Awareness and management of hepatitis B vaccination nonresponse in healthcare workers

Lacey Marie Kane
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2012
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INTRODUCTION

Several major diseases such as smallpox and polio, which can bear serious consequences, have been virtually eliminated through the implementation of vaccines. One malady modern medicine is still working to control is hepatitis B, caused by the hepatitis B virus (HBV), a major cause of liver disease worldwide killing an estimated 620,000 annually (U. S. Centers for Disease Control and Prevention [CDC], 2011). More transmissible than HIV (human immunodeficiency virus) or Hepatitis C, it continues to be an important cause of morbidity and mortality (Hibberd, 1995). Healthcare workers (HCWs) are a population at an increased risk of exposure to HBV (Figure 2), as this virus can be transmitted parenterally, via blood and blood products, fomites, and is capable of surviving outside the body for at least seven days (Counard et al., 2010; CDC, 2011). Many body fluids have demonstrated levels of hepatitis B, but only serum, saliva and semen have been demonstrated to be infectious (Mast et al., 2006). Very small amounts of blood are needed to transmit the virus, a concerning fact because the main route of exposure for HCWs is likely to be needle sticks (Levinson, 2010). Though the vaccine has been extremely helpful, there remain gaps in effective coverage in some populations. According to Louther et al. (1998), “declination of vaccine and failure to respond to vaccine continue to thwart achievement of full control of this preventable occupational exposure” (p.423). Many factors contribute to the body’s inability to develop antibodies to the HBV, and there is little information about how to manage and elicit immunity in this set of individuals. Mitchell, Colvin & Beasley (2010) explain that “the extent and seriousness of this public health problem is not appreciated, inadequate resources are being allocated to prevention, control and surveillance programs” (p.729). It appears through research and clinical experience that there is an ill-defined meaning of what “immunity” is and how to manage it within the healthcare field. The purpose of this
study was to examine the policies and procedures of local hospitals to determine if there is a consensus on the definition, management and implications of HCWs who do not appear to possess immunity against the HBV.
LITERATURE REVIEW

HEPATITIS B VIRUS

Ioannou states that (2011) “Hepatitis B virus infection is the most important cause of liver disease in the world, causing acute hepatitis, chronic liver disease, cirrhosis, and hepatocellular carcinoma” (p.319). Hepatitis B develops in a person infected with the hepatitis B virus. In developed countries such as the United States, the main routes of transmission between adults are sexual and percutaneous, either from intravenous drug use or nosocomial accidental exposure (Counard et al., 2010; Greenberger, Blumberg, & Burakoff, 2012). Children may also pass HBV horizontally, and the virus is capable of surviving outside of the body and remain virulent (CDC, 2011; Greenberger et al., 2012). Less commonly it is also possible to get HBV from blood transfusion. Animals are not known to carry hepatitis B (Levinson, 2010). The virus is an enveloped virion containing three antigens within it, hepatitis B surface antigen (HBsAg), hepatitis B core antigen (HBcAg), and hepatitis B e antigen (HBeAg) (Greenberger et al., 2012; Levinson, 2010). Levels of hepatitis B core antibody (anti-HBc, HBcAb), hepatitis B surface antibody (anti-HBs, HBsAb) and HBsAg are used in laboratory testing to determine the infectious state; susceptible, immune, acute or chronic infection (CDC, 2011; Mast et al., 2006) (Table 1). HBV itself is not cytopathic, liver damage is a result of the immune attack of cytotoxic T cells against the antigens attached to the hepatocytes, hence, it is a cell-mediated immune injury (Greenberger et al., 2012; Hibberd, 1995; Levinson, 2010). Eight genotypes of the virus are distributed geographically (Greenberger et al., 2012), and immunization or infection with one serotype confers immunity to all serotypes (Mast et al., 2006).
HEPATITIS B INFECTION

HBV infection is often asymptomatic, with an incubation period of four weeks to six months, averaging three months (Greenberger et al., 2012; Levinson, 2010). Sometimes the infection presents as flu-like symptoms. Exposure to HBV is seventeen times more common nationally than chronic infection (Ioannou, 2011). An acute infection occurs when a patient has levels of HBsAg in their blood for less than six months, and frequently the disease is limited to the acute stage, while conferring immunity to the subject following resolution of the virus (Levinson, 2010). The majority (95%) of primary infections in healthy adults with normal immune function are self-limited (Greenberger et al., 2012; Mast et al., 2006). If the body is unable to clear the infection within six months, the disease has entered the chronic state and may persist for life. Most carriers in the chronic state are asymptomatic, though the risk of the patient developing cirrhosis and liver failure remains (Counard et al., 2010; Greenberger et al., 2012). Patients infected chronically as infants and children are at an increased risk of developing chronic hepatitis B and hepatocellular carcinoma (Greenberger et al., 2012; Levinson, 2010).

