated population (children over 1 year old) decreased faster than the population over 60 years old. The RI of 1–5-year-old age group was significantly higher than the others after 2009. Thus, the 1–5-year-old and oldest age groups had the greatest risk for hepatitis A in 2016. Notably, the oldest and young age groups (1–9 years) also had obvious peaks of RI in 2007. Additionally, people aged 10–19 years old had the greatest decline in mortality from 2004 to 2007, and the highest mortality rate was in the oldest age group.

We also performed a more detailed analysis of the effect of age (Fig. 4 and Table 2). Almost all age groups had significantly decreasing RIs from 2004 to 2016. However, 1–2 and 2–3-year-old groups had no significant downward trends during the past 12 years, which might be due to that these age groups usually have no symptomatic infection and therefore are not diagnosed and reported. The lowest OR (under 0.80) was in children aged 5–10 years old, meaning this group had the greatest relative change. The mortality rate remained very low, and there were no reported deaths in the 9–10-year-old group during the past 12 years. The overall OR for all age groups was 0.9998 (95% CI: 0.9997–0.9998; $P = 0.002$), indicating a small but statistically significant nation-wide downward trend. However, people aged 0–9 (might because there were so few deaths in any year among young children), 20–25 and 70 or more years old had no significant changes in mortality.

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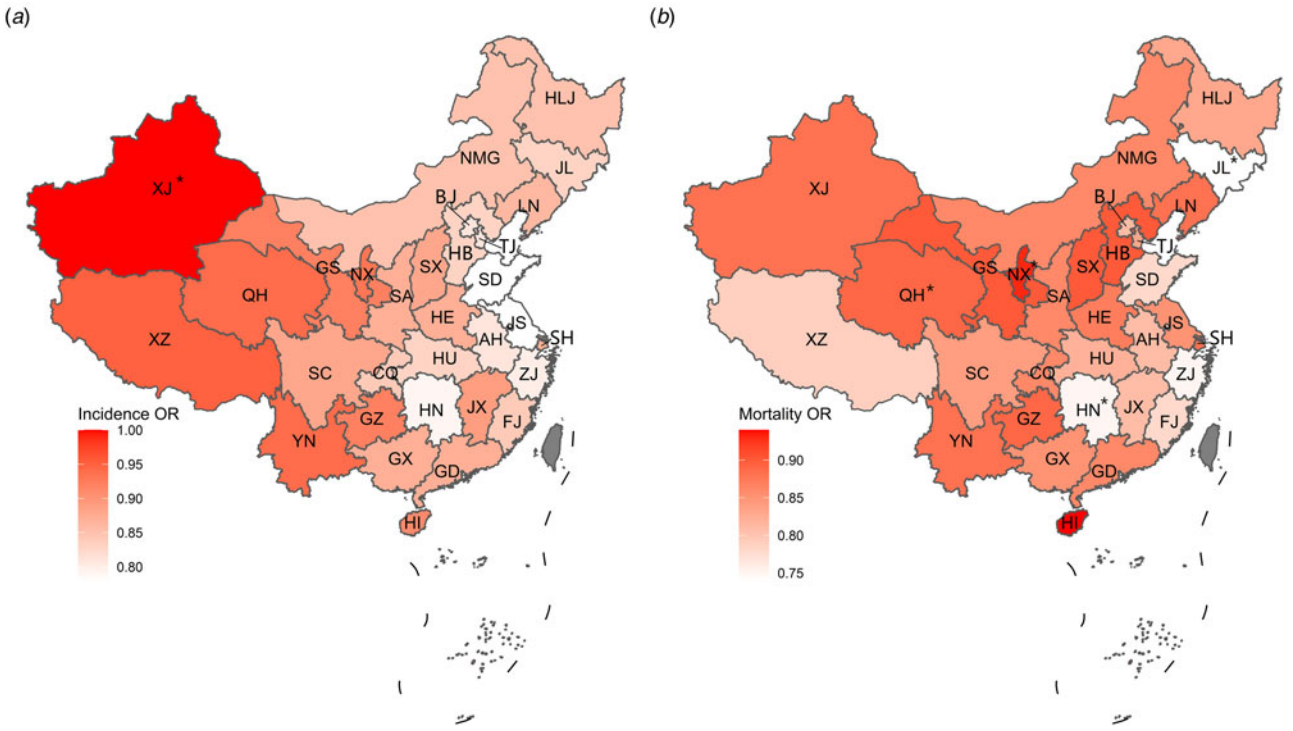

Fig. 2. Relative changes in hepatitis A RI (a) and mortality (b) in different provinces of China from 1990 to 2016. *$P > 0.05$ for incidence in XJ and for mortality in QH, NX, JL and HN. Changes in all other provinces were significant ($P < 0.05$; see Table 1). AH, Anhui; BJ, Beijing; CQ, Chongqing; FJ, Fujian; GD, Guangdong; GS, Gansu; GX, Guangxi; GZ, Guizhou; HB, Hebei; HE, Henan; HI, Hainan; HLJ, Heilongjiang; HN, Hunan; HU, Hubei; JL, Jilin; JS, Jiangsu; JX, Jiangxi; LN, Liaoning; NMG, Inner Mongolia; NX, Ningxia; QH, Qinghai; SA, Shaanxi; SC, Sichuan; SD, Shandong; SH, Shanghai; SX, Shanxi; TJ, Tianjin; XJ, Xinjiang; XZ, Tibet; YN, Yunnan; ZJ, Zhejiang.

