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ORIGINAL ARTICLE

Targeted antiviral treatment of hepatitis B virus in culturally and linguistically diverse populations to achieve elimination targets in Australia

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Abstract

The majority of Australia's hepatitis B virus (HBV) burden is borne by culturally and linguistically diverse (CALD) populations, and antiviral treatment is the mainstay of intervention. Using modelling, we estimated the impact of targeted antiviral treatment scale-up and changes in migration on HBV-related mortality and HBV elimination in CALD populations in Australia. We fitted a deterministic mathematical model based on the natural history of HBV and the Australian migration effect in four CALD population groups according to country of birth. We used three antiviral treatment scale-up scenarios: *baseline* (9.3% coverage); *intermediate* (coverage of 80% of patients eligible for antiviral therapy by 2030); and *optimistic* (coverage of 20% of all patients living with HBV by 2022). Our model predicted that if the *baseline* treatment is followed between 2015 and 2030, the number of chronic HBV cases and HBV-related mortality will increase. Following the *optimistic* scale-up, the number of new HBV cases could be reduced by 78%, 73%, 74% and 83% in people born in Asia-Pacific, Europe, Africa and the Middle East, and Americas, respectively, between 2015 and 2030. An *optimistic* treatment scale-up could result in a 19.2%–24.5% reduction in HBV-related mortality and a 15%–25% reduction in HCC-related mortality in CALD populations between 2015 and 2030. In conclusion, our findings highlight that targeted antiviral treatment for CALD populations provides significant health system benefits by reducing HBV-related complications from cirrhosis and HCC. Expanded antiviral treatment programmes focusing on high-prevalence CALD populations may be an effective strategy to reduce HBV-related morbidity and mortality.

KEYWORDS
culturally diverse populations, elimination, hepatitis B virus, modeling, targeted antiviral treatment

1 | INTRODUCTION

Chronic hepatitis B (HBV) is the leading cause of hepatocellular carcinoma (HCC), and more than 820,000 HBV-related deaths occur worldwide every year mostly due to liver cirrhosis and HCC.[1,2]

Migrants from most of the world regions usually come from high or moderate HBV-endemic countries and have a higher rate of HBV infection than that of the prevalence in the country where they settle into.[3] In Australia, migrants born in Asia-Pacific, Africa and eastern Europe have the highest burden of HBV infection.[4] For example, in Western Australia, an increasing trend of HBV-associated referrals was reported and most of them were patients born in Asia (57%) and Africa (35%).[5] Reekie et al.[6] reported high prevalence rates of HBV in Australian migrant women born in Cambodia (8.6%), Taiwan (8.1%), Vietnam (7.5%), China (6.8%) and Tonga (6.5%). The high rates of HBV in migrants increase the risk of transmission to other migrants and the local community in the receiving country and shape the epidemiology of HBV in a country.[7,8]

The World Health Organization has identified viral hepatitis (VH) elimination targets, which include a 65% reduction in hepatitis-related mortality and a 90% reduction in new infections by 2030.[9,10] Over 90% of new HBV cases in Australia are attributable to migration,[11] which cannot be prevented by local routine vaccination programmes. The control and elimination of HBV in Australia therefore depends on improved rates of testing and treatment of HBV infection with more attention to people from culturally and linguistically diverse (CALD) backgrounds born overseas and is reflected in the Commonwealth National Strategy for HBV.[10] The Australian Government recommends testing and vaccination of patients migrating from HBV-endemic countries, which is a key entry point to initiate treatment for eligible individuals.[12]

There are several barriers to receiving treatment in CALD populations such as language, health literacy, cultural competency of healthcare providers and cost of diagnostics at the primary care. The HBV treatment coverage rate in Australia is 9.3%. There are no CALD-specific treatment uptake rates, but in areas where a large number of people with CALD backgrounds live, the rates are estimated at 7.3%.[13] Disease and mortality estimates based on national-level data on transmission probability, and treatment uptake rates may not be representative of the situation in migrants. Modelling studies that consider CALD population-specific risk factors and data may provide better disease estimates to develop a more focused intervention. We aimed to estimate and predict the impact of targeted antiviral treatment scale-up and migration on HBV burden, HBV-related mortality and elimination in people with CALD backgrounds in Australia.

2 | METHODS

2.1 | Model structure and differential equations

We developed a dynamic, deterministic compartmental model of ordinary differential equations[14] based on the transmission dynamics and natural history of HBV infection in four groups of CALD Australians born in African and the Middle East, European, American and Asia-Pacific regions. These regions are conveniently grouped areas from where migrants come, and although there are variations in their HBV prevalence across nations, we grouped them for technical feasibility reasons. The model incorporated net migration and prevalence in the country of birth.

We constructed the model based on the clinical progression of HBV infection using data from recent literature.[18-20] Following general infective modelling conventions, the model included transmission states as susceptible (S), infective, vaccinated (V) and resolved (R) within the transmission paradigm. Furthermore, in the model state 'infective' we included those HBV clinical stages with a persistent viral load including acute infection (immune-tolerant phase) (A), chronic hepatitis (immune-control phase) (C), cirrhosis (immune-active phase) (Cr) and hepatocellular carcinoma (H).[9] Susceptible model state included those who were non-infected and non-vaccinated. Resolved (sero-clearance phase) model state included those who had undergone immune clearance of the virus (loss of surface antigen) or those who are censored due to death or emigration out of Australia. We also included patients on antiviral treatment as resolved, assuming they are effectively removed from the pool of transmission risk. We fitted the model separately for four groups of CALD Australians born in African and the Middle East, European, American and Asia-Pacific regions. Migration of susceptible and HBV infections in each disease state including chronic, immune and recovered infections was incorporated. Migration with acute infection, cirrhosis and HCC was not included because of the symptomatic nature and severity of these disease conditions (Figure 1). The model parameter and initial state symbols are described in Table S1.