HEPATITIS B VACCINE

Following a 1991 recommendation by the Centers for Disease Control and prevention (CDC), the Occupational Safety & Health Administration (OSHA) implemented its Bloodborne Pathogen Standard, designed to decrease illness and death resulting from blood borne infections (Louther et al., 1998). Included in this standard was the vaccination against HBV. The vaccine is a yeast-derived recombinant form developed in the mid-1980s, successor to the original plasma-derived vaccine of the early 1980s (Stephenne, 1990). The hepatitis B vaccine is one of the safest available (Lemon & Thomas, 1997). In the United States there are five vaccines in use, two single antigens and three combination forms (CDC, 2011). Most subjects receive either
Recombivax HB™ or Energix-B™, the two single antigen vaccines, as they are equally immunogenic and interchangeable (Lemon & Thomas, 1997). This vaccine has been so effective worldwide it was discovered that the number of liver cancers decreased dramatically, demonstrating that the HBV vaccine appears to be the first vaccine known to prevent a human cancer (Levinson, 2010). Separate dosing schedules have been established, one for infants, children and adolescents, and another for adults. Both are three dose treatments. While the campaign has been largely successful worldwide, among those who received the three dose regimen, some fail to demonstrate immunity. Most concerning are those in high risk populations, specifically healthcare workers, as HBV is the most commonly transmitted blood-borne virus in the healthcare setting (Mast et al., 2006). Facilities in which health care is delivered have changed from mainly acute hospitals to outpatient offices as well, where infection control practices may not be as strictly enforced or affordable (Mast et al., 2006; Thompson, Perz, Moorman, & Holmberg, 2009). Due to changing medical practices involving needle use and the influx of ethnic groups more at risk for HBV, it has been a challenge to determine whether the prevalence of HBV infection is indeed decreasing within the United States, as the success of the vaccination program would suggest (Ioannou, 2011).

**VACCINATION MEASUREMENTS**

Immunizations are required of every HCW, with the specific vaccinations varying dependent on the risk of exposure and type of patient contact the worker is likely to experience (Figure 2). Some employees refuse vaccines, while others have less than optimal responses to an appropriate vaccination regimen (Louther et al., 1998). This leaves some employees not only susceptible to illness themselves, but also in transmitting an illness and perhaps even in keeping their job (Jarrosson et al., 2004). Most hospitals follow the guidelines established by the CDC
when it comes to vaccination protocols and questions. The standards are available to the public as well at the CDC websites. Since the implementation of the childhood vaccination program against hepatitis B in the early and mid-1990s, most adults today have already received their series of shots. For any adult without a complete series, the typical dosing schedule for adults (>20 years) is an intramuscular vaccination at zero, one and six months, with other schedules available depending on the circumstances under which the patient is being vaccinated, and are generally equally as successful (Mast et al., 2006) (Figure 1). To determine whether or not the vaccination was successful, at an interval of one to two months following the third injection, antibody titers are sometimes drawn to show response and thus protection, by measuring the level of HBsAb (anti-HBs) (Greub, Zysset, Genton, Spertini, & Frei, 2001; U. S. Centers for Disease Control and Prevention, 2011). There is no defined value of anti-HBs that demonstrates successful vaccination, however, the CDC recognizes levels of >10 mIU/mL for seroconversion (responders), and levels of <10 mIU/mL nonresponders (Alimonos, Nafziger, Murray, & Bertino, 1998; Jarrosson et al., 2004; McMahon et al., 2009; Zuckerman, Sabin, Craig, Williams, & Zuckerman, 1997). There are also recommendations for subjects who do not demonstrate immunity (response) with the first three dose series. According to the results of the National Health and Nutrition Examination Survey (NHANES), the number of children and adolescents with a level of anti-HBs that would indicate response to the vaccine and thus immunity is significantly lower than the reported number of completed vaccination series in the same population (Ioannou, 2011). Lack of universal immunity to a disease significantly restricts the ability to eradicate the disease.
VACCINATION CHALLENGES

