MEETING REPORT

Technical meeting on hepatitis A outbreak response

Riga, November 2008

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Acknowledgements

ECDC would like to thank Dr. Jurijs Perevoscikovs and Dr. Uldis Līkops of the Public Health Agency of Latvia for hosting this meeting.

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Abbreviations

ALT	alanine transaminase
ECDC	European Centre for Disease Prevention and Control, Stockholm
HAV	hepatitis A virus
IDUs	injecting drug users
MSM	men having sex with men
PEP	post-exposure prophylaxis
PHPA	public health protection authorities
RT-PCR	real-time polymerase chain reaction

Executive summary

Although the overall incidence and burden of hepatitis A in the EU has continued to decrease in the last decade, there remains a high risk for sporadic and localised outbreaks. In the absence of vaccination strategies, specific risk groups such as IDUs and MSM continue to be at risk. The general population can also be at risk through subsequent person-to-person spread from localised outbreaks, as a consequence of decreasing general population immunity.

General measures available in outbreak situations include health education, good hygiene measures and limitation of spread from person-to-person. Timely diagnosis and surveillance reporting are crucial for implementing subsequent response control options and limiting the spread among at-risk groups and the general population. Outbreak investigation studies can help in identifying risks, rule out common source outbreaks, and assist in guiding short-term and long-term control measures. Furthermore, molecular laboratory methods can provide a tool to assist in delineating and possibly linking outbreaks, helping to identify characteristics of the affected population.

It was agreed that vaccination is an important control measure to be considered in outbreak situations. In view of the changing epidemiology across the EU, there is an identified need for accessible technical guidelines on control options for outbreak situations, particularly different vaccination strategies. Identifying the relative effectiveness of different vaccination strategies in controlling outbreaks, and the cost-effectiveness of vaccination options compared to general measures, would be useful supporting evidence when deciding on the control measures to be implemented in a specific outbreak.

Hepatitis A remains highly endemic worldwide. Global travel will continue to present added opportunities for introduction of infection to non-immune populations in the EU. Thus effective outbreak control measures combined with a preventive approach will be important in reducing the possible impact of sporadic outbreaks in the EU.

1 Introduction

The founding regulation[1] establishing the European Centre for Disease Prevention and Control (ECDC) gives ECDC a mandate in strengthening the capacity of the EU for the prevention and control of infectious diseases. In autumn 2008, the Czech Republic, Latvia and the Slovak Republic reported being affected by large hepatitis A outbreaks. Though each outbreak appeared to be independent, the Czech Republic and Latvia reported similar epidemiological observations with injecting drug users (IDU) being primarily affected, followed by community spread within the general population. Information exchange among MS through the Early Warning and Response System (EWRS) identified few isolated cases linked to either outbreaks in Latvia and Czech Republic, indicating limited spread within the EU from both events.

ECDC, in collaboration with the Public Health Agency of Latvia, organised a technical meeting on response options to hepatitis A outbreaks. The meeting intended to share experiences among affected Member States and review options available in response to community outbreaks of hepatitis A, with a particular focus on vaccination.

To achieve this aim, the meeting brought together public health representatives from the Czech, Latvian and Slovak ministries of health and/or public health institutes with experts in outbreak investigation, laboratory diagnosis and response strategies for hepatitis A outbreaks from other Member States, and with the support of The World Health Organization (WHO) European Region.

2 Objectives of the consultation

The objectives of this technical consultation were 1) to share the Member States' experiences in response activities to the current hepatitis A outbreaks and 2) review general response options available during hepatitis A outbreaks, in order to support ongoing response actions in the affected Member States, and identify any technical support needs related to hepatitis A outbreak response.

[1] Regulation (EC) No 851/2004 of the European Parliament and of the Council

3 Overview of hepatitis A epidemiology

3.1 European perspective

A general overview of hepatitis A and epidemiological trends in the EU was presented, based on statistical data available through The European Surveillance System (TESSy), which is organised and maintained by ECDC. Hepatitis A is a communicable disease under EU surveillance[2], with the case definition for reporting at community level available under the Commission Decision No 2008/426/EC[3].

