Received: 9 November 2020 | Revised: 13 January 2021 | Accepted: 11 February 2021

DOI: 10.1111/liv.14821

ORIGINAL ARTICLE

Liver INTERNATIONAL WILEY

The impact of universal hepatitis B vaccine on the trend of liver cancer from the Global Burden of Disease Study 2017

Chenxi Li | **Wen-Qiang He**

School of Population Health, UNSW Sydney, Sydney, Australia

Correspondence
Dr. Wen-Qiang He, Samuels Building, F25, Samuel Terry Ave, Kensington NSW 2033, Australia.
Email: wen-qiang.he@unsw.edu.au

Funding information
This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Handling Editor: Pierre Nahon

Abstract

Aims: This study aims to assess the trend of hepatitis B virus (HBV)-attributable liver cancer as well as the impact of HBV vaccine on it.

Methods: We retrieved data from Global Burden Disease study to estimate trends of HBV-attributable liver cancer by region and age from 1990 to 2017 and HBV vaccine data from World Health Organization to assess its impact on these trends for children (0-14 years), adolescents and young adults (15-29 years). Change of cancer cases, age-standardized incidence rate (ASR) and estimated annual percentage change (EAPC) were used to quantify the trends of HBV-attributable liver cancer.

Results: In this study, reduction in HBV-attributable cancer incident cases was found among children (from 2080 to 1430), adolescents and young adults (from 10 890 to 9090). In terms of ASR, overall reduction was observed globally by an average of −0.45% (95% CI: −0.62 to −0.29) per year in the same period. The highest reduction in ASR was found in adolescents and young adults with EAPC of −3.02 (95% CI: −3.57 to −2.46). Although the ASR has decreased from all the five regions with universal HBV immunization programme, it has increased in the region without universal vaccination and the highest increase was found among children with EAPC of 1.97 (95% CI: 1.71-2.23).

Conclusion: Significant reduction in HBV-attributable liver cancer among children was mainly because of the universal HBV vaccination. However, the increasing trend of HBV-attributable liver cancer in region without universal HBV vaccination suggested the necessity of introducing universal immunization.

KEYWORDS

global trends, HBV-attributable liver cancer, universal HBV vaccination

Abbreviations: 95% CI, 95% confidence interval; 95% UI, 95% uncertainty interval; ASR, age-standardized rate; EAPC, estimated annual percentage change; GBD, Global Burden Disease; HBV, hepatitis B virus; HepB3, 3rd-dose HBV vaccine; SDI, sociodemographic index; UNICEF, United Nations International Children's Emergency Fund; WHO, World Health Organization.

1 | INTRODUCTION

Infection with hepatitis B virus (HBV) is a global public health problem and it can lead to long-term carriage of the virus and often resulting in chronic liver damage or primary liver cancer or death.[1] To date, it has been shown that the age at infection with HBV is the most important factor governing whether an individual will become chronically infected or not.[2] Nearly all newborns who acquire HBV in utero or around the time of birth from their infected mothers become chronic carriers and the carrier rate drops to about 23% among preschool children and is about < 5% among healthy adults.[3,4] Therefore, a mass childhood immunization could postpone the average age at infection in the unvaccinated community and thus reducing the probability of chronical infection or hepatocellular carcinoma in children.[5] The HBV vaccine has been in place since 1981, and a 3-dose childhood schedule has been shown to be greater than 90% effective in preventing infection.[6] However, HBV is still the major cause of liver cancer accounting for 42.3% (405 000/953 000) of total primary liver cancer globally in 2017,[7] owing in part to the failure to implement vaccination programmes and also to a high number of perinatal infections in endemic areas.[1,8]

Since 1984, countries have begun introducing the vaccine into their universal childhood immunization programme with an estimated 3rd-dose HBV vaccine (HepB3) coverage of 84% in 2017.[9] Therefore, increasing evidences have suggested the decreasing prevalence of HBV in many countries with good implementation of universal vaccination, while the prevalence remained stable or increased in some African countries with poor HepB3 vaccination programme[5] or countries with large immigrants from regions of high and intermediate HBV prevalence.[10,11] However, few studies have investigated the trends of HBV-attributable liver cancer worldwide in detail[7] and the impact of HBV vaccine on HBV-attributable liver cancer was only reported in some parts of China, Taiwan, Korea, Thailand and USA.[12-16] For instance, the cluster randomized control trial in China revealed that neonatal HBV vaccine significantly reduced the risk of liver cancer over 30 years of follow-up periods in Jiangsu Province.[13] Another study in Taiwan suggested significant reduction in liver cancer in children and adolescents and young adults from 2003 to 2011 since the first nationwide HBV universal vaccination programme in 1984.[12] After the successful implementation of universal HepB3 vaccination programme worldwide for the past 3 decades, it is important to assess the impact on the serious sequelae of HBV, in particular primary liver cancer in children (0-14 years) and adolescents and young adults (15-29 years) in a systematic way.

The Global Burden Disease (GBD) study assessed the primary liver cancer burden overall and by specific aetiologies in 195 countries and territories from 1990 to 2017.[17] In this study, the incidence of HBV-attributable liver cancer by age was retrieved from GBD 2017, which was used to estimate the trend of primary liver cancer caused by HBV. Together with the availability of estimated HepB3 vaccination information from the World Health Organization (WHO) and United Nations International Children's Emergency Fund (UNICEF),[9] this study aims to understand the trends of HBV-attributable liver cancer by age as well as the impact of HepB3 vaccine on HBV-attributable liver cancer in children, adolescents and young adults.

Lay Summary

Few studies have reported that the universal neonatal HBV vaccination has reduced the risk of HBV-attributable liver cancer. We aim to understand the trends of HBV-attributable liver cancer by age as well as the impact of national HBV immunization on HBV-attributable liver cancer in children, adolescents and young adults. HBV-attributable liver cancer has reduced significantly among children in countries since the introduction of universal HBV vaccination. In contrast, it increased in countries without universal HBV vaccination suggesting the importance of introducing universal immunization.

Key Points

- This study estimated the trends of HBV-attributable liver cancer by country, region and age from 1990 to 2017 by using data from Global Burden Disease study 2017 and the impact of universal HBV vaccination programmes on these trends among children (0-14 years), adolescents and young adults (15-29 years).
- This study showed HBV-attributable liver cancer decreased significantly among children, adolescents and young adults and from countries with national HepB3 vaccination programme, while it increased in the general population from countries without HepB3 vaccine programme or countries from high-SDI regions.
- These results confirm previously reported regional trends, correlated well with universal HBV vaccination programme and underscore the need for introducing universal HBV immunization of newborns as well as targeting vaccination of high-risk groups in countries without such campaign.

2 | METHOD

2.1 | Study data

Annual incidence rates and age-specific rates of HBV-attributable liver cancer with 95% Uncertainty Interval (95% UI) from 1990 to 2017 overall, by region and country, were collected from the Global Health Data Exchange query tool.[18] Data from a total of 195 countries and territories were available from the dataset. The countries with similar development status were grouped into 5 categories by using a Sociodemographic Index (SDI) including low SDI, low-middle SDI, middle SDI, middle-high SDI and high SDI. These countries were also categorized into 21 regions based on their geographical location.

