

RESEARCH ARTICLE



Global, regional, and national burden of chronic hepatitis B, 1990–2021, and projections to 2030: An urgent call for action to achieve hepatitis B elimination goals by 2030

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ABSTRACT

Chronic hepatitis B (CHB) represents a major barrier to achieving the hepatitis B elimination goals by 2030. We aimed to estimate the burden of CHB and its temporal trend from 1990 to 2021, and to project the extent of this burden up to 2030. We extracted data on the incidence, prevalence, mortality, and disability-adjusted life years (DALYs) of CHB from Global Burden of Diseases, Injuries, and Risk Factors Study 2021. Temporal trends of age-standardized rates from 1990 to 2021 were assessed by Joinpoint regression model. Bayesian Age-Period-Cohort model was employed to predict the incidence, prevalence, mortality, and DALYs of CHB up to 2030. Global prevalent cases of CHB were estimated at 283.64 million in 2021, with a slight decline of 8.32% in the number of prevalent cases from 1990 to 2021. CHB resulted in 431.96 thousand global deaths in 2021, and the number of CHB-related deaths increased by 20.04% during these periods. East Asia, South Asia, Western Sub-Saharan Africa, Southeast Asia, and Eastern Sub-Saharan Africa remained among the regions with the highest burden of CHB in 2021. Age-standardized rates of CHB significantly decreased during 1990–2021, and these rates were projected to continuously decline during 2022–2030. Despite evident declines in age-standardized incidence, prevalence, mortality, and DALYs of CHB over the past three decades, significant challenges remain in achieving hepatitis B elimination goals by 2030. Findings stress the need for comprehensive hepatitis B interventions, including vaccination, screening, and antiviral therapy, to reduce CHB burden and speed elimination.

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Introduction

Hepatitis B virus (HBV) infection represents a major public health concern worldwide, affecting around 2 billion people at some point in their lives.¹ Perinatal infection carries the highest risk of chronicity, with 80%–90% of infected newborns and 30%–50% of children infected before age 5 developing chronic hepatitis B (CHB), compared to only 5% of acutely infected adults who become chronic carriers.² Patients with CHB account for approximately 42% of cirrhosis cases and over 75% of hepatocellular carcinoma (HCC) cases worldwide.³ Currently, CHB affects around 300 million people globally, and 820,000 individuals with HBV infection die annually from complications such as cirrhosis and HCC.⁴

Significant efforts have been made to manage and eliminate hepatitis B. In 2016, the World Health Organization Global Health Sector Strategy on Viral Hepatitis (WHO-GHSS) articulated the goal for hepatitis B elimination by 2030, aiming for a 95% reduction in new infections and a 65% reduction in hepatitis B-related deaths compared with the 2015 baseline.^{4–6} The WHO-GHSS has advocated for reducing

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hepatitis B surface antigen (HBsAg) prevalence among children under 5 y to less than 0.1% by 2030 and proposed a target for an absolute mortality rate of less than or equal to 4 per 100,000 individuals annually.^{4–6} Furthermore, effective immunizations, testing, and antiviral treatments help prevent HBV spread and liver disease progression.⁶ Since 1992, WHO has recommended that countries include the three-dose hepatitis B vaccine series (HepB3) in their national immunization programs.⁷ In the 1990s and 2000s, the availability of HepB3 vaccine increased due to lower costs and support from Gavi, the Vaccine Alliance, facilitating routine vaccination of newborns in resource-limited countries.^{8,9} In 2009, WHO recommended integrating universal infant and birth-dose hepatitis B vaccination into national vaccination programs.¹⁰ However, as of 2021, more than 50 countries, mostly low- and middle-income countries (LMICs), had not yet implemented the birth-dose policy. Most LMICs were hyperendemic areas with HBsAg prevalence exceeding 8%.¹ In Europe, HBsAg prevalence varied geographically, with the lowest rates in Western and Northern Europe (<1%) and higher rates (4%–8%) in some middle-income countries in Eastern Europe.¹¹ Accumulating data indicate that disparities in the burden of CHB exist globally. Therefore, a better understanding of these disparities is crucial to reduce the impact of CHB.

The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) employs highly standardized analytical methods. It provides a comprehensive and up-to-date assessment of population health loss and attributable risk factors across over 300 diseases and injuries globally.^{12–14} Previous studies have reported the global burden of hepatitis B and related liver diseases using data from GBD 2019 and earlier versions.^{4,15–17} However, systematic analyses of the changing burden of CHB during the COVID-19 pandemic remain limited. Additionally, vaccination coverage for routine childhood vaccines, particularly HBV vaccine, was disrupted by COVID-19 lockdowns.¹⁸ The latest GBD dataset (GBD 2021) provides the most up-to-date assessments of the burdens due to 371 diseases and injuries, as well as 288 causes of death from 1990 to 2021.^{13,14} Using GBD 2021, we assessed the incidence, prevalence, mortality, and disability-adjusted life years (DALYs) of CHB and their temporal trends at global, regional, and national levels from 1990 to 2021, projected these metrics to 2030, and evaluated gaps relative to the WHO hepatitis B elimination goals. These findings will provide valuable insights to inform health policies and facilitate the efficient allocation of healthcare resources for CHB prevention and control.

