

# Distribution of hepatitis B infection in Brazil: the epidemiological situation at the beginning of the 21<sup>st</sup> century

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## ABSTRACT

Brazil was formerly considered a country with intermediate hepatitis B endemicity, with large heterogeneity between Brazilian regions and areas of high prevalence, especially in the Amazon basin. Systematic vaccination of children was initiated in 1998. Between 2004 and 2009, a large population-based study reported decreased prevalence in all regions of Brazil. This review analyzed the current hepatitis B epidemiological situation in Brazil through a systematic search of the scientific literature in MEDLINE, LILACS, and CAPES thesis database, as well as disease notifications to the Information System for Notifiable Diseases. The search strategy identified 87 articles and 13 theses, resulting in 100 total publications. The most recent results indicate reduced hepatitis B prevalence nationwide, classifying Brazil as having low endemicity. Most studies showed HBV carrier prevalence less than 1%. However, there are still isolated regions with increased prevalence, particularly the Amazon, as well as specific groups, such as homeless people in large cities and isolated Afro-descendant communities in the center of the country. This review also detected successful vaccination coverage reported in a few studies around the country. The prevalence of anti-HBs alone ranged from 50% to 90%. However, isolated and distant localities still have low coverage rates. This review reinforces the downward trend of hepatitis B prevalence in Brazil and the need to intensify vaccination strategies for young people and adults in specific regions with persisting higher HBV infection prevalence.

**Keywords:** HBV. Brazil. Epidemiology. Prevalence. Incidence. Vaccine.

## INTRODUCTION

Hepatitis B is a viral infectious disease responsible for significant worldwide human morbidity and mortality. This disease burden is due mainly to complications of chronic infections, such as liver cirrhosis and hepatocellular carcinoma<sup>(1)(2)</sup>. The hepatitis B virus (HBV) is transmitted person-to-person through contact with blood, exudates, and other body fluids such as semen and vaginal secretions. Although iatrogenic dissemination was a common route of transmission throughout the second half of the 20<sup>th</sup> century due to blood product transfusion and sharing or reuse of syringes and needles, natural routes of transmission are mainly responsible for the high disease prevalence, including sexual, vertical (perinatal, from mother to newborn), and horizontal transmission from environmental exposure in the home, prisons, and other confinement institutions.

## PREVALENCE AND GLOBAL DISTRIBUTION OF HEPATITIS B VIRUS

The World Health Organization (WHO) classifies hepatitis B endemicity according to the prevalence of the serological marker of viremia, the hepatitis B surface antigen (HBsAg)<sup>(3)</sup>. The WHO currently categorizes endemicity as low, intermediate low, intermediate high, or high (**Table 1**).

The disease distribution is quite heterogeneous, with higher prevalence in densely populated Asiatic locations and regions lacking economic and hygienic resources. The most affected region with high endemicity is Southeast Asia. Sub-Saharan Africa, Oceania, and the Amazon basin are other hyperendemic areas. This last region is traditionally considered hyperendemic despite being sparsely inhabited. Indeed, high prevalence rates also have been reported in other populations in remote and poorly inhabited locations, such as among the native Inuits of the Arctic Circle<sup>(4)</sup>. Industrialized countries (North America, Australia, Western Europe, and Scandinavia) have lower endemicity rates. As countries become industrialized, there is a progressive reduction of hepatitis B endemicity concomitant with increasing access to better housing conditions, hygiene, and infrastructure, as reported in Taiwan<sup>(5)</sup>.

Vaccination is another crucial factor for disease control, with effective and safe HBV vaccines first developed in the 1970s. Although initially very expensive, genetic engineering increased production and reduced costs, allowing their use in wide-ranging

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**TABLE 1 - World Health Organization classification of hepatitis B virus endemicity, 2015<sup>(3)</sup>.**

	Prevalence			
	low	intermediate low	intermediate high	high
HBsAg+ individuals	<2%	2-4%	5-7%	≥8%

HBsAg: hepatitis B surface antigen.

campaigns and public policies. Evidence from across the globe reveals the effectiveness of vaccination to achieve medium- and long-term endemicity reductions<sup>(6) (7) (8) (9) (10)</sup>. Follow-up of children in Taiwan indicated that it was possible to transform hyperendemic levels to low endemicity<sup>(5)</sup>. Even more striking was the significant decrease in the incidence of liver cancer because of the universal vaccination of youngsters.

The WHO suggests that these changes have decreased the number of HBV carriers and estimates that there are currently about 240 million carriers worldwide<sup>(3) (11) (12)</sup>.

### HISTORICAL DISTRIBUTION OF HEPATITIS B VIRUS IN BRAZIL

At the end of the 20<sup>th</sup> century, Brazil was classified as having moderate hepatitis B endemicity. Detailed analysis showed a highly heterogeneous distribution of the disease in Brazil. It was long known that the prevalence of hepatitis B increased from the Southern to the Northern regions of the country. The Amazon region has the highest endemicity in Brazil, particularly in Acre, south of the Amazon, as well as Rondônia, Pará, and Northwestern Mato Grosso<sup>(13) (14) (15) (16) (17)</sup>. Data available up to 1999 classified the Southeast, Northeast, and Midwest as regions with low to moderate prevalence, with the exception of the North of Mato Grosso and the mountainous region of Espírito Santo. However, even in southern parts of the country with relatively low endemicity, populations with moderate or high endemic state have been identified, especially in the western parts of the States of Paraná and Santa Catarina<sup>(18)</sup>.

