Review Article

Global epidemiology of occult HBV infection

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Abstract: Defining the epidemiology of occult HBV infection (OBI) is difficult because it relies on disparate sets of data and on the respective performance of both hepatitis B surface antigen (HBsAg) and HBV DNA detection and quantification. Higher sensitivity of HBsAg decreases OBI prevalence while increased HBV DNA detection increases such prevalence as two sliding indexes. In addition there is, at best, poor correlation in the levels of these two parameters. The prevalence of OBI in a general population depends on the prevalence of the infection, being in the 1:100–1,000 in high prevalence areas (East Asia and West Africa) but below 1:5,000 in Western Europe, North America and Australasia. As a percentage of overall infection OBI remains small ranging between 0.1% and 0.6%. Many studies selected individuals with anti-HBc as only serologic marker of HBV infection providing a biased view of the epidemiology since a larger number of cases are seen in anti-HBs positive individuals. The prevalence of OBI is higher in males than in females and also varies according to genotype, being particularly high for genotype D and E. It is typically identified in people ≥50 years, decades post-infection but at a younger age in sub-Saharan Africa. OBI prevalence is elevated in chronic liver disease (CLD), percentages ranging between 40% and 75% in HBsAg negative hepatocellular carcinoma (HCC). Immunodeficiency whether acquired or induced triggers OBI as a minor expression of HBV reactivation in anti-HBc carriers. As methods of HBV DNA detection increase in sensitivity, more OBI will be identified but the clinical significance of these extremely low levels of viral genome remains to be determined. In the meantime, proper epidemiologic, unbiased, studies should be conducted in general populations, particularly where the infection prevalence is high.

Keywords: HBV; occult HBV infection (OBI); epidemiology

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Introduction

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The detection of HBV DNA in patients with chronic liver disease (CLD) negative for hepatitis B surface antigen (HBsAg) was first noticed in 1985 (1). Until the mid-1990s, this observation remained controversial with nearly equal number of studies reproducing or not the initial discovery (2). Such discrepancies were attributed to differences in epidemiology and performance of the now archaic methods utilized for HBV DNA detection. Nevertheless, the concept of occult HBV infection (OBI) progressively rooted and triggered a large number of studies confirming the reality and scientific importance of this new feature of this 'old' viral infection. In 2008, an international workshop was convened in Taormina, Italy, where a group of specialists led by G Raimondo defined OBI as: the presence of HBV DNA in the liver (with detectable or undetectable HBV DNA in the serum) of individuals testing HBsAg negative by currently available assays (3). It added that the amount of HBV DNA in the serum is usually very low (<200 IU/mL). As a result, the definition clearly indicated that the diagnosis of OBI was closely dependent on the performance of the key assays: HBsAg and HBV DNA. In the past 15 years, the sensitivity of both assays has progressively increased, decreasing the number of OBI with

Table 1 Limit of detection (LOD) of assays for HBsAg and HBV DNA

HBsAg	LOD IU/mL	HBV NAT	95% LOD in individual samples
PRISM ×12	0.03	Ultrio ×24	13
Murex ×4	0.03	Ultrio Plus ×2	3–4
AxSYM ×7	0.1	Cobas Ampliscreen ×6	3.4–5
Architect ×2	0.03	Roche MPX ×6	4–6.7
BioRad ×2	0.1	Artus ×2	3.8–50
BioMerieux ×6	0.1	In-house 1	20
Wantai ×2	2	In-house 2	<6
Kehua	0.2	In-house 3	20
Huakang	0.2	In-house 4	20
Xiamen	0.1	In-house 5	5
Dade	0.1	In-house 6	20

The number following the × sign indicates the number of studies utilizing each particular assay. NAT, nucleic acid testing

increased sensitivity of HBsAg assays and increasing this number with increased sensitivity of HBV DNA assays.

