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Significance of anti-HB levels below 10 IU/L after vaccination against hepatitis B in infancy or adolescence: an update in relation to sex

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ABSTRACT

Hepatitis B vaccination (three-dose series) induces long-term immunity, but it is not uncommon to find antibody levels below 10 IU/L long after vaccination. However, the majority of the subjects with low antibody levels have a prompt response to a booster dose. A population of 10,294 students at Padua University Medical School, who were subjected to hepatitis B vaccination during infancy or adolescence according to the law, was tested for the presence of anti-HBs, usually during the first year of matriculation. Among the students offered a booster dose, 1,030 were vaccinated, and the antibody titre was re-tested. The present research provides further evidence from a larger number of students (1,030) that an anti-HB level higher than 2 IU/L is predictive of a prompt response to a booster. There are also differences related to sex. The results clearly confirm that an antibody titre equal to or greater than 2 IU/L is enough to prompt a response after a booster dose, even several years after the initial vaccination cycle, and to predict effective immune protection. The length of the interval between the booster/post-booster analyses increases the probability of finding a low response to the booster; furthermore, females show a more rapid response to the booster than males. The importance for healthcare workers of measuring the antibody titre four weeks after a booster is highlighted, and the results suggest that females have a better response than males to booster vaccination.

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Introduction

It is well established that vaccination against hepatitis B virus (HBV) induces long-term immunity after a three-dose series of the vaccine.[1,2] However, it is possible to find anti-HBs levels lower than 10 IU/L several years after vaccination. This phenomenon has become especially evident among those to whom the vaccine was administered within the first year of life[3] according to the vaccination schedule introduced in Italy in 1991 (at time 0, after a month and after six months for adolescents and during the third, fifth and eleventh months of life for infants). The vaccination schedule initially included two cohorts (both mandatory): those vaccinated at three months old (for those born after the introduction of mandatory vaccination) and adolescents in the twelfth year of life (for those born between 1980 and 1991). Once the two cohorts overlapped in 2003, the vaccination of adolescents was discontinued.

The relevant question is: do subjects with anti-HBs levels below 10 IU/L, who are exposed to biological risk, need a booster dose? Surely, these subjects should not be considered as non-responders; according to the definition from the Centers for Disease and Control and Prevention,[4] a non-responder is "a person who does not develop protective surface antibodies after completing two full series of the HBV vaccine and for whom an acute or chronic HBV infection has been ruled out". Only after assessing these criteria can a subject be labelled as a non-responder, with the understanding that immunological memory commonly persists after vaccination.[5]

Further, an anamnestic response was defined as an increase in the anti-HBs concentration of four times or more after the booster vaccine or an antibody concentration of at least 10 IU/L after the booster.[6] A new criterion to evaluate anti-HBs levels lower than 10 IU/L at the time of analysis was recently introduced;[7] in fact, subjects with anti-HBs levels equal to or higher than 2 IU/L have a prompt response to a booster dose, reaching a post-booster level that is largely protective. An antibody level higher than 1 IU/L probably has the same significance.[8]

Four years after our attempt to introduce the different management of subjects with waning or disappearing circulating antibodies after HBV vaccination,[7] the population was largely examined with particular attention to sex differences.

Methods

Study design

The study is based on data collected by health surveillance, according to the law, in university medical school students. The Italian law (legislative decree n. 81, 2008) requires health surveillance of workers in the presence of a chemical, physical or biological risks (students are considered as workers). The

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health protocol is prepared by the occupational physician according to national guidelines. Regarding transmissible infectious diseases, the markers of these diseases are monitored and, if necessary, the vaccination or a recall must be suggested (not mandatory).

This is an observational-retrospective study of fourteen years. Anti-HBs were detected using the commercially available Chemiluminescent Microparticle Immunoassay (CMIA) until 2017. At the end of 2017, the clinical microbiology laboratory changed the instruments and commercial kits used to measure HBV antibodies. This new procedure uses a Chemiluminescent Immunoassay (CLIA) named LIAISON® anti-HBs plus by Sorin (Saluggia, Italy), and the lower cutoff is expressed only as "below 3 IU/L" without knowing the values below this value.

Health surveillance is mandatory in Italy, and studies based on surveillance data do not require evaluation by an ethics committee. All subjects submitting to health surveillance signed a privacy document permitting the elaboration and publication of anonymous data.