### INITIATION OF CHILD VACCINATION IN BRAZIL AND THE NATIONAL EPIDEMIOLOGICAL SURVEY IN BRAZILIAN STATE CAPITALS

In 1998, the National Immunization Program [*Programa Nacional de Imunizações* (PNI)] of the Ministry of Health in Brazil mandated vaccination of children against hepatitis B in their first years of life. This policy was gradually extended to cover larger parts of the population as the vaccine became more accessible and the country became self-sufficient in its production. Currently, the hepatitis B vaccine is widely available and recommended for citizens up to 49 years of age. Vaccine coverage has been considered satisfactory, despite the persistent challenge of vaccinating difficult-to-access populations. However, more precise information was required to analyze the effectiveness of the vaccination strategy and the current endemic situation.

Thus, in the past decade, the Ministry of Health has sponsored an ambitious project to estimate the prevalence of

viral hepatitis in Brazil. The survey, based on a robust multistage random sampling methodology, evaluated almost 20,000 residents from more than 9,000 households in the 27 Brazilian capitals between 2004 and 2009<sup>(19)</sup>. The results indicated a lower than expected prevalence of hepatitis B in all regions<sup>(20)</sup>. Exposure to HBV [measured by levels of antibodies against the core antigen (anti-HBc)] varied in participants 10 to 19 years of age, from 0.6% in the southeast to 1.6% in the South. Among individuals 20 to 69 years of age, the prevalence ranged from 7.9% in the Southeast to 14.7% in the North. The prevalence rates of virus carriers (HBsAg-positive) among those 10 to 19 years of age did not exceed 0.2% in any region. For those between 20 and 69 years of age, the HBsAg prevalence ranged from 0.4% in the Southeast and the Federal District to 0.9% in the Northern region (**Table 2**). These numbers moved Brazil to a low-prevalence hepatitis B endemicity classification<sup>(3)</sup>.

### CURRENT HEPATITIS B EPIDEMIOLOGICAL DATA IN BRAZIL

This decline was expected, considering the significant socioeconomic improvements for a large portion of the Brazilian population and effective vaccination coverage, especially among children, from the end of the 20<sup>th</sup> century. However, the findings of the National Survey remain controversial. The main criticism, acknowledged by the authors, was that limiting the sample to large urban centers (state and federal capitals) could have underestimated the true hepatitis B prevalence in localities with worse health and economic conditions<sup>(21)</sup>.

By excluding the more remote and poorer regions, the study did not sample localities with the highest historical prevalence of hepatitis B in Brazil. For example, the Purus and Juruá River basins in Amazonas historically had the highest rates<sup>(22)</sup>. In the State of Espírito Santo, Cachoeiro de Itapemirim municipality was hyperendemic<sup>(23)</sup>, such as some municipalities in Northwestern Mato Grosso near the border with States of Rondônia and Amazonas<sup>(17) (24)</sup>. The same situation was reported in Cascavel and Francisco Beltrão municipalities of the State of Paraná, and in other countryside of the States of Santa Catarina and Minas Gerais<sup>(18) (25)</sup>. These regions are far from the capital, where improvements in living and hygiene conditions are usually implemented more slowly.

By the beginning of the 21<sup>st</sup> century, Brazil had become a cosmopolitan and urbanized country, with 84% of the population living outside rural areas [Censo 2010, *Instituto Brasileiro de Geografia e Estatística* (IBGE)]. Considering that less than one-fifth of the population lives in rural areas, it remains unclear whether the results of the National Survey reflect the overall hepatitis B prevalence.

In short, although the results of the National Survey of the Ministry of Health are promising, it is important to continue analyzing data from new Brazilian studies to better understand the current epidemiological environment of hepatitis B, a disease with considerable burdens<sup>(2) (12)</sup>. New data will help assess the impact of vaccination strategies used so far and therapeutic guidelines adopted in recent years, suggesting complementary measures for control of this endemic disease.

**TABLE 2 - Prevalence of markers of current infection (HBsAg-positive) and HBV exposure (anti-HBc-positive) in a population-based survey of capitals of Brazil, coordinated by the UPE and supported by the Ministry of Health and the PAHO<sup>(20)</sup>.**

Region	Households/ participants	Age group (years)	HBsAg+ (%)	95%CI of HBsAg (%)	Anti-HBc + (%)	95%CI of anti-HBc (%)
North	1,084	10–19	0.0	-	0.9	0.4–1.5
	2,306	20–69	0.9	0.3–1.5	14.7	12.2–17.8
Northeast	1,695	10–19	0.1	0.0–0.3	2.1	1.4–2.8
	3,650	20–69	0.5	0.20–0.9	11.7	10.0–13.3
Midwest	1,763	10–19	0.2	0.0–0.3	1.3	0.7–1.8
	3,653	20–69	0.8	0.3–1.2	12.7	10.9–14.5
Federal District	870	10–19	0.2	0.0–0.5	1.2	0.4–2.0
	1,966	20–69	0.4	0.0–0.8	8.4	6.6–10.2
Southeast	1,842	10–19	0.0	-	0.6	0.3–0.9
	3,689	20–69	0.4	0.1–0.7	7.9	6.2–9.2
South	2,047	10–19	0.2	0.0–0.4	1.6	0.8–2.3
	4,189	20–69	0.5	0.2–0.9	11.3	9.9–12.7
Brazil	9,671	10–19	0.05	0.0–0.1	1.1	0.9–1.4
	19,634	20–69	0.6	0.4–0.8	11.6	10.7–12.4

**HBsAg:** hepatitis B surface antigen; **HBV:** hepatitis B virus; **anti-HBc:** antibodies against hepatitis B core antigen; **UPE:** University of Pernambuco; **PAHO:** Pan American Health Organization; **95%CI:** 95% confidence interval.