The epidemiology of hepatitis A in the EU is as follows:

- Incidence of hepatitis A in the EU has declined steadily since 1995, from around 16 cases per 100 000 population to 4 per 100 000 population in 2006, representing over 20 000 cases reported in 2006 (data reported from 29 of the EU and EEA/EFTA countries) [1].
- Incidence varies among countries within the EU, with higher incidences in 2006 reported from Romania, Bulgaria and the Slovak Republic.
- In most EU Member States, lower incidence of hepatitis A over the years has led to an increase in the susceptibility of young people.
- Age-specific notification rates in 2006 showed that children aged less than 15 years were most affected.
- Hepatitis A in the EU shows a marked seasonal pattern with higher notification rates in the months of September and October. This may reflect increases related to travel during the summer holiday season, in addition to seasonal variation of domestic cases observed within some EU countries.
- Various outbreaks, varying in size and suspected cause, have been reported in Europe over the last 10 years. These include examples of outbreaks caused by contaminated water [2], contaminated seafood [3], contaminated food products imported into Europe [4] and infected food handlers [5]. Outbreaks have also been associated with injecting drug users (IDU) [6] and men having sex with men (MSM) [7], and previously, clusters identified among haemophiliacs receiving solvent/detergent inactivated factor VIII blood products [8].
- No overview of vaccination uptake throughout the EU is currently available through a common database at EU level.

3.2 The occurrence of hepatitis A in the Czech Republic

Data on hepatitis A in the Czech Republic were presented, including overall trends. Special attention was given to the 2008 outbreak and control measures implemented in response to this community outbreak.

The epidemiological situation of hepatitis A in the Czech Republic is as follows:

- Hepatitis A is a mandatory reportable disease in Czech Republic.
- The overall incidence of hepatitis A virus (HAV) infections has declined from around 3 500 cases per year (35 per 100 000 population) in the early 1980s to around 100 cases annually from 2002 (1 per 100 000 population).
- The 2008 outbreak is considered to have started in Prague around week 26. The incidence of hepatitis A within Prague city varied per neighbourhood and is considered to be linked to the distribution of the IDU population, which is estimated to be 10 000 in Prague.
- By calendar week 45, 1 233 cases had been reported, with the outbreak peak identified in week 39 (162 cases). Person-to-person spread of infection could be concluded from the outbreak curve with increasing incidence within each generation cycle until measures started to have an impact.
- The current outbreak has a different age distribution than that observed from surveillance trends under 1993–2007. In this outbreak, the peaks observed are among persons aged 20–40 years, compared to trends between 1993–2007 where younger persons aged <25 years were mostly affected.

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[2] Annex I of Commission Decision No 2000/96/EC of 22 December 1999 on the communicable diseases to be progressively covered by the Community network under Decision No 2119/98/EC of the European Parliament and of the Council, as amended by Decisions No 2003/534/EC,2003/542/EC and No 2007/875/EC.

[3] 2008/426/EC: Commission Decision of 28 April 2008 amending Decision No 2002/253/EC laying down case definitions for reporting communicable diseases to the Community network under Decision No 2119/98/EC of the European Parliament and of the Council (notified under document number C(2008) 1589) (Text with EEA relevance).

- Between calendar week 26 and 32 of the outbreak, the majority of cases were among the IDU population, but this proportion dropped because of an increase of incidence in the general population.
- Control measures implemented under the outbreak include general measures such as isolation of cases and quarantine in hospitals, surveillance of contacts, disinfection of contaminated environments, restrictions of work activities for high-risk occupations and health education in schools and to the public. A targeted vaccination campaign to IDUs was also implemented.
- The targeted measure of vaccination to IDUs in the outbreak areas was undertaken in Prague. The IDU population was reached through crisis centres, street workers and specific campaigns. Vaccination was implemented from week 33, with an approximate total of 2 500 of the estimated 10 000 IDU population vaccinated during the entire campaign.
- In clusters associated with schools, classmates of cases received vaccination.
- Post-exposure prophylaxis (PEP) is funded by the Czech ministry of health and organised by public health protection authorities in cooperation with GPs. Over 4 500 persons received HAV PEP between weeks 26–43 of 2008.
- Research activities were initiated to investigate the risks for infection among IDUs.