Performance of HBsAg assays

Since the first assays available in 1970, HBsAg testing has been steadily improving until enzyme immunoassays utilizing monoclonal antibodies reached in 2002 a sensitivity of 0.13–0.62 ng/mL for licensed assays and 0.07–0.12 ng/mL for three investigational assays since released for use by FDA (4). In 2006, a comparative evaluation of 17 HBsAg CE marked assays indicated 0.018 to 0.1 IU/mL sensitivity range for serotype AD and 0.012–0.11 IU/mL for AY (5). *Table 1* summarizes the performance of current HBsAg assays utilized in articles reporting on OBI. Since then, several assays with higher sensitivity were developed and clinically evaluated that used chemiluminescence enzyme immunoassay (CLEIA) or chemiluminescence immunoassay (CLIA) (6-8). The limit of detection (LOD) reached 0.025 ng/mL compared to 0.2 ng/mL for CLIA. A modified CLEIA claimed to reach a sensitivity of 0.005 IU/mL (9). These improved assays were developed for two main purposes: improve the detection of the early infection window period (4,8) and monitor antiviral treatment (7,9,10). The latest assays claim to be able to replace HBV DNA detection in monitoring treated patients. However none of these assays specifically compared HBsAg and DNA in the circumstances of OBI. As shown below, the hope of LOD similar to HBV DNA was defeated by the very nature of OBI.

In a range of circumstances, the major hydrophobic region (MHR) of the HBV surface protein can be mutated with amino acid changes potentially affecting detection with HBsAg assays. This situation is particularly frequent in OBI of genotype A2-D, less so in genotypes A1 and E (11). In addition to sensitivity, ability to detect variants is critical for the diagnosis of OBI. It is recommended to retest HBV DNA positive samples, anti-HBc positive with an alternative sensitive HBsAg assay that may more effectively detect particular HBsAg variants.

Performance of HBV nucleic acid testing (NAT)

The detection of HBV DNA was clearly key to the identification of OBI and commercial assays with increased sensitivity became recently available (12). The LOD of assays reported in articles on OBI are shown in *Table 1*. The impact of sensitivity was particularly illustrated in a study conducted in Hong Kong comparing two commercial assays (Ultrio and Ultrio Plus, Grifols) from the same manufacturer with LOD of 13 and 3 IU/mL, respectively (13). The yield of both OBI and window period cases doubled with the more sensitive assay applied to random blood donor samples. In general, assays enabling to quantify HBV DNA are derived from the detection assays but the dynamic range of quantification is higher than the 3–5 IU/mL LOD so that a significant proportion of positive HBV DNA samples are below the limit of quantification (LOQ). Since then, a new real-time PCR based assay was developed by Roche (Cobas CTX) with a claimed 95% LOD of 1.6 IU/mL or 7.4 copies/mL and LOD 50% of 0.3 IU/mL or 1.6 copies/mL. Such sensitivity should considerably increase OBI detection but at the same time make the assay highly susceptible to contamination (14). Irrespective of this issue, all reactive results with any HBV NAT need to be confirmed with an alternative assay of similar sensitivity. Short of an alternative test with sensitivity matching the screening method, 5–10 repeats of the screening assay on the same or an alternative sample has been advocated (15) arguing of the Poisson distribution of HBV DNA template in OBI samples. There are algorithms allowing to transform the number of repeat reactive into viral load at very low concentration (16). In