## METHODOLOGY

In order to validate and extend the findings of the National Survey, a systematic review was performed using data from independent epidemiological studies on disease prevalence and incidence in Brazil, including historical series.

Scientific publications with primary data on the epidemiology, prevalence, or incidence of hepatitis B in Brazil from 1999 to early 2015 were systematically analyzed. This time interval was defined based on the existence of a publication from 1999 that had compiled all available data available to that time<sup>(18)</sup>.

The MEDLINE, LILACS, CAPES/MEC, and SINAN/MS (*Sistema Nacional de Agravos de Notificação, Ministério da Saúde*) databases were accessed. In MEDLINE, the following descriptors were entered only in the title/abstract field: (brazil OR brazil\*) AND (epidem\* OR survey OR prevalence OR incidence OR cross-sectional) AND (hepatitis B OR HBV OR HBsAg). In LILACS, the following descriptor terms in Portuguese, Spanish, and English were used: hepatitis OR *hepatite* [Words in Title] and *epidemiologia* OR epidemiology OR *prevalencia* OR prevalence OR *incidencia* OR incidence OR survey OR *inquerito* OR *encuesta* [Words in Title], and *brasil* OR brazil [Country of affiliation].

The CAPES/MEC database was queried to find unpublished data. The search strategy used as descriptors *hepatitis B* and *epidemiology* or *prevalence* and *incidence* or *survey* in the field *title* or *abstract*. We had the helpful assistance of the call center staff, available through the electronic address (mec.cube.callsp.inf.br/auto-atendimento). The SINAM/MS database was used to collect data on hepatitis B incidence (<http://dtr2004.saude.gov.br/sinanweb/>).

## RESULTS

The MEDLINE search (<http://www.ncbi.nlm.nih.gov/pubmed>) performed on April 4, 2015, resulted in 304 citations. After reviewing the titles and abstracts, studies referring to aspects other than the prevalence or incidence of hepatitis B were discarded, as well as those that focused on subpopulations with increased risk for HBV infection, such as patients with human immunodeficiency virus (HIV), patients in renal replacement therapy, poly-transfused patients, patients with chronic liver disease or scleral jaundice, or patients with sexually transmitted diseases. Articles on prevalence in prison inmates, sex workers, or injectable drug users were discarded because these subpopulations were also considered to have increased risk. Non-injectable drug users, however, were retained in this review. Studies that focused on describing the genotypic distribution of HBV among chronic carriers and research on occult infections were also discarded. After this evaluation, 76 articles remained. Two publications had no data on infection prevalence. One focused only on seroprevalence of vaccine coverage<sup>(26)</sup>, while the other was part of the results of the National Epidemiological Survey in Brazilian State Capitals<sup>(20)</sup>. Thus, 74 articles were retrieved.

A LILACS/BIREME (<http://lilacs.bvsalud.org>) search on the same day identified 144 studies. First, references that dealt with hepatitis other than hepatitis B were removed from consideration. Results from subpopulations were also discarded, following the same criteria used for the MEDLINE search. After removing articles already identified in the MEDLINE search, 13 additional articles were identified. Thus, from these two databases, 87 publications were retrieved.

The CAPES database query identified 136 masters or doctoral theses. Most dealt with other aspects of HBV infection, ranging from molecular biology to vaccine considerations. Thirty-four reported prevalence in cross-sectional studies. Among these, 12 had already been identified in the MEDLINE and LILACS searches. Of the remaining 22, two studies were based in other countries, and seven included only risk groups. Finally, 13 dissertations were identified with unique data, resulting in 100 studies.

The results of these studies are presented below, in four groups. **Table 3** presents the results of studies from the beginning of the current millennium, among which many references were related to research and surveys carried out in the 1990s. The most recent population studies or those in specific groups (without increased risk) are shown in **Table 4**. **Table 5** and **Table 6** contain data specific to pregnant women and blood donors, respectively. The results in pregnant women are presented separately owing to the fact that these studies have become very common in recent years in Brazil and because they represent in particular the risk of vertical transmission. Blood donors were also separated as a group, with notably reduced prevalence due to increasingly insightful recruitment by blood banks to select individuals with minimal risk.

### Results from the turn of the century

The data in **Table 3** show prevalence across the country, with the highest rates concentrated in the Amazon region, including Mato Grosso<sup>(27) (28) (29) (30) (31) (32) (33) (34) (35) (36) (37) (38) (39) (40) (41) (42) (43) (44)</sup>. In all, there were 21 reports, nine (42.8%) with intermediate to high prevalence (>2%). Of these nine, two had prevalence rates above 9%, namely indigenous people in Lábrea, Amazonas, and isolated African descendants in the State of Mato Grosso do Sul<sup>(30) (36)</sup>. The high prevalence was concentrated, as expected, in the northern region. However, two studies identified high endemicity outside the Amazon basin, in the semi-arid region of the State of Bahia and in African descendants from the *Cerrado* of the State of Mato Grosso do Sul<sup>(34) (36)</sup>. Five studies reported prevalence below 1%, and the other six assessed anti-HBc positivity rather than HBsAg. The prevalence of this marker in these studies ranged from 1.2% to 58.4%<sup>(27) (29) (44)</sup>.

