Review Article

Occult Hepatitis B infection (OBI) in vaccinated groups, a metanalysis

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Abstract

Nowadays, the presence of HBV DNA in the absence of HBsAg; occult hepatitis B infection; (OBI), is a known clinical entity along with the rapid influx of research being conducted on its clinical relevance. Biologists and clinicians alike have a recent-standing interest in this regards. OBI has been described in several clinical settings. However, the data on its prevalence among immunized and non-immunized healthy general population, in particular, among health care workers (HCWs) is ambigous. This review attemps to explore the significance of OBI in vaccinated groups as a special subject. The prevalence of OBI among general population, vaccinated children/general population and health care workers were: 157 (5.2%), 222 (6.7%) and 33 (1.8%), respectively. The prevalence of anti-HBc among OBI-positive subjects were: 64 (40.7%), 133 (82.7%) and 27 (81.8%), respectively. OBI is partly prevalent in general population and in vaccinated individuals, especially in those who born to HBsAg positive mothers. HBV serological surveys are not enough adequate and sensitive to rule out the presence of HBV DNA. For high-risk groups (subjects born to HBsAg mothers, health care workers, isolated anti-HBc, etc) sensitive molecular tests based on real time PCR should be applied for a proper diagnosis.

Keywords: occult hepatitis B infection, general population, Health care workers, HBV vaccine

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Clinical Relevance

The clinical importance of occult hepatitis B (OBI) has been a matter of debate for the past few years, given its clinical and epidemiological implications. Although OBI has been described in various clinical settings (Fig 1), the clinical significance and associated risks of occult HBV infection may differ in various patient populations. Two studies have explored the distribution of hepatitis B virus (HBV) in the livers of patients with OBI; these studies showed that the percentage of hepatocytes containing HBV DNA and the level of intrahepatic HBV DNA were statistically lower in OBI-infected patients than in chronic HBsAg carriers [1, 2]. However, the molecular mechanism, dynamic fluctuation, and health risk of occult hepatitis cannot be accurately delineated through cross-sectional, case series, or case-control studies. The best approach is a population-based and long-term follow-up study on a randomly selected cohort with repeated measurements of HBV infection markers including serology and HBV DNA.

OBI has been implicated in the transmission of HBV via transfusion of blood and realted products [3]. Other studies have also documented the transmission and development of OBI via organ

