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Changing incidence of reported viral hepatitis in China from 2004 to 2016

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Title: Changing incidence of reported viral hepatitis in China from 2004 to 2016

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Specific author contributions: MZ was first author, MZ wrote the first draft of the manuscript, collected data in the study site, RW, HX assisted MZ to run the study, interpret the data, JU, RGG contributed in manuscript discussion. XW, QJ contributed to the data collection. GYM, MHN contributed to data analysis and interpretation and major revision of the manuscript. YG advised on study design and contributed to the manuscript discussion. The corresponding author JN designed and organised the study and had full access to all the data in the study and had final responsibility for the decision on content and publication submission.

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Changing incidence of reported viral hepatitis in China from 2004 to 2016

Abstract:

Objective: China's hepatitis burden is high in the world. This study aim to provide a detailed national-level description of the reported incidence of viral hepatitis in China during 2004 -2016.

Design: Observational study

Setting: Data were obtained from China's National Notifiable Disease Report System, reported trends were estimated by Joinpoint regression analysis

Participants: In this system, 16,927,233 patients with viral hepatitis during 1995–2015 were identified

Primary outcome measure: Incidence rates per 100 000 person-years and 95% CIs were calculated.

Results: There were 16,927,233 new cases of viral hepatitis reported in China from 2004 to 2016. Hepatitis B (n=13,543,137, 80.00%) and hepatitis C (n=1,844,882, 10.90%) accounted for >90% of cases. Overall APC of reported cases of viral hepatitis and hepatitis B were 0.3% (95% CI -2.0 to 0.8, P=0.6), and -0.2% (95% CI -1.6 to 1.2, P=0.8), respectively, a stable trend. HBV rates were highest in the 20-29 age group and lowest in younger ages, consistent with the universal HBV vaccination. Reported incidence of HCV and HEV showed increased trends, the APC was 14.5% (95% CI 13.1 to 15.9, P<0.05) and 4.7% (95% CI 2.8 to 6.7, P<0.05), respectively. Hepatitis A reporting decreased, APC was -13.1% (95% CI -15.1 to -11.0, P<0.05). There were marked differences in the reporting of hepatitis amongst provinces.

Conclusions: Hepatitis B continue to constitute the majority of viral hepatitis cases in China. Over the entire study period, HBV reporting was stable, HCV and HEV increased, while HAV decreased. There were significant interprovincial disparities in the burden of viral hepatitis with higher rates in economically less developed areas. Vaccination is important for viral hepatitis prevention and control.

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Strengths and limitations of this study

► Latest comprehensive descriptions of trends in the national and provincial reporting incidence for viral hepatitis in China, since 2004, were provided.

► Highlights the magnitude and importance of viral hepatitis in China, provide key data to help determine where efforts need to be focused.

► We analysed age distribution among different types of viral hepatitis, provided the prevalence characteristics of viral hepatitis in China.

► Since the studies collected data almost across the whole country, heterogeneity across reporting centers were existed, which might be the weakness.

Introduction

Viral hepatitis is an important challenge to public health globally. In 2013, the greatest number of deaths and disability-adjusted life years (DALYs) attributable to viral hepatitis, occurred in East and South Asia, including China.[1] According to WHO, approximately 100 million people in China – that's 1 in 13 people – are living with chronic HBV and HCV infection.[2] In 2016, the WHO approved the first global health sector strategy on viral hepatitis, with the goal of eliminating viral hepatitis as a major public health threat by 2030.[3] To achieve this goal, a review of the current status of viral hepatitis and the different types was essential. Since Age distribution is an important for obtaining a clear understanding of changing trends in viral hepatitis reporting, and its future burden. China is a vast and diverse country with 32 provinces, province-level data are also required for effective disease prevention, control and management. Therefore, the present study examined the reported rates of newly diagnosed cases of viral hepatitis and documented temporal trends across age groups and provinces.

Materials and Methods

In 2004, the Chinese government established a centralized web-reporting system for notifiable infectious diseases and public health emergencies. The fundamental database for this project was

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maintained by the Chinese Communicable Disease Control(CCDC). A standardized case reporting form (CRF) was established for the collection of demographic and diagnostic information for each case afflicted by reportable diseases (Appendix Table1).

We collected data for viral hepatitis between 2004 and 2016 from the Center's website [4,5]and the Health Yearbooks.[6] In this system, cases were defined with diagnostic criteria issued by the law on the prevention and control of infectious diseases of the People's Republic of China in 2004.(Appendix Table2). Based on patient histories, clinical manifestations, and laboratory test results, cases were categorized as hepatitis A, B, C, E and unidentified hepatitis. [7] In this research, unidentified hepatitis cases were excluded. For provincial analyses, Hong Kong, Macao and Taiwan were not enrolled in this research.

Incidence (per 100,000) was defined as the number of annual newly diagnosed cases divided by the population size. What should be mentioned that, in this surveillance system the cases were newly diagnosed rather than new infections, to avoid misunderstanding, we used reported incidence in this research.

Statistical analysis

Descriptive epidemiological methods were used to examine and analyze reported data. APC (*Annual percent change*), AAPC (*Average annual percent change*) and 95% confidence intervals (CI) were calculated for viral hepatitis overall and for individual categories of viral hepatitis (A, B, C, and E). Additionally, we investigated trends and made comparisons among different provinces by heatmap. For age distributions, cases were divided annually into 10 groups for each category of viral hepatitis. Joinpoint regression models were used to describe temporal trends in the reporting of newly diagnosed cases. In describing trends, we used the terms "increase" and "decrease" when the slope (APC) was significant (two-tailed $P< 0.05$). The term "stable" refers to a non-significant annual percent change ($P \geq 0.05$) and indicates the incidence was maintained at a perennially stable level. R language (version 3,3.0) and Joinpoint (version 4.6.0.0, April,2018, IMS, Inc., https://surveillance.cancer.gov/joinpoint/) were used in this study. The conduct of this study was consistent with the Declaration of Helsinki.

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Patient and public involvement

No patients were involved in developing the research question or the outcome measures, no patients were involved in planning the design, recruitment to and conduct of the study. The data were collected from the on-line reporting system, patients were anonymous， we are unable to disseminate the results of the research directly to study participants.

Results

National and Provincial reporting incidence of viral hepatitis

National reporting incidence

Between 2004 and 2016, a total of 16,927,233 newly diagnosed cases of viral hepatitis were reported in China. Hepatitis B (n=13,543,137, 80.00%) and hepatitis C (n=1,844,882, 10.90%), jointly accounted for over 90% of cases. The remaining cases consisted of the following: 595,982 (3.52%) hepatitis A and 300,505 (1.78%) hepatitis E. (Figure 1)

Viral hepatitis reporting incidence increased from 85.49/100,000 in 2004 to 108.44/100,000 in 2007 (P<0.05). After 2007, there was a significant downward trend to 89.11/100,000 in 2016(P<0.05). Overall, the APC was 0.3% (95% CI -2.0 to 0.8, P=0.6), indicating a stable trend. (Appendix Figure1.1)

Reporting incidence for hepatitis B increased from 2004 (67.96/100,000) to 2009 (88.82/100,000), and then decreased in 2016(68.74/100,000). From 2004 to 2007, the APC was 10.3% (95% CI 4.1 to 16.9, *P*<0.05), while from 2007 to 2016, the APC was -3.5% (95% CI -4.5 to -2.5, *P*<0.05). Overall, the APC of hepatitis B was -0.2% (95% CI -1.6 to 1.2, P=0.8), indicated a stable trend (Appendix Figure1.2).

Reporting incidence for HCV increased from 2004 (2.92/100,000) to 2016 (15.09/100,000). From 2004 to 2007, the APC was 34.4% (95% CI 27.7 to 41.3, *P*<0.05), indicating a significant increase. Thereafter, the APC from 2007 to 2012 was 15.9% (95% CI 13.6 to 18.2, *P*<0.05),

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indicating a significant but slower increase, and from 2012 to 2016, the APC was 0.1% (95% CI -1.5 to 1.7, *P*=0.9), indicating a stable trend. Overall, the APC was 14.5% (95% CI 13.1 to 15.9, P<0.05), indicating an increased trend (Appendix Figure1.3).

For hepatitis A, the reporting incidence decreased from 2004 (6.94/100,000) to 2016 (1.55/100,000). The APC for the entire period was -13.1% (95% CI -15.1 to -11.0, *P*<0.05) (Appendix Figure1.4). For hepatitis E, reporting incidence increased from 1.22/100,000 in 2004 to 2.18/100,000 in 2011, with the APC of 8.1% (95% CI 5.2 to 11.0, *P*<0.05). From 2011 to 2016, they decreased to 2.04/100,000, APC was stable (0.3%; 95% CI -3.4 to 4.1, *P*=0.9). Overall, the APC for hepatitis E was 4.7% (95% CI 2.8 to 6.7, P<0.05), indicating an increasing trend (Appendix Figure1.5).

Detailed information of Joinpoint analysis results are provided in Appendix Table 3.

Reporting incidence in relation to age

Marked differences in the reporting incidence of hepatitis B were evident amongst the various age groups. Overall, HBV reporting incidence were highest in the 20-29 age group. When divided into those 20-25 and 26-29 years of age, the highest incidence were in the 26-29 group. The lowest reporting incidence of viral hepatitis occurred in the age group between 1 and 9 years old. In terms of trends from 2004 to 2013, the ages "<1", "30-39", "40-49" were stable, while those "1-9", "10-19", "20-29" decreased. Reporting incidence for all subjects over the age of 50 increased. More recently (beyond 2007), most age groups showed a significant decrease or stable trend, however, the trend increased in the "50-59" age group. (Figure 2)

For hepatitis C, aside from the <1 age group, reporting incidence in the different age groups increased with age. The highest reporting incidence were in those >80 years and the lowest in those between 1 and 19 years of age. From 2004 to 2013, each age group showed an increasing trend but more recently (beyond 2011) rates were stable in the "10-19", "30~39", "30~49" age groups. (Figure 3)

For hepatitis A, the highest reporting incidence were in the "1~9" age group with incidence

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in the “5-9” group being higher than the “1-4” age group. The lowest reporting incidence was in the “Age<1” group. In terms of trends, incidence in the “5~9” group were stable as were those in the “10~29” age group after 2007. All the other age groups showed decreasing trends during this period. (Figure 4)

For hepatitis E, the highest reporting incidence were in the older age group (60-79 years). Aside from the “1~9” age group, where incidence was stable and the “Age>=80” where incidence decreased after 2011, the other age groups showed increasing trends during this period. (Figure 5)

More detailed information is provided in Appendix Table 4.

Provincial incidence

In 2015, analysis of reporting incidence for viral hepatitis demonstrated that Xinjiang was the province with the highest rates (>200/100,000). Qinghai, Hainan, Guangdong, Shanxi, Fujian, Hubei, Inner Mongolia, Guangxi, and Hunan provinces had intermediate rates (>100 and <200/100,000); while Shanghai, Heilongjiang, Zhejiang, Jiangsu, Tianjin, Beijing had the lowest rates (<50/100,000). Specific analyses for hepatitis B and hepatitis C by province are provided in Appendix Figure 2.

To document trends in reporting incidence for viral hepatitis from 2004 to 2015 by provinces, data and a heatmap of reporting incidence for viral hepatitis in general as well as for the different viruses are provided in Appendix Figure 3,4. For most provinces, reporting incidence for hepatitis A have decreased, while those for hepatitis C have increased. Most northern areas of China (Beijing, Tianjin, Hebei, Liaoning, Jilin, Heilongjiang) had decreasing incidence of hepatitis E reporting, while the other provinces (Jiangxi, Shandong, Hubei, Guangxi, Hainan, Chongqing, Sichuan, Guizhou, Yunnan) revealed increasing trends.

Discussion

Viral hepatitis is a significant global public health issue, it is responsible for an estimated 1.4

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million deaths per year from acute infection and hepatitis-related liver cirrhosis and cancer. Of those deaths, approximately 47% are attributable to hepatitis B, 48% hepatitis C and the remainder, hepatitis A and hepatitis E infections.[1] In 2015, an estimated 257 million people were living with chronic HBV infections and 71 million chronic HCV infections.[8] China's hepatitis burden is the highest in the world: according to WHO, one-third of the world's 240 million people living with chronic HBV are in China, while approximately 7% of the world's 130-150 million people living with HCV are in China [2].

In this study, HBV reporting incidence were lowest in children under 10 years of age and highest in the "20~29" age group. Similar results have been reported previously. [9] Further analysis of the "20-29" age group revealed that those "25-29" years of age (i.e. born in 1975-1988) had significantly higher reporting incidence than the "20-24" age group, suggesting a possible vaccine effect. Indeed, the hepatitis B vaccine was first introduced into China in 1985, and integrated into the National Expanded Program on Immunization (EPI) in 1992[10]. Thus, the majority of individuals in the "25-29" age group were born in a period without HBV vaccine protection and hence, susceptible to transmission via the maternal-infant route. Of note, HBV reporting in individuals older than 50 years, showed an increase from 2004 to 2013. This could be explained by: (1) the elderly being more likely to establish contact with the health care system. (2) A higher prevalence of chronic HBV and therefore, greater likelihood of presenting with complications such as portal-hypertensive bleeding, encephalopathy, ascites, jaundice or HCC leading to diagnosis of HBV-related disease. (3) Behaviors like sexual contact, invasive medical procedures, sharing shavers and towels with HBV carriers were independent risk factors for acute hepatitis B, which is an important way for HBV transmission in adult. (4) Older groups didn't have vaccine protection in the early age, they would be more easier to be infected with HBV, after successfully vaccination for children, to decrease the prevalence of HBV, vaccination among people aged from 15~59 years old should also be conducted. [11]

Regarding hepatitis C, reporting incidence increased with age, the lowest incidence occurred in children and adolescents, while the highest incidence was documented in the "Age>=80" group. However, from 2004 to 2013, reporting incidence increased in all age groups, which likely reflects

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increased disease awareness, older individuals seeking medical care, increases in new infections, progression to complications of cirrhosis, and adopting new generation HCV testing[8,12,13]. Of note, in China, the implementation of HCV screening of blood donors and products occurred in 1993,[14] and associated with this intervention was a decline in transfusion-related HCV from 72% to 47%.[13] However, relatively high rates of HCV infections among patients undergoing hemodialysis and other invasive therapies and high-risk sexual behaviours remain a potential source for HCV transmission.[15] While the success achieved with recent directing antiviral agents (DAA) for chronic HCV predict further declines in HCV reporting, complete eradication of HCV might not be possible without an effective vaccine.[16]

Provincial analyses demonstrated large differences in reporting incidence for viral hepatitis in various provinces. Specifically, Xinjiang and Qinghai provinces had the highest incidence of viral hepatitis in general and hepatitis B and hepatitis C in particular, while incidence were lowest in Shanghai, Zhejiang, Jiangsu, Tianjin and Beijing. These findings suggest that viral hepatitis is more prevalent in less economically developed areas, where health care resources and awareness of public health suboptimal.

During this period, for hepatitis A, the highest reported incidence was found in "1~9" age group. For hepatitis E, the highest reported incidence was in the older age groups (between 60 to 79 years old), similar results as Ren's Research.[17] Heatmap analysis of changing trends within the provinces documented that hepatitis A reporting has decreased. This finding likely reflects the impact of effective HAV vaccination (a live attenuated hepatitis A vaccine was introduced in 1992 and incorporated into the Expanded Program of Immunization in 2008).[18] Regarding reporting incidence for hepatitis C and hepatitis E in most provinces, the increased trends might be ascribed to a lack of effective vaccines, more wide-spread application of HCV testing, and more sensitive and specific hepatitis E diagnostics.[19] Also potentially important is the increased insurance coverage and patient reimbursement in China, resulting in increased exposure of large segments of the population to the health care system.[20] Indeed, between 2003 and 2011, insurance coverage increased from 30% to 96% and physical access to health services was achieved for 83% of the general population.

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There are certain limitations to this study that warrant emphasis. First, protocols were not in place to evaluate data quality and consistency across reporting centers. Second, it is unknown which diagnostic tests and when those tests were introduced into the various laboratories throughout the country. Third, the distinction between acute and recently identified chronic infections was difficult and in some cases, not possible. Fourth, certain demographic characteristics were not provided in this web-site system, therefore, trends in gender reporting could not be ascertained.

In conclusion, this study underscores the magnitude of viral hepatitis reporting in China. Overall reporting of new cases of viral hepatitis and hepatitis B have been stable. Hepatitis B infections continue to be the most commonly reported hepatotropic virus, but the minimal reporting in the young underscore the value of the HBV vaccine. Similarly, HAV reporting which had mainly occurred in children and adolescents has decreased with the introduction of HAV vaccination. HCV and HEV reporting was relatively higher among the elderly and increased during the study period. Thus, for these viruses, increased awareness and effective vaccines are urgently needed.

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Potential conflicts of interest:

The authors declare no conflicts of interest.