Approximately 10-15% of the population does not develop antibodies to the vaccine (Kruskall, Alper, Awdeh, Yunis, & Marcus-Bagley, 1992; Mast et al., 2006; Zuckerman et al., 1997). The CDC states that in subjects without adequate levels of anti-HBs, they may be primary nonresponders or are infected with HBV, as well as possible genetic factors (Alper et al., 1989; Kruskall et al., 1992; Mast et al., 2006). Populations at an increased risk of poor response to the vaccine include males, the immunocompromised, smokers, those of increasing age (>40), and subjects with higher body mass indexes (BMI) (Louther et al., 1998; Poland, 1998; Stephenne, 1990). However, some nonresponders appear to have no risk factors that suggest a lack of ability to respond to the vaccine. One study examined the efficacy of the two common vaccines (Recombivax HB™ and Energix-B™) in these higher risk populations, finding that Energix-B™ was more efficacious in older adults (Poland, 1998). Conferring life-long immunity to HBV through vaccination has been hypothesized to occur in several different ways. Multiple studies indicate that protection from HBV is not reflected in long-term antibody titers if the immunization was successful, as indicated with an initial positive titer. Though difficult and expensive to measure, plasma and memory B cells, along with T helper cells, appear to be important, with the memory B cells most critical for long-term protection (Greub et al., 2001; McMahon et al., 2009; Rosado et al., 2011; Ward, Phalora, Bradshaw, Leyendeckers, & Klenerman, 2008). Plasma cells are thought to be short- or long-lived and unable to divide further, while memory B cells may be able to differentiate to secrete antibodies once an antigen is present (Ward et al., 2008). Changing the dose and location of vaccine administration may also play a role in effectiveness. A study by Zuckerman et al. (1997) examined the success of a new generation of vaccine in nonresponders, finding it to be more effective in conferring
immunity (Zuckerman et al., 1997). Development of a new vaccine may also be useful for individuals with certain HLA haplotypes, who appear to have alterations in their major histocompatibility complex (MHC) determinants, suggesting that vaccine nonresponse may be inherited in a recessive fashion resulting in an absence or decrease of T-cell help (Alper et al., 1989; Kruskall et al., 1992). Exposure to HBV is more common than chronic infection, and though individuals may appear to clear the infection and sustain immunity, it is possible that some components of the virus may remain in the body, leaving the subject at risk for subsequent liver damage or cancer (Ioannou, 2011). Infection risk in hyporesponders and nonreponders is unknown (Greub et al., 2001; Jarrosson et al., 2004).

MANAGEMENT OF NONRESPONSE

There is no set procedure to do further testing to determine a cause for the lack of response. Jarrosson et al. (2004) found that “serological nonresponders are able to develop a cellular immune response after HBV vaccination, and retain significant although small numbers of sensitized T-cells, liable to expand again upon further encountering the antigen” (p. 3794). As it would not be possible to study the effect of exposing a nonresponder to the virus, these individuals should be considered at risk for infection (Weissman et al., 1988). It appears there is no guideline to report to the CDC any subject that appears to be a nonresponder. Though the percentage of the population of nonresponders that are healthcare workers is likely to be small, this is a population that is continually at an increased risk of contracting and potentially spreading hepatitis B. Regardless of the universal vaccination of all newborns and anyone else at risk not vaccinated as a baby, with such a virulent disease it is imperative to keep the HCW protected. “To protect individuals at high risk for hepatitis B exposure against becoming infected with HBV, there is a need for effective regimes that can make nonresponders respond to
hepatitis B vaccine” (Cardell, Akerlind, Sallberg, & Fryden, 2008, p. 300). On a daily basis HCWs are interacting with patients who likely have diminished immune capacity, and may be capable of contracting the disease should they be exposed by an unprotected HCW who unknowingly has contracted HBV. This is underscored in a statement by Thompson et al. (2009), who state there is an “inadequacy of current surveillance for viral hepatitis in the US to detect health care-related HBV infection” (p. 37). This threatens the foundation of the immunization program if a secondary means of vaccination or vaccine itself cannot be developed to confer immunity in this subset of individuals.
METHODS