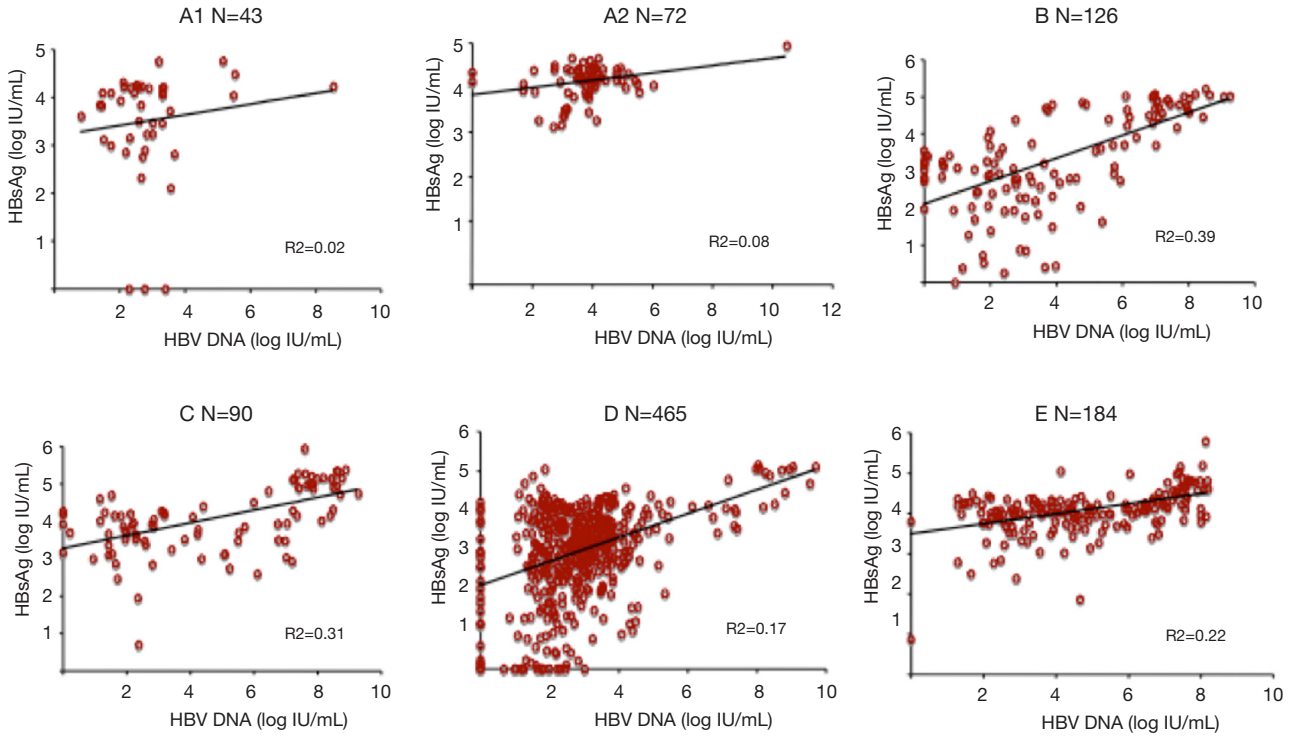

Figure 1 Correlation between HBsAg and HBV DNA in IU/mL in individuals infected with different genotypes. Correlation between the two markers is very poor irrespective of genotype but particularly in genotype D. In each genotype graph, some samples contain high HBsAg level without detectable HBV DNA. In others, relatively high viremia coexists with very low HBsAg levels.

addition, HBV serology can be helpful, particularly in excluding samples without anti-HBc or anti-HBs as likely false positive (17). This strategy has its own limitations since several studies have identified OBIs in anti-HBs only or serologically negative samples. Ultimately, follow-up of individuals with uncertain diagnosis of HBV DNA yield cases can differentiate between window period and OBI, although fluctuating levels of OBI HBV DNA between low positive and undetectable is frequently encountered (18). In several studies targeting HBV DNA+/HBsAg– blood donors, follow-up testing for HBV markers showed that 20–80% of OBI cases (mean 50%) remained HBV DNA positive 1–3 months after the index sample was collected (17-22).

Relation between HBsAg and HBV DNA levels

During the window period, two studies showed clearly the correlation between HBsAg and viremia (4,23). They also showed that below 300 IU/mL of HBV DNA, HBsAg was no longer detectable when tested with an assay with LOD 0.1 IU/mL. In this case, it appears that most of the detected HBsAg corresponds to full, infectious, complete virus Dane particles. In contrast, after chronic infection is established, there seem to be a switch in infected cells, enhancing S protein production in large but variable excess found in circulation as free or aggregated protein together with lipids forming pseudo-particles. These pseudo-particles are the majority of what is detected as HBsAg. As reported in several articles and shown in *Figure 1*, months post-infection, there is a poor correlation between HBsAg and HBV DNA that are both quantified in IU/mL against their respective international standard (24-28). Irrespective of genotype, but particularly frequent in genotype D, a substantial proportion of HBsAg positive samples (3–15%) carry no detectable HBV DNA. However, when increasing the NAT sensitivity, more of these samples are DNA positive, suggesting that the discrepancy is mostly related to assay sensitivity (14,29). In cases of OBI, among other mechanisms, specific amino acid substitutions in the S protein prevent the export of HBsAg explaining the lack of detection of HBsAg in circulation (30).

Further difficulties in assessing the viral load and determining the level of infectious virions is related to the co-circulation of spliced and unspliced (complete) HBV genomes in Dane particles (31). Spliced genomes are non-infectious but the percentages of these modified genomes vary according to individual, time in the infection course and genotype.