**TABLE 3 - Prevalence of hepatitis B virus infection in Brazilian studies from the early 2000s, including data from the 1990s, according to geographic region.**

Region	State	Subregion	Municipalities	Sample	Number	HBsAg (%)	Anti-HBc (%)	Endemicity*	Year	Ref.	
North	Acre	East	Rio Branco	General population	2,684	-	58.4	-	2000	27	
	"	"	"	"	390	3.3	40.0	Intermediate	2004	28	
	Amazonas	Center	Manaus	"	613	-	21.4	-	2000	29	
	"	Southwest	Lábrea	Indigenous	688	9.7	54.5	High	2001	30	
	"	Southwest	Purus	General population	349	5.2	66.2	High intermediate	2001	31	
"	Southwest	Southwest	Lábrea	"	605	3.3	49.4	Low intermediate	2004	32	
Northeast	Pará	Northeast	Igarapé	"	58	0.0	12.4	Low	2003	33	
	Ceará	Fortaleza	Fortaleza	"	489	-	1.2	"	2000	29	
	Bahia	Semi-arid	Rural area	"	476	2.6	9.8	Low intermediate	2006**	34	
Midwest	Mato Grosso do Sul	Central	Sidrolândia	Indigenous	312	0.0	2.2	Low	2002	35	
	"	Central	Furnas Dionísio	IADC	260	9.2	42.7	High	2003	36	
	Goiás	Central	Goiania	Dentists	90	0.0	10.0	Low	2003	37	
	"	"	"	Psychiatric patients	433	1.6	22.4	"	2004	38	
	Mato Grosso	Mid-North	Nova Mutum	General population	754	3.0	31.0	Low intermediate	2001	39	
	"	North	Apiacás	Prospectors	520	7.1	82.9	High intermediate	2001	40	
	"	North	Peixoto e Azevedo	Schoolchildren	487	1.2	11.1	Low	2004	41	
	"	Northwest	Cotriguaçu	General population	838	2.1	40.0	Low intermediate	2004	42	
	Southeast	São Paulo	North	Ribeirão Preto	"	632	0.3	13.9	Low	2000	43
		Rio de Janeiro	Central	Rio de Janeiro	"	2,090	-	5.5	-	2000	29
"		North	Macaé	"	1,100	-	15.3	-	2002	44	
South	Rio Grande do Sul	Porto Alegre	Porto Alegre	"	461	-	7.6	-	2000	29	

**HBsAg:** hepatitis B surface antigen; **anti-HBc:** antibodies against hepatitis B core antigen; **HBV:** hepatitis B virus; **WHO:** World Health Organization; **IADC:** isolated Afro-descendant communities. **Ref:** references. \*The HBV infection endemicity classification was based on the WHO categorization using HBsAg positivity prevalence. When there were only results for anti-HBc, we used previous WHO classifications: ≤20%, low; 21-60%, intermediate; and >60%, high. \*\*Article was published in the 2000s, but presented data from the 1990s.

TABLE 4 - Prevalence of hepatitis B virus infection in Brazilian studies since 2005 by geographic region.

Region	State	Subregion	Municipalities	Sample	Number	HBsAg (%)	Anti-HBc (%)	Endemicity*	Year	Ref.	
North	Acre	-	Several	General population	2,656	3.3	61.2	Low intermediate	2005	45	
	Amazonas	Southwest	Lábrea	"	1,510	6.2	52.1	High intermediate	2012	46	
	Rondônia	North	Montenegro	Rural population	267	4.8	61.8	"	2005	47	
	"	North	Porto Velho	"	660	1.8	50.7	Low	2012	48	
	Pará	North	Belém	Recruits	298	0.3	6.0	"	2007	49	
	"	Southeast	Altamira	Indigenous	167	5.4	55.7	High intermediate	2007	50	
	"	West	Juruti	Rural population	232	0.0	2.2	Low	2010	51	
	"	North	Cametá	"	181	0.0	1.1	"	2011	52	
	"	"	Belém	Dentists	98	0.0	6.2	"	2012	53	
	"	"	Belém	Laboratory technicians	528	0.4	8.0	"	2012	54	
	"	"	Tucuruí	"	668	1.9	28.0	"	2012	55	
	Northeast	Bahia	Southeast	São Felix do Araguaia	"	91	1.1	49.5	"	"	"
"		Coast	Salvador	Dentists	120	0.0	5.8	Low	2005	56	
"		"	"	NIDU	125	0.8	-	"	2007	57	
"		"	"	University students	766	0.0	1.7	"	2012	58	
"		"	"	General population	780	1.3	-	"	2013	59	
Maranhão		B. Munim	Morros, Arixá	"	1,249	1.7	39.6	"	2014	60	
Midwest		Mato Grosso do Sul	Rural area	Several	IADC	1,058	2.2	19.8	Low intermediate	2005	61
		"	Central	Campina Grande	Dentists	474	0.6	10.8	Low	2006	62
		"	Pantanal	Corumbá	General population	321	1.6	36.5	"	2009	63
		"	Central	Campina Grande	PPL	409	0.5	17.8	"	2009	64
	"	"	Goiânia	Firemen	308	1.0	6.5	"	2012	65	
	Goiás	"	"	Laboratory technicians	648	0.7	24.1	"	2005	66	
	"	"	"	Dentists	680	0.0	6.0	"	2008	67	
	"	All	Several	Truck drivers	641	1.4	18.9	"	2008	68	
	"	North	Cavalcante	IADC	878	1.8	35.4	"	2009	69	
	"	Central	Goiânia	PPL	148	0.7	18.9	"	2010	70	
	"	"	"	Garbage collectors	431	0.7	12.8	"	2014	71	
	Mato Grosso	East	Barra do Garças	Adolescents	576	0.7	5.0	"	2011	72	
"	Central	Várzea Grande	Leprosy patients	191	1.0	27.7	"	2011	73		
Southeast	All	-	-	NIDU	852	1.0	14.0	"	2009	74	
	São Paulo	North	Ribeirão Preto	Health workers	1,433	0.8	9.4	Low	2005	75	
	"	"	"	Administ. workers	872	0.2	-	"	"	"	
	"	East	São Paulo	Homeless	330	3.3	30.6	Low intermediate	2007	76	
	"	Coast	Santos	Children	4,680	0.02	0.1	Low	2014	77	
	Rio de Janeiro	"	Rio de Janeiro	"	1,217	1.8	3.6	"	2014	78	
	"	"	"	Recruits	433	0.0	4.1	"	2015	79	
	Espírito Santo	Central	Vitória	Women	1,029	0.9	4.2	"	2008	80	
	Santa Catarina	Coast	Florianópolis	Recruits	371	0.0	1.6	Low	2011	81	
	"	"	"	Adolescents	384	0.0	0.5	"	2010	82	
	"	"	Itajaí	"	353	0.6	1.1	"	2011	83	
	"	West	Chapecó	"	418	0.2	1.4	"	2011	84	
"	East	Blumenau	Children	393	0.8	1.0	"	"	85		
"	South	Tubarão	Elderly	820	0.6	15.1	"	2013	86		
Paraná	South	Rural area	Indigenous	214	0.0	15.4	"	2006	87		
Rio Grande do Sul	Central	Caxias do Sul	General population	60,604	1.6	-	"	2014	88		
Brazil	Multicenter	"	Several	Psychiatric patients	2,238	1.6	14.7	Low	2009	89**	
	"	"	"	"	2,206	2.0	17.1	Low intermediate	2014	90**	

