

# EUROPEAN RECOMMENDATIONS FOR THE MANAGEMENT OF HEALTHCARE WORKERS OCCUPATIONALLY EXPOSED TO HEPATITIS B VIRUS AND HEPATITIS C VIRUS

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Exposure prevention is the primary strategy to reduce the risk of occupational bloodborne pathogen infections in healthcare workers (HCW). HCWs should be made aware of the medicolegal and clinical relevance of reporting an exposure, and have ready access to expert consultants to receive appropriate counselling, treatment and follow-up.

Vaccination against hepatitis B virus (HBV), and demonstration of immunisation before employment are strongly recommended. HCWs with postvaccinal anti-HBs levels, 1-2 months after vaccine completion, >10 mIU/mL are considered as responders. Responders are protected against HBV infection: booster doses of vaccine or periodic antibody concentration testing are not recommended. Alternative strategies to overcome non-response should be adopted.

Isolated anti-HBc positive HCWs should be tested for anti-HBc IgM and HBV-DNA: if negative, anti-HBs response to vaccination can distinguish between infection (anti-HBs >50 mIU/ml 30 days after 1<sup>st</sup> vaccination: anamnestic response) and false positive results (anti-HBs >10 mIU/ml 30 days after 3<sup>rd</sup> vaccination: primary response); true positive subjects have resistance to re-infection and do not need vaccination.

The management of an occupational exposure to HBV differs according to the susceptibility of the exposed HCW and the serostatus of the source. When indicated, post-exposure prophylaxis with HBV vaccine, hepatitis B immunoglobulin or both must be started as soon as possible (within 1-7 days).

In the absence of prophylaxis against hepatitis C virus (HCV) infection, follow-up management of HCV exposures depends on whether antiviral treatment during the acute phase is chosen. Test the HCW for HCV-Ab at baseline and after 6 months; up to 12 for HIV-HCV co-infected sources. If treatment is recommended, perform ALT (amino alanine transferase) activity at baseline and monthly for 4 months after exposure, and qualitative HCV-RNA when an increase is detected.

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## Introduction

Bloodborne pathogens such as hepatitis B (HBV) and C virus (HCV) represent an important hazard for healthcare workers (HCWs) [1]. In the general population, HCV prevalence varies geographically from about 0.5% in northern countries to 2% in Mediterranean countries, with some 5 million chronic carriers estimated in Europe; while HBV prevalence ranges from 0.3% to 3%. The World Health Organization (WHO) estimates that each year in Europe 304 000 HCWs are exposed to at least one percutaneous injury with a sharp object contaminated with HBV, 149 000 are exposed to HCV and 22 000 to HIV.

The probability of acquiring a bloodborne infection following an occupational exposure has been estimated to be on average <0.3% for HIV, 0.5% for HCV and 18%-30% for HBV, depending on the type of exposure (percutaneous injuries with hollow-bore, blood-filled needles carry the highest risk of infection), the body fluid involved, and the infectivity of the patient [1].

To implement and standardise a rational management of occupational exposures to HIV, HBV and HCV among HCWs in Europe, representatives of nine European countries participated in a project funded by the European Commission, and developed a comprehensive set of recommendations.

We present here recommendations for the general management of occupational risk of bloodborne infections, HBV vaccination and management of HBV and HCV exposures. A description of the project and recommendations for HIV post-exposure management, including antiretroviral prophylaxis, has been previously published [2], and so issues related to occupational risk and prevention of HIV infection following an occupational exposure will not be discussed further.

## General policies

Exposure prevention is the primary strategy to reduce the risk of occupational bloodborne pathogen infections. All preventive efforts should be made to reduce the risk of occupational exposures.

Healthcare organisations should have a system readily available to their personnel that includes educational programmes, written protocols for prompt reporting, evaluation, counselling, treatment, and follow-up of occupational exposures that might place HCWs at risk of acquiring a bloodborne infection.

## Educational programmes and training

All HCWs should be informed, educated and trained about:

- The possible risks and prevention of bloodborne infections after an occupational exposure;
- The measures to prevent bloodborne pathogen exposures:
  - Implementation of standard precautions,
  - Provision of personal protective equipment and safety devices,
  - Implementation of safer procedures,
  - HBV vaccination,
  - The principles of post-exposure management and the importance of seeking urgent advice following any occupational exposure immediately after it occurs, as certain indicated interventions must be initiated promptly to maximise their effectiveness.

