Changing Epidemiology of Hepatitis A and Hepatitis E Viruses in China, 1990–2014

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We compared the epidemiology of hepatitis A and hepatitis E cases in China from 1990–2014 to better inform policy and prevention efforts. The incidence of hepatitis A cases declined dramatically, while hepatitis E incidence increased. During 2004–2014, hepatitis E mortality rates surpassed those of hepatitis A.

Hepatitis A virus (HAV) and hepatitis E virus (HEV) cause acute hepatitis in humans and are transmitted mainly through the fecal–oral route. Hepatitis A and hepatitis E became notifiable in China in 1990 and 1996, respectively. Since the introduction of the hepatitis A vaccine and the start of mass vaccination in several countries in the 1980s, hepatitis A incidence declined substantially, not only among vaccinated children but in the population as whole (*1*,*2*). China first licensed its live attenuated hepatitis A vaccine in 1992 and later the inactivated hepatitis A vaccine in 2002 (*3*). The hepatitis A vaccine was initially introduced into the private market, although some provinces provided subsidies through the World Health Organization Expanded Programme on Immunization (http://www.wpro.who.int/china/areas/immunization/en/). Starting in May 2008, hepatitis A vaccinations were incorporated into the routine national childhood immunization program for children >18 months of age (*3*).

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HEV is a substantial cause of illness and death worldwide, particularly among pregnant women (*4*). Until the introduction of the first hepatitis E vaccine to private markets in China in 2011, there were no specific pharmaceutical interventions for HEV (*5*). Given the similarity in diseases caused by HAV and HEV and the recent decline in hepatitis A incidence, we compared the epidemiology of human cases infected with the 2 pathogens in China.

The Study

We obtained data on cases of hepatitis A reported during 1990–2014 and hepatitis E for 1997–2014 from China's National Notifiable Disease Report System and collated demographic information from the China National Bureau of Statistics. We defined confirmed cases on the basis of dates of disease onset and updated diagnostic criteria issued by the Chinese Ministry of Health in 2008; these critera are based on epidemiologic history, clinical signs, and laboratory test results (online Technical Appendix Table, https://wwwnc.cdc.gov/EID/article/23/2/16-1095-Techapp1.pdf)

We used R version 3.0.1 (R Foundation for Statistical Computing, Vienna, Austria) and SAS version 9.2 (SAS Institute Inc., Cary, NC, USA) to estimate annual incidence and mortality rates for hepatitis A and hepatitis E according to patient age and sex. Notified cases were geocoded into provinces and mapped by ArcGIS 10 (Esri Inc., Redlands, CA, USA). To examine seasonality, we created heat maps by using monthly incidence normalized to the maximum incidence each year. We used a similar approach to examine seasonality across latitudes. We assessed potential associations between incidence and demographic and economic factors by using Poisson regression.

Hepatitis A incidence dropped from 55.7 cases/100,000 person-years in 1991 to 1.9 cases/100,000 person-years in 2014, a decrease of 96.6% (Figure 1). In contrast, hepatitis E incidence increased significantly over this period, from 0.21 cases/100,000 person-years in 1997 to 1.99 cases/100,000 person-years in 2014, an 8-fold increase ($p<0.0001$ by Poisson regression) (Figure 1). The mortality and incidence rates for hepatitis E overtook those for hepatitis A in 2004 and 2011, respectively (Figure 1). Hepatitis E cases across the country were most frequently reported in March (online Technical Appendix Figures 4, 5). This change may result from increased temperature and rainfall in the spring, which could increase the likelihood of acquiring

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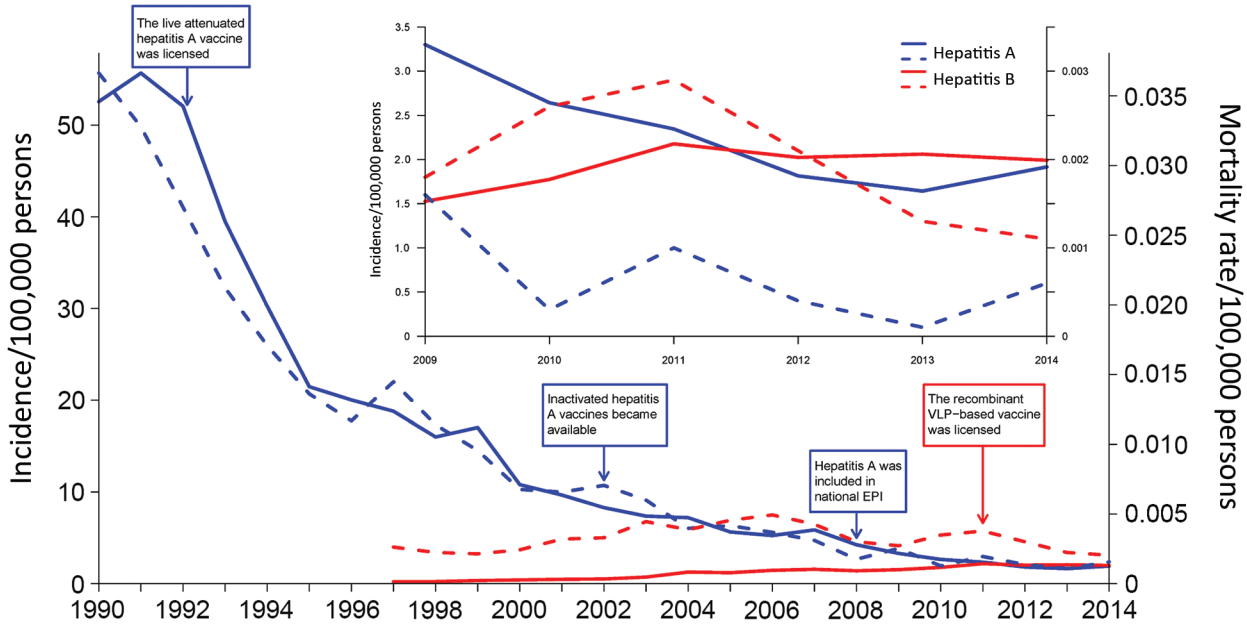

Figure 1. Annual incidence (solid lines) and mortality rates (dashed lines) of notified hepatitis A (blue) and E (red) cases in China, 1990–2014. The inset shows an enlarged view of rates during 2009–2014. EPI, Expanded Program on Immunization; VLP, virus-like particle.