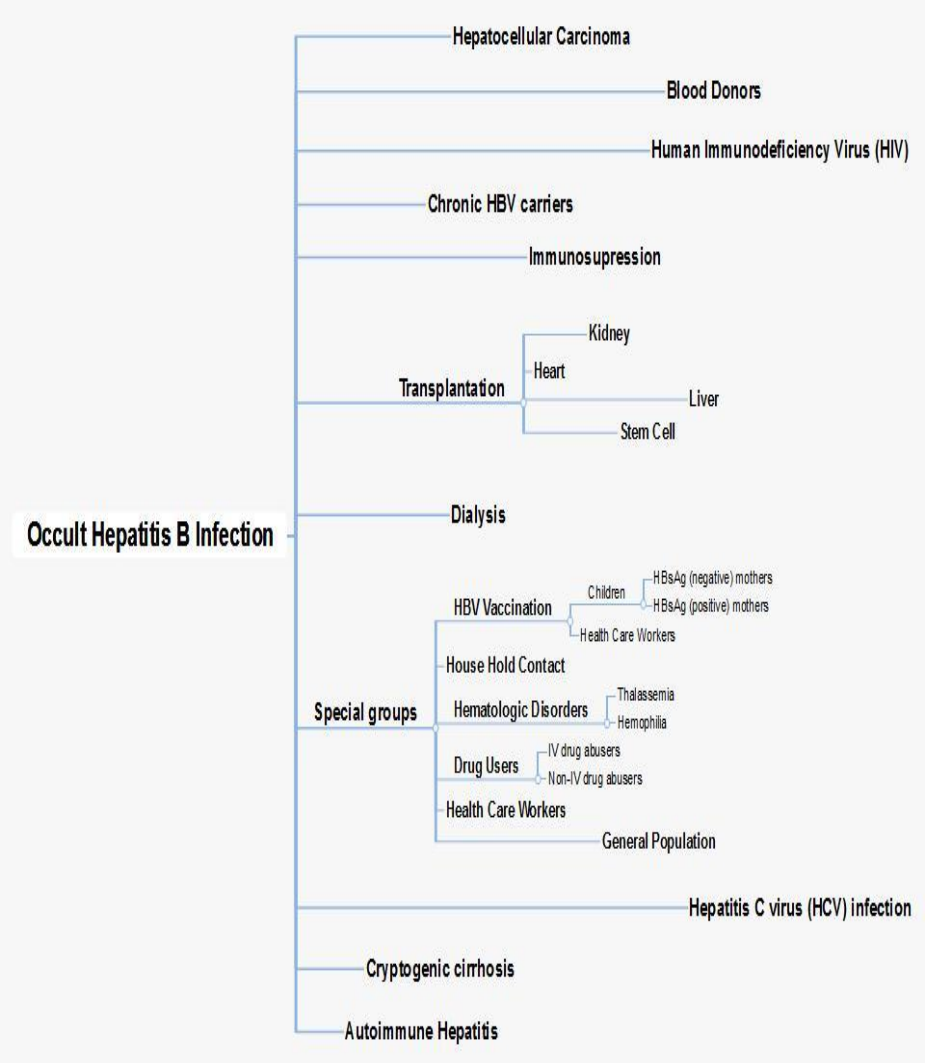

Figure 1. A schematic phylogenetic tree showing the association of occult hepatitis B in different clinical settings. The length of each branch symbolizes the weight of published papers for those settings.

transplantation, from mother to child, and from humans to chimpanzees [4-8]. Finally, occult HBV can be transmitted with few or no signs of ongoing viral replication [5, 9-12].

A major question about occult HBV is whether such small amounts of HBV DNA are associated with progressive liver damage in the individual. In the vast majority of patients with OBI infection, however, a low threshold level of HBV DNA (<1,000 copies/mL) may not be sufficient to cause progressive liver disease in immunocompetent chronic HCV patients, as demonstrated in previous studies [13].

The literature has discussed OBI in diverse clinical settings (Fig 1). However, no study has been focused on the reported prevalence of OBI among health care workers and immunized as well as nonimmunized general population yet. The aim of this review was to explore the details of diagnosed OBI in these special groups.

Evidence Acquisition

A comprehensive electronic literature search using Pubmed was carried out by following medical subject headings (MeSH) and combination of free text words: occult hepatitis B infection along with keywords: general population, health care workers and vaccinated subjects. The inclusion of health care workers in this category was due to the fact that this group of people is a part of general population (and not patients) who involved in health care settings. Also, recent published data globally indicated that a majority of HCWs have been received at least a single dose of vaccine prior or after they engagement

Table 1: Details of occult hepatitis B infection prevalence among general population.
Note *: prevalence of anti-HBc in OBI-positive cases.

No	Author	Country	Number of Samples	Number (%) of OBI positive cases	Number (%) of Anti-HBc positive*	Mutational study results
1	Fang/2009 [14]	China	359	38 (10.6)	14 (33.3)	-
2	Kim/2007 [15]	Korea	195	31 (16)	16 (51.6)	-
3	Minuk/2012 [19]	Canada	706	9 (1.3)	2 (22)	-
4	Minuk/2005 [17]	Canada	487 I-seronegative:407 II-seropositive:80	47 (9.6) I:33 (8) II: 14 (18)	14 (29.7)	I:12 (86%) II:17 (52%) contained surface protein mutations
5	Song/2009 [50]	Korea	1047	7 (0.7)	2 (28.5)	Three cases contained mutation within and outside of "a" determinant.
6	Hwang/2010 [20]	USA	118	9 (7.6)	6 (66.6)	-
7	Raimondo/2008 [18]	Italy	98	16 (16.3)	10 (62.5)	-
	Total		**3010**	**157 (5.2)**	**64 (40.7)**	-

in health care settings. All published data since 2001 (the explanation of OBI) until April 2014 have been included in the study. The inclusion criteria for the study were: all studies showing the presence of HBV DNA in the absence of HBsAg regardless of antibodies to core and/or surface proteins.

General population

The OBI prevalence for healthy individuals who were tested negative for HBsAg and positive or negative for either anti-HBs or anti-HBc or both ranges from 0.7% to 18% (Table 1), whereas the prevalence of previous HBV exposure in these populations has been found to range between 6.1 and 51% [14-18]. The prevalence of anti-HBc positivity in OBI cases in general population-studied was between 22% and 66.6% as a whole (Table 1).

