

# Misleading hepatitis B serology following Rho (D) immune globulin (human) injection and influenza vaccine

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## Abstract

Having a hepatitis B surface antibody (HBsAb) titre of more than 10 mIU/mL after hepatitis B vaccination is generally considered to confer immunity to hepatitis B. This case report discusses an unusual case of a false positive hepatitis B core total antibody (HBcAb) following administration of either Rho (D) immune globulin (Human) injection or influenza vaccine in a patient who was previously immunised against hepatitis B.

## Introduction

Abnormal hepatitis B serology results often times lead to further investigations and possibly, treatment. Physicians are sometimes faced with unexpected hepatitis B serology results. Previous studies have highlighted some cases of misleading hepatitis B serology results which led to either unnecessary or delay in treatment.<sup>1-4</sup> Having a HBsAb titre of more than 10 mIU/mL after hepatitis B vaccination is generally considered to confer immunity to hepatitis B.<sup>5,6</sup> This case report describes an unusual case of a patient who was immunised against hepatitis B, presenting with a transitory false positive HBcAb, possibly as a result of administration of either Rho (D) immune globulin (Human) injection or influenza vaccine.

## Case Report

In March 2017, a 35-year old woman, gravidity 3, parity 2 was seen at the staff clinic following a needlestick injury (NSI). She was 22 weeks pregnant at the time of the NSI. As part of the NSI protocol, the source patient had his blood sample screened for hepatitis B, hepatitis C and human immunodeficiency virus (HIV). All three were non reactive. Her blood sample was also screened for hepatitis B, hepatitis C and HIV. Her HIV screen and hepatitis C screen were non reactive. Her hepatitis B

screen was negative for hepatitis B surface antigen (HBsAg), with a HBsAb titre of 92 mIU/mL, undetectable hepatitis B virus (HBV) DNA load but a positive HBcAb.

The patient has been working as a healthcare worker for 10 years and was immunised against hepatitis B before the start of her employment. She had the same hepatitis B, hepatitis C and HIV workup done in 2008, 2011, 2013 and 2015. Her HIV and hepatitis C screen were non reactive. She had a negative HBsAg and HBsAb titre of more than 10 mIU/mL. Of note, her HBcAb was negative on all four occasions.

The patient did not recall any overt exposure to hepatitis B infected blood or body fluid before the NSI. She received an intramuscular Rho (D) immune globulin (Human) injection when she was 8 weeks pregnant and received an intramuscular influenza vaccine (2016-2017 northern hemisphere influenza vaccine) when she was 17 weeks pregnant.

The results of the hepatitis serology were discussed with the patient. This led to a lot of anxiety in the patient. Many queries were raised regarding the causes of a positive HBcAb on a background of hepatitis B immunisation, the implications on her health and the health of her fetus, the ability to continue with cord blood storage, as well as the ability to continue working as a healthcare worker. She was referred to a hepatologist and the results of the hepatitis serology were discussed with her obstetrician.

Blood samples from the healthcare worker were repeated 7 weeks after the NSI and again at 18 weeks after the NSI. The HBcAb was negative and HBV DNA was undetectable in both repeated blood tests. The rest of the results were unremarkable.

Due to the serial blood tests showing negative HBcAb, the positive HBcAb in the initial results was treated as a false positive. The patient was discharged from follow up.

## Discussion

Interpretation of hepatitis B serology involves analyzing HBV specific antigens and antibodies. Table 1 shows a summary of the interpretation of hepatitis B serology results.<sup>7</sup>

Individuals who have been immunised against hepatitis B are expected to have negative HBsAg, negative HBcAb and positive HBsAb. This patient had 4 baseline sets of hepatitis B serology results consistent with that of an individual with past immunisation. The abnormal hepatitis B serology results after the NSI were unexpected, making the interpretation of results

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challenging. Subsequent repeated tests showed that the HBcAb was negative on two separate occasions, suggesting that the initial positive HBcAb was a false positive result.