Population

Among the 10,294 students at Padua University Medical School (medicine and surgery, dentistry, and health professions), 49.8% were vaccinated against HBV within the first year of life, and 50.2% were vaccinated later. The study includes the period from 2004 to 2018. Students with anti-HBs levels lower than 10 IU/L (3,246, 31.5%) were included in the study; of those students, 79.5% were vaccinated within the first year of life, and 20.5% were vaccinated later. Of these students, 1,497 (46.1%) adhered to the suggested booster dose, and 1,122 (74.9%) had measured antibody levels after the booster. The inclusion criteria for the study are: (1) born in Italy after January 1, 1980, and then subjected to the vaccination schedule according to the Italian law implemented in 1991; (2) provided with a vaccination certificate released by the Public Health Office; (3) only submitted to three doses of HBV vaccine during infancy or adolescence according to the law; and (4) neither a carrier of HBV antigens nor previously infected with HBV.

Further evaluation excluded additional subjects, including: (1) 12 students with values of antibody levels measured after receiving the booster but who failed to submit an updated vaccination certificate were excluded (this is relevant because the interval between the booster and analysis significantly influenced post-booster antibody levels); and (2) the records of 80 students tested with LIAISON® (see above) were excluded, since their anti-HBs levels were < 3 IU/L. Finally, 1,030 students, of whom 64.8% were vaccinated within the first year of life and 35.2% were vaccinated during adolescence, were included in the study.

Statistics

Descriptive analysis was performed using the means, median and standard deviations for continuous variables, and absolute and relative frequencies (proportion) for categorical variables. Further, unpaired t-test non-parametric Mann-Whitney test, χ^2 distribution with Yates correction, simple linear correlations, and multiple linear regressions were used in statistical analysis. The following outcomes were considered for the purpose of multiple linear regression: (1) antibody levels analyzed after the booster dose (post-booster markers); (2) antibody levels analyzed during health surveillance (pre-booster markers); (3) interval between booster and post-booster analyses (post-booster markers); (4) age at the first dose of the vaccine; (5) interval between the third dose of the vaccine and the analysis during health surveillance (pre-booster markers); (6) age at the time of pre-booster markers; and (7) sex. Post-booster markers (1) are the dependent variable, and the remaining (2–7) are the independent variables. Statistical significance was set at $P < .05$. Statsdirect version 3.1.20 (Statsdirect Ltd, UK) was used for the statistical analyses.

Results

Multiple regression analysis (Table 1) shows that only the three following independent variables influenced the response to booster vaccination: (a) the level of pre-booster markers ($P < .0001$); (b) the interval between booster and post-booster antibody analyses ($P < .0001$); and (c) sex ($P = .009$). The influence of the interval between booster and analysis particularly attracted our attention, prompting us to perform data analysis to determine the temporal limit that influences the evaluation of antibodies.

As shown in Table 2, five subjects of 347 (1.4%) with anti-HBs higher than 2 IU/L showed a level below 10 IU/L after the booster, contrary to what was expected by previous results.[7] Step-by-step evaluation (every thirty days) of the delay between the booster dose and post-booster antibody measurement revealed that these subjects had their post-booster antibody levels measured 824 to 2,268 days later. Because the analysis of the post-booster was performed more than one year later, there was an increase in the negative correlation between the variables (increasing the interval decreases the post-booster anti-HB levels, data not shown); 70 subjects (6.8%) for whom the analysis was performed after 365 days were further excluded from the study, leaving 960 eligible subjects.

Multiple regression analysis on these 960 subjects confirms what is highlighted in the overall case study regarding

Table 1. Multiple linear regression among post-booster markers (dependent variable) and the independent variables age, sex, pre-booster markers, age at first dose of vaccine, interval between third dose of vaccine and analysis of markers at the time of health surveillance, and interval between booster and post-booster markers (independent variables) in all 1030 students. Significant results are shown in bold.

	b	r	t	P
Intercept	597.133496		3.810411	=0.0001
Age	−0.263358	−0.0497	−1.590827	=0.112
Sex	**56.674998**	**0.081581**	**2.616769**	**=0.009**
Pre-booster markers	**71.826128**	**0.470908**	**17.064896**	**<0.0001**
Age 1st dose	0.238392	0.045889	1.468557	=0.1423
Interval 3rd dose/analysis	0.224232	0.042664	1.365168	=0.1725
Interval booster/ analysis	**−0.290415**	**−0.277095**	**−9.219373**	**<0.0001**

Post-booster markers = 597.133496 - 0.263358 age + 56.674998 sex + 71.826128 pre-booster markers + 0.238392 age at 1st dose + 0.224232 interval 3rd dose/ analysis - 0.290415 interval booster/analysis.