3.3 Update of the hepatitis A outbreak in Latvia

The Public Health Agency of Latvia presented the epidemiology of hepatitis A in Latvia in the last 30 years, an update on the situation of the current hepatitis A outbreak, and response actions taken.

- Hepatitis A is a mandatory notifiable disease in Latvia.
- There has been a sharp decrease in the number of reported HAV cases in Latvia in the last 30 years: from a peak of 12 000 annual cases in the early 1980s (c. 480 per 100 000 population) to less than 100 cases per year since the year 2000 (c. 5 per 100 000). This decrease in incidence can be attributed to overall hygiene improvement. A nationwide serological survey from 1998 showed anti-HAV serology in around 15 % of 1–6 year olds and 90 % among the 60+.
- The current outbreak started in late autumn 2007, with the outbreak then taking off from August to September.
- Riga was principally affected at the start of the outbreak, with up to 35 % of cases among IDUs in the first few months, declining to <1 % of new cases in October 2008. The outbreak has spread to other regions and the general population.
- As of 11 November 2008, 2 235 cases had been reported for the year. A specific restaurant outbreak was identified within the larger community outbreak, as well as several clusters among people with low income.
- The 2008 outbreak can be attributed to the large number of susceptible individuals as a result of rapidly decreasing population immunity to hepatitis A.
- Control measures taken include:
  – contact tracing of cases;
  – PEP vaccination recommended to contacts of cases, but not financed by the health care system;
  – quarantine and medical observation of cases;
  – health education to the public through mass media; and
  – specific recommendations for prevention targeted to food handlers, schools, and to the general public, published on the website of the Public Health Agency of Latvia.
- An uptake of HAV vaccination by the population has been observed from September 2008;
- Research studies have been undertaken at schools to investigate risks factors for hepatitis A in closed settings.

3.4 Hepatitis A and outbreak in the village of Lomnicka, Slovak Republic

An overview of hepatitis A surveillance in Slovakia was presented. Special attention was given to recent trends and response control measures.

- Hepatitis A is a mandatory reportable disease in the Slovak Republic.
- Incidence has decreased from 50 cases per 100 000 in the early 1980s, to 7 per 100 000 in 2007.
- Higher incidences were observed in 1992–1993, relating to outbreaks among specific groups of the population.
- The current outbreak occurred in October–November 2008, mainly among children <10 years of age. A total of 569 cases were reported between January–October 2008.
- 80 % of the reported cases were from four districts of East Slovakia (out of a total 79 districts in Slovakia). Cases in other districts were considered sporadic cases.

- One village in East Slovakia was particularly affected, with a total of 275 cases reported during 2008. The residents were living in very poor hygienic conditions as the water distribution to the village had been stopped due to unpaid water bills.
- Specific control measures targeted to the populations of the affected districts and in particular to the affected village, included:
  – standard control measures of: hospitalisation and treatment; contract tracing and treatment with medical supervision; disinfection of the environment in affected areas; PEP and preventive vaccination;
  – drinking water tanks provided in the affected village;
  – information provided to the general public, especially on preventative measures;
  – vaccination campaigns targeted to family members of cases, school contacts and children aged <15 years. Additional vaccination campaigns were targeted to children 15–18 years old, and other risk groups associated as contacts;
  – by 29 October 2008, more than 1 200 persons were vaccinated in the affected village.
- Vaccination is funded for children up to 15 years of age and partially reimbursed for adults.