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Figures:

Figure 1. Report cases of viral hepatitis in total and its different categories

Figure 2. Reported incidence of hepatitis B from 2003 to 2013

Figure 3. Reported incidence of hepatitis C from 2003 to 2013

Figure 4. Reported incidence of hepatitis A from 2003 to 2013

Figure 5. Reported incidence of hepatitis E from 2003 to 2013

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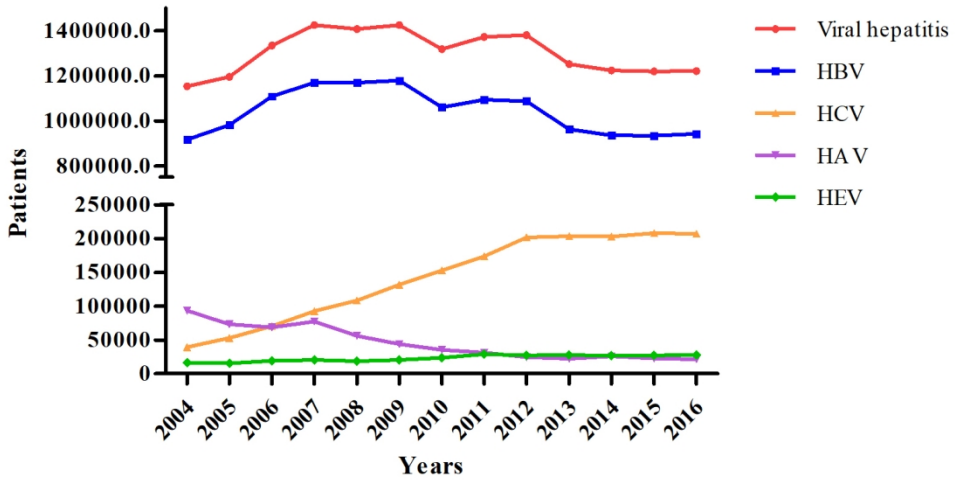

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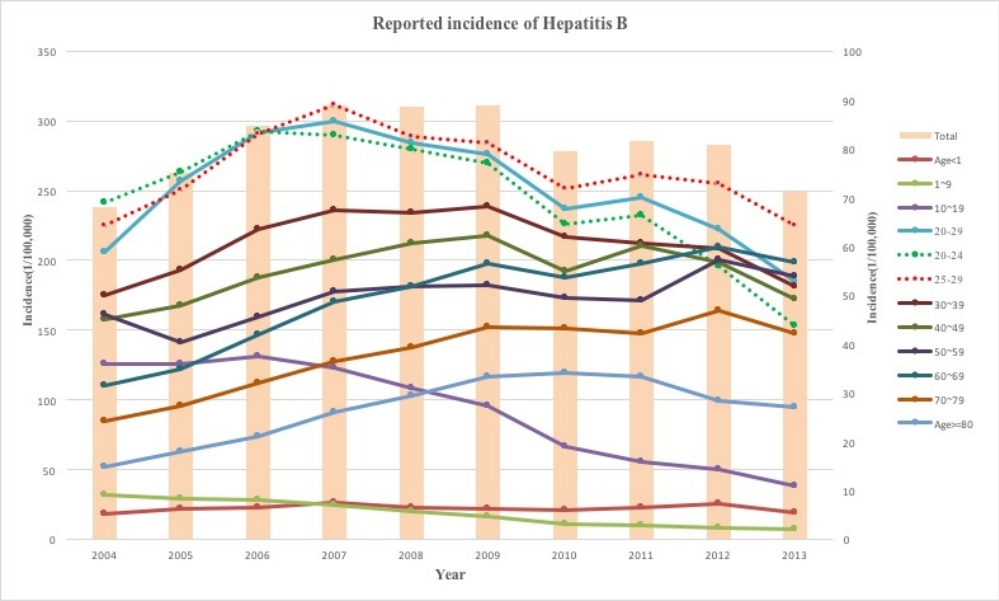

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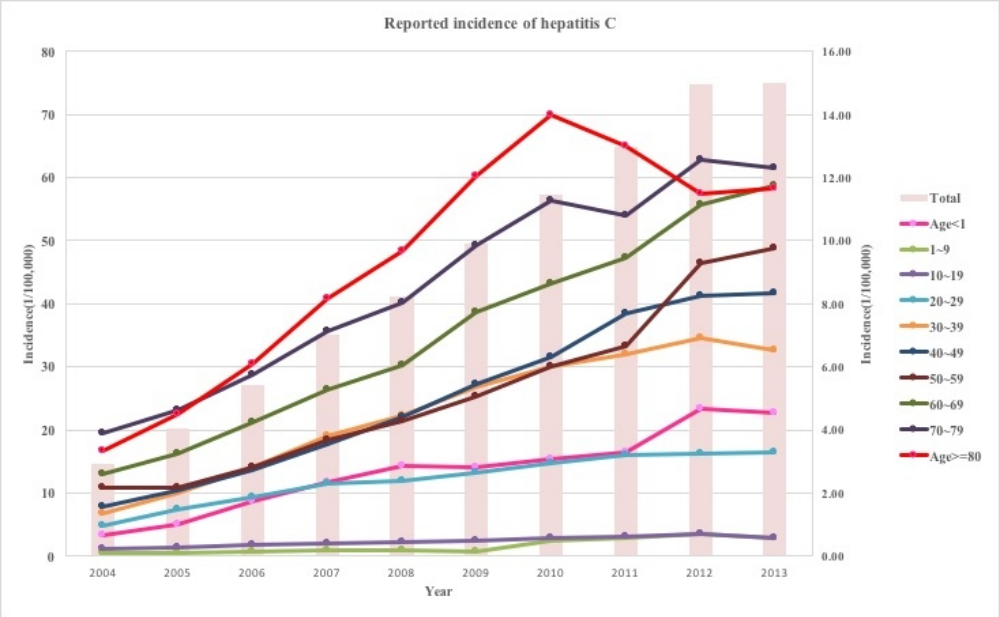

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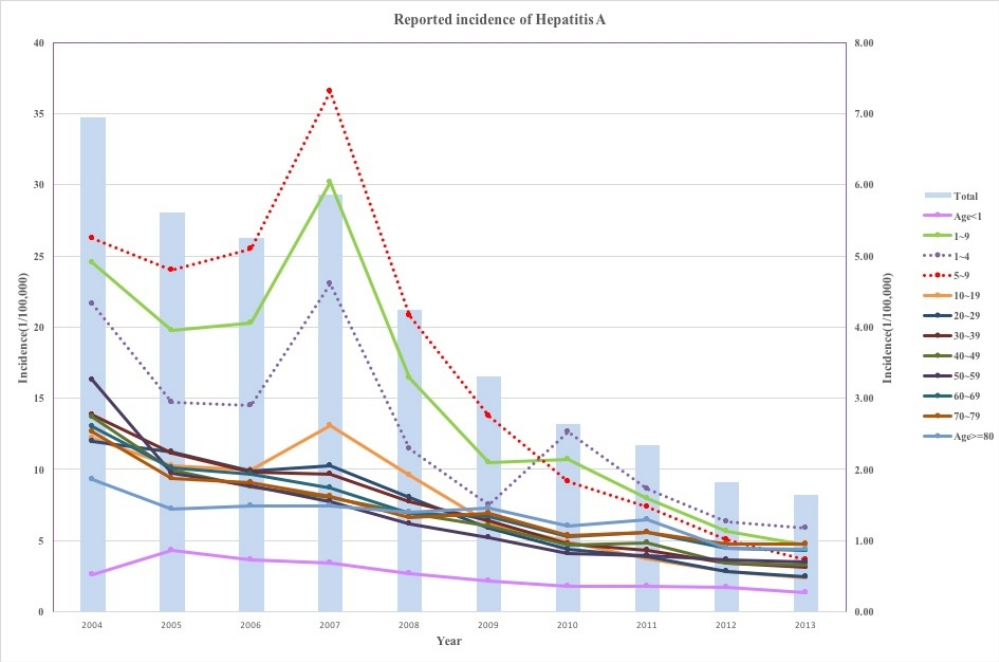

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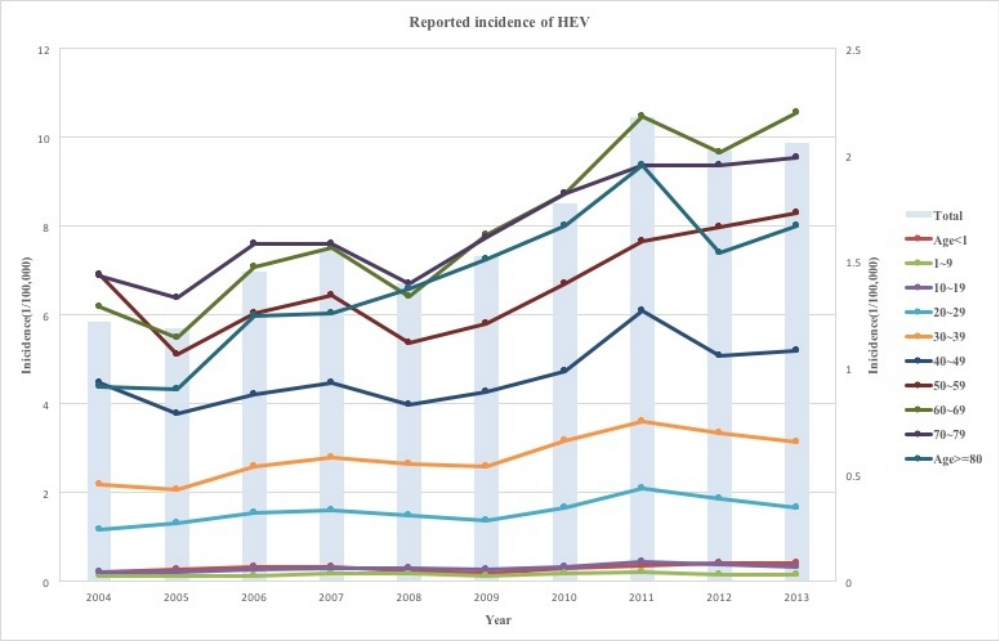
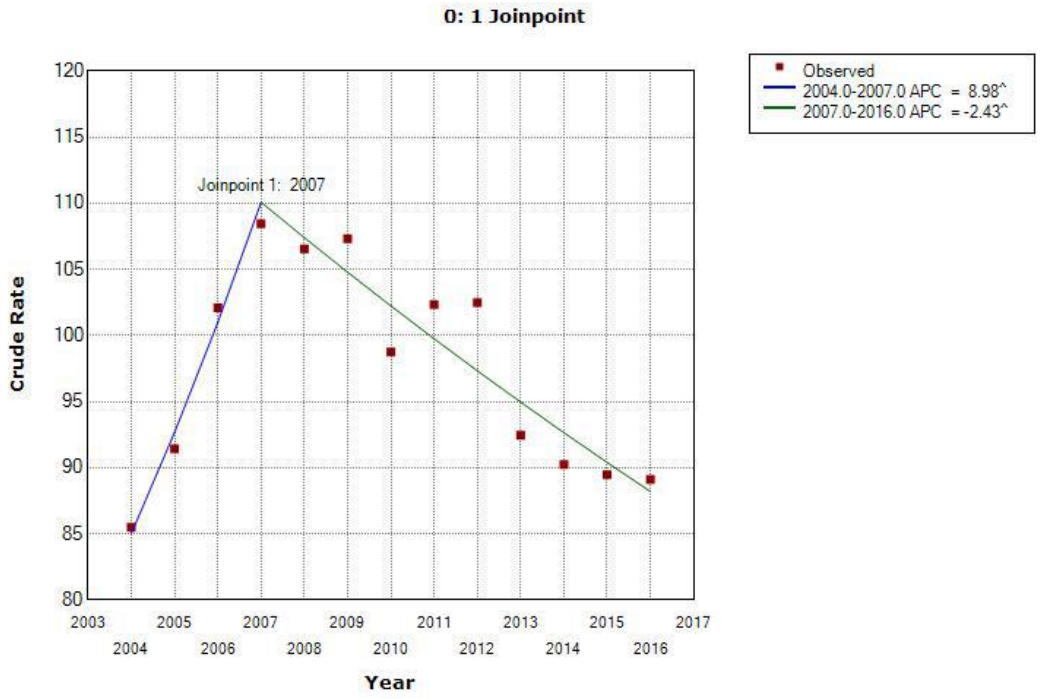


273x175mm (72 x 72 DPI)

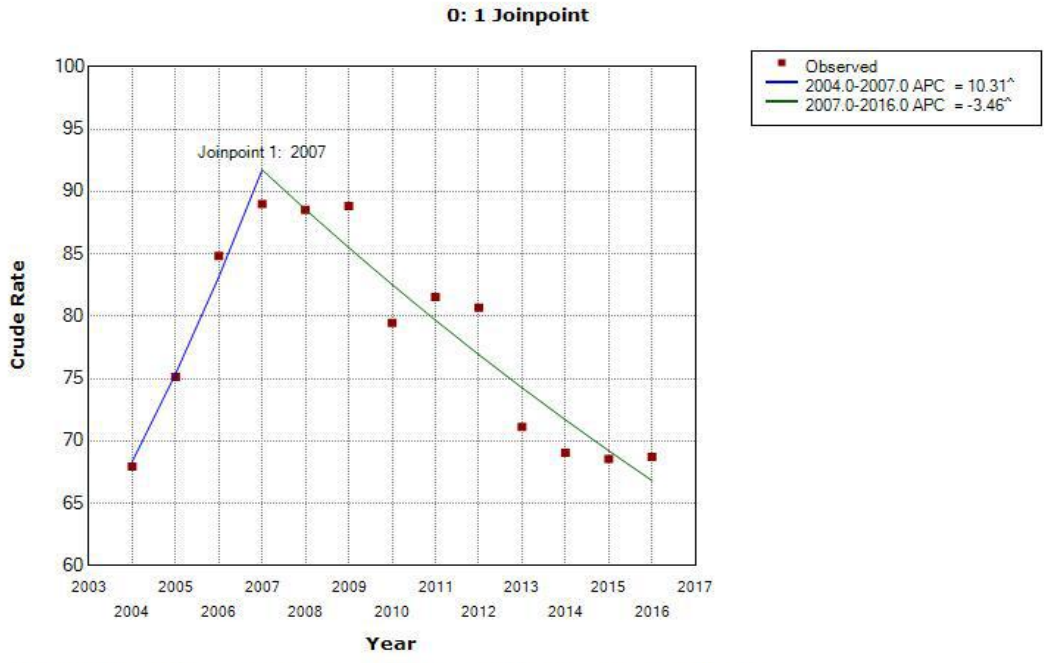
Appendix Figure1. Joinpoint analysis of viral hepatitis and hepatitis B, hepatitis C, hepatitis A and hepatitis E

1.1 Viral hepatitis



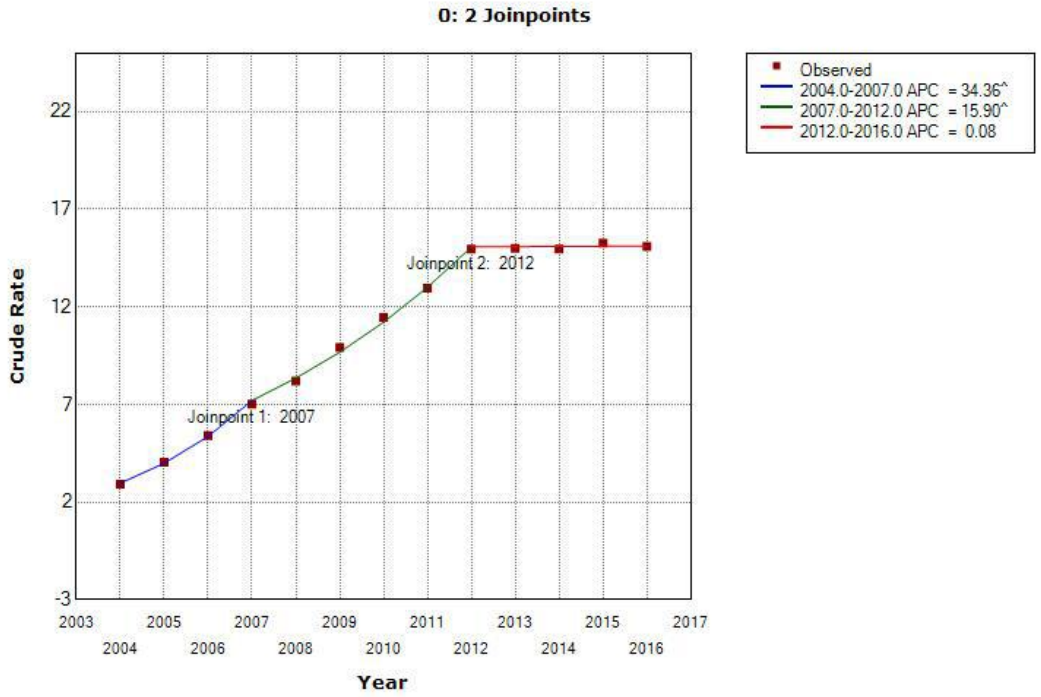
^ Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 1 Joinpoint.

1.2 Hepatitis B



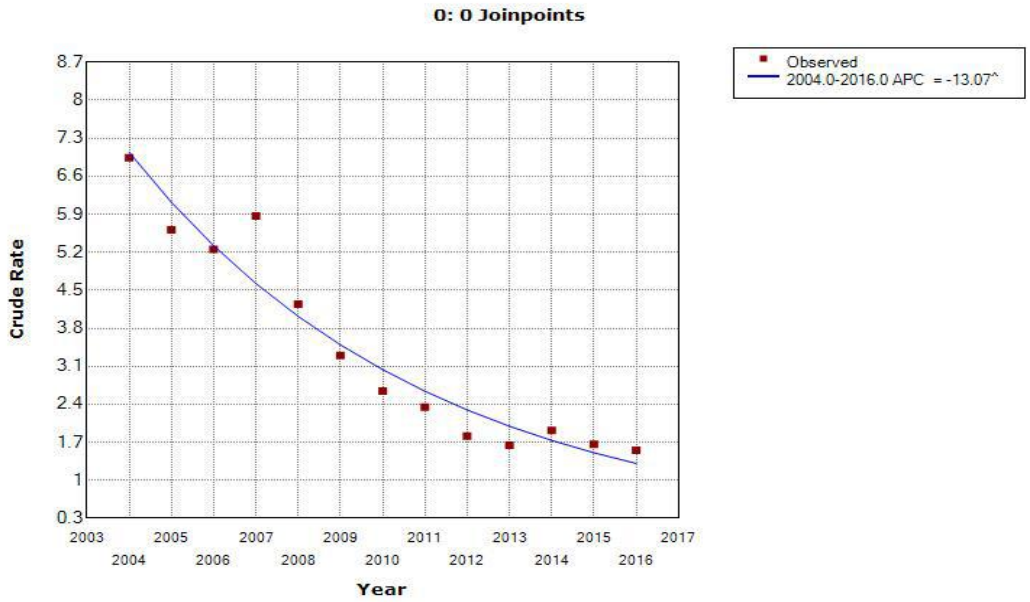
^ Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 1 Joinpoint.

1.3 Hepatitis C



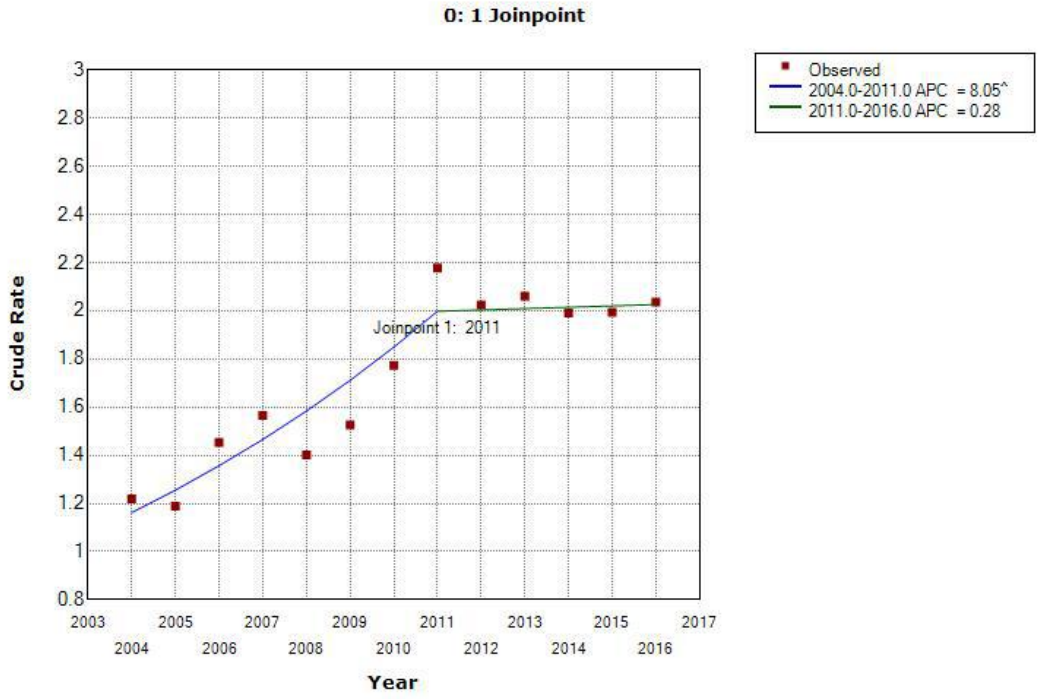
^ Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 2 Joinpoints.

1.4 Hepatitis A



^ Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 0 Joinpoints.

1.5 Hepatitis E



^ Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 1 Joinpoint.