Table 2. Distribution (number and percentage) of all (1030) students according the level of anti-HBs antibodies after booster administration.

Pre-booster		Post-booster Anti-HBs levels							
IU/L	No.	0.00–9.99	%	10–99	%	100–1000	%	>1000	%
0.00–0.09	108	35	32.4	34	31.5	36	33.3	3	2.8
0.10–0.99	321	33	10.3	120	37.4	146	45.5	22	6.9
1.00–1.99	254	9	3.5	46	18.1	150	59.1	49	19.3
2.00–9.99	347	5	1.4	34	9.8	135	38.9	173	49.9
All	1030	82	8.0	234	22.7	467	45.3	247	24.0

Table 3. Multiple linear regression among post-booster markers (dependent variable) and the independent variables age, sex, pre-booster markers, age of first dose of vaccine, interval between third dose of vaccine and analysis of markers at the time of health surveillance, and interval between booster and post-booster markers (independent variables) in 960 students with check of antibody level less than one year after booster. In bold significant results.

	b	r	t	P
Intercept	639.633055		3.917674	=0.0001
Age	−0.268772	−0.051849	−1.602757	=0.1093
Sex	**62.683428**	**0.089948**	**2.788052**	**=0.0054**
Pre-booster markers	**77.556552**	**0.493004**	**17.492981**	**<0.0001**
Age 1st dose	0.244005	0.048039	1.48471	=0.138
Interval 3rd dose/analysis	0.230044	0.04476	1.383148	=0.1669
Interval booster/ analysis	**−1.342746**	**−0.154398**	**−4.824238**	**<0.0001**

Post-booster markers = 639.633055 − 0. 0.268772 age + 62.683428 sex + 77.556552 pre-booster markers + 0.244005 age first dose + 0.230044 interval 3rd dose/analysis −1.342746 interval booster/analysis

level of pre-booster marker, interval between analysis and booster, and sex (Table 3). Unlike in the complete population, no subjects with pre-booster markers greater than or equal to 2 IU/L showed non-protective post-booster values (Table 4).

The third independent variable influencing post-booster markers is sex. As shown in Table 5, females showed a significantly more protective post-booster response than males (χ^2 = 5.286, P = .0215). In particular, if the pre-booster marker was lower than 1 IU/L, the booster response in females was significantly higher than in males (P = .013). Statistically, the female subjects were slightly younger (P = .0025) and had slightly delayed post-booster analysis (P = .0128) than the male subjects. Further, with similar pre-booster anti-HBs levels, age of the 1st dose of vaccine during infancy or adolescence, interval between the 3rd dose of vaccine and HBV marker analysis, and (although statistically significant) time of analysis after the booster, anti-HBs levels were significantly higher in females (P = .0016 in the whole population and P = .0011 in the sub-group with an anti-HBs level lower than 1 IU/L) than in males. The other variables did not apparently influence anti-HBs levels after the booster dose. The predictivity of pre-booster anti-HBs levels according to sex was calculated with a simple linear correlation (Table 6). Pre- and post-booster markers were more closely correlated in females (r = 0.560) than in males (r = 0.489). Finally, a protective anti-HBs level was reached by females starting by a hypothetical pre-booster level two times lower (0.58 IU/L) than males (1.05 IU/L).

Discussion

Recently, we proposed a cutoff at 2 IU/L as an anti-HBs level that is predictive of a prompt immune response to prevent HBV infection after virus exposure[6] according to evidence that a booster dose is enough to stimulate the immune system to produce protective antibodies despite the waning of circulating antibodies. A booster dose appears to be unnecessary if the anti-HBs level is higher than this value. Although the sample size was numerically small (279 subjects), the results appeared highly suggestive.

