Hepatology International (2019) 13:157–164
https://doi.org/10.1007/s12072-019-09931-w

ORIGINAL ARTICLE

The impact of national viral hepatitis therapy program and hepatitis B vaccination program on mortality from acute and chronic viral hepatitis in Taiwan

Shih-Yung Su[1]

Received: 22 August 2018 / Accepted: 14 January 2019 / Published online: 31 January 2019

Abstract

Background In Taiwan, the national hepatitis B virus vaccination program and national viral hepatitis therapy program were implemented to control the infections of hepatitis viruses and their progressive illnesses. Studies have evaluated the impacts of two national health programs on many liver-related diseases, but not on acute and chronic viral hepatitis. The purpose of this study was to evaluate the impact on the mortality of acute and chronic viral hepatitis.

Methods Poisson regression models were used to estimate the adjusted rate ratios of the different period groups and corresponding 95% confidence intervals for childhood, adulthood and elderhood, and to estimate the adjusted rate ratios of vaccinated cohorts and corresponding 95% confidence intervals.

Results Compared with period of 2000–2003, the adjusted rate ratios for period groups of 2008–2011 and 2012–2015 reported a significantly increasing risk of acute and chronic viral hepatitis mortality, except for the childhood and female adulthood. For population without vaccination, the adjusted rate ratios of acute and chronic viral hepatitis B mortality were 0.99 (95% CIs 0.88–1.12), 1.30 (95% CIs 1.17–1.45) and 1.42 (95% CIs 1.28–1.55) for periods of 2004–2007, 2008–2011 and 2012–2015, respectively, comparing with unimplemented period of national viral hepatitis therapy program. Compared with 1967–1983 cohorts, the adjusted rate ratio of 1984–2000 cohorts was 0.46 (95% CIs 0.28–0.75), and the adjusted rate ratios were 0.49 (95% CIs 0.28–0.87) and 0.35 (95% CIs 0.11–1.05) for male and female, respectively.

Conclusion This study revealed the significantly higher mortality rates of acute and chronic viral hepatitis during the implemented period of national viral hepatitis therapy program, comparing the unimplemented period. Such ineffectiveness may be attributable to the low coverage rate. The national vaccination program was currently an effective strategy for controlling the mortality of viral hepatitis.

Keywords Mortality · Acute and chronic viral hepatitis · Hepatitis B vaccination

Abbreviations

HBV	Hepatitis B virus
HCV	Hepatitis C virus
ICD	International classification of disease
CIs	Confidence intervals
DAAs	Direct-acting antiviral agents
AAs	Aristolochic acids and their derivatives
WHO	World Health Organization

Introduction

Globally, approximately 292 million people have developed hepatitis B virus (HBV) infections and 71 million people have developed hepatitis C virus (HCV) infections according to estimations from polaris observatory collaborators [1, 2]. Viral hepatitis is the seventh leading cause of death worldwide, with 1.45 million deaths [3].

Taiwan is a high-epidemic region of HBV infection, and approximately 2.5 and 0.7 million patients are infected with HBV and HCV in Taiwan, respectively; more than 90% of cases of end-stage liver diseases are related to infection with

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s12072-019-09931-w) contains supplementary material, which is available to authorized users.

✉ Shih-Yung Su
d01849007@ntu.edu.tw

[1] Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Rm. 541, No. 17, Xuzhou Rd, Taipei 100, Taiwan

HBV and HCV [4, 5]. To control viral hepatitis infections and their progressive illnesses, the government of Taiwan has implemented 2 national programs: the national HBV vaccination program for infants (since July 1984) and the national viral hepatitis therapy program for patients infected with HBV and HCV (since October 2003) [6, 7]. Many studies have indicated that these national health programs have significantly reduced morbidity and mortality from infant fulminant hepatitis, chronic liver diseases, liver cirrhosis, and hepatocellular carcinoma [8–13]. However, the impact of the 2 national programs on acute and chronic viral hepatitis mortality in various age groups and both genders has not been investigated.

This study evaluated the impact of the national HBV vaccination program and national viral hepatitis therapy program on mortality from acute and chronic viral hepatitis in Taiwan.

Materials and methods

Study population

Data on all causes of death were extracted from the National Death Certificates Database from 1981 to 2015 provided by the Ministry of Health and Welfare in Taiwan. All death certificates are coded using the ninth edition of the International Classification of Disease (ICD) during 1981–2007 and using the tenth edition after 2008. The mortality cases of acute and chronic viral hepatitis (ICD-9 code 070 and ICD-10 codes B15–B19) were selected in this study. A total of 4382 mortality cases of acute and chronic viral hepatitis (3058 and 1324 in male and female, respectively, aged 0–99 years) over the 1981–2015 period were collected. Age was categorized into 20 groups (0–4, 5–9, …, 95–99), and period was categorized by single year. Data on population numbers from 1981 to 2015 were extracted from the Household Registration Census Database provided by the Department of Statistics of the Ministry of the Interior in Taiwan.