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### **Reporting an occupational exposure**

Local health policies should specifically identify a designated healthcare provider to whom HCWs can be urgently referred in case of exposure, and who will be responsible for post-exposure management, provision of prophylaxis and clinical and serological follow-up. Access to clinicians who can provide post-exposure care should be available during all working hours, including nights and weekends.

HCWs should be made aware in advance of the medicolegal and clinical relevance of reporting an occupational exposure, how to report it and to whom it should be reported, and have ready access to expert consultants to receive appropriate counselling, treatment and follow-up.

### **HBV vaccination**

- HCWs should be vaccinated against HBV, with a standard vaccination schedule [3].

- Before entering nursing and medical schools and before employment in healthcare settings, vaccination or demonstration of immunisation against HBV is strongly recommended [4].

- Pre-vaccination screening is not routinely indicated [5].

- Antibody titre against HBsAg (anti-HBs) should be assessed 1-2 months after completion of a 3-dose vaccination series [6].

- New vaccines or alternative schedules that could determine a higher response rate or a stronger response should be used if available [7-8].

- Combined hepatitis A and hepatitis B vaccine is recommended in case of susceptible HCWs with HCV infection or other liver diseases [9], and could be considered for all HCWs regardless of their clinical status [10].

### **Definitions**

Primary 3-dose vaccination: three standard doses (according to manufacturers) of recombinant HBV vaccine administered intramuscularly in the deltoid region, preferably with a 25 mm needle [11], at 0, 1, and 6 months.

Responders: subjects with post-vaccinal anti-HBs levels, determined at 1-2 months from the last dose of vaccine, equal to or greater than 10 mIU/mL.

Non-responders: subjects with post-vaccinal anti-HBs levels, determined at 1-2 months from the last dose of vaccine, lower than 10 mIU/mL, who tested negative for HBsAg, and anti-HBc [see section 2c].

### **Post-vaccination management**

#### **HBV vaccination responders**

- Responders are protected against HBV infection [12].

- Routine booster doses of HBV vaccine are not recommended for known responders, even if anti-HBs levels become low or undetectable [13].

- Periodic antibody concentration testing after completion of the vaccine series and assessment of the response is not recommended [14].

#### **HBV vaccination non-responders**

- 5%-10% of the adult population will not respond to standard HBV vaccination.

- Risk factors for vaccine non-response include: male sex, older age, cigarette smoking, obesity, immunodeficiency, renal failure, intragluteal vaccine administration, chronic diseases, certain HLA haplotypes and coeliac disease [15-16].

- If non-responders test HBsAg/anti-HBc negative:

- Administer a fourth dose and then retest the HCWs for response 1-2 months later [17];

- If no response has been elicited, complete a full course of conventional vaccine at the standard doses (i.e. administer a fifth and sixth dose), and retest the HCW for response 1-2 months after the last dose of vaccine [17-18].

- Possible alternative strategies, that need further evaluation, to overcome nonresponse to standard HBV vaccination are: Vaccines

containing S subunit, pre-S1 and pre-S2 particles [19-20]; Three intradermal 5 µg doses of standard vaccine, given every two weeks [21]; Combined hepatitis A and hepatitis B vaccines [22]; High-dose standard vaccine series [18, 23-24].

### **Management of isolated anti-HBc**

- Test isolated anti-HBc positive HCWs for IgM anti-HBc and HBV-DNA [25], possibly with sensitive PCR assays, to determine whether these subjects are low-level HBsAg carriers, or in the window phase, or have occult HBV infection [26-27].

- If negative for anti-HBc IgM and HBV-DNA, initiate vaccination, and test the HCW 30 days after the first dose of vaccine: an anti-HBs titre exceeding or equal to 50 mIU/mL indicates an anamnestic response (isolated anti-HBc indicated infection with HBV) [28-29]. True positive subjects with isolated anti-HBc (those with anamnestic response) have resistance to HBV re-infection and do not need to complete vaccination or to receive HBV post-exposure prophylaxis [30].

- If anti-HBs response is <50 mIU/mL 30 days after the first dose of vaccine, complete the vaccination schedule and test the HCW: an anti-HBs titre exceeding or equal to 10 mIU/mL 30 days after the third dose of vaccine indicates a primary response (isolated anti-HBc was a false positive result).