Prevalence of OBI in several populations (*Table 2*)

Prevalence studies have been conducted, often partially, in three types of populations: general population, hospital population and blood donors. Hospital populations are assumed to be biased towards higher prevalence of liver diseases, therefore of HBV infection. They are made of random samples coming to hospital laboratories. Blood donor populations are also biased because a variable percentage of samples come from repeat donors who have already been tested for HBV markers, lowering prevalence. Volunteer donors are also biased as they are often young adults and in many countries are 70–95% males. Only one study indicated testing first-time donors with gender distribution close to equivalent (45). In addition, the majority of the reported studies concentrated on samples carrying anti-HBc as only marker of HBV infection. The few studies testing for HBV DNA in all anti-HBc positive samples or in all samples carrying an HBV serological marker can be taken as a base to calculate OBI prevalence although some OBI are anti-HBc negative (anti-HBs only or primary OBI without serological markers). Finally, over time, and according to assays utilized, the NAT sensitivity varies considerably adding difficulties in comparing data sets.

Only three studies reporting on OBI prevalence in general populations have been published (32-34). A single study tested all 1,091 samples from random check-up seekers for HBsAg, anti-HBc, anti-HBs and HBV DNA. However HBV NAT was tested with Cobas MPX in pools of six samples reducing the clinical sensitivity to 18–24 IU/mL and therefore the detection of potential OBI (33). The distribution of markers was HBsAg+ 2%, anti-HBs+/anti-HBc+ 33.4%, anti-HBc only 2%, anti-HBs only 42% and no serological marker 18.6%. From these five categories, HBV DNA was detected in 7 samples (0.6%), 2 anti-HBc+/anti-HBs+, 4 anti-HBs only (presumably HBV vaccinated) and 1 negative for all markers. This unique observation draws serious doubts on the significance of the many studies conducted in anti-HBc or anti-HBc-only positive samples to assess the prevalence of OBI. Such was the case in the other two studies of populations that could be considered representative of Germans and Koreans, respectively where only samples presenting with the anti-HBc-only profile were tested for HBV DNA with assay LOD of 20 and 4–12 IU/mL, respectively. OBI with anti-HBs+/anti-HBc+ or anti-HBs-only or no HBV markers profiles were not included decreasing the true OBI prevalence by a factor of at least 2. Prevalence of OBI extrapolated to the total starting populations of 5,305 and 14,253 was 0.1% and 0.2%, respectively. Therefore the true prevalence of OBI is far from being reliably known. Such prevalence is assumed to increase with infection prevalence and possibly according to genotype but there is no evidence of either. Multiple studies have been conducted in various populations in which anti-HBc-only samples have been selected for HBV DNA testing. Among those samples, selected from biased hospital patients or laboratory populations, the percentage of HBV DNA positive samples ranges between 2.3% and 20.8%. The lowest was observed with a LOD of 350 IU/mL, the highest with an assay that did not confirm in 16/37 DNA positive samples, reducing the prevalence from 20.8% to 11.8%.

In ten studies (33,39,42,44-49) testing all anti-HBc positive/HBsAg negative samples for HBV DNA (sensitivity ranging between 4 and 230 IU/mL but 4/10 did not provide LOD), the prevalence of OBI ranged between 0.25% and 0.8% of total population (*Table 2*). No HBV DNA was found in a large UK study (39) but the sensitivity of the assay in 1998 was too low to detect OBI (median viral load 20 IU/mL). The low prevalence in the study by Seo contrasts with the Song data, which are clearly more representative of the general population of Korea (33,49). The high prevalence in Banerjee's study (4.9%) might be biased by other unknown factors (46) when compared to another Indian study (*Table 2*) (48). The higher prevalence of OBI in Ghana is likely related to one of the highest anti-HBc prevalence in the world (76% in adult blood donors) and chronic HBV infection (15% HBsAg positive) (42).

OBI prevalence in 16 studies of samples carrying anti-HBc as unique marker of HBV ranges between 0 (2 studies) and >20% (4 reports). Studies from India and Pakistan indicate an average of 20.6% OBI in anti-HBc-only blood donor samples in areas where anti-HBc prevalence is approximately 20% (46-48). In six studies of OBI in samples carrying both anti-HBc and anti-HBs, the prevalence of OBI ranged between 0.07% and 17.8%. Here again studies by Seo and Banerjee appear exceptions, the others averaging

Table 2 Prevalence of OBI in general or blood donor populations tested for HBV markers