HEV infection from exposure to contaminated water, such as water sourced from a stream near a free-range pig farm (*6–8*). In contrast, the seasonal pattern of HAV infections varied by latitude; cases were reported most frequently in the spring in southern provinces and in the autumn in most northern provinces (online Technical Appendix Figure 5). The decline in the incidence of hepatitis A cases in winter and summer varies by province, and reasons for the differential latitudinal pattern are unclear (*7–9*).

Hepatitis A incidence was highest among children and young adults (Figure 2). In contrast, hepatitis E incidence was highest among older adults and low among children and young adults (Figure 2). For both diseases, incidence and mortality rates were higher among male patients, and mortality rates tended to increase with age (Figure 2). The percentage of infections resulting in death were generally similar among men and women within each age group for most years (online Technical Appendix Figure 2).

We found considerable changes in the epidemiology of hepatitis A and E over time in mainland China. The major decline in hepatitis A incidence during 1992–2014 cannot be explained solely by the introduction of the vaccine because implementation of vaccinations in the general population had been relatively low until the inactivated hepatitis A vaccine was included in the national Expanded Program on Immunization in May 2008 (*3*). Other key reasons could be heightened public awareness, improved social hygiene, and upgrades in sewage treatment and water quality (*9-11*). Decreasing incidence was also accompanied by a change Hin the age distribution of reported hepatitis A case-patients; the average age increased over time (Figure 2), possibly a consequence of inclusion of the vaccine in the national Expanded Program on Immunization, which targets children >18 months of age. The incidence of hepatitis A is now highest in northwestern China, which is a comparatively less developed region of the country (online Technical Appendix Figure 1).

Our findings in China are similar to those documented in other countries, where HEV infection is now more common than HAV infection (*12*,*13*). The increase in hepatitis E incidence could result from either a true increase in the number of cases or from improved case diagnosis. Hepatitis E case-patients are mostly adults, particularly older adults (Figure 2). Although we did not have data on HEV genotypes for this study, it is possible that the change in age distribution of hepatitis E patients may result from the shift of the prevalent HEV genotype in China from genotype 1 to genotype 4 (and, to a lesser extent, genotype 3). Genotype 3 and genotype 4 are known to infect older men (*14*,*15*). The increase in the number of HEV infections in eastern China (online Technical Appendix Figure 1) could also be caused by this genotype shift and improved surveillance in these more developed provinces (*15*), rather than by true geographic heterogeneity in risk factors.

There are some limitations to our study (online Technical Appendix). Our findings are inferred from case notification data, and the data quality could vary because of changes in case definitions. Other limitations include

