Enhanced surveillance of hepatitis B in the EU, 2006–2012

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SUMMARY. Robust epidemiological information on hepatitis B is important to help countries plan prevention and control programmes and evaluate public health responses to control transmission. European Centre Disease Prevention and Control (ECDC) introduced enhanced surveillance of hepatitis B at EU/EEA level in 2011 to collate routine surveillance data from national notification systems. Analysis of the data collected for the years 2006–2012 shows a high burden of hepatitis B across Europe with 110 005 cases reported over the period with the majority of these cases being chronic infections. The most commonly reported routes of transmission in acute cases included heterosexual transmission, nosocomial transmission, injecting drug use and transmission among men who have sex with men. Mother-to-child transmission was the most common route reported for chronic cases. Trends over time were difficult to analyse as national reporting practices changed, but data suggest a downward trend in acute cases, which probably reflects the impact of the widespread implementation of vaccination programmes. Notifications of chronic infection varied across countries and showed discrepancy with the expected results based on findings from recent prevalence surveys. This indicated that notifications mirror local testing practices rather than real occurrence of disease. Improving the quality of the data and considering reported notifications alongside other data sources, such as local screening practices and vaccination policies, will improve the utility of the data.

Keywords: epidemiology, Europe, hepatitis B, surveillance.

INTRODUCTION

Infection with the hepatitis B virus (HBV) results in inflammation of the liver and is a major cause of cirrhosis and liver cancer around the world. The natural history of HBV infection is influenced by the age at which an individual is infected. Neonatal infections are mostly asymptomatic, but usually lead to chronic infection whereas infections among adults are more likely to result in symptomatic acute hepatitis, but are associated with a lower risk of persistent infection [1].

Recent estimates suggest that around 350 million people worldwide are chronically infected with HBV [2,3]. Across Europe, the incidence and prevalence of HBV infections vary between countries [4]. The mode of transmission also varies markedly between countries [5–7]. In countries with a high prevalence of HBV (defined as prevalence of HBsAg ≥ 2%), transmission is usually perinatal or during childhood through horizontal transmission from close household contacts. In countries with a lower prevalence, HBV transmission usually occurs later in life through injecting drug use (IDU) or sexual exposure [8].

Robust epidemiological information underpins the effectiveness of public health action. A survey undertaken by the European Centre for Disease Prevention and Control (ECDC) in 2009/2010 identified specific hepatitis B surveillance systems in all European Union (EU) and European Economic Area (EEA) countries, but marked differences between these systems in the type of data collected [9]. The results of this survey confirmed the findings of a previous review of the published literature which had found variability in case definitions in use and an inability for many countries to distinguish between acute and chronic cases [10].

In 2010, ECDC established a network for enhanced surveillance of hepatitis B with national experts from each EU/EEA country. Surveillance at the EU level is facilitated by the European Surveillance System (TESSy), a platform for web-based data submission, warehousing and retrieval of communicable diseases under EU surveillance.

This paper presents the results from the first enhanced surveillance data collections of HBV infections across EU/EEA countries. It aims to describe epidemiological trends for HBV between 2006 and 2012 and to consider these findings critically in light of the limitations of surveillance and findings from seroprevalence surveys.
MATERIALS AND METHODS

Viral hepatitis B is a statutorily notifiable disease in all EU/EEA Member States. EU countries, Norway, Iceland and Liechtenstein were requested to follow the 2012 EU case definition for hepatitis B reporting at the European level [11] (see text box), but data defined according to other case definitions were also accepted, provided this was explained.

EU 2012 case definition for hepatitis B

Hepatitis B:
Clinical criteria: Not relevant for surveillance purposes
Laboratory criteria:
Positive results of at least one or more of the following tests or combination of tests:
IgM hepatitis B core antibody (anti-HBc IgM)
• Hepatitis B surface antigen (HBsAg)
• Hepatitis B e antigen (HBeAg)
• Hepatitis B nucleic acid (HBV-DNA)
Epidemiological criteria: Not relevant for surveillance purposes
Case classification:
Possible case – N/A
Probable case – N/A
Confirmed case – Any person meeting the laboratory criteria
NOTE: The following combination of laboratory tests shall not be included or reported:
• Resolved hepatitis - Hepatitis B total core antibody (anti-HBc) positive and hepatitis B surface antibody (anti-HBs) positive
• Immunity following vaccination - Hepatitis B total core antibody (anti-HBc) negative and hepatitis B surface antibody (anti-HBs) positive
• Anti-HBc IgG positivity only

Data on the acute and chronic hepatitis B infections were differentiated by countries using defined criteria (Table 1).