The estimation process for the GBD 2017 in liver cancer has been described in detail from previous studies. In brief, cancer incidence was obtained from vital registration system (83% of data), cancer registry (16% of data) and verbal autopsy data (1% of data) using an ensemble model approach.[17] Although the changes between coding systems can lead to artificial differences in disease estimates, the GBD study group had adjusted for this by mapping the different coding systems to the GBD causes. In addition, underreporting of liver cancer can be an issue in cancer registries from low-income countries as it requires advanced diagnostic techniques. Proportions of HBV-attributable liver cancer were identified by using a systematic review.[17]

Data for HepB3 coverage were obtained from the 2018 WHO Global Health Observatory estimates of vaccine coverage provided by WHO and UNICEF since the start of national programme[9] and the method of estimation was described previously.[19] Briefly, administrative data based on reports from service providers and surveys with items on children's vaccination history were the main sources of empirical data on immunization coverage. As both administrative and survey methods are vulnerable to inadvertent recording, calculation and transcription errors, WHO and UNICEF began a retrospective review of data using reports by national authorities to WHO, surveys data and grey literature. These agencies jointly estimated the most likely immunization coverage for the years 1980-1999 and it has been continued annually since. Vaccination coverage data for the US territories and Puerto Rico were obtained from the National Immunization Survey among children aged 19-35 months.[20] The 195 countries or territories were thus categorized into 6 groups by their HepB3 coverage (Table A1), including those without universal immunization, 20%-50%, 51%-70%, 71%-80%, 81%-90% and > 90%. As for countries without universal HepB3 vaccination, it included Iceland, United Kingdom, Denmark, Greenland, Norway, Finland, Japan, Switzerland, Slovenia and Hungary, where universal HBV vaccine is not routinely administrated in infants.

2.2 | Statistical analysis

The trends of HBV-attributable liver cancer were investigated by using age-standardized rates (ASR) and estimated annual percentage change (EAPC). ASR was calculated using the year 2000 world population from WHO as reference with every 5-year age as a group,[21] i.e. the sums of the products of age-specific rates and the weight in the same age group of the reference population were divided by the sum of weights of each age group from the standard population. This was calculated overall, by regions (SDI, vaccination coverage and geographical regions) and by four age groups (children: 0-14 years, adolescents and young adults: 15-29 years, adults: 30-64 years, elders: 65 + years). All rates were computed per 100 000 person-years with 95% uncertainty intervals for all estimates.

EAPC (95% confidence interval, 95% CI) was used to estimate the trend of ASR over the period. It was calculated as $100 \times (\exp(\beta) - 1)$, where β was obtained from the regression line fitting to the natural logarithm of the ASR in the following formula, i.e. $y = \alpha + \beta x + \varepsilon$, where y = ln(ASR) and x = calendar year. The trend of ASR was considered as significant reduction if ASR and its upper estimate of 95% CI were less than 0 and it was considered as significant increase if ASR and its lower estimate of 95% CI were greater than 0. Otherwise, the trend of ASR was considered as no change or stable over the period.

All analyses were performed using R version 3.5.1.[22] A two-sided *P* value less than 0.05 was considered statistically significant.

3 | RESULTS

In 2017, the global number of HBV-attributable liver cancer is 403 960 (95% UI: 378 260-434 130) (Table 1), which is about 1.8 times of that in 1990 (219 830, 95% UI: 201 200-241 570). However, slight reduction was found among children, adolescents and young adults in the same period (children: from 2080 in 1990 to 1430 in 2017, adolescents and young adults: from 10 890 in 1990 to 9090 in 2017). In terms of ASR, overall reduction was observed by an average of −0.45% (95% CI: −0.62 to −0.29) per year in the same period (from 5.15 per 100 000 in 1990 to 5.10 per 100 000 in 2017). The highest reduction in ASR was found in the young adults with EAPC of −3.02 (95% CI: −3.57 to −2.46), followed by children with EAPC of −2.72 (95% CI: −3.11 to −2.34) and middle-aged adults with EAPC of −0.76 (95% CI: −0.94 to −0.59), while increase was found among those elder people with EAPC of 0.59 (95% CI: 0.45 to 0.73).

In the five SDI regions, increase in cancer cases was found across the regions among the whole population (Table 1), while decrease in cancer cases was found among those children, adolescents and young adults in the middle SDI (children: from 847 to 350, adolescents and young adults: from 5244 to 3591) and high-middle SDI regions (children: from 420 to 218, adolescents and young adults: from 2999 to 2302) (Figure 1A). As for the trend of ASR, consistent increase in ASR from high SDI region was found across the four age groups with the highest increase found among those elder people with EAPC of 1.08 (95% CI: 0.84-1.32), while significant reduction was found among children, adolescents and young adults, and middle-aged adults in low, low-middle, middle and high-middle SDI regions (Figure 1B). And the highest reduction in ASR was found among children from middle SDI region with EAPC of −4.46 (95% CI: −5.05 to −3.86) (Figure 2A).

As for 6 regions by HepB3 vaccine coverage, apart from the 10 countries without universal immunization till the end of 2017, the average national vaccine coverage of the rest of the 185 countries or territories was 84% (range: 20% to 98.6%) and the average vaccination year was 18 years (range: 3 to 31 years, Table A1). Throughout the study period, increase in cancer cases was found across the 6 regions overall, while decrease in cancer cases was only observed from countries with vaccine coverage greater than 80% for children (from 1435 to 731) and adolescents and young adults (from 9175 to 6815, Figure 1C). As for ASR, it only increased in the region without universal vaccination and the highest increase was found among children with EAPC of 1.97 (95% CI: 1.71-2.23, Figure 2B). The ASR

TABLE 1 The incident cases and age-standardized incidence of HBV-attributable liver cancer in 1990 and 2017, and its temporal trends from 1990 to 2017