2.2 | Model assumptions

We assumed that immunity after successful vaccination is lifelong.[21-24] We also considered a failure rate of HBV vaccination to be 5%. We assumed that resolution and viral clearance in chronic infection occurred in 2%[25] and that subsequent immunity to HBV from a previous infection is lifelong.[26] As a result, transition from recovered to acute infection or susceptible states was not possible. With the current state of hepatitis care, we assumed no cure for hepatitis B. Patients with cirrhosis also enter the HCC state. Recovery occurs from acute infection, chronic HBV and cirrhosis states; however, due to the acute nature of HCC, recovery was not considered. Mortality due to acute infection occurs because of fulminant hepatitis occurring in a small proportion of patients.[19,27] Patients on antiviral treatment for HBV transition through different disease states at different rates and separate equations were included. Transmission from patients on antiviral treatment was considered negligible and not included in the calculation of force of infection.

2.3 | Force of infection (λ)

The force of infection is the rate at which susceptible individuals contract infection, and is determined by both infective viral dynamics reflecting infection risk with exposure, and the probability of that

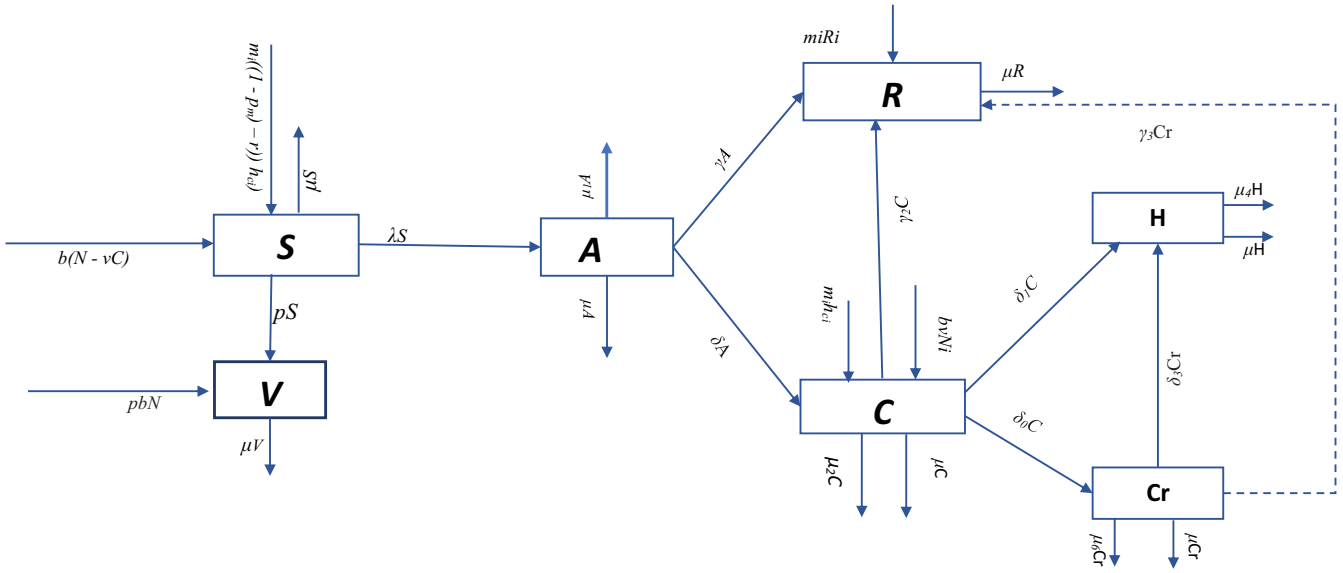

FIGURE 1 Hepatitis B transmission model structure. The model depicts the transmission and progression of the hepatitis B virus. Individuals transition from susceptible state (S) to acute infection (immune-tolerant phase) (A), which in turn progresses to chronic hepatitis B (immune-control phase) (C) or recovers (sero-clearance phase) (R). Patients from chronic hepatitis progress to cirrhosis (Cr) or hepatocellular carcinoma (H). Patients with any state of hepatitis B could leave the disease state due to recovery, natural deaths or hepatitis B-related mortality

exposure based on HBV prevalence. We calculated the force of infection for each CALD population group based on the variation in migrant population born in different regions and the variation in HBV prevalence in the countries of origin. We used an average regional prevalence of HBV for patients whose country of birth was in the same region. We used an average transmission coefficient (β) of 2% for all migrants.[28,29] Transmission risk was estimated in acute infection and chronic HBV states including chronic hepatitis, cirrhosis and HCC, and was included in the calculation of force of infection. The acute infection state was assumed as the early immune-tolerant phase, characterized by higher viral loads and greater infectivity. In chronic HBV (here assumed as the immune-control phase, characterized by lower HBV viral load), the transmission risk is expected to be lower and a multiplier for reduced transmission of 0.16 was used.[29] Transmission from patients with chronic HBV on antiviral treatment was considered negligible, and those treated were excluded from the calculation of force of infection.

We computed a dynamic force of infection for each CALD population group based on the proportion of infection in the population (β), the number of infectives (i.e. acute infection [A_i], chronic infection [C_i], cirrhosis cases [Cr_i] and hepatocellular carcinoma [H]) and the total population at time t (N_i). Therefore, the force of infection for each CALD population group i of total size N was determined as:

$$\lambda_i = \beta\,[A_i + 0.16\,(C_i + Cr_i + H_i)]\,/\,N_i.$$

2.4 | Model inputs and initial states

2.4.1 | Demographic states

The initial states of the model are presented in Table S2. We used the total population of migrants born in Asia-Pacific, European, African and the Middle East, and American regions using data from the Australian Bureau of Statistics. The total population of migrants in Australia in 2011 (when modelling commences) was 5,280,676.[30] The total population size of the four population groups was 2,347,466 for those born in Asia-Pacific, 2,131,147 for those born in Europe, 578,426 for those born in Africa and the Middle East, and 223,637 for those born in American regions.[30,31] We used 2011 as a starting point because of the global resolution of the World Health Assembly,[32] which addresses viral hepatitis care, and the national hepatitis B strategy, which was published close to the end of 2010.[33] The estimate of HBV burden in 2011 from the baseline treatment coverage was used as a reference of outcomes against treatment scenarios over time.