Joinpoint patterns for incidence

Our joinpoint regression model of incidence indicated the presence of joinpoints in 2002, 2007 and 2012 (Fig. 5). Only the period of 2002–2006 had no statistically significant changes. The annual percent change (APC) was −15.2 (95% CI: −16.8 to −13.6) for the first period, −8.8 (95% CI: −17.8 to 1.2) for the second period, −18.4 (95% CI: −26.5 to −9.5) for the third period and −6.2 (95% CI: −11.3 to −0.9) for the fourth period. The average APC was −12.8 (95% CI: −15.2 to −10.4), and there was a significant change in the APC of incidence at the 2007 joinpoint. Analysis of mortality indicated a statistically significant joinpoint in 2006 (no significance in 2010). The APC was −14.5 (95% CI: −17.2 to −11.6) for the first period and −34.1 (95% CI: −61.9 to 14) for the second period, and −7.16 (95% CI: −11.6 to −3.4) for the third period. Because all the APC and average APC values for incidence and mortality were negative, this confirms decreasing trends in both parameters.

Effectiveness of EPI on infection and death based on ITS analysis

We also analysed the effect of the EPI on hepatitis A (Fig. 6). By generalised least squares estimation, linear regression is an appropriate model to use (the transformed Durbin–Watson statistic of incidence and mortality are 1.078 and 1.183, respectively). Before the EPI, the average incidence of hepatitis A was 21.3673/100 000 and decreased by an average of 2.9657/100 000 per year ($t = -11.274$; $P < 0.0001$). The average mortality rate was 0.0127/100 000 and decreased by an average of 0.0018164/100 000 per year ($t = -11.168$; $P < 0.0001$). After the EPI, the average incidence was 2.1617/100 000 and decreased by an average of 0.2571 per 100 000 per year ($t = 4.429$; $P < 0.0058$). Meanwhile, the average mortality was 0.0006/100 000 and declined by an average of 0.0000736 per 100 000 per year ($t = 4.609$; $P = 0.0031$).

Evidence of regional clustering

The global Moran's *I* for hepatitis A incidence in China was positive from 1990 to 2016, except for during 1994 (Table 3), indicating positive spatial autocorrelation. Additionally, Moran's *I* was significant ($P < 0.05$) from 1997 to 2000 and from 2002 to 2016. Analysis of mortality using Moran's *I* indicated significantly positive autocorrelation during several years. These results provide evidence for the spatial clustering of hepatitis A incidence and mortality in southwest and northwest China. To explore the relationship between this spatial clustering of hepatitis A and vaccination rates by province, we collected data on valid inoculation rate (%) among different ages since 2008 in each province. The result shows a large gap of inoculation rate (%) of children from 2 to 15 years old among different provinces since 2008, in which Yunnan and Gansu present a relatively lower vaccination rate in most age groups than other regions (Table S2).

Discussion

China has experienced great declines in the incidence and mortality of hepatitis A from 1990 to 2018. The control of hepatitis A in eastern, northern and northeastern regions of China is better than that in northwestern and southwestern regions, although the incidence and reported cases in the eastern

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Table 1. Relative change of hepatitis A RI and mortality in different provinces from 1990 to 2016

