



Tehran University  
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# Occult HBV Infection (OBI) In Vaccination Settings

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## Introduction



- \* Mother-to-child transmission (MTCT) is responsible for more than one third of chronic HBV infections worldwide.
- \* HBIG and hepatitis B vaccine within 24 hours of birth, followed by completion of the vaccine series, is 85% to 95% effective in preventing HBV infection and the chronic carrier state in children born to HBsAg positive mothers.
  - Therefore, despite appropriate immunoprophylaxis, HBV vertical transmission occurs in 5-15% of these infants.
  - This percentage is also attributable to vaccine immunization in general population.

**Occult hepatitis B infection prevalence among vaccinated Adults in general population.**

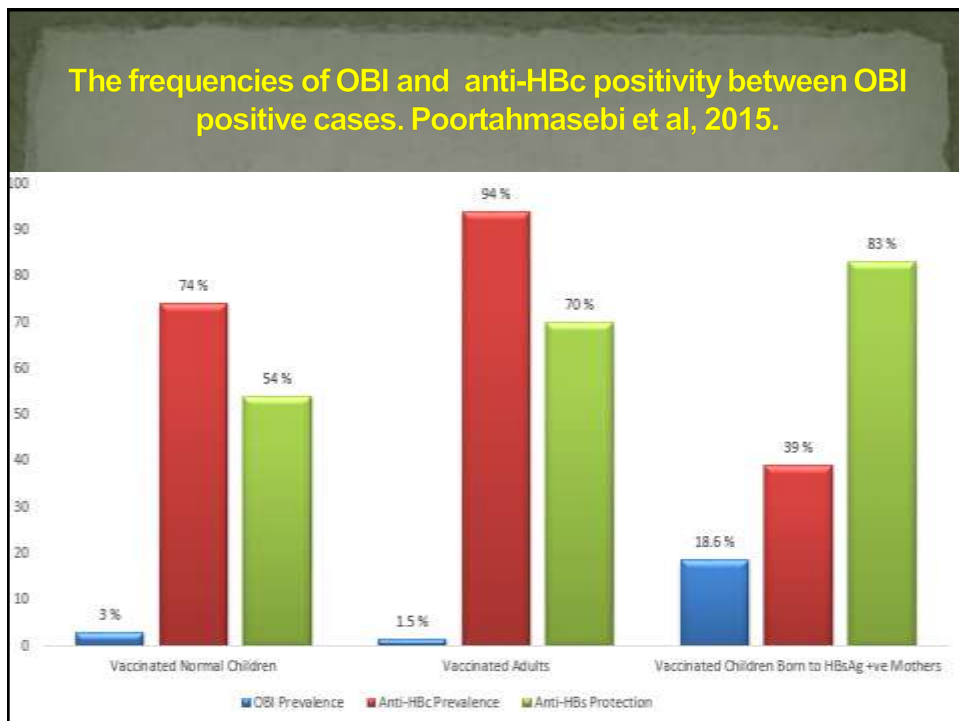
Author	Country	No Samples	OBI (%)	% Anti-HBs	% Anti-HBc
Koh/2005	Korea	34	0	70	100
Fytli/2008	Germany	43	2 (4.6)	Neg	Neg
Xu/2010	China	2919	81 (2.7)	44	100
Chen/2012	China	1146	9 (0.8)	66	100
Hudu/2013	Malaysia	804	20 (5)	80	100
He/2015	China	3955	27 (0.6)	63	63

**Occult hepatitis B infection prevalence among vaccinated children in general population.**

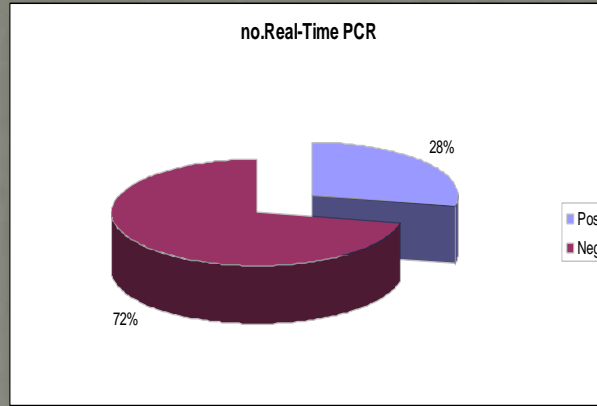
No	Author	Country	No Samples	Number (%) of OBI positive cases	Number (%) of Anti-HBc +	%Protective Anti-HBs
1	Karthigesu/1994	Gambia	31	6 (19.4)	6 (100)	100
2	Mu/2009	Taiwan	46	5 (10.9)	0	60
3	Meschi/2010	Tanzania	282	1(0.35)	1 (100)	0
4	Utsumi/2010	Indonesia	229	5 (2.1)	4(80)	60
5	Ni/2012	Taiwan	142	6* (4.2)	6 (100)	50