	Incident cases N x10^3 (95% UI) 1990	ASR per 100 000 N (95% UI) 1990	Incident cases N x10^3 (95% UI) 2017	ASR per 100 000 N (95% UI) 2017	EAPC % (95% CI)
Overall	219.83 (201.20, 241.57)	5.15 (4.53, 5.79)	403.96 (378.26, 434.13)	5.1 (4.56, 5.71)	−0.45 (−0.62, −0.29)
Age group					
0-14	2.08 (1.71, 2.50)	0.12 (0.10, 0.15)	1.43 (1.26, 1.63)	0.07 (0.06, 0.08)	−2.72 (−3.11, −2.34)
15-29	10.89 (9.59, 12.64)	0.76 (0.67, 0.88)	9.09 (8.16, 10.04)	0.48 (0.44, 0.54)	−3.02 (−3.57, −2.46)
30-64	153.21 (134.83, 171.17)	8.76 (7.71, 9.78)	258.84 (231.12, 289.93)	8.07 (7.20, 9.04)	−0.76 (−0.94, −0.59)
65+	53.65 (47.32, 61.16)	16.23 (14.31, 18.51)	134.61 (120.44, 150.45)	20.11 (17.99, 22.48)	0.59 (0.45, 0.73)
Gender					
Male	164.52 (146.96, 183.17)	7.91 (6.81, 9.06)	321.17 (297.6, 347.97)	8.38 (7.42, 9.48)	−0.22 (−0.39, −0.05)
Female	55.31 (48.01, 60.90)	2.50 (2.11, 2.88)	82.8 (76.78, 89.15)	2.00 (1.76, 2.26)	−1.17 (−1.31, −1.03)
Social-demographic index					
Low	9.7 (6.82, 19.24)	2.55 (1.64, 5.30)	15.12 (13.02, 19.69)	1.92 (1.49, 2.55)	−0.96 (−1.03, −0.89)
Low-middle	17.59 (14.87, 22.96)	2.71 (2.15, 3.67)	29.63 (26.26, 36.62)	2.33 (1.93, 3.00)	−0.67 (−0.82, −0.53)
Middle	93.05 (84.68, 100.14)	8.6 (7.48, 9.71)	170.94 (157.02, 186.09)	7.55 (6.58, 8.61)	−0.83 (−0.97, −0.68)
Middle-high	74.71 (68.15, 80.36)	7.69 (6.60, 8.65)	141.26 (128.85, 155.42)	7.96 (6.87, 9.24)	−0.53 (−0.77, −0.29)
High	21.96 (20.49, 23.40)	1.91 (1.68, 2.15)	41.99 (38.88, 46.66)	2.29 (1.95, 2.70)	0.47 (0.36, 0.59)
Vaccine coverage					
No universal immunization	4.90 (4.20, 5.71)	0.76 (0.53, 1.08)	5.45 (4.04, 7.01)	0.80 (0.48, 1.23)	0.22 (0.09, 0.36)
20%-50%	5.40 (3.86, 8.10)	3.32 (1.47, 8.97)	14.1 (11.56, 17.45)	2.12 (1.14, 3.98)	−2.10 (−2.30, −1.90)
51%-70%	7.01 (4.54, 10.55)	3.42 (1.98, 5.78)	12.61 (7.88, 18.69)	3.09 (1.58, 5.04)	−0.62 (−0.82, −0.41)
71%-80%	8.02 (4.76, 15.93)	4.06 (2.09, 9.07)	12.36 (7.49, 21.07)	3.07 (1.56, 5.86)	−0.96 (−1.02, −0.90)
81%-90%	172.43 (148.38, 203.63)	3.98 (2.15, 9.04)	318.05 (277.16, 370.04)	3.15 (1.96, 5.12)	−0.73 (−0.80, −0.66)
>90%	19.27 (14.60, 24.78)	2.24 (1.54, 3.15)	36.39 (25.51, 49.63)	2.08 (1.28, 3.06)	−0.52 (−0.65, −0.40)
Region					
East Asia	166.1 (152.81, 177.02)	16.55 (14.65, 18.26)	305.35 (283.91, 329.71)	14.95 (13.33, 16.77)	−0.89 (−1.09, −0.69)
Southeast Asia	11.61 (9.95, 13.31)	3.93 (2.97, 5.01)	23.31 (19.60, 27.40)	3.73 (2.78, 4.82)	−0.38 (−0.49, −0.27)
High-income Asia Pacific	10.45 (9.56, 11.32)	5.15 (4.39, 5.99)	15.65 (14.08, 17.46)	4.64 (3.49, 5.90)	−0.42 (−0.48, −0.36)
Central Asia	0.99 (0.79, 1.24)	1.97 (1.35, 2.73)	1.59 (1.32, 1.87)	2.00 (1.40, 2.71)	−0.21 (−0.31, −0.10)
South Asia	5.15 (4.30, 6.05)	0.74 (0.59, 0.90)	14.56 (13.18, 15.95)	1.02 (0.88, 1.17)	1.26 (1.20, 1.33)
Australasia	0.07 (0.06, 0.08)	0.32 (0.26, 0.39)	0.28 (0.24, 0.32)	0.7 (0.50, 0.97)	3.06 (2.79, 3.34)
Oceania	0.17 (0.10, 0.27)	4.79 (2.65, 8.14)	0.37 (0.24, 0.50)	4.62 (2.83, 6.86)	−0.02 (−0.07, 0.02)

(Continues)

TABLE 1 (Continued)

	Incident cases N x10^3 (95% UI) 1990	ASR per 100 000 N (95% UI) 1990	Incident cases N x10^3 (95% UI) 2017	ASR per 100 000 N (95% UI) 2017	EAPC % (95% CI)
North Africa and Middle East	2.68 (2.20, 3.42)	1.38 (1.00, 1.89)	6.04 (5.27, 6.86)	1.33 (1.04, 1.68)	−0.03 (−0.15, 0.09)
Central Sub-Saharan Africa	0.83 (0.55, 1.64)	3.08 (1.82, 6.46)	1.10 (0.79, 1.69)	1.82 (1.17, 3.00)	−1.85 (−2.07, −1.63)
Eastern Sub-Saharan Africa	2.03 (1.55, 2.55)	2.24 (1.46, 3.20)	3.67 (3.01, 4.43)	1.95 (1.32, 2.71)	−0.74 (−0.88, −0.60)
Southern Sub-Saharan Africa	1.17 (0.67, 3.21)	3.56 (1.86, 10.15)	1.32 (1.19, 1.48)	2.13 (1.70, 2.64)	−1.49 (−2.05, −0.93)
Western Sub-Saharan Africa	7.07 (4.89, 15.14)	6.85 (4.30, 15.4)	9.57 (8.02, 12.03)	4.46 (3.29, 5.91)	−1.51 (−1.59, −1.43)
Eastern Europe	2.25 (2.03, 2.51)	0.83 (0.71, 0.97)	2.44 (2.24, 2.65)	0.81 (0.70, 0.93)	−0.58 (−0.77, −0.39)
Central Europe	1.38 (1.12, 1.66)	0.94 (0.64, 1.28)	1.77 (1.40, 2.14)	0.93 (0.63, 1.29)	−0.08 (−0.26, 0.11)
Western Europe	3.51 (3.05, 4.03)	0.65 (0.50, 0.83)	5.91 (5.12, 6.84)	0.81 (0.61, 1.06)	0.79 (0.67, 0.91)
High-income North America	1.45 (1.36, 1.55)	0.44 (0.39, 0.50)	5.21 (4.84, 5.58)	0.98 (0.84, 1.13)	3.03 (2.71, 3.35)
Caribbean	0.42 (0.36, 0.48)	1.54 (1.17, 1.98)	0.66 (0.57, 0.77)	1.34 (1.01, 1.73)	−0.83 (−0.97, −0.70)
Andean Latin America	0.62 (0.56, 0.68)	2.72 (2.25, 3.27)	1.35 (1.21, 1.52)	2.48 (2.00, 3.03)	−0.4 (−0.61, −0.19)
Central Latin America	0.9 (0.77, 1.04)	0.94 (0.68, 1.24)	1.71 (1.44, 2.00)	0.72 (0.52, 0.98)	−1.17 (−1.27, −1.08)
Southern Latin America	0.13 (0.11, 0.14)	0.27 (0.21, 0.34)	0.19 (0.16, 0.21)	0.24 (0.19, 0.30)	−0.82 (−0.95, −0.68)
Tropical Latin America	0.86 (0.80, 0.91)	0.83 (0.73, 0.93)	1.93 (1.81, 2.04)	0.83 (0.73, 0.93)	−0.16 (−0.27, −0.04)

FIGURE 1 The number of cancer cases and ASR of HBV-attributable liver cancer worldwide and in region levels by age. (A) The number of liver cancer by age and SDI regions; (B) The ASR of liver cancer by age and SDI regions. (C) The number of liver cancer by age and vaccine coverage; (D) The ASR of liver cancer by age and vaccine coverage. ASR, age-standardized rate; SDI, social-demographic index

in the other five regions with vaccination decreased significantly across the four age groups with the highest reduction observed in the children across the 5 regions (EAPC from −2.29 to −1.16, 95% CI: −2.58 to −1.05, Figure 2B).

In terms of the trend for the 21 geographical regions, increase in cancer cases was found across the 21 regions overall (Table 1), while the ASR only increased in four regions (South Asia, Australasia, Western Europe and High-income North America) with the highest observed in Australasia with EAPC of 3.06 (95% CI: 2.79-3.34) (Figure 2C). Another 17 regions either had some reduction or the only reduction among children with the highest reduction found in East Asia with EAPC of −3.95 (95% CI: −4.72 to −3.17).