In the present research, the sample size is about four-fold (1,030 subjects) higher than those of previous studies, and the results show further evidence that anti-HBs levels equal to or higher than 2 IU/L are enough to predict a protective immune response after virus exposure. Furthermore, it is highly probable that a titre above 1 IU/L is also enough. In addition, subjects that tended to be prone to waning circulating antibodies over time also showed similar behavior after a booster if the measurement of the marker was excessively delayed. This observation could lead to misinterpretation of the results and to a false decision to label the subject as a non-responder (if a completely new vaccination cycle is not performed).

The third piece of evidence is that females show a significantly higher rate of seroconversion after the booster than males, particularly if the pre-booster anti-HBs levels were lower than 1 IU/L. In fact, an anti-HBs level is achieved in females even if they exhibit a lower level of pre-booster anti-HBs, and they have a stronger correlation between pre- and post-booster anti-HBs levels.

Table 4. Distribution (number and percentage) of 960 students with check of antibody level less than one year after booster, according the level of anti-HBs antibodies after booster administration.

Pre-booster		Post-booster Anti-HBs level							
IU/L	No.	0.00–9.99	%	10–99	%	100–1000	%	>1000	%
0.00–0.09	105	33	31.4	33	31.4	36	34.3	3	2.9
0.10–0.99	308	28	9.1	112	36.4	146	47.4	22	7.1
1.00–1.99	240	6	2.5	41	17.1	145	60.4	48	20.0
2.00–9.99	307	0	0.0	20	6.5	118	38.4	169	55.0
All	960	67	7.0	206	21.5	445	46.4	242	25.2

Table 5. Influence of sex on post-booster response (in 960 subjects). Significant results are shown in bold.

	Post-booster					
	Males			Females		
Pre-booster	No.	≥10 IU/L	%	No.	≥10 IU/L	%
0.00–0.09 IU/L	30	21	70.0	75	51	68.0
0.10–0.99 IU/L	**106**	**86**	**81.1**	**202**	**194**	**96.0[a]**
Lower than 1.00 IU/L	**136**	**107**	**78.7**	**277**	**245**	**88.4[b]**
Age (years, mean ± SD)	20.9 ± 1.3			20.6 ± 1.3		
Age first dose (days, median and range)	91 (3 days-13 years)			92 (0 day-12 years)		
Interval 3rd dose/analysis (years, mean ± SD)	17.5 ± 4.1			17.6 ± 3.9		
Interval booster/analysis (days, median and range)	**42 (24–294)**			**44[c] (21–335)**		
Anti-HBs level pre-booster (IU/L, median and range)	0.49 (0.00–0.99)			0.36 (0.00–0.99)		
Anti-HBs level post-booster (IU/L, median)	**48.5 (0.00–1000)**			**125[d] (0.00–1000)**		
1.00–1.99 IU/L	91	88	96.7	149	146	98.0
2.00–9.99 IU/L	101	101	100.0	206	206	100.0
All students (0.00–9.99 IU/L)	**328**	**296**	**90.2**	**632**	**597**	**94.5[e]**
Age (years, mean ± SD)	**21.0 ± 1.5**			**20.7 ± 1.6[f]**		
Age first dose (days, median and range)	97 (1 day-13 years)			97 (0 day-13 years)		
Interval 3rd dose/analysis (years, mean ± SD)	16.3 ± 4.6			16.4 ± 4.5		
Interval booster/analysis (days, median and range)	**43 (24–294)**			**46[g] (20–345)**		
Anti-HBs level pre-booster (IU/L, median and range)	1.335 (0.00–9.94)			1.19 (0.00–9.98)		
Anti-HBs level post-booster (IU/L, median and range)	**246 (0.00–1000)**			**361[h] (0.00–1000)**		

Legend: the first part of the table refers to subjects with pre-booster anti-HBs levels divided in three classes: lower than 1.00 IU/L, 1.00–1.99 IU/L, and 2.00–9.99 IU/L; the second part refers to all subjects (between 0.00 and 9.99 pre-booster anti-HBs levels)
[a]P<0.0001, [b]P = 0.013, [c]P = 0.0156, [d]P = 0.0011,[e]P = 0.0215, [f]P = 0.025, [g]P = 0.0128, [h]P = 0.0016