Minuk et al investigated the prevalence of OBI in two publications from Canada. In the first study, 487 samples were collected from Eskimo community. They classified into two groups: 80 and 407 for HBV serologic markers positive and negative, respectively. The prevalence of OBI was 18% and 8%, respectively. Moreover, 86% and 52% were contained surface protein mutations, respectively[17]. In the second study, 706 HBsAg-negative sera were collected from three Northern Canadian communities with known HBsAg prevalence of 11–12%. The rate of OBI was 1.3% [19]. Both of these studies have

Table 2: Reported prevalence of OBI obtained from blood specimens collected from vaccinated individuals. Note *: prevalence of anti-HBc in OBI-positive cases.

No	Author	Country	No Samples	Number (%) of OBI positive cases	Number (%) of Anti-HBc positive*	Study Subjects	Mutational study results
1	Mu/2009 [24]	Taiwan	46	5 (10.9)	None	Normal children	C139S vaccine escape mutant and variation and deletion were found in pre-S1.
2	Meschi/2010 [22]	Tanzania	282	1(0.35)	1 (100)	Normal children	-
3	Utsumi/2010 [23]	Indonesia	229	5 (2.1)	4 (80)	Normal children	All contained mutations in S and or Pre-S proteins.
4	Xu/2010 [25]	China	2218	81 (2.7)	81 (100)	Gen population Anti-c and anti-s positive	Various mutations within "a" determinant. 3 contained G145R.
5	Shahmoradi/2012 [27]	Iran	75	21 (28)	5 (23.8)	Children born to HBsAg positive mothers	13 infected children (62%) had at least one mutation. 10 had G145R mutations.
6	Chakvetadze/2011 [26]	France (Africans)	100	2 (2)	1 (50)	Children born to HBsAg positive mothers	-
7	Pande/2013 [28]	India	213	89 (42)	NI	Children born to HBsAg positive mothers	-
8	Pereira/2006 [30]	Brazil	I: 100 II: 50	I: 6 (6%) II: 12 (24%)	18 (100)	I:Blood donors II: HCV positive	-
	Total		**3313**	**222 (6.7)**	**133 (82.7)**		

NI, not identified.

been carried out in Northern region of Canada, especially amongst either Eskimo or Northwest Territories, known for high endemicity for HBV infection.

Raimondo et al found a massive prevalence (16.3%) of OBI in 98 patients who admitted to the hospital for abdominal surgery (non-liver disease complaints). In details, 10 out of these 16 patients were anti-HBc positive. Despite authors claimed that almost 6.1 of the Italian general population might be carriers of occult HBV infection, however, the relative small number of cases in Raimondo's study prevents to draw a net conclusion and it must surely be simplistic to extend this finding to general population.

Hwang et al. found a prevalence of 7.6% of OBI amongst 118 Asian-American general population from the USA [20]. The prevalence of positive HBV

Table 3: Reported prevalence of OBI from health care workers.

No	Author	Country	No Samples	Number (%) of OBI positive cases	Number (%) of Anti-HBc positive*	Vaccination status
1	Borzooie/unpublished	Iran	122	4 (3.3%)	0 (0)	Vaccinated Non-Responders
2	Chiarakul /2011(35)	Thailand	36	4 (11%)	4 (100)	Non- Responders
3	Slusarczyk /2012(37)	Poland	961	6 (4%)	4 (100)	vaccinated
4	Shim/2011(36)	Korea	334	0%	0	Responders /non- Responders
5	Sukriti/2008(34)	India	120	6 (5%)	6 (100)	Responders
6	Yen/2005(33)	Taiwan	250	13 (6.4%)**	13 (100)	Non Responders
	Total		**1823**	**33 (1.8)**	**27 (81.8)**	

Note *: prevalence of anti-HBc in OBI-positive cases. **: 16/23 samples were available for HBV DNA testing

markers; as overt HBV infection, was 10.2% among patients-studied. There are numerous reports coming up from the USA regarding a high prevalence of HBV serologic markers in Asian-American who already migrated to the USA.