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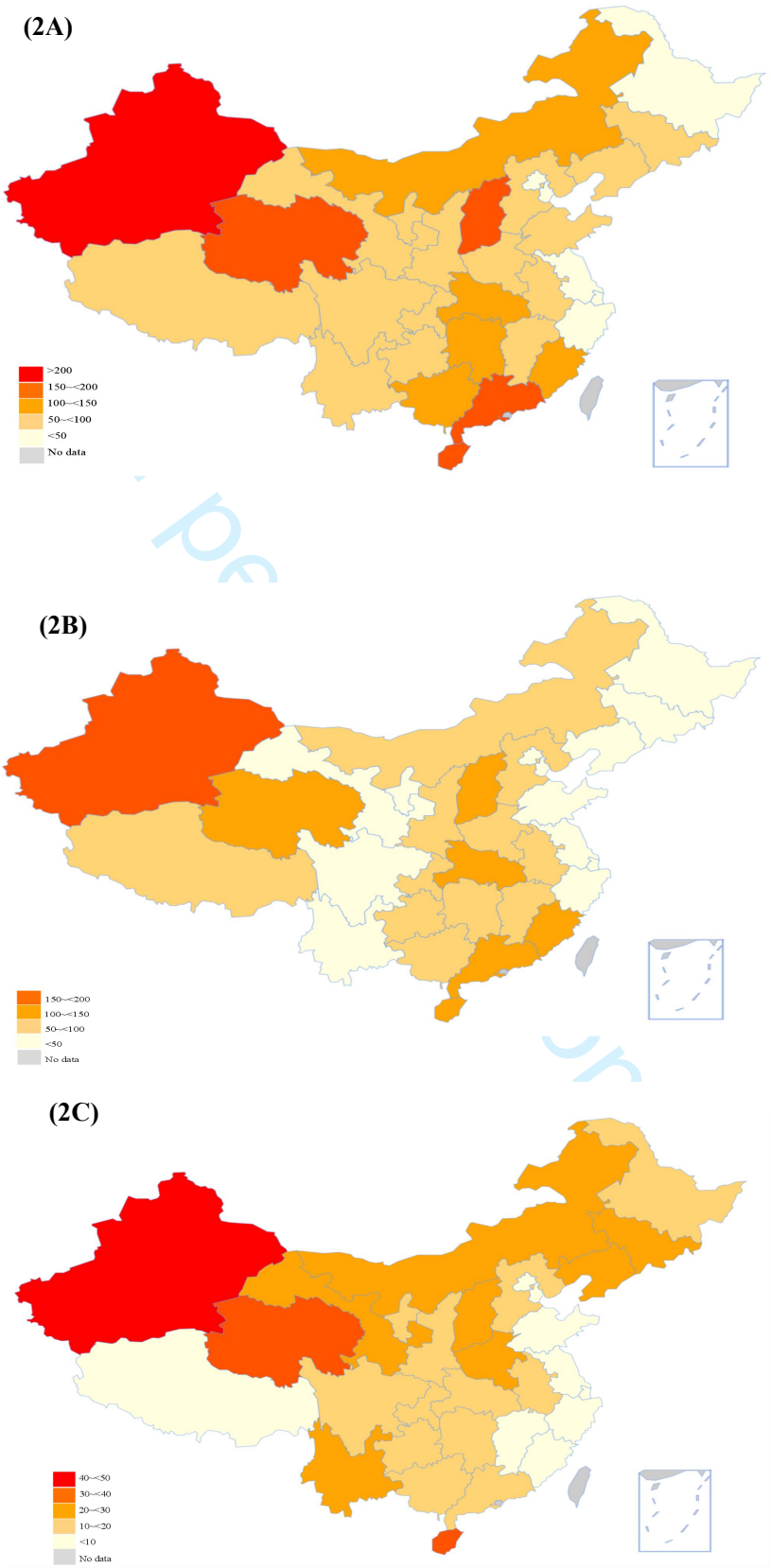
Appendix Figure 2: Reported incidence of viral hepatitis(2A), hepatitis B(2B), and hepatitis C(2C) in different provinces of China, 2015



Data Source: National Health and Family Planning Commission of the People's Republic of China, Health and family planning

statistical Yearbook of China, Beijing, 2016

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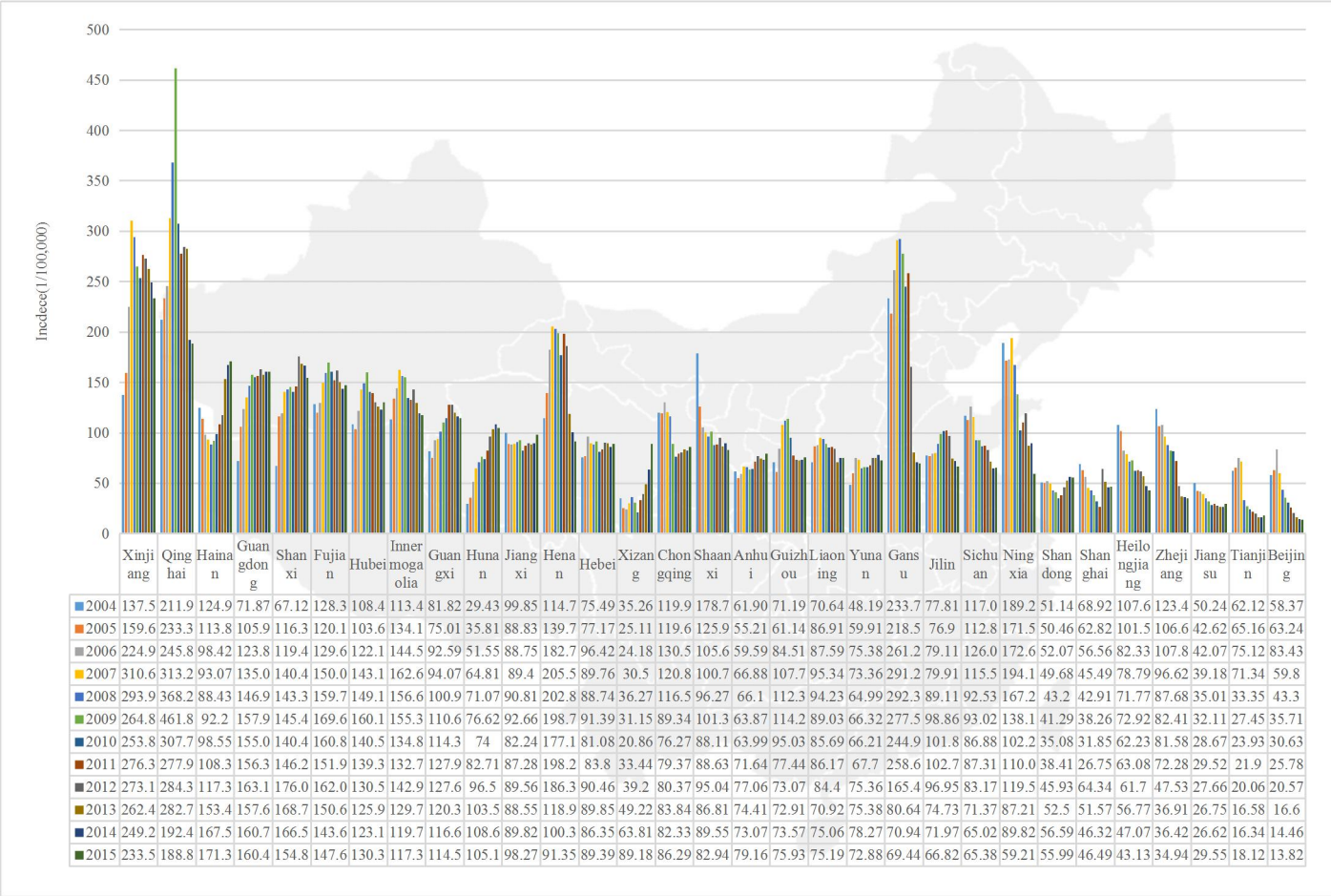
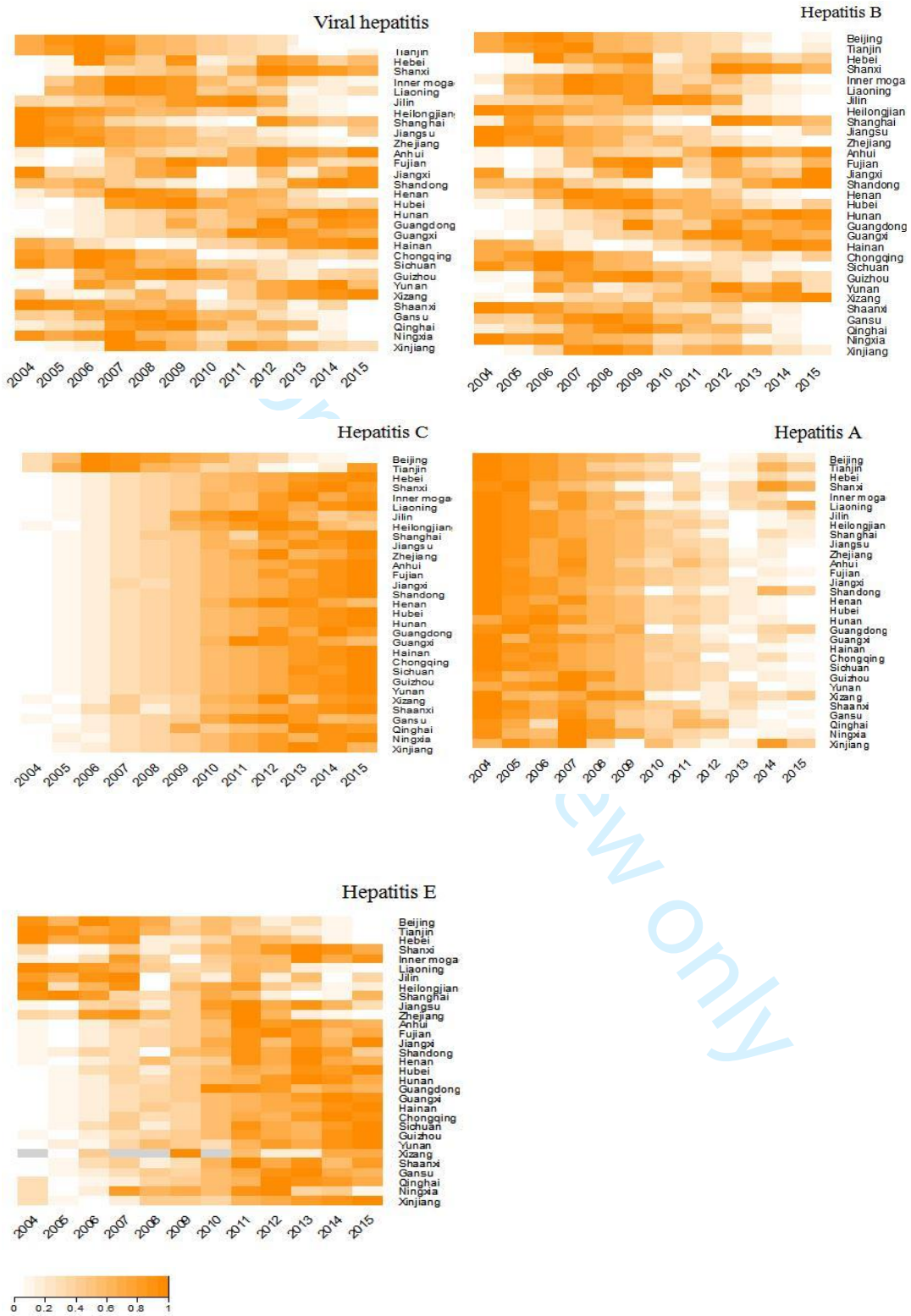
Appendix Figure 3: Annual reported incidence of viral hepatitis overall in different provinces, China,2004-2015



	Xinjiang	Qinghai	Hainan	Guangdong	Shanxi	Fujian	Hubei	Innermogalia	Guangxi	Hunan	Jiangxi	Henan	Hebei	Xizang	Chongqing	Shaanxi	Anhui	Guizhou	Liaoning	Yunan	Gansu	Jilin	Sichuan	Ningxia	Shandong	Shanghai	Heilongjiang	Zhejiang	Jiangsu	Tianjin	Beijing
2004	137.5	211.9	124.9	71.87	67.12	128.3	108.4	113.4	81.82	29.43	99.85	114.7	75.49	35.26	119.9	178.7	61.90	71.19	70.64	48.19	233.7	77.81	117.0	189.2	51.14	68.92	107.6	123.4	50.24	62.12	58.37
2005	159.6	233.3	113.8	105.9	116.3	120.1	103.6	134.1	75.01	35.81	88.83	139.7	77.17	25.11	119.6	125.9	55.21	61.14	86.91	59.91	218.5	76.9	112.8	171.5	50.46	62.82	101.5	106.6	42.62	65.16	63.24
2006	224.9	245.8	98.42	123.8	119.4	129.6	122.1	144.5	92.59	51.55	88.75	182.7	96.42	24.18	130.5	105.6	59.59	84.51	87.59	75.38	261.2	79.11	126.0	172.6	52.07	56.56	82.33	107.8	42.07	75.12	83.43
2007	310.6	313.2	93.07	135.0	140.4	150.0	143.1	162.6	94.07	64.81	89.4	205.5	89.76	30.5	120.8	100.7	66.88	107.7	95.34	73.36	291.2	79.91	115.5	194.1	49.68	45.49	78.79	96.62	39.18	71.34	59.8
2008	293.9	368.2	88.43	146.9	143.3	159.7	149.1	156.6	100.9	71.07	90.81	202.8	88.74	36.27	116.5	96.27	66.1	112.3	94.23	64.99	292.3	89.11	92.53	167.2	43.2	42.91	71.77	87.68	35.01	33.35	43.3
2009	264.8	461.8	92.2	157.9	145.4	169.6	160.1	155.3	110.6	76.62	92.66	198.7	91.39	31.15	89.34	101.3	63.87	114.2	89.03	66.32	277.5	98.86	93.02	138.1	41.29	38.26	72.92	82.41	32.11	27.45	35.71
2010	253.8	307.7	98.55	155.0	140.4	160.8	140.5	134.8	114.3	74	82.24	177.1	81.08	20.86	76.27	88.11	63.99	95.03	85.69	66.21	244.9	101.8	86.88	102.2	35.08	31.85	62.23	81.58	28.67	23.93	30.63
2011	276.3	277.9	108.3	156.3	146.2	151.9	139.3	132.7	127.9	82.71	87.28	198.2	83.8	33.44	79.37	88.63	71.64	77.44	86.17	67.7	258.6	102.7	87.31	110.0	38.41	26.75	63.08	72.28	29.52	21.9	25.78
2012	273.1	284.3	117.3	163.1	176.0	162.0	130.5	142.9	127.6	96.5	89.56	186.3	90.46	39.2	80.37	95.04	77.06	73.07	84.4	75.36	165.4	96.95	83.17	119.5	45.93	64.34	61.7	47.53	27.66	20.06	20.57
2013	262.4	282.7	153.4	157.6	168.7	150.6	125.9	129.7	120.3	103.5	88.55	118.9	89.85	49.22	83.84	86.81	74.41	72.91	70.92	75.38	80.64	74.73	71.37	87.21	52.5	51.57	56.77	36.91	26.75	16.58	16.6
2014	249.2	192.4	167.5	160.7	166.5	143.6	123.1	119.7	116.6	108.6	89.82	100.3	86.35	63.81	82.33	89.55	73.07	73.57	75.06	78.27	70.94	71.97	65.02	89.82	56.59	46.32	47.07	36.42	26.62	16.34	14.46
2015	233.5	188.8	171.3	160.4	154.8	147.6	130.3	117.3	114.5	105.1	98.27	91.35	89.39	89.18	86.29	82.94	79.16	75.93	75.19	72.88	69.44	66.82	65.38	59.21	55.99	46.49	43.13	34.94	29.55	18.12	13.82

Data Source: China Center for Disease Control and Prevention. The Public Health Science Data Center. http://www.phsciencedata.cn/Share/index.jsp

Appendix Figure 4 Heatmap of annual reported incidence of viral hepatitis in total and by different types of hepatitis, different data provinces of China, 2004-2015



Lightgray: means that data were not availiable

Data Source: China Center for Disease Control and Prevention. The Public Health Science Data Center. http://www.phsciencedata.cn/Share/index.jsp

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Appendix Table1.

Web-based Clinical reporting form(CRF)

<table>
<tr><td>Name:</td><td>Family member's Name:</td><td>Date of birth:</td><td>Age:</td><td>Gender:</td><td>Marital status:</td><td>Family address:</td></tr>
<tr><td colspan="2">ID number:</td><td colspan="2">Telephone number:</td><td colspan="3">Occupation:</td></tr>
<tr><td colspan="2">Degree of education:</td><td colspan="2">Nationality:</td><td colspan="3">Report disease name:</td></tr>
<tr><td colspan="2" rowspan="4">Classification of disease:</td><td colspan="5">i: Clinical diagnosis</td></tr>
<tr><td colspan="5">ii: Laboratory confirmationdiagnosis</td></tr>
<tr><td colspan="5">iii: Suspected cases</td></tr>
<tr><td colspan="5">iv: Pathogen carriers</td></tr>
<tr><td>Dates of onset:</td><td colspan="2">Date of being diagnosed:</td><td colspan="2">Methods of diagnose:</td><td colspan="2">Date of death:</td></tr>
<tr><td colspan="3">Date of completing the CRF:</td><td colspan="3">Name of reporting doctor:</td><td>Department:</td></tr>
</table>

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Appendix Table2.