**Reported prevalence of OBI from vaccinated children born to HBsAg-positive mothers.**

No	Author	Country	No Samples	Vaccine (%) / HBIG (%)	Protective Anti- HBs (%)	No (%) of OBI positive cases	No (%) of Anti- HBc positive
1	Shahmoradi /2012	Iran	75	100/100	100	21 (28)	5 (23.8)
2	Chakvetadze /2011	France (Africans)	100	100/90	76	2 (2)	1 (50)
3	Pande/2013	India	213	100/49	85	89 (42)	NI
4	Hoffman /2014	South Africa	14	100*/0	NI	3 (21.5)	NI
5	Su/2013	China	183	100/78	66.6	9 (4.9)	1 (11)
6	Chen/2013	China	148	100/100	0	7 (4.7)	NI
7	Hsu/2014	Taiwan	16	100/8	100	9 (56)	9 (100)



## Real Time PCR Results

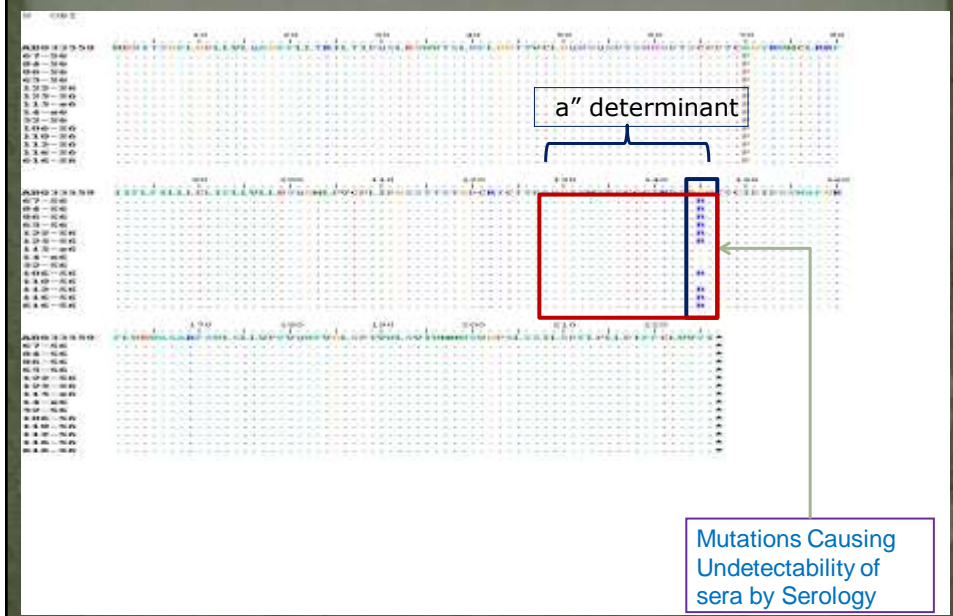


Real Time PCR (TaqMan) was positive in 21 (28%)

### Demographic, serologic and virologic data of occult HB-positive patients.

Sample Code	Age <sup>a</sup>	Sex*	Anti-HBc	Anti-HBs Titer(mIU/mL)	HBV DNA (copy/mL)
14	16	2	+	>100	2100
40	15	1	-	30	2000
42	61	1	-	28	55
46	128	1	-	18	77
52	17	2	-	>100	1270
56	18	1	-	>100	81
65	32	1	-	95	3800
67	38	2	-	38	415
72	37	1	-	>100	223
84	57	1	-	36	9240
86	63	2	-	>100	474
103	12	1	-	>100	468
106	66	2	-	>100	1920
108	35	2	-	>100	347
110	10	1	+	>100	500
112	22	1	-	47	450
115	10	1	+	38	1200
116	64	2	-	25	4560
616	23	1	-	47	2330
122	12	2	+	>100	2300
125	72	2	+	94	205