An interesting study from Korea, apreviously-known region with high prevalence for HBsAg carriers reported that the rate of OBI was 0.7% (7 out of 1047) (Table 1). The mean age of participants was not mentioned in this paper; however, 1000 out of 1047 population were ≥30 years old, born long before the commencement of HBV immunization in Korea in 1983. Sequencing of HBV *S* gene in three cases revealed one wild-type and two mutant strains. Similarly, An et al. from Korea reported a low prevalence of OBI between vaccinated children (0.9%). On the other hand, previous studies from the same area reported prevalence of 11.4 [21] to 16% [15] using more sensitive techniques. The age differences could be the reason for these wide gaps between different prevalence of OBI.Specifically, it can be related to the vaccine coverage rate started in 1983 in Korea which lowered the endimicity of HBV infection as a whole. Collectively, among 3010 population-studied, 157 (5.2%) were positive for OBI of whom 64 (40.7%) were anti-HBc positive (Figure 2).

HBV-vaccinated Individuals

Of nine studies undertaken for OBI in vaccinated individual, three were carried out on normal children who received the vaccine according to standard protocols. The prevalence of OBI among these populations was ranged between 0.35% and 10.9% [22-24] (Table 2). Another study carried out on vaccinated general population with a mean age of 19-21 years who were positive for both anti-HBs and anti-HBc, showed 2.7% OBI frequency [25]. 124.16 anti-HBc and anti-HBs positive cases were born from HBsAg positive mothers. This investigation was included the adults who had been vaccinated during 1980s-1990s. Only 9.8% showed mutations at the "a" epitope and three of them were G145A. The other class of studies was undertaken on high risk communities who were born to HBsAg positive

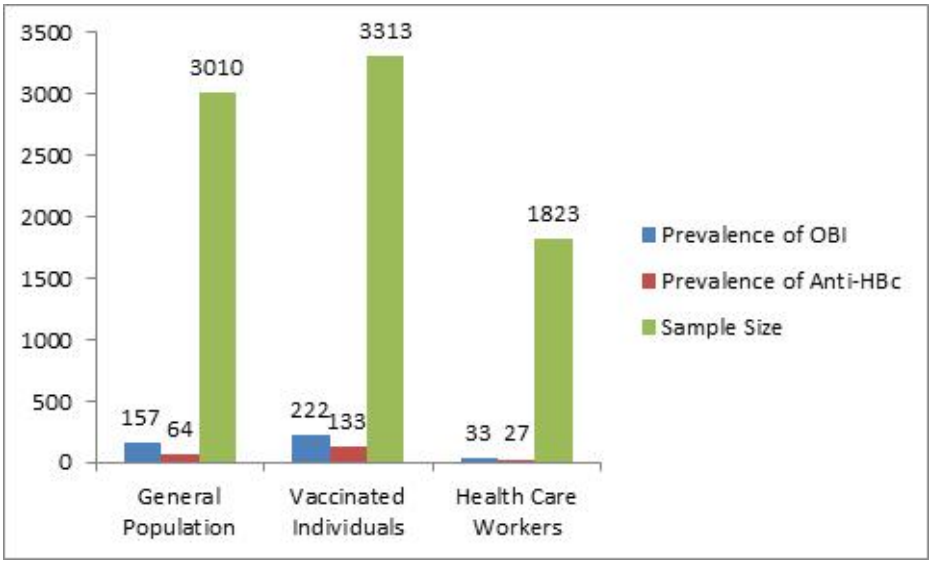

Figure 1. A diagram showing the percentages of positive HBV occult infection and the frequency of positive anti-HBc between OBI positive cases in the selected studies. The light green columns show the number of samples, blue columns indicate the number of OBI-positive cases and red columns show the number of positive cases between OBI patients.

mothers. The frequency of OBI was between 2% and 42% [26-28]. In a majority of these studies, vaccine failure was observed due to occult HBV infection despite the presence of adequate levels of anti-HBs (Table 2). In a study from Taiwan, of 46 vaccinated children, 5 (10.9%) were found to have OBI [24]. Another study from Iran, indicated the presence of HBV DNA in 21 of 75 (28%) children borrn to HBsAg-positive mothers who had already been immunized with an HBIG and vaccine prophylaxis regimen [29]. All OBI-infected children were anti-HBs positive with protection titers (>10IU/mL). In both studies, multiple-point mutations (including *a*-determinant vaccine escape mutants) and deletions were found in different parts of the HBV genome in OBI-positive individuals. In a similar study from India, Pande et al. found that 142 out of 222 (64%) of babies born to HBsAg positive mothers acquired OBI at the end of primary end point of the study (week 18th after birth). At month 24, 89 (42%) were OBI-positive. Authors were found that the anti-HBs status at 18 weeks of babies who acquired OBI was an important indicator for subsequent outcomes. Also, 85% of babies had adequate anti-HBs titers at 18 weeks, while 15% had inadequate anti-HBs titres. From the former group, 36% lost their infection, while from the latter group, only 15% lost their infection ($P < 0.05$). These two latter studies which showed a massive prevalence of OBI (28% and 42%, respectively) among children born to HBsAg positive mothers despite immunoprophylaxis with vaccine and HBIG, underscore the importance of OBI as a clinical entity in these high-risk group individuals.