Diagnostic criteria for viral hepatitis by the law on the prevention and control of infectious diseases of the People's Republic of China, 2004

Viral hepatitis				
Clinical description	(I).Recently, there has been a loss of appetite, nausea, refused fatty food, fatigue, jaundice, tea color urine, liver enlargement, liver pain, fatigue, etc, exclude other diseases;			
Laboratory test	(II).Serum ALT elevated repeatedly and cannot be explained by other causes.			
Diagnose	**Suspected cases:(I)+(II)**			
Classification	**Hepatitis A**	**Hepatitis B**	**Hepatitis C**	**Hepatitis E**
Clinical description	1.One month (2-6 weeks) before the onset of illness, patients have been exposed to patients with Hepatitis A, or have been working or travelling, and eating, or directly coming from the prevalence area.	1. No more than half a year accepted treatment of blood and blood products, or have any medical damage such as insanitary injection, acupuncture, puncture, operation, or have a close contaction with HBV patients or carriers.	1.Have received blood and blood products in half a year, or have any medical damage.	1.Two months before the onset of the disease, patients had been exposed to hepatitis E infected patients, or went to the hepatitis E outbreak place, working, travelling, eating, or dinner together.
Laboratory test	2.1 Serum ALT elevated. 2.2 Serum anti-HAV-IgM positive. 2.3 Double serum anti-HAV-IgG titer increased by four times during convalescence after acute infection. 2.4 immuno-electron microscopy found 27nm HAV's particles in the feces.	2.1 Serum ALT elevated. 2.2 Serum HBsAg positive and anti-HBc IgM positive (greater than 1:1000) or HBV-DNA positive.	2.1 Serum ALT increased. 2.2 Not consistent with hepatitis A, hepatitis B, hepatitis E, CMV, EBV infection. 2.3 Serum anti-HCV positive.	2.1 Serum ALT elevated. 2.2 Serum anti-HEV IgM positive. 2.3 The immune electron microscopy showed 30-32nm particles in feces. 2.4 It is not consistent with hepatitis A, hepatitis B, CMV, EBV infection.
Diagnose	**Clinical diagnosis:** suspected cases+1+2.1 **Laboratory confirmation**	**Clinical diagnosis:** suspected cases+1+2.1 **Laboratory confirmation**	**Clinical diagnosis:** suspected cases+2.1+2.2, with 1 as supporting evidence	**Clinical diagnosis:** suspected cases+2.1+2.4, with 1 as supporting evidence

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	diagnosis: suspected cases+2.2 or suspected cases+2.3 or suspected cases+2.4	**diagnosis**: suspected cases+2.2	**Laboratory confirmation diagnosis**: suspected cases+2.3	**Laboratory confirmation diagnosis:** in accordance with the clinical diagnosis +2.2 or 2.3

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Appendix Table 3. Average annual percentage change(AAPC) and Annual percentage change(APC) of reported incidence of Viral hepatitis, hepatitis B, hepatitis C, hepatitis A, hepatitis E, with age distribution

Viral hepatitis	**Year**	**AAPC/APC(95%CI)**		**Trend**	**P-Value**
Viral hepatitis	2004-2016	AAPC	0.3%(-0.9～1.5)	Stable	0.6
	2004-2007	APC[1]	9.0%(3.7～14.6)	Increase	<0.05
	2007-2016	APC[2]	-2.4%(-3.3～-1.6)	Decrease	<0.05
HBV	**Year**	**AAPC/APC(95%CI)**		**Trend**	**P-Value**
	2004-2016	AAPC	-0.2%(-1.6～1.2)	Stable	0.8
	2004-2007	APC[1]	10.3%(4.1～16.9)	Increase	<0.05
	2007-2016	APC[2]	-3.5%(-4.5～-2.5)	Decrease	<0.05
HCV	**Year**	**AAPC/APC(95%CI)**		**Trend**	**P-Value**
	2004-2016	AAPC	14.5%(13.1～15.9)	Increase	<0.05
	2004-2007	APC[1]	34.4%(27.7～41.3)	Increase	<0.05
	2007-2012	APC[2]	15.9%(13.6～18.2)	Increase	<0.05
	2012-2016	APC[3]	0.1%(-1.5～1.7)	Stable	0.9
HAV	**Year**	**AAPC/APC(95%CI)**		**Trend**	**P-Value**
	2004-2016	AAPC	-13.1%(-15.1, -11.0)	Decrease	<0.05
HEV	**Year**	**AAPC/APC(95%CI)**		**Trend**	**P-Value**
	2004-2016	AAPC	4.7%(2.8～6.7)	Increase	<0.05
	2004-2011	APC[1]	8.1%(5.2～11.0)	Increase	<0.05
	2011-2016	APC[2]	0.3%(-3.4～4.1)	Stable	0.9

APCC: Average annual percentage change; APC:Annual percentage change; HBV: Hepatitis B, HCV: Hepatitis C, HAV: Hepatitis A, HEV: Hepatitis E.

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Appendix Table 4. Average annual percentage change(AAPC) and Annual percentage change(APC) of reported incidence of hepatitis B, hepatitis C, hepatitis A, hepatitis E, with age distribution

HBV	Year	AAPC/APC(95%CI)		Trend	P-Value
Age<1	2004-2013	APC	0.4%(-2.7～3.6)	Stable	0.8
1~9	2004-2013	AAPC	-15.5%(-18.4～-12.4)	Decrease	<0.05
	2004-2006	APC[1]	-3.9%(-18.8～13.7)	Decrease	0.6
	2006-2013	APC[2]	-18.5%(-21.3～-15.5)	Decrease	<0.05
10~19	2004-2013	AAPC	-12.1%(-14.4～-9.7)	Decrease	<0.05
	2004-2007	APC[1]	0.9%(-6.1～8.4)	Stable	0.8
	2007-2013	APC[2]	-18.0%(-21.1～-14.7)	Decrease	<0.05
20~24	2004-2013	AAPC	-4.4%(-7.7～-1.0)	Decrease	<0.05
	2004-2008	APC[1]	4.3%(-3.4～12.6)	Stable	0.2
	2008-2013	APC[2]	-10.8%(-15.7～-5.7)	Decrease	<0.05
25~29	2004-2013	AAPC	0.2%(-2.0～2.5)	Stable	0.9
	2004-2007	APC[1]	10.9%(3.1～19.4)	Increase	<0.05
	2007-2013	APC[2]	-4.8%(-7.1～-2.4)	Decrease	<0.05
30~39	2004-2013	AAPC	-1.1%(-1.0～3.2)	Stable	0.3
	2004-2007	APC[1]	12.0%(4.8～19.7)	Increase	<0.05
	2007-2013	APC[2]	-3.9%(-6.1～-1.7)	Decrease	<0.05
40~49	2004-2013	AAPC	1.2%(-1.2～3.5)	Stable	0.3
	2004-2006	APC[1]	6.8%(2.7～11.0)	Stable	<0.05
	2006-2013	APC[2]	-5.5%(-9.9～-0.8)	Decrease	<0.05
50~59	2004-2013	APC	2.5%(0.8～4.3)	Increase	<0.05
60~69	2004-2013	AAPC	7.1%(4.9～9.4)	Increase	<0.05
	2004-2008	APC[1]	14.3%(8.7～20.3)	Increase	<0.05
	2008-2013	APC[2]	1.6%(-1.1～4.5)	Stable	0.2
70~79	2004-2013	AAPC	6.4%(3.8～9.0)	Increase	<0.05
	2004-2009	APC[1]	12.0%(7.3～16.9)	Increase	<0.05
	2009-2013	APC[2]	-0.2%(-4.8～4.7)	Stable	0.9
Age>=80	2004-2013	AAPC	6.8%(4.8～8.9)	Increase	<0.05
	2004-2009	APC[1]	18.5%(14.4～22.8)	Increase	<0.05
	2009-2013	APC[2]	-6.1%(-9.4～-2.8)	Decrease	<0.05
HCV	**Year**	**AAPC/APC(95%CI)**		**Trend**	**P-Value**
Age<1	2004-2013	AAPC	23.2%(13.1～34.2)	Increase	<0.05
	2004-2007	APC[1]	50.0%(9.2～106.0)	Increase	<0.05
	2007-2013	APC[2]	11.7%(5.5～18.2)	Increase	<0.05
1~9	2004-2013	APC	25.9%(15.9～36.8)	Increase	<0.05
10~19	2004-2013	AAPC	10.4%(6.9～14.0)	Increase	<0.05
	2004-2011	APC[1]	15.3%(12.4～18.3)	Increase	<0.05
	2011-2013	APC[2]	-5.1%(-19.7～12.1)	Stable	0.5
20~29	2004-2013	AAPC	14.2%(9.7～18.8)	Increase	<0.05
	2004-2007	APC[1]	31.6%(14.0～51.8)	Increase	<0.05

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	2007-2013	APC[2]	6.3%(3.0～9.8)	Increase	<0.05
30~39	2004-2013	AAPC	17.7%(13.8～21.9)	Increase	<0.05
	2004-2009	APC[1]	29.7%(21.5～38.4)	Increase	<0.05
	2009-2013	APC[2]	4.4%(-1.8～10.9)	Stable	0.1
40~49	2004-2013	AAPC	18.8%(15.8～21.9)	Increase	<0.05
	2004-2011	APC[1]	24.0%(20.5～27.5)	Increase	<0.05
	2011-2013	APC[2]	2.5%(-8.7～15.1)	Stable	0.6
50~59	2004-2013	AAPC	19.5%(17.4～21.7)	Increase	<0.05
60~69	2004-2013	AAPC	18.1%（15.6～20.7）	Increase	<0.05
	2004-2009	APC[1]	23.7%（18.6～29.0）	Increase	<0.05
	2009-2013	APC[2]	11.5%（7.8～15.4）	Increase	<0.05
70~79	2004-2013	AAPC	14.0%（10.9～17.2）	Increase	<0.05
	2004-2009	APC[1]	21.0%（14.7～27.6）	Increase	<0.05
	2009-2013	APC[2]	5.8%(0.9～11.0)	Increase	<0.05
Age>=80	2004-2013	AAPC	12.6%(9.5～15.8)	Increase	<0.05
	2004-2010	APC[1]	24.6%(19.6～29.9)	Increase	<0.05
	2010-2013	APC[2]	-8.1%(-14.6～-1.2)	Increase	<0.05
HAV	**Year**	**AAPC/APC(95%CI)**		**Trend**	**P-Value**
Age<1	2004-2013	APC	-11.1%(-15.9～-5.9)	Decrease	<0.05
1~4	2004-2013	APC	-12.3%(-19.2～-4.9)	Decrease	<0.05
5~9	2004-2013	AAPC	-20.1%(-22.4～-17.7)	Decrease	<0.05
	2004-2007	APC[1]	9.7%(2.0～17.9)	Increase	<0.05
	2007-2013	APC[2]	-31.7%(-34.8～-28.6)	Decrease	<0.05
10~19	2004-2013	AAPC	-16.6%(-19.4～-13.7)	Decrease	<0.05
	2004-2007	APC[1]	2.3%(-6.1～11.5)	Stable	0.5
	2007-2013	APC[2]	-24.8%(-28.5～-20.8)	Decrease	<0.05
20~29	2004-2013	APC	-16.7%(-18.9～-14.5)	Decrease	<0.05
	2004-2007	APC[1]	-5.8%(-12.3～1.1)	Stable	0.1
	2007-2013	APC[2]	-21.7%(-24.5～-18.7)	Decrease	<0.05
30~39	2004-2013	APC	-15.1%(-16.8～-13.4)	Decrease	<0.05
40~49	2004-2013	APC	-14.3%(-15.9～-12.7)	Decrease	<0.05
50~59	2004-2013	APC	-16.1%(-19.2～-12.9)	Decrease	<0.05
60~69	2004-2013	APC	-11.6%(-13.1～-10.1)	Decrease	<0.05
70~79	2004-2013	APC	-10.1%(-12.0～-8.2)	Decrease	<0.05
Age>=80	2004-2013	APC	-6.7%(-9.3～-3.9)	Decrease	<0.05
HEV	**Year**	**AAPC/APC(95%CI)**		**Trend**	**P-Value**
Age<1	2004-2013	APC	5.8%(0.7～11.2)	Increase	<0.05
1~9	2004-2013	APC	3.0%(-2.0～8.2)	Stable	0.2
10~19	2004-2013	APC	6.8%(3.3～10.5)	Increase	<0.05
20~29	2004-2013	APC	4.5%(1.5～7.7)	Increase	<0.05

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30~39	2004-2013	APC	5.4%(2.9～7.9)	Increase	<0.05
40~49	2004-2013	APC	3.6%(0.8～6.5)	Increase	<0.05
50~59	2004-2013	APC	4.2%(1.1～7.4)	Increase	<0.05
60~69	2004-2013	APC	7.1%(4.7～9.6)	Increase	<0.05
70~79	2004-2013	APC	4.6%(2.8～6.3)	Increase	<0.05
Age>=80	2004-2013	APC	6.2%(2.7～9.9)	Increase	<0.05
	2004-2011	APC[1]	10.6%(2.1～14.2)	Increase	<0.05
	2011-2013	APC[2]	-7.6%(-21.6～8.9)	Decrease	0.3

APCC: Average annual percentage change; APC:Annual percentage change; HBV: Hepatitis B, HCV: Hepatitis C, HAV: Hepatitis A, HEV: Hepatitis E.

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Appendix Table 5. Date of birth of reported HBV cases in different age groups from 2004-2013

Age groups	Date of birth	Trend	*P* value	Joinpoint	Date of birth	Trend	*P* value
10~19	1985-2003	Decrease	<0.05	2007	1985-1997	Stable	0.8
					1988-2003	Decrease	<0.05
20~24	1980-1993	Decrease	<0.05	2008	1980-1988	Stable	0.2
					1984-1993	Decrease	<0.05
25~29	1975-1988	Stable	0.9	2007	1975-1982	Increase	<0.05
					1978-1988	Decrease	<0.05
30~39	1965-1983	Stable	0.3	2007	1965-1977	Increase	<0.05
					1968-1983	Decrease	<0.05

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract （Page 3）	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale （Page 4）	2	Explain the scientific background and rationale for the investigation being reported
Objectives （Page 4）	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design （Page 4&5）	4	Present key elements of study design early in the paper
Setting （Page 4&5）	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants （Page 4&5）	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables （Page 5）	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement （Page 4&5）	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size （Page 4）	10	Explain how the study size was arrived at
Quantitative variables （Page 5）	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods （Page 5）	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

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Results		
Participants （Page 5&6）	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data （Page 5&6）	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data （Page 5&6&7&8）	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results （Page 5&6&7&8）	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses （Page 5&6&7&8）	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results （Page 8&9&10）	18	Summarise key results with reference to study objectives
Limitations （Page 10）	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation （Page 8,9,10,11）	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability （Page 10&11）	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding （Page 11）	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at

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http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Title: Changing incidence of reported viral hepatitis in China from 2004 to 2016: an observational study

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Title: Changing incidence of reported viral hepatitis in China from 2004 to 2016: an observational study

Abstract:

Objective: China's national hepatitis burden is high. This study aims to provide a detailed national-level description of the reported incidence of viral hepatitis in China during 2004-2016.

Design: Observational study

Setting: Data were obtained from China's National Notifiable Disease Reporting System, and changing trends were estimated by joinpoint regression analysis.

Participants: In this system, 16,927,233 reported viral hepatitis cases occurring during 2004-2016 were identified.

Primary outcome measure: Incidence rates per 100,000 person-years and changing trends were calculated.

Results: There were 16,927,233 new cases of viral hepatitis reported in China from 2004 to 2016. Hepatitis B (HBV) (n=13,543,137, 80.00%) and hepatitis C (HCV) (n=1,844,882, 10.90%) accounted for >90% of the cases. The overall annual percent change (APC) in reported cases of viral hepatitis and HBV were 0.3% [95% confidence interval (CI) -2.0 to 0.8, P=0.6)] and -0.2% (95% CI -1.6 to 1.2, P=0.8), respectively, showing a stable trend. HBV rates were highest in the 20-29 year old age group and lowest in younger individuals, likely resulting from the universal HBV vaccination. The reported incidence of HCV and hepatitis E (HEV) showed increasing trends; the APCs were 14.5% (95% CI 13.1 to 15.9, P<0.05) and 4.7% (95% CI 2.8 to 6.7, P<0.05), respectively. The hepatitis A (HAV) reporting incidence decreased, and the APC was -13.1% (95% CI -15.1 to -11.0, P<0.05). There were marked differences in the reporting of hepatitis among provinces.

Conclusions: HBV continues to constitute the majority of viral hepatitis cases in China. Over the entire study period, the HBV reporting incidence was stable, the HCV and HEV incidence increased, and the HAV incidence decreased. There were significant interprovincial disparities in the burden of viral hepatitis, with higher rates in economically less-developed areas. Vaccination is important for viral hepatitis prevention and control.

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Strengths and limitations of this study

► The latest comprehensive description of trends in the national and provincial reporting incidence for viral hepatitis in China since 2004 were provided.

► This study highlighted the magnitude and importance of viral hepatitis in China and provided key data to help determine where efforts need to be focused.

► We analyzed the age distributions among different types of viral hepatitis and provided the prevalence characteristics of viral hepatitis in China.

► Since the study collected data from across almost the whole country, heterogeneity across reporting centers existed, which might be a weakness.

Introduction

Viral hepatitis is an important challenge to public health globally. In 2013, the greatest number of deaths and disability-adjusted life years (DALYs) attributable to viral hepatitis occurred in East and South Asia, including China. [1] According to the World Health Organization (WHO), approximately 100 million people in China – that is 1 in 13 people – live with chronic hepatitis B (HBV) and hepatitis C (HCV) infections. [2] In 2016, the WHO approved the first global health sector strategy on viral hepatitis, with the goal of eliminating viral hepatitis as a major public health threat by 2030. [3] To achieve this goal, a review of the current status of viral hepatitis and the different types was essential. Age distribution is important for obtaining a clear understanding of changing trends in viral hepatitis reporting and its future burden. China is a vast and diverse country with 32 provinces, and province-level data are also required for effective disease prevention, control and management. Therefore, the present study examined the reported rates of newly diagnosed cases of viral hepatitis and documented temporal trends across age groups and provinces.

Materials and Methods

In 2004, the Chinese government established a centralized web-reporting system for notifiable infectious diseases and public health emergencies. The fundamental database for this project was maintained by the Chinese Communicable Disease Control (CCDC). A standardized case

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reporting form (CRF) was established for the collection of demographic and diagnostic information for each case of a reportable diseases (Appendix Table 1).

We collected data for viral hepatitis between 2004 and 2016 from the CCDC Center's website (http://www.chinacdc.cn/). [4,5] and the Yearbooks of Health for the People's Republic of China. [6] In the system, cases were defined with diagnostic criteria issued by the law on the prevention and control of infectious diseases of the People's Republic of China in 2004. (Appendix Table 2). In this system, the reported cases numbers and the rates among the total population were provided, and we calculated the total population number each year accordingly. Based on patient histories, clinical manifestations, and laboratory test results, cases were categorized as hepatitis A, B, C, E and unidentified hepatitis. [7] In this study, unidentified hepatitis cases were excluded. For the provincial analyzes, Hong Kong, Macao and Taiwan were not included in this research. The data were collected from the notifiable infectious disease reporting database, which is open and available to the public, and no specific permissions were required. The conduct of this study was consistent with the Declaration of Helsinki.

Incidence (per 100,000) was defined as the number of annual newly diagnosed cases divided by the population size. In this surveillance system, the cases were newly diagnosed rather than new infections. To avoid misunderstanding, we used the reported incidence in this research.

Statistical analyses

Descriptive epidemiological methods were used to examine and analyze the reported data. The annual percent change (APC), average annual percent change (AAPC) and 95% confidence intervals (CIs) were calculated for viral hepatitis overall and for individual categories of viral hepatitis (A, B, C, and E). Additionally, we investigated trends and made comparisons among different provinces by a heatmap analysis. For age distributions, cases were divided annually into 10 groups for each category of viral hepatitis. Joinpoint regression models were used to describe temporal trends in the reporting of newly diagnosed cases. In describing trends, we used the terms "increase" and "decrease" when the slope (APC) was significant (two-tailed $P< 0.05$). The term "stable" refers to a nonsignificant APC ($P \geq 0.05$) and indicates that the incidence was maintained

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at a perennially stable level. The R language (version 3,3.0) and Joinpoint (version 4.6.0.0, April 2018, IMS, Inc., https://surveillance.cancer.gov/joinpoint/) were used for the analyses in this study. The conduct of this study was consistent with the Declaration of Helsinki.

Patient and public involvement

No patients were involved in developing the research question or the outcome measures, and no patients were involved in the design, recruitment and conduct of the study. The data were collected from the on-line reporting system, and patients were anonymous. We were unable to disseminate the results of the research directly to study participants.