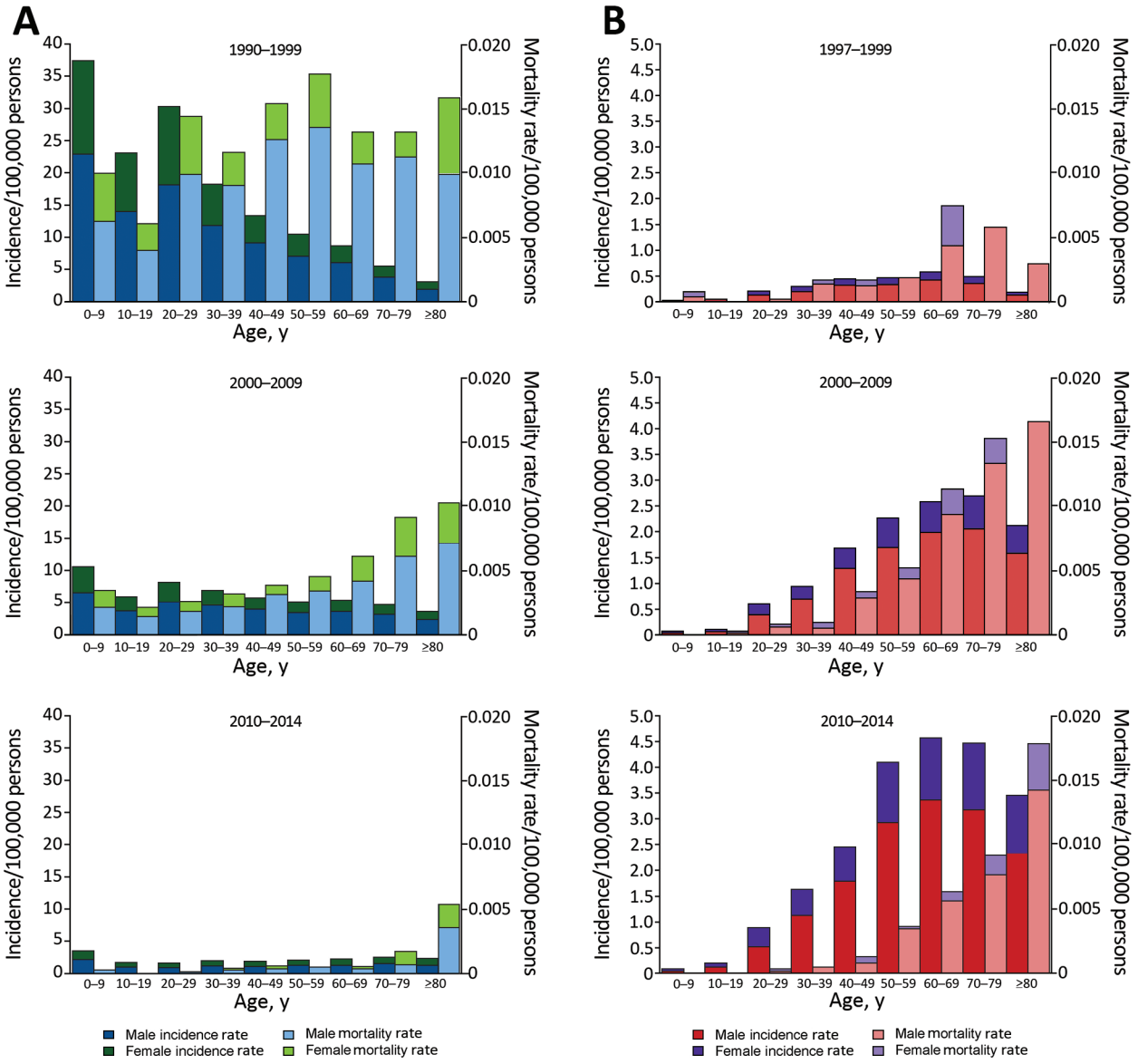

Figure 2. Age distribution of patients with reported cases of A) hepatitis A (blue, male patients; green, female patients) and B) hepatitis E (red, male patients; purple, female patients) in China for 1990–1999, 2000–2009, and 2010–2014. Incidence and mortality rates were calculated in 10-year age groups for the 3 periods. For each color, the darker shade represents incidence and the lighter shade represents mortality rate.

variable availability of laboratory diagnostics and lack of hepatitis E genotype data.

Conclusions

Reports of hepatitis A in China have declined substantially, while reports of hepatitis E cases have continued to rise. The mortality rate for hepatitis E surpassed that for hepatitis A in 2004. Decreasing trends of hepatitis A incidence after implementation of a vaccination program targeting children >18 months of age indicate a similar strategy for hepatitis E could be considered as a means to curtail incidence. In addition, variations in demographic, geographic and seasonal distributions of hepatitis A and E may inform future prevention strategies in China.

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Technical Appendix

Regional Hepatitis Incidence

Provinces along the Yangtze River and some northeastern provinces had relatively higher hepatitis A incidence in the 1990s, while a higher incidence has been observed in western China since 2000 (Technical Appendix Figure 1). In contrast, hepatitis E incidence s have remained highest in eastern China (Technical Appendix Figure 1). In the Poisson regression models, both GDP and GDP per capita (Technical Appendix Figure 3) showed a strong association with the incidence s of hepatitis A ($p < 0.0001$) and the incidence s of hepatitis E ($p < 0.0001$). GDP and GDP per capita were inversely correlated with incidence of hepatitis A but positively associated with the incidence of hepatitis E.