## Direct Sequencing Results of HBV surface Protein obtained from Occult-Infected Children



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Research Article

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Viral Hepatitis

### High prevalence of occult hepatitis B virus infection in children born to HBsAg-positive mothers despite prophylaxis with hepatitis B vaccination and HBIG

Sajad Shahmoradi<sup>1</sup>, Yousef Yahyapour<sup>2</sup>, Mahmood Mahmoodi<sup>3</sup>, Seyed Moayed Alavian<sup>4</sup>,  
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<sup>3</sup>Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences (TUMS), Tehran, Iran;

<sup>4</sup>Baqiyatollah University of Medical Sciences, Baqiyatollah Research Center for Gastroenterology and Liver Disease, Tehran, Iran

See Editorial, pages 484–485

### Iranian Study Details (2013)



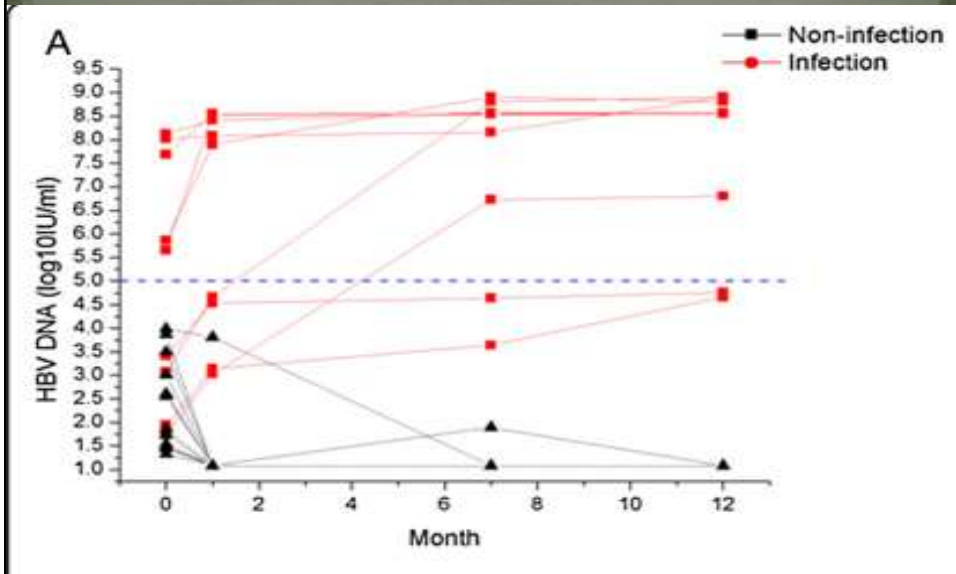
- The initial sampling of children was on 2009. After recruitment of children (36 months after the initial sampling, 2013), 17 out of 21 were available for further study.
- All 17 samples were re-checked by Real Time PCR (Abbott m 2000) with detection limit of 10 IU/mL.
- All but one case were negative for HBV DNA.
- On follow-up, 18 months later (54 months after initial sampling), another sample was drawn and was checked by real-time PCR twice. The results showed that HBV DNA was undetectable. He had G145R in 2009.
- The anti-HBs level in the last sample of index case was 18 IU/mL.