Region	Province	HAV RI in 2016 ($1/10^5$)	Relative change of incidence		HAV mortality in 2016 ($1/10^5$)	Relative change of mortality	
			OR (95% CI)	*P* value		OR (95% CI)	*P* value
All		1.5528	0.86 (0.85–0.87)	**<0.0001**	0.0004	0.84 (0.83–0.85)	**<0.0001**
North	Beijing	0.6496	0.81 (0.79–0.83)	**<0.0001**	0	0.81 (0.74–0.89)	**0.0002**
	Tianjin	0.3943	0.81 (0.79–0.83)	**<0.0001**	0	0.83 (0.71–0.96)	**0.0199**
	Hebei	0.5360	0.83 (0.82–0.85)	**<0.0001**	0.0013	0.90 (0.82–0.98)	**0.0223**
	Shanxi	2.6009	0.88 (0.87–0.90)	**<0.0001**	0	0.90 (0.85–0.96)	**0.0021**
	Inner Mongolia	0.8323	0.85 (0.84–0.86)	**<0.0001**	0	0.86 (0.81–0.90)	**<0.0001**
Northeast	Liaoning	6.7725	0.86 (0.84–0.88)	**<0.0001**	0	0.88 (0.84–0.92)	**<0.0001**
	Jilin	0.8644	0.83 (0.81–0.84)	**<0.0001**	0	0.74 (0.55–0.99)	0.0565
	Heilongjiang	0.7608	0.85 (0.84–0.87)	**<0.0001**	0.0026	0.83 (0.80–0.87)	**<0.0001**
East	Shanghai	0.9688	0.87 (0.85–0.88)	**<0.0001**	0	0.88 (0.82–0.94)	**0.0008**
	Jiangsu	0.7535	0.78 (0.76–0.81)	**<0.0001**	0	0.85 (0.83–0.88)	**<0.0001**
	Zhejiang	0.8576	0.80 (0.79–0.82)	**<0.0001**	0	0.75 (0.73–0.78)	**<0.0001**
	Anhui	0.8155	0.81 (0.80–0.83)	**<0.0001**	0	0.81 (0.78–0.85)	**<0.0001**
	Fujian	1.1748	0.84 (0.83–0.85)	**<0.0001**	0	0.78 (0.74–0.83)	**<0.0001**
	Jiangxi	0.5979	0.89 (0.88–0.91)	**<0.0001**	0	0.81 (0.78–0.83)	**<0.0001**
	Shandong	0.3788	0.78 (0.76–0.81)	**<0.0001**	0	0.78 (0.74–0.82)	**<0.0001**
Centre	Henan	0.2395	0.87 (0.85–0.89)	**<0.0001**	0	0.87 (0.81–0.93)	**0.0005**
	Hubei	1.4219	0.83 (0.82–0.85)	**<0.0001**	0	0.82 (0.79–0.84)	**<0.0001**
	Hunan	0.8398	0.79 (0.76–0.81)	**<0.0001**	0.0015	0.75 (0.69–0.83)	**<0.0001**
South	Guangdong	1.4812	0.87 (0.86–0.89)	**<0.0001**	0	0.86 (0.82–0.90)	**<0.0001**
	Guangxi	1.1739	0.87 (0.85–0.88)	**<0.0001**	0.0021	0.85 (0.82–0.88)	**<0.0001**
	Hainan	0.6807	0.91 (0.89–0.93)	**<0.0001**	0	0.94 (0.84–1.06)	0.3230
Southwest	Chongqing	2.9371	0.84 (0.82–0.86)	**<0.0001**	0	0.86 (0.76–0.97)	**0.0241**
	Sichuan	2.4122	0.88 (0.86–0.89)	**<0.0001**	0.0012	0.84 (0.82–0.86)	**<0.0001**
	Guizhou	0.7791	0.92 (0.90–0.94)	**<0.0001**	0	0.89 (0.86–0.93)	**<0.0001**
	Yunnan	2.0920	0.94 (0.92–0.96)	**<0.0001**	0	0.88 (0.85–0.91)	**<0.0001**
	Tibet	2.3768	0.95(0.93–0.98)	**0.0004**	0	0.79(0.76–0.82)	**<0.0001**
Northwest	Shaanxi	0.7778	0.87(0.85–0.88)	**<0.0001**	0	0.86(0.80–0.93)	**0.0004**
	Gansu	2.6197	0.92(0.90–0.94)	**<0.0001**	0	0.90(0.86–0.94)	**<0.0001**
	Qinghai	5.5742	0.94(0.93–0.95)	**<0.0001**	0	0.89(0.76–1.05)	0.1770
	Ningxia	2.5454	0.93(0.91–0.95)	**<0.0001**	0	0.93(0.83–1.06)	0.2820
	Xinjiang	15.1525	1.00(0.98–1.02)	0.9640	0	0.88(0.85–0.91)	**<0.0001**

CI, confidence interval; OR, odds ratio.
Linear models were applied to the RI and mortality data on the logit scale. Relative changes in incidence and mortality during the study period are presented as ORs relative to 1990. The bold values are of great statistical significance ($P < 0.05$).

and northern regions were highest during the early 1990s [20]. This may be related to differences in per capita GDP, the quality of drinking water and general sanitation practices in these regions [20]. The greatest relative decreases in incidence were in Hunan, Shandong and Jiangsu, and the decline in incidence was slowest in Xinjiang, Qinghai and other provinces in northwestern China. These differences are likely related to differences in hygiene awareness, economic conditions and access to clean drinking water and sanitation practices [21]. For instance, the use of sanitary toilets in central and western China is obviously less than that in eastern regions [22], where 17 million households have serious hygiene issues resulting from poor toilets [23]. Another similar study also showed that drinking water and sanitation access varied markedly among provinces, in that there was 99% coverage in Shanghai but only 23% coverage in Tibet [24].