In the country level, the highest number of HBV-attributable liver cancer was found in China with 290 945 accounting for around 72% of total cases globally in 2017, followed by India (12 155) and South Korea (10 999). As for ASR (Figure 3A), the highest was found in Mongolia with 22.33 per 100 000 (95% UI: 14.70-31.75), followed by Gambia (17.08, 95% UI: 5.73-28.48), Guinea (16.06, 95% UI: 4.46-29.05) and China (14.97, 95% UI: 13.36-16.77). As for change of cancer cases (Figure 3B), the reduction was only found among 13 countries with the highest reduction of 50% in Sierra Leone (from 446 in 1990 to 223 in 2017), while the rest 182 countries had increase in cancer cases with the highest increase of 876% in United Arab Emirates (from 10 in 1990 to 97 in 2017). As for the change of ASR, a total of 115 countries or territories had seen significant reduction with the highest EAPC observed in Burkina Faso (−3.94, 95% CI: −4.37 to −3.51), followed by Kazakhstan, Sierra Leone and Chad (Figure 3B). Another 56 countries or territories had significant increase in ASR with the highest EAPC in Moldova of 4.45 (95% CI: 3.87-5.03), followed by Netherlands, United Kingdom, Australia and United States (Figure 3C). The ASR of the rest of the 24 countries or territories remained stable over the study period (Figure 3C).

The change of cancer cases and ASR over the study period varied across four age groups (Figure 4 and Figure A1). As for the change of cancer cases (Figure 4A-4B), a total of 108 countries had reduced number of cancer cases among children with greatest relative reduction of 83% found in Thailand (40 in 1990 to 7 in 2017) and 56 countries had reduction in cancer cases among adolescents and young adults with the greatest relative reduction of 52.8% in South Korea (133 in 1990 to 63 in 2017). In term of absolute reduction, China has the highest reduction among children

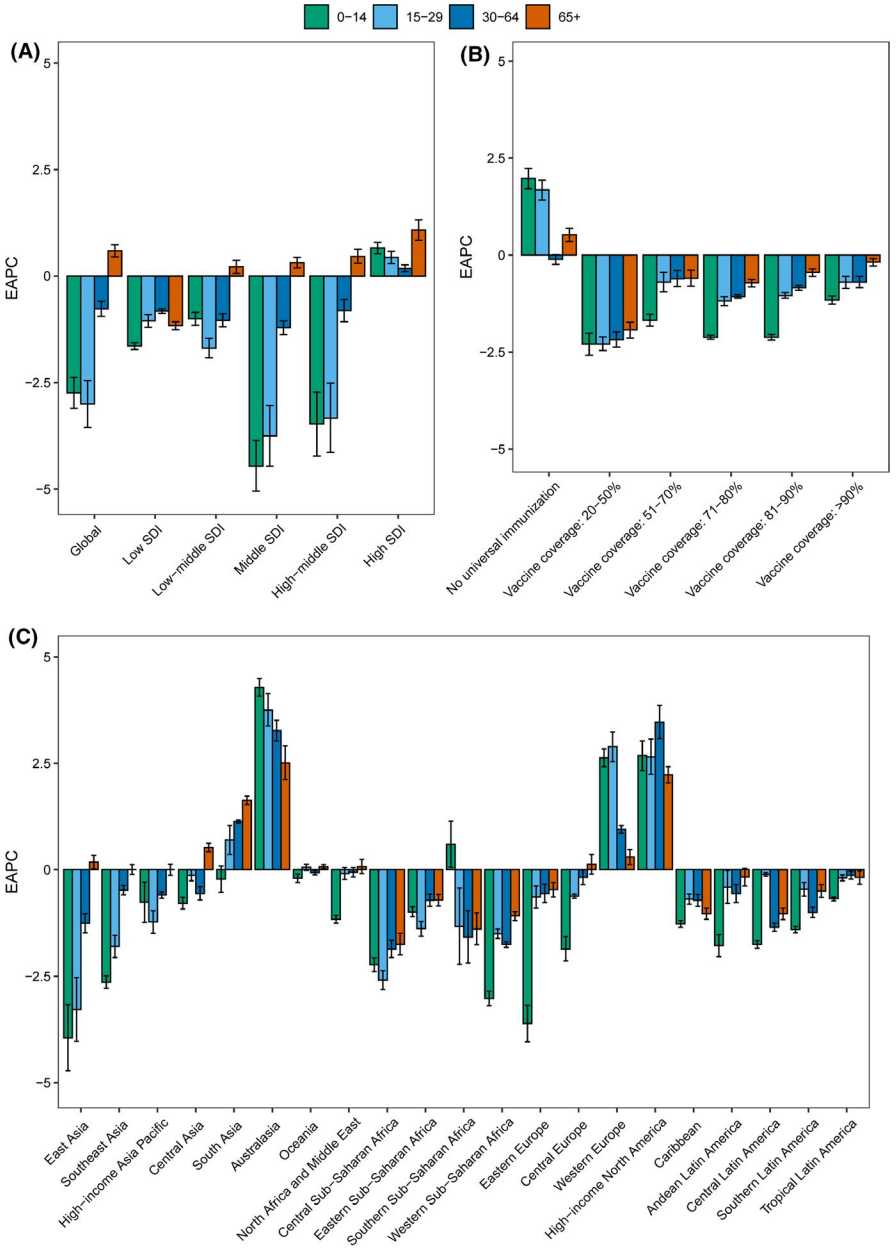

FIGURE 2 The EAPCs of HBV-attributable liver cancer worldwide and in regions by age groups. (A) The EAPC from 1990 to 2017 by SDI region. (B) The EAPC of liver cancer ASR from 1990 to 2016 by vaccination category. (C) The EAPC of liver cancer by geographical regions. Error bars represent 95% CI. EAPC, estimated annual percentage change; SDI, social-demographic index

(957 in 1990 to 375 in 2017) and adolescents and young adults (7594 in 1990 to 4954 in 2017). In contrast, only 16 and 13 countries had reduction in cancer cases among middle-aged adults and elder people respectively (Figure A1 A-B). As for change of ASR, a total of 132 countries or territories had significant reduction among children with the highest reduction in EAPC −7.41 (95% CI: −8.00 to −6.81) in Sierra Leone (Figure 4C) and another 42 countries or territories had increase in ASR with the highest increase in Netherlands with EAPC of 6.14 (95% CI: 5.59-6.70). For adolescents and young adults, 113 had significant decrease in ASR with the highest observed in Burkina Faso of −3.74 (95% CI: −4.22 to −3.26) and 55 countries had significant increase in ASR with highest found in Netherlands of 6.64 (95% CI: 6.28-7.00) (Figure 4D). In addition, slight reduction in ASR was also found in 123 and 108 countries among middle-aged adults and elder people respectively (Figure A1 C-D).

4 | DISCUSSION

In this study, HBV-attributable liver cancer decreased significantly among children, adolescents and young adults and from regions with national HepB3 vaccination programme. In contrast, it increased in the general population from countries without HepB3 vaccine programme or countries from high-SDI regions.