In a study by Pereira et al. 100 blood donors and 50 anti-HCV positive individuals who were positive for anti-HBc only found to be positive for OBI; 6 (6%) and 12 (24%), respectively. 22 HCV-positive patients and all blood donors received three doses of HBV vaccine. All (100%) and 12.9 (75%) of OBI-positive became HBV DNA negative after few months post-diagnosis, respectively [30].

Altogether, of total 3313 subjects-studied, 222 (6.7%) were OBI-positive of whom 133 (60%) were positive for anti-HBc (Figure 2).

Health Care workers

Health care workers are at the front line for acquisition of blood-borne viruses. Compared to general population, the risk of acquiring HBV for HCW is estimated to be 16 to 30% [31, 32]. Regarding the prevalence of OBI in this special group, as it shown in Table 3, these values ranged between 3.3 and 11%.

In an unpublished data from Iran, our group found a prevalence of 3.3% of HCW who harbored OBI. All subjects in this study were chosen from individuals who did not respond to 3 standard doses

of HBV vaccine. None of index patients were positive for anti-HBc. In molecular analysis, no subjects were contained mutations in the whole surface proteins.

In another study, 250 health care workers who completed their hepatitis B vaccination, were divided into 2 groups: anti-HBc positive (n=78) and anti-HBc negative (n=172). Both groups were vaccinated by three doses of HBV vaccine. 23 (29.5%) and 11 (6.4%) were non-responders in both groups, respectively. Among 23 non-responders in anti-HBc positive subjects, blood samples were obtained from 16 subjects. HBV DNA was positive in all these 16 subjects.

23 were nonresponders, and of 16 available samples, 13 had OBI (Table 3) [33].

In a study from India [34], a vast number of HCWs was screened for HBV markers. Of the 2141 HCWs who were negative for HBsAg, anti-HBc testing was done in 700 subjects. A total of 200 (24.7%) were found to be positive, showing evidence of past exposure to hepatitis B infection. Of these 200 subjects, 120 were tested for OBI. 6 (5%) were OBI positive with adequate levels of anti-HBs. Among the 115 subjects who had prior exposure, but not reported to have occult HBV infection, 87% were anti-HBs-positive even though they did not receive any vaccination. These results underscore the fact that a fair proportion of HCWs might be infected by cryptic feature of HBV without any acknowledge that would never been explored by current molecular techniques.

In a group of 548 Thai HCWs, Chiarakul et al, found a frequency of 11% (n=4) OBI among 36 HCW with isolated anti-HBc. None of persons were responded to a single dose of booster vaccine[35].

In a study from Korea, a known endemic area for HBV, a group of 334 HCWs were divided into two groups: isolated anti-HBc (n=40) and 294 who were negative for all HBV markers. After 3 doses of vaccine, 10 (25%) and 98 (33.3%) were showed an amnestic response to vaccine and the rest were failed to response. Interestingly, none groups were positive for OBI [36]. This finding came as something of a surprise, as the total isolated anti-HBc subjects were only 2.2% (40 out of 1757).

In Poland, of 961 HCWs, 151 (15.7%) were positive for anti-HBc, of whom 98.7% (149) were positive for anti-HBs as well. OBI was detected in 6 (4%) of cases [37].

None of such studies on HCWs contained mutational analysis. However, in our unpublished study, we did not find any mutations in surface proteins of subjects. Interestingly, the prevalence for OBI and anti-HBc positivity in OBI cases were 1.8% and (81.8%), respectively (Figure 2).

Discussion

A growing body of literatures have shown that occult HBV infection could be expected to occur any clinical settings (Fig 1). Adequate molecular epidemiology databases of this clinical entity are important for infection prevention and control managements and treatment programs.