Materials and methods

Data source

The data used in this study are from the GBD 2021, a standardized framework for integrating, validating, analyzing, and disseminating disease burden data. It evaluates the burden of premature death, health loss, and disability due to diseases, injuries, and risk factors across 204 countries and territories from 1990 to 2021.^{13,14} The GBD 2021 includes multiple data sources such as national censuses, household surveys, vital statistics, disease registries, health service use databases, and other relevant databases. Raw data from various sources undergo processing and integration through DisMod-MR 2.1, a Bayesian meta-regression tool specifically designed for epidemiological modeling within GBD studies. DisMod-MR 2.1 is used to generate internally consistent estimates of incidence, prevalence, remission duration, and excess mortality, thereby reducing the likelihood of biases and heterogeneity across different data sources.^{13,14}

Data collection

According to the GBD 2021 cause hierarchy, CHB is defined as chronic infection with HBV (HBsAg seropositivity persisting for ≥ 6 months), encompassing both cirrhosis and non-cirrhotic cases.¹³ Acute hepatitis B cases (infection duration <6 months) are categorized separately in GBD 2021 and were excluded from this analysis. Data on the burden of CHB were extracted from the GBD 2021 study. These included absolute numbers and age-standardized rates for incidence, prevalence, mortality, and DALYs stratified by age, sex, region, and country/territory from 1990 to 2021 along with their 95% uncertainty intervals (UIs). DALYs equal the sum of years of life lost (YLLs) and years lived with disability (YLDs), which are used to quantify the loss of health due to both fatal and non-fatal disease burden. Moreover, the data on burden

were classified geographically into 21 GBD regions, such as High-income Asia Pacific, Central Asia, and Australasia.^{13,14} We included 20 age groups ranging from under-5 y to 95 y and older, with 5-y intervals.

Statistical analysis

Age-standardized rates for incidence, prevalence, mortality, and DALYs were calculated using the GBD world population age standard. The average annual percentage change (AAPC) and its corresponding 95% confidence interval (CI) were estimated by Joinpoint regression model to assess the temporal trends of these rates from 1990 to 2021. The value of AAPC indicated an increasing, decreasing, or stable trend in annual rate, whereby an AAPC and its 95% CI higher than zero represented an upward trend and vice versa.¹⁹ We incorporated sex-specific global population projections from the United Nations (UN) World Population Prospects 2022 (separate projections for males and females) and applied the Bayesian Age-Period-Cohort (BAPC) model to predict the incidence, prevalence, mortality, and DALYs of CHB stratified by sex from 2022 to 2030.²⁰ The BAPC model was fitted separately for males and females to account for sex-specific trends in CHB epidemiology, vaccination response, and mortality patterns observed during 1990–2021. Projections were calculated by applying forecasted age-, sex-, and period-specific rates to the respective UN population projections for each sex. The BAPC model employed an integrated nested Laplacian approximation (INLA) approach to estimate the marginal posterior distributions, effectively addressing mixing and convergence issues that are often encountered with conventional Bayesian methods using Markov Chain Monte Carlo sampling.²⁰ Furthermore, based on the results of BAPC model, we assessed the progress needed to achieve the hepatitis B elimination goals proposed by WHO-GHSS. These targets were operationalized from GBD 2021 data as follows: (1) a 95% reduction in new chronic HBV infections was calculated as the percentage reduction in absolute incident cases from the 2015 baseline to 2030; (2) a 65% reduction in hepatitis B related deaths was calculated as the percentage reduction in absolute deaths from the 2015 baseline to 2030; (3) HBsAg prevalence among children <5 y (<1% by 2020 and <0.1% by 2030) was directly extracted from GBD 2021 estimates of HBsAg seroprevalence in the <5 y age group; and (4) the mortality rate target of ≤ 4 per 100,000 by 2030 was operationalized as the age-standardized mortality rate per 100,000 population.^{4–6} All Statistical analyses were performed using R software (version 4.3.3, Vienna, Austria).

Results

Global and regional burden and trend

Globally, incident cases of CHB witnessed a notable decrease from 7.75 (95% UI = 6.47 to 9.07) million in 1990 to 4.77 (95% UI = 4.08 to 5.42) million in 2021, representing a 38.45% decline. Age-standardized incidence rate exhibited a decreasing trend from 134.58 (95% UI = 113.24 to 156.39) per 100,000 population in 1990 to 61.51 (95% UI = 52.44 to 69.81) per 100,000 population in 2021, with an AAPC of -2.61% (95% CI = -2.72 to -2.50) (Table S1). In 2021, CHB had 283.64 (95% UI = 260.11 to 307.69) million prevalent cases, with an age-standardized prevalence rate of 3490.14 (95% UI = 3197.57 to 3789.02) per 100,000 population. This represented an 8.32% reduction in prevalent cases and a decrease of 1.59% (95% CI = -1.62 to -1.56) in the age-standardized prevalence rate during 1990–2021 (Table S2). CHB caused an estimated 359.85 (95% UI = 306.10 to 423.84) thousand deaths in 1990 and 431.96 (95% UI = 365.20 to 502.42) thousand deaths in 2021, with a 20.04% increase in deaths from 1990 to 2021. However, age-standardized mortality rate showed a decreasing trend [AAPC 95% CI: -1.83% (-1.90 to -1.77)] (Table S3). Similar to the mortality, DALYs increased from 12.47 (95% UI = 10.66 to 14.63) million in 1990 to 13.88 (95% UI = 11.75 to 16.00) million in 2021, while the age-standardized DALY rate declined [AAPC 95% CI = -1.86% (-1.93 to -1.80)] (Table S4).

Among the 21 GBD regions, those with the highest burden of CHB were East Asia, South Asia, Western Sub-Saharan Africa, Southeast Asia, and Eastern Sub-Saharan Africa. From 1990 to 2021, the most significant declines in age-standardized incidence and prevalence rates occurred in East Asia and Tropical Latin America. The largest decreases in age-standardized mortality and DALY rates were in High-income Asia Pacific and East Asia, whereas a significant increase was only observed in Eastern Europe (Tables S1–S4).