Results

National and provincial reporting incidence of viral hepatitis

National reporting incidence

Between 2004 and 2016, a total of 16,927,233 newly diagnosed cases of viral hepatitis were reported in China. HBV (n=13,543,137, 80.00%) and HCV (n=1,844,882, 10.90%) jointly accounted for over 90% of cases. The remaining cases consisted of the following: 595,982 (3.52%) cases of HAV and 300,505 (1.78%) cases of HEV (Figure 1). The total population and the definite number of reported viral hepatitis in total and different categories were provided. (Appendix Table3)

Viral hepatitis reporting incidence increased from 85.49/100,000 in 2004 to 108.44/100,000 in 2007 (P<0.05). After 2007, there was a significant decrease to 89.11/100,000 in 2016 (P<0.05). Overall, the APC was 0.3% (95% CI -2.0 to 0.8, P=0.6), indicating a stable trend. (Appendix Figure 1.1)

The reporting incidence for HBV increased from 2004 (67.96/100,000) to 2009 (88.82/100,000) and then decreased in 2016 (68.74/100,000). From 2004 to 2007, the APC was 10.3% (95% CI 4.1 to 16.9, P<0.05), while from 2007 to 2016, the APC was -3.5% (95% CI -4.5

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to -2.5, P<0.05). Overall, the APC of HBV was -0.2% (95% CI -1.6 to 1.2, P=0.8), indicating a stable trend (Appendix Figure 1.2).

The reporting incidence for HCV increased from 2004 (2.92/100,000) to 2016 (15.09/100,000). From 2004 to 2007, the APC was 34.4% (95% CI 27.7 to 41.3, P<0.05), indicating a significant increase. Thereafter, the APC from 2007 to 2012 was 15.9% (95% CI 13.6 to 18.2, P<0.05), indicating a significant but slow increase, and from 2012 to 2016, the APC was 0.1% (95% CI -1.5 to 1.7, P=0.9), indicating a stable trend. Overall, the APC was 14.5% (95% CI 13.1 to 15.9, P<0.05), indicating an increased trend (Appendix Figure 1.3).

For HAV, the reporting incidence decreased from 2004 (6.94/100,000) to 2016 (1.55/100,000). The APC for the entire period was -13.1% (95% CI -15.1 to -11.0, P<0.05) (Appendix Figure 1.4). For HEV, the reporting incidence increased from 1.22/100,000 in 2004 to 2.18/100,000 in 2011, with an APC of 8.1% (95% CI 5.2 to 11.0, P<0.05). From 2011 to 2016, the reporting incidence decreased to 2.04/100,000, and the APC was stable (0.3%; 95% CI -3.4 to 4.1, P=0.9). Overall, the APC for HEV was 4.7% (95% CI 2.8 to 6.7, P<0.05), indicating an increasing trend (Appendix Figure 1.5).

Detailed information of the joinpoint analysis results are provided in Appendix Table 4.

Reporting incidence in relation to age

Marked differences in the reporting incidence of HBV were evident among the various age groups. Overall, the HBV reporting incidence was highest in the 20-29 year old age group. When subdivided into 20-25 and 26-29 year old age groups, the highest incidence was in the 26-29 year old group. The lowest reporting incidence of viral hepatitis occurred in the age group between 1 and 9 years old. In terms of trends from 2004 to 2013, the age groups <1, 30-39, and 40-49 were stable, while the age groups 1-9, 10-19, and 20-29 decreased. The reporting incidence for all subjects over the age of 50 increased. More recently (beyond 2007), most age groups showed a significant decrease or stable trend; however, the trend increased in the “50-59” age group. (Figure 2)

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For HCV, aside from the <1 year old age group, the reporting incidence in the different age groups increased with age. The highest reporting incidence was in those >80 years old and the lowest was in those between 1 and 19 years old. From 2004 to 2013, each age group showed an increasing trend, but more recently (beyond 2011) rates were stable in the 10-19, 30~39, and 30~49 age groups. (Figure 3)

For HAV, the highest reporting incidence was in the 1~9 age group, with incidence in the 5-9 age group higher than that in the 1-4 age group. The lowest reporting incidence was in the <1 age group. In terms of trends, incidence in the 5~9 age group was stable, as was that in the 10~29 age group after 2007. All other age groups showed decreasing trends during this period. (Figure 4)

For HEV, the highest reporting incidence was in the relatively older age group (60-79 years). Aside from the 1~9 age group, where the incidence was stable, and the >=80 age group, where the incidence decreased after 2011, the other age groups showed increasing trends during this period. (Figure 5)

More detailed information is provided in Appendix Table 5.

Provincial incidence

In 2015, an analysis of the reporting incidence for viral hepatitis demonstrated that Xinjiang was the province with the highest rates (>200/100,000). Qinghai, Hainan, Guangdong, Shanxi, Fujian, Hubei, Inner Mongolia, Guangxi, and Hunan provinces had intermediate rates (>100 and <200/100,000), while Shanghai, Heilongjiang, Zhejiang, Jiangsu, Tianjin, Beijing had the lowest rates (<50/100,000). Specific analyses for HBV and HCV by province are provided in Appendix Figure 2.

To document trends in the reporting incidence for viral hepatitis from 2004 to 2015 by province, data and a heatmap of reporting incidence for viral hepatitis in general as well as for the different viruses are provided in Appendix Figure 3,4. For most provinces, reporting incidence for HAV decreased, while those for HCV increased. Most northern areas of China (Beijing, Tianjin, Hebei, Liaoning, Jilin, Heilongjiang) had a decreasing incidence of HEV, while the other

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provinces (Jiangxi, Shandong, Hubei, Guangxi, Hainan, Chongqing, Sichuan, Guizhou, Yunnan) revealed increasing trends.

Discussion

Viral hepatitis is a significant global public health issue, and it is responsible for an estimated 1.4 million deaths per year from acute infection, hepatitis-related liver cirrhosis and cancer. Of those deaths, approximately 47% are attributable to HBV, 48% to HCV and the remainder to HAV and HEV infections. [1] In 2015, an estimated 257 million people were living with chronic HBV infections and 71 million with chronic HCV infections. [8] China's hepatitis burden is the highest in the world. According to the WHO, one-third of the world's 240 million people living with chronic HBV live in China, while approximately 7% of the world's 130-150 million people living with HCV live in China. [2]

In this study, HBV reporting incidence was lowest in children under 10 years of age and highest in the 20~29 age group. Similar results have been reported previously. [9] Further analysis of the 20-29 age group revealed that those 25-29 years of age (i.e., born in 1975-1988) had a significantly higher reporting incidence than the 20-24 age group, suggesting a possible vaccine effect (Appendix Table 6). Indeed, the HBV vaccine was first introduced into China in 1985 and integrated into the National Expanded Program on Immunization (EPI) in 1992. [10] Thus, the majority of individuals in the 25-29 age group were born in a period without HBV vaccine protection and were thus susceptible to transmission via the maternal-infant route. Of note, HBV reporting in individuals older than 50 years old showed an increase from 2004 to 2013. This could be explained by the following: (1) elderly individuals may be more likely to establish contact with the health care system. (2) There is a higher prevalence of chronic HBV and therefore a greater likelihood of presenting with complications, such as portal-hypertensive bleeding, encephalopathy, ascites, jaundice or hepatocellular carcinoma (HCC), leading to a diagnosis of HBV-related disease. (3) Elderly individuals engage in high-risk behaviors such as sexual contact, invasive medical procedures, and sharing shavers and towels, which are all important HBV transmission

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routes in adults. (4) Older individuals do not have vaccine protection when they were young, and they are be more easily infected with HBV compared with successfully vaccinated children. To decrease the prevalence of HBV, vaccination among people aged 15~59 years old should also be conducted. [11]

Regarding HCV, the reporting incidence increased with age; the lowest incidence occurred in children and adolescents, while the highest incidence was documented in the >=80 age group. However, from 2004 to 2013, the reporting incidence increased in all age groups, which likely reflects increasing disease awareness, an increase in older individuals seeking medical care, increases in new infections, progression to complications of cirrhosis, and providing HCV testing to a new generation [8,12,13]. Notably, in China, the implementation of HCV screening for blood donors and blood products occurred in 1993, [14] and a decline in transfusion-related HCV, from 72% to 47%, was associated with this intervention. [13] However, relatively high rates of HCV infections among patients undergoing hemodialysis and other invasive therapies and engaging in high-risk sexual behaviors remain a potential source for HCV transmission. [15] While the success achieved with recent directing antiviral agents (DAA) for chronic HCV predict further declines in HCV reporting, complete eradication of HCV might not be possible without an effective vaccine. [16]

Provincial analyses demonstrated large differences in the reporting incidence for viral hepatitis in various provinces. Specifically, Xinjiang and Qinghai provinces had the highest incidence of viral hepatitis in general and HBV and HCV in particular, while incidence was lowest in Shanghai, Zhejiang, Jiangsu, Tianjin and Beijing. These findings suggest that viral hepatitis is more prevalent in less economically developed areas, where health care resources and awareness of public health are suboptimal.

During this period, for HAV, the highest reported incidence was found in the 1~9 age group. For HEV, the highest reported incidence was in the older age groups (between 60 and 79 years old), similar to Ren's research. [17] A heatmap analysis of changing trends within the provinces documented that HAV reporting decreased. This finding likely reflects the impact of effective

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HAV vaccination (a live attenuated HAV vaccine was introduced in 1992 and incorporated into the EPI in 2008). [18] Regarding the reporting incidence for HCV and HEV in most provinces, the increased trends might be ascribed to a lack of effective vaccines, more widespread application of HCV testing, and more sensitive and specific HEV diagnostics. [19] Also potentially important is the increased insurance coverage and patient reimbursement program in China, resulting in the increased exposure of large segments of the population to the health care system. [20] Indeed, between 2003 and 2011, insurance coverage increased from 30% to 96%, and physical access to health services was achieved for 83% of the general population.

There are certain limitations to this study that warrant emphasis. First, protocols were not in place to evaluate data quality and consistency across reporting centers. Second, it is unknown which and when certain diagnostic tests were introduced into the various laboratories throughout the country. Third, the distinction between acute and recently identified chronic infections was difficult and, in some cases, not possible. Fourth, certain demographic characteristics were not provided in the electronic system; therefore, trends in sex reporting could not be ascertained.

In conclusion, this study underscores the magnitude of viral hepatitis reporting in China. Overall, the reporting of new cases of viral hepatitis and HBV has been stable. HBV continues to be the most commonly reported hepatotropic virus, but the minimal reporting in the young underscores the value of the HBV vaccine. Similarly, HAV, which mainly occurred in children and adolescents, decreased with the introduction of the HAV vaccination. HCV and HEV cases was relatively higher among elderly individuals and increased during the study period. Thus, for these viruses, increased awareness and effective vaccines are urgently needed.

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Figure 5. Reported incidence of hepatitis E from 2003 to 2013

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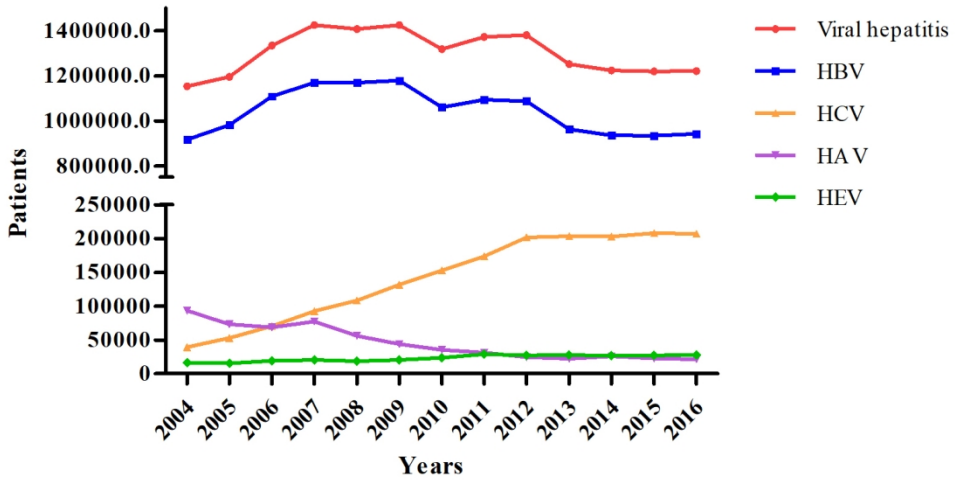

Report cases of viral hepatitis in total and its different categories

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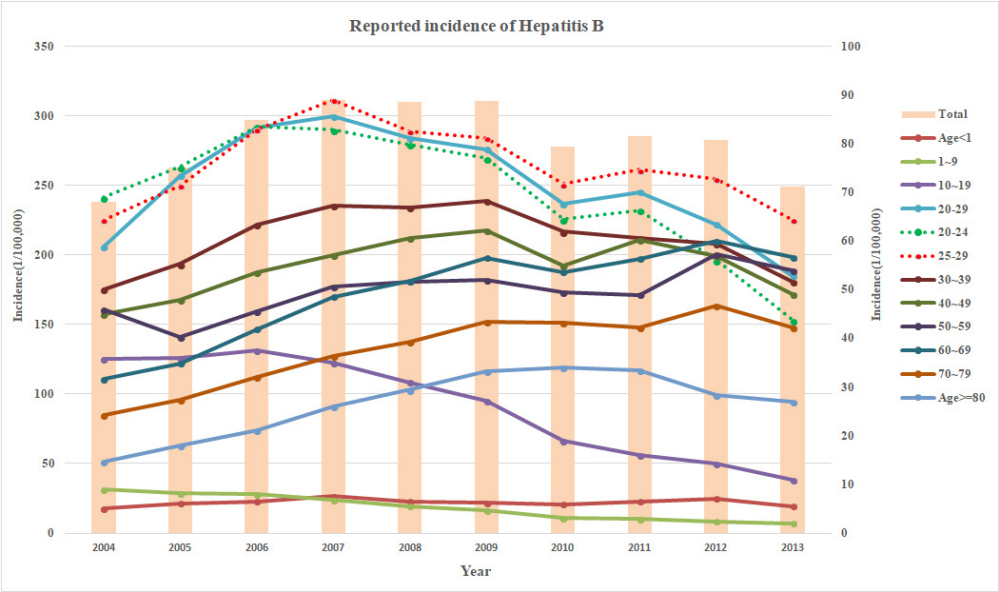

Reported incidence of hepatitis B from 2003 to 2013

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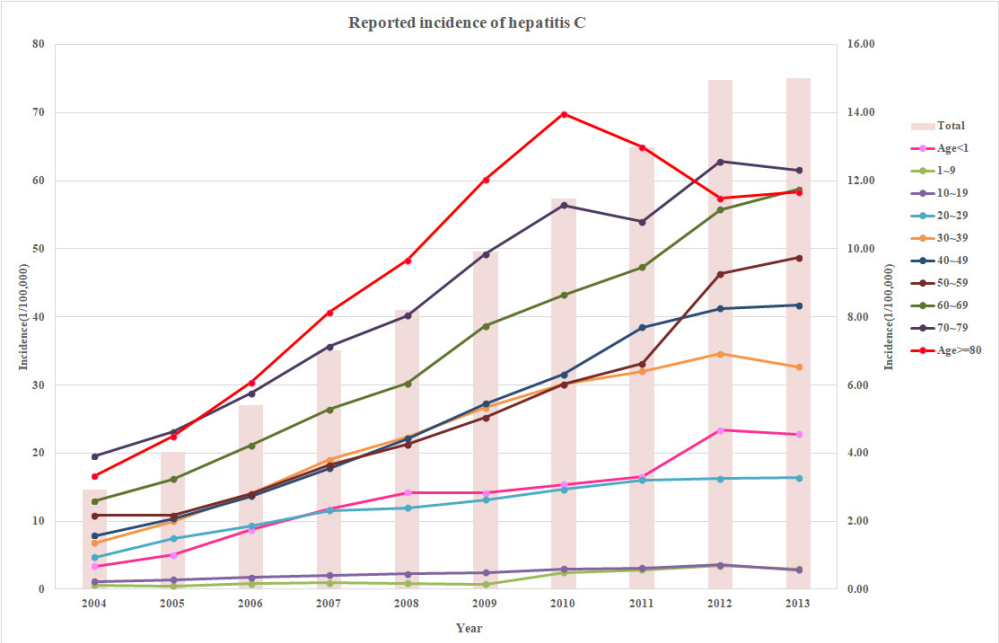

Reported incidence of hepatitis C from 2003 to 2013

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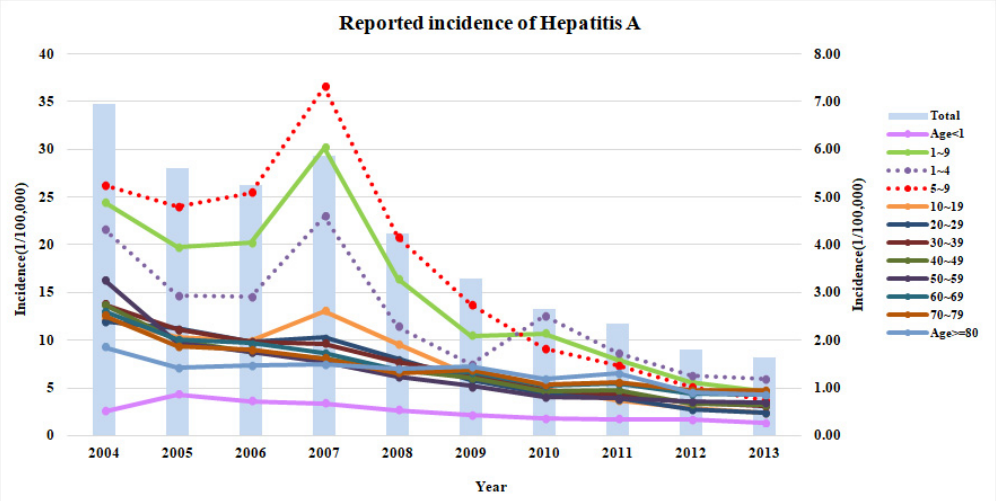

Reported incidence of hepatitis A from 2003 to 2013

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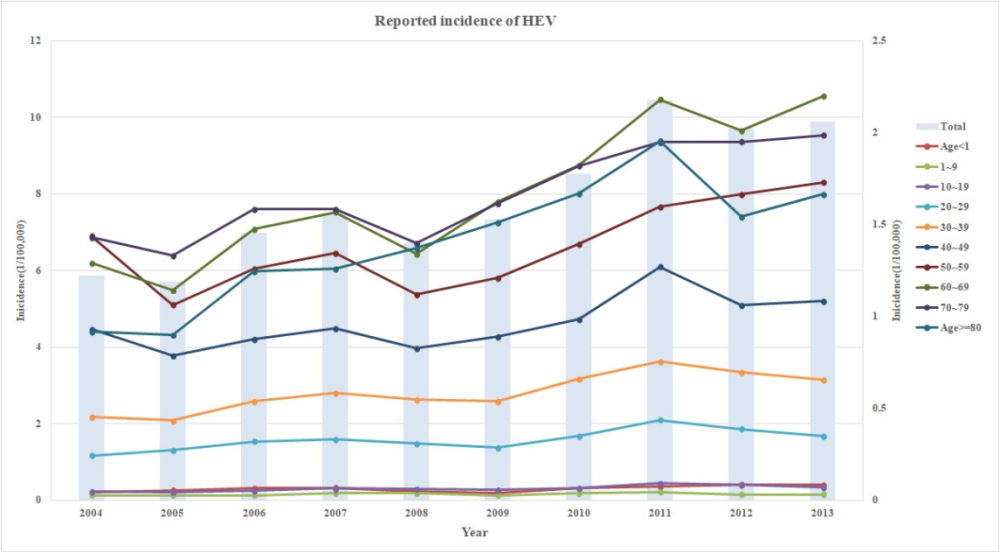

Reported incidence of hepatitis E from 2003 to 2013

102x56mm (300 x 300 DPI)

Appendix Table1.