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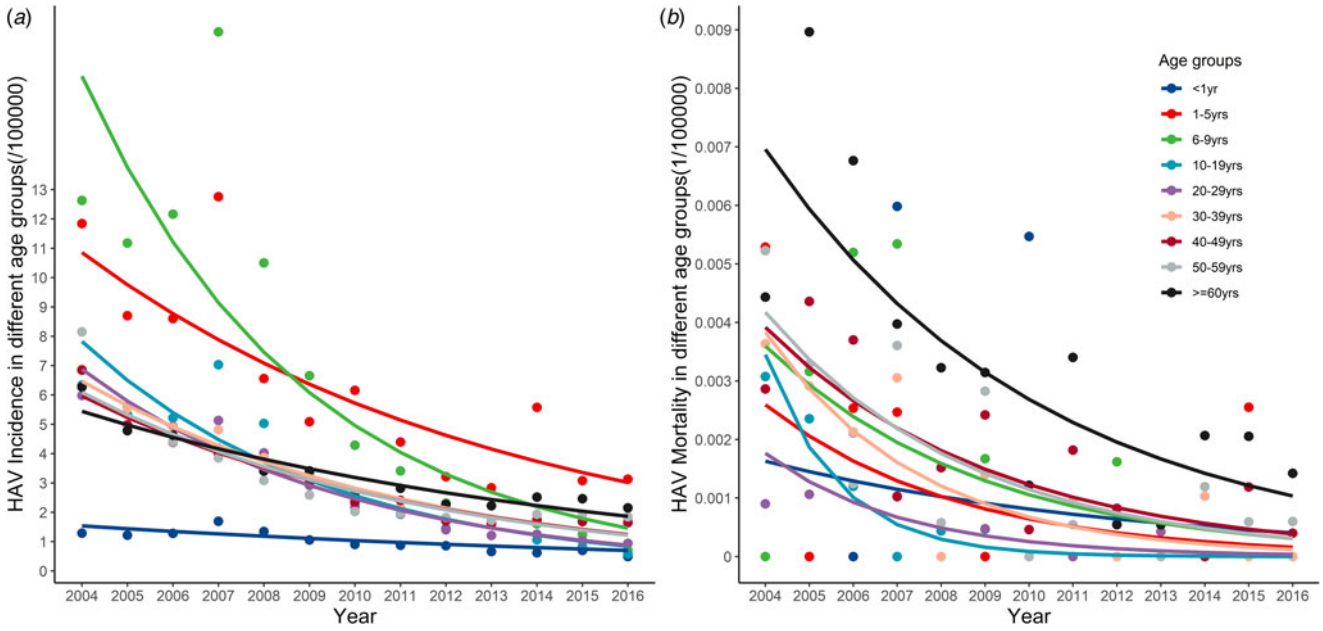

Fig. 3. Annual RI (a) and mortality (b) of hepatitis A in China in different age groups from 2004 to 2016. The lines are fits to logistic regression equations.

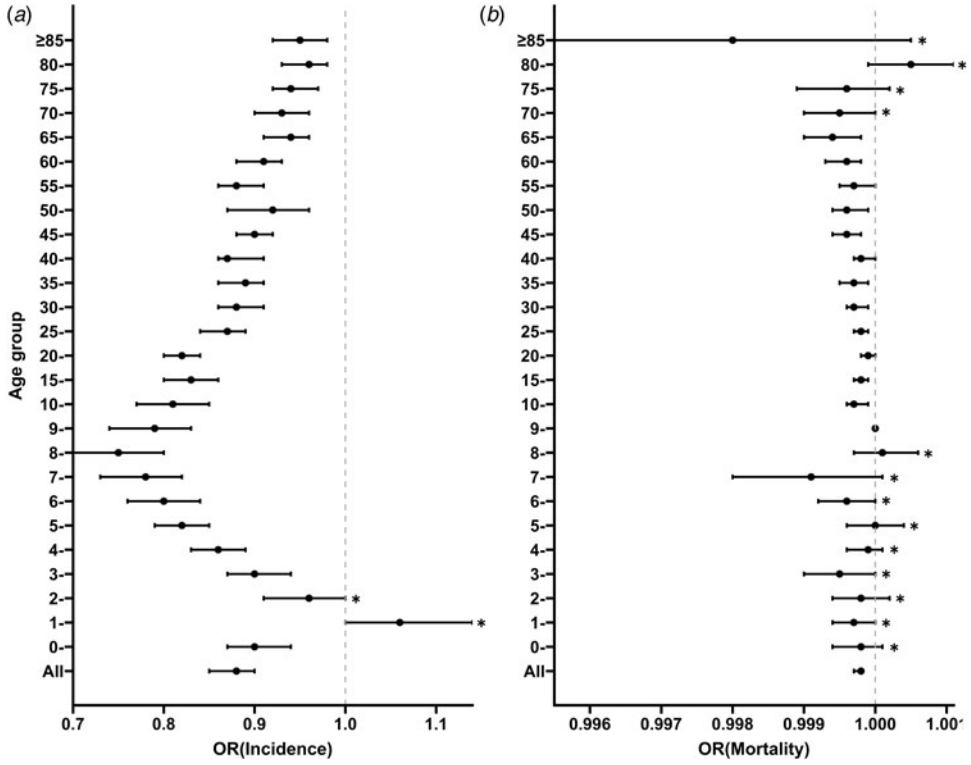

Fig. 4. Relative change in hepatitis A incidence (a) and mortality (b) in different age groups from 2004 to 2016. *$P > 0.05$.