HBsAg: hepatitis B surface antigen; anti-HBc: antibodies against HBV core antigen; NIDU: non-injectable drug user; IADC: isolated Afro-descendant communities; PPL: people deprived of their freedom; HBV: Hepatitis B Virus; WHO: World Health Organization; Ref: references. \*The HBV infection endemicity classification was based on WHO categorization using HBsAg positivity prevalence. When only anti-HBc results were available, we used previous WHO classifications: ≤20%, low; 21–60%, intermediate; >60%, high. \*\*These publications report on the same historical series.

**TABLE 5 - Prevalence of hepatitis B virus infection among pregnant women in Brazilian studies since 2000, according to geographic region.**

Region	State	Subregion	Municipalities	Number (%)	HBsAg (%)	Anti-HBc (%)	Endemicity*	Year	Ref.
North	Amazonas	Juruá	-	218	8.7	75.9	High	2003	91
	"	Middle Amazon	-	118	0.0	12.7	Low	"	"
	"	East	Manaus	674	0.7	-	"	2010	92
	Acre	East	Rio Branco**	283	2.1	-	Low intermediate	2006	93
Northeast	Pernambuco	Coast	Recife	1,584	0.6	-	Low	2003	94
	Maranhão	Coast	São Luís	541	0.9	6.4	"	2012	95
	Bahia	Coast	Salvador	692	0.3	-	"	2014	96
Midwest	Mato Grosso do Sul	Central	Campo Grande	119,774	0.3	0.6	Low	2008	97
	"	All	Several	32,512	0.3	-	"	2007	98
	Goiás	South	Catalão	2,037	-	5.6	"	2014	99
Southeast	São Paulo	East	São José dos Campos	224	0.9	4.5	Low	2003	100
	"	"	São Paulo	554	1.8	-	"	2010	101
	"	North	Ribeirão Preto	5,191	0.5	-	"	2005	102
	Rio de Janeiro	Central	Rio de Janeiro	874	0.5	7.2	"	2002	103
	Espírito Santo	"	Vitória	1,608	1.1	-	"	2001	104
	"	"	Vitória	534	1.1	-	"	2009***	105
South	Paraná	North	Londrina	1,502	0.8	-	Low	2000	106
	"	West	Cascavel	496	1.4	24.0	"	2006	107
	"	"	Francisco Beltrão	442	3.8	38.5	Low intermediate	"	"
	"	East	Curitiba	458	0.7	7.2	Low	"	"
	"	North	Londrina	335	0.6	12.8	"	"	"
	"	"	Maringá	379	1.8	10.8	"	"	"
	"	Northwest	Several	1,534	0.5	-	"	2013	108
	Santa Catarina	Coast	Itajaí	10,147	0.4	-	"	2012	109
Rio Grande do Sul	North	Passo Fundo	3,573	0.7	-	"	2009	110	

**HBsAg:** hepatitis B surface antigen; **anti-HBc:** antibodies against HBV core antigen. \*The HBV infection endemicity classification was based on WHO categorization using HBsAg positivity prevalence. When only anti-HBc results were available, we used previous WHO classifications:  $\leq 20\%$ , low; 21–60%, intermediate;  $>60\%$ , high. **Ref:** references. \*\*The study by Santos included seven municipalities bordering the Rio Amazonas: Bragança, Castanhal, Combu, Alenquer, Santarém, Óbidos and Oriximiná. \*\*\*Article published later in the 2000s but included data from the 1990s.