Table 6. Influence of sex on linear correlation (part a) and predictivity of achievement anti-HBs level higher than 2 IU/L (part b) in 960 subjects.

part a	Equation	r	95% C.I. for r (Fisher's z transformed)
All	Pre-booster markers = 0.0036 post-booster markers + 0.719	0.537[a]	0.490–0.580
Males	Pre-booster markers = 0.0031 post-booster markers + 1.017	0.489[a]	0.402–0.567
Females	pre-booster markers = 0.0040 post-booster markers + 0.536	0.560[a]	0.504–0.611
Part b (to achieve)	10 IU/L	100 IU/L	1000 IU/L
All (pre-booster marker)	0.76	1.08	4.32
Males (pre-booster marker)	1.05	1.33	4.12
Females (pre-booster marker)	0.58	0.94	4.54

[a]P<.0001.

It is known that females (both children and adults) produce a higher levels of antibodies than males[9,10] and have a higher rate of seroconversion[11] after HBV vaccination. No differences were observed in the waning of antibodies during the first ten years of life.[12] Males also show a higher rate of nonresponse to the vaccine than do females.[13]

As reviewed by Klein et al.,[14] there are relevant gender-related differences in innate and adaptive immune responses to vaccination, showing that females have a greater immune response, both humoral and cell-mediated.[15] These differences are related to genes for the toll-like receptor pathway and type I interferon induction.[16] Furthermore, several genes that are immune-related are located on the X chromosome and play a pivotal role in immune competence.[17]

Finally, the age of the patient at primary HBV vaccination (three doses), despite the large difference in the percentage of anti-HBs levels lower than 10 IU/L and the interval between the third dose of vaccine and the time of antibody titre analysis, does not influence the response to the booster dose. Rather, considering all subjects with a pre-booster anti-HBs level less than 2 IU/L, the probability to find levels lower than 10 IU/L is greater in subjects vaccinated after (16.0%) than in those vaccinated before the first year of age (9.0%, $\chi^2 = 4.416$, $P = .0356$). What does this mean? Further research is necessary to provide a satisfactory answer to this question.

In conclusion, the results of this study (1) confirm that anti-HBs levels of 2 IU/L or more many years after vaccination during infancy or adolescence is predictive of an immune response to HBV infection after virus exposure with complete protection; (2) suggest that antibody measurement should be performed less than one year after the booster administration and possibly after the suggested interval of 30 days; and (3) highlight that females have a prompter response to a booster dose than males.

The study has some weaknesses: (1) despite careful counseling work, since this an observational-retrospective study, this study does not have the influence to convince all the subjects with anti-HBs levels lower than 10 IU/L to undergo a booster dose and, above all, to evaluate the markers within the recommended time after the vaccination booster; furthermore, based on our previous research, 7 students with anti-HBs levels higher than 2 IU/L were not offered a booster dose, except in the event of biological accidents with sharp instruments; finally, the use of a new kit to measure anti-HBs levels has effectively excluded a significant number of subjects from the study.

As concluding remarks, we suggest that (1) health care workers are subjected to an accurate screening of HBV markers to promote protection of this population potentially exposed to biological risk;[18] (2) a booster dose (with a new complete cycle of three doses, if applicable) should be suggested only to subjects showing an anti-HBs level lower than 2 IU/L or who have been injured with sharp instruments; and (3) if the laboratory results show an anti-HBs titre lower than 3 IU/L, a booster dose should be required.

Authorship

All the authors collaborated in the data collection, in the elaboration of the results and in the drafting of the manuscript, and all approve the final draft.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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References