Author	Country	Year	Sample type	Number tested (%)	HBV DNA+/number tested (%)					LOD (IU/mL)
					Whole population	Anti-HBc+ total	Anti-HBc+ Anti-HBs+	Anti-HBs only	Anti-HBc only	
Jilg (32)	Germany	2001	General pop	5,305						
			Anti-HBc	544 (10.3)					5/81 (6.2)	20
Song (33)	South Korea	2009	General pop	1,091						
			Anti-HBc	364 (33.4)	7 (0.6)		2/364 (0.5)	4/458 (0.9)	0/22 (0)	18-24
Kang (34)	South Korea	2014	General pop	14,253						
			Anti-HBc	846 (5.9)					27/571 (4.7)	4–12
Knöll (35)	Germany	2006	Hospital pop						44/545 (8.1)	NA
Vitale (36)	Italy	2008	Hospital pop	6,544					5/85 (5.9)	20
Launay (37)	France	2011	Hospital pop						8/349 (2.3)	350
Hui (38)	Hong Kong	2005	HSC donors	124	19 (15.3)	94 (17.0)		3/30 (10.0)		2
Allain (39)	UK	1999	Bd	103,869	0 (0)					~260
				584 (0.6)		0/584			0/69 (0)	
Chaudhuri (40)	India	2003	Bd	6,159					48/230 (20.9)	20
			Bd	3,304					40/147 (27.2)	
Kleinman (41)	USA	2003	Anti-HBc	3,350					4/387 (1.0)	10
Allain (42)	Ghana	2003	Bd	576	22 (3.8)					15–50
García-Montalvo (43)	Mexico	2005	Bd	11,240						
			Anti-HBc	475 (4.2)					13/158 (8.2)	6–60
Behzad (44)	Iran	2006	Bd	2,000	16 (0.8)					
			Anti-HBc	131 (6.6)		16 (12.2)	6/85 (7.0)		10/46 (21.7)	NA
Manzini (45)	Italy	2007	1st time bd	6,313	16 (0.25)	16 (0.25)			0/39 (0)	4.9
Banerjee (46)	India	2007	Bd	1,294	63 (4.9)					NA
			Anti-HBc	303 (23.4)		60/289 (20.8)	21/118 (17.8)		39/171 (22.8)	
Bhatti (47)	Pakistan	2007	Bd	966	4 (0.4)					10
			Anti-HBc	190 (19.7)		4/185 (2.2)	1/162 (1.2)		3/23 (13.0)	
Asim (48)	India	2010	Bd	2,175	31 (1.4)					NA
			Anti-HBc	413 (19.0)		31 (7.5)	12/260 (4.6)		19/153 (12.4)	
Seo (49)	South Korea	2011	Bd	12,461	2 (0.02)					
			Anti-HBc	1,674 (13.4)		2 (0.12)	1/1522 (0.07)		1/152 (0.7)	3.7
Mahgoub (50)	Sudan	2011	Anti-HBc	145		4 (4.1)	6/81 (7.4)		0/64 (0)	10
Muselmani (51)	Syria	2013	Bd	1,939	5 (0.26)					NA
			Anti-HBc	215 (11.1)		5 (2.3)				
Apica (52)	Uganda	2016	ER Popul	314	90 (30)					NA
Sondlane (53)	RS Africa	2016	HCW	333	21 (6.7)					NA
Sosa-Jurado (54)	Mexico	2016	Bd	156		27 (17.3)				NA
Alshayea (55)	Saudi Arabia	2016	Bd	198		17 (8.6)				NA
Hudu (56)	Malaysia	2016	Bd	1,000	55 (5.5)					NA
Blanco (57)	Argentina	2017	Bd	168,215	3 (0.002)					2.3–3.8

Data are from HBsAg negative samples. It is assumed that the vast majority of OBIs is anti-HBc positive and can be equated to true prevalence. However, as shown in the Song study, anti-HBs only sample can be HBV DNA positive. Bd, blood donor; HCW, health care workers; Pop, population; LOD, limit of detection; HSC, hematopoietic stem cell; OBI; occult HBV infection; NA, not available.