4 Characterisation of hepatitis A outbreaks through laboratory testing and sequencing

- Diagnosis of hepatitis A by laboratory tests may include biochemical tests (raised alanine transaminase [ALT] levels), serology (positive HAV IgM), molecular tests (positive RT-PCR).
- There is only one serotype of hepatitis A virus, but several genotypes, and molecular diagnostics exist to differentiate genotypes.
- Molecular tests include real-time polymerase chain reaction (RT-PCR) techniques with the following advantages:
  – detection possible from serum or faeces;
  – new methods use single set of nested primers for VP1/2A region;
  – sensitivity of PCR is still around 60 % after 1 month of onset of illness.
- Accurate sequencing techniques are needed to differentiate between the genotypes I, II and III, as there is little variation within the subtypes.
- RIVM, the Dutch National Institute for Public Health and the Environment, maintains a database of sequences from Dutch samples. Over 700 samples are from other EU Member States as well as some non-European countries. Sequences are used to create phylogenetic trees to identify how closely related (or distant) the various strains are.
- This database can assist in investigating how outbreaks may be linked to other reported outbreaks or cases elsewhere. For example, the database has been used in an analysis of a hepatitis A outbreak in the Netherlands among men having sex with men (MSM).
- Inter-laboratory collaboration between the Netherlands and Latvia has shown that 95 % of the Latvian strains are identical, which implies that the outbreak could have originated from one single primary case.
- Recent analyses of a sample of strains from the outbreak in Latvia and a strain from a Dutch patient reported to be recently infected in Czech Republic have identified sequences from these two countries to differ. Further samples from Czech Republic could add to the phylogenetic trees and allow an analysis of the similarity or disparity of both outbreaks.

5 Options for the prevention and control of hepatitis A

5.1. General overview

An overview of elements that can assist in the prevention and control of hepatitis A were presented. This was followed by examples from outbreaks investigated and published by the Netherlands, used to further illustrate some of the challenges in implementing control measures.

- Prevention of hepatitis A in the community can include:
  - ensuring good hygiene practices (environmental health, food safety, engineering structures for sanitation, education); and
  - immunisation of the population at risk, either by passive immunisation using immunoglobulins, pre- or post-exposure to HAV, or active immunisation: primer and booster vaccination provides long-lasting immunity and can be used in post-exposure prophylaxis protection.
- Control options under an outbreak can include various HAV vaccine strategies:
  - Accelerated universal vaccination (general population vaccination using an accelerated schedule) can be considered an option for controlling a community-wide outbreak. Demonstrated effective in reducing virus circulation even with relatively low coverage levels [9-12].
  - Vaccination of contacts: transmission to direct contacts including household transmission can play an important role in sustaining community-wide outbreaks. Household contact vaccination has been shown to be effective under clinical trials [13,14]. Implementation may need to take into account feasibility and costs.
  - Selected risk groups: targeted vaccination to risk groups may help control and prevent outbreaks, but may need high vaccination coverage rates and may be difficult to implement.
- Hepatitis A vaccine is safe and effective. Efficacy of hepatitis A vaccine has been demonstrated very high even after the first dose (60 % after 14 days, up to 100 % after one month) [15-16].
- Effective control of outbreaks depends on:
  - timely diagnosis and notification of cases;
  - appropriate definition of contacts at risk around each case. This is preferably done in a standardised way supported by a written protocol;
  - timely post-exposure prophylaxis of contacts for each case (within 14 days after onset of index case); if this is done by multiple professionals (e.g. general practitioners), then coordination and monitoring of the process is required;
  - availability of vaccine/immunoglobulin, allowing timely administration of PEP to each of the contacts at risk;
  - identification of sources of the infection (including identifying any common source, use of epidemiological studies); and
  - specific control activities in closed institutions with cases.
- Some epidemic situations may require mass vaccination.

Experiences from outbreaks in the Netherlands highlighted:

- Similarly, a low-incidence country since a sharp decrease of cases from 1960s.
- Yearly incidence peak after summer, considered attributed to travellers returning from HAV endemic countries with subsequent transmission among close contacts [17].
- An HAV outbreak occurred in Rotterdam in 1998 [7], with a case control study undertaken among affected men having sex with men (MSM). Another outbreak occurred among the IDU and homeless population in 2004. Mass vaccination was undertaken among the homeless population in response. However the latter was not as effective as anticipated due to the high level of exposure in the homeless population.

5.2. Experiences from Italy on using vaccination in hepatitis A outbreak response

Experiences from Italy were presented, giving an example of an EU Member State with low national incidence and occasional outbreaks of hepatitis A among specific risk groups.