Statistical analysis

Age-specific mortality rates of acute and chronic viral hepatitis were calculated for both genders and for 5 period groups (1996–1999, 2000–2003, … , 2011–2015). Age-adjusted mortality rates of acute and chronic viral hepatitis from 1996 to 2015 were estimated using 2000 World Standard Population for the 2 genders and were plotted in a log scale. To clearly understand the effect on age on mortality, all ages were categorized into 3 stages: childhood (between 0 and 29 years), adulthood (between 30 and 69 years), and elderhood (between 70 and 99 years). To estimate the effect of the national viral hepatitis therapy program since 2003, Poisson regression models were used to estimate the adjusted rate ratios of the different period groups and the corresponding 95% confidence intervals (CIs) for childhood, adulthood, and elderhood, and the 2000–2003 period group was used as the reference. Additional Poisson regression was performed to estimate the adjusted rate ratios of acute and chronic viral hepatitis B mortality for the population without HBV vaccination (the 1996–2003 period group was used as the reference).

The annual period group and 5-year age group were used to collect the birth cohort (period – age = cohort), which was categorized into 2 cohorts (namely 1967–1983 and 1984–2000 cohorts). To estimate the effect of the HBV vaccination program in childhood since 1984, Poisson regression models were used to estimate the adjusted rate ratios of the 1984–2000 period group and the corresponding 95% CIs and the 1967–1983 period group was used as the reference.

All statistical analyses were conducted using SAS software 9.4 version (SAS® Institute Inc., Cary, NC, USA).

Results

Figure 1 presents the age-specific mortality rates of acute and chronic viral hepatitis per 1,000,000 population for both genders and the 5 period groups. The magnitude of acute and chronic viral hepatitis mortality rates was similar across age groups for both genders. For the youngest age group of 0–19 years, the mortality rates for both genders were lower in later period groups during 2008–2015 than in early period groups during 1996–2003, except for the 2008–2011 period group in male. For the age group of 20–69 years, the mortality rates for both genders and the 5 period groups all dramatically increased with age (less than 10 and 5 deaths to more than 100 and 80 deaths per 1,000,000 population were observed for male and female, respectively). For the oldest age group of 70–99 years, the mortality rates for both genders were higher in later period groups during 2008–2015 than in early period groups during 1996–2007, except for the 2008–2011 period group in female.

Figure 2 presents the age-adjusted mortality rates of acute and chronic viral hepatitis per 1,000,000 population for both genders from 1996 to 2015. Different trends were observed for both genders; however, the age-adjusted mortality rate in male was much higher (approximately twofold higher). The age-adjusted mortality rates of acute and chronic viral hepatitis showed slightly decreasing trends from 1996–1999 to 2004–2007 (39–34 deaths per 1,000,000 population) and increasing trends thereafter (50 deaths per 1,000,000 population) in male and showed gradually increasing trends in female (16–22 deaths per 1,000,000 population).

Table 1 displays the results of statistical tests for determining temporal effects on acute and chronic viral hepatitis