In order to assess hospital policies on the management of nonresponders to the hepatitis B vaccine, a survey was developed and distributed to infection control personnel at several local facilities. The survey collected basic demographic data about the facilities (name, location, number of staff, year opened) and thirteen questions immediately pertinent to the evaluation of nonresponder management (Appendix A). A cover letter accompanied the survey explaining the purpose and procedures to follow (Appendix A). The target population was Michigan and Ohio hospitals. The initial method of distributing the survey was through the use of a national infection control resource website, APIC (Association for Professionals in Infection Control and Epidemiology, Inc.). It was delivered by electronic mail to 82 members within Ohio, with a request to be completed within four weeks and returned in the same manner it was delivered (electronic mail). Once the four week deadline had passed, the number of responses was reviewed to see if another method of distribution was appropriate. The second method used to contact hospitals for survey data was through contact information gathered from local hospital websites. This method was largely used to contact the Michigan hospitals, and a few Ohio facilities. The cover letter and survey were again delivered by electronic mail. All data was tallied and organized using Microsoft Excel. Epidemiology information was gathered from the Michigan Department of Community Health (MDCH), Ohio Department of Health (ODH) and the CDC website.
RESULTS

A total of 7 surveys were returned from both Michigan and Ohio facilities. Of those seven, two were from hospitals that belonged to systems which each consisted of multiple facilities. Four surveys were returned from the APIC group, the remaining were collected after contacting facilities using the contact information found on their websites. The results are tabulated in Table 2.

Several questions were consistently answered with the same response from all hospitals. These were questions one, two, eight, nine, eleven and thirteen. Very few facilities had any data regarding the prevalence of acute, chronic or perinatal hepatitis B infections within the last ten years. There was not a lot of consistency with which immunity was defined among the facilities (Question 4: How do you define response to the vaccine (what minimum titer value)? & Question 5: How do you define nonresponse to the vaccine (what titer value)?), and there was also a lot of variance within the policies regarding a second three-step vaccination series (Question 6: For nonresponders, is a second 3-step series optional or required?).

Though the answers varied among facilities, there did not appear to be any increased limitation placed on employees who were not considered responders (Questions 11: Are there any additional requirements of employees who are nonresponders? & Question 12: Are any limitations imposed on nonresponder staff?). No facility reports their non-responding employees to the CDC (Questions 8: For staff not responding to two complete series, are they reported to the CDC? & Question 9: How many years have you been reporting nonresponders to the CDC?).
DISCUSSION

Owing to the fact that there was no easy way to contact a large number of hospitals and therefore get a high survey return, no statistics were calculated for this data. Hepatitis B is a reportable infectious disease in both Michigan and Ohio. In the question regarding the number of cases within the last ten years (Question 10), only one case was reported, and it was chronic. It is possible this question was not worded to facilitate accurate collection of this data, or that the appropriate department was not reached that had access to the information. This is more evident when looking at the ODH website, which collects and reports data on notifiable diseases. In 2010 alone there were a total of 1,903 cases of acute, chronic or perinatal hepatitis B infection within the entire state of Ohio. Broken down by county, there were a total of 129 cases of chronic hepatitis B within the seven counties represented by the returned surveys (Ohio Department of Health, 2012). Where did the information come from that was reported to the ODH if not from a hospital? A five-year summary (2005-2009) of reportable communicable diseases in Michigan listed 133 acute cases of hepatitis B, near the average reported during the entire five year period, 139 (Michigan Department of Community Health, 2010). No listing was made of chronic cases for the Michigan data. Nationally there were 3,374 cases of acute hepatitis B reported in 2010 (Adams et al., 2012).

All responding facilitates reported that they know the CDC guidelines for PEP (Question 13). This parallels the requirement of reporting hepatitis B infections to the CDC, which all facilitates reportedly do. However, it is not a requirement of the CDC to receive report of exposure to hepatitis B, and the viral hepatitis surveillance system is poorly developed and fragmented (Mitchell et al., 2010). For individuals who have been vaccinated successfully this
should not be an issue, but for those whose immune status is questionable, it may be of benefit to track this more closely.