- Since 1985 a national surveillance system for acute viral hepatitis (SEIEVA) exists in Italy.
- Incidence in Italy has remained stable in the northern central part of Italy at around <5 cases per 100 000 per year. In southern Italy, yearly incidence has dropped from 15 per 100 000 in 1985 to 1 per 100 000 in 2006. A large outbreak was reported in 1996 in Puglia, southern Italy, contributing to a total of 5 620 cases reported during 2006. The outbreak was identified to be associated with shellfish consumption [3] and contributed to a 2006 incidence rate of 45 cases per 100 000 population in southern Italy.
- Principle reported risk factors for hepatitis A infection are shellfish consumption, travel abroad and household contact with a day-care child. Other factors include injecting drug use and sexually transmitted infections among MSM.
- An outbreak of HAV among IDUs was identified in Italy in 2002–2003 with 37 cases, during which three people with underlying liver disease died.
- Anti-HAV vaccination in Italy is recommended for travellers to endemic areas, IDUs, patients with chronic liver diseases, MSM and contacts of HAV cases.
- A randomised control trial was carried out in Italy in 1998 to test the efficacy of hepatitis A vaccine in preventing secondary HAV infections to household contacts. The study identified the number needed to vaccinate as 18, i.e. 18 persons need to be vaccinated to prevent one further HAV case [13].
- In Italy, contacts of hospitalised cases are offered free vaccination within 7–8 days after onset of symptoms in the initial case.

6 Discussion

Epidemiology of hepatitis A in the EU:

- Similar situations of declining hepatitis A immunity in the general population can be observed in other Member States, especially among the younger adult age groups.
- Since hepatitis A is not included in childhood vaccination schedules, outbreaks will likely continue to occur within EU Member States due to declining population immunity.
- It is important to understand the dynamics of hepatitis A infection and how infection can be introduced into at-risk populations and the general population of a Member State, as this understanding offers the opportunity for prevention and control. For example, returning travellers could act as 'seeding events' (i.e. introduction of an infective case) in low-incidence countries.

Available control measures:

- It was agreed that health education and information to the public during outbreaks were key in limiting spread of infection through good hygiene measures.
- Quarantine and isolation of cases in health care facilities can have the effect of reducing the spread of infection within a community, but may represent higher medical or other economic costs compared to other control measures and corresponding effectiveness in controlling the outbreak.
- Experts agreed that vaccination of contacts is useful as a control measure. This requires timely diagnosis, contact tracing for each case, and unrestricted and timely availability of vaccine for all contacts at risk.
- As infected persons may also be asymptomatic virus shedders, control measures should include consideration of the impact of asymptomatic carriers on the effectiveness of available control measures.
- The definition of a 'contact' under an outbreak is vital for effective contact tracing and implementation of household or other targeted vaccination control measures — a guidance definition may be useful.
- The role of immunoglobulin in future vaccination strategy is unclear, as the donor population is becoming less immune, so obtaining the immunoglobulins is more difficult. Furthermore the effectiveness and cost of immunoglobulins are similar to vaccine [14], yet immunity is short-lived.
- In order to prevent or limit outbreaks in low-endemic countries, vaccine strategies could consider:
  – reducing the risk of importation of primary cases through international travel;
  – containing outbreaks at early stages through targeted vaccination of at-risk groups or other strategies;
  – limiting any wide-spread community outbreaks with accelerated universal preventative and post-exposure prophylaxis vaccination.
- It was recognised that it is often difficult to reach specific at-risk groups for targeted vaccination. Guidance on when to consider a universal accelerated vaccine strategy versus the required targeted vaccination coverage of at-risk populations for an impact on the outbreak would be helpful.
- Implementing large-scale vaccine campaigns in response to sporadic hepatitis A outbreaks has the added challenge of planning stockpiling of vaccines or mobilising vaccine stocks.
- The impact on blood donations and the blood donor system during a community outbreak situation may need to be considered, as there is the risk for a greater proportion of asymptomatic infections in the general population, outside of affected high-risk groups (e.g. IDUs). The latter would likely already be exempt from blood donation.
- Reliable and updated information on hepatitis A epidemiology worldwide, including current outbreaks is important to assist effective travel medicine advice and vaccine uptake among travellers, contributing to the prevention of outbreaks which possibly result from imported infections.