- In case of an exposure to an HBsAg positive source, manage subjects with 'unresolved' isolated anti-HBc as susceptible.

### **Management of HBsAg-positive and HCV-Ab-positive HCWs**

- HCWs who prove to be HBsAg-positive and/or HCV-Ab positive should be counselled regarding the need for medical evaluation and regarding prevention of HBV and/or HCV transmission to others.

- Evaluation of the risk they pose to patients by an expert review panel according to national and international recommendations to prevent worker-to-patient transmission is strongly recommended [31].

### **Management of occupational exposures**

#### **Immediate treatment of the exposure site**

- Percutaneous exposure: encourage bleeding and wash with soap and water.

- Cutaneous contaminations: wash with soap and water.

- Mucous membranes contamination: flush with water.

- Eyes should be irrigated with clean water, saline, or sterile irrigants.

- Although no evidence exists that using antiseptics/disinfectants reduces the risk of bloodborne pathogen transmission, their use is not contraindicated, as both viruses are enveloped and are supposed to be relatively sensitive to many chemical agents.

- The application of caustic agents (i.e. bleach) or the injection of antiseptics or disinfectants onto the wounds is not recommended [1].

#### **Risk assessment**

- In case of an occupational exposure to an at risk bloodborne infection, baseline HBV, HCV, HIV immune status of the exposed HCW should be available.

- For medicolegal reasons, store a plasma and serum sample of the exposed HCW at baseline.

- Evaluate the exposure's potential to transmit HBV, HCV, and HIV, based on the type of exposure and body material involved [2].

- Evaluate the source patient's serostatus for antibodies against HIV (HIV-Ab), HCV (HCV-Ab) and for HBsAg. If unknown, inform the source patient of the incident and obtain an informed consent. Results should be readily available. Source testing for HBsAg can be avoided when the HCW is known to be protected by vaccine or natural immunity. Direct virus assays (e.g. HBV-DNA or HCV-RNA/HCV Ag) are not recommended.

- Store a plasma and a serum sample from the source for further investigations.

- Consider as infected sources who refuse testing or cannot be tested.

**Management of exposures to HBV**

The management of a possible occupational exposure to HBV differs according to the susceptibility and serostatus of the exposed HCW [TABLES 1,2]. When necessary, post-exposure prophylaxis with HBV vaccine, hepatitis B immunoglobulin (HBIG) or both must be started as soon as possible, preferably within 24 hours from the exposure and no later than one week [32-33]. This management is no different in pregnant HCWs [34].

HBsAg-positive HCWs should receive clinical evaluation and their serostatus, as well as risk for hepatitis D, should be assessed.

If, notwithstanding optimal post-exposure management, acute B hepatitis develops, the person should be referred for medical management to a specialist knowledgeable in this area.

**Follow up**

• Serological follow-up is not recommended when post-exposure management is in accord with the above mentioned recommendations.

**Management of exposures to HCV**

Currently, there is no available prophylaxis for HCV.

Data from the literature suggest that therapy (interferon or PegIFN +/-Ribavirin) may prevent chronicisation when administered to patients with acute HCV infection [35]. However, while it is documented that viral clearance can spontaneously occur after acute infection [36], it is unclear whether treatment of the acute or early

(first six months) phase is more effective than early treatment of chronic C hepatitis [37-38]. Further studies to clarify these issues are ongoing. As medical advice and personal choices could change in the near future, an optimal follow up management of occupational HCV exposure should allow prompt identification of infection, and be cost effective, bearing in mind that estimated incidence of HCV infection following an occupational exposure is on average 0.5%.

**1. HCV-Ab positive, untested or unidentifiable source**

• Test the HCW for HCV-Ab (EIA) at baseline and 6 months from exposure; extend to 12 months for exposures to HIV-HCV co-infected sources Confirm positive results with a recombinant immunoblot assay or qualitative HCV-RNA.

• Perform ALT activity at baseline, and then monthly for 4 months after exposure.

• Perform qualitative HCV-RNA when an increased transaminase level is detected.

• Some experts would also test for HCV-Ab at 3 months, as most seroconverters are already positive at this time, and in order to reduce loss to follow-up and the anxiety of the exposed HCW.