Although the incidence of HBV caused liver cancer among middle-aged adults and elder people still increased, we found it decreased among children, adolescents and young adults throughout the study period. This could be attributed to improving socioeconomic conditions, demographic changes (smaller size of families), better hygiene, changes in risky behaviour, refinement in blood screening and adoption of universal precautions in medical settings.[23] However, we assume the reduction was largely attributable to the national HepB3 vaccination programme. For instance, the highest relative

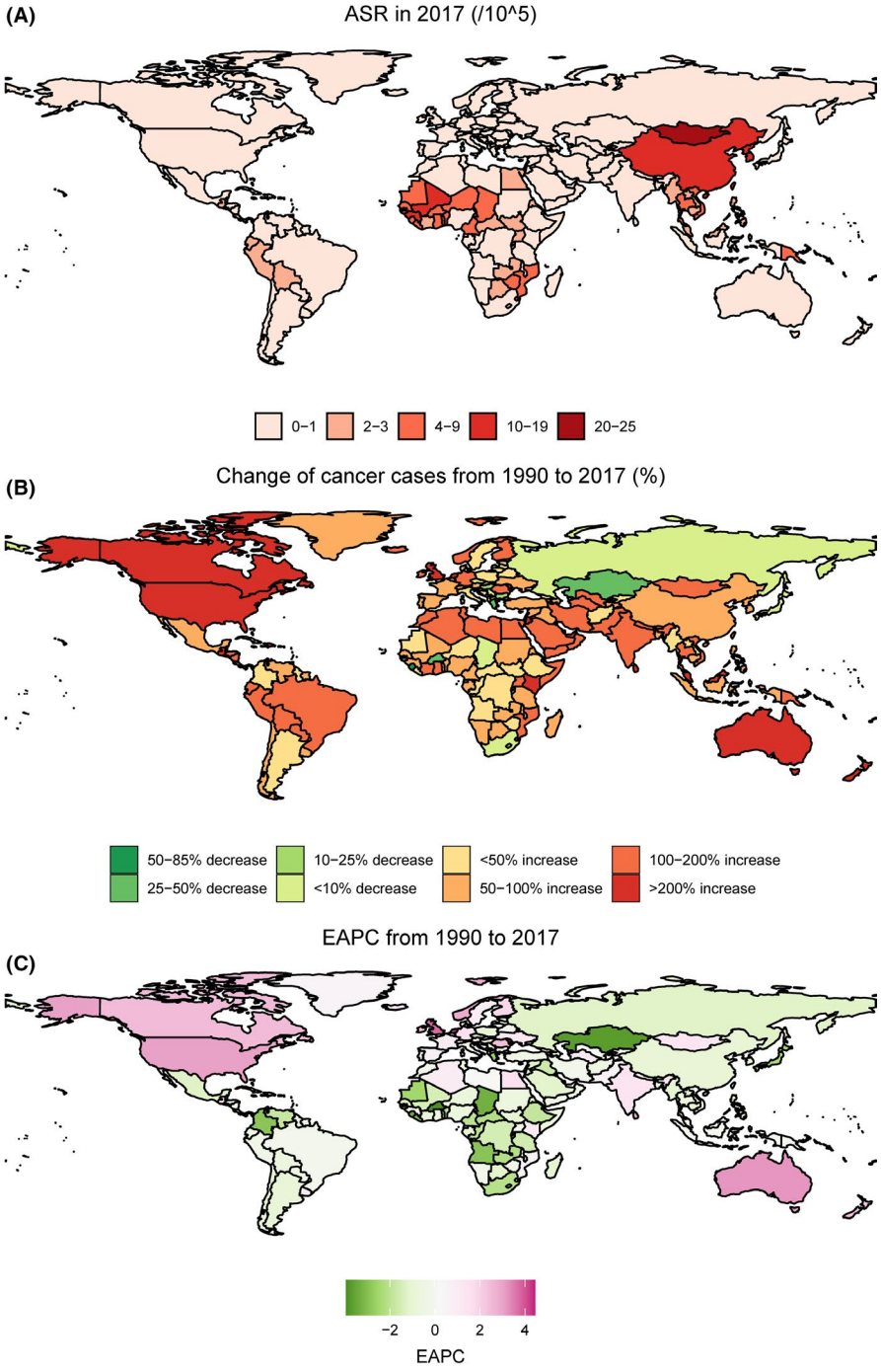

FIGURE 3 The trends of HBV-attributable liver cancer and their correlation with HBV vaccine. (A) ASR in 2017. (B) Change of cancer cases from 1990 to 2017. (C) EAPC from 1990 to 2017. Grey area indicated no available universal vaccination data. ASR, age-standardized rate; EAPC, estimated annual percentage change

reduction in cancer cases among children was found in Thailand and the highest reduction among adolescents and young adults in South Korea, both of which had introduced universal immunization since early 1990s and with vaccine coverage of > 93% since 1995.[9] This is consistent with the report that Thailand is one of the few countries reported the reduced burden of liver cancer in children 10 years after introduction of universal infant vaccination.[16] The highest absolute reduction in cancer cases among children, adolescents and young adults in China highlighted the success of national neonatal HBV vaccination since 1992.[24] The strong reduction was further supported by the highest reduction in ASR of HBV caused liver cancer among children in the regions with universal HepB3 vaccination programme. In addition, the reduction in HBV-attributable liver cancer was only found among children but not among adolescents and young adults in South Asia. This was mainly driven by India as it has the second highest number of HBV-attributable liver cancer in the world, from where the number has decreased from 175 in 1990 to 140 among children in 2017, which was correlated well with their recent start of universal HBV immunization in 2004 and low vaccine coverage prior to 2012 (ranged from 6% in 2004 to 44% in 2011).[25] However, the incidence of liver cancer in India among adolescents and young adults has increased from 258 in 1990 to 420 in 2017 with EAPC of 0.48 (95% CI: 0.04 to 0.92). Therefore, the impact of HBV vaccination in India among adolescents and young adults will