National burden and trend

In 2021, among 204 countries and territories, age-standardized incidence rates of CHB ranged from 4.76 (95% UI = 4.01 to 5.62) per 100,000 population in the United States, as the lowest, to 284.07 (95% UI = 226.51 to 343.93) per 100,000 population in Somalia, being the highest (Figure 1(A)). In the past three decades, Poland had the greatest drop in age-standardized incidence rate [AAPC: -5.44% (95% CI = -5.78 to -5.10)], followed by Italy and Belarus (Figure 1(B)). In 2021, the top five countries and territories with the highest age-standardized prevalence rates were Democratic Republic of the Congo, Somalia, Chad, Niger, and Angola,

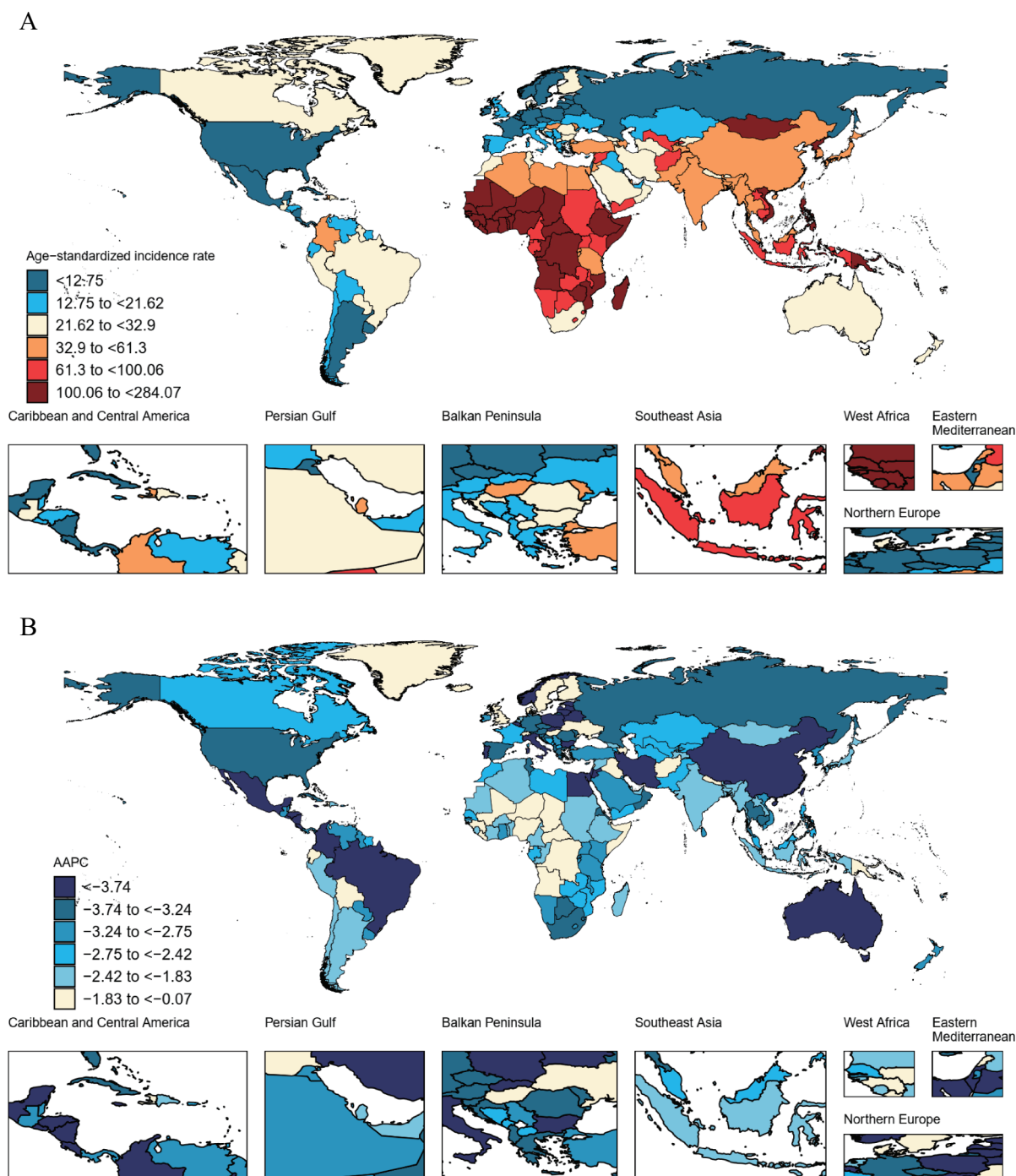


Figure 1. Global map of age-standardized incidence rate of chronic hepatitis B in 2021 and its AAPC from 1990 to 2021. (A) Age-standardized incidence rate in 2021. (B) AAPC of age-standardized incidence rate from 1990 to 2021. AAPC, average annual percentage change.

in descending order (Figure S1(A)). The age-standardized prevalence rates were most significantly decreased in Saudi Arabia and Poland (Figure S1(B)). Egypt had the highest age-standardized mortality and DALY rates in 2021, followed by Somalia, Central African Republic, Sao Tome and Principe, Chad, Guinea-Bissau, and South Sudan (Figures S2(A) and S3(A)). Significant increases in these rates were observed in ten countries, including Russian Federation, Kazakhstan, Belarus, Lithuania, United Kingdom, Ukraine, Estonia, Turkmenistan, Lesotho, and United States (Figures S2(B) and S3(B)).

Age composition of global burden

As shown in Figure 2, age-specific rates for incidence, prevalence, mortality, and DALYs of CHB generally declined in all age groups over the past three decades, with the largest decrease in those under 24 y old. Incident and prevalent cases increased in individuals aged ≥ 30 y in 2021 compared to 1990, while mortality and DALYs increased in those aged ≥ 45 y. Age-specific incidence rate had the most significant reduction in children under five. Additionally, age-specific prevalence rate increased with age, peaking at 30–34 y, then stabilized until 50–54 y, and declined continuously in those older than 55 y. Age-specific mortality rate gradually rose with advancing age and reached peak level at 85–89 y age range, then declined slightly. Age-specific DALY rate increased first and then decreased, with the highest rate observed in the 65–69 y age range in 2021.