**2. HCV-Ab negative source**

• In case of HIV infection, immunosuppression or other conditions (i.e. dialysis) associated with possible false negative results in the source, follow recommendations for exposure to an HCV positive source.

TABLE 1

Post-exposure management in case of an HBsAg+, untested or unidentifiable source

Vaccinal status against HBV in the exposed HCW	Anti-HBs	HBIG (0.06 mL/kg)	HBV vaccine	Comment
Not vaccinated	Obtain rapid results If anti-HBs >10 mUI/mL: no treatment	If anti-HBs <10 mUI/mL: administer HBIG 1 dose ASAP and repeat after 1 month	1 <sup>st</sup> dose ASAP and then accelerated schedule 1-2-12 months	Administer HBV vaccine in the deltoid muscle; HBIG can be administered i.m. simultaneously at a separate site. Assess response 1-2 months after last dose
Incompletely vaccinated or does not recall a complete vaccination schedule	As above	1 dose ASAP	Complete according to documentation or restart 0-1-2-12 months	As above
Vaccinated with an unknown antibody response	As above	As above	1 booster ASAP	As above
Non-responder to primary vaccination		1 dose ASAP and repeat after 1 month	1 <sup>st</sup> dose ASAP and then accelerated schedule 1-2-12 months	As above
Previously vaccinated with 4 doses or two complete vaccine series but non-responder		As above	Possible alternative vaccine?	
Previously vaccinated and known responder	No	No	No	

Abbreviations

HBsAg: hepatitis B surface antigen; HBV: Hepatitis B Virus; HCW: Health Care Worker; anti-HBs: antibodies against hepatitis B surface antigen; HBIG: hepatitis B immune globulins; ASAP: as soon as possible; i.m.: intramuscular

TABLE 2

Post-exposure management in case of an HBsAg-source

Vaccinal status against HBV in the exposed HCW	Anti-HBs Testing	HBV vaccine	Comment
Not vaccinated		Initiate standard schedule	Assess response 1-2 months after last dose
Incompletely vaccinated or does not recall a complete vaccination schedule		Complete according to documentation or restart standard schedule	As above
Vaccinated with an unknown antibody response	Test for anti-HBs	If anti-HBs <10 mIU/mL administer 1 booster and retest after 1-2 months If still < 10 mIU/mL complete as a 2 <sup>nd</sup> standard vaccination schedule	As above
Non-responder to primary vaccination		Repeat standard schedule	As above
Previously vaccinated with 4 doses or two complete vaccine series but non-responder		Possible alternative vaccine?	
Previously vaccinated and known responder	No	No	

Abbreviations

HBsAg: hepatitis B surface antigen; HBV: Hepatitis B Virus; HCW: Health Care Worker; anti-HBs: antibodies against hepatitis B surface antigen; HBIG: hepatitis B immune globulins; ASAP: as soon as possible; i.m.: intramuscular

## Conclusions

Accidental blood and body fluid exposures entail the risk of occupational infection by bloodborne pathogens in HCWs, mainly HBV, HCV, and HIV [39-41].

Notwithstanding effective pre- and post-exposure prophylaxis for HBV and the availability of post-exposure prophylaxis against HIV, the best approach to avert cases of occupational bloodborne infection remains to prevent these exposures.

However, the adoption of a rational pre- and post-exposure management could help to minimise consequences and costs. In this regard, the recommendations here presented are complementary to the European recommendations for post-exposure prophylaxis of HIV infection in healthcare workers [2], both being developed within a project funded by the European Commission with the aim to standardise the management of occupational exposures to HIV/bloodborne infections in Europe. These recommendations must be considered dynamic documents. Indeed, scientific evidence appearing in the literature after the consensus meetings was also included in these documents, and recommendations may change in the future with further research and scientific information, as some issues remained unresolved or controversial.

Among issues related to HBV vaccination, there was no unanimous consensus regarding the post-vaccinal anti-HBs level to be considered as protective. A minority of the expert panel suggested a more conservative approach, in which those HCWs who have post-vaccinal anti-HBs levels between 10 and 100 mIU/mL are considered as low-responders. These subjects may, due to waning antibodies, develop asymptomatic hepatitis B infection and seroconversion after exposure, although only very rare cases of chronic infection/disease have been reported [42]. For these subjects, the same recommendations used for non-responders could be applied, including HBsAg determination. Indeed, among these subjects, concurrence of hepatitis B surface antibodies and surface antigen is also possible [43].