EU/EEA Member States agreed to report data on all newly diagnosed hepatitis B cases from 2006 to 2012 to TESSy. The data set includes basic demographic variables and enhanced variables specific to hepatitis B such as serological markers, transmission factors and risk groups. The deadline for submitting data was 15 September 2013, and the data presented were retrieved from TESSy on 5 November 2013.

Data were collected in case-based format, but if case-based data were not available, aggregate format was accepted. Aggregated data allowed only basic analysis of the origin of cases and classification of the disease as either acute or chronic. Liechtenstein did not provide any data and was omitted from the tables presenting data. A few countries who provided data using alternative case definitions submitted cases with ‘unknown’ or ‘probable’ case classification.

STATA 11 (StataCorp LP, College Station, Texas, USA) and Excel 2010 (Microsoft, Redmond, WA, USA) were used for data analyses. A descriptive analysis of the reported data was undertaken to assess burden and trends of hepatitis B in EU/EEA countries. For countries with comprehensive surveillance systems covering the entire population, annual notification rates were calculated per 100 000 population based on the denominator data published by Eurostat.¹ For hepatitis B infections in the UK, 2008 population data from the Office for National Statistics were used to exclude Scotland which was unable to provide any hepatitis B data.

The trends over time are difficult to interpret due to the many changes in reporting practice. A comparison of data across countries over time was undertaken through considering countries with stable reporting over the whole reporting period.

RESULTS

For the period from 2006 to 2012, 110 005 cases of hepatitis B were reported by 30 EU/EEA countries. The data provided showed varying degrees of completeness across countries and over time. Although 19 countries were able to provide national data in 2012 defined according to the current EU case definition (EU 2012), five of these countries (France, Hungary, Lithuania, Portugal and Romania) submitted data on acute cases only (Table 2). Data were provided by six countries according to previous EU case definitions (EU 2008 and EU 2002) and only included acute cases of hepatitis B. Four countries (Denmark, Germany, Italy and Luxembourg) provided data according to their national case definitions, which included both acute and chronic cases for Denmark and only acute cases for the others. In a few countries, the case definitions changed between 2006 and 2012 as countries adapted to using the new case definition.

For 2012, 17 315 cases of hepatitis B were reported from 29 countries (no data from Belgium and Liechtenstein), resulting in an overall crude rate of 3.5 per 100 000 population. Of these cases, 2796 cases (16.1%) were reported as acute, 12 295 (71.0%) as chronic, 1864 (10.8%) as ‘unknown’ and 360 cases (2.1%) could not be classified as data were provided in an incompatible format.

For 2012, 22 countries provided data on acute infections and the number of cases ranged from three cases in Iceland to 561 cases in Germany. Rates of reported acute cases ranged from 0.1 cases per 100 000 in Portugal to 4.4 cases per 100 000 in Bulgaria (Fig. 1).
### Table 1 Criteria for differentiating acute and chronic hepatitis B

| Disease          | Stage  | Definition                                                                                     |
|------------------|--------|-----------------------------------------------------------------------------------------------|
| Hepatitis B      | Acute  | Detection of IgM antigen-specific antibody (anti-HBc IgM) or                                   |
|                  |        | Detection of hepatitis surface antigen (HBsAg) and previous negative hepatitis B virus (HBV) markers <6 months ago or |
|                  |        | Detection of hepatitis B nucleic acid (HBV-DNA) and previous negative HBV markers <6 months ago and |
|                  |        | Any of the above with or without symptoms and signs (e.g. jaundice, elevated serum aminotransferase levels, fatigue, abdominal pain, loss of appetite, intermittent nausea, vomiting, fever) |
| Chronic          |        | Detection of HBsAg or HBeAg or HBV-DNA and                                                     |
|                  |        | No detection of anti-HBc IgM (negative result)                                                  |
|                  |        | or Detection of HBsAg or HBeAg or HBV-DNA on two occasions that are 6 months apart*           |
| Unknown          |        | Any newly diagnosed case which cannot be classified according to the above definition of acute or chronic infection |

*In the event that the case was not notified the first time.