Sex disparities of global burden

Globally, males were responsible for 2.88 (95% UI = 2.49 to 3.26) million incident cases, accounting for 60.38% of all incident cases in 2021, compared with 39.62% [1.89 million (95% UI = 1.58 to 2.17)] in females. The male-to-female ratio was 1.38 for prevalent cases in 2021, having increased from 1.34 in 1990 (Table S5). This widening disparity was more pronounced for mortality (from 2.24 to 2.63) and DALYs (from 2.50 to 2.91). Male deaths from CHB exceeded female deaths [304.20 (95% UI = 252.90 to 355.81) thousand vs. 127.77 (95% UI = 104.40 to 155.89) thousand]. DALYs related to CHB were more in males [10.20 (95% UI = 8.57 to 11.91) million] than those in females [3.69 (95% UI = 3.08 to 4.47) million], with a male-to-female ratio of 2.77 in 2021 (Tables S1–S4). Although age-standardized rates for incidence, prevalence, mortality, and DALYs were higher in males, females experienced greater reductions in these rates over time (Figure 3).

Prediction of global burdens from 2022 to 2030

As depicted in Figure 4, age-standardized incidence, prevalence, mortality, and DALYs rates of CHB for both sexes are projected to decline gradually from 2022 to 2030. By 2030, age-standardized incidence rate will decrease to 57.24 (95% UI = 45.10 to 69.38) per 100,000 population with an AAPC of -0.64% (95% CI = -0.84 to -0.43) (Table S6). Prevalent cases will decrease from 287.01 (95% UI = 277.96 to 296.07) million in 2022 to 272.96 (95% UI = 235.79 to 310.12) million by 2030. Males are expected to have a larger decline in age-standardized prevalence rate than females during 2022–2030, with AAPCs of -1.78% (95% CI = -1.82 to -1.75) for males and -1.59% (95% CI = -1.63 to -1.55) for females (Table S7 and Figure 4(B)). The age-standardized mortality rate will decrease to 4.58 (95% UI = 3.73 to 5.44) per 100,000 population by 2030 (Table S8). It is projected that the age-standardized DALY rate will decrease from 162.43 (95% UI = 150.49 to 174.37) per 100,000 population in 2022 to 146.63 (95% UI = 117.67 to 175.59) per 100,000 population by 2030, with an AAPC of -1.27% (95% CI = -1.28 to -1.26) (Table S9). BAPC Model validation was performed using a hold-out approach (training period: 1990–2015; validation period: 2016–2021). The high concordance between predicted and observed values (correlation coefficients >0.95 for all metrics) supported model reliability (Figure S4).

Progress toward hepatitis B elimination goals at global and regional levels

Based on BAPC model projections, the global and 21 GBD regions fail to meet the 95% reduction target for new chronic HBV infections between 2015 and 2030 (Figure S5). Only four regions (Central Asia, Australasia, Southern Latin America, and Central Europe) are expected to reach or exceed the 65% decrease