The number of susceptible individuals was obtained by subtracting those with acute and chronic hepatitis B and those recovered from the total number of patients not vaccinated. An average incidence of 0.77 cases per 100,000 population was used as a multiplier to compute the initial number of acute infections across all population groups.[34] The number of patients positive for chronic HBV was calculated by multiplying the prevalence of HBV in migrants born in a specific group by the total population in each group.[31] Hepatocellular carcinoma cases were calculated using data for the incidence of HCC in the general Australian population, accepting that disease state-specific and region-specific differences in HCC incidence were not possible to accurately estimate.[35] The number of vaccinated individuals in each group was estimated from vaccination coverage in Australia.[36]

2.5 | Migration

According to the Australian Bureau of Statistics, in 2010, 180,030 people migrated from the four regions into Australia including people

from the Asia-Pacific (45.1%), $m_1 = 81{,}194$; European region (40.3%), $m_2 = 72{,}552$; Africa and the Middle East (2.8%), $m_3 = 50{,}408$; and American (4.1%), $m_4 = 7381$, regions.[37] To obtain the number of immigrants for each year extending to 2030, we used data from the Australia Bureau of Statistics, which assumed the net overseas migration will remain constant from 2021 onwards.[38]

The number of new susceptible immigrants per year for each population category (m_iS_i) was calculated by subtracting the expected number of chronic carriers, and vaccinated and recovered patients from the total immigrant number (m_i) given as $m_iS_i = m_i\left(\left[1-p_m\right]-r\right)h_{ci}$. Migration with hepatocellular carcinoma and acute HBV infection was considered zero because of the severity of the illness.

As the burden of HBV infection varies across the four regions, we used different prevalence estimates for all patients born in each region. The regional HBV prevalence estimates for patients born in the Asia-Pacific region (5%), European region (2%), Africa and the Middle East (5%), and in the American (0.8%) region were used. Based on available estimates, we assumed an HBV vaccination coverage of 85% in Asia-Pacific, 91% in European, 77% in Africa and the Middle East, and 82% in American regions and applied it to the calculation of force of infection.[39,40]

2.6 | Disease progression parameters

We extracted the model parameters for HBV transition and mortality rates from the literature and presented them in detail in Table S3. Individuals join the susceptible state through birth without vaccination, failure of immunization (p_f) and migration ($miSi$) as susceptible. The transition from susceptible (S) state to acute infection (A) occurs at a rate of the force of infection (λ; see above). Susceptible individuals also leave this state through vaccination (p) or as a result of natural mortality (μ). Patients with acute infection (A) exit this state due to natural recovery (γ), or transition to chronic HBV (δ), HBV-related deaths or natural mortality (μ). Mortality from acute infection occurs in 1% of patients because of fulminant hepatitis.[28]

Individuals join the chronic HBV infection state (immune-control phase) (C) through a transition from acute infection (immune-tolerant phase) (δ), immigration with infection (m_iC_i) or vertical transmission (v), and leave this state through recovery (γ), transition to cirrhosis (immune-active phase) or HCC (δ), and HBV-related or natural deaths (μ).[42]

2.7 | Antiviral treatment scenarios

2.7.1 | Baseline treatment scenario (status quo)

We assumed the current level of antiviral treatment rate of 9.3% of people diagnosed with HBV remains constant until 2030.[43] HBV antiviral treatment was performed with any of entecavir, tenofovir, lamivudine or (rarely) adefovir.

2.7.2 | Intermediate treatment scale-up

This scenario is a treatment scale-up to achieve treatment for 80% of patients medically eligible for antiviral therapy, assuming that 32.3% of people with chronic HBV are eligible (i.e. 25.8% of all chronic HBV cases).[28] To reach this goal, there is a need to increase treatment uptake at an average annual rate of 1.4%.[28]

2.7.3 | Optimistic treatment scale-up

This scenario is a scale-up of treatment to achieve a treatment coverage of 20% of people living with HBV on antiviral therapy by 2022. This strategy requires a potential increase in the rate of annual treatment uptake by 2.7%.[29]

2.8 | Outcomes estimated in the model

There were two related outcomes evaluated in this model, HBV prevalence and morbidity through cirrhosis and HCC. The number of persons with chronic HBV over time in CALD populations by country of birth was modelled. Additionally, the number of people with liver cirrhosis and HCC from 2015 to 2030 was estimated for each population group by differing treatment scenarios. We reported the number of HBV-related deaths per year from 2015 to 2030 by the three antiviral treatment coverage scenarios. Finally, to indicate the impact of targeted antiviral treatment scale-up towards achieving HBV elimination targets, we estimated the number of new HBV infections, and compared HBV-related mortality with the 2015 baseline.

2.9 | Sensitivity analysis

Sensitivity analysis was performed to identify parameters that had the highest impact on model outputs. We calculated the partial rank correlation coefficient (PRCC)[43-45] for the prevalence of HBV in the country of birth, transmission coefficient, rate of vertical transmission and HBV vaccination coverage in the country of birth with model outputs (the number of HBV cases, HBV-related mortality, HCC incidence and HCC-related deaths).

3 | RESULTS

3.1 | Prevalence of chronic hepatitis B

In 2011 (when the modelling commences), there were an estimated 83,335 Asia-Pacific-born people living with HBV (prevalence of 3.55%), 21,951 European-born, 15,560 Africa and the Middle East-born, and 1789 American-born. If the baseline treatment scenario is followed, the number of patients living with chronic HBV will slightly increase from 81,065 in 2015 to 82,598 cases in 2030 in

persons born in Asia-Pacific, from 23,012 in 2015 to 27,139 in 2030 in European born, and from 15,892 in 2015 to 18,042 in 2030 in African and the Middle East born, and slightly decrease from 1720 cases in 2015 to 1693 cases in 2030 in Persons born in the region of Americas.