### Recent prevalence data

Analysis of data from more recent studies (Table 4) suggests lower prevalence rates nationwide<sup>(45) (46) (47) (48) (49) (50) (51) (52) (53) (54) (55) (56) (57) (58) (59) (60) (61) (62) (63) (64) (65) (66) (67) (68) (69) (70) (71) (72) (73) (74) (75) (76) (77) (78) (79) (80) (81) (82) (83) (84) (85) (86) (87) (88) (89) (90)</sup>. These studies represent more than 90,000 individuals. Among 48 reports, only seven (14.6%) found intermediate to high prevalence. In 28 (58.3%) studies, the prevalence of HBsAg-positive individuals was below 1%. However, there is no guarantee that individuals were not sampled in more than one such study.

Three Amazonian communities had prevalence higher than 4%, namely Lábrea (6.2%), a rural population in Rondônia (4.8%), and indigenous peoples in Southeastern Pará (5.4%)<sup>(46) (47) (50)</sup>. However, in general, the prevalence rates in most recent studies were systematically lower than those in previous studies. Only two studies showed intermediate-low endemicity outside the Amazon Region (3.3% among homeless in São Paulo, a population considered to be at increased risk, and isolated populations of African descendants in the State of Mato Grosso do Sul)<sup>(61) (66)</sup>. It should also be emphasized that, contrary to

studies performed in the 1990s, the prevalence in more recent studies was less than 7%.

### Evaluation of pregnant and postpartum women

Table 5 presents the results of 25 surveys carried out in pregnant and postpartum women that reported low prevalence, with 16 (64%) of 25 reports showing that HBsAg was present in less than 1.0% of women<sup>(91) (92) (93) (94) (95) (96) (97) (98) (99) (100) (101) (102) (103) (104) (105) (106) (107) (108) (109) (110)</sup>. Three studies reported intermediate or high endemicity. Two studies were in the Amazon: in Juruá, Amazonas (8.7% of carriers) in a study from 2003 and in Rio Branco, Acre (2.1%)<sup>(9) (93)</sup>. The third study took place in Francisco Beltrão, in Paraná, with 3.8% endemicity in this population<sup>(107)</sup>.

### Blood donor data

The 15 reports on blood donors totaled over 500,000 donations (Table 6)<sup>(75) (111) (112) (113) (114) (115) (116) (117) (118) (119) (120)</sup>. It was also not possible to rule out double participation between these studies. None of the studies showed prevalence above 0.7%, and 10 reported prevalence below 0.4%.

**TABLE 6 - Prevalence of hepatitis B virus infection among blood donors in Brazilian studies since 2005, according to geographic region.**

Region	State	Subregion	Municipality	Number	HBsAg (%)	Anti-HBc (%)	Endemicity*	Year	Ref.
North	Amazonas	Manaus	Manaus	1,199	0.2	4.7	Low	2008	111
Northeast	Bahia	Coast	Salvador	1,201	0.2	4.0	Low	2008	111
	Pernambuco	Coast	Recife	28,364	0.3	5.1	“	2013	112
Midwest	Goiás	Southwest	Several	984	-	6.9	Low	2011	113
	Mato Grosso do Sul	Central	Campo Grande	8,840	0.2	3.0	“	2013	114
Southeast	São Paulo	North	Ribeirão Preto	2,583	0.2	-	Low	2005	75
	“	East	Sao Paulo	1,198	0.7	5.2	“	2008	111
	“	“	“	43,523	0.2	3.0	“	2013	112
	“	“	“	25,891	0.6	8.7	“	2005	115
	Rio de Janeiro	Central	Rio de Janeiro	128,497	0.3	3.7	“	2006	116
	Minas Gerais	Southeast	Belo Horizonte	21,823	0.3	3.7	“	2013	112
South	Paraná	North	Maringá	8,337	0.1	2.2	Low	2013	117
	Santa Catarina	Coast	Florianópolis	3,180	0.1	2.1	“	2013	118
	“	Coast	Florianópolis	2,583	0.7	9.2	“	2000	119
	Rio Grande do Sul	All	-	263,795	0.6	5.3	“	2003	120

**HBsAg:** hepatitis B surface antigen; **anti-HBc:** antibodies against hepatitis B core antigen; **WHO:** World Health Organization; **Ref:** references. \*The classification of HBV infection prevalence was based on WHO categorization using HBsAg positivity prevalence. When only anti-HBc results were available, we used the previous WHO classification:  $\leq 20\%$ , low; 21-60%, intermediate;  $> 60\%$ , high.

### Vaccine coverage

Among studies included in this review, some also analyzed vaccine coverage by measuring the seroprevalence of antibodies against HBsAg (anti-HBs)<sup>(26) (52) (58) (72) (78) (79) (82) (83) (85)</sup>. These reports were predominantly conducted in adolescents and young adults. As it is common for people to lose documents certifying vaccination in Brazil, authors often use positivity for anti-HBs positivity alongside negativity for HBsAg and anti-HBc as evidence of vaccine coverage. Most of these reports found a prevalence of anti-HBs alone between 55% and 60%, considering the cutoff of 10UI/L as the lower level of anti-HB positivity. When anti-HB titers lower than 10UI/L were considered, prevalence reaches approximately 90% (Table 7). However, two studies (Amazon and northeast) suggested low vaccine coverage<sup>(52) (60)</sup>.