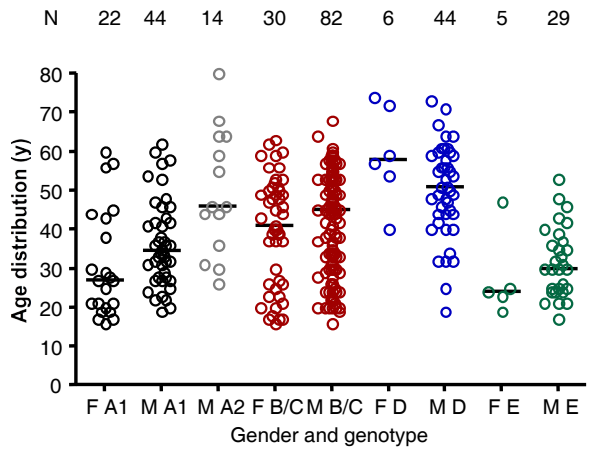

Figure 2 Distribution of age and gender in 276 OBI cases from areas where genotype A1-E are prevalent. Data of Genotype A1 are from South African blood donors. Data on genotype A2 are from Germany, Italy, Spain and Poland (42). Data on genotype B/C are from China, Hong Kong, Malaysia, Singapore and Taiwan (44). Data on genotype D are from Italy, Poland and Spain (42). Data on genotype E are from Ghana (32,46). F is for female, M for male.

at 4% (46,49). This data is in line with approximately 50% of OBIs in the northern hemisphere carrying anti-HBs and anti-HBc, the other 50% anti-HBc only. Recent studies conducted in Uganda and South Africa indicated very high prevalence of OBI in emergency patients and health care workers (30% and 6.7%, respectively (52,53).

Age and gender of OBI carriers

In the many reports on OBI, age and gender of individuals carrying the infection is not often given. When the information is provided, it is biased by the generally higher prevalence of HBV infection in men. In blood donor populations, particularly in developing countries with high prevalence of infection, males are by far predominant over female donors making calculation of prevalence according to gender difficult by lack of denominator. However blood donors in developed countries are most often with a male/female ratio close to 1 allowing a comparison of OBI prevalence according to gender. *Figure 2* shows the distribution of OBI cases in blood donors from our group data reinforced with published data from the literature covering a total of 276 OBI cases from areas where genotype A1–E are prevalent. In areas of dominance of genotype A2 (Europe), B/C (South East Asia) and D (Mediterranean basin), median age, irrespective of gender, ranges between 45 and 55 years (17,18,58). In contrast, in South Africa where genotype A1 is dominant or in Ghana where genotype E is dominant, age of OBI carriers is considerably younger with a median around 30 years, irrespective of gender (59,60). It is not known whether this difference is related to genotype or to a less effective immune system of Africans. The duration span of the HBV infection acquired vertically or in early childhood is ranging between 15 and 60 years for African blood donors but a similar range is present in South East Asia where infection is mostly vertical mode. In Europe where many HBV infections occur later (older than 15 years) with IV drug use or sexually, it may take up to an older age to develop OBI.

Figure 2 also shows that in areas where gender ratio in blood donors is approximately 1, 67% of OBI are males in South Africa (genotype A1), 100% males in Western Europe (on a small number of cases), 62% in South East Asia (genotype B/C) and 88% in Italy, Spain, Poland (genotype D). This difference might be related to the generally more efficient anti-viral activity of the female immune system but this hypothesis would require further studies to be supported by firm evidence.

Identification of OBI in patients with CLD

OBI was first described in patients with CLD in 1985 and subsequently in patients with hepatocellular carcinoma (HCC). OBI in HCC literature is divided into two groups: without co-infection with hepatitis C virus (HCV) and with co-infection. Studies of patients with HCC negative for anti-HCV and HBsAg published since 2000 are shown in *Table 3*. The prevalence of HBV DNA ranges between 40.5% in Taiwan (90% genotype B) and 76.2% in Egypt (100% genotype D). Three of the studies tested for HBV DNA in liver tissue (prevalence 67.6–76.2%) and the other five studies in serum (47.6–75.4%). It is difficult to determine whether the difference in prevalence suggesting higher frequency of OBI when examining liver tissue is related to true increased prevalence or to increased sensitivity of assays over time. In few studies where a control population was included, the difference in prevalence was highly significant (P<0.001). In anti-HCV positive HCC, the prevalence of OBI ranges between 22% and 73.3% in studies conducted between 2002 and 2011 (69). The lower prevalence found in HCC negative for anti-HCV suggests an etiologic role of both viruses. The potential impact of

Table 3 Prevalence of HBV DNA in HCC negative for HBsAg

Study	Year	Country	Number of patients	Dominant genotype	Percentage of OBI (%)	Percentage OBI in controls (%)	P value
Yotsuyanagi (61)	2000	Japan	42	C	47.6	2.4	<0.001
Shiota (62)	2000	Japan	26	C	69.2		
Hsia (63)	2003	USA/Canada	31	A/C/D	59.4		
Pollicino (64)	2004	Italy	34	D	67.6		
Kew (65)	2008	South Africa	118	A1	75.4		
Fang (66)	2009	China	135	C/B	70.4	10.6	<0.001
Chen (67)	2009	Taiwan	222	B	40.5	8.0	
Wong (68)	2011	Hong Kong	33	B/C	72.7		
Hassan (69)	2011	Egypt	21	D	76.2		

HCC, hepatocellular carcinoma.