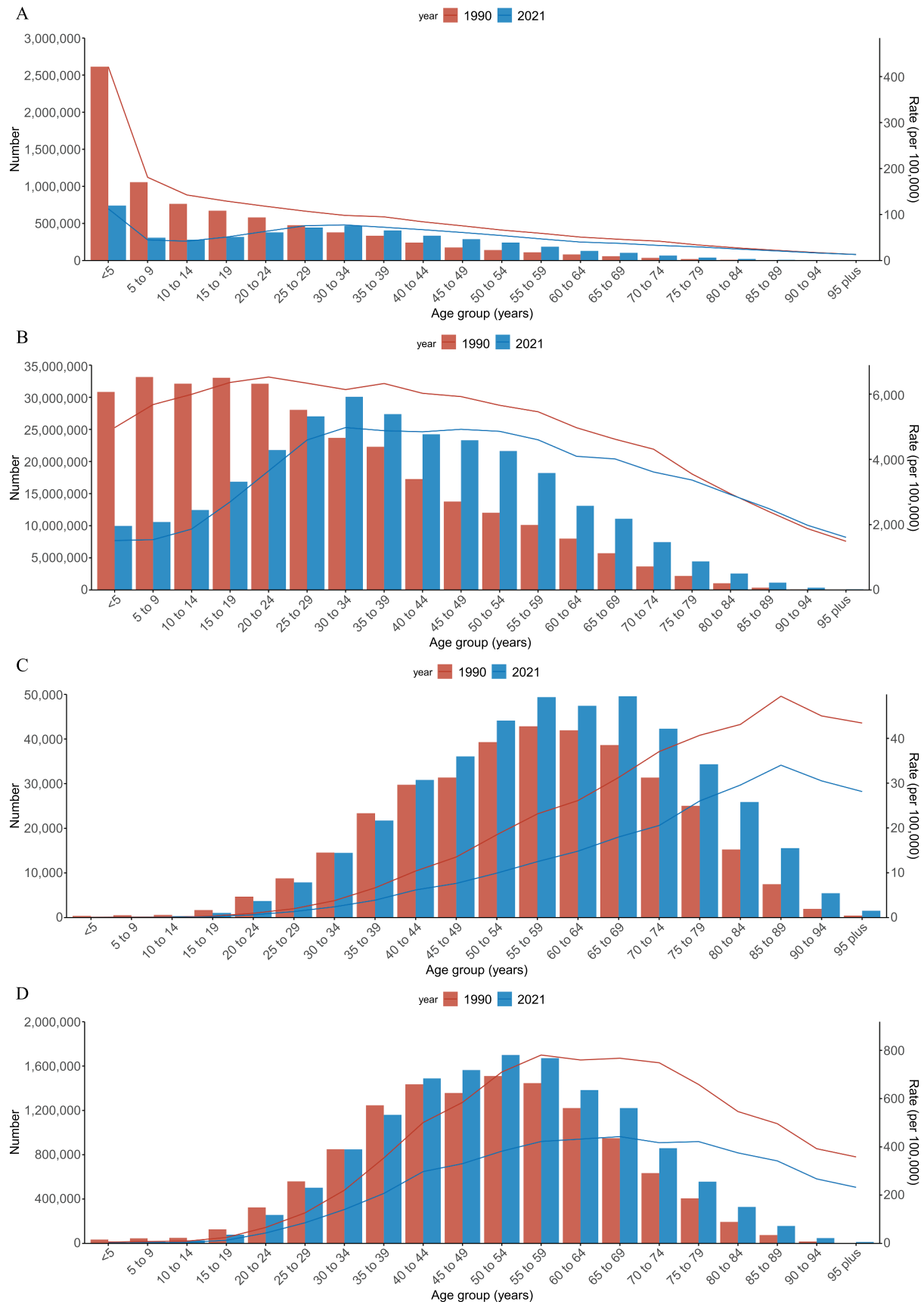


Figure 2. Global age-specific numbers and rates for incidence, prevalence, mortality, and DALYs of chronic hepatitis B in 1990 and 2021. (A) Age-specific numbers and rates for incidence. (B) Age-specific numbers and rates for prevalence. (C) Age-specific numbers and rates for mortality. (D) Age-specific numbers and rates for DALYs. Each lines represent age-specific rates for age group, and each bars represent the number for age group. DALY, disability-adjusted life year.

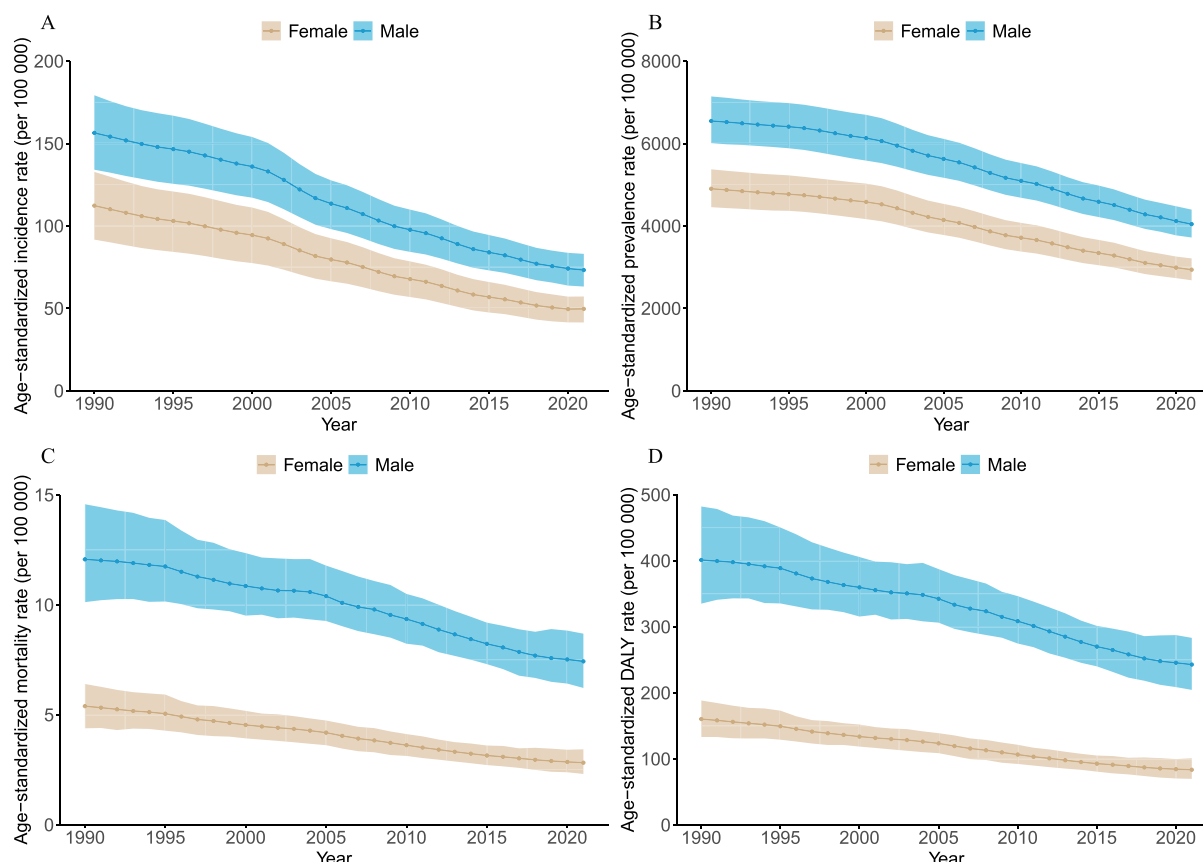


Figure 3. Trends in age-standardized rates for incidence, prevalence, mortality, and DALY of chronic hepatitis B stratified by sex globally, 1990–2021. (A) Age-standardized incidence rates. (B) Age-standardized prevalence rates. (C) Age-standardized mortality rates. (D) Age-standardized DALY rates. DALY, disability-adjusted life year.

in hepatitis B-related deaths, whereas Eastern Europe witnesses a 31.18% increase in deaths by 2030 (Figure S6). The global and five regions failed to achieve the goal of less than 1% in HBsAg prevalence among children younger than 5 y in 2020, and the global and eleven regions did not meet the goal of less than 0.1% in HBsAg prevalence by 2030 (Figure S7). Only twelve regions will achieve the all-age mortality rate goal of less than or equal to 4 per 100,000 population annually by 2030 (Figure S8).