Study Limitations

There are some potential limitations to our work. First, the data quality may be influenced by changes in the national notifiable disease reporting system including changes in case definitions, reporting methods, availability of health facilities and laboratory diagnostics, under reporting, and completeness and accuracy of data over the years. Diagnosis and notification of cases may vary across the country, affecting our geographic comparisons of incidence. Second, we inferred the relative disease burden of hepatitis A and E on the basis of case notification data, but underestimation of hepatitis A or E cases may have biased our comparison since many cases may not have been diagnosed and reported. Information on hepatitis E genotypes was not available in the case reports, and therefore we could not explore the potential effect of changing patterns in the genotypes on HEV infections in. In addition, the increase in hepatitis E could be due to increased awareness of the disease and use of diagnostic testing and. We cannot be certain if there has been a true increase in incidence as data on the total number of cases tested for HEV

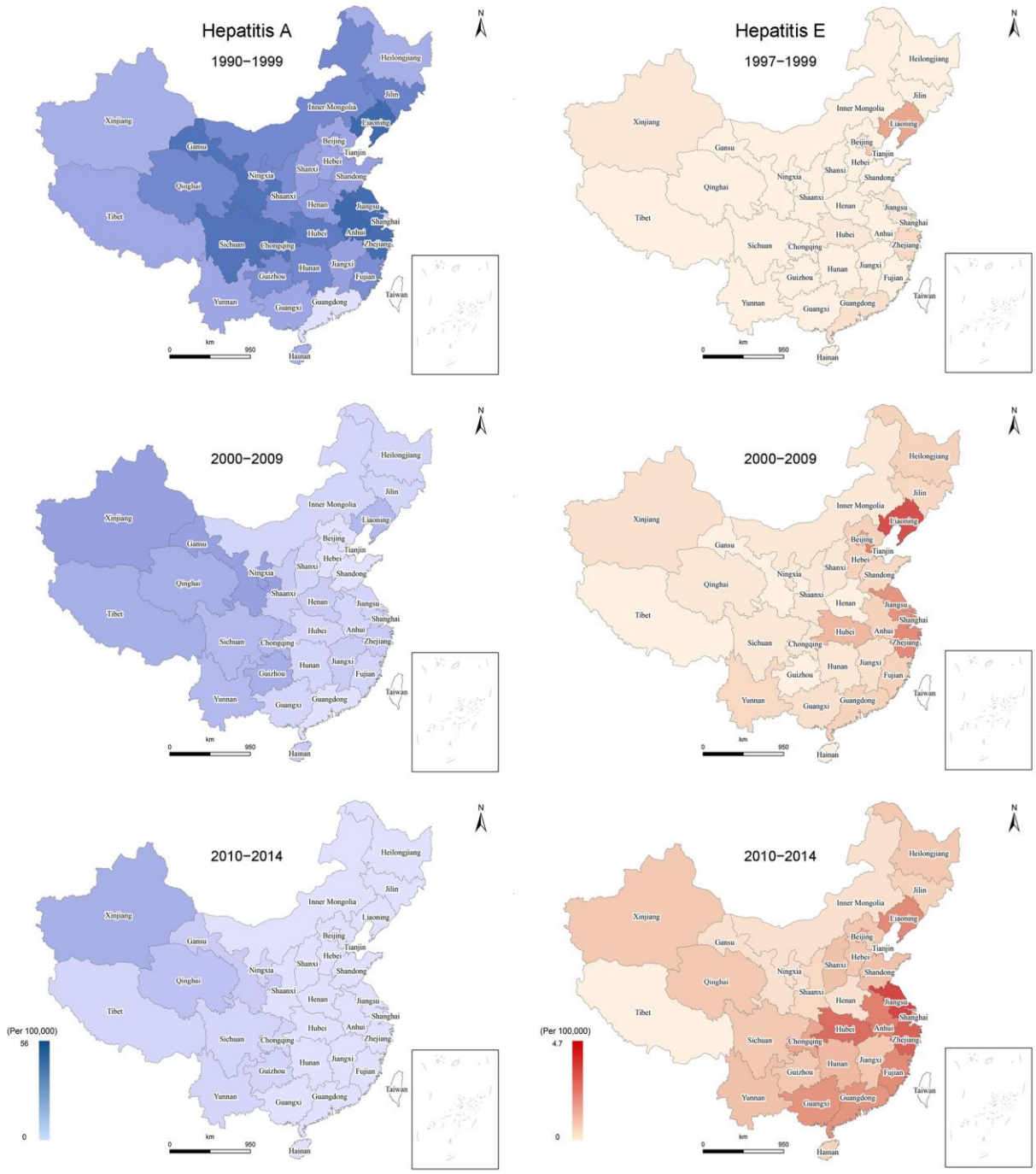
over the study period are not available. Finally, we did not have information on the total number of laboratory tests performed over time, and increase in laboratory capacity may have led to gradual increases in the incidence of notified cases of hepatitis A and E over time.