3.2 | Impact of treatment on hepatitis B-related morbidity and mortality

3.2.1 | Incidence of liver cirrhosis

Table 1 presents the number of new cases of cirrhosis in each population group by all three treatment scale-up scenarios. In 2015, in migrants born in the Asia-Pacific region, there were an estimated 1465 new cases of liver cirrhosis. Using the optimistic treatment scale-up, the number of new cases of liver cirrhosis by 2030 could be reduced by 40% in the Asia-Pacific-born population and 30% in migrants born in the European region compared with the number of new cases of liver cirrhosis in 2015.

3.2.2 | Incidence of hepatocellular carcinoma

Compared with the 2015 baseline estimate, following the baseline treatment coverage, the number of new HCC cases in 2030 will increase in CALD population born in Africa and the Middle East (92 vs. 96 cases), Asia-Pacific (477 vs. 446 cases) and Europe (132 vs. 145 cases), and remains approximately similar in migrant Australians born in the region of the Americas. The optimistic treatment scale-up approach is projected to reduce the incidence of HCC to 331 cases (vs. 477 cases) in Asia-Pacific-born, and 72 cases (vs. 92 cases) in Africa and the Middle East-born Australians by 2030 (Table 2).

3.2.3 | Hepatocellular carcinoma-related mortality

The number of deaths due to HCC per year increased in all CALD population groups compared with that in 2015 following the baseline treatment. In migrants born in Asia-Pacific regions, the annual number of HCC-related deaths rose from 378 deaths in 2015 to 443 deaths in 2030. A nearly 50% increase in HCC mortality is projected in CALD Australians born in the European region. In the Africa and the Middle East-born population, HCC-related mortality would increase by 28% from 72 deaths in 2015 to 92 deaths in 2030.

Following the optimistic HBV treatment scale-up, HCC-related mortality is projected to decline by 15%–25% compared with the pretreatment year in 2020. For example, in the Asia-Pacific-born population, HCC-related deaths are projected to decrease by 25.5% from 462 deaths in 2020 to 344 deaths in 2030 (Figure 2).

3.3 | Impact of targeted antiviral treatment scale-up on hepatitis B elimination

3.3.1 | Hepatitis B-related mortality

The number of HBV-related deaths is projected to increase between 2015 and 2030 if the baseline treatment scenario were followed. An estimated 1054 HBV-related deaths could occur in CALD populations born in the Asia-Pacific region, followed by 334 deaths in European-born, 108 deaths in Africa and the Middle East-born and 10 deaths in American region-born populations.

Both intermediate and optimistic antiviral treatment scale-up for HBV in CALD populations reduced the number of HBV-related deaths in all subpopulation groups. Optimistic antiviral treatment scale-up can achieve a reduction in the annual number of HBV-related deaths from 19.2% (European-born migrants) to 24.5% by 2030 compared with the 2020 pretreatment number of deaths (Figure 3).

3.4 | Reduction in new hepatitis B virus infections

Our antiviral treatment scale-up scenario does not achieve the WHO HBV elimination targets of reduction in new HBV infections by 90% compared with the baseline. In all the four groups by 2030, a reduction in new HBV infections would be observed compared with the 2015 baseline if an optimistic antiviral treatment scale-up is followed. An estimated reduction of 78%, 74%, 73% and 83%

TABLE 1 Number of new cases of liver cirrhosis across three treatment scenarios in culturally and linguistically diverse populations, 2015–2030

	Treatment coverage scenario/number of cases								
	Baseline coverage			Intermediate scale-up			Optimistic scale-up		
Region of birth	2015	2025	2030	2015	2025	2030	2015	2025	2030
Asia-Pacific	1465	1214	1159	1465	1121	968	1465	1053	874
Europe	414	390	386	414	360	322	414	337	290
Africa and the Middle East	286	261	256	286	241	213	241	226	192
Americas	31	25	24	31	23	20	31	22	18

TABLE 2 Number of incident hepatocellular carcinoma cases in culturally and linguistically diverse populations by antiviral treatment coverage, 2015–2030

	Treatment coverage scenario								
	Baseline coverage			Intermediate scale-up			Optimistic scale-up		
Region of birth	2015	2025	2030	2015	2025	2030	2015	2025	2030
Asia-Pacific	477	464	446	477	426	367	477	398	331
Europe	132	144	145	132	133	119	132	124	107
Africa and the Middle East	92	97	96	92	89	79	92	84	72
Americas	10	10	9	10	9	8	10	8	7