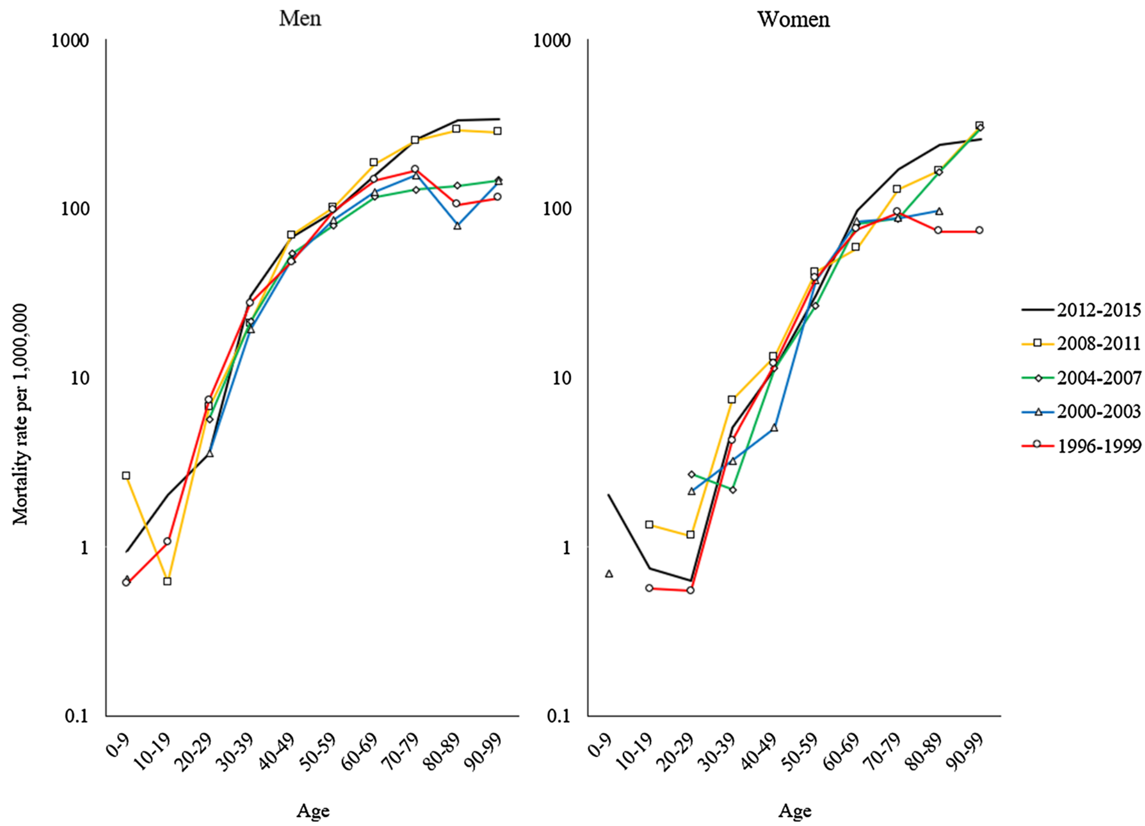

Fig. 1 Age-specific mortality rates per 1,000,000 population of acute and chronic viral hepatitis for two genders in Taiwan

mortality rates and provides the adjusted rate ratios and corresponding 95% CIs for childhood (0–29 years), adulthood (30–68 years), and elderhood (70–99 years). During 1996–2015, for both genders, a total of 82, 2706, and 1288 deaths occurred during childhood, adulthood, and elderhood, respectively. For both genders and the 3 stages of age, the crude mortality rates in the later period groups of 2008–2011 and 2012–2015 were higher than the rates in the 2000–2003 period group. Compared with the 2000–2003 period group, the adjusted rate ratios of the later period groups of 2008–2011 and 2012–2015 all revealed a significantly increasing risk of acute and chronic viral hepatitis mortality, except for childhood and female adulthood. During 2012–2015, the gender- and age-adjusted rate ratios were 1.27 (95% CI 0.60–2.71), 1.23 (95% CI 1.09–1.39), and 2.06 (95% CI 1.72–2.48) in childhood, adulthood, and elderhood, respectively.

Figure 3 presents the adjusted rate ratios and corresponding 95% CIs of acute and chronic viral hepatitis B mortality in the 2004–2007, 2008–2011, and 2012–2015 period groups. Compared with 1996–2003, the adjusted rate ratios in 2008–2011 and 2012–2015 all revealed a significantly higher risk of acute and chronic viral hepatitis B mortality for both genders. The gender- and age-adjusted rate ratios were 0.99 (95% CI 0.88–1.12), 1.30 (95% CI 1.17–1.45), and 1.42 (95% CI 1.28–1.55) for the periods of 2004–2007, 2008–2011, and 2012–2015, respectively.

Table 2 shows the results of statistical tests for determining cohort effects on acute and chronic viral hepatitis mortality rates and provides the adjusted rate ratios and corresponding 95% CIs. In the 1967–2000 birth cohorts, a total of 76 deaths occurred in 0–29 age groups for both genders (58 deaths in male and 18 deaths in female). The crude mortality rate in the 1984–2000 cohorts was 2.20 per 1,000,000 population (3.44 deaths in male and 0.87 deaths in female), which is approximately 0.5-fold lower than that in the 1967–1983 cohorts. Compared with the 1967–1983 cohorts, the gender- and age-adjusted rate ratio of the 1984–2000 cohorts was 0.46 (95% CI 0.28–0.75), and the age-adjusted rate ratios were 0.49 (95% CI 0.28–0.87) and 0.35 (95% CI 0.11–1.05) for male and female, respectively.

Discussion

The secular trend of the age-adjusted mortality rates and adjusted rate ratios indicated that the national viral hepatitis therapy program did not significantly change the mortality rates of acute and chronic viral hepatitis in Taiwan since October 2003. In addition, in adulthood and elderhood,