Web-based Clinical reporting form(CRF)

<table>
<tr><td>Name:</td><td>Family member's Name:</td><td>Date of birth:</td><td>Age:</td><td>Gender:</td><td>Marital status:</td><td>Family address:</td></tr>
<tr><td colspan="2">ID number:</td><td colspan="2">Telephone number:</td><td colspan="3">Occupation:</td></tr>
<tr><td colspan="2">Degree of education:</td><td colspan="2">Nationality:</td><td colspan="3">Report disease name:</td></tr>
<tr><td colspan="2" rowspan="4">Classification of disease:</td><td colspan="5">i: Clinical diagnosis</td></tr>
<tr><td colspan="5">ii: Laboratory confirmationdiagnosis</td></tr>
<tr><td colspan="5">iii: Suspected cases</td></tr>
<tr><td colspan="5">iv: Pathogen carriers</td></tr>
<tr><td>Dates of onset:</td><td colspan="2">Date of being diagnosed:</td><td>Methods of diagnose:</td><td colspan="3">Date of death:</td></tr>
<tr><td colspan="3">Date of completing the CRF:</td><td colspan="3">Name of reporting doctor:</td><td>Department:</td></tr>
</table>

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Appendix Table2.

Diagnostic criteria for viral hepatitis by the law on the prevention and control of infectious diseases of the People's Republic of China, 2004

Viral hepatitis				
Clinical description	(I).Recently, there has been a loss of appetite, nausea, refused fatty food, fatigue, jaundice, tea color urine, liver enlargement, liver pain, fatigue, etc, exclude other diseases;			
Laboratory test	(II).Serum ALT elevated repeatedly and cannot be explained by other causes.			
Diagnose	**Suspected cases:(I)+(II)**			
Classification	**Hepatitis A**	**Hepatitis B**	**Hepatitis C**	**Hepatitis E**
Clinical description	1.One month (2-6 weeks) before the onset of illness, patients have been exposed to patients with Hepatitis A, or have been working or travelling, and eating, or directly coming from the prevalence area.	1. No more than half a year accepted treatment of blood and blood products, or have any medical damage such as insanitary injection, acupuncture, puncture, operation, or have a close contaction with HBV patients or carriers.	1.Have received blood and blood products in half a year, or have any medical damage.	1.Two months before the onset of the disease, patients had been exposed to hepatitis E infected patients, or went to the hepatitis E outbreak place, working, travelling, eating, or dinner together.
Laboratory test	2.1 Serum ALT elevated. 2.2 Serum anti-HAV-IgM positive. 2.3 Double serum anti-HAV-IgG titer increased by four times during convalescence after acute infection. 2.4 immuno-electron microscopy found 27nm HAV's particles in the feces.	2.1 Serum ALT elevated. 2.2 Serum HBsAg positive and anti-HBc IgM positive (greater than 1:1000) or HBV-DNA positive.	2.1 Serum ALT increased. 2.2 Not consistent with hepatitis A, hepatitis B, hepatitis E, CMV, EBV infection. 2.3 Serum anti-HCV positive.	2.1 Serum ALT elevated. 2.2 Serum anti-HEV IgM positive. 2.3 The immune electron microscopy showed 30-32nm particles in feces. 2.4 It is not consistent with hepatitis A, hepatitis B, CMV, EBV infection.
Diagnose	**Clinical diagnosis:** suspected cases+1+2.1 **Laboratory confirmation**	**Clinical diagnosis:** suspected cases+1+2.1 **Laboratory confirmation**	**Clinical diagnosis:** suspected cases+2.1+2.2, with 1 as supporting evidence	**Clinical diagnosis:** suspected cases+2.1+2.4, with 1 as supporting evidence

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	diagnosis: suspected cases+2.2 or suspected cases+2.3 or suspected cases+2.4	**diagnosis**: suspected cases+2.2	**Laboratory confirmation diagnosis**: suspected cases+2.3	**Laboratory confirmation diagnosis:** in accordance with the clinical diagnosis +2.2 or 2.3

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Appendix Table 3. Total Population, reported cases of viral hepatitis in total and different categories in China, from 2004-2016

Year	Total Population	Viral hepatitis （Rate）	HBV （Rate）	HCV （Rate）	HAV （Rate）	HEV （Rate）
2004	1,348,440,164	1,152,874(85.50)	916,426(67.96)	39,381(2.92)	93,587(6.94)	16,444(1.22)
2005	1,307,513,434	1,195,355(91.42)	982,297(75.13)	52,927(4.05)	73,349(5.61)	15,541(1.19)
2006	1,307,566,387	1,334,859(102.09)	1,109,130(84.82)	70,681(5.41)	68,667(5.25)	19,007(1.45)
2007	1,314,481,770	1,425,428(108.44)	1,169,946(89.00)	92,378(7.03)	77,135(5.87)	20,577(1.57)
2008	1,321,305,046	1,407,664(106.54)	1,169,569(88.52)	108,446(8.21)	56,052(4.24)	18,525(1.40)
2009	1,328,023,190	1,425,020(107.30)	1,179,607(88.82)	131,849(9.93)	43,841(3.30)	20,275(1.53)
2010	1,334,701,299	1,317,982(98.75)	1,060,582(79.46)	153,039(11.47)	35,277(2.64)	23,682(1.77)
2011	1,340,936,879	1,372,344(102.34)	1,093,335(81.54)	173,872(12.97)	31,456(2.35)	29,202(2.18)
2012	1,347,349,640	1,380,800(102.48)	1,087,086(80.68)	201,622(14.96)	24,453(1.81)	27,271(2.02)
2013	1,354,058,016	1,251,872(92.45)	962,974(71.12)	203,155(15.00)	22,244(1.64)	27,902(2.06)
2014	1,355,173,143	1,223,021(90.25)	935,702(69.05)	202,803(14.97)	25,969(1.92)	26,988(1.99)
2015	1,362,466,732	1,218,946(89.47)	934,215(68.57)	207,897(15.26)	22,667(1.66)	27,169(1.99)
2016	1,370,784,890	1,221,479(89.11)	942,268(68.74)	206,832(15.09)	21,285(1.55)	27,922(2.04)

Rate: indicates the proportion of reported cases among total population, the unit is 1/100,000

Data from the Chinese Communicable Disease Control Center's website (http://www.chinacdc.cn/) and the Yearbooks of Health in the people's republic of China

Appendix Table 4. Average annual percentage change(AAPC) and Annual percentage change(APC) of reported incidence of Viral hepatitis, hepatitis B, hepatitis C, hepatitis A, hepatitis E, with age distribution

Viral hepatitis	**Year**	**AAPC/APC(95%CI)**		**Trend**	**P-Value**
Viral hepatitis	2004-2016	AAPC	0.3%(-0.9～1.5)	Stable	0.6
	2004-2007	APC[1]	9.0%(3.7～14.6)	Increase	<0.05
	2007-2016	APC[2]	-2.4%(-3.3～-1.6)	Decrease	<0.05
HBV	**Year**	**AAPC/APC(95%CI)**		**Trend**	**P-Value**
	2004-2016	AAPC	-0.2%(-1.6～1.2)	Stable	0.8
	2004-2007	APC[1]	10.3%(4.1～16.9)	Increase	<0.05
	2007-2016	APC[2]	-3.5%(-4.5～-2.5)	Decrease	<0.05
HCV	**Year**	**AAPC/APC(95%CI)**		**Trend**	**P-Value**
	2004-2016	AAPC	14.5%(13.1～15.9)	Increase	<0.05
	2004-2007	APC[1]	34.4%(27.7～41.3)	Increase	<0.05
	2007-2012	APC[2]	15.9%(13.6～18.2)	Increase	<0.05
	2012-2016	APC[3]	0.1%(-1.5～1.7)	Stable	0.9
HAV	**Year**	**AAPC/APC(95%CI)**		**Trend**	**P-Value**
	2004-2016	AAPC	-13.1%(-15.1, -11.0)	Decrease	<0.05
HEV	**Year**	**AAPC/APC(95%CI)**		**Trend**	**P-Value**
	2004-2016	AAPC	4.7%(2.8～6.7)	Increase	<0.05
	2004-2011	APC[1]	8.1%(5.2～11.0)	Increase	<0.05
	2011-2016	APC[2]	0.3%(-3.4～4.1)	Stable	0.9

APCC: Average annual percentage change; APC:Annual percentage change; HBV: Hepatitis B, HCV: Hepatitis C, HAV: Hepatitis A, HEV: Hepatitis E.

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Appendix Table 5. Average annual percentage change(AAPC) and Annual percentage change(APC) of reported incidence of hepatitis B, hepatitis C, hepatitis A, hepatitis E, with age distribution

HBV	Year	AAPC/APC(95%CI)		Trend	P-Value
Age<1	2004-2013	APC	0.4%(-2.7～3.6)	Stable	0.8
1~9	2004-2013	AAPC	-15.5%(-18.4～-12.4)	Decrease	<0.05
	2004-2006	APC[1]	-3.9%(-18.8～13.7)	Decrease	0.6
	2006-2013	APC[2]	-18.5%(-21.3～-15.5)	Decrease	<0.05
10~19	2004-2013	AAPC	-12.1%(-14.4～-9.7)	Decrease	<0.05
	2004-2007	APC[1]	0.9%(-6.1～8.4)	Stable	0.8
	2007-2013	APC[2]	-18.0%(-21.1～-14.7)	Decrease	<0.05
20~24	2004-2013	AAPC	-4.4%(-7.7～-1.0)	Decrease	<0.05
	2004-2008	APC[1]	4.3%(-3.4～12.6)	Stable	0.2
	2008-2013	APC[2]	-10.8%(-15.7～-5.7)	Decrease	<0.05
25~29	2004-2013	AAPC	0.2%(-2.0～2.5)	Stable	0.9
	2004-2007	APC[1]	10.9%(3.1～19.4)	Increase	<0.05
	2007-2013	APC[2]	-4.8%(-7.1～-2.4)	Decrease	<0.05
30~39	2004-2013	AAPC	-1.1%(-1.0～3.2)	Stable	0.3
	2004-2007	APC[1]	12.0%(4.8～19.7)	Increase	<0.05
	2007-2013	APC[2]	-3.9%(-6.1～-1.7)	Decrease	<0.05
40~49	2004-2013	AAPC	1.2%(-1.2～3.5)	Stable	0.3
	2004-2006	APC[1]	6.8%(2.7～11.0)	Stable	<0.05
	2006-2013	APC[2]	-5.5%(-9.9～-0.8)	Decrease	<0.05
50~59	2004-2013	APC	2.5%(0.8～4.3)	Increase	<0.05
60~69	2004-2013	AAPC	7.1%(4.9～9.4)	Increase	<0.05
	2004-2008	APC[1]	14.3%(8.7～20.3)	Increase	<0.05
	2008-2013	APC[2]	1.6%(-1.1～4.5)	Stable	0.2
70~79	2004-2013	AAPC	6.4%(3.8～9.0)	Increase	<0.05
	2004-2009	APC[1]	12.0%(7.3～16.9)	Increase	<0.05
	2009-2013	APC[2]	-0.2%(-4.8～4.7)	Stable	0.9
Age>=80	2004-2013	AAPC	6.8%(4.8～8.9)	Increase	<0.05
	2004-2009	APC[1]	18.5%(14.4～22.8)	Increase	<0.05
	2009-2013	APC[2]	-6.1%(-9.4～-2.8)	Decrease	<0.05
HCV	**Year**	**AAPC/APC(95%CI)**		**Trend**	**P-Value**
Age<1	2004-2013	AAPC	23.2%(13.1～34.2)	Increase	<0.05
	2004-2007	APC[1]	50.0%(9.2～106.0)	Increase	<0.05
	2007-2013	APC[2]	11.7%(5.5～18.2)	Increase	<0.05
1~9	2004-2013	APC	25.9%(15.9～36.8)	Increase	<0.05
10~19	2004-2013	AAPC	10.4%(6.9～14.0)	Increase	<0.05
	2004-2011	APC[1]	15.3%(12.4～18.3)	Increase	<0.05
	2011-2013	APC[2]	-5.1%(-19.7～12.1)	Stable	0.5
20~29	2004-2013	AAPC	14.2%(9.7～18.8)	Increase	<0.05
	2004-2007	APC[1]	31.6%(14.0～51.8)	Increase	<0.05

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	2007-2013	APC[2]	6.3%(3.0～9.8)	Increase	<0.05
30~39	2004-2013	AAPC	17.7%(13.8～21.9)	Increase	<0.05
	2004-2009	APC[1]	29.7%(21.5～38.4)	Increase	<0.05
	2009-2013	APC[2]	4.4%(-1.8～10.9)	Stable	0.1
40~49	2004-2013	AAPC	18.8%(15.8～21.9)	Increase	<0.05
	2004-2011	APC[1]	24.0%(20.5～27.5)	Increase	<0.05
	2011-2013	APC[2]	2.5%(-8.7～15.1)	Stable	0.6
50~59	2004-2013	AAPC	19.5%(17.4～21.7)	Increase	<0.05
60~69	2004-2013	AAPC	18.1%（15.6～20.7）	Increase	<0.05
	2004-2009	APC[1]	23.7%（18.6～29.0）	Increase	<0.05
	2009-2013	APC[2]	11.5%（7.8～15.4）	Increase	<0.05
70~79	2004-2013	AAPC	14.0%（10.9～17.2）	Increase	<0.05
	2004-2009	APC[1]	21.0%（14.7～27.6）	Increase	<0.05
	2009-2013	APC[2]	5.8%(0.9～11.0)	Increase	<0.05
Age>=80	2004-2013	AAPC	12.6%(9.5～15.8)	Increase	<0.05
	2004-2010	APC[1]	24.6%(19.6～29.9)	Increase	<0.05
	2010-2013	APC[2]	-8.1%(-14.6～-1.2)	Increase	<0.05
HAV	**Year**	**AAPC/APC(95%CI)**		**Trend**	**P-Value**
Age<1	2004-2013	APC	-11.1%(-15.9～-5.9)	Decrease	<0.05
1~4	2004-2013	APC	-12.3%(-19.2～-4.9)	Decrease	<0.05
5~9	2004-2013	AAPC	-20.1%(-22.4～-17.7)	Decrease	<0.05
	2004-2007	APC[1]	9.7%(2.0～17.9)	Increase	<0.05
	2007-2013	APC[2]	-31.7%(-34.8～-28.6)	Decrease	<0.05
10~19	2004-2013	AAPC	-16.6%(-19.4～-13.7)	Decrease	<0.05
	2004-2007	APC[1]	2.3%(-6.1～11.5)	Stable	0.5
	2007-2013	APC[2]	-24.8%(-28.5～-20.8)	Decrease	<0.05
20~29	2004-2013	APC	-16.7%(-18.9～-14.5)	Decrease	<0.05
	2004-2007	APC[1]	-5.8%(-12.3～1.1)	Stable	0.1
	2007-2013	APC[2]	-21.7%(-24.5～-18.7)	Decrease	<0.05
30~39	2004-2013	APC	-15.1%(-16.8～-13.4)	Decrease	<0.05
40~49	2004-2013	APC	-14.3%(-15.9～-12.7)	Decrease	<0.05
50~59	2004-2013	APC	-16.1%(-19.2～-12.9)	Decrease	<0.05
60~69	2004-2013	APC	-11.6%(-13.1～-10.1)	Decrease	<0.05
70~79	2004-2013	APC	-10.1%(-12.0～-8.2)	Decrease	<0.05
Age>=80	2004-2013	APC	-6.7%(-9.3～-3.9)	Decrease	<0.05
HEV	**Year**	**AAPC/APC(95%CI)**		**Trend**	**P-Value**
Age<1	2004-2013	APC	5.8%(0.7～11.2)	Increase	<0.05
1~9	2004-2013	APC	3.0%(-2.0～8.2)	Stable	0.2
10~19	2004-2013	APC	6.8%(3.3～10.5)	Increase	<0.05
20~29	2004-2013	APC	4.5%(1.5～7.7)	Increase	<0.05

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30~39	2004-2013	APC	5.4%(2.9～7.9)	Increase	<0.05
40~49	2004-2013	APC	3.6%(0.8～6.5)	Increase	<0.05
50~59	2004-2013	APC	4.2%(1.1～7.4)	Increase	<0.05
60~69	2004-2013	APC	7.1%(4.7～9.6)	Increase	<0.05
70~79	2004-2013	APC	4.6%(2.8～6.3)	Increase	<0.05
Age>=80	2004-2013	APC	6.2%(2.7～9.9)	Increase	<0.05
	2004-2011	APC[1]	10.6%(2.1～14.2)	Increase	<0.05
	2011-2013	APC[2]	-7.6%(-21.6～8.9)	Decrease	0.3

APCC: Average annual percentage change; APC:Annual percentage change; HBV: Hepatitis B, HCV: Hepatitis C, HAV: Hepatitis A, HEV: Hepatitis E.