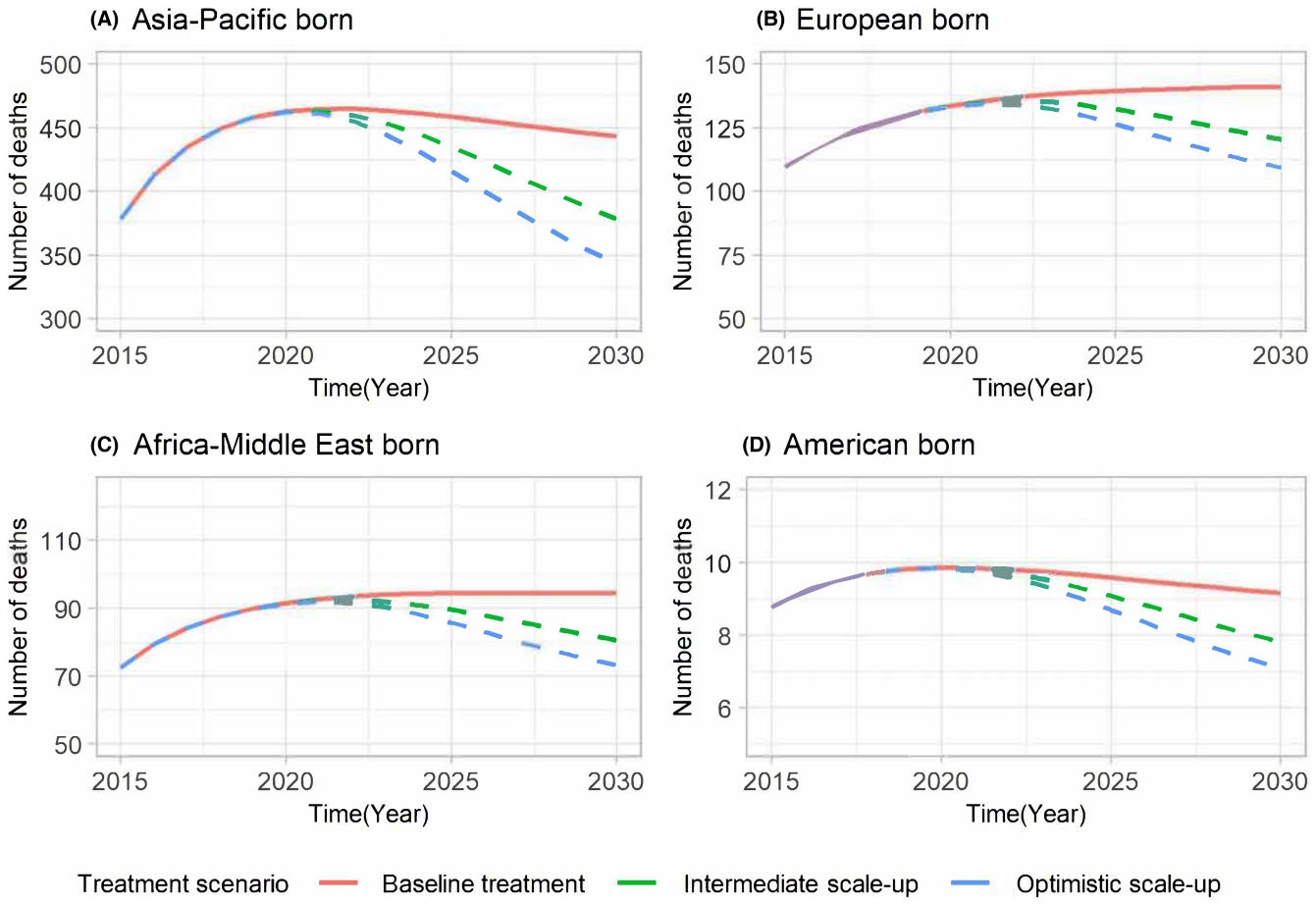

FIGURE 2 Hepatocellular carcinoma (HCC)-related mortality in culturally and linguistically diverse (CALD) populations. HCC-related deaths per year are presented in CALD Australians born in Asia-Pacific (A), Europe (B), Africa and the Middle East (C), and Americas (D) compared between baseline antiviral treatment coverage (red line), intermediate scale-up (green line) and optimistic scale-up (blue line). Treatment scale-up starts in 2020, and comparisons are made from the pretreatment baseline

in incident HBV infections is projected to occur in CALD populations born in Asia-Pacific, Africa and the Middle East, European and American regions (Figure 4).

3.5 | Sensitivity analysis

The prevalence of HBV in the country of birth was significantly correlated with all the outcomes. It was found to have the strongest correlation with the number of HBV cases over time (PRCC = 0.999) and the incidence of HCC (PRCC = 0.998). The transmission coefficient was the second important factor influencing the outcomes (Figure S2).

4 | DISCUSSION

Expanding the access and uptake of antiviral therapy for HBV provides big public health benefits by preventing viral transmission and