The western provinces had severe epidemics of hepatitis A, with the highest incidences compared to other provinces during 2016. This pattern is similar to those of other infectious diseases that are also targeted by vaccines [25, 26]. Our results on valid inoculation rate (%) among different age groups since 2008 in each province show large gap, especially in Yunnan and Gansu. Although the data are incomplete even missing in some provinces, it can be associated with the spatial clustering of hepatitis A incidence and mortality in southwest and northwest China, suggesting there may be problems in the routine immunisation of children in these areas. Another interesting phenomenon is that the only increase of hepatitis A incidence in recent years was in Liaoning, which might be ascribed to the consumption of contaminated seafood from coastal areas [27]. Further investigations

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Table 2. Relative change of hepatitis A RI and mortality in different age groups from 2004 to 2016 (comparison is relative to 2004)

		Relative change of incidence		Relative change of mortality	
Age, years	HAV RI in 2016 (/10^5)	OR (95% CI)	*P* value	OR (95% CI)	*P* value
All	1.55	0.88 (0.85–0.90)	**<0.0001**	0.9998 (0.9997–0.9998)	**0.0002**
<1	0.49	0.90 (0.87–0.94)	**0.0005**	0.9998 (0.9994–1.0001)	0.2374
1 to <2	2.69	1.06 (1.00–1.14)	0.0892	0.9997 (0.9994–1.0000)	0.1112
2 to <3	4.18	0.96 (0.91–1.00)	0.1067	0.9998 (0.9994–1.0002)	0.3548
3 to <4	3.71	0.90 (0.87–0.94)	**0.0009**	0.9995 (0.9990–1.0000)	0.0596
4 to <5	3.02	0.86 (0.83–0.89)	**<0.0001**	0.9999 (0.9996–1.0001)	0.4467
5 to <6	1.88	0.82 (0.79–0.85)	**<0.0001**	1.0000 (0.9996–1.0004)	0.8555
6 to <7	1.33	0.80 (0.76–0.84)	**<0.0001**	0.9996 (0.9992–1.0000)	0.0805
7 to <8	0.62	0.78 (0.73–0.82)	**<0.0001**	0.9991 (0.9980–1.0001)	0.1169
8 to <9	0.43	0.75 (0.70–0.80)	**<0.0001**	1.0001 (0.9997–1.0006)	0.6147
9 to <10	0.65	0.79 (0.74–0.83)	**<0.0001**	1[a]	
10 to <15	0.60	0.81 (0.77–0.85)	**<0.0001**	0.9997 (0.9996–0.9999)	**0.0061**
15 to <20	0.55	0.83 (0.80–0.86)	**<0.0001**	0.9998 (0.9997–0.9999)	**0.0022**
20 to <25	0.60	0.82 (0.80–0.84)	**<0.0001**	0.9999 (0.9998–1.0000)	0.0852
25 to <30	1.36	0.87 (0.84–0.89)	**<0.0001**	0.9998 (0.9997–0.9999)	**0.0041**
30 to <35	1.81	0.88 (0.86–0.91)	**<0.0001**	0.9997 (0.9996–0.9999)	**0.0012**
35 to <40	1.76	0.89 (0.86–0.91)	**<0.0001**	0.9997 (0.9995–0.9999)	**0.0064**
40 to <45	1.73	0.87 (0.86–0.91)	**<0.0001**	0.9998 (0.9997–1.0000)	**0.0389**
45 to <50	1.57	0.90 (0.88–0.92)	**<0.0001**	0.9996 (0.9994–0.9998)	**0.0048**
50 to <55	2.42	0.92 (0.87–0.96)	**0.0034**	0.9996 (0.9994–0.9999)	**0.0364**
55 to <60	1.33	0.88 (0.86–0.91)	**<0.0001**	0.9997 (0.9995–1.0000)	**0.0456**
60 to <65	2.07	0.91 (0.88–0.93)	**<0.0001**	0.9996 (0.9993–0.9998)	**0.0129**
65 to <70	2.16	0.94 (0.91–0.96)	**0.0006**	0.9994 (0.9990–0.9998)	**0.0085**
70 to <75	2.13	0.93 (0.90–0.96)	**0.0004**	0.9995 (0.9990–1.0000)	0.0527
75 to <80	2.21	0.94 (0.92–0.97)	**0.0020**	0.9996 (0.9989–1.0002)	0.1970
80 to <85	2.36	0.96 (0.93–0.98)	**0.0091**	1.0005 (0.9999–1.0011)	0.1151
≥85	2.20	0.95 (0.92–0.98)	**0.0144**	0.9980 (0.9955–1.0005)	0.1484

CI, confidence interval; OR, odds ratio; RI, reported incidence.
Linear models were applied to the RI and mortality data on the logit scale. Relative changes in incidence and mortality during the study period are presented as OR relative to 2004.
[a]No reported deaths in this age group from 2004 to 2016.
The bold values are of great statistical significance ($P < 0.05$).

should seek to identify risk factors in an effort to reduce the outbreaks of hepatitis A. The hepatitis A mortality rate has had an overall downward trend throughout the country, indicating successful overall prevention and treatment interventions during recent years.