There was also consistency within the knowledge of the vaccination guidelines and schedule, with all hospitals reporting that they know both (Questions 1 & 2). However, not all facilities require titers to prove immunity. Within those that do require titers, there is a variance in what value immunity is represented as (Questions 4 & 5). Two facilities listed the CDC value as the reference they use, while two others simply used the “lab reference” as demonstrating immunity without explaining what that reference was, two did not give a response, while the last uses a Mayo Clinic value of above or below 12.0 mIU/mL. Perhaps this question could have been clarified further by lab personnel who work directly with the equipment and values daily. This still leaves a gray area in regards to what hospitals define as immunity for healthcare workers, even though the CDC information suggests that the value should be \( \geq 10 \) mIU/mL (Mast et al., 2006). Standardization should be a goal.

It is interesting that not all facilities require the antibody titer, as this is a largely preventable disease (Question 3). The low acute occurrence rate within Ohio (123 of the 1,903 cases) can both argue for and against the titer draw (Ohio Department of Health, 2012). Clearly the vaccination program is effective and so perhaps drawing a titer is not of the benefit for this disease that it may be for others. However, the frequency with which healthcare workers are exposed to potential carriers of the disease makes knowledge of their immune status that much more important. For the 2010 data on Ohio notifiable diseases, hepatitis B was second only to hepatitis C, which is not preventable (Ohio Department of Health, 2012). For the Michigan data, acute cases of hepatitis B surpassed those of hepatitis C in each year of the report (Michigan
Department of Community Health, 2010). This further emphasizes the importance of monitoring vaccination effectiveness.

Two facilities had additional requirements of a nonresponder, and that was to have their surface antigen (HbAg) drawn to look for current infection (Question 11). It was expected that there would not be any extra limitations placed on employees who did not receive immunity through the hepatitis B vaccine (Question 12). This would fall under the umbrella of discrimination and really has no direct effect on the ability of an individual to carry out their job responsibilities. Similarly, it was anticipated that the facilities would not report their non-responders to the CDC, as there is no requirement to do so (Questions 8 & 9).

Several facilities listed that upon the lack of demonstrated immunity in an individual (as defined by their respective titer value), they would be referred for counseling of their immune status against hepatitis B, or that their employer or department director would be made aware (Question 7). There was no detail in what defines “counseling”. It is important that employees are conscious of their susceptibility to infectious diseases they have been vaccinated against so they are aware of the steps to take should they be exposed. In a study using multiple enzyme-linked immunoassays (EIA) to look at the antibody levels in nonresponders, it was found that the results of the antibody level depended on the sensitivity or specificity of the assay, questioning the label of true nonresponder, and suggest that additional doses of vaccine should not necessarily be given (Greub et al., 2001).

Along those lines, three of the facilities that responded had a routine practice of repeating the three-dose series (Question 6). The Occupational Safety and Health Administration (OSHA) require use of the U.S. Public Health Service (USPHS) guidelines current at the time of the
evaluation or procedure, found in the *Quick Reference Guide to the Bloodborne Pathogens Standard* (U. S. Department of Labor), which state:

Employees who have ongoing contact with patients or blood and are at ongoing risk for percutaneous injuries must be tested for antibody to hepatitis B surface antigen, one to two months after the completion of the three-dose vaccination series. Employees who do not respond to the primary vaccination series must be revaccinated with a second three-dose vaccine series and retested. Non-responders to the second series must be medically evaluated. (para 17)

This is not to say that these facilities surveyed are in violation of federal regulations, but it is fascinating that a standard exists and is followed in fragments. Though the CDC promotes revaccination, several studies have concluded revaccination and even booster shots are not necessary (Greub et al., 2001; Ioannou, 2011; Jarrosson et al., 2004; Lemon & Thomas, 1997; McMahon et al., 2009; World Health Organization, 2010), while others indicate the success of a second series (Greenberger et al., 2012), leaving a gray area of how best to proceed in the treatment of a nonresponder to the primary vaccination. Should subsequent doses be given, no more than two complete three-dose series are recommended in an individual who is considered a nonresponder (Mast et al., 2006).

**LIMITATIONS**

There were a few limitations of this research study. Most importantly was the surprisingly low response rate. Of the ninety hospitals contacted to complete the survey, only seven responded. This may have been due in part to the survey being delivered electronically, which does not allow an individual to hold the survey, making easier to set aside in a digital world and never be seen again. Also, it could be possible that the survey was sent to the wrong department and that
it was not returned because much of the information was not easily available to the person in possession of the survey. We submitted the email to infection control personnel, but many of the questions were lab based, and perhaps the hospital laboratory would have been more appropriate to contact with the survey, as well as the infection control personnel.