OBI in the development of HCC in HCV co-infected patients has been debated. Several studies suggest that the incidence of HCC in co-infected patients is significantly higher than in OBI negative patients (70). However, the likelihood that patients have been HBV infected early in life (at birth or during childhood) and developed chronic LD is very high in both Japanese and Italian incidence studies. HCV infection was most likely acquired at a considerably later date after years or decade of asymptomatic HBV infection in the process of becoming OBI. The question really is: do individuals long-term infected with HBV possibly reaching the status of OBI who became co-infected with HCV are at an increased risk of HCC? So far, no long-term prospective studies have been conducted examining this side of the co-infection coin. However, several epidemiological studies conducted in Europe and Asia provided convincing evidence that OBI associated with either HCV infection or alcoholism-related CLD was a significant risk factor for the development of HCC (71). Such evidence was not confirmed in the USA (72). In addition, there was recent evidence that reactivation of OBI might take place after successful treatment of HCV with direct-acting antiviral drugs (73,74).

In studies comparing different populations of patients with CLD, the prevalence of OBI in HCC was significantly higher than in other types of CLD. Whether examined in areas where genotype A, B, C or D are prevalent, no difference in prevalence was observed (70). Molecular studies of tumor and non-tumor tissue showed that HBV DNA was significantly more found in tumor tissue of OBI HCC and that mutations and deletions in the Pre-S/S region were frequent (75).

OBI and hemodialysis

Relatively high prevalence of HBV infection identified by positivity of HBsAg was described in many cohorts of patients in chronic renal dialysis. It was largely recognized as being nosocomial. The availability of HBV DNA detection prompted many investigators to examine the prevalence of OBI in small and large cohorts of patients. In 24 studies from 11 countries the prevalence of OBI ranged between 0 and 26.6% (median 3%). In countries where multiple large studies were conducted such as in Italy, Turkey, Iran and Brazil, prevalence ranged between 0 and 26.6%, 1.3% and 12.4%, 0 and 3.1%, 1.5% and 15%, respectively. Only in Egypt, an area of moderate HBV infection prevalence, consistent OBI prevalence of approximately 4% was found in two studies. Such prevalence is quite close to what is observed in the general population of each of the countries involved. In the countries with discrepant data, differences in prevalence might be related to levels of infection risk prevention or to assay performance. These data were recently reviewed (76).

OBI and immunodeficiency

HBV remains detectable in the liver of virtually all infected individuals, whether with chronic or recovered infection. It is well known that anti-HBc positive patients receiving

massive drug-induced immunosuppression for organ transplantation (OT) or bone marrow transplantation (BMT) are at high risk of reactivation of HBV replication, endangering patients' lives. In many ways, OBI can be considered as an intermediary stage of the infection to a large extent dependent on the efficacy of the host immune system. In the relatively immunodeficient group of patients with leukemia, the prevalence of OBI was 10.5% compared to 2.9% in non-leukemic patients in China, most of them infected with HBV genotype C (77). Therefore, when immunodeficient either naturally or drug-induced, HBV infected patients were predicted to move from undetectable to detectable DNA without full reactivation indicated by HBsAg and high viral load. This situation explains the interest of hemodialysis centers in OBI detection since many of their patients undergo kidney transplantation and receive immunosuppressive treatment.

OBI and immunodeficiency is an issue for patients with lymphoma, leukemia or other types of cancer because they receive immunosuppressive drugs that might trigger the reactivation of these 'dormant' HBV infections. In such cases, the main factor of reactivation is the drug used. In a study of 127 patients with lymphoma, 32 patients were treated with rituximab and two of them reactivated HBV while none of 16 not receiving the drug reactivated (78). Such post-rituximab reactivation can be delayed for up to a year after discontinuation of the drug (79). In another study (80) of 80 patients with lymphoma, 46 were anti-HBc positive. Twenty-one of them were treated with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) and rituximab with five reactivations but in 25 patients treated with CHOP alone no reactivation was observed. A new assay detecting HBV core antigen has been proposed to detect reactivation in patients with OBI on chemotherapy (81).