No data directly assess the efficacy of HBIG in post-exposure prophylaxis in HCWs. The use of hepatitis B vaccine alone after exposure to HBsAg-positive blood seems to achieve comparable results to HB vaccine combined with HBIG [44]; however, the vast majority of the expert panel agrees on HBIG administration. Nonetheless, in the discussion, several reservations were expressed regarding the administration of HBIG. For exposures to a source of unknown serostatus, while the majority of the expert panel would treat as if HBsAg positive, some experts would consider the option of HBIG administration according to the probability of infection of source patient (e.g. drug user, coming from high endemicity country, etc.). In unvaccinated HCWs testing anti-HBs negative, it was suggested that testing for anti-HBc would avoid HBIG administration if the subject had natural immunity. Moreover, as a protective response should be elicited in these subjects after the first three doses of vaccine during the accelerated vaccination schedule, the administration of the second dose of HBIG could be avoided; this same reservation was expressed for vaccinated HCWs with an unknown antibody response, in view of the high probability that the subject would respond to a booster dose, and for non-responders to primary vaccination, in view of the high probability that the subject would respond to a second, accelerated vaccination schedule.

Cost-effectiveness issues could also be considered; for example, in young subjects, low-dose intramuscular or intradermal vaccination provides long-term effective protection and can be used as a cost-saving vaccination strategy [45-46].

Finally, for the management of non-responders, nucleic acid vaccines or DNA vaccines are candidate vaccines to prevent and treat viral hepatitis, and hepatitis B DNA vaccine seems to induce protective antibody responses in human non-responders to conventional vaccination [47]. The preliminary results of an ongoing trial are promising in this regard.

Regarding the management of HCV exposures, until new anti-HCV drugs such as HCV serine protease inhibitors, which may eventually be used for post-exposure prophylaxis, neutralising antibodies to

hepatitis C virus [48], or an anti-HCV vaccine are available [49], the discussion focuses on the opportunity of treating acute infection, an issue thoroughly discussed during the consensus meeting. The resulting dichotomy is mirrored in the follow-up schedule. Further well-conducted, randomised clinical trials are needed to conclusively support the treatment option. Whether treatment during the acute phase could avoid the establishment of HCV reservoirs and therefore ultimately contribute to decrease the risk of cirrhosis and hepatocellular carcinoma, however, remains to be determined. New data will be necessary to give definitive indications on these and other issues.

In the meantime, it is important to maintain surveillance of occupationally exposed HCWs, and to promote a widespread implementation of preventive strategies such as standard precautions, education on exposure risk, better sharps disposal systems, personal protective equipment, and safety-engineered sharp devices to ensure a safer working environment in the healthcare setting.

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## ORIGINAL ARTICLES

## Outbreak report

## HUMAN-TO-HUMAN TRANSMISSION OF AVIAN INFLUENZA A/H7N7, THE NETHERLANDS, 2003

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An outbreak of highly pathogenic avian influenza A virus subtype H7N7 began in poultry farms in the Netherlands in 2003. Virus infection was detected by RT-PCR in 86 poultry workers and three household contacts of PCR-positive poultry workers, mainly associated with conjunctivitis. To determine the magnitude of and risk factors for human-to-human transmission of influenza A/H7N7 in the Netherlands, a retrospective cohort study among household members of infected poultry workers was undertaken. In total, 33 (58.9%) of 56 (among 62) participants who provided blood samples had positive H7 serology, using single convalescent serum samples obtained at least 3 weeks after onset of symptoms of the

index case. Eight household members (12.9%) reported symptoms (conjunctivitis and/or ILI), of which four of five (80.0%) tested seropositive. On univariate analysis, significant risk factors for seropositivity included having at least two toilets, a pet bird, and using cloth handkerchiefs. It was not possible to obtain a stable model for binomial regression for the outcome of A/H7N7 infection. Further seroprevalence studies among contacts of asymptomatic H7 cases should be conducted.

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### Background

On 28 February 2003, the highly pathogenic avian influenza A virus subtype H7N7 (HPAI A/H7N7) was isolated for the first time in the Netherlands from poultry on a farm, identifying the start of