Immunoglobulin products are derived from pooled plasma. Despite stringent donor screening, these products may contain antibodies and proteins that may be passively transferred to the patient, clouding the interpretation of serology results. The administration of intravenous immunoglobulin (IVIG) has been reported to cause unexpected hepatitis B serology results, namely a positive HBcAb in several cases. Ilboudo *et al.* reported two cases of misleading hepatitis B results following IVIG administration in children.<sup>1</sup> One child who had Evans syndrome and systemic lupus erythematosus received IVIG in the form of Gamunex<sup>TM</sup>. She received 3 doses of hepatitis B vaccination at birth. Post IVIG, her hepatitis screen showed positive HBcAb and positive antibody to hepatitis B e antigen (HBeAb). The misleading results led to a delay in the administration of rituximab. The other child who had high-risk pre B-cell lymphoblastic leukemia was given IVIG in the form of Gamunex<sup>TM</sup>. She also received 3 doses of hepatitis B vaccination at birth and had a negative HBcAb prior to IVIG administration. Following IVIG, she had positive HBcAb, resulting in a delay in bone marrow transplantation. Benwell *et al.* reported false positive HBcAb and HBsAg

following IVIG administration for a patient with chronic inflammatory demyelinating polyneuropathy.<sup>2</sup> The patient received lamivudine antiviral prophylaxis prior to cyclophosphamide immunosuppression therapy. His baseline HBcAb was negative. Lamivudine was ceased following confirmation that the IVIG sample was positive for HBcAb. Positive HBcAb has also been associated with subcutaneous administration of immunoglobulin.<sup>3</sup>

This patient received a dose of intramuscular Rho (D) immune globulin (Human) injection 14 weeks before she tested positive for HBcAb. Even though the intramuscular route has not been reported to cause false positive HbcAb, it is nonetheless a consideration.

H1N1 vaccination has been reported by Araújo *et al.* to cause transitory false positive for HBcAb.<sup>4</sup> In that case control study, it was found that recent H1N1 vaccination resulted in false positive HBcAb which became negative in blood samples collected later. The authors therefore suggested that blood donors be temporarily deferred from blood donation after recent H1N1 vaccination to avoid loss of a unit and to avoid con-

fusion caused by this false positive HBcAb result. This patient received an intramuscular 2016-2017 northern hemisphere influenza vaccine 5 weeks prior to being tested positive for HBcAb. This trivalent vaccine contained an A/California/7/2009 (H1N1) pdm09-like virus, an A/Hong Kong/4801/2014 (H3N2)-like virus and a B/Brisbane/60/2008-like virus,<sup>8</sup> which may be the potential cause of the false positivity to HBcAb.

## Conclusions

Having an abnormal hepatitis B serology may lead to further work up and treatment. Clinicians should remain alert when faced with unexpected hepatitis B serology results and consider the possibility of a false positive result when clinical signs do not tie in, such as a normal baseline serology, absence of clear source of infection, positive HBc Ab in the absence of HBV DNA and negative HBsAg and subsequent clearance of HBcAb.<sup>9</sup> They should be think of the unusual causes of a false positive

HBcAb to avoid causing unnecessary worry in patients, unnecessary investigations and treatment.

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**Table 1. Interpretation of hepatitis B serologic test results.**

Tests	Results	Interpretation
HBsAg anti-HBc anti-HBs	Negative Negative Negative	Susceptible
HBsAg anti-HBc anti-HBs	Negative Positive Positive	Immune due to natural infection
HBsAg anti-HBc anti-HBs	Negative Negative Positive	Immune due to hepatitis B vaccination
HBsAg anti-HBc IgM anti-HBc anti-HBs	Positive Positive Positive Negative	Acutely infected
HBsAg anti-HBc IgM anti-HBc anti-HBs	Positive Positive Negative Negative	Chronically infected
HBsAg negative Interpretation unclear; four possibilities: anti-HBc positive 1. Resolved infection (most common) anti-HBs negative 2. False-positive anti-HBc, thus susceptible 3. Low level chronic infection 4. Resolving acute infection	Negative	Interpretation unclear; four possibilities