Our analysis of hepatitis A also indicated declining trends for incidence and mortality in all age groups. The highest incidence was in the 2–10-year-old group during 2004 (specific data on age is 2004–2016). Nevertheless, hepatitis A was relatively common among older adults (>50 years old) and preschool children (1–5 years old) in 2016. We can suggest four possible explanations for this: (i) the national HAV vaccination programme for newborns and catch-up vaccinations for children provided inadequate protection of older adults [28]; (ii) the weaker immune responses of young children and older adults makes them more vulnerable to infection; (iii) there was a low vaccination rate among children in some rural regions [29] and (iv) insufficiency of specific hygienic measures for children in institutions such as nurseries [30] and schools. Since HAV is transmitted via the faecal–oral route, high hepatitis A infection can be contributed by inadequate habits of hygiene, intensive contact and susceptibility in children [31]. The decline in the overall incidence of hepatitis A in China has led to the elderly becoming a high-risk group. Thus, further efforts are needed to protect the youngest and oldest age groups in China from hepatitis A.

Our joinpoint regression model indicated that key points and different stages in the epidemiology of hepatitis A can be explained by major policy changes. For example, the outbreak of hepatitis A in Shanghai during 1988 accelerated the use of vaccination. Thus, the Chinese government permitted L-HepA in

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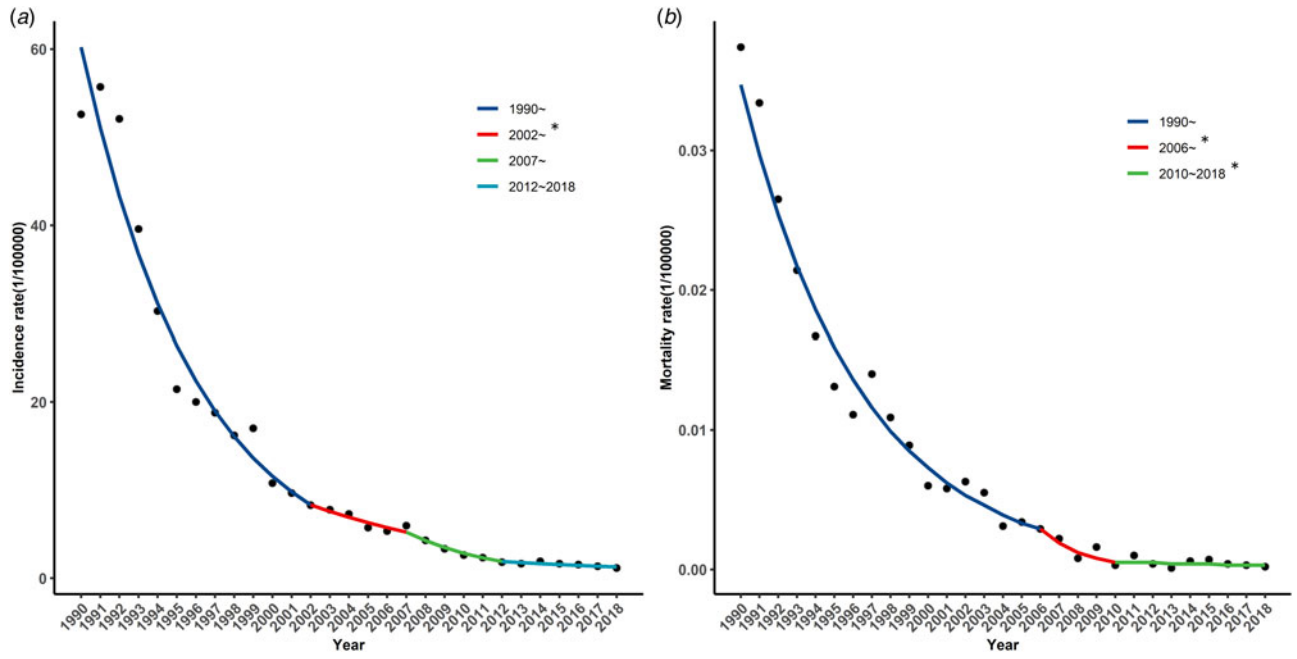

Fig. 5. Joinpoint regression analysis of hepatitis A RI (a) and mortality (b) from 1990 to 2018. *$P > 0.05$; APC in other periods was significantly different from zero ($P < 0.05$).

