ECDC Risk Assessment

Hepatitis A and blood donations

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Public health issue

Large scale outbreaks of hepatitis A in Latvia, Czech Republic and Slovakia and possible impact on the safety of blood donations in these countries

Consulted experts

This ECDC assessment does not represent necessarily the views of the experts consulted. It represents ECDC views, on the basis of the information obtained from the experts.

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Disease background information

Clinical picture

Acute hepatitis A (HAV) can be divided into 4 different clinical phases[1]:

1) Incubation/pre-clinical period: ranging from 10-50 days, the patient is asymptomatic and there is active replication of the virus, resulting in a high risk of transmission;
2) Prodromal/pre-icteric phase: the person experiences fever, malaise, anorexia, nausea and abdominal discomfort [2]. This phase can last from a few days to more than one week;
3) Icteric phase: this period is characterized by jaundice, usually within 10 days of initial symptom onset;
4) Convalescent period: the disease resolves slowly and in 3-20% of patients there is the possibility of relapsing hepatitis from 4-15 weeks after the initial symptoms resolved.

The overall case fatality ratio for hepatitis A is estimated around 0.01-0.03% [2, 3]. The severity of disease appears to be related to the age of the patient [4] or existence of underlying liver disease or other chronic diseases [1]. The case fatality ratio in hospitalised patients has been reported to be 0.23% in persons under 30, 0.38% in persons 30-39 years of age and 1.76% in persons over the age of 49 years [5]. Hepatitis A during pregnancy is not associated with more severe disease, higher maternal mortality, foetal loss or identifiable chromosomal abnormalities [6].

HAV is usually transmitted through the faecal-oral route and from person to person. Outbreaks in the past have been related to contaminated water, contaminated food items and in communities of injecting and non-injecting drug users. The incubation period varies from 2 to 6 weeks. The proportion of symptomatic infections with HAV range between 40-90% [7], a recent outbreak among children in France determined that 83.6% were symptomatic for HAV [8]. Therefore a potentially significant proportion of persons are asymptomatic, but active virus carriers, during outbreak settings.

Detection of the virus [1]

The diagnosis of HAV is usually done by detection of anti-HAV IgM in the serum and saliva [8] or virus/antigen in the faeces of patients during the acute phase of the disease. There exist commercial serological assays for the detection of Anti-HAV IgM and IgG. Molecular tests exist for the detection of viral RNA in serum, stool and the liver [9].

Changing epidemiology of hepatitis

Central and eastern Europe have intermediate HAV rates [10] when previously they were highly endemic. The average age of infection in countries like Poland has shifted from early to mid-adulthood. Reasons for this shift in epidemiological picture include rising economic status and improvements in the water quality in these countries [11]. In countries that move from endemic situations for HAV to more epidemic-prone situations (such as Latvia, Czech Republic and Slovak Republic), there is a risk that the adults that become infected experience a more severe disease [11].

Events background

Slovakia [12]

Between October and November 2008, there was a sudden increase in reported cases of HAV in the Slovak Republic. The majority of reported cases were under the age of 10 years and 80% of reported cases were from 4 districts in eastern Slovakia. The majority of these cases were restricted to a village of the Roma community.

Control measures implemented included: hospitalization and treatment, contact tracing, disinfection, post-exposure and preventative vaccination and public information campaigns.

Czech Republic [13]

In 2008, a steady increase in the number of reported cases of HAV was observed in the Czech Republic, by week 39 of 2008, the reported 602 cases were 8 times higher than the same period in 2007. The two most affected regions were the city of Prague and the central Bohemian region. The age distribution of the reported cases was 78.5% in persons between the ages of 15-64 years. No deaths were reported.

The implemented outbreak measures included [13]: patient isolation, quarantine, surveillance of contacts, disinfection, targeted vaccination in the outbreak areas, post-exposure prophylaxis by vaccine was provided to HAV contacts in foci, preventive vaccination was offered to IDUs and homeless people in Prague.