1. Zanetti AR, Mariano A, Romanò L, D'Amelio R, Chironna M, Coppola RC, Cuccia M, Mangione R, Marrone F, Negrone FS, et al. Long-term immunogenicity of hepatitis B vaccination and policy for booster: an Italian multicentre study. Lancet. 2005;366 (9494):1379–84. doi:10.1016/S0140-6736(05)67568-X.
2. Trevisan A. Long-term persistence of immunity after hepatitis B vaccination: a fact, not a fancy. Hum Vaccin Immunother. 2017;13(4):916–17. doi:10.1080/21645515.2016.1257451.
3. Chiara F, Bartolucci GB, Mongillo M, Ferretto L, Nicolli A, Trevisan A. Hepatitis B vaccination at three months of age: a successful strategy? Vaccine. 2013;31(13):1696–700. doi:10.1016/j.vaccine.2013.01.046.
4. Advisory Committee on Immunization Practices; Centers for Disease Control and Prevention (CDC). Immunization of health-care personnel: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2011;60(RR–7):1–45.
5. Carollo M, Palazzo R, Bianco M, Pandolfi E, Chionne P, Fedele G, Tozzi AE, Carsetti R, Romanò L, Ausiello CM. Hepatitis B specific T cell immunity induced by primary vaccination persists independently of the protective serum antibody level. Vaccine. 2013;31 (3):506–13. doi:10.1016/j.vaccine.2012.11.029.
6. Zanetti AR, Romanò L, Giambi C, Pavan A, Carnelli V, Baitelli G, Malchiodi G, Valerio E, Barale A, Marchisio MA, et al. Hepatitis B immune memory in children primed with hexavalent vaccines and given monovalent booster vaccines: an open-label, randomised, controlled, multicentre study. Lancet Infect Dis. 2010;10 (11):755–61. doi:10.1016/S1473-3099(10)70195-X.
7. Chiara F, Bartolucci GB, Cattai M, Piazza A, Nicolli A, Buja A, Trevisan A. Hepatitis B vaccination of adolescents: significance of non-protective antibodies. Vaccine. 2013;32(1):62–68. doi:10.1016/j.vaccine.2013.10.074.
8. Spradling PR, Xing J, Williams R, Masunu-Faleafaga Y, Dulski T, Mahamud A, Drobeniuc J, Teshale EH. Immunity to hepatitis B virus (HBV) infection two decades after implementation of universal infant HBV vaccination: association of detectable residual antibodies and response to a single HBV challenge dose. Clin Vaccine Immunol. 2013;20(4):559–61. doi:10.1128/CVI.00694-12.
9. Morris CA, Oliver PR, Reynolds F, Selkon JB. Intradermal hepatitis B immunization with yeast-derived vaccine: serological response by sex and age. Epidemiol Infect. 1989;103(2):387–94. doi:10.1017/S0950268800030740.
10. Fang JW, Lai CL, Chung HT, Wu PC, Lau JY. Female children respond to recombinant hepatitis B vaccine with a higher titre than male. J Trop Ped. 1994;40(2):104–07. doi:10.1093/tropej/40.2.104.
11. Zeeshan M, Jabeen K, Ali AN, Ali AW, Farooqui SZ, Mehraj V, Zafar A. Evaluation of immune response to Hepatitis B vaccine in health care workers at a tertiary care hospital in Pakistan: an observational prospective study. BMC Infect Dis. 2007;7:120. doi:10.1186/1471-2334-7-120.
12. Wu JS, Hwang LY, Goodman KJ, Beasley RP. Hepatitis B vaccination in high-risk infants: 10-year follow-up. J Infect Dis. 1999;179(6):1319–25. doi:10.1086/314768.
13. Yang S, Tian G, Cui Y, Ding C, Deng M, Yu C, Xu K, Ren J, Yao J, Li Y, et al. Factors influencing immunologic response to hepatitis B vaccine in adults. Sci Rep. 2016;6:27251. doi:10.1038/srep27251.
14. Klein SL, Jedlicka A, Pekosz A. The Xs and Y of immune responses to viral vaccines. Lancet Infect Dis. 2010;10(5):338–49. doi:10.1016/S1473-3099(10)70049-9.
15. Fish EN. The X-files in immunity: sex-based differences predispose immune responses. Nat Rev Immunol. 2008;8(9):737–44. doi:10.1038/nri2394.
16. Hannah MF, Bajic VB, Klein SL. Sex differences in the recognition of and innate antiviral responses to Seoul virus in Norway rats. Brain Behav Immun. 2008;22(4):503–16. doi:10.1016/j.bbi.2007.10.005.
17. Abramowitz LK, Olivier-Van Stichelen S, Hanover JA. Chromosome imbalance as a driver of sex disparity in disease. J Genomics. 2014;2:77–88. doi:10.7150/jgen.8123.
18. Trevisan A, Nicolli A, Chiara F. Hepatitis B: prevention, protection, and occupational risk. Future Virol. 2015;10(1):53–61. doi:10.2217/fvl.14.90.