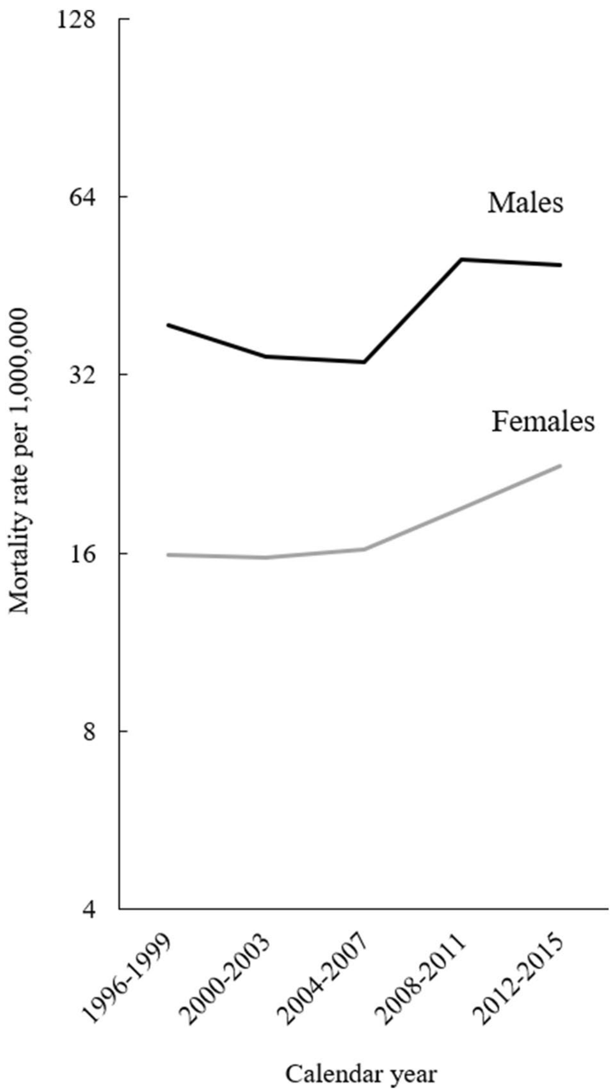

Fig. 2 Age-adjusted mortality rates per 1,000,000 population of acute and chronic viral hepatitis for two genders in Taiwan

the mortality rates of acute and chronic viral hepatitis in male were significantly higher during the period with national therapy program implementation than during the period without national therapy program implementation. The national therapy program is covered by the National Health Insurance program in Taiwan, which was founded in 1995 and has a coverage rate of nearly 100%. The antiviral treatments in this national therapy program are reimbursed for patients with HBV or HCV infection. Until 2016, the reimbursed treatments included lamivudine, interferon α, pegylated interferon α, entecavir, telbivudine, tenofovir, and adefovir. Among them, lamivudine and interferon α were used after 2003, pegylated interferon α after 2005, entecavir and telbivudine after 2008, and adefovir after 2011. The eligibility criteria for patients who can receive the reimbursed treatments are provided in Appendix 1 in Supplementary Material. Higher biochemical and virological responses have been demonstrated for viral hepatitis [14, 15]. However, the role of antiviral therapy for HBV is unclear. A systematic review and meta-analysis indicated that the short-term survival of patients with acute exacerbation of chronic HBV who were treated with lamivudine was not different from that of untreated patients, and treatment with entecavir exerted higher effects on short-term mortality than treatment with lamivudine [16].

The cure rate in patients with HCV who receive antiviral treatment is higher than the rate in HBV patients. In Taiwan, interferon treatment in the national viral hepatitis therapy program was the major reimbursed treatment provided for patients with HCV. In January 2017, the National Health Insurance program in Taiwan further covered new direct-acting antiviral agents (DAAs) for patients with HCV infection. DAAs are more effective than interferon [17]. However, the effect of DAAs could not be estimated in this study because the data after 2017 are unavailable. If the coverage rate of the national therapy program substantially increases in the future, mortality from progressive illnesses of HCV infection will be lower than the mortality reported in the current study.

The low coverage rate of the national viral hepatitis therapy program may explain why acute and chronic viral hepatitis mortality did not significantly change. Until 2011, a total of 219,393 patients received the reimbursed treatments in the national therapy program in Taiwan [11]. Such cumulative numbers of patients from 2004 to 2011 were approximately 15–25% of all patients with HBV or HCV who were eligible for the reimbursed treatments [18, 19]. It revealed a concern that more than half of the patients with HBV or HCV were not protected by this national therapy program.

The result (no significant change in acute and chronic viral hepatitis mortality) of this study is inconsistent with those of previous studies, which attributed the decreasing trend (after 2004) of morbidity and mortality from chronic liver diseases, cirrhosis, and liver cancer to the national therapy program. However, in addition to hepatitis viruses, other causes, including obesity, metabolic syndrome, alcohol use, smoking, and family history, contribute to such liver diseases [20]. In addition, the coverage rate of the national therapy program is too low to interpret that the decreasing trends of chronic liver diseases, liver cirrhosis, and liver cancer after 2004 are caused by or even associated with the national therapy program since October 2003. In contrast, the government of Taiwan had introduced a law prohibiting the use of herbal medicines containing aristolochic acids (AAs) and their derivatives since November 2003. In Taiwan, mutations caused by AAs were found in the hepatocytes of 78% of patients with liver cancer [21, 22]. However, further study is required to clarify the association between AAs and liver cancer.