Technical Appendix Table. Change of diagnostic criteria for viral hepatitis A and viral hepatitis E in China*

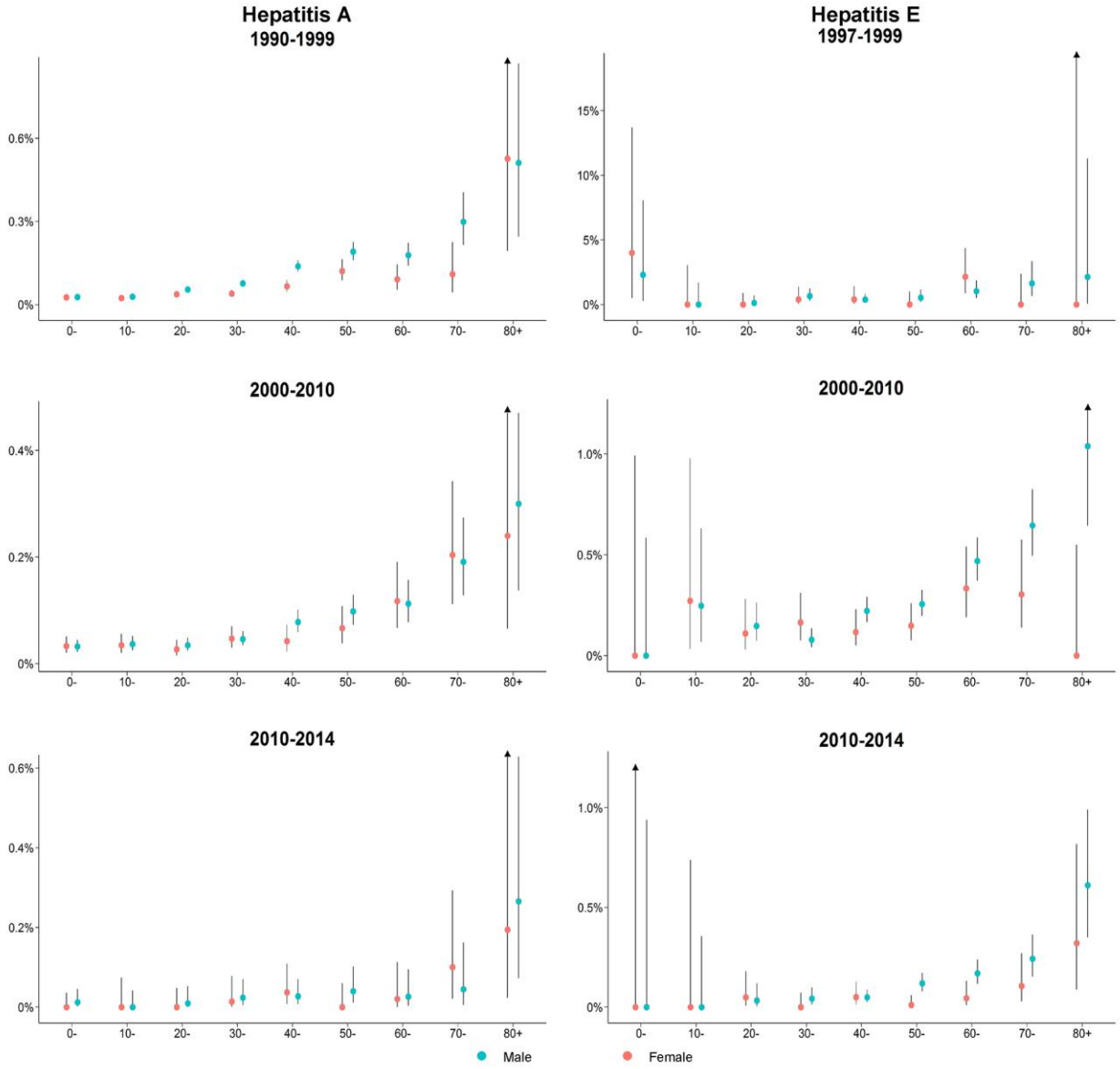
Standard Name	Diagnostic Criteria and Principles of Management for Viral Hepatitis A	Diagnostic Criteria of Viral Hepatitis A	Diagnostic Criteria and Principles of Management for Viral Hepatitis E	Diagnostic Criteria for Hepatitis E
Chinese Standard Number	GB 17010—1997	WS 298–2008	GB 17011—1997	WS 301–2008
Issued by	Chinese Ministry of Health	Chinese Ministry of Health	Chinese Ministry of Health	Chinese Ministry of Health
Date issued	1997/10/6	2008/12/11	1997/10/6	2008/12/11
Date Enforced	1998/10/1	2009/6/15	1998/10/1	2009/6/15
Epidemiologic Linkage	1.1 has epidemiologic history of contact with acute hepatitis A patient or having ingested contaminated food or water in 45 d before onset of illness	1.1 has epidemiologic history of contact with a laboratory-confirmed acute hepatitis A patient or has ingested contaminated food or water in 2–7weeks before onset of illness, or lives in the place with recent hepatitis A epidemic or outbreak, or has history of travel to hepatitis A epidemic area	1.1 has epidemiologic history of contact with hepatitis patient or ingested contaminated food or water in 2–6 weeks before onset of illness or has history of travel to high hepatitis E prevalence area or hepatitis E epidemic area	1.1 has epidemiologic history of contact with a laboratory-confirmed hepatitis E patient, or ingested contaminated food or water in 15–75 d before onset of illness, or has history of travel to hepatitis E high prevalence area or hepatitis E epidemic area
Clinical Description	2.1 has symptoms of fever, fatigue, loss of appetite, nausea and vomiting in the recent week with exclusion of other diseases, and has hepatomegaly with tenderness or percussion pain 2.2 has jaundice with exclusion of other diseases 2.3 has Obstructive jaundice for over 3 weeks with exclusion of other diseases 2.4 has acute onset with severe gastrointestinal symptoms and neuropsychiatric symptoms occur within 10 d since the onset(over grade 2 of the Parsons-Smith Scale of Hepatic Encephalopathy) with exclusion of other diseases 2.5 has a rapidly shrinking liver 2.6 starts with onset of acute hepatitis, has extreme fatigue, severe loss of appetite, rapidly deepened jaundice, ascites and bleeding tendency, progressively shrinking liver. During 10 d to 8 weeks since the onset has impaired consciousness (over grade 2 of the Parsons-Smith Scale of Hepatic Encephalopathy) with exclusion of other diseases 2.7 has liver pathological characteristics	2.1 has symptoms of fever, fatigue, loss of appetite, nausea, vomiting, or abdominal distension, constipation and etc. and has hepatomegaly with tenderness or percussion pain 2.2 has jaundice with exclusion of other diseases	2.1 has symptoms of fatigue, loss of appetite lasting over 1 week or other gastrointestinal symptom or hepatomegaly with tenderness or percussion pain with exclusion of other diseases 2.2 has jaundice with exclusion of other diseases 2.3 has jaundice rapidly deepened 2.4 has mental or neurologic symptoms (Hepatic Encephalopathy) within 10 d after the onset with exclusion of other reasons 2.5 has severe abdominal distention or ascites	2.1 has symptoms of fatigue, loss of appetite, or other gastrointestinal symptom and/or hepatomegaly with tenderness or percussion pain with exclusion of other diseases 2.2 has dark urine and jaundice with exclusion of other diseases 2.3 for patients with liver failure, has progressive symptoms like fatigue, gastrointestinal symptoms and jaundice, with ascites and/or neuropsychiatric symptoms (dysphoria, disorientation, even delirious, drowsiness and coma)
Laboratory Tests	3.1 has abnormal serum alanine aminotransferase (ALT) 3.2 tests positive for the IgM antibody to hepatitis A virus by MAC ELISA or tests IgG antibody to hepatitis A virus 4 times of increasing by competitive inhibition ELISA	3.1 has increasing serum alanine aminotransferase (ALT) 3.2 has total serum bilirubin (TBIL) over 1 times larger than the normal upper limits and/or positive urinary bilirubin tests	3.1 has increasing serum alanine aminotransferase (ALT) 3.2 excludes the acute hepatitis A/B/C/G through serum test 3.3 has serum bilirubin(BIL)>17.1 μmol/L (>10mg/L) or positive	3.1 tests positive for the IgG antibody to hepatitis E virus and/or IgM antibody to hepatitis E virus by EIA kit 3.2 has increasing serum alanine aminotransferase (ALT)