### Incidence data

Several studies presented incidence data, including three studies conducted in Santa Catarina. Kupeck (2001) estimated the risk of HBsAg transmission by studying historical blood donor series in the State of Santa Catarina in the 1990s<sup>(109)</sup> and concluded that despite reduced risk, the incidence density would be three infections per 1,000 person-years. More recently, Silva et al.<sup>(121)</sup> analyzed notifications to the Information System for Notifiable Diseases and estimated that the incidence in 2009 in Brazil and Santa Catarina was 11.5 and 17 infections per 100,000 inhabitants, respectively<sup>(121)</sup>. Finally, Marcon et al.<sup>(122)</sup> also studied notifications in the same state and concluded that there was a decrease in incidence starting in 2006<sup>(122)</sup>.

The Brazilian official data about hepatitis (SVS/MS, 2012) presents data relating to hepatitis B case notifications from

1999 to 2011<sup>(123)</sup>. There is a trend of year-to-year growth. There were fewer notifications among youth  $< 20$  years of age in Brazil and in all macroregions.

Figure 1 presents reported case data in Brazil from 2007 to 2013 (SINAN) according to age group, with an increasing number of notifications each year. The majority of the cases are concentrated in the 20- to 59-year-old age group. However, below 20 years of age, the number of reported cases is stable. Reports among this age range were 10% and 5.9% of the total cases in 2007 and 2013, respectively.

### DISCUSSION

This review shows an improved epidemiological environment in Brazil compared to the end of the last century, likely due to improved quality of life and the increasingly comprehensive deployment of systematic youth vaccination programs. The results presented in Table 3, which correspond to samples obtained at the end of the 1990s, are similar to reports from previous studies, with carrier prevalence exceeding 7% in some regions, characterizing them as highly endemic<sup>(30) (36) (39)</sup>. In more recent studies, however, this situation has improved, with low to intermediate-high prevalence and no prevalence rates above 7% (Table 4).

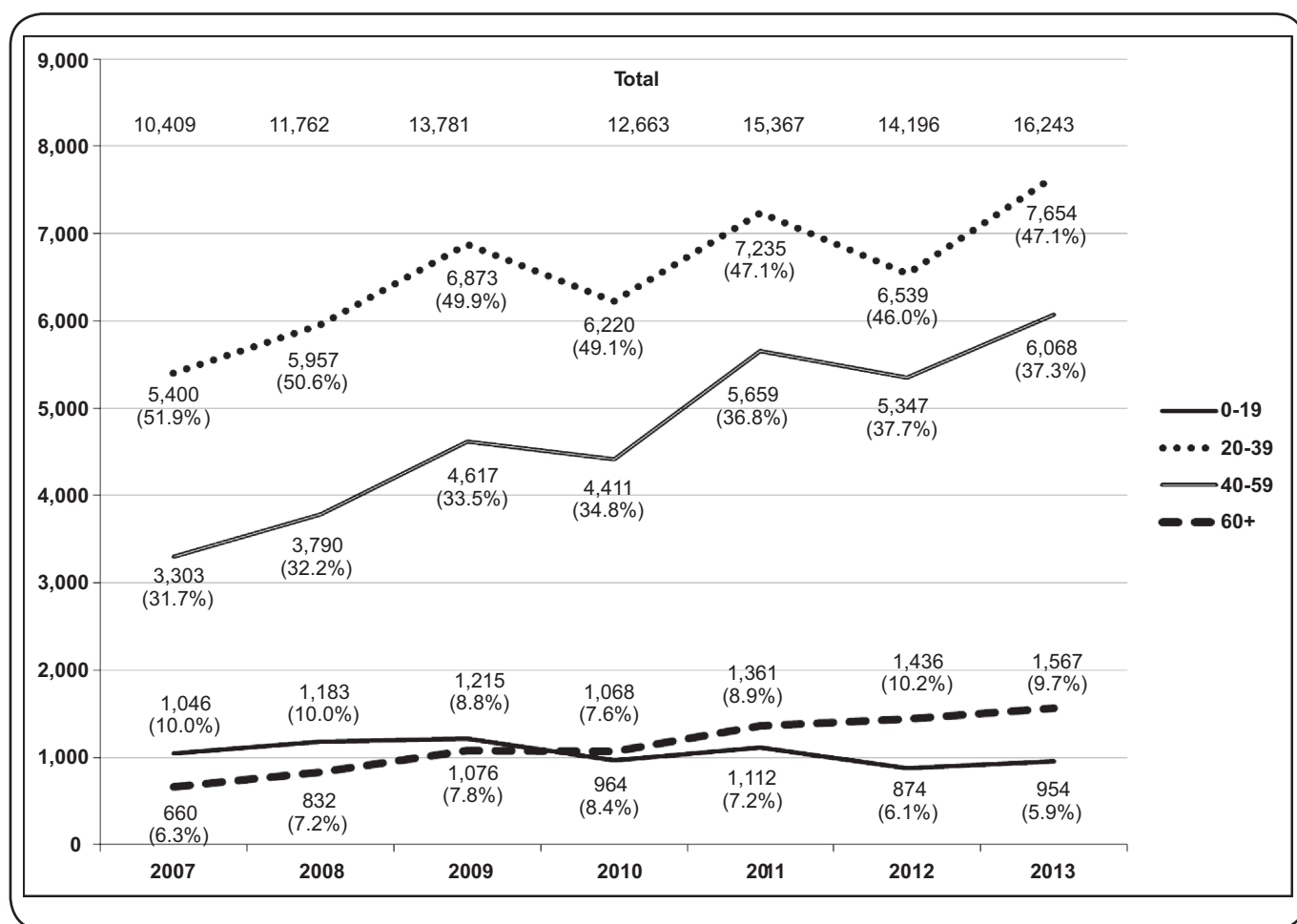
However, there are still foci of intermediate endemicity, especially in areas difficult to access or with low population densities, such as riverine populations in the Amazon Basin and among isolated populations of African descendants (quilombolas) in the Midwest<sup>(30) (36)</sup>.