Table 1 Mortality rates of viral hepatitis in childhood (0–29), adulthood (30–69), and elderhood (70–99) from 1996 to 2015 in Taiwan

Year	0–29 years old				30–69 years old				70–99 years old			
	Population under observation	No. of cases	Mortality rate[a]	Adjusted rate ratio (95% CIs)[b]	Population under observation	No. of cases	Mortality rate[a]	Adjusted rate ratio (95% CIs)[b]	Population under observation	No. of cases	Mortality rate[a]	Adjusted rate ratio (95% CIs)[b]
Overall												
1996–1999	10,543,872	19	1.80	1.45 (0.72–2.94)	10,153,946	436	42.94	1.10 (0.96–1.25)	1,110,366	139	125.18	1.08 (0.86–1.36)
2000–2003	10,182,725	13	1.28	[Reference]	10,921,480	427	39.10	[Reference]	1,335,212	155	116.09	[Reference]
2004–2007	9,605,009	16	1.67	1.24 (0.60–2.59)	11,693,574	463	39.59	0.98 (0.86–1.12)	1,523,388	189	124.07	1.07 (0.86–1.32)
2008–2011	8,822,447	20	2.27	1.66 (0.83–3.34)	12,586,818	655	52.04	1.25 (1.10–1.41)	1,719,698	353	205.27	1.78 (1.47–2.15)
2012–2015	8,104,610	14	1.73	1.27 (0.60–2.71)	13,392,218	725	54.14	1.23 (1.09–1.39)	1,904,285	452	237.36	2.06 (1.72–2.48)
Men												
1996–1999	5,438,121	17	3.13	2.11 (0.91–4.90)	5,156,473	324	62.83	1.11 (0.95–1.30)	594,393	93	156.46	1.11 (0.84–1.47)
2000–2003	5,255,212	8	1.52	[Reference]	5,489,915	309	56.29	[Reference]	707,894	100	141.26	[Reference]
2004–2007	4,963,019	11	2.22	1.38 (0.56–3.44)	5,840,222	337	57.70	1.00 (0.85–1.16)	771,038	102	132.29	0.93 (0.71–1.23)
2008–2011	4,563,000	16	3.51	2.15 (0.92–5.02)	6,245,162	493	78.94	1.32 (1.14–1.52)	826,871	221	267.27	1.89 (1.49–2.39)
2012–2015	4,204,837	10	2.38	1.46 (0.58–3.71)	6,606,918	524	79.31	1.26 (1.09–1.45)	879,548	251	285.37	2.01 (1.59–2.54)
Women												
1996–1999	5,105,751	2	0.39	0.39 (0.08–2.03)	4,997,473	112	22.41	1.06 (0.82–1.38)	515,973	46	89.15	1.02 (0.69–1.51)
2000–2003	4,927,513	5	1.01	[Reference]	5,431,565	118	21.72	[Reference]	627,318	55	87.67	[Reference]
2004–2007	4,641,990	5	1.08	1.03 (0.30–3.55)	5,853,352	126	21.53	0.95 (0.74–1.22)	752,350	87	115.64	1.31 (0.93–1.83)
2008–2011	4,259,447	4	0.94	0.88 (0.24–3.28)	6,341,656	162	25.55	1.08 (0.85–1.37)	892,827	132	147.84	1.65 (1.21–2.27)
2012–2015	3,899,773	4	1.03	0.97 (0.26–3.61)	6,785,300	201	29.62	1.16 (0.92–1.45)	1,024,737	201	196.15	2.17 (1.61–2.92)