### Indian Study Details (Pande, 2014)

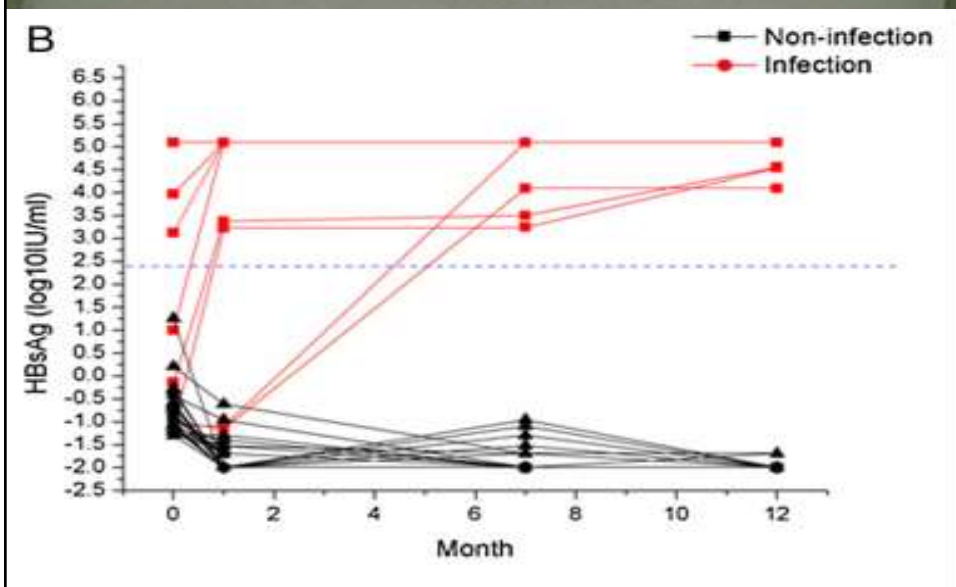


- Pande et al found that 142 out of 222 (64%) of babies born to HBsAg positive mothers acquired OBI at the end of primary end point of the study (week 18<sup>th</sup> after birth).
- At month 24, 89 (42%) were OBI-positive.
- Authors were found that the anti-HBs status at 18 weeks of babies who acquired OBI was an important indicator for subsequent outcomes.
- 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 ( $P < 0.05$ ).

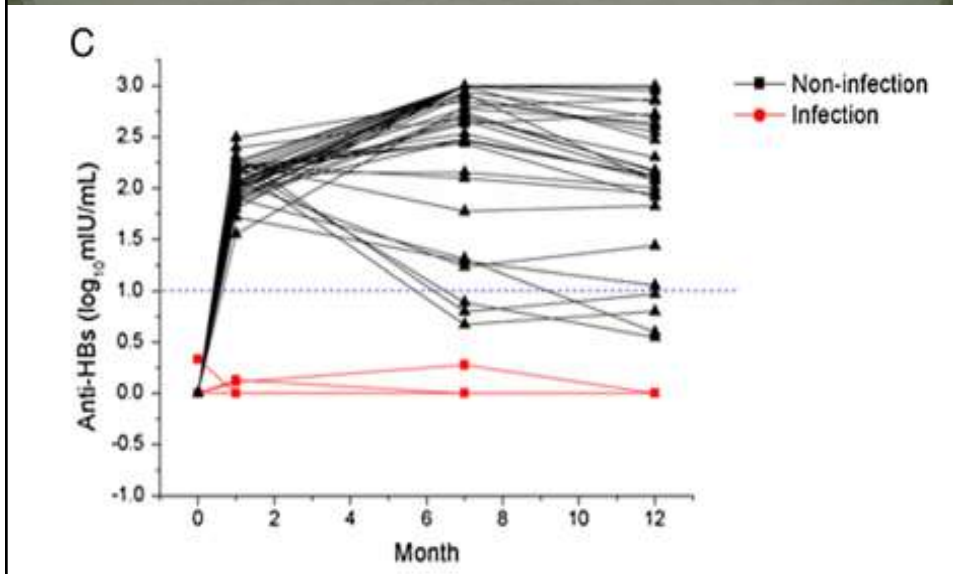
Dynamic changes in HBV DNA titer in infants who were HBsAg(+) and HBV DNA(+) at birth. Taken from chen, 2013.



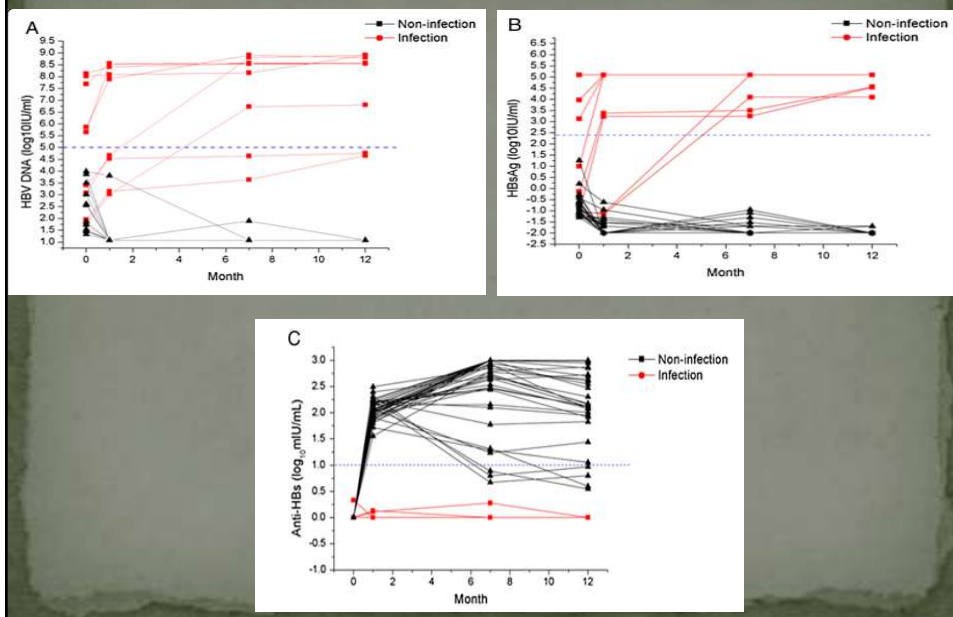
Dynamic changes in HBsAg titer in infants who were HBsAg(+) and HBV DNA(+) at birth. Taken from chen, 2013.