Latvia [14, 15]

In Latvia, since February 2008, a gradual increase in reported hepatitis A cases was seen in national surveillance data. Between February and July 2008 around 30% of these reported cases were amongst Intravenous Drug Users (IDUs). In April 2008, an outbreak was identified to be linked to a single source in a restaurant. Since then, the outbreak has extended to the general population [14]. At present the outbreak continues to affect between 100-200 new cases per week nationwide with around 80% of new cases occurring in the city of Riga and around 80% of these cases in adults over 18 years of age (personal communication J. Perevoščikovs). Up to November 2008, 16 deaths have been reported due to HAV infection.

Implementation of control measures were initiated early and included: hospitalization and treatment of affected cases, epidemiological investigations around each reported case, quarantine of identified cases and health information campaigns targeted at the general public, food handlers and staff of educational facilities and seminars and trainings for healthcare workers and medical staff of educational facilities.

Blood supplies and measures

Slovakia **(personal communication J. Rosochová and J. Koller)**

As the two outbreaks were highly localized in isolated communities, a risk assessment undertaken by the Public Health Institute with the national transfusion service and national organ, tissues and cells transplantation system stated that the risk of disease transmission by organ/tissue donation was very low in this particular case. Recommendations for blood donors from outbreak affected areas were put into place, these included:

- Informing donors about the epidemic situation;
- Asking donors actively about their stay in the outbreak affected areas;
- Deferring all donors from affected areas during the outbreaks and for an additional 2 months;
- Deferring all donors that visited the outbreak affected area up to 2 months after leaving the epidemic region.

***Czech Republic* (Personal communication D. Starkova)**

Blood banks were informed of the epidemiological situation and asked to take measures accordingly, these included:

- IDUs and homeless people are excluded from blood donation;
- Anybody who was in close contact with serious contagious disease (incl. HA) is temporarily deferred for period longer than incubation period;
- Donors are tested for alanine aminotransferase (ALT) in each donation;
- Donors are trained to inform blood establishment in case of complication / illness (incl. HAV) after donation;
- Public health service inform blood establishments on regular basis about new hepatitis cases (HAV, hepatitis B, Hepatitis C etc.) in the region.

***Latvia* (personal communication J. Perevoščikovs)**

The central blood bank in Latvia routinely screens donations on ALT levels using levels >90 UI/L as a cut-off for the level of enzymes that would indicate an impaired liver function. No blood products are exported outside of Latvia. Additionally the following measures are routinely implemented in the central blood bank:

- Persons with high risk of infection are excluded from blood donation, for instance IDUs and homeless people;
- Donors who have been in contact with communicable diseases (including HAV) are temporarily deferred;
- Epidemiologists who conduct epidemiological investigations should inform the blood donor centers in the case that an HAV patient indicates during his interview that he donated blood prior to his disease onset. Also, the interview includes questions related to the reception of blood products during the incubation period;
- Blood donors are asked to inform the blood donor centre in case they are diagnosed with an infectious disease soon after blood donation.

EU blood directive and hepatitis A [16]

The current EU Blood Directive 2004/33/EC includes the following recommendations specific for blood donations relevant to Hepatitis A and infectious disease outbreak situations:

- If a person has received the Hepatitis A vaccine, but has not recently been exposed to a known source of Hepatitis A infection, they will not be deferred from donating blood;
- Member States may choose to defer blood donations during specific epidemiological situations (such as outbreaks) and should be notified to the European Commission with a view to Community action.

Risk for blood supplies in Latvia

Theoretical risk associated with current level of hepatitis A transmission in Latvia

The transmission of HAV through blood and clotting factors has been reported, but rarely [4]. However, due to the nature of the outbreak reported in Latvia, ECDC was requested by the Commission to estimate the risk of obtaining contaminated blood products with HAV in Latvia during the current outbreak. The methods used were similar to Biggerstaff and Petersen [17, 18] and the 'Working Group Afssaps, EFS, INTS, InVS' [7] to estimate contamination of blood donations with west Nile virus and other infectious diseases respectively.