With a low response rate such as this, it does make the ability to draw conclusions more challenging. While there were no statistics calculated for this data, we believe that the range of information within the few responses demonstrates that there is clearly a gray area in the definition and management of vaccine nonresponse among HCWs. Thus the objective of our research was met, to highlight an area of infection control practice that needs to be examined for clarity and conciseness.
CONCLUSION

Vaccinations were created in an effort to improve morbidity and mortality and have saved countless lives. The hepatitis B vaccine is the first given at birth and one of the few required of new employees entering many healthcare settings. It is generally effective and cost efficient. Some individuals appear to be less susceptible to the effects of the vaccine and research needs to be performed in understanding what hepatitis B exposure means to these people. Will they be adequately protected against an acute or chronic infection? Will their children also be subject to similar concerns? Equally as important, does a poor response to this vaccine indicate that these individuals will have a similar reaction to other vaccines that are not routinely tested for, as a study by Cardell et al. suggests? (Cardell et al., 2008) Perhaps an OSHA requirement with support from the CDC of hepatitis B titers and a standard of re-vaccination or more detailed serologic testing would be appropriate among healthcare professionals and facilities. This may help “provide occupational medicine with a way to stop the revaccination of nonresponders who display specific cellular responses” (Jarroson et al., 2004, p. 3795). It would allow for continuity and awareness of the effectiveness of the vaccine among individuals most at risk. It may even lead to a prompting of further investigation among the general population for nonresponse to the vaccine, or a more universally effective one.
REFERENCES


### Interpretation of Hepatitis B Serologic Test Results

<table>
<thead>
<tr>
<th>Tests</th>
<th>Results</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>negative</td>
<td>Susceptible</td>
</tr>
<tr>
<td>anti-HBc</td>
<td>negative</td>
<td></td>
</tr>
<tr>
<td>anti-HBs</td>
<td>negative</td>
<td></td>
</tr>
<tr>
<td>HBsAg</td>
<td>negative</td>
<td>Immune due to natural infection</td>
</tr>
<tr>
<td>anti-HBc</td>
<td>positive</td>
<td></td>
</tr>
<tr>
<td>anti-HBs</td>
<td>positive</td>
<td></td>
</tr>
<tr>
<td>HBsAg</td>
<td>negative</td>
<td>Immune due to Hepatitis B vaccination</td>
</tr>
<tr>
<td>anti-HBc</td>
<td>negative</td>
<td></td>
</tr>
<tr>
<td>HBsAg</td>
<td>positive</td>
<td>Acutely infected</td>
</tr>
<tr>
<td>anti-HBc</td>
<td>positive</td>
<td></td>
</tr>
<tr>
<td>IgM anti-HBc</td>
<td>positive</td>
<td></td>
</tr>
<tr>
<td>anti-HBs</td>
<td>positive</td>
<td></td>
</tr>
<tr>
<td>HBsAg</td>
<td>positive</td>
<td>Chronically infected</td>
</tr>
<tr>
<td>anti-HBc</td>
<td>negative</td>
<td></td>
</tr>
<tr>
<td>IgM anti-HBc</td>
<td>negative</td>
<td></td>
</tr>
<tr>
<td>anti-HBs</td>
<td>negative</td>
<td></td>
</tr>
</tbody>
</table>

**Interpretation unclear; four possibilities:**
1. Resolved infection (most common)
2. False-positive anti-HBc, thus susceptible
3. "Low level" chronic infection
4. Resolving acute infection

**Hepatitis B surface antigen (HBsAg):** A protein on the surface of HBV; it can be detected in high levels in serum during acute or chronic HBV infection. The presence of HBsAg indicates that the person is infectious. The body normally produces antibodies to HBsAg as part of the normal immune response to infection. HBsAg is the antigen used to make Hepatitis B vaccine.

**Hepatitis B surface antibody (anti-HBs):** The presence of anti-HBs is generally interpreted as indicating recovery and immunity from HBV infection. Anti-HBs also develops in a person who has been successfully vaccinated against Hepatitis B.

**Total Hepatitis B core antibody (anti-HBc):** Appears at the onset of symptoms in acute Hepatitis B and persists for life. The presence of anti-HBc indicates previous or ongoing infection with HBV in an undefined time frame.