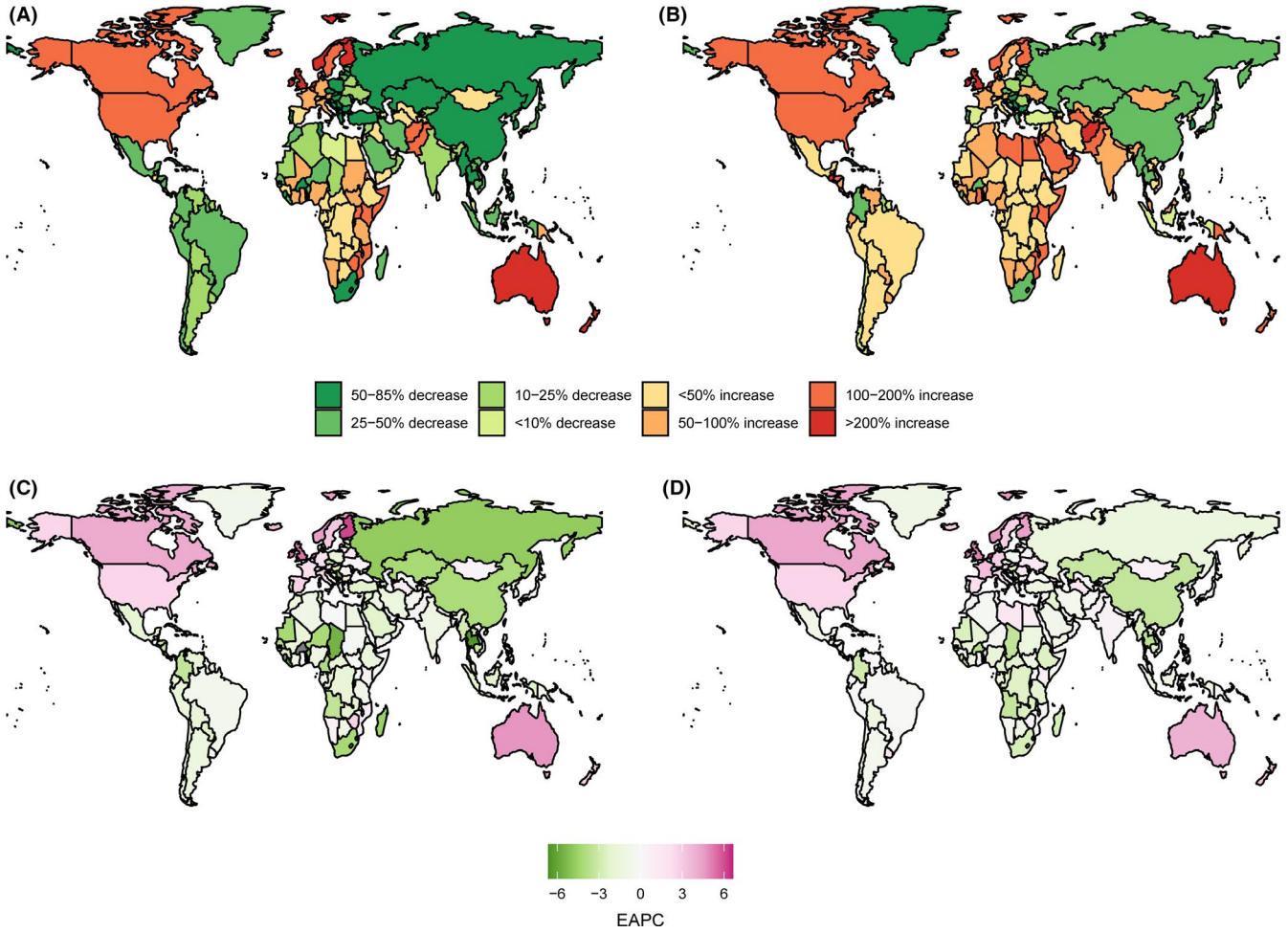

FIGURE 4 The trends of HBV-attributable liver cancer among children, adolescents and young adults. The change of cancer cases from 1990 to 2017 for children (A), adolescents and young adults (B). The EAPC for children (C), adolescents and young adults (D). Grey area indicated no available universal vaccination data. EAPC, estimated annual percentage change

not be observed until at least another 10 years, given the universal vaccination programme has not reached the country nationwide until 2012.

In contrast to the reduction in HBV-attributable liver cancer observed in countries with universal HepB3 vaccination programme and those from middle to high-middle SDI regions, significant increase in liver cancer was observed in countries without universal vaccine programme and those from high-SDI regions (including Western Europe, High-income North America and Australasia). Therefore, for countries without universal vaccination, we propose a campaign of universal vaccination of newborns and catch-up vaccination for adolescents could reduce the risk of HBV from parental transmission as supported by reports from Italy,[26] Australia[27] and Taiwan[28] and the burden of HBV attributable liver cancer in the longer term as suggested by studies in Taiwan.[12,28] Nevertheless, such universal vaccination campaign of newborns and adolescents might not reach the immigrants population[29] with increasing number of migrants from countries with high and intermediate prevalence of HBV significantly contributing to the increased risk of HBV-attributable liver cancer in these countries with low HBV prevalence.[30,31] Therefore, some countries with low prevalence of HBV have developed targeted risk-group vaccination programmes in addition to screening pregnant mothers from high prevalence regions and immunization of their newborns as an alternative to universal immunization.[32] Yet, such selective programmes are difficult to implement and have so far failed to control viral hepatitis infection in the general population.[33,34]

For countries from high-SDI regions, despite some of them from North America and Australasia had a relative long history of universal HBV vaccination, the domestic immunization programme will not have any noticeable effect on the burden of chronic HBV because of the immigrants from countries with high and intermediate prevalence and thus negligible impact on the burden of HBV-attributable liver cancer in these countries.[10,11] This was supported by the increased incidence of HBV-attributable liver cancer from United States, Canada, Australia and New Zealand found in this study. Because of a lack of universal standards for screening, vaccination and treatment of viral hepatitis, the burden of chronic liver disease and liver cancer continues to increase among migrant populations globally.[31] Taking together, all these results suggest the importance to strengthen efforts to implement universal HBV vaccination as well as targeting vaccination including migrant population

from countries with high and intermediate prevalence of HBV. This includes countries with high vaccine coverage maintaining their immunization and countries with low vaccine coverage increasing their vaccine coverage. Furthermore, countries without universal vaccination should initiate such programmes.[32] Indeed, changing demography with increasing immigration and increased risk of HBV introduction from HBV endemic countries make the cost-benefit ratios strongly in favour of universal HBV vaccination. Irrespective of universal vaccination, programmes targeting high-risk groups are further needed until all countries have a generation of adolescents and young adults among whom transmission has been interrupted. Finally, for prevention through immunization, early diagnosis and effective treatment should be implemented to contribute to the reduction in transmission.

The strength of this study is to use the data from GBD study to estimate the burden of HBV-attributable liver cancer in 195 countries and territories and data from WHO and UNICEF for national HepB3 vaccination coverage to estimate its impact on the change of HBV-attributable liver cancer.[7,35] However, the major limitation of the study is that the GBD estimates largely depend on the quality and quantity of data used in the modeling.[17] This included the miscoding of liver metastases as primary liver cancers and underestimation of liver cancer in some countries because of lack of diagnostic capacity. Although the quality of such registry has improved significantly over the period in some of the countries, the quality in some low-income countries was still far behind. As such, some results in this region might not be accurate. Although the small number of HBV-attributable cases in some countries might provide inaccurate estimate of the trend, the grouping of countries by their SDI level, HepB3 vaccination coverage and geographical location will generate more acute estimate of trends in this study. Another limitation of this study is the inability to assess the impact of the birth dose of HBV vaccine within the first 24 hours of life on the change of HBV-attributable liver cancer, which is considered as the most effective intervention for the prevention of HBV-associated disease worldwide.[36] However, it has only been introduced in 109 countries by the end of 2018 and the global coverage is 42%.[37] Therefore, the reduction in liver cancer cases among children identified in this study might also partially caused by the birth dose of HBV vaccine. Lastly, the reduction in HBV-attributable liver cancers among children found in this study could also be contributed to reducing other risk factors.[38,39] For instance, liver cancer decreased in young adults was also found as a result of the reduction in aflatoxin in food storage and HepB3 vaccination programme in China[38] and adherence to the Mediterranean diet appears to be protective against liver cancer in Italy and Greece.[39] However, the consistent reduction in HBV-attributable liver cancer among children found in so many countries could possibly only be explained by the national HepB3 vaccination programme.

In conclusion, significant reduction in HBV-attributable liver cancer observed among children was mainly caused by the universal HBV vaccination. However, the increasing trend of HBV-attributable liver cancer was found in countries without universal HBV vaccination, suggesting the necessity of introducing universal HBV immunization of newborns as well as targeting vaccination of high-risk groups in these countries.

ACKNOWLEDGEMENT

We appreciate the works by the Global Burden of Disease study 2017 and Global Health Observatory data: Hepatitis B 3rd-dose (HepB3) immunization coverage from World Health Organization.

CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this study.