Dynamic changes in anti-HBs titer in infants who were HBsAg(+) and HBV DNA(+) at birth. Taken from chen, 2013.



Comparison between HBV DNA, HBsAg and Anti-HBs dynamics and outcome of HBV infection. Chen et al, BMC Infectious Diseases, 2013. 13: 524.





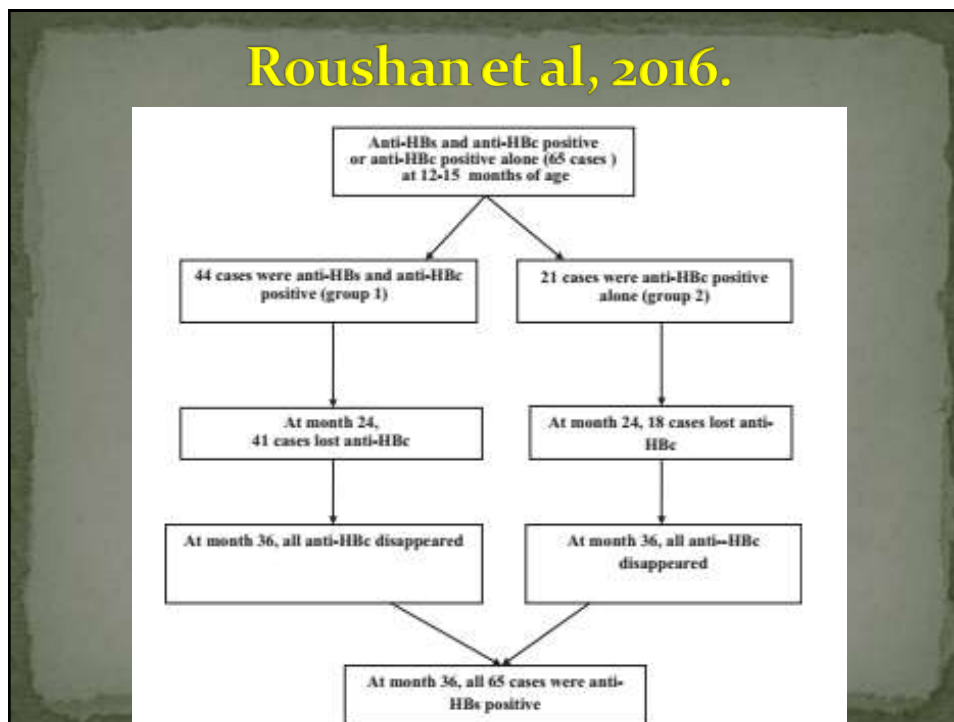
Positive likelihood ratio of diagnostic indicators for chronic HBV-infected infants . Chen et al, 2013.

Diagnostic Indicator	Total 1 month after birth	Infected 12 month N	Uninfected 12 month N (%)	Positive Likelihood Ratio
HBV DNA Positivity	21	9	12 (57%)	11.6
HBsAg Positivity	41	9	32 (78%)	4.34
Both HBV DNA and HBsAg Positivity	18	9	9 (50%)	15.4
Anti-HBs Positivity	9	9	0 (0%)	+∞

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Anti-HBs Positivity	9	9	0 (0%)	+∞

## Roushan et al, 2016.



## Summary of OBI-positive cases who became OBI negative.

No	Author	Country	No (%) of OBI positive cases	Protective Anti-HBs (%)	No (%) of cases who became HBV DNA negative	Age (year) At the time of HBV DNA clearance
1	Shahmoradi /2012	Iran	21 (28)	100	17/17 (100)	8 (Mean Age)
2	Hsu /2014	Taiwan	9 (56)	100	3/9 (33)	>20
3	Pande /2013	India	89 (42)	85	53/142 (37)	2
4	Chen /2013	China	7 (4.7)	100	5/7 (71.5)	1