Standard Name	Diagnostic Criteria and Principles of Management for Viral Hepatitis A	Diagnostic Criteria of Viral Hepatitis A	Diagnostic Criteria and Principles of Management for Viral Hepatitis E	Diagnostic Criteria for Hepatitis E
	3.3 has serum bilirubin (BIL)>17.1 μmol/L and positive urinary bilirubin tests 3.4 has serum bilirubin (BIL) increased, especially the direct bilirubin,with alkalinephosphatase(ALP), glutaminepeptideenzyme(GGT) and cholesterol increased, and serum alanine moderately increased 3.5 has abnormal liver function, serum bilirubin increased to over 171 μmol/L within a few days or increased by more than 17.1 μmol/L per day, and prothrombin activity less than 40% 3.6 has abnormal liver function, transaminase level decreased but the serum bilirubin continued to be elevated, Albumin globulin ratio(A/G)<1, cholesterol decreased and prothrombin activity less than 40%	3.3 tests positive for the IgM antibody to hepatitis A virus by ELISA or tests IgG antibody to hepatitis A virus 4 times of increasing by competitive inhibition ELISA or tests hepatitis A RNA positive by RT-PCR	urinary bilirubin tests 3.4 tests positive for the IgM antibody to hepatitis E virus or tests IgG antibody to hepatitis E virus from negative to positive or titer from low to high or high to low with over quadruple of change by EIA kit 3.5 serum bilirubin increased to over 171 μmol/L 3.6 has prolonged prothrombin time and prothrombin activity less than 40% 3.7 serum bilirubin increased by 17.1 μmol/L daily	3.3 has total serum bilirubin (TBIL) >17.1 μmol/L (>10mg/L) and/or positive urobilirubin tests 3.4 for patients with liver failure, has prothrombin activity progressively decreased to less than 40% 3.5 excludes the acute hepatitis A/B/C from serum test
Diagnosis and Classification	4.1 Acute anicteric hepatitis 4.1.1 Probable case:2.1+3.1 4.1.2 Confirmed case: 4.1.1+3.2 4.2 Acute icteric hepatitis 4.2.1 Probable case: 2.1+2.2+3.1+3.3 4.2.2 Confirmed case: 4.2.1+3.2 4.3 Cholestasis hepatitis 4.3.1 Probable case: 2.1+2.2+2.3+3.4 4.3.2 Confirmed case: 4.3.1+3.2 or 2.7+3.2 4.4 Acute severe hepatitis 4.4.1 Probable case: 2.4+2.5+3.5 4.4.2 Confirmed case: 4.4.1+3.2 or 2.5+2.7 4.5 Sub-acute severe hepatitis 4.5.1 Probable case: 2.6+3.6 4.5.2 Confirmed case:4.5.1+3.2 or 2.7+3.2	4.1 Hepatitis A 4.1.1 Probable case:1.1+2.1+2.2+3.1 or 1.1+2.1+2.2+3.1+3.2 or 2.1+2.2+3.1 or 2.1+2.2+3.1+3.2 4.1.2 Confirmed case: 4.1.1+3.3 4.2 Acute anicteric hepatitis A 4.2.1 Probable case:1.1+2.1 or 1.1+3.1 or 2.1+3.1 4.2.2 Confirmed case: 4.2.1+3.3 4.3 Acute icteric hepatitis A 4.3.1 Probable case: 1.1+2.1+2.2+3.2 or 1.1+2.2+3.1+3.2 or 2.1+2.2+3.1+3.2 4.3.2 Confirmed case: 4.3.1+3.3	4.1 Acute anicteric hepatitis E 4.1.1 Probable case:2.1+3.1+3.2 4.1.2 Confirmed case: 4.1.1+3.4 4.2 Acute icteric hepatitis E 4.2.1 Probable case: 2.1+2.2+3.1+3.2+3.3 4.2.2 Confirmed case: 4.2.1+3.4 4.3 Acute severe hepatitis E 4.3.1 Probable case: 2.1+2.2+2.3+3.1+3.2+3.3+3.5 4.3.2 Confirmed case:4.3.1+2.4+3.6 4.4 Sub-acute severe hepatitis E 4.4.1 Probable case: 2.1+2.2+2.5+3.1+3.2+3.3+3.5 or 2.1+2.2+2.5+3.1+3.2+3.3+3.7 4.4.2 Confirmed case:4.4.1+3.6 or 4.4.1+2.4+3.6	4.1 Acute anicteric hepatitis E 4.1.1 Probable case:1.1+2.1+3.2+3.5 4.1.2 Confirmed case: 4.1.1+3.1 4.2 Acute icteric hepatitis E 4.2.1 Probable case: 1.1+2.1+2.2+3.2+3.3+3.5 4.2.2 Confirmed case: 4.2.1+3.1 4.3 Hepatitis E with acute liver failure 4.3.1 Probable case: 1.1+2.1+2.2+3.2+3.3+3.5+2.3a+3.4a a: has these symptoms within 14 d since the onset 4.3.2 Confirmed case: 4.3.1+3.1 4.4 Hepatitis E with sub-acute liver failure 4.4.1 Probable case: 1.1+2.1+2.2+3.2+3.3+3.5+2.3b+3.4b b: has these symptoms after 14 d till 6 mo since the onset 4.4.2 Confirmed case:4.4.1+3.1