[a]Indicates mortality rate per 1,000,000 population

[b]Adjusts age and gender in overall, and adjusts age in two genders

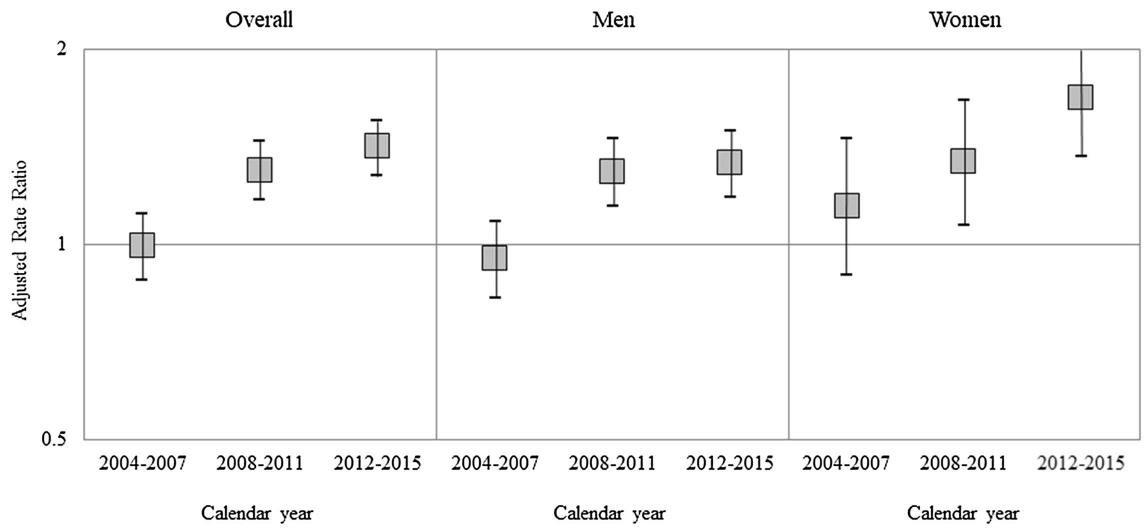

Fig. 3 The adjusted rate ratio and corresponding 95% CIs of acute and chronic viral hepatitis B mortality in 2004–2007, 2008–2011 and 2012–2015 period groups in Taiwan (reference group was 1996–2003 period and all subjects did not receive the hepatitis B virus vaccine)

Table 2 Mortality rates of viral hepatitis of birth cohorts born before and after the implementation of hepatitis B vaccination program in 1984 in Taiwan

Birth years	Population under observation	No. of cases	Mortality rates[a]	Adjusted rate ratio (95% CIs)[b]
Overall				
1967–1983	11,654,636	55	4.72	[Reference]
1984–2000	9,546,346	21	2.20	0.46 (0.28–0.75)**
Men				
1967–1983	5,983,184	41	6.85	[Reference]
1984–2000	4,941,798	17	3.44	0.49 (0.28–0.87)*
Women				
1967–1983	5,671,452	14	2.47	[Reference]
1984–2000	4,604,548	4	0.87	0.35 (0.11–1.05)

*$p < 0.05$; **$p < 0.01$

[a]Indicates mortality rate per 1,000,000 population

[b]Adjusts age and gender in overall, and adjusts age in two genders

This study indicated that the national HBV vaccination program significantly reduced mortality from acute and chronic viral hepatitis in Taiwan. This finding is consistent with that of a previous study, which used a similar statistical method and revealed significant reduction in the incidence of acute HBV for vaccine protected cohorts during 1986–1994 [23]. The reduction of the mortality rates of acute and chronic viral hepatitis may be attributed to the reduced incidence of acute hepatitis B. In the early 1980s, researchers and decision-makers comprehended that Taiwan is a high-epidemic region of HBV. Thus, researchers cautiously pre-evaluated the cost-effectiveness of a national vaccination program and found that mortality and financial loss in the period without implementation are higher than the cost of medicine and vaccination in the period with implementation. Currently, HBV prevalence is still higher in Taiwan (especially in adults and elderly people), and the HBV vaccination program is crucial for disease control. After HBV vaccination, hepatitis B surface antibody titers gradually decrease over time. The health authority in Taiwan recommended that high risk groups for HBV infection (hemodialysis, immunodeficiency, primary immunodeficiency diseases, etc.) should be paid for HBV vaccination. The vaccine protected cohorts in this study could reach the age of 15 and 30 years in 2015. When they reach the adulthood and elderhood in the next few decades, the mortality rate of acute and chronic viral hepatitis is expected to further decrease in Taiwan. In the future, the final step of the elimination or eradication of HBV can be achieved in Taiwan [24].

For a fair comparison, unvaccinated cohorts aged less than 30 years were selected in this study, and these cohorts could reach the age of 15 and 30 years in 1998. The National Health Insurance program in Taiwan was launched in March 1995, and notably, the age-adjusted mortality rates dramatically increased during 1995–1998 (see Figure S1 in Supplementary Material). Due to the lack of information, the coincidence between National Health Insurance program establishment and dramatically increasing mortality is difficult to clarify. Nevertheless, this dramatic increasing mortality may influence the results of this study and probably lead an unavoidable bias for the adjusted rate ratio in the vaccinated cohort. Most data for unvaccinated cohorts were collected before 1995. Thus, this bias is incalculable, but toward the null.

In 2015, the World Hepatitis Summit announced a Glasgow declaration on viral hepatitis and hoped to eliminate HBV and HCV infection [25]. In 2016, the World Health Organization (WHO) released a global health sector strategy on viral hepatitis for the period 2016–2021, which aimed to achieve a 65% reduction of viral hepatitis B and C mortality from 2015 to 2030 [26]. In Taiwan, the earliest vaccinated cohort will reach the age of 46 years in 2030, and the age-specific mortality rates are still lower in the age group of 40–49 years than in the oldest age group of 90–99 years. This study revealed that mortality rates showed fivefold and 20-fold increases in male and female across age groups from 40–49 to 90–99 years, respectively. Although a 53% reduction (based on the adjusted rate ratio) of viral hepatitis mortality can be achieved for the Taiwanese vaccinated cohort aged less than 30 years, it is extremely difficult to reach the WHO target in 2030. According to the invalid of the national viral hepatitis therapy program, the national HBV vaccination program may be the only strategy for controlling mortality from viral hepatitis. Other efficiency strategies for disease control and improving public health are urgently required to be developed.