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Appendix Table 6. Date of birth of reported HBV cases in different age groups from 2004-2013

Age groups	Date of birth	Trend	*P* value	Joinpoint	Date of birth	Trend	*P* value
10~19	1985-2003	Decrease	<0.05	2007	1985-1997	Stable	0.8
					1988-2003	Decrease	<0.05
20~24	1980-1993	Decrease	<0.05	2008	1980-1988	Stable	0.2
					1984-1993	Decrease	<0.05
25~29	1975-1988	Stable	0.9	2007	1975-1982	Increase	<0.05
					1978-1988	Decrease	<0.05
30~39	1965-1983	Stable	0.3	2007	1965-1977	Increase	<0.05
					1968-1983	Decrease	<0.05

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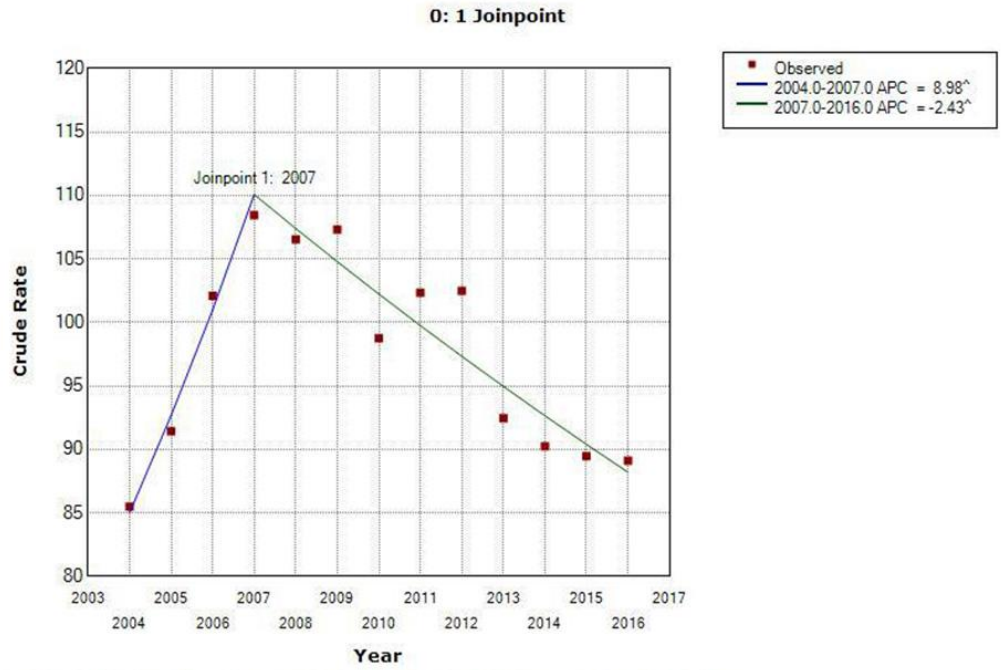
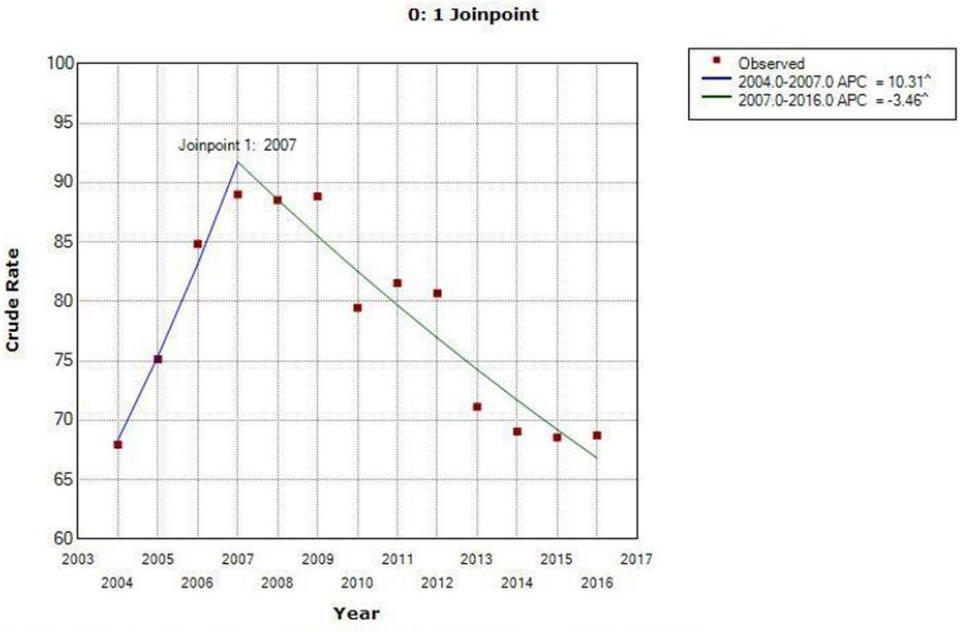
Appendix Figure 1. Joinpoint analysis of viral hepatitis and hepatitis B, hepatitis C, hepatitis A and hepatitis E

1.1 Viral hepatitis



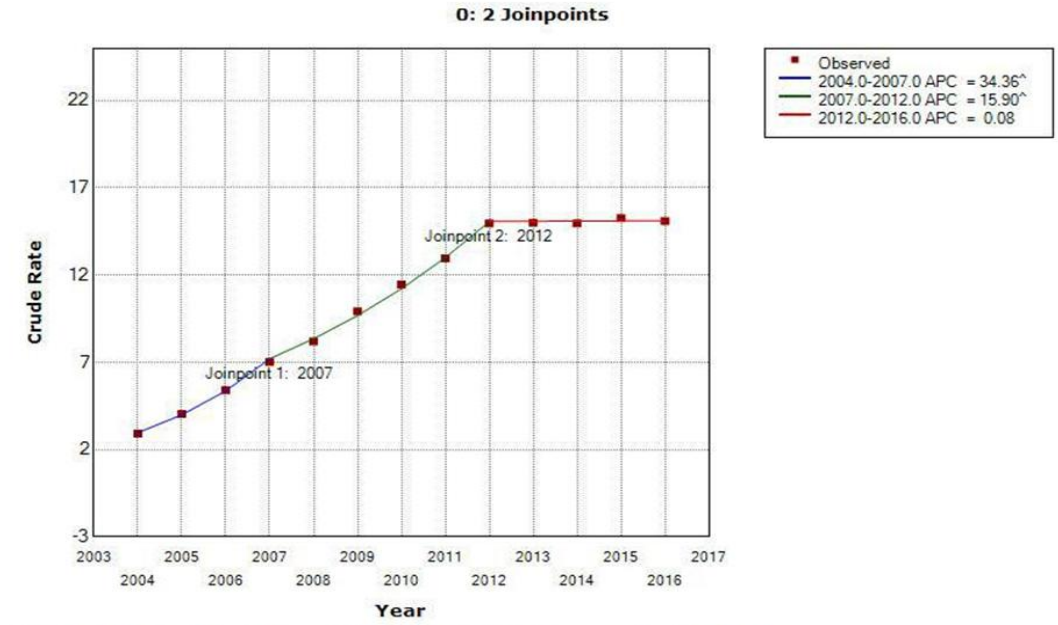
^ Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 1 Joinpoint.

1.2 Hepatitis B



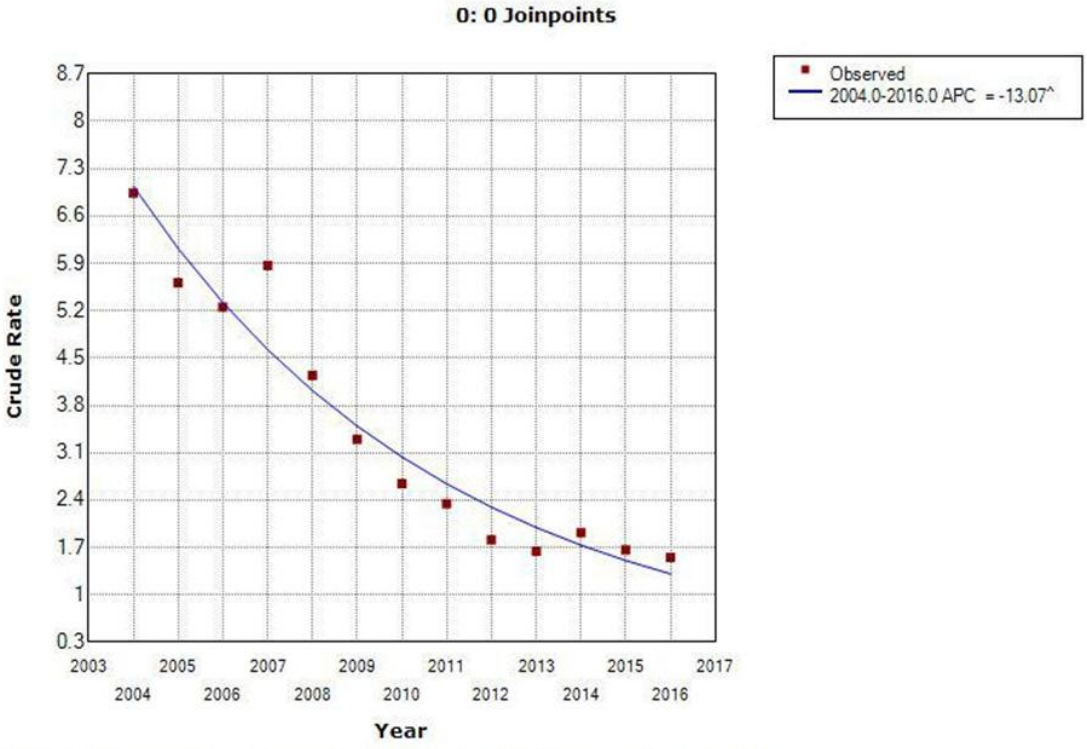
^ Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 1 Joinpoint.

1.3 Hepatitis C



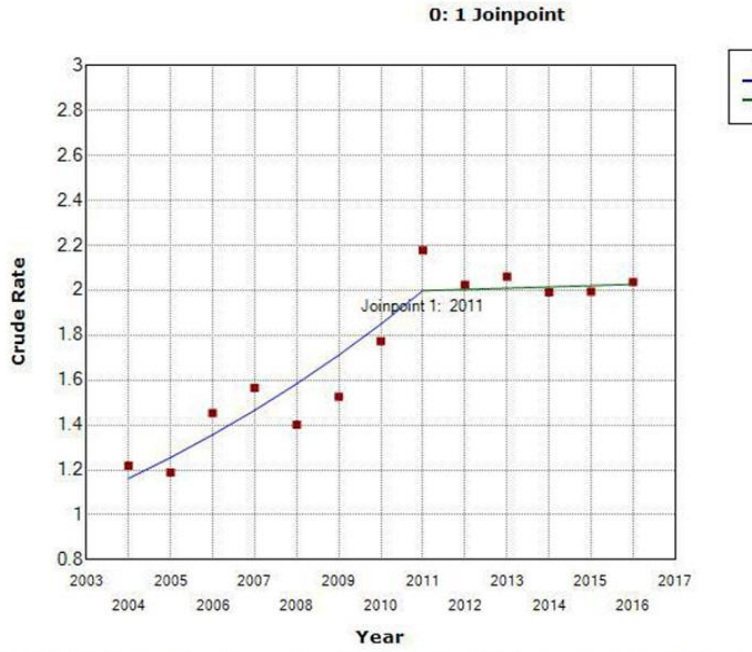
^ Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 2 Joinpoints.

1.4 Hepatitis A



^ Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 0 Joinpoints.

1.5 Hepatitis E



^ Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 1 Joinpoint.

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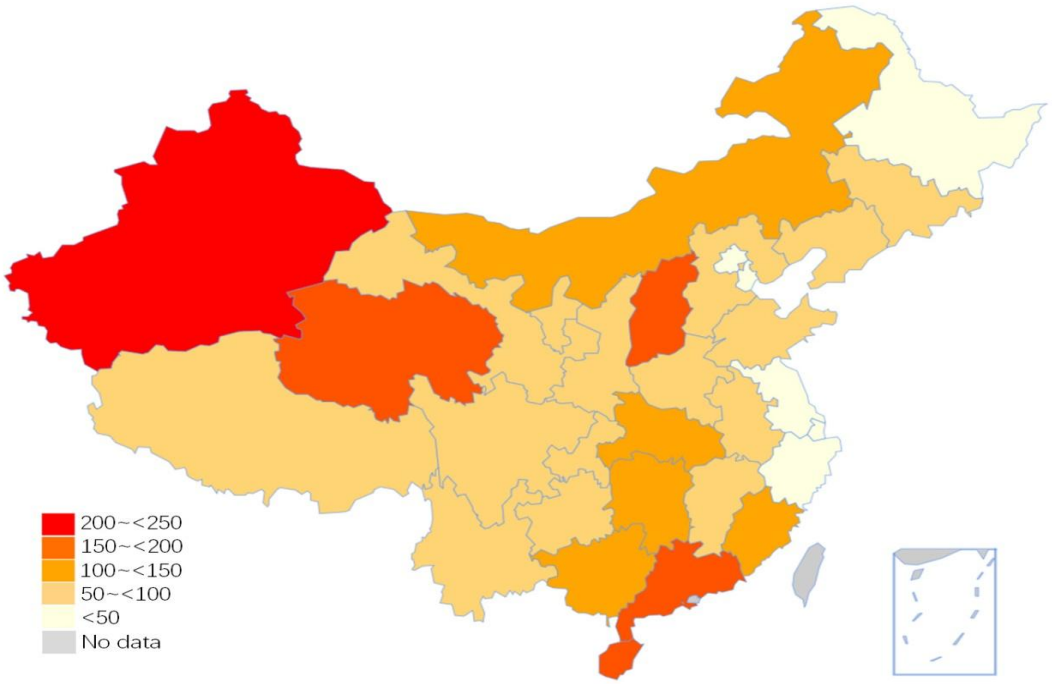
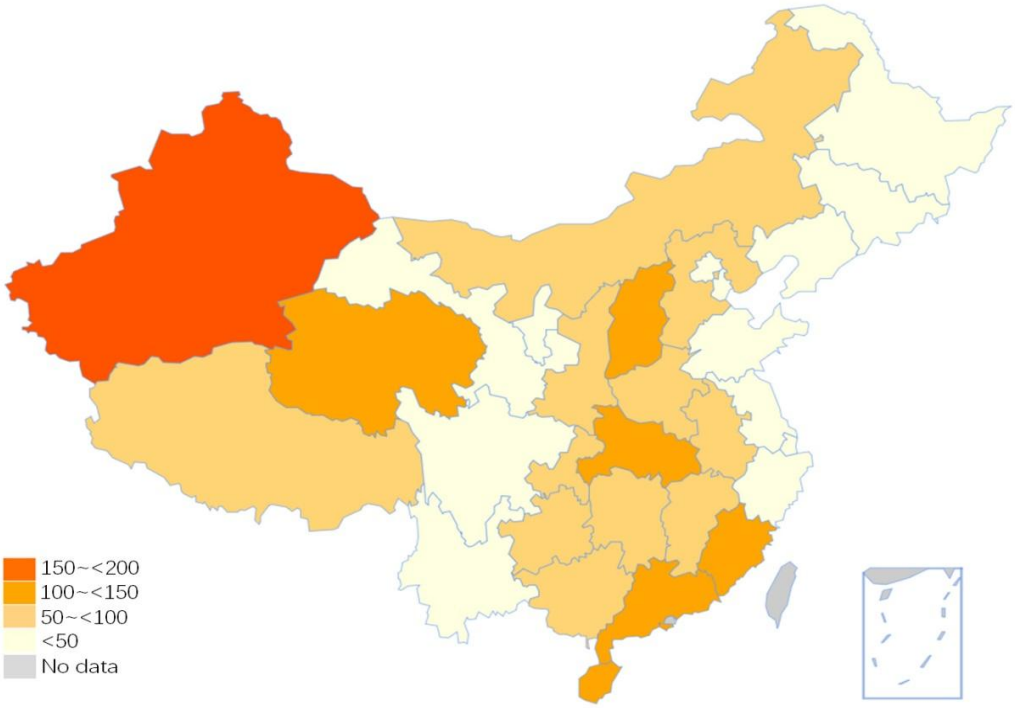
Appendix Figure 2: Reported incidence of viral hepatitis(2A), hepatitis B(2B), and hepatitis C(2C) in different provinces of China, 2015 (The authors generated all these maps by R language software, no copyright issue)

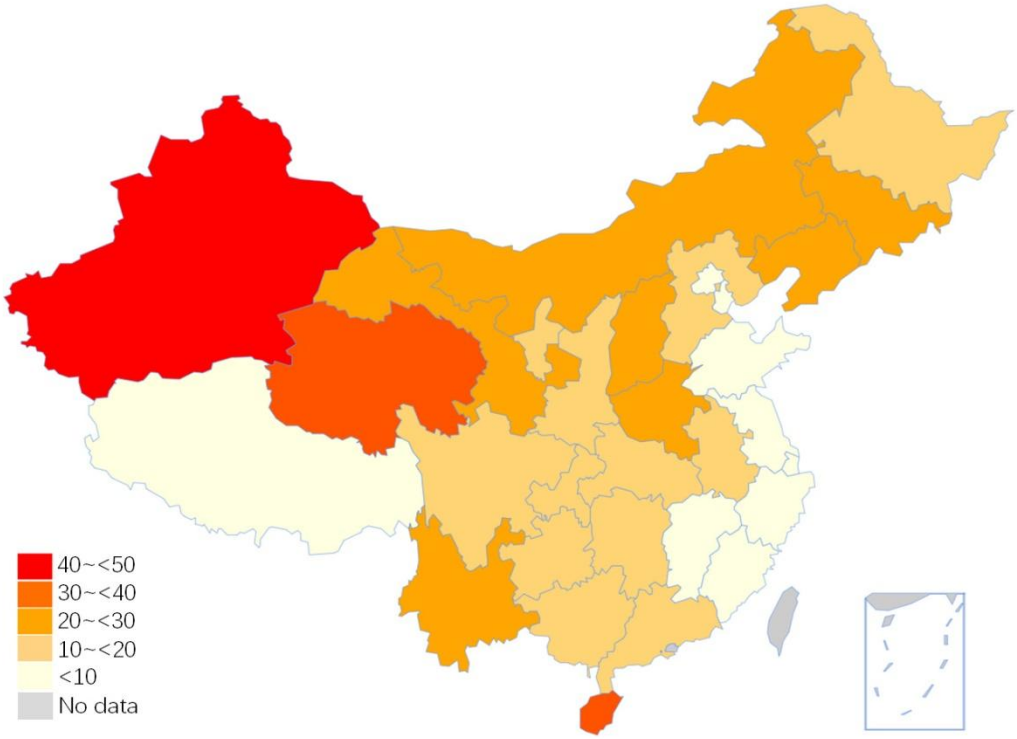
(2A)



(2B)



(2C)



Data Source: National Health and Family Planning Commission of the People's Republic of China, Health and family planning statistical Yearbook of China, Beijing, 2016

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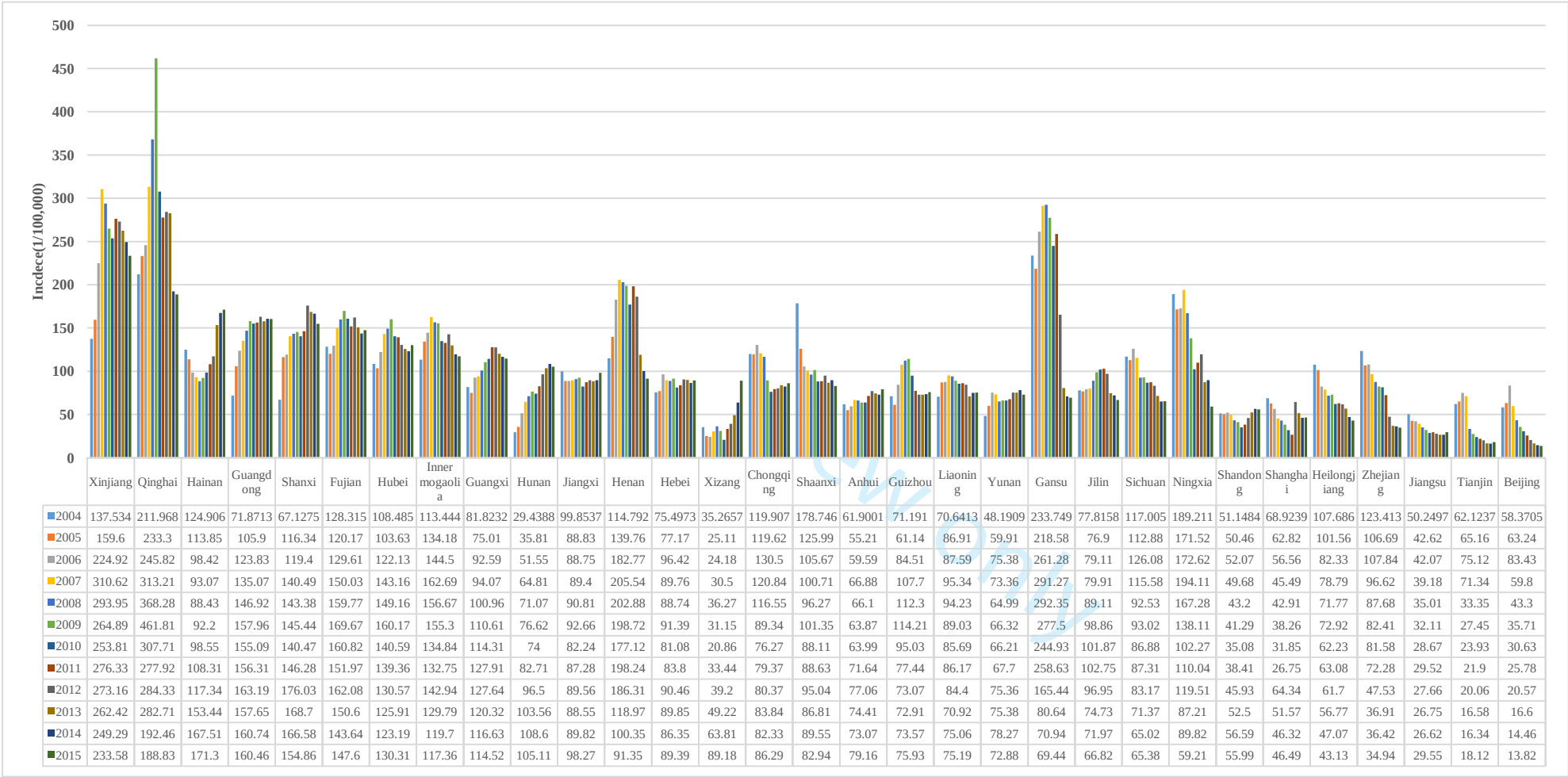
Appendix Figure 3: Annual reported incidence of viral hepatitis overall in different provinces, China, 2004-2015