Discussion

Significant progress has been made toward eliminating CHB, yet CHB remains a major global public health challenge. In 2021, CHB was responsible for 4.77 million incident cases, 283.64 million prevalent cases, 431.96 thousand deaths, and 13.88 million DALYs worldwide. From 1990 to 2021, incident and prevalent cases decreased, while deaths and DALYs increased. Meanwhile, age-standardized rates for incidence, prevalence, mortality, and DALYs showed significant declines, which were largely in line with previous studies.^{4,15} The decline in the age-standardized rates is likely attributed to increased hepatitis B vaccination coverage, enhanced detection and diagnosis of HBV infection, and effective antiviral therapies.^{4,21} It should be noted that while these therapies effectively suppress viral replication, they are not curative. Consequently, treated patients experience prolonged survival with chronic infection, which contributes to sustained high prevalence rates despite declining incidence.¹ In 1992, the World Health Assembly endorsed a global initiative to vaccinate newborns against HBV.^{4–6} For example, China was among the first developing countries to implement a universal neonatal HBV vaccination program, starting in 1992. From 1992 to 2015, the national coverage rates for timely hepatitis B vaccine birth-dose (HepB-BD) and HepB3 increased significantly, from 22.2% to 95.6% and from 30.0% to 99.6%, respectively.^{4,15,21} By 2014, the coverage rate of HepB-BD and HepB3 in the Western Pacific Region reached 81.5% and 92.2%, respectively, preventing

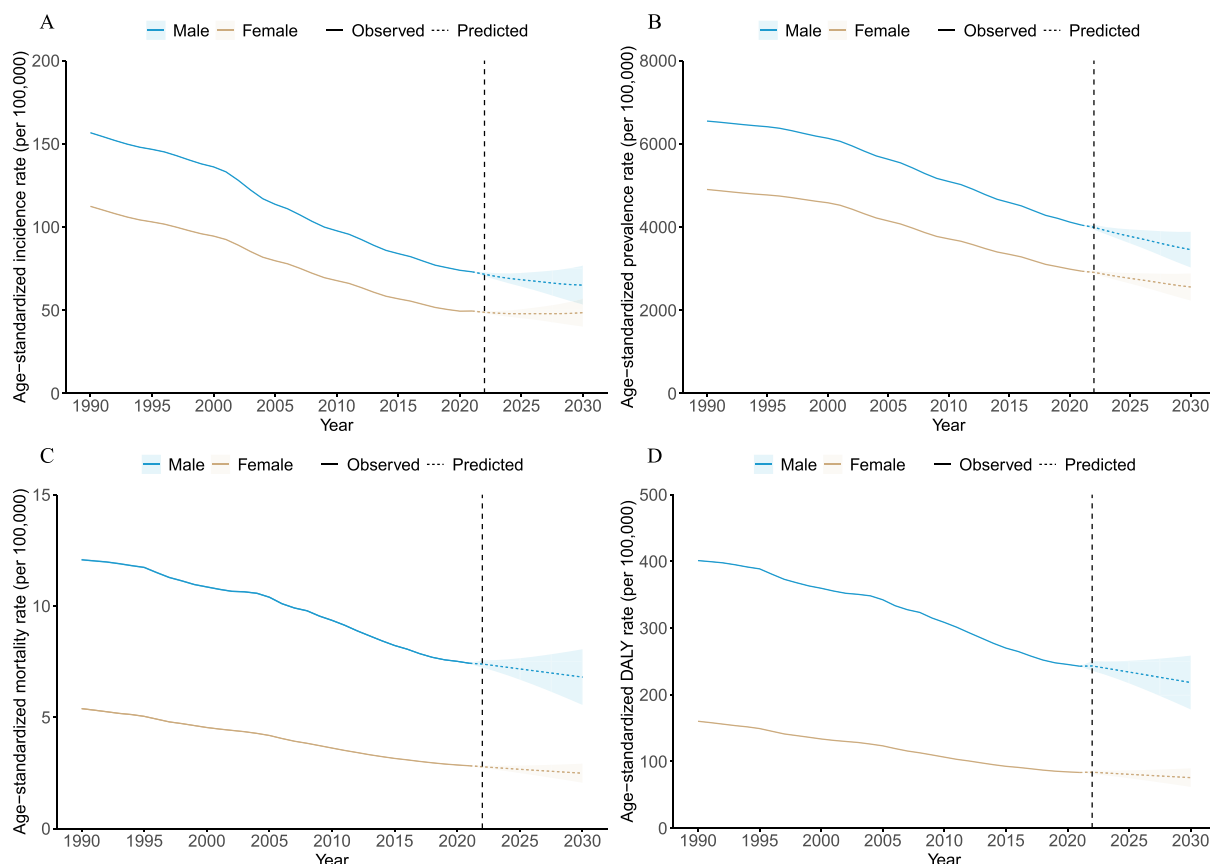


Figure 4. The predictions of age-standardized rates for incidence, prevalence, mortality, and DALY of chronic hepatitis B in males and females from 2022 to 2030. (A) Age-standardized incidence rates. (B) Age-standardized prevalence rates. (C) Age-standardized mortality rates. (D) Age-standardized DALY rates. DALY, disability-adjusted life year. Shaded areas represent 95% uncertainty intervals derived from the full posterior distribution of the Bayesian Age-Period-Cohort model, validated to provide appropriate coverage of observed data during 2016–2021 including the COVID-19 period.

nearly 3 million chronic infections and 570 thousand deaths.²² Thus, HBV vaccination is considered the most effective measure to control CHB burden.