7 Next steps

Based on the discussion above, the following next steps were proposed by the group:

In the short term:

- Further direct information exchange between affected Member States is considered useful for:
  – information sheets provided to the public;
  – epidemiological study protocols related to investigating risks during current outbreaks, particularly with regard to injecting drug users; and
  – molecular laboratory methods for hepatitis A.
- ECDC to explore impact on blood donations and implications of the EU Blood Directive during community outbreak situations.

In the long term, consider:

- the potential use of serological surveys across the EU to assess overall population susceptibility as well as serological surveys in several countries after community-wide outbreaks to study the real scale of the epidemic and the proportion of asymptomatic cases;
- the usefulness of a review of post-exposure prophylaxis practices for hepatitis A among Member States;
- a literature review or other study on the cost-effectiveness of PEP under outbreak situations;
- developing technical guidelines on hepatitis A outbreak response including e.g. vaccination strategies, definition of 'contacts' in hepatitis A contact tracing, guidance on environmental sampling for hepatitis A, and surveillance data to be collected; and
- providing information updates on countries worldwide where hepatitis A is endemic or where outbreaks occur — this could be considered as part of an ECDC travel medicine support function.

References

Note: Updated descriptions of the outbreaks from the Czech Republic, Latvia and the Slovak Republic were published in Eurosurveillance, 2009 Jan 22;14(3)).

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Annex 1. Agenda of the consultation

09:00 - 09:15	Opening of the meeting and objectives Dr. Uldis Līkops, Director, Public Health Agency of Latvia Dr. Denis Coulombier, ECDC
09:15 - 09:30	Overview of hepatitis A epidemiology in the EU Dr. Therese Westrell, ECDC
09:30 - 10:00	The occurrence of viral hepatitis A in the Czech Republic Dr. Michael Vít, Ministry of Health of the Czech Republic
10:00 - 10:30	Update of hepatitis A outbreak in Latvia Dr. Jurijs Perevoscikovs, Public Health Agency of Latvia
10:30 - 11:00	Hepatitis A and outbreak in the village of Lomnicka Dr. Lucia Hrivniakova and Mgr. Helena Hudakova, Public Health Authority of the Slovak Republic
11:00 - 11:30	Coffee break
11:30 - 12:15	Characterisation of hepatitis A outbreaks through laboratory testing and sequencing Dr. Harry Vennema, RIVM, Netherlands
12:15 - 13:00	Options for the prevention and control of hepatitis A Dr. Arnold Bosman, ECDC
13:00 - 14:00	Lunch
14:00 - 14:30	Specific examples of using vaccination in hepatitis A outbreak response Dr. Alfonse Mele, ISS, Italy
14:30 - 15:30	Discussion and next steps
15:30 - 16:00	Coffee break
16:00 - 16:30	Conclusion of the meeting

Annex 2. List of participants

Michael Vit	Ministry of Health, Czech Republic
Vratislav Nemecek	National Institute of Public Health, Czech Republic
Irina Dontsenko	Health Protection Inspectorate, Estonia
Christina Frank	Robert Koch Institute, Germany
Alfonso Mele	Instituto Superiore di Sanità, Italy
Baiba Rozentale	Centre for Infections, Latvia
Helena Storozenko	Centre for Infections, Latvia
Dace Viluma	Ministry of Health, Latvia
Laura Bundule	Public Health Agency of Latvia
Uldis Līkops	Public Health Agency of Latvia
Irine Lucenko	Public Health Agency of Latvia
Sandra Magone	Public Health Agency of Latvia
Jurijs Perevoscikovs	Public Health Agency of Latvia
Renata Pavinksnyte	Centre for Communicable Diseases Prevention and Control, Lithuania
Hannelore Gotz	National Institute for Public Health and the Environment, The Netherlands
Harry Vennema	National Institute for Public Health and the Environment, The Netherlands
Lucia Hrivniakova	Public Health Authority of the Slovak Republic, Slovak Republic
Helena Hudecova	Public Health Authority of the Slovak Republic, Slovak Republic
Rosy McNaught	Health Protection Agency, United Kingdom
Aiga Rurane	World Health Organization, Country Office Latvia
Arnold Bosman	Preparedness and Response Unit, ECDC
Denis Coulombier	Preparedness and Response Unit, ECDC
Lara Payne	Preparedness and Response Unit, ECDC
Therese Westrell	Surveillance Unit, ECDC