The selected, available papers on the prevalence of OBI in general population suffer from bias on sample collections according to age, HBV hyperendemicity, methodology used and vaccine coverage. Almost all the data have come from areas with high HBV endemicity (Eskimos, south-east Asian countries, Italy, etc). More cross -sectional studies from low to intermediate HBV endemic regions need to be carried out to explore the exact prevalence of OBI in general population. Worldwide coverage rate of 80% for HBV vaccine is another issue which should be taken into account. This factor would influence the results of such investigations dramatically. In addition, other limitation for above mentioned studies is the lack of clarification for the status of HBV immunization in their investigations, despite anti-HBs positivity in some of cases, adding more confusion about either past history of HBV infection or outstanding of antibody after immunization.

The occurrence of OBI in immunized individuals with adequate, protective levels of anti-HBs is a matter of debates. For high risk subjects, previous contact with HBV (vertical or horizontal) might prevent the effects of vaccine/HBIg for proper neutralization of HBsAg. To add to the confusion, the tiny amount of HBV DNA in the presence of anti-HBs may not be quiet efficient for HBV replication. Pande et al., found that 36% of OBI-positive high-risk infants lost their infection after a period of six

month post-diagnosis. All of these patients had protective levels of anti-HBs at the time of diagnosis. If it is the case, therefore, testing of sequential samples in certain intervals would explore the real situation of OBI in cohort, longitudinal studies which could reveal the outcomes of this complicated clinical situation.

There are scarce data on the prevalence of OBI in HCWs worldwide. However, the presented data in this section underscores the importance of this clinical entity in this high risk group. In a majority of the following studies, the molecular tests were carried out on anti-HBc positive samples (regardless of being either isolated or being also positive for anti-HBs). However, our unpublished results are the only data on screening of HBsAg negative HCWs regardless of other HBV serologic markers results.

What is the significance of OBI in these individuals? Several epidemiological and molecular studies which are supported by animal models encouraged the hypothesis that OBI retains the same pro-oncogenic features and accelerates the progression of liver disease and the development of cirrhosis [38, 39]. Moreover, despite the strong association between HCC and seropositivity of HBsAg, almost all clinical and epidemiological studies have observed HBsAg-sero negative patients affected with HCC and liver cirrhosis [10, 18, 40, 41].

The other issue includes the reactivation of hepatitis due to OBI. HBV is now a well-recognized complication in patients with chronic HBV infection receiving cytotoxic, corticosteroid, or immunosuppressive therapy. In these cases, reactivation of the virus may occasionally be present, leading to severe or even fulminant hepatic failure sometimes indistinguishable from *de novo* acute infection [42-44]. In this respect, HBV reactivation has been observed in advanced immune deficiency in patients with hematological-malignancy disorders, at a prevalence of 3.3% to 24% [45-48]; and subjects who were HBsAg negative prior to chemotherapy (alkylators, antimetabolites, antitumor antibiotics, corticosteroids, etc.) who underwent treatment and transplantation especially those treated with rituximab (anti-CD20), alemtuzumab (anti-CD52), and infliximab (anti-TNF) [47-49].

A vast majority of publication highlighted the importance of anti-HBc, either isolated or in the presence of anti-HBs, as a useful serologic marker for the probability of OBI diagnosis. Naively speaking, one would expect that anti-HBc testing can be helpful for identification of cases for HBV DNA testing in terms of patients' selection and cost benefit issues. However, it is not the case. Rather, as described earlier [39], results from this study confirmed that a fair proportion of anti-HBc negative cases were OBI-positive. Therefore, relying on this serologic marker would underestimate the real prevalence of OBI.

Concluding Remarks

This metanalysis clearly showed that OBI cannot be ignored even in immunized individuals. In the process of moving from evidence to recommendations, the following were considered. First, HBV serological surveys are not enough and sensitive to rule out the presence of HBV DNA. For high-risk groups (subjects born to HBsAg mothers, health care workers, isolated anti-HBc, etc) sensitive molecular tests based on real time PCR should be applied for a proper diagnosis. Secondary, due to intermittent HBV replication and hopefully clearance of HBV, those who have been diagnosed with OBI, should be monitored periodically by molecular tests to verify the persistence of OBI (especially in those who showed protective levels of anti-HBs).

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Conflicts of Interest

The authors declare that there are no conflicts of interest.

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