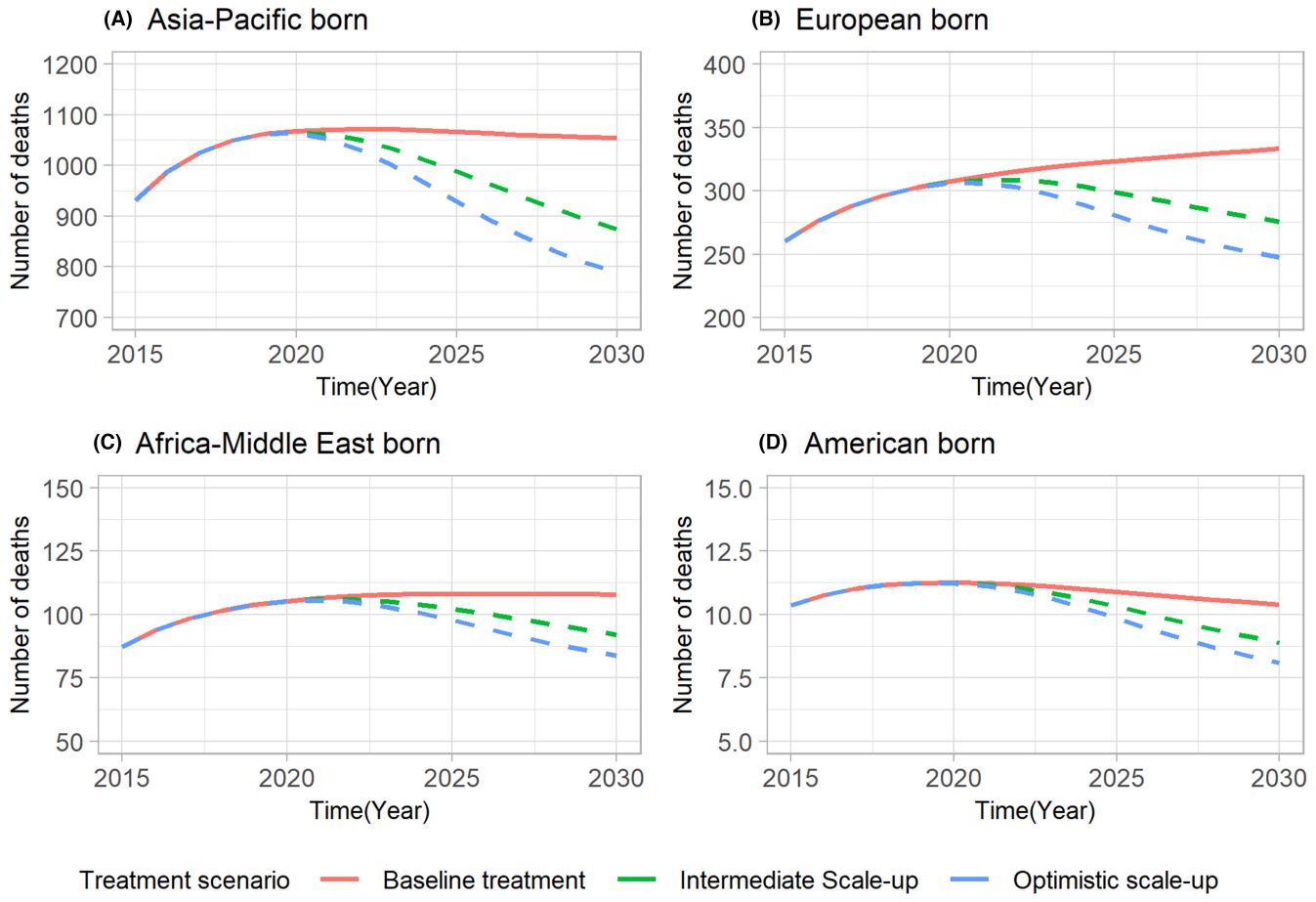

FIGURE 3 Hepatitis B virus (HBV)-related mortality in culturally and linguistically diverse (CALD) Australians. The figure presents the annual number of deaths in CALD populations born in Asia-Pacific (A), Europe (B), Africa and the Middle East (C), and Americas (D). Red (baseline), green (intermediate scale-up) and blue (optimistic scale-up) represent antiviral treatment scenarios

the occurrence of liver disease.[47] Migration contributes significantly to the epidemiology of HBV in Australia, and infant vaccination and immunoprophylaxis through vaccination alone may not be sufficient to achieve the desired elimination goals. An optimistic scale-up of antiviral treatment of HBV with innovative approaches to increasing screening and treatment uptake in CALD populations is needed.

We developed a mathematical model for antiviral treatment scale-up for the control of HBV in targeting migrant Australians born in Asia-Pacific, Europe, Africa and the Middle East, and American regions. Our model predicted the number of chronic HBV cases will be stable, and HBV-related morbidity and mortality will increase if the current treatment coverage rates are maintained through 2030. Hepatitis B elimination at the CALD population level is not on track to be achieved. Implementing the optimistic treatment scale-up (increased treatment uptake to achieve 20% treatment for all patients living with chronic HBV by 2022) could reduce the number of new cases of liver cirrhosis by 30% in European-born and 40% in Asia-Pacific-born migrants by 2030. Following the optimistic scale-up approach, the incidence of HCC is projected to decrease by about 30% across the four population subgroups by 2030 compared with the 2015 baseline, and a 15%–25% reduction in HCC-related mortality could be achieved. The number of patients with chronic HBV, the incidence of HBV infection, cirrhosis and HCC, and HBV-related deaths vary by CALD population group could be associated with the underlying differences in the prevalence of HBV in the countries of origin that reflects the prevalence at the time of migration in a population group leading to high incidence rates and mortality. These could also be due to possible undiagnosed cases because of several barriers to accessing health care faced by CALD populations. We found antiviral treatment in migrants—with most cases of HBV infection attributable to migration from high-burden countries—may be an effective and preferred strategy to significantly reduce HBV-related hospitalizations, mortality and healthcare costs.

Sensitivity analysis was done to identify the parameters that had the highest impact on the model outputs. Our sensitivity analysis suggested that prevalence in the country of origin, and transmission coefficient had the highest impact on the model outputs. The findings from the sensitivity analysis helped frame impacts by country of origin. Presenting without the sensitivity analyses would result in wrong estimates of the impact of interventions and relevant parameters, which might have masked the impact of HBV prevalence in CALD populations from the Asia-Pacific region. We have also interpreted the findings in the context of factors that impact the transmission coefficient.