### A Summary of OBI Studies in Hepatitis B Lab, TUMS

Clinical Presentation	No Samples	OBI Prevalence	No Anti-HBc	Notes
Children born to HBsAg-Positive Mothers	75	21 (28%)	5 (23%)	
Cryptogenic Cirrhosis	29	11 (38%)	2 (18%)	
Children Autistic Disorders	53	1 (1.8%) ??	1	To be Continued....
Health Care Workers	120	4 (3.3%)	0	
Vaccinated Children	100	27 (27%) ??	0	To be Continued....
Behcet Syndrome	105	7 (6.6%)	NI	To be Continued....
HIV-Positive	172	31 (18%)	20 (64.5%)	
HTLV-1 Positive	109	1 (0.9%)	1	
Dentists	55 (1628)	1 (1.8%)	1	
Serodiscordant Chronic	5	5	1 (20%)	

Results of Pilot study on vertical OBI.

OBI	Parents Vaccine	Real time & Nested PCR	Anti HBs	Anti HBc	HBsAg	Cases	No
⊖	NI	Neg	0.1	Neg	Neg	Index	1
*	NI	Pos	>1000	Pos	Neg	F	
		Neg	2.43	Neg	Neg	M	2
*	+	Pos	1.57	Neg	Neg	Index	
		Pos	>1000	Pos	Neg	F	
	+	Neg	>1000	Pos	Neg	M	
	No	Neg	0.1	Neg	Neg	Index	3
*	No	Pos	1.27	Neg	Neg	F	
		Pos	0.1	Neg	Neg	M	
			1.11	Neg	Neg	Index	4
*	No	Pos	>1000	Pos	Neg	F	
	No	Neg	0.47	Neg	Neg	M	
			0.1	Neg	Neg	Index	5
*	+	Pos	12.87	Neg	Neg	F	
	No	Neg	0.3	Neg	Neg	M	
			7.26	Neg	Neg	Index	6
*	idose+	Pos	0.55	Neg	Neg	F	
	No	Pos	0.1	Neg	Neg	M	
			0.1	Neg	Neg	Index	7
*	No	Pos	0.1	Neg	Neg	F	
⊖	No	Neg	97.81	Pos	Neg	M	
			1.67	Neg	Neg	Index	8
*	No	Pos	0.1	Neg	Neg	F	
⊖	No	Neg	>1000	Pos	Neg	M	
			0.1	Neg	Neg	Index	9
	No	Neg	0.3	Neg	Neg	F	
*	No	Pos	1.5	Neg	Neg	M	
			4.06	Neg	Neg	Indexes	10
	No	Neg	1.6	Neg	Neg	F	
*	No	Pos	0.1	Neg	Neg	F	
	No	Neg	0.3	Neg	Neg	M	11
⊖	No	Neg	6.05	Neg	Neg	Index	
*	No	Pos	>1000	Pos	Neg	F	
			6.41	Neg	Neg	M	12
*	No	Pos	3.94	Neg	Neg	Index	
	+	Neg	14	Neg	Neg	F	
			25	Neg	Neg	M	13
*			5.62	Neg	Neg	Index	
	NI	Pos	35.42	Neg	Neg	F	
	NI	Neg	0.1	Neg	Neg	M	14
			1.1	Neg	Neg	F	
			1.16	Neg	Neg	Index	
*	No	Neg	0.71	Neg	Neg	F	15
	No	Pos	0.1	Neg	Neg	M	
			0.1	Neg	Neg	Index	
*	No	Neg	0.15	Neg	Neg	F	
	No	Pos	0.1	Neg	Neg	M	



- Loss of HBsAg or HBV DNA may occur in a proportion of vertically exposed infants later in their life (**vertical infection**).
- Sometimes it is really difficult to distinguish between “**occult HBV infections**” versus “**vertical HBV infections**”.

## **Conclusion; Diagnostic**



- All of these patients had protective levels of anti-HBs at the time of diagnosis.
- The presence of anti-HBs following HBV vaccine administration in combination with HBIG could eventually neutralize HBV in children sometimes after being diagnosed as OBI.
- Anti-HBs may be considered as a predictive indicator for HBV infection in the children with positive HBV DNA, especially for those with low levels of HBV DNA load.