This study is the first to reveal a concerning result that the mortality rates of acute and chronic viral hepatitis were higher in later period groups (2008–2015) than in early period groups (1996–2007) for the oldest age group of 70–99 years. Whether similar trends are applicable for other infectious diseases is unclear. Nevertheless, this result may imply the negligence of the geriatric population and a deficiency in geriatric care services in Taiwan. The geriatric population will soon represent a severe health burden on viral hepatitis mortality in Taiwan due to the immediate and unavoidable problem of aging. A recent study estimated the growth of the elderly population in Taiwan and found that 20% of the population in 2025 and 41% in 2060 will be older than 65 years [27]. To meet respond the growing need for geriatrics care, a national 10-year long-term care plan was introduced in 2007 [28]. However, family and paid caregivers and their professional training are lacking in this long-term care plan. The government of Taiwan approved the 2.0 version of the national long-term care plan in September 2016, and this version of the plan was implemented in January 2017 [29]. This plan aims to minimize the years lived with disability and integrate hospice care at home with other home care service for the end stage of life. However, the efficiency of the implementation of the program is still unclear. To prevent deaths from acute and chronic viral hepatitis in elderhood, health workers and policy-makers should cautiously and immediately assess the geriatrics care system during the implementation of the program.

This study could not clarify the influence of duration of viral hepatitis infection for mortality rates in different periods, because the database of national death certificates does not provide information for etiology and condition of patient. Viral resistance induced by early antiviral drugs or treatment interruption may influence the effectiveness during treatment of hepatitis viruses and confound the finding of the study. However, this study also could not clarify due to lack of information. The data connection between the national health insurance database and national death certificates database is a method for addressing these needs. The national health insurance database constitutes a rich source of medical information such as prescriptions, treatment, outpatient clinic service, and hospital admission service. A further record-linkage study is required.

Acknowledgements This manuscript was edited by Wallace Academic Editing. I would like to thank the Editors of the journal and all reviewers for their comments.

Funding None.

Compliance with ethical standards

Conflict of interest No reported conflicts.

References

1. Polaris Observatory C. Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study. Lancet Gastroenterol Hepatol 2018;3(6):383–403. https://doi.org/10.1016/S2468-1253(18)30056-6
2. Polaris Observatory HCVC. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. Lancet Gastroenterol Hepatol 2017;2(3):161–176. https://doi.org/10.1016/S2468-1253(16)30181-9
3. Stanaway JD, Flaxman AD, Naghavi M, Fitzmaurice C, Vos T, Abubakar I, et al. The global burden of viral hepatitis from 1990 to 2013: findings from the Global Burden of Disease Study 2013. Lancet 2016;388(10049):1081–1088. https://doi.org/10.1016/S0140-6736(16)30579-7
4. Chen DS. Hepatocellular carcinoma in Taiwan. Hepatol Res 2007;37(Suppl 2):S101–S105. https://doi.org/10.1111/j.1872-034X.2007.00170.x
5. Centers for Disease Control, Department of Health, Taiwan, ROC. Annual report 2012. http://www.cdc.gov.tw/uploads/files/20120