We used the following assumptions:

- 70% of cases are symptomatic;
- all symptomatic cases are reported through the surveillance system;
- the period of asymptomatic viremia is 16 days in symptomatic cases;
- the period of asymptomatic viremia is up to 70 days in asymptomatic cases [7];
- symptomatic persons are excluded from blood donation;
- blood donors are representative of the population aged 18-65 years in Riga.

We calculated the potential number of contaminated blood donations with HAV per 10,000 donations from 18 to 65 year old residents of Riga City where 80% of cases were reported. These calculations were performed for three defined outbreak periods: February-April, May-July and August-October. The results are shown in the Table 1.

Table 1: Risk of HAV contamination of blood donation in the city of Riga, Latvia, among persons 18-65 years of age, 2008.

Period	HAV+ blood donation /10,000 blood donations	CI95%
February – April 2008	1.36	1.16 - 1.56
May – July 2008	2.03	1.80 - 2.27
August – October 2008	10.59	10.05 - 11.13

Risk of infection in Latvia

Considering that Latvia is currently screening blood donors using ALT levels, and that a proportion of recipients have acquired natural immunity, the model can be reapplied taking into consideration the additional assumptions:

- ALT levels will be over the threshold of 90 UI/L after 16 days of infection for symptomatic and asymptomatic cases;
- A proportion of recipients have acquired natural immunity. On the basis of the sero-epidemiological survey carried-out in 1998, the following assumptions can be proposed:
    - 15% of persons aged 0 to 14 years have developed immunity;
    - 30% of persons aged 15 to 39 years have developed immunity;
    - 60% of persons the age of 40 have developed immunity.

Table 2: Risk of HAV infection for recipients of blood donation by age group, in the city of Riga, Latvia, among persons 18-65 years of age, August- October, 2008.

Age group	HAV infection /10,000 blood recipient	CI95%
0-14	4.47	4.24 – 4.70
15-39	3.68	3.49 – 3.87
40 &+	2.10	1.99 – 2.21

Implications for affected countries for blood supply

Hepatitis A infection following blood transfusion or the receipt of blood products appears rare [1] however parenteral transmission is possible [19]. For this reason, recipients of blood products are recommended in some countries to receive HAV vaccines [20, 21].

Between August and October 2008 in Latvia, the residual risk for being infected by hepatitis A when receiving blood products ranges from 2/10,000 recipients for adults over 40 years of age to 4.5/10,000 for children below the age of 15. It should be noted that not all control measures currently implemented in Latvia for blood safety could be taken into consideration when performing the risk calculation. It is therefore possible that the actual risk is reduced in relation with such additional deferral measures. It is important to note that during a large-scale outbreak of this kind, the risk of becoming infected in the general population is also high. However, the importance of calculating the risk in blood supplies remains important as these are infections that could be preventable through deferral measures and screening protocols on blood donations.

Considerations for blood donations in the current outbreaks:

- There is a risk that fresh blood products become contaminated by hepatitis A because the virus is not sensitive to the inactivation techniques used for these products;
- In highly localised outbreaks, deferring blood donations from the affected area would substantially reduce the risk of obtaining contaminated blood with HAV;
- It is possible that the risk associated with receiving a contaminated long lasting blood product is higher in the current scenario, as these products are usually prepared from many thousands of donors. However, as we have limited knowledge of the inactivation procedures used for long lasting blood products in Latvia, it is difficult to quantify this additional risk.

In outbreaks with a high incidence and where the general population is affected, especially the blood-donating population, the risk to the safety of the blood donation increases, and therefore additional options can be considered:

- Consider HAV antibody testing of each blood donor up to 2 months after the end of the outbreak;
- Development of HAV RNA detection capacity in the central blood bank (allowing for pooled blood screening);
- Consider the active implementation of HAV vaccination or IgG-HAV for persons receiving blood products (haemophiliacs, immunocompromised persons).