Two other findings from this review should be emphasized. First, the disease seems to be under control in the Southern region

**TABLE 7 - Prevalence of vaccine-induced protection profile (anti-HBs-positive only) in Brazilian studies.**

Region	State	Municipalities	Number	Age group (years)	Anti-HBs isolated (%)	Year	Ref.
North	Pará	Cametá	181	32*	18.0	2011	52
Northeast	Bahia	Salvador	766	17–66**	92.7	2012	58
	Maranhão	Axixá, Morros	286	1–10	34.3	2014	60
	“	“	301	11–20	28.2	“	“
Midwest	Mato Grosso	Barra do Garças	576	12–20	56.1	2011	71
Southeast	Rio de Janeiro	Rio de Janeiro	1,217	0–18	85.0	2014	78
	“	“	433	18–25	57.0	2015	79
South	Santa Catarina	Florianópolis	384	10–16	58.8	2010	82
	“	“	371	18–19	57.0**	2011	26
	“	Itajaí	353	10–15	83.6**	2011	83
	“	Blumenau	371	10–15	89.8**	2011	85

**Anti-HBs:** antibodies against HBV surface antigen; **Ref:** references. \*Average sample age. The study was conducted in a riverside community in the Amazon interior. \*\*Study of university students between 17 and 66 years of age. \*\*Considering any anti-HBs titer.



**FIGURE 1 - Number (and percentages) of notified cases of hepatitis B (HBsAg+) in Brazil by age ranges between 2007 and 2013 by age. Source: SINAN/SVS/MS. HBsAg:** HBV surface antigen; **SINAN/SVS/MS:** Sistema Nacional de Notificação de Agravos/Secretaria de Vigilância à Saúde/Ministério da Saúde.



of the country. A hepatitis B intermediate to high endemicity condition was observed in West States of Paraná and Santa Catarina in the 1990s. Since then, many studies have been conducted, and the states and regional health authorities have worked to identify risk groups and increase vaccine coverage. More recent studies from the Southern regions have reported prevalence rates lower than previously observed, with the exception of pregnant women in Francisco Beltrão<sup>(107)</sup>. These findings suggest successful vaccination coverage in this region<sup>(26) (82) (83) (85)</sup>.

Second, data from northeast Brazil remain relatively scarce, perhaps because hepatitis B has never been a major problem in this region compared to the Northern and Southern states. However, there may be locations in the interior that require a better approach, as observed by Almeida et al.<sup>(34)</sup> in the semi-arid region of Bahia during the 1990s<sup>(34)</sup>.

At-risk groups were not addressed in this review because they are a significant minority of the Brazilian population. However, they are a potential reservoir for dissemination of HBV. Groups such as prisoners, homeless people, drug addicts, people with HIV, and sex workers need specialized approaches to benefit from vaccination and, where appropriate, antiviral therapy.

The data obtained in the SINAN are unreliable as a historical series, as there is no separation between acute and chronic cases, making it impossible to determine when the infection occurred. As a result, the data do not represent incidence rates of new cases. Furthermore, recent infections are added to previous infections that were only recently detected. In addition, the increase in the number of notifications appears to correspond to improvements in the epidemiological surveillance system and notifications for communicable diseases in Brazil. Despite improved socioeconomic conditions and hygiene in a large part of the country, notifications have increased, generating the false impression that the prevalence of many infectious diseases is increasing in Brazil. The same phenomenon has also been observed in hepatitis A. Although analysis of the raw numbers of notifications does not suggest imminent control of hepatitis B in Brazil, the positive trend of decreased or stabilized prevalence among children under 20 years of age indicates the positive effects of vaccination.

Although fewer in number than studies on the prevalence of HBV infection, studies reporting the prevalence of anti-HBs antibodies alone indicate that the levels of coverage offered by vaccination are comparable to those in countries with high vaccine coverage<sup>(5) (8)</sup>. Similar to reports of reduced HBV incidence and prevalence in these countries, Brazil should detect a similar downward trend in the next decade. It is, however, worrying that vaccine coverage was insufficient in remote communities of the Amazon Region and in the Northeast. Efforts must be made to increase vaccination coverage in these localities. In a remote Amazonian community of the State of Mato Grosso, efforts to increase vaccination coverage resulted in reduced prevalence from the high levels previously reported<sup>(17) (42)</sup>.

In short, a systematic literature review of 100 studies on hepatitis B prevalence, incidence, and vaccine coverage suggest that Brazil is progressing toward low endemicity, with specific

foci of increased fragility, mainly in the interior of the Amazon region and among remote small communities. The National Survey of the last decade captured the declining trend in major urban regions of the country<sup>(20)</sup>. This review also observed decreasing prevalence in Brazil's innermost part. However, the situation is far from safe. On the contrary, this review underscores the need for increased efforts to control HBV in these specific communities and populations.

## CONFLICT OF INTEREST

The author declare that there is no conflict of interest.

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