**IgM antibody to Hepatitis B core antigen (IgM anti-HBc):** Positivity indicates recent infection with HBV (≤6 months). Its presence indicates acute infection.

---

<table>
<thead>
<tr>
<th>#</th>
<th>Question</th>
<th>Yes</th>
<th>%</th>
<th>No</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Do you know the guidelines for Hepatitis B vaccination?</td>
<td>7</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Do you follow the vaccination schedule recommended by the CDC?</td>
<td>7</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Do you require Hepatitis B titers?</td>
<td>4</td>
<td>57.1</td>
<td>3</td>
<td>42.9</td>
</tr>
<tr>
<td>4</td>
<td>How do you define response to the vaccine (what minimum titer value)?</td>
<td>2 (29%) use CDC value of &gt;10mIU/mL</td>
<td>2 (29%) listed a &quot;positive&quot; titer without defining a value</td>
<td>1 (14%) uses a Mayo Clinic value of &gt;12mIU/mL</td>
<td>1 (14%) did not respond</td>
</tr>
<tr>
<td>5</td>
<td>How do you define nonresponse to the vaccine (what titer value)?</td>
<td>2 (29%) use CDC value of &lt;10mIU/mL</td>
<td>2 (29%) listed a &quot;negative&quot; titer without defining a value</td>
<td>1 (14%) uses a Mayo Clinic value of &lt;12mIU/mL</td>
<td>1 (14%) did not respond</td>
</tr>
<tr>
<td>6</td>
<td>For nonresponders, is a second 3-step series optional or required?</td>
<td>3</td>
<td>42.9</td>
<td>4</td>
<td>57.1</td>
</tr>
<tr>
<td>7</td>
<td>For nonresponders to two 3-step series, what procedure is followed?</td>
<td>2 (29%)-HbAg drawn</td>
<td>2 (29%)-counseling</td>
<td>2 (29%)-no answer given</td>
<td>1 (14%)-booster dose</td>
</tr>
<tr>
<td>8</td>
<td>For staff not responding to two complete series, are they reported to the CDC?</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>100</td>
</tr>
<tr>
<td>9</td>
<td>How many years have you been reporting nonresponders to the CDC?</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>100</td>
</tr>
<tr>
<td>10</td>
<td>How many cases of acute, chronic and perinatal Hepatitis B infections have you had in each of the following years? (2000-2009)</td>
<td>No responses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Are there any additional requirements of employees who are nonresponder?</td>
<td>1</td>
<td>14.3</td>
<td>6</td>
<td>85.7</td>
</tr>
<tr>
<td>12</td>
<td>Are any limitations imposed on nonresponder staff?</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>100</td>
</tr>
<tr>
<td>13</td>
<td>If a nonresponder is exposed to Hepatitis B, do you follow the CDC guidelines for PEP (post-exposure prophylaxis)?</td>
<td>7</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Figures

<table>
<thead>
<tr>
<th>0, 1, and 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>0, 1, and 4 months</td>
</tr>
<tr>
<td>0, 2, and 4 months</td>
</tr>
<tr>
<td>0, 1, 2, and 12 months*</td>
</tr>
</tbody>
</table>

* All schedules are applicable to single-antigen hepatitis B vaccines: Twinrix® (combined hepatitis A and hepatitis B vaccine) may be administered at 0, 1, and 6 months.

† A 4-dose schedule of Engerix-B® is licensed for all age groups.

Figure 1. Hepatitis B vaccine schedules for adults (aged >20 years)*(Mast et al., 2006)
Persons at risk for infection by sexual exposure

- Sex partners of hepatitis B surface antigen (HBsAg)-positive persons
- Sexually active persons who are not in a long-term, mutually monogamous relationship (e.g., persons with more than one sex partner during the previous 6 months)
- Persons seeking evaluation or treatment for a sexually transmitted disease
- Men who have sex with men

Persons at risk for infection by percutaneous or mucosal exposure to blood

- Current or recent injection-drug users
- Household contacts of HBsAg-positive persons
- Residents and staff of facilities for developmentally disabled persons
- Health-care and public safety workers with reasonably anticipated risk for exposure to blood or blood-contaminated body fluids
- Persons with end-stage renal disease, including predialysis, hemodialysis, peritoneal dialysis, and home dialysis patients