ORCID

Wen-Qiang He https://orcid.org/0000-0002-7475-8485

REFERENCES

1. Ringelhan M, McKeating JA, Protzer U. Viral hepatitis and liver cancer. *Philos Trans R Soc Lond B Biol Sci*. 2017;372(1732).
2. Edmunds WJ, Medley GF, Nokes DJ, Hall AJ, Whittle HC. The influence of age on the development of the hepatitis B carrier state. *Proceedings Biological sciences*. 1993;253(1337):197-201.
3. Beasley RP, Hwang L-Y, Lin C-C, et al. Incidence of hepatitis B virus infections in preschool children in Taiwan. *J Infect Dis*. 1982;146(2):198-204.
4. McMahon BJ, Alward WLM, Hall DB, et al. Acute hepatitis B virus infection: relation of age to the clinical expression of disease and subsequent development of the carrier state. *J Infect Dis*. 1985;151(4):599-603.
5. Ott JJ, Horn J, Krause G, Mikolajczyk RT. Time trends of chronic HBV infection over prior decades – a global analysis. *J Hepatol*. 2017;66(1):48-54.
6. World Health Organization. Hepatitis B. 2019. https://www.who.int/news-room/fact-sheets/detail/hepatitis-b Accessed April 21, 2020
7. Fitzmaurice C, Abate D, Abbasi N, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2017: a systematic analysis for the global burden of disease study. *JAMA oncology*. 2019;5(12):1749-1768.
8. Trépo C, Chan HL, Lok A. Hepatitis B virus infection. *Lancet (London, England)*. 2014;384(9959):2053-2063.
9. World Health Organization. Global Health Observatory (GHO) data: Hepatitis B 3rd dose (HepB3) immunization coverage. 2019. https://www.who.int/gho/immunization/hepatitis/en/. Accessed April 27, 2020
10. MacLachlan JH, Allard N, Towell V, Cowie BC. The burden of chronic hepatitis B virus infection in Australia, 2011. *Aust N Z J Public Health*. 2013;37(5):416-422.
11. Kim WR. Epidemiology of hepatitis B in the United States. *Hepatology (Baltimore, MD)*. 2009;49(5 Suppl):S28-S34.
12. Hung GY, Horng JL, Yen HJ, Lee CY, Lin LY. Changing incidence patterns of hepatocellular carcinoma among age groups in Taiwan. *J Hepatol*. 2015;63(6):1390-1396.
13. Qu C, Chen T, Fan C, et al. Efficacy of neonatal HBV vaccination on liver cancer and other liver diseases over 30-year follow-up of the Qidong hepatitis B intervention study: a cluster randomized controlled trial. *PLoS Medicine*. 2014;11(12):e1001774.
14. McMahon BJ, Bulkow LR, Singleton RJ, et al. Elimination of hepatocellular carcinoma and acute hepatitis B in children 25 years

after a hepatitis B newborn and catch-up immunization program. *Hepatology (Baltimore, MD)*. 2011;54(3):801-807.
15. Gwack J, Park SK, Lee EH, Park B, Choi Y, Yoo KY. Hepatitis B vaccination and liver cancer mortality reduction in Korean children and adolescents. *Asian Pacific journal of cancer prevention : APJCP*. 2011;12(9):2205-2208.
16. Wichajarn K, Kosalaraksa P, Wiangnon S. Incidence of hepatocellular carcinoma in children in Khon Kaen before and after national hepatitis B vaccine program. *Asian Pacific journal of cancer prevention : APJCP*. 2008;9(3):507-509.
17. Akinyemiju T, Abera S, Ahmed M, et al. The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level: results from the global burden of disease study 2015. *JAMA oncology*. 2017;3(12):1683-1691.
18. Global Burden of Disease Collaborative Network. *Global Burden of Disease Study 2017 (GBD 2017) Results*. Institute for Health Metrics and Evaluation (IHME); 2017. http://ghdx.healthdata.org/gbd-results-tool. Accessed March 13, 2019
19. Burton A, Monasch R, Lautenbach B, et al. WHO and UNICEF estimates of national infant immunization coverage: methods and processes. *Bull World Health Organ*. 2009;87(7):535-541.
20. Hepatitis B (HepB) vaccination coverage among children 19-35 months by State, HHS Region, and the United States, National Immunization Survey-Child (NIS-Child), 1995 through 2017. Centers for Disease Control and Prevention; 2018. https://www.cdc.gov/vaccines/imz-managers/coverage/childvaxview/data-reports/hepb/trend/index.html. Accessed January 30, 2020
21. Ahmad OB, Boschi-Pinto C, Lopez AD, Murray CJ, Lozano R, Inoue M. Age standardization of rates: a new WHO standard, World Health Organization, Geneva 2001. 2001. http://www.who.int/healthinfo/paper31.pdf. Accessed March 13, 2019.
22. Team RC. *R A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing; 2016.
23. World Health Organization. Global hepatitis report 2017. 2018. http://www.who.int/iris/handle/10665/255016. Accessed Mar 13, 2019
24. Liao X, Liang Z. Strategy vaccination against Hepatitis B in China. *Human vaccines & immunotherapeutics*. 2015;11(6):1534-1539.
25. John TJ. Hepatitis B immunization in public health mode in India. *Indian Pediatr*. 2014;51(11):869-870.
26. Sagnelli E, Sagnelli C, Pisaturo M, Macera M, Coppola N. Epidemiology of acute and chronic hepatitis B and delta over the last 5 decades in Italy. *World J Gastroenterol*. 2014;20(24):7635-7643.
27. Reekie J, Kaldor JM, Mak DB, et al. Long-term impact of childhood hepatitis B vaccination programs on prevalence among Aboriginal and non-Aboriginal women giving birth in Western Australia. *Vaccine*. 2018;36(23):3296-3300.
28. 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.
29. Nelson NP, Easterbrook PJ, McMahon BJ. Epidemiology of hepatitis B virus infection and impact of vaccination on disease. *Clin Liver Dis*. 2016;20(4):607-628.
30. Marschall T, Kretzschmar M, Mangen MJ, Schalm S. High impact of migration on the prevalence of chronic hepatitis B in the Netherlands. *Eur J Gastro Hepatol*. 2008;20(12):1214-1225.
31. Sharma S, Carballo M, Feld JJ, Janssen HL. Immigration and viral hepatitis. *J Hepatol*. 2015;63(2):515-522.
32. Lernout T, Hendrickx G, Vorsters A, Mosina L, Emiroglu N, Van Damme P. A cohesive European policy for hepatitis B vaccination, are we there yet? *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases*. 2014;20(Suppl 5):19-24.
33. François G, Hallauer J, Van Damme P. Hepatitis B vaccination: how to reach risk groups. *Vaccine*. 2002;21(1–2):1-4.
34. Pollard AJ. Hepatitis B vaccination. *BMJ*. 2007;335(7627):950.
35. James SL, Abate D, Abate KH. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet (London, England)*. 2018;392(10159):1789-1858.
36. Hepatitis B. vaccines: WHO position paper – July 2017. *Releve epidemiologique hebdomadaire*. 2017;92(27):369-392.
37. World Health Organization. Immunization coverage. 2019. https://www.who.int/news-room/fact-sheets/detail/immunization-coverage. Accessed March 27, 2020
38. Sun Z, Chen T, Thorgeirsson SS, et al. Dramatic reduction of liver cancer incidence in young adults: 28 year follow-up of etiological interventions in an endemic area of China. *Carcinogenesis*. 2013;34(8):1800-1805.
39. Turati F, Trichopoulos D, Polesel J, et al. Mediterranean diet and hepatocellular carcinoma. *J Hepatol*. 2014;60(3):606-611.