In patients who receive OT or BMT or hematopoietic stem cell transplantation (BMT or HSCT), the impact of OBI is seen at the donors level as well at the recipient level that might reactivate their own HBV infection or OBI depending on the drug regiment they receive or the OBI from the donor. For instance, in a study by Hui *et al.* in 2006, in 118 HCV positive patients receiving a liver transplantation, 41 patients carried OBI and 77 were HBV DNA negative. Of 90% received ciclosporin (82) reactivation occurred in 9.8% of OBIs and 1.3% of non-OBI patients. In another study, six BMT recipients were anti-HBc and anti-HBs positive, the four OBI patients reactivated and the two patients HBV DNA negative did not (83). The general conclusion of these studies is that among anti-HBc positive patients treated with immunosuppressive drugs, those carrying OBI are at higher risk of reactivation than those negative for HBV DNA but at lower risk than those with overt HBV infection indicated by detectable HBsAg.

Another situation of immunodeficiency is related to HIV infection that induces progressively increasing deterioration of the host immune system. Sub-Saharan Africa being an area of high prevalence of both HIV and HBV, several studies were conducted in that region. Few of the studies directly compared the prevalence of OBI in HIV infected and non-infected patients carrying anti-HBc as evidence of previous contact with HBV. In two studies where such comparison was made (84,85) the prevalence of OBI in HIV infected patients was significantly higher than in non-infected patients (*Table 4*). In other studies in Africa and other continents, prevalence in anti-HBc positive patients was higher than in non-infected population although not comparatively tested (*Table 4*). As in immunodeficiencies induced by drugs, HIV-1 infection seems to allow individuals who have recovered from HBV infection to move from that status to OBI and in some cases to overt HBV infection HBsAg positive (86). These data are indirect evidence that efficacy of the host immune system is to a large extent determining the status of OBI.

Conclusions

This review of some aspects of the epidemiology of HBV infection expressed as OBI is disappointing since there is a remarkable paucity of studies determining the true prevalence of OBI in representative general populations. Studies provide disparate results related to multiple biases whether in terms of assay performance, subject selection in terms of gender or age or health status (too healthy for blood donors, not enough for hospital populations). Epidemiologically adequate studies remain to be conducted to provide a reliable answer to this critical question.

One interesting question is whether OBI status is a new branch of the natural history of HBV infection in its own right as an intermediate state between recovery and chronicity or is it a secondary turn in the long-term history of HBV infection recovery or asymptomatic chronic infection. Only long-term careful studies of recent infection might provide the answer.

There is presently no evidence that individuals carrying OBI can be infectious vertically, horizontally or sexually.

Table 4 Prevalence of OBI in individuals infected and non-infected with HIV-1 HBsAg negative, anti-HBc positive

Author (year)	Country	HBV DNA positive/total in anti-HBc positive/HBsAg negative (%)		HIV+ no HBV marker
		HIV negative	HIV positive	
Mphahlele, 2006 (84)	South Africa	2/105 (1.9)	31/142 (22.1)	
Bell, 2012 (86)	South Africa		45/181 (24.9)	0/79
Barth, 2011 (87)	South Africa		6/62 (9.7)	
Firnhaber, 2012 (88)	South Africa			12/222 (5.4)
Compston, 2009 (85)	Ghana	2/88 (2.3)	28/238 (11.8)	
Pourkarim, 2011 (89)	Belgium		27/175 (15.4)	
Tramuto, 2013 (90)	Italy	0.25 (Manzini) (45)	14/159 (8.8)	
Morsica, 2009 (91)	Italy		27/175 (15.0)	
Bell, 2012 (86)	The Netherlands		6/187 (3.2)	
Khorvash, 2014 (92)	Iran	0.8 (Behzad) (44)	3/12 (25.0)	
Gupta, 2010 (93)	India	1.4 (Asim) (48)	24/42 (57.1)	
		4.9 (Banerjee) (46)		
Araujo, 2008 (94)	Brazil		6/43 (14.0)	
Oliveira, 2016 (95)	Brazil		19/505 (3.8)	

Authors in parenthesis refer to data presented in Table 3 for comparison.

Only massive exposure to blood products prepared from blood of OBI carrier contains sufficient amount of infectious virions to cause infection. It is however possible that lower infectious doses might be infectious in severely immunodeficient individuals but no evidence was yet provided.

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Footnote

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