Comparison with GBD 2019 estimates reveals both consistencies and important refinements in the current analysis. While GBD 2019 reported approximately 296 million prevalent CHB cases globally in 2019, our GBD 2021 analysis estimated 283.64 million cases in 2021, representing a slight reduction attributable to updated demographic projections and refined seroprevalence modeling in high-burden regions, particularly sub-Saharan Africa and East Asia.^{1,13} However, the trajectory toward 2030 appears somewhat less optimistic than was projected in GBD 2019. Whereas earlier projections anticipated steeper declines in mortality following universal vaccination scale-up, our 2021-based BAPC projections indicate that absolute death numbers will likely remain elevated longer due to the aging of historical chronic carrier cohorts, a demographic reality not fully captured in previous estimates.¹⁵ Furthermore, GBD 2021 incorporated COVID-19 related disruptions in vaccination coverage and healthcare access during 2020–2021, contributing to slightly higher incident case projections for 2030 compared with GBD 2019 forecasts. These refinements suggest that while age-standardized rates continue declining as previously reported, the absolute burden reduction will require more intensive intervention efforts than earlier anticipated to achieve WHO elimination targets.

While recent analyses examined specific complications of HBV such as cirrhosis or acute hepatitis phases, our study addressed the total chronic disease burden required for elimination planning.^{23,24} Notably, our CHB burden trends differed from acute hepatitis patterns, reflecting distinct epidemiological drivers. While acute infection rates correlated closely with recent vaccination coverage gaps, CHB prevalence reflected historical accumulation in aging cohorts, which explained why declining acute trends

coexisted with substantial chronic burdens. Furthermore, although Gao et al. provided essential insights into HBV burden among aging populations aged 65 y and older,²⁵ our life-course approach revealed the full demographic transition of the disease. By analyzing all age strata, we demonstrated that while the elderly currently bore the highest mortality burden, the most significant epidemiological success, specifically the 95% reduction target in new cases, needed to be measured in birth cohorts of children under 5 y, a population excluded from Gao's analysis.²⁵ Our comprehensive scope and age stratification were therefore necessary to evaluate both the immediate impact of infant vaccination and the long-term elimination trajectory.

It is important to interpret our findings in the context of demographic transitions. While age-standardized incidence, mortality, and DALY rates declined significantly from 1990 to 2021 (reflecting genuine epidemiological improvements from vaccination and treatment), the absolute numbers of deaths and DALYs increased (deaths: +20.04%; DALYs: +11.3%). This apparent paradox reflects two major demographic forces: (1) global population growth expanding the at-risk pool, and (2) aging shifting the demographic structure toward older age groups where CHB-related complications predominantly occur. Consequently, despite reduced per-capita risk (age-standardized rates), the growing and aging population generates higher absolute numbers of cases and deaths.^{1,3,15} This distinction is crucial for policymakers: while public health interventions have successfully reduced individual risk, the escalating absolute burden necessitates sustained and intensified healthcare resources to manage the expanding cohort of aging patients with chronic HBV complications.^{21,26}

Regional disparities in the burden of CHB remained significant. In 2021, East Asia, South Asia, Western Sub-Saharan Africa, Southeast Asia, and Eastern Sub-Saharan Africa emerged as the regions with the highest CHB burden among the 21 GBD regions. During 1990–2021, most regions saw declining trends in age-standardized rates for incidence, prevalence, mortality, and DALYs. However, Eastern Europe, High-income North America, and Central Asia experienced increasing or stable trends in age-standardized mortality and DALY rates. The concerning rise in Eastern Europe may reflect delayed implementation of universal vaccination compared to Western Europe,²⁷ higher prevalence of HBV genotype D which has been associated with accelerated progression, co-epidemics of HBV with hepatitis C virus (HCV) and human immunodeficiency virus (HIV),²⁸ and potentially compounding alcohol consumption.¹ Unlike Western Europe where control measures were established decades earlier, Eastern European countries may be experiencing a cohort effect of aging chronic carriers now developing end-stage complications.³ For sub-Saharan Africa, where 34% of countries reached $\geq 90\%$ HepB3 coverage but only 4% achieved $\geq 90\%$ timely HepB-BD coverage by 2021, scaling up birth-dose vaccination remains the critical unmet need.^{29,30} Point-of-care testing scale-up may also be critical, which involves deploying WHO-prequalified HBsAg rapid diagnostic tests in antenatal care settings to identify infected mothers for treatment and infant prophylaxis.^{6,7} Task-shifting for treatment should be implemented by training primary healthcare workers to initiate and monitor tenofovir therapy, supported by the WHO AFRO viral hepatitis framework.³⁰ Nigeria's experience in achieving 50% HepB-BD coverage through Gavi support and domestic resource mobilization demonstrates feasibility even in resource-constrained settings.²⁹ Oceania, identified in our analysis as having the largest gap in reducing incident cases, may require urgent attention to birth-dose delivery in remote island communities. These priorities align with our finding that regions with low birth-dose coverage consistently show the largest gaps in reducing new chronic infections.³¹

Males generally exhibited higher age-standardized rates for CHB incidence, prevalence, mortality, and DALYs than females. For example, a prospective cohort study found that prevalence of CHB was higher in males (10.7%) than females (4.4%) among those vaccinated at birth.³² Sex disparities in the occurrence of HBV-related liver diseases are well recognized. Estrogens have an immune-boosting effect, which may contribute to a lower prevalence of HBV infection and better disease outcomes in females.³³ Conversely, androgens have an immune-suppressing effect and may also directly interact with HBV genome, promoting viral replication and disease progression in males. These hormonal differences are reflected in gene expression patterns, immune responses, and xenobiotic metabolism between males and females.³³ Females have higher immune clearance rates for HBsAg and HBV e antigen (HBeAg) compared to males. HBeAg and HBsAg seroconversion also occurred more frequently in females than males.³⁴ Males tend to have a less effective response to HBV vaccination during the neonatal period, which is associated with a reduced protective effect against HBV infection.³² In an

immunocompetent HBV persistence mouse model, female mice exhibited lower levels of serum viral loads and antigens compared to male mice.³⁵ Our study also showed a significant decline in CHB incident and prevalent cases among individuals under 24 y old in 2021 compared to 1990. Notably, the most substantial decrease in incidence rates was observed in children under five, suggesting that CHB prevention efforts are particularly effective in this age group. Therefore, enhancing targeted prevention and control strategies for children under five could potentially offer the greatest benefits to the overall population.