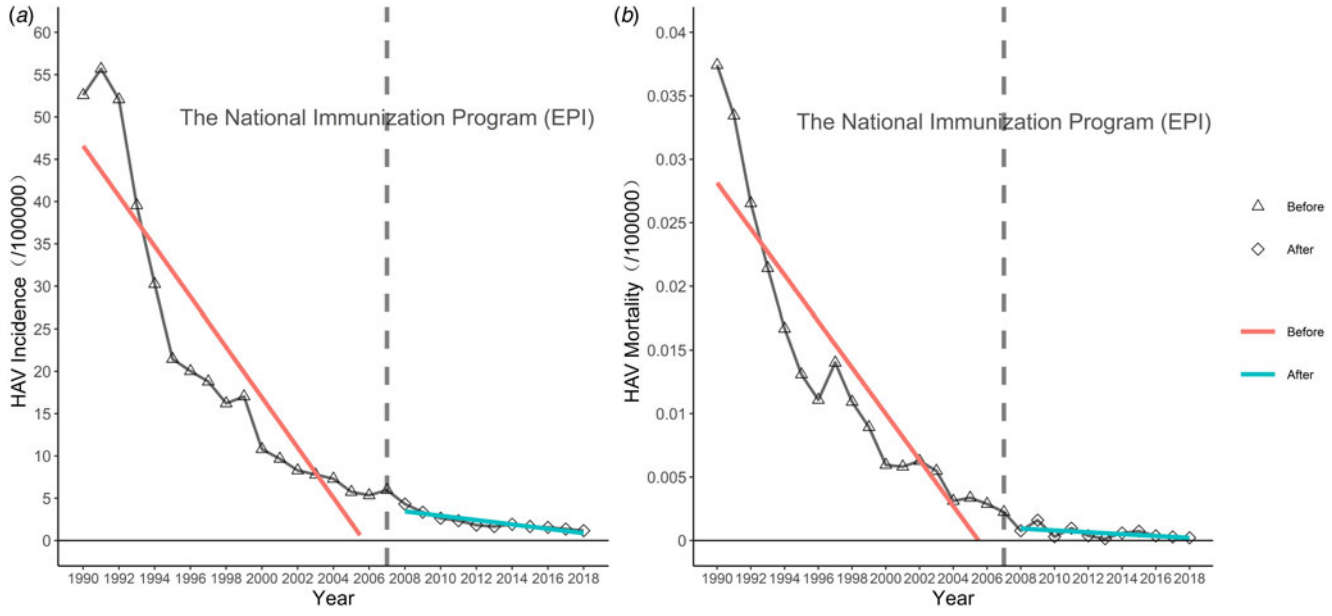

Fig. 6. ITS analysis of the RI (a) and mortality (b) of hepatitis A from 1990 to 2018 based on level and slope change.

1992 and I-HepA was licensed in 2002 [7]. In 2007, hepatitis A vaccination was included in the nationwide EPI, and I-HepA was subsequently administered as a free childhood vaccine [32]. In 2010, the World Health Assembly adopted resolutions to take comprehensive measures for the prevention and control viral hepatitis, and updated its recommendations on use of hepatitis A vaccines in 2012 [33].

We, therefore, attribute the main decline in the incidence and mortality of hepatitis A in China to the increased use of vaccination, as described previously [9]. To reduce the burden of liver diseases caused by the different hepatitis viruses, the Chinese government has continuously increased investments in prevention and control measures for prevention of infections by HAV [34], hepatitis B virus and hepatitis C virus [35]. Based on our ITS analysis, the incidence and mortality of hepatitis A significantly decreased after inclusion of hepatitis A vaccine in EPI (the average incidence of hepatitis A was 2.1617/100 000 and decreased by an average rate of 0.2571/100 000 per year), showing the EPI strategy had a continuous effect on the decreasing trend of hepatitis A burden. This supports other evidence [10] that the EPI reduced infections and deaths from hepatitis A. However, the observed decrease of hepatitis A incidence and mortality during 1990–2018 was a

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Table 3. Global spatial autocorrelation analysis of RI and mortality of hepatitis A in China from 1990 to 2016

Year	Moran's *I* value			Moran's *I* value		
	Incidence	*Z* value	*P* value	Mortality	*Z* value	*P* value
1990	0.0327	0.8305	0.4062	0.0510	1.0877	0.2767
1991	0.0176	0.6455	0.5186	0.1366	2.4155	**0.0157**
1992	0.1077	1.8141	0.0697	−0.0062	0.4265	0.6697
1993	0.0666	1.2800	0.2006	−0.1038	−0.9075	0.3641
1994	−0.0158	0.2344	0.8147	0.1767	3.2066	**0.0013**
1995	0.0441	0.9928	0.3208	0.1699	2.5934	**0.0095**
1996	0.0655	1.2308	0.2184	−0.0445	−0.1266	0.8993
1997	0.1685	2.5630	**0.0104**	0.0229	1.4110	0.1582
1998	0.2933	4.4448	**<0.0001**	0.1008	1.8399	0.0658
1999	0.1479	2.4001	**0.0164**	0.1299	2.1123	**0.0347**
2000	0.2631	3.9406	**0.0001**	0.0124	0.6953	0.4869
2001	0.0850	1.6872	0.0916	0.0625	1.4724	0.1409
2002	0.1489	2.4396	**0.0147**	0.0621	1.3238	0.1856
2003	0.2757	4.0714	**<0.0001**	0.0420	1.3421	0.1796
2004	0.3269	4.7695	**<0.0001**	0.1484	2.4974	**0.0125**
2005	0.2730	4.3223	**<0.0001**	0.0801	1.5233	0.1277
2006	0.2991	4.5244	**<0.0001**	0.3264	4.8098	**<0.0001**
2007	0.1885	3.0865	**0.0020**	−0.0693	−0.4984	0.6186
2008	0.2847	4.1825	**<0.0001**	0.0288	0.8565	0.3917
2009	0.2934	4.3710	**<0.0001**	−0.0234	0.1624	0.8710
2010	0.1987	3.4479	**0.0006**	−0.0368	−0.0499	0.9602
2011	0.2367	3.7882	**0.0002**	−0.0391	−0.0777	0.9381
2012	0.2592	4.1320	**<0.0001**	0.0941	1.7875	0.0739
2013	0.2090	3.4644	**0.0005**	−0.0418	−0.1402	0.8885
2014	0.0934	2.5732	**0.0101**	−0.0818	−0.6894	0.4906
2015	0.1505	3.0105	**0.0026**	0.0278	0.8602	0.3897
2016	0.0860	2.0075	**0.0447**	−0.0605	−0.3799	0.7040