References

1. WHO, *Hepatitis A*. 2005.

2. McNeil, M., et al., *Aetiology of fatal viral hepatitis in Melbourne. A retrospective study.* Med J Aust, 1984. **141**(10): p. 637-40.

3. Willner, I.R., et al., *Serious hepatitis A: an analysis of patients hospitalized during an urban epidemic in the United States.* Ann Intern Med, 1998. **128**(2): p. 111-4.

4. *Control Of Communicable Diseases Manual* 18th Edition ed, ed. D. Heymann. 2004: American Public Health Association.

5. *Fields Virology*. 5th edition ed, ed. D. Knipe and P. Howley. Vol. Volume 1. 2007: Lippincott, Williams & Wilkins.

6. Koff, R.S., *Viral Hepatitis*. 1978, New York: John Wiley. 161-165.

7. Groupe de travail Afssaps, E., INTS, InVS, *Estimation quantitative du risque de contamination d'un don de sang par des agents infectieux*. 2007.

8. Santa-Olalla, P., et al., *Utilisation de tests salivaires dans l'investigation d'une epidemie d'hepatite A, Auvergne, decembre 2004.* Bulletin epidemiologique hebdomaire, 2006. **2-3**: p. 13-15.

9. Koff, R.S., *Clinical manifestations and diagnosis of hepatitis A virus infection.* Vaccine, 1992. **10 Suppl 1**: p. S15-7.

10. Cianciara, J., *Hepatitis A shifting epidemiology in Poland and Eastern Europe.* Vaccine, 2000. **18 Suppl 1**: p. S68-70.

11. Jacobsen, K.H. and J.S. Koopman, *Declining hepatitis A seroprevalence: a global review and analysis.* Epidemiol Infect. , 2004. **132**(6): p. 1005-22.

12. Hrivniakova, L., H. Hudecova, and M. Slacikova, *Hepatitis A Outbreak in Gypsy Village of Lomnicka*, in *Technical meeting on Hepatitis A outbreak response, Riga, European centre for Disease Control and Prevention, November 11, 2008*. 2008, Public Health Authority of the Slovak Republic.

13. Fabianova, K., et al., *Increase in hepatitis A cases in the Czech Republic in 2008--preliminary report.* Euro Surveill, 2008. **13**(40).

14. Perevoščikovs, J., *Community wide outbreak of Hepatitis A in Latvia in 2008*, in *Technical meeting on Hepatitis A outbreak response, Riga, European centre for Disease Control and Prevention, November 11, 2008*. 2008, Latvian Public Health Agency.

15. Perevoscikovs, J., et al., *Increase in hepatitis A cases in Latvia, in 2008, including an ongoing outbreak associated with a restaurant in Riga--preliminary report.* Euro Surveill, 2008. **13**(20).

16. EC, *Directive 2004/33/EC implementing Directive 2002/98/EC of the European Parliament and of the Council as regards certain technical requirements for blood and blood components,.*

17. Biggerstaff, B.J. and L.R. Petersen, *Estimated risk of West Nile virus transmission through blood transfusion during an epidemic in Queens, New York City.* Transfusion, 2002. **42**(8): p. 1019-26.

18. Biggerstaff, B.J. and L.R. Petersen, *Estimated risk of transmission of the West Nile virus through blood transfusion in the US, 2002.* Transfusion, 2003. **43**(8): p. 1007-17.

19. Franco, E., et al., *Risk groups for hepatitis A virus infection.* Vaccine, 2003. **21**(19-20): p. 2224-33.

20. Crowcroft, N.S., et al., *Guidelines for the control of hepatitis A virus infection.* Communicable Disease and Public Health, 2001. **4**(3): p. 213-227.

21. Arankalle, V.A. and M.S. Chadha, *Who should receive hepatitis A vaccine?* J Viral Hepat, 2003. **10**(3): p. 157-8.