How to cite this article: Li C, He W-Q. The impact of universal hepatitis B vaccine on the trend of liver cancer from the Global Burden of Disease Study 2017. *Liver Int*. 2021;00:1–13. https://doi.org/10.1111/liv.14821

APPENDIX

TABLE A1 Countries by HBV vaccine categories and summary of vaccine coverage

Vaccine coverage (n)	Vacciation coverage (%)		Year of vaccination		Countries or territories
	Mean (SD)	Range	Mean (SD)	Range	
No universal immunization (10)					Denmark, Finland, Greenland, Hungary, Iceland, Japan, Norway, Slovenia, Switzerland, United Kingdom
20%-50% (8)	37.4 (9.2)	20.0, 47.1	9.12 (4.7)	3, 15	Canada, Central African Republic, Chad, Equatorial Guinea, India, Nigeria, Somalia, South Sudan
51%-70% (21)	61.9 (6.4)	51.1, 69.7	17.52 (7.9)	5, 30	Afghanistan, Angola, Ethiopia, France, Guam, Guinea, Haiti, Indonesia, Iraq, Laos, Liberia, Marshall Islands, Netherlands, Pakistan, Papua New Guinea, Philippines, Sweden, Syria, Ukraine, Yemen, Zimbabwe
71%-80% (34)	74.8 (3.1)	70.3, 79.9	18.2 (6.1)	9, 30	American Samoa, Azerbaijan, Belgium, Benin, Brazil, Comoros, Congo, Cote d'Ivoire, Democratic Republic of the Congo, Djibouti, Dominican Republic, Gabon, Georgia, Germany, Greece, Kiribati, Lebanon, Madagascar, Mali, Mauritania, Mozambique, Myanmar, Nepal, Niger, Northern Mariana Islands, Poland, Samoa, South Africa, Sudan, Timor-Leste, Togo, Uganda, Vanuatu, Venezuela
81%-90% (58)	86.9 (2.5)	80.2, 89.9	17.5 (5.0)	8, 28	Andorra, Argentina, Armenia, Austria, Bangladesh, Barbados, Bhutan, Bolivia, Bosnia and Herzegovina, Botswana, Burkina Faso, Cambodia, Cameroon, Cape Verde, China, Colombia, Costa Rica, Cyprus, Dominica, Ecuador, El Salvador, Federated States of Micronesia, Ghana, Guatemala, Guinea-Bissau, Ireland, Kenya, Kyrgyzstan, Lesotho, Luxembourg, Malawi, Maldives, Malta, Mongolia, Montenegro, Morocco, Namibia, New Zealand, North Korea, Panama, Paraguay, Peru, Portugal, Saint Lucia, Sao Tome and Principe, Senegal, Sierra Leone, Solomon Islands, Suriname, Swaziland, Tajikistan, The Bahamas, Tonga, Trinidad and Tobago, Turkey, United States, Vietnam, Zambia
>90% (64)	94.1 (2.2)	90.1, 98.6	21.0 (5.2)	11, 32	Albania, Algeria, Antigua and Barbuda, Australia, Bahrain, Belarus, Belize, Bermuda, Brunei, Bulgaria, Burundi, Chile, Croatia, Cuba, Czech Republic, Egypt, Eritrea, Estonia, Fiji, Grenada, Guyana, Honduras, Iran, Israel, Italy, Jamaica, Jordan, Kazakhstan, Kuwait, Latvia, Libya, Lithuania, Macedonia, Malaysia, Mauritius, Mexico, Moldova, Nicaragua, Oman, Palestine, Puerto Rico, Qatar, Romania, Russian Federation, Rwanda, Saint Vincent and the Grenadines, Saudi Arabia, Serbia, Seychelles, Singapore, Slovakia, South Korea, Spain, Sri Lanka, Taiwan (Province of China), Tanzania, Thailand, The Gambia, Tunisia, Turkmenistan, United Arab Emirates, Uruguay, Uzbekistan, Virgin Islands, US

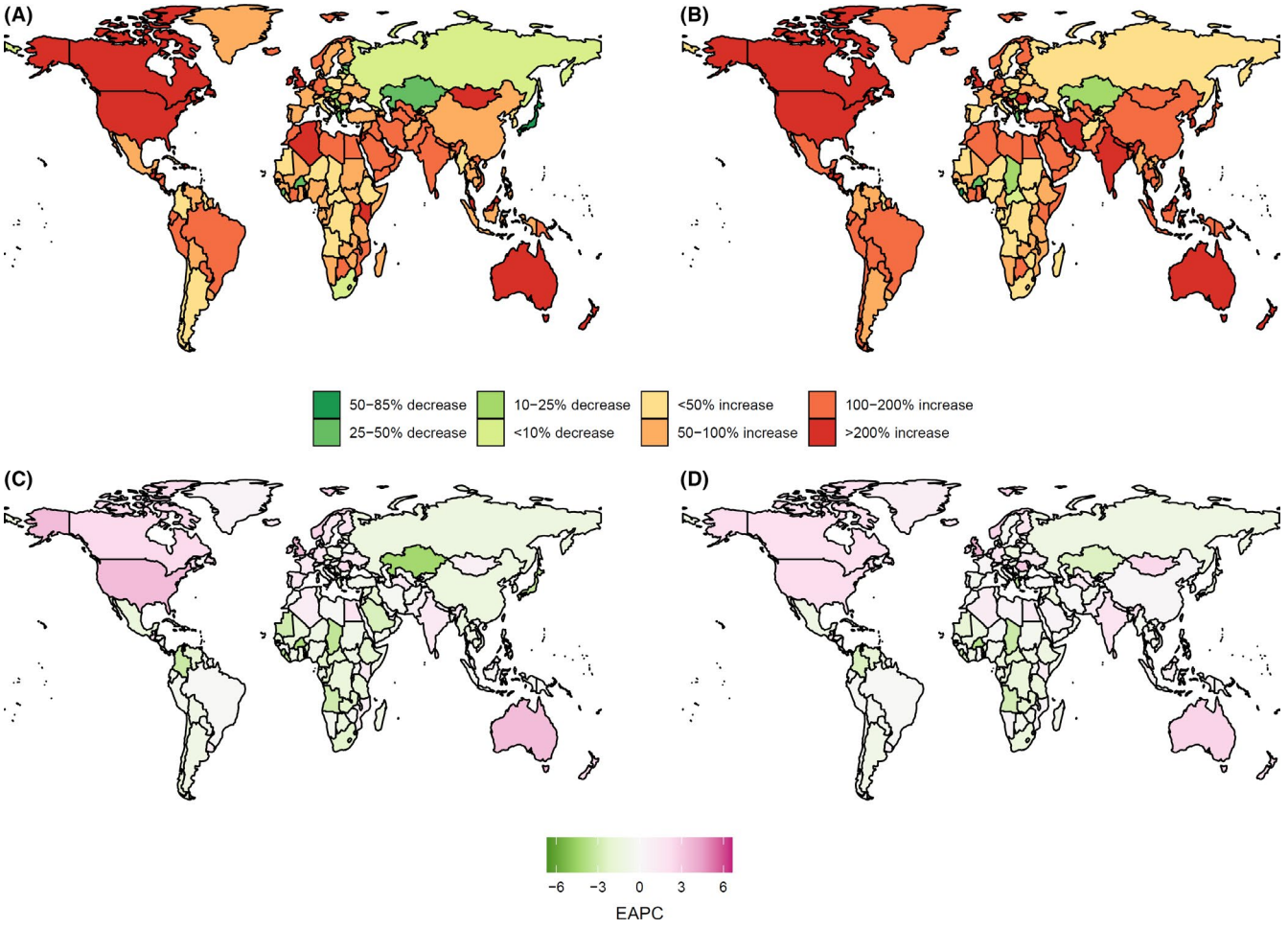

FIGURE A1 The global disease burden of HBV-attributable liver cancer in 195 countries and territories. (A) Change of cancer cases among middle-aged adults. (B) Change of cancer cases among elder people. (C) EAPC from 1990 to 2017 among middle-aged adults. (D) EAPC from 1990 to 2017 among elder people. EAPC, estimated annual percentage change