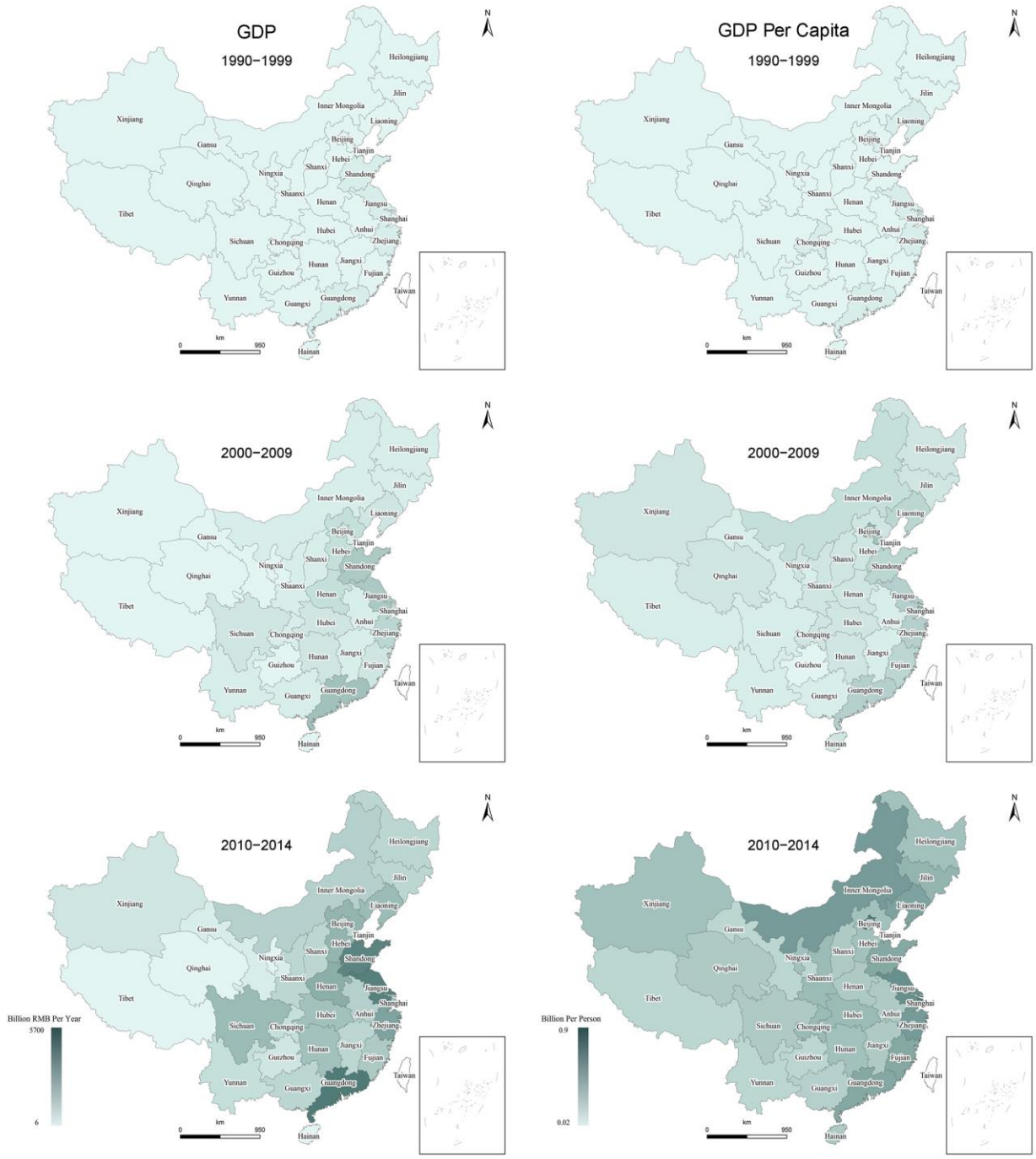
*The revised diagnostic criteria in 2008 provided a simplified disease categorization for hepatitis A and clarified laboratory confirmation for IgG and IgM antibody using ELISA and HAV RNA using RT-PCR. The hepatitis E laboratory testing guidelines were changed in 2008 to include quantification of IgG and IgM antibody using suggested assays.



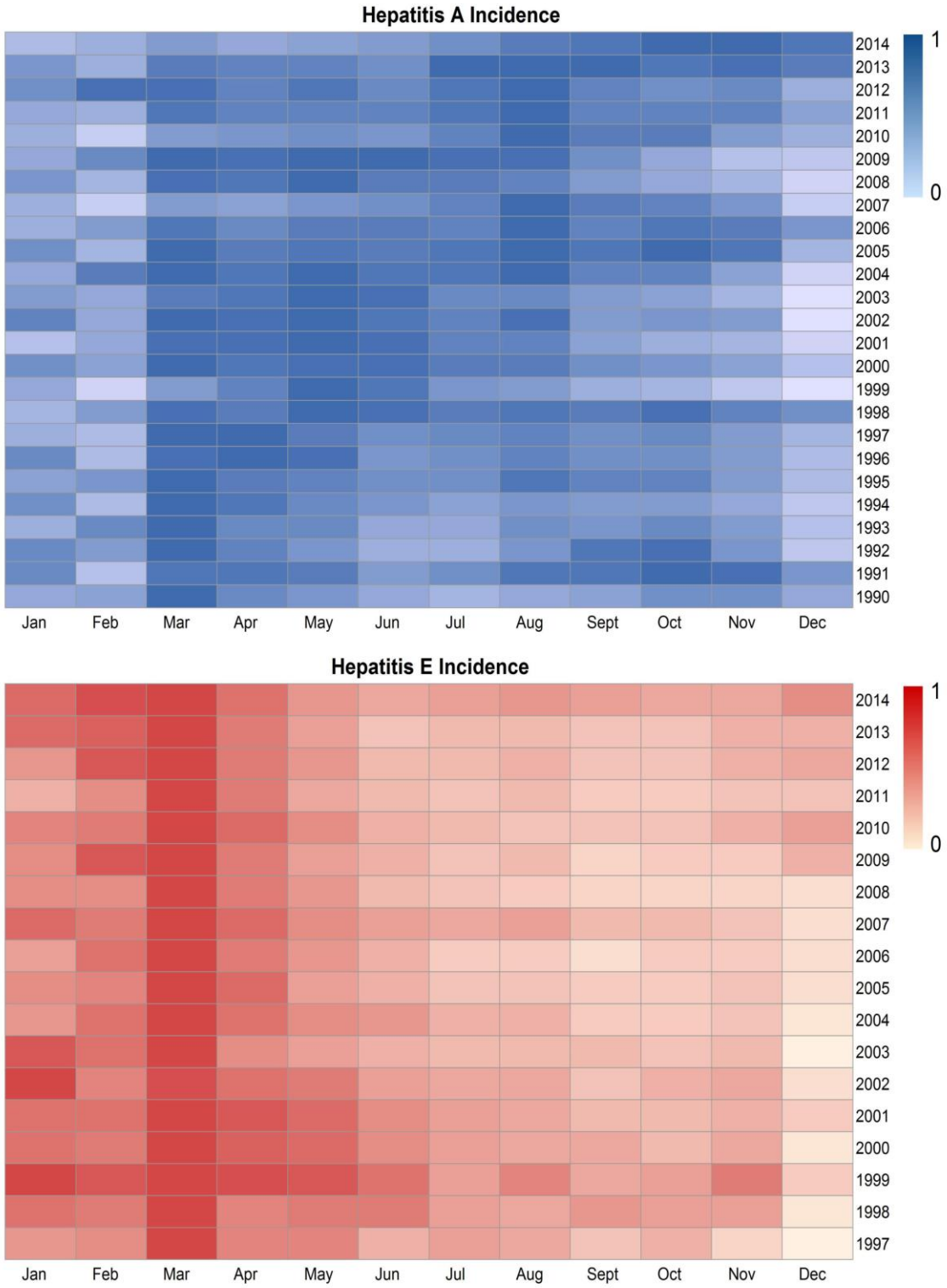
Technical Appendix Figure 1. Averaged annual incidence of notifications of hepatitis A (left column) and hepatitis E (right column) in each province of China in 1990–1999, 2000–2009 and 2010–2014. Data were not available on hepatitis A and E cases in Hong Kong SAR, Macau SAR, and Taiwan. Chongqing municipality has been administratively separated from Sichuan province since 1997, and therefore estimates of incidence and mortality rates of hepatitis A in Sichuan province before 1997 were calculated by using data that included Chongqing.