Others

- International travelers to regions with high or intermediate levels (HBsAg prevalence of ≥2%) of endemic HBV infection (Figure 4, Box 2)
- Persons with chronic liver disease
- Persons with HIV infection
- All other persons seeking protection from HBV infection

Figure 2. Adults recommended to receive hepatitis B vaccination (Mast et al., 2006)
Appendix A

Cover letter:

To whom it may concern,

My name is Lacey Kane, I am a second year Physician Assistant student at The University of Toledo College of Medicine. Currently I am working on a scholarly project, a research paper. The topic I am interested in is the management of healthcare workers who do not respond to the hepatitis B vaccine. No patient demographic data is going to be collected; I am more interested in the hospital policies regarding these employees. I am trying to assess if there is a lack of clarification regarding how to manage this population. All information will remain anonymous. Even though I am asking for facility names on the survey, each will be assigned an ID number. Any help with this project is greatly appreciated. Please refer to the following instructions and definitions as you complete the survey.

Sincerely,

Lacey Kane, PA-S2

Brian Fink, PhD, MPH, CHES (Principal Investigator)

University of Toledo College of Medicine

Physician Assistant Studies

Instructions/Definitions

- “Staff”: personnel providing direct patient care who perform tasks involving contact with blood, other body fluids and sharp medical instruments or other sharp objects (not just the number of people the facility employs, but the number meeting this criteria)

- When selecting an answer, please place an “X” in the box in front of your choice, or type in the boxes provided when appropriate.

- Upon completion of the survey, please return to: lacey.kane@rockets.utoledo.edu
Scholarly Project Survey: Hepatitis B Vaccine Response Policies

Facility name:________________________________________________________________

City, state:_______________________________________________________________

Number of staff:__________________________________________________________

Year opened:_____________________________________________________________

For the following questions, please answer as it applies to the protocols of your facility. Mark Yes/No when appropriate, or type in the space provided. Thank you for your participation.

1. Do you know the guidelines for Hepatitis B vaccination?
   □ Yes  □ No

2. Do you follow the vaccination schedule recommended by the CDC?
   □ Yes  □ No

3. Do you require Hepatitis B titers?
   □ Yes  □ No

4. How do you define response to the vaccine (what minimum titer value)?

   __________________________________________________________

5. How do you define nonresponse to the vaccine (what titer value)?

   __________________________________________________________

6. For nonresponders, is a second 3-step series optional or required?
   □ Required  □ Optional
7. For nonresponders to two 3-step series, what procedure is followed?

8. For staff not responding to two complete series, are they reported to the CDC?
   - Yes  - No

9. How many years have you been reporting nonresponders to the CDC?
   - Yes  - No

10. How many cases of acute, chronic and perinatal Hepatitis B infections have you had in each of the following years?

<table>
<thead>
<tr>
<th></th>
<th>Acute</th>
<th>Chronic</th>
<th>Perinatal</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>2002</td>
<td></td>
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<td></td>
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<td>2003</td>
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<td>2004</td>
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<td>2005</td>
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<td></td>
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<tr>
<td>2006</td>
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<td></td>
<td></td>
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<tr>
<td>2007</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>2008</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
11. Are there any additional requirements of employees who are nonresponders? If yes please explain.

☐ Yes  ☐ No

12. Are any limitations imposed on nonresponder staff? If yes, please list below.

☐ Yes  ☐ No

13. If a nonresponder is exposed to Hepatitis B, do you follow the CDC guidelines for PEP (post-exposure prophylaxis)?

☐ Yes  ☐ No
Abstract

BACKGROUND: Standard vaccination against Hepatitis B began 31 years ago. Healthcare workers are required to prove immunity with titers, some do not possess antibodies. Their immune status is unknown. We found there is conflicting information regarding policies for vaccination challenges.

METHOD: A survey was delivered by electronic mail to hospitals within Michigan and Ohio assessing their policies regarding definitions and management of nonresponders to the Hepatitis B vaccine.

RESULTS: About 57% of the facilities require Hepatitis B titers, with 43% requiring a second 3-dose series if the titers are negative. Much variation existed in the value of a positive titer. None of the facilities imposed limitations on employees who did not seroconvert.

CONCLUSION: The efficacy of the Hepatitis B vaccine among some individuals is questionable. There is no standard on how to approach an individual without immunity. This research highlights the lack of consistency regarding how to proceed.