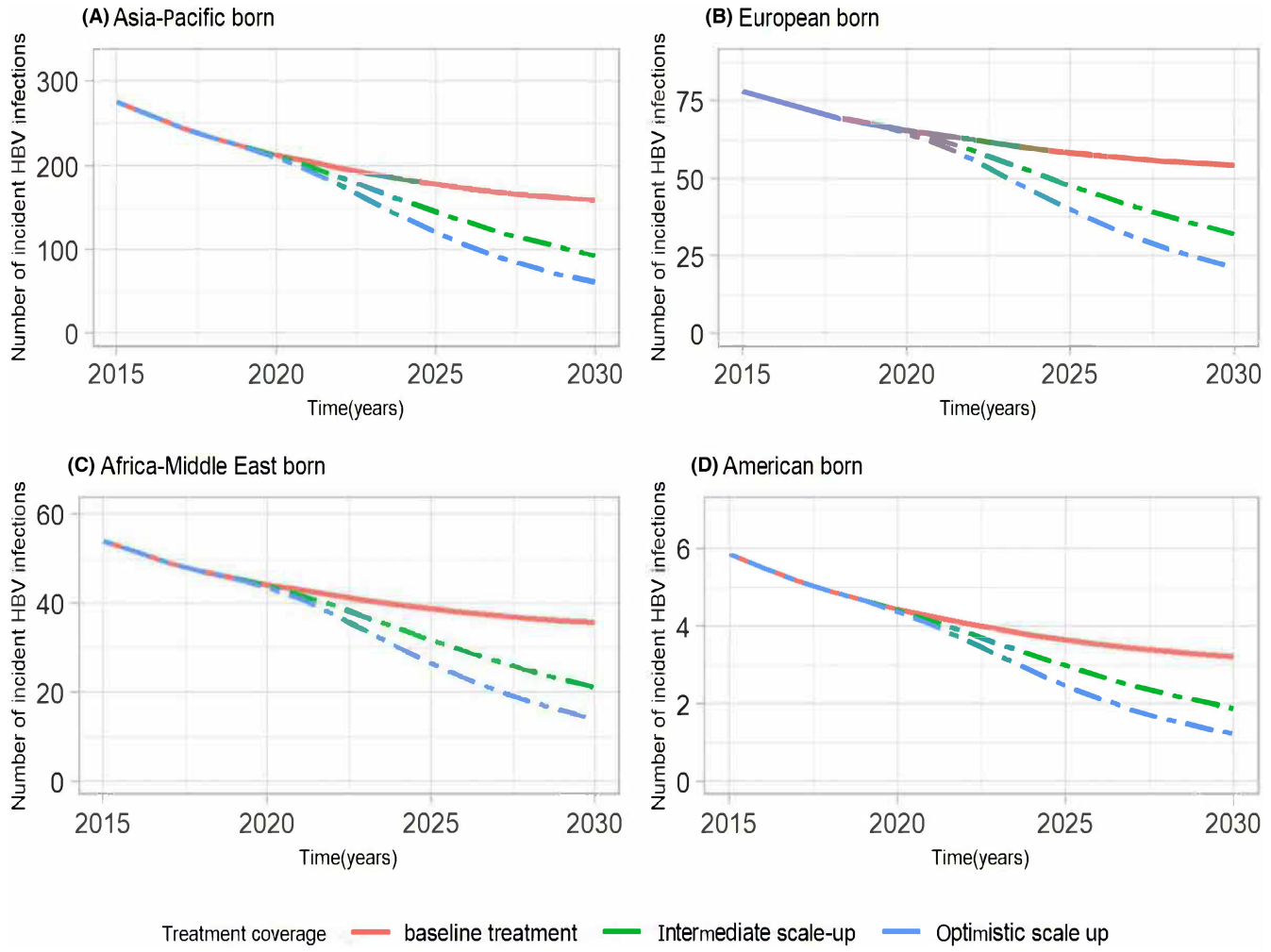

FIGURE 4 New hepatitis B virus (HBV) infections in culturally and linguistically diverse Australian born in Asia-Pacific (A), Europe (B), Africa and the Middle East (C), and Americas (D). The figure shows a reduction in incident HBV infections between 2020 and 2030. Colours show intervention scenarios: baseline antiviral treatment (red line), intermediate antiviral treatment scale-up (green line) and optimistic treatment scale-up (blue line)

Our model demonstrated that focused antiviral treatment scale-up in CALD populations significantly reduces chronic HBV incidence, the burden of liver cirrhosis, HCC and HBV-related deaths. Increasing the rate of screening and treatment of HBV in high-risk populations cuts down mortality and is cost-effective.[44] CALD populations might have a high prevalence of HBV including immigrants arriving in Australia, and screening provides an opportunity as an entry point for increasing treatment uptake. Screening and treatment of HBV could be increased by testing migrants at the time of entry, improving the health literacy of CALD populations such as using culturally appropriate techniques such as involvement of community-based organizations and language-specific messages,[45,46] and engagement of general practitioners.[45] Community engagement and education are key to expanding HBV screening and treatment programmes, to ensure accessibility for people with CALD backgrounds, as well as making them sustainable and cost-effective, and improving continuity to chronic disease care.[47] Test-and-treat strategies focused on geographic areas with a large population of migrants (who collectively contribute two-thirds of the national HBV burden) may be effective to reduce the HBV burden and prevent clinical complications. Treatment in high-risk population groups with a prevalence >2% is recommended in some countries.[48,49] Treatment roll-out at current rates is insufficient to achieve elimination targets and will see HBV prevalence and complications rise over time. Mechanisms to ensure priority populations access HBV treatment and that those opportunities are optimized are critical to reduce the burden of HBV. Although effective treatment is available for HBV, limited access among CALD populations limits the universal benefits of treatment and halts the progress towards HBV elimination.[50] There is a need to ensure that people with HBV, particularly CALD populations who bear the highest HBV burden, are not denied treatment. HBV treatment access for high-risk population groups, such as CALD people, can be achieved through decentralized treatment using task shifting in the primary care settings.[51] The significant incremental cost-effectiveness of antiviral therapy has been reported in modelling studies elsewhere.[52,53]

Despite the evidence for successful HBV vaccination and global efforts to support implementation to control HBV infection, the HBV prevalence in CALD populations in Australia remains relatively stable and markedly higher than in other Australians. This represents a disjuncture between the lofty targets of WHO vaccination and the reality of giving birth in lower income countries of the developing world. The success of control and elimination of HBV in the CALD population, and at the national level, requires narrowing the viral hepatitis treatment access gap in people with CALD backgrounds through community involvement, building the capacity of primary care physicians and reducing cost through universal funding of diagnostic services and treatments. Treatment scale-up may give particular emphasis to migrants coming from high-prevalence countries such as the Asia-Pacific, eastern European and African regions. Migrants arriving from moderate to high HBV prevalence countries including the Asia-Pacific, Africa and the Middle East, and eastern European regions may have a high rate of HBV infection, which contributes to the relatively steady prevalence of HBV.[5,54] Reprioritizing health spending to widen the scope for a rapid antiviral treatment to reach populations such as people with CALD backgrounds at high risk of getting infected with HBV is an effective investment strategy for the health system for elimination of HBV.[55] The two major HBV antiviral treatments, such as the use of entecavir and tenofovir, are now off-patent, and generic medications make wider availability more economically feasible.