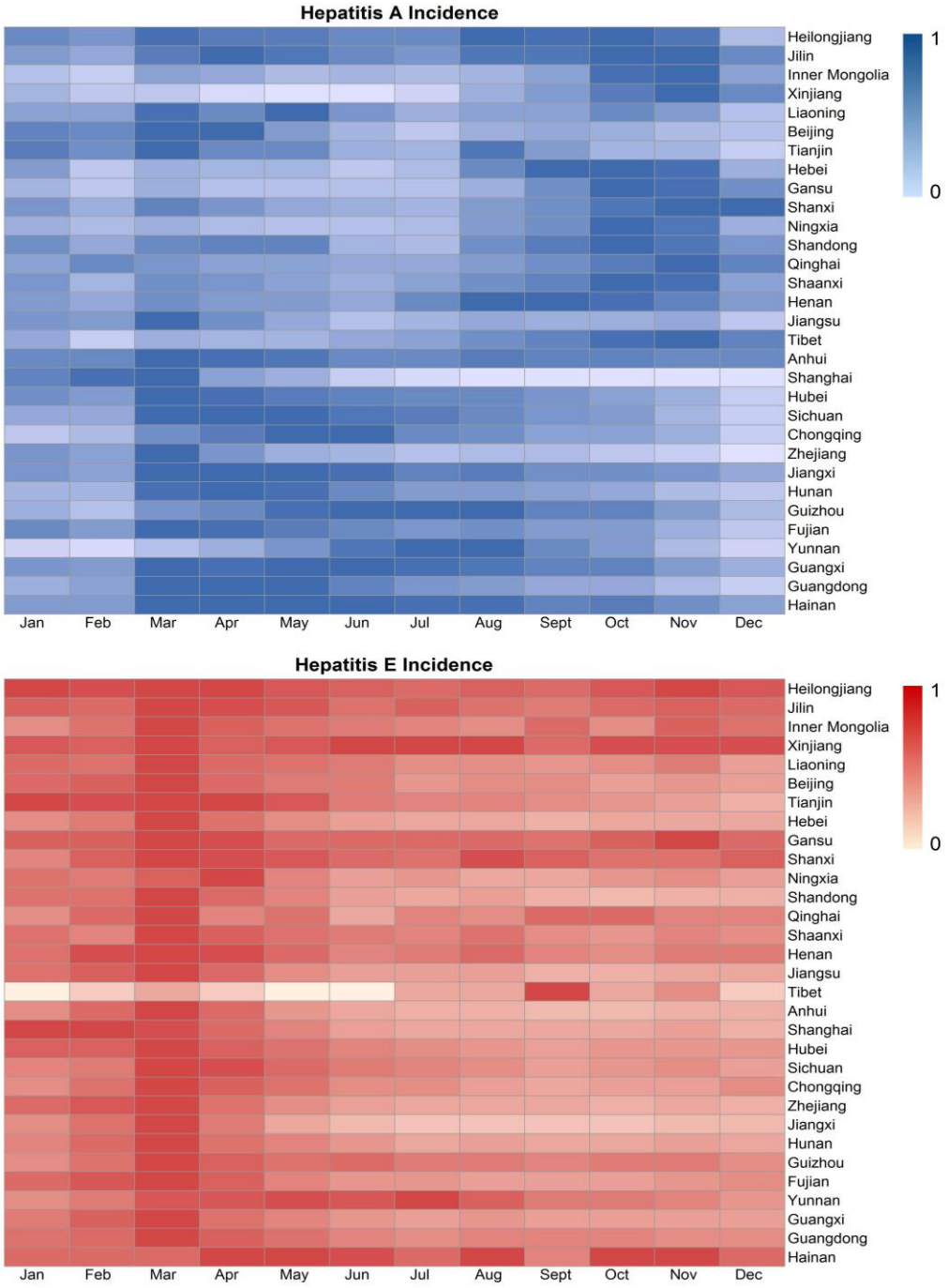
Technical Appendix Figure 2. Point estimates (dots) and 95% confidence intervals (vertical gray lines) of the case fatality ratio (defined as notified deaths divided by all notifications) of hepatitis A and E by age group among males (blue) and females (red) in 1990–1999, 2000–2009 and 2010–2014.



Technical Appendix Figure 3. Averaged annual GDP and GDP per capita in each province of China in 1990–1999, 2000–2009 and 2010–2014.



Technical Appendix Figure 4. Seasonal patterns in incidence of notified hepatitis A (upper panel) and hepatitis E (lower panel) cases by year in China from 1990 through 2014. The monthly incidence was calculated for each year and then divided by the maximum monthly incidence in each year.



Technical Appendix Figure 5. Seasonal patterns in incidence of notified hepatitis A (upper panel) and hepatitis E (lower panel) cases by province from 1990 through 2014. The monthly incidence was calculated for each province and then divided by the maximum monthly incidence in each province. The provinces are sorted by latitude from north to south.