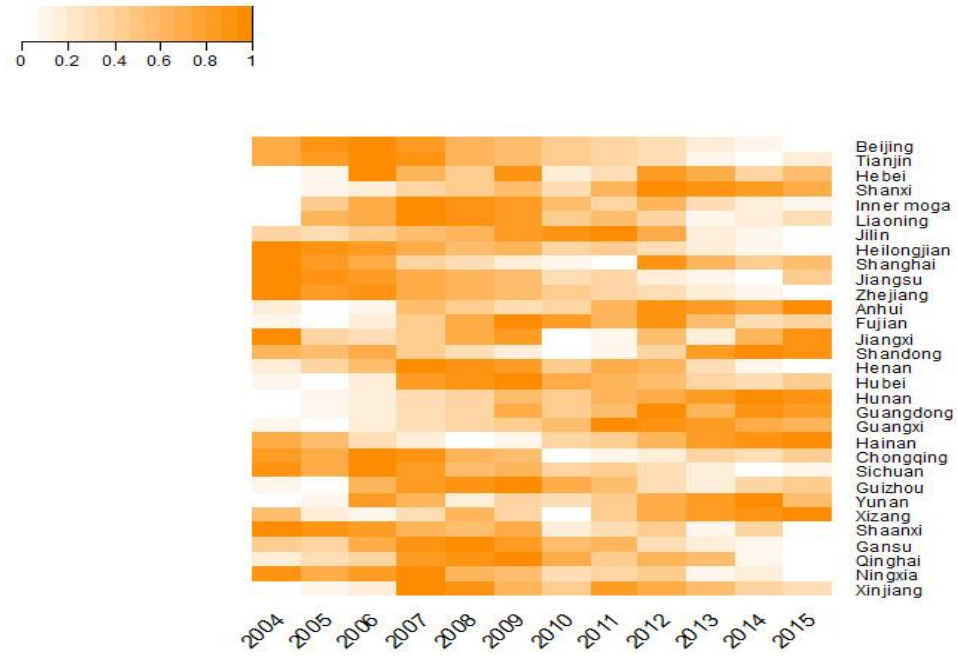


	Xinjiang	Qinghai	Hainan	Guangdong	Shanxi	Fujian	Hubei	Inner mogaolia	Guangxi	Hunan	Jiangxi	Henan	Hebei	Xizang	Chongqing	Shaanxi	Anhui	Guizhou	Liaoning	Yunan	Gansu	Jilin	Sichuan	Ningxia	Shandong	Shanghai	Heilongjiang	Zhejiang	Jiangsu	Tianjin	Beijing
2004	137.534	211.968	124.906	71.8713	67.1275	128.315	108.485	113.444	81.8232	29.4388	99.8537	114.792	75.4973	35.2657	119.907	178.746	61.9001	71.191	70.6413	48.1909	233.749	77.8158	117.005	189.211	51.1484	68.9239	107.686	123.413	50.2497	62.1237	58.3705
2005	159.6	233.3	113.85	105.9	116.34	120.17	103.63	134.18	75.01	35.81	88.83	139.76	77.17	25.11	119.62	125.99	55.21	61.14	86.91	59.91	218.58	76.9	112.88	171.52	50.46	62.82	101.56	106.69	42.62	65.16	63.24
2006	224.92	245.82	98.42	123.83	119.4	129.61	122.13	144.5	92.59	51.55	88.75	182.77	96.42	24.18	130.5	105.67	59.59	84.51	87.59	75.38	261.28	79.11	126.08	172.62	52.07	56.56	82.33	107.84	42.07	75.12	83.43
2007	310.62	313.21	93.07	135.07	140.49	150.03	143.16	162.69	94.07	64.81	89.4	205.54	89.76	30.5	120.84	100.71	66.88	107.7	95.34	73.36	291.27	79.91	115.58	194.11	49.68	45.49	78.79	96.62	39.18	71.34	59.8
2008	293.95	368.28	88.43	146.92	143.38	159.77	149.16	156.67	100.96	71.07	90.81	202.88	88.74	36.27	116.55	96.27	66.1	112.3	94.23	64.99	292.35	89.11	92.53	167.28	43.2	42.91	71.77	87.68	35.01	33.35	43.3
2009	264.89	461.81	92.2	157.96	145.44	169.67	160.17	155.3	110.61	76.62	92.66	198.72	91.39	31.15	89.34	101.35	63.87	114.21	89.03	66.32	277.5	98.86	93.02	138.11	41.29	38.26	72.92	82.41	32.11	27.45	35.71
2010	253.81	307.71	98.55	155.09	140.47	160.82	140.59	134.84	114.31	74	82.24	177.12	81.08	20.86	76.27	88.11	63.99	95.03	85.69	66.21	244.93	101.87	86.88	102.27	35.08	31.85	62.23	81.58	28.67	23.93	30.63
2011	276.33	277.92	108.31	156.31	146.28	151.97	139.36	132.75	127.91	82.71	87.28	198.24	83.8	33.44	79.37	88.63	71.64	77.44	86.17	67.7	258.63	102.75	87.31	110.04	38.41	26.75	63.08	72.28	29.52	21.9	25.78
2012	273.16	284.33	117.34	163.19	176.03	162.08	130.57	142.94	127.64	96.5	89.56	186.31	90.46	39.2	80.37	95.04	77.06	73.07	84.4	75.36	165.44	96.95	83.17	119.51	45.93	64.34	61.7	47.53	27.66	20.06	20.57
2013	262.42	282.71	153.44	157.65	168.7	150.6	125.91	129.79	120.32	103.56	88.55	118.97	89.85	49.22	83.84	86.81	74.41	72.91	70.92	75.38	80.64	74.73	71.37	87.21	52.5	51.57	56.77	36.91	26.75	16.58	16.6
2014	249.29	192.46	167.51	160.74	166.58	143.64	123.19	119.7	116.63	108.6	89.82	100.35	86.35	63.81	82.33	89.55	73.07	73.57	75.06	78.27	70.94	71.97	65.02	89.82	56.59	46.32	47.07	36.42	26.62	16.34	14.46
2015	233.58	188.83	171.3	160.46	154.86	147.6	130.31	117.36	114.52	105.11	98.27	91.35	89.39	89.18	86.29	82.94	79.16	75.93	75.19	72.88	69.44	66.82	65.38	59.21	55.99	46.49	43.13	34.94	29.55	18.12	13.82

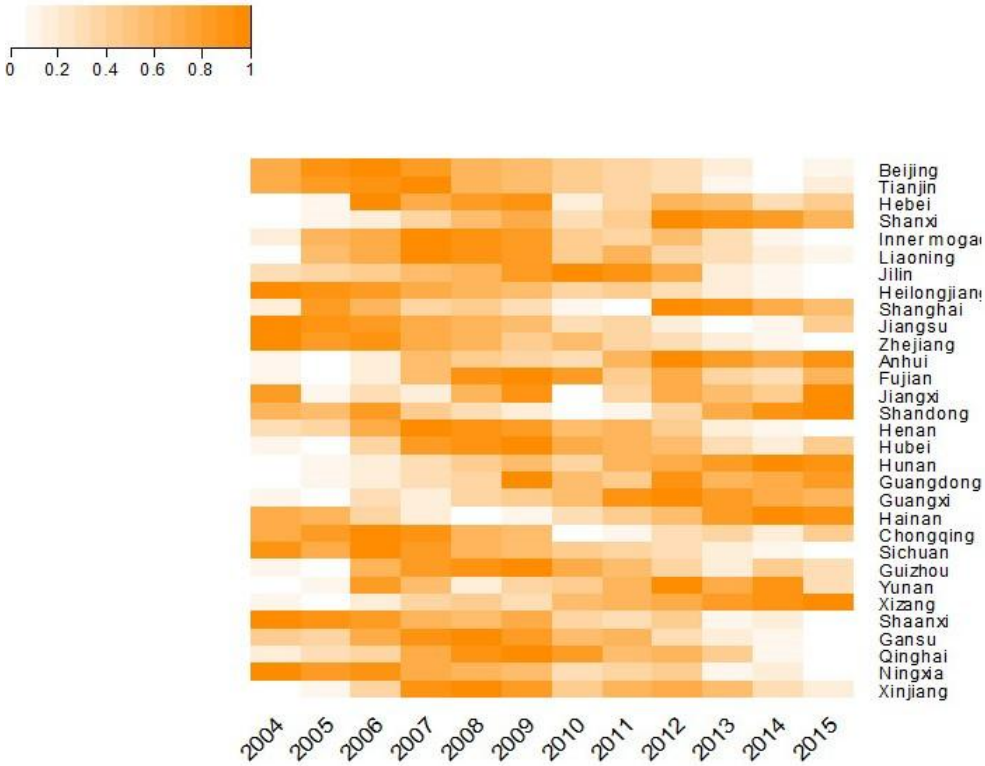
Data Source: China Center for Disease Control and Prevention. The Public Health Science Data Center. http://www.phsciencedata.cn/Share/index.jsp

Appendix Figure 4. Heatmap of annual reported incidence of viral hepatitis in total and by different types of hepatitis, different data provinces of China, 2004-2015

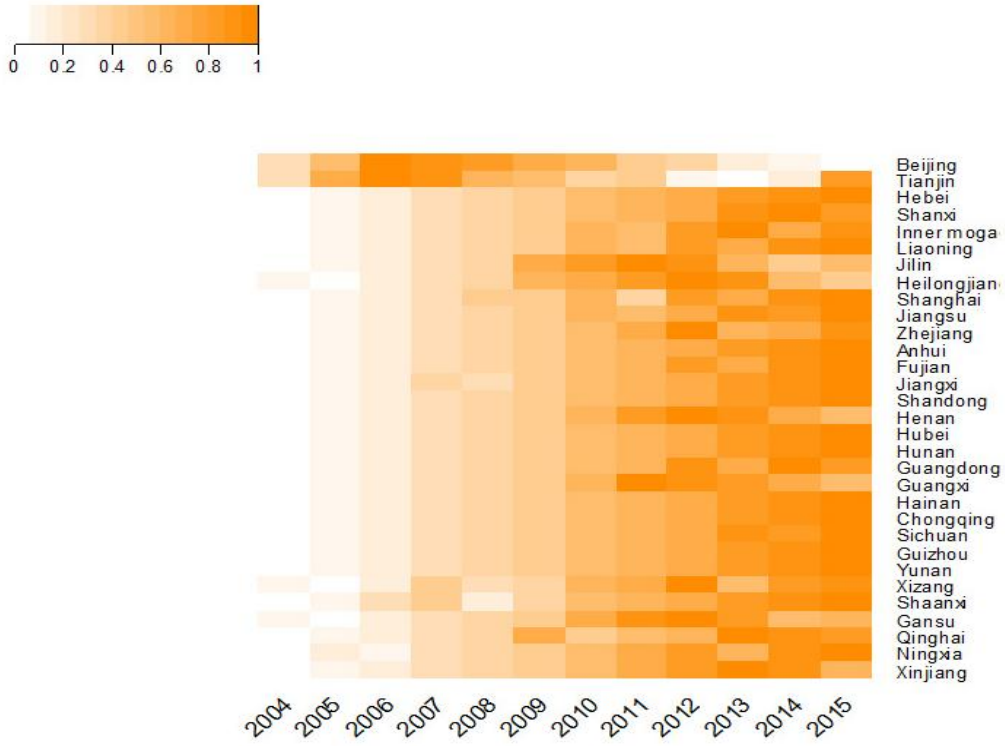
4.1 Viral hepatitis



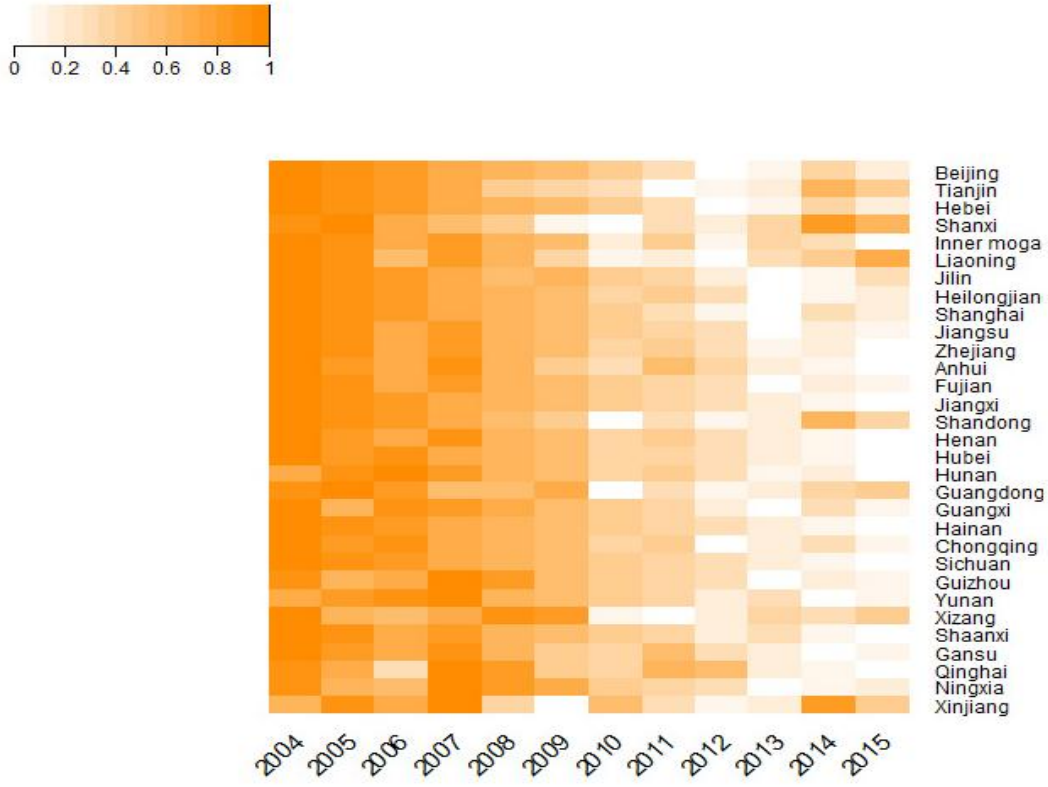
4.2 Hepatitis B



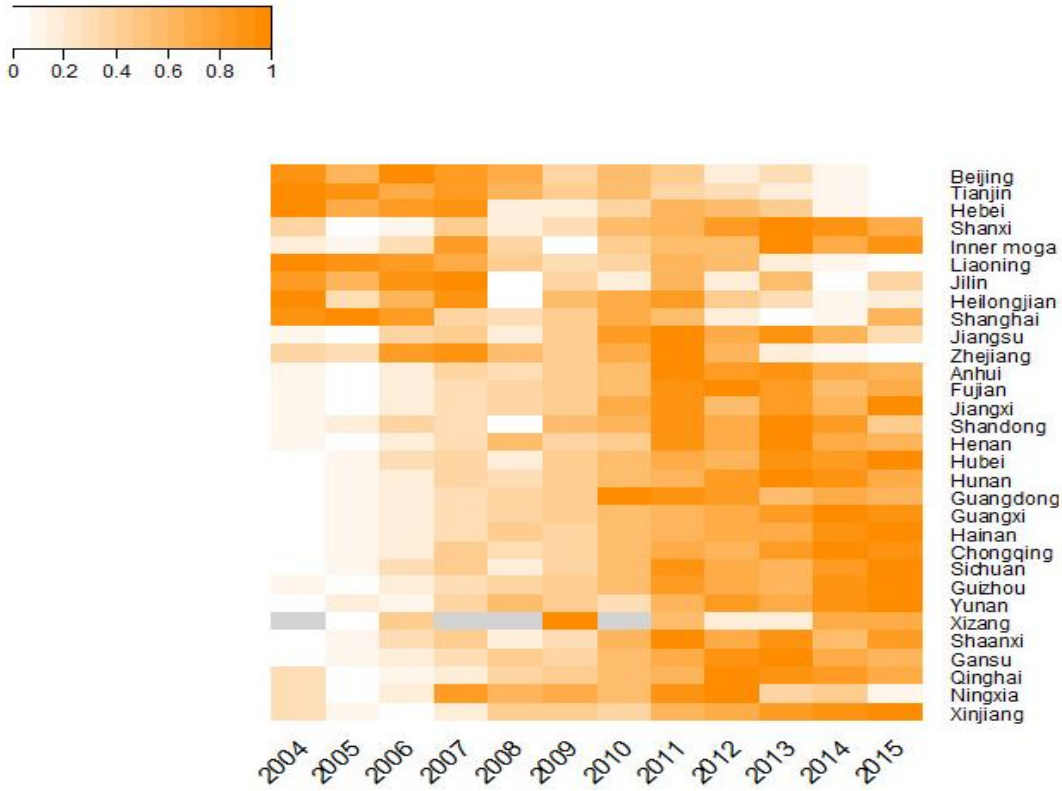
4.3 Hepatitis C



4.4 Hepatitis A



4.5 Hepatitis E



Lightgray: means that data were not availiable

Data Source: China Center for Disease Control and Prevention. The Public Health Science Data Center. http://www.phsciencedata.cn/Share/index.jsp

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract （Page 3）	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale （Page 4）	2	Explain the scientific background and rationale for the investigation being reported
Objectives （Page 4）	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design （Page 4&5）	4	Present key elements of study design early in the paper
Setting （Page 4&5）	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants （Page 4&5）	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables （Page 5）	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement （Page 4&5）	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size （Page 4）	10	Explain how the study size was arrived at
Quantitative variables （Page 5）	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods （Page 5）	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

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Results		
Participants （Page 5&6）	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data （Page 5&6）	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data （Page 5&6&7&8）	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results （Page 5&6&7&8）	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses （Page 5&6&7&8）	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results （Page 8&9&10）	18	Summarise key results with reference to study objectives
Limitations （Page 10）	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation （Page 8,9,10,11）	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability （Page 10&11）	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding （Page 11）	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at

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http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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