Based on BAPC projections, age-standardized incidence, prevalence, mortality, and DALYs rates of CHB are predicted to continuously decline from 2022 to 2030 in both males and females, similar to the trends in China.³⁶ Our projection model was based on the population age structure and sex disparities observed between 1990 and 2021, combined with the WHO's estimates of the future global population. The projected rates reflect the global CHB landscape as it was in 2021. Our projections represented a 'business-as-usual' scenario based on gradual evolution of current trends. While the 6-y validation demonstrated robust performance as shown in Figure S4, our hold-out validation specifically indicated that observed 2020–2021 values remained within projected 95% UIs despite COVID-19 disruptions, suggesting immediate pandemic effects had limited impact on mortality trajectories.¹⁸ Joinpoint analysis detected no significant inflection points in 2020. However, we acknowledged that indirect effects including delayed childhood vaccinations and reduced screening might manifest as increased future incidence which our projections cannot capture.²⁰ While the validation demonstrated robust performance, projections cannot account for structural breaks such as rapid scale-up of birth-dose vaccination in currently uncovered regions, breakthroughs in curative therapies, or future pandemic disruptions. The 95% UIs provided bounds for plausible variations under current trajectory assumptions. Remarkable progress toward hepatitis B elimination goals has been made, but the targets for reducing the burden of CHB by 2030 remain unmet. Notably, the gap in reducing new chronic HBV infections is particularly significant in Oceania and Western Sub-Saharan Africa. Despite efforts by champion countries such as Nigeria, which introduced HepB-BD in 2004, incident cases of CHB in Oceania, Central Sub-Saharan Africa, and Western Sub-Saharan Africa increased. However, by 2021, only 16 (34%) African countries had reached or exceeded 90% HepB3 coverage, and two (4%) countries had reached or exceeded 90% timely HepB-BD coverage.²⁴ Moreover, regions such as Oceania, African regions, and Southeast Asia are unlikely to achieve the global goals of reducing HBsAg prevalence among children under 5 y to less than 0.1% and all-age mortality rates to 4 per 100,000 population or lower by 2030. Given the proven effectiveness of the hepatitis B vaccine, prioritizing widespread administration to infants from birth and to high-risk adults in these regions is essential.

Our study has several limitations. First, the data were sourced from GBD 2021 database, with limitations inherent in the methodology of GBD databases, which potentially affected the accuracy and reliability of our findings.^{12,13} Second, while GBD 2021 uses various statistical methods to improve data precision, high-quality raw data are scarce in some LMICs, potentially introducing bias. Specifically, under-diagnosis and under-reporting in these regions likely lead to underestimation of both incidence and prevalence, as limited serosurvey coverage and weak vital registration systems fail to capture asymptomatic infections and out-of-facility deaths. Conversely, expanded screening intensity in high-income settings may artifactually inflate apparent prevalence trends through ascertainment bias, despite stable or declining true epidemiological risk. Variability in diagnostic criteria such as rapid test thresholds and confirmatory laboratory standards further complicates cross-regional comparisons. Third, this study encountered a scarcity of data regarding the global distribution of HBV genotypes, which adds another layer of complexity to the analysis. Fourth, coinfections of HBV with HIV or HCV accelerate disease progression but cannot be isolated from GBD 2021 CHB estimates. While GBD stratifies liver disease outcomes by etiology, coinfecting populations are not disaggregated within CHB and are instead primarily classified under HIV or HCV burden estimates rather than retained in CHB-specific outputs.¹ Fifth, our assessment of WHO-GHSS targets relied on GBD 2021 estimates of HBsAg prevalence in children <5 y, which were model-based predictions where empirical serosurvey coverage was incomplete. Validation of these estimates against population-based serosurveys in high-burden regions, particularly in sub-Saharan Africa, remains a priority for future research. Finally, we acknowledge that GBD 2023 estimates were released after completion of our primary analyses. While our

2022–2023 projections showed concordance with available GBD 2023 summary estimates, future studies should utilize GBD 2023 or subsequent iterations for updated elimination progress assessments.

Conclusions

Significant progress has been made globally toward the hepatitis B elimination goals by 2030. From 1990 to 2021, the number of incident and prevalent cases of CHB, as well as the age-standardized rates for incidence, prevalence, mortality, and DALYs, had significantly decreased. Burden attributable to CHB varied by region, with East Asia, South Asia, Western Sub-Saharan Africa, Southeast Asia, and Eastern Sub-Saharan Africa having the highest burden, while Eastern Europe experienced a significant increase in age-standardized mortality and DALY rates. Although age-standardized rates for CHB are expected to continue declining, few regions are on track to meet the proposed hepatitis B elimination goals by 2030. Therefore, accelerating the implementation of hepatitis B control strategies is crucial to meet these goals. Our findings provide precise and reliable data on the burden of CHB, helping assess progress toward hepatitis B elimination and informing effective preventive strategies and resource allocation.

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Data availability statement

All the data used for analyses are publicly available at the Global Health Data Exchange GBD 2021 website (<https://ghdx.healthdata.org/gbd-2021>).

Ethics approval statement

This study was approved by the Institutional Review Board and Human Research Ethics Committee of Shandong First Medical University & Shandong Academy of Medical Sciences (No. S2025320).

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