Although a reduction in HBV incidence is demonstrated in the model, the WHO elimination targets (a 90% reduction in new HBV infections by 2030) are not on track to be achieved in both intermediate and even optimistic antiviral treatment scale-up scenarios. The contribution to HBV prevalence is via influx from migration, where HBV prevalence in countries of birth is static in migration age groups, or via refugee populations, where country-of-origin health systems are often fractured through conflict or civil strife interfering with vaccination programmes. From a domestic health security perspective, Australia should place more effort into supporting Maternal-Child Transmission prevention vaccination programmes, even if such efforts were limited to countries of highest migration contribution. On the contrary, the countries of origin for CALD populations may sustain and increase vaccination coverage, and increase treatment rates, which will significantly contribute to the reduced number of chronic HBV cases attributable to migration. Although Australia has high coverage of HBV vaccination, this only effectively limits vertical transmission domestically but will not significantly reduce horizontal transmissions.[7] As increasing migration reflects the true 'global village', Australia's domestic horizons must look wider. Offering vaccination to unvaccinated immigrants with no prior exposure to HBV infection could increase protection in the population and reduce the risk of transmission in Australia. The target of reducing HBV-related mortality by 65% is not on track to be achieved in these subpopulations. Many individuals with HBV infection may already have advanced liver disease at the time of diagnosis due to early childhood exposure to HBV infection, and the opportunity to prevent mortality with curative treatments is very low. Chronic HBV infections take more than 15 years to progress to HCC, and HBV-related mortality may remain high for years to come even after incidence is reduced.[20,56]

Hepatitis B control activities in low-prevalence countries such as Australia may benefit from targeted screening and treatment of high-risk populations such as people with CALD backgrounds or expansion of aid programmes in countries of origin to address HBV risk.[4] Micro-elimination is recommended as a cost-effective approach in high-risk populations. Adaptive treatment strategies that address the challenges faced by migrants including treatment cost, linguistic barriers and health literacy (knowledge of transmission, prevention and treatment of HBV, and knowledge about the health system) could be effective in improving treatment access and may be associated with improved health outcomes,[7] contributing significantly to micro-elimination.

Innovative strategies for improved rates of testing and treatment for HBV are available for migrants facing multiple challenges to accessing health care. If implemented in a community-based model of care, an optimistic scale-up of antiviral treatment for HBV may be more achievable.[55] This enables communities to access HBV testing and treatment services at primary care, in a more familiar environment closer to their residence with minimal travel and associated costs. Migrants may also have the option of getting a healthcare provider who speaks their preferred language or is more attuned to cultural issues relevant to the patient.[7] Hepatitis B prevention-focused health messages could be important to raise awareness and increase testing and follow-up rates.

We presented a detailed model of the transmission dynamics and natural history of HBV based on Australia's migration pattern and prevalence in countries of birth. We demonstrated the continuing impact of migration from regions with different HBV prevalence rates on the future natural history of HBV-related liver disease epidemiology in Australia. Detailed subgroup analysis of the impact of treatment scale-up on micro-elimination of HBV helps to better understand the burden of HBV in CALD populations and provides an opportunity to plan responsive healthcare programmes for these special healthcare needs.

This study has several limitations. Although regional assumptions provide a better reflection of the prevalence of HBV and vaccination coverage in member countries, there are differences between countries within regions, which impact the accuracy of estimates of HBV prevalence and mortality. The prevalence of HBV in countries of origin may change over time owing to the introduction of treatment and increasing vaccination coverage, yet these prevalence data lag, particularly in lower income countries with reduced epidemiological health infrastructure. Future projections depend on whether past trends in HBV prevalence rates and vaccination coverage remain steady in the future in countries of birth, which may be associated with differing numbers of migrants with chronic HBV. Improved screening and treatment for HCC are dynamic, and HCC-related mortality rates may decline

over time. Regression of cirrhosis may be observed in treated patients, which is likely to impact complications and improve mortality moving forward. The population projection for the number of migrants per year into Australia might significantly change owing to regional and global circumstances, for example, the emergence of the SARS-CoV-2 pandemic and the situation in Afghanistan, which result in significant fluctuation in migrant numbers in unpredictable ways. Changing migration might have an impact on the transmission of HBV during transition and on the rate of screening for HBV upon entry. Immunity after vaccination may not be lifelong, and there might be a possibility of HBV infection many years after vaccination or recovery from infection, which might increase the numbers of HBV cases than that predicted by our model. Moreover, our model predictions may be affected by the shortage of migrant-specific data on treatment uptake, transition probabilities, mortality rates and birth rates. Whenever evidence was available, we used data that included CALD populations as study participants.

In conclusion, targeted antiviral treatment of HBV in people with CALD backgrounds is associated with a significant reduction in HBV incidence, and lower HBV-associated morbidity and mortality, and might achieve control. In people with CALD backgrounds by 2030, HBV-related mortality will increase if current treatment rates remain static. The number of people with chronic HBV will increase if the current antiviral treatment rates do not increase. Our model projected that HBV elimination targets are not on track to be achieved by 2030. However, with scale-up of testing and treatment, the HBV prevalence significantly reduces as do associated complications such as liver cirrhosis, HCC and consequently HBV-related mortality. The use of expanded screening and antiviral treatment for HBV-prioritizing high-risk CALD populations will prevent transmission, reducing incidence and preventing healthcare costs associated with hospitalizations and care of advanced liver disease. More work is required to determine the incremental cost-effectiveness of expanded antiviral therapy for HBV infection, focused on high-risk populations, and how it may contribute to achieving HBV control.

AUTHOR CONTRIBUTIONS

BT, PV and PC conceived and designed the study. BT developed the methods, performed the mathematical modelling and drafted the manuscript. PV and PC reviewed the analysis and wrote the manuscript. All the authors have revised the manuscript and approved it for submission.

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CONFLICT OF INTEREST

The authors state that they have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are included in the Supplementary File.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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