The bold values are of great statistical significance ($P < 0.05$).

complicated process, because the incidence and mortality of hepatitis A has declined to a relatively low level under the comprehensive prevention and control measures based on vaccination during 2007–2018. Therefore, the role of hepatitis A vaccine in reducing the incidence of hepatitis A may be underestimated after it was included in the EPI. A study in 2012 found that the universal childhood hepatitis A vaccination would decrease 20 deaths and 51 deaths per million in the regions with higher and highest infection rates of China, respectively [36]. Bauch's result showed that universal hepatitis A vaccine for children aged 1, 4, 9 and 15 years would, respectively, reduce 60%, 52%, 36% and 3% of cases and reduce the fatality rate of hepatitis A by 56%, 45%, 26% and 25% apart [37]. It is a pity that we could not distinguish the specific contribution of the EPI by ITS because data on water quality, urbanisation, economic level, health care service level and environmental sanitation are unavailable for us, but our results certainly showed that the EPI strategy had a continuous effect on the decreasing trend of hepatitis A burden.

Since the 1980s, access to safe drinking water and sanitation has been national priorities within China's rural development projects [22]. Access to sanitary toilets in rural areas has increased from 7.5% in 1993 to 78.5% in 2015, and access to 'harmless sanitary toilets' in rural areas was 57.5% by the end of 2015 [23]. However, there are still 280 million rural and urban people in China without safe drinking water [38]. Urban drinking water is far superior to rural drinking water in China, and provinces with poor water quality are mainly in the economically underdeveloped and rural areas of central and western China, such as Yunnan and Guizhou [39].

Areas with high rates of viral transmission have lower rates of severe morbidity and mortality compared to areas with low transmission rates, mainly because there are fewer susceptible adults in areas with high-transmission rates [40]. Although the disease burden caused by acute hepatitis A has rapidly decreased in China, there is still a probability of outbreaks due to increases in the infection of susceptible individuals, especially the elderly [41]. Moreover, hepatitis A will remain a public-health challenge as

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long as people engage in unhealthy habits, such as insufficient hand-washing [42] and eating raw food [43], and have limited access to high-quality drinking water, especially in western China [44]. Therefore, implementing more effective measures to prevent and treat hepatitis A and preventing outbreaks of hepatitis A and in specific regions and populations are keys to controlling hepatitis A in the future.

Some limitations of our study should be noted. First, the data on HAV infections and deaths were from a passive surveillance system and there may be some under-reporting, especially during the earlier years, and this could have led to underestimates of incidence and mortality in some provinces. Second, because of the introduction of improved clinical testing methods, the number of false-positives has likely declined over time, and this could have affected our reported time trends. Third, the increased access to health care likely increased the use of testing, and this may have increased the number of people testing positive for HAV. These limitations might have altered our reported temporal trends in the incidence and mortality of hepatitis A.

In conclusion, we used a longitudinal dataset spanning 29 years to investigate hepatitis A incidence and death in China. Our results indicated that some western provinces had more severe epidemic areas. We also found that school children, adolescents and adults were mostly well-protected from HAV infection, but there were higher incidences in older people and preschool children. In addition, all the key epidemiological changes identified by our joinpoint regression model were related to changes in vaccine policy, thus indicating that routine immunisation is an indispensable measure for prevention of hepatitis A. Our ITS analysis indicated that inclusion of the hepatitis A vaccine in the EPI promoted the decline in the numbers of hepatitis A infections and deaths in China. Increasing the vaccination rate, improving hygiene conditions and providing access to high-quality of drinking water in rural areas are key measures needed to control hepatitis A in China.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0950268821001552

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Author contributions. ZW and BZ designed the study. JP extracted the data and constructed the database. BZ and ZW analysed the data and drafted the manuscript. WW and JP conducted critical revisions of the manuscript. All authors read and approved the final manuscript.

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Conflict of interest. The authors declare that they have no known competing financial interests or personal relationships that could influence the work reported in this paper.

Ethical standards. This study does not use any personal information and animals were not involved. Therefore, no ethical approval was necessary.

Data availability statement. Readers may contact the authors for accessing data used in this study.

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