8/67addf76-04934d7b-aa72-cd51beff6654.pdf. Accessed 17 Feb 2013
6. Chen DS, Hsu NH, Sung JL, Hsu TC, Hsu ST, Kuo YT, et al. A mass vaccination program in Taiwan against hepatitis B virus infection in infants of hepatitis B surface antigen-carrier mothers. JAMA 1987;257(19):2597–2603
7. Ministry of Health and Welfare, Taiwan, ROC. Taiwan Public Health Report 2012. http://www.mohw.gov.tw/EN/Ministry/DM2_P.aspx?f_list_no5475&fod_list_no5853&doc_no529943. Accessed 16 Aug 2013
8. Chien YC, Jan CF, Kuo HS, Chen CJ. Nationwide hepatitis B vaccination program in Taiwan: effectiveness in the 20 years after it was launched. Epidemiol Rev 2006;28:126–135. https://doi.org/10.1093/epirev/mxj010
9. Chiang CJ, Yang YW, You SL, Lai MS, Chen CJ. Thirty-year outcomes of the national hepatitis B immunization program in Taiwan. JAMA 2013;310(9):974–976. https://doi.org/10.1001/jama.2013.276701
10. Chang CH, Lin JW, Wu LC, Liu CH, Lai MS. National antiviral treatment program and the incidence of hepatocellular carcinoma and associated mortality in Taiwan: a preliminary report. Med Care 2013;51(10):908–913. https://doi.org/10.1097/MLR.0b013e3182a502ba
11. Chiang CJ, Yang YW, Chen JD, You SL, Yang HI, Lee MH, et al. Significant reduction in end-stage liver diseases burden through the national viral hepatitis therapy program in Taiwan. Hepatology 2015;61(4):1154–1162. https://doi.org/10.1002/hep.27630
12. Ni YH, Chang MH, Jan CF, Hsu HY, Chen HL, Wu JF, et al. Continuing decrease in hepatitis B virus infection 30 years after initiation of infant vaccination program in Taiwan. Clin Gastroenterol Hepatol 2016;14(9):1324–1330. https://doi.org/10.1016/j.cgh.2016.04.030
13. Chang MH, You SL, Chen CJ, Liu CJ, Lai MW, Wu TC, et al. Long-term effects of hepatitis B immunization of infants in preventing liver cancer. Gastroenterology 2016;151(3):472–480 e1. https://doi.org/10.1053/j.gastro.2016.05.048
14. Tillmann HL, Zachou K, Dalekos GN. Management of severe acute to fulminant hepatitis B: to treat or not to treat or when to treat? Liver Int 2012;32(4):544–553. https://doi.org/10.1111/j.1478-3231.2011.02682.x
15. Wong VW, Wong GL, Yiu KK, Chim AM, Chu SH, Chan HY, et al. Entecavir treatment in patients with severe acute exacerbation of chronic hepatitis B. J Hepatol 2011;54(2):236–242. https://doi.org/10.1016/j.jhep.2010.06.043
16. Yu W, Zhao C, Shen C, Wang Y, Lu H, Fan J. The efficacy and safety of Nucleos(t)ide analogues in patients with spontaneous acute exacerbation of chronic hepatitis B: a systematic review and meta-analysis. PLoS One 2013;8(6):e65952. https://doi.org/10.1371/journal.pone.0065952
17. Spengler U. Direct antiviral agents (DAAs)—a new age in the treatment of hepatitis C virus infection. Pharmacol Ther 2018;183:118–126. https://doi.org/10.1016/j.pharmthera.2017.10.009
18. Chen CF, Lee WC, Yang HI, Chang HC, Jen CL, Iloeje UH, et al. Changes in serum levels of HBV DNA and alanine aminotransferase determine risk for hepatocellular carcinoma. Gastroenterology 2011;141(4):1240-1248, 8 e1-2. https://doi.org/10.1053/j.gastro.2011.06.036
19. Lee MH, Yang HI, Lu SN, Jen CL, Yeh SH, Liu CJ, et al. Hepatitis C virus seromarkers and subsequent risk of hepatocellular carcinoma: long-term predictors from a community-based cohort study. J Clin Oncol 2010;28(30):4587–4593. https://doi.org/10.1200/JCO.2010.29.1500
20. Global Burden of Disease Cancer C, Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the global burden of disease study. JAMA Oncol 2017;3(4):524–548. https://doi.org/10.1001/jamaoncol.2016.5688
21. Poon SL, Pang ST, McPherson JR, Yu W, Huang KK, Guan P, et al. Genome-wide mutational signatures of aristolochic acid and its application as a screening tool. Sci Transl Med 2013;5(197):197ra01. https://doi.org/10.1126/scitranslmed.3006086
22. Ng AWT, Poon SL, Huang MN, Lim JQ, Boot A, Yu W, et al. Aristolochic acids and their derivatives are widely implicated in liver cancers in Taiwan and throughout Asia. Sci Transl Med 2017;9(412):eaan6446. https://doi.org/10.1126/scitranslmed.aan6446
23. Su WJ, Liu CC, Liu DP, Chen SF, Huang JJ, Chan TC, et al. Effect of age on the incidence of acute hepatitis B after 25 years of a universal newborn hepatitis B immunization program in Taiwan. J Infect Dis 2012;205(5):757–762. https://doi.org/10.1093/infdis/jir852
24. Wait S, Chen DS. Towards the eradication of hepatitis B in Taiwan. Kaohsiung J Med Sci 2012;28(1):1–9. https://doi.org/10.1016/j.kjms.2011.10.027
25. Su S-Y, Chiang C-J, Yang Y-W, Lee W-C. Secular trends in liver cancer incidence from 1997 to 2014 in Taiwan and projection to 2035: an age-period-cohort analysis. J Formosan Med Assoc 2019;118:444–449. https://doi.org/10.1016/j.jfma.2018.07.001
26. World Health Organization. Global health sector strategy on viral hepatitis 2016–2021. http://www.who.int/hepatitis/strategy2016-2021/ghss-hep/en/. Accessed June 2016
27. Lin YY, Huang CS. Aging in Taiwan: building a society for active aging and aging in place. Gerontologist 2016;56(2):176–183. https://doi.org/10.1093/geront/gnv107
28. Wang HH, Tsay SF. Elderly and long-term care trends and policy in Taiwan: challenges and opportunities for health care professionals. Kaohsiung J Med Sci 2012;28(9):465–469. https://doi.org/10.1016/j.kjms.2012.04.002
29. Executive Yuan, Taiwan, ROC. Long-term care 2.0 plan for greater peace of mind. https://english.ey.gov.tw/News_Hot_Topic.aspx?n=FE8C5966F81D8273&sms=BBB420E471DAF6C0. Accessed Mar 6 2018