### Table 2 Hepatitis B: Case definitions and type of data provided in 2012

| Country          | Case definition (s) used | Acute | Chronic |
|------------------|--------------------------|-------|---------|
| Austria          | EU 2008                  | x     |         |
| Belgium          | National                 | x     |         |
| Bulgaria         | EU 2002                  | x     |         |
| Croatia          | EU 2012                  | x     | x       |
| Cyprus           | EU 2008                  | x     |         |
| Czech Republic   | EU 2012                  | x     | x       |
| Denmark          | National                 | x     | x       |
| Estonia          | EU 2012                  | x     | x       |
| Finland          | EU 2012                  | x     | x       |
| France           | EU 2012                  | x     |         |
| Germany          | National                 | x     |         |
| Greece           | EU 2008                  | x     |         |
| Hungary          | EU 2012                  | x     |         |
| Iceland          | EU 2012                  | x     | x       |
| Ireland          | EU 2012                  | x     | x       |
| Italy            | National                 | x     |         |
| Latvia           | EU 2012                  | x     | x       |
| Lithuania        | EU 2012                  | x     |         |
| Luxembourg       | National                 | x     |         |
| Malta            | EU 2012                  | x     | x       |
| Netherlands      | EU 2012                  | x     | x       |
| Norway           | EU 2012                  | x     | x       |
| Poland           | EU 2008                  | x     |         |
| Portugal         | EU 2012                  | x     |         |
| Romania          | EU 2012                  | x     |         |
| Slovakia         | EU 2012                  | x     | x       |
| Slovenia         | EU 2012                  | x     | x       |
| Spain            | EU 2008                  | x     |         |
| Sweden           | EU 2012                  | x     | x       |
| United Kingdom   | EU 2012                  | x     | x       |
Thirteen countries provided data on chronic infections in 2012. The number and rates of reported chronic infections were generally higher and showed greater variation than acute cases. Numbers of reported chronic cases ranged from 26 cases in Slovenia to 7368 cases in the UK. Rates of newly diagnosed chronic infections ranged from 0.1 case per 100 000 in Romania to 14.9 per 100 000 population in Sweden (Fig. 2).

In 2012, 9971 of all reported cases were in males (4.2 per 100 000) and 7014 cases in females (2.8 per 100 000). This represents an overall male-to-female ratio of 1.5. A third of all hepatitis B cases reported (33.4%) were in the 25–34 age group. The age distributions of reported cases of acute and chronic infections were similar, with 14.8% of acute cases and 16.9% of chronic cases aged under 25 years (Fig. 3).

Between 2006 and 2012, the annual number of reported cases increased from 12 642 cases to 17 315. Rates of reported acute cases declined from 1.0 per 100 000 in 2006 to 0.6 in 2012 whilst the rates of reported chronic cases increased over the period from 1.4 cases to 2.5 cases per 100 000. The numbers and rates of reported unknown infections remained fairly stable over time.

Among nine countries that provided continuous data on both acute and chronic cases, there was a decline in the rates of acute infections and a rise in rates of newly identified chronic infections (Fig. 4).

The most commonly reported route of transmission was mother-to-child transmission which accounted for 41.1% of all cases. Among acute cases in 2012, heterosexual transmission was reported as the most common route of transmission (31.1%), followed by nosocomial transmission (20.7%) (Table 3). Mother-to-child transmission was the most common route (66.9%) for chronic cases, followed by ‘other’ routes (9.0%) and heterosexual transmission (6.7%).

There were no major changes in the reported routes of transmission over time. There were differences between countries; however, it is difficult to identify any clear geographical trends as reporting across most countries was so patchy and incomplete.

In 2012, 19 countries provided information for 6033 cases (34.8%) on whether the case was considered to have
been ‘imported’ from outside the reporting country. Of these cases, 3576 (59.3%) were reported as being imported. There was considerable variation in the proportion of imported cases between acute and chronic infections. 9.7% of acute cases with available information were classified as imported compared to 84.1% of chronic cases. Data were collected on the probable country of infection for imported cases; however, the completeness of the data was low and this restricted any meaningful analysis of this data.

Among 1544 cases classified as ‘imported’ with complete information on transmission, 1119 (72.5%) were recorded as mother-to-child transmission. Of these, 1110 cases (99.2%) were reported as chronic. Among the 937 cases classified as not being ‘imported’, 261 (27.9%) were reported to have been infected through heterosexual transmission, 138 (14.7%) through injecting drug use and 154 (16.4%) through nosocomial transmission.

**DISCUSSION**

This paper presents first results from the enhanced surveillance of hepatitis B in the EU/EEA [12,13]. The data originate from national routine surveillance with most countries defining cases according to the new EU case...
definition based on laboratory criteria. The implementation of this surveillance system has been a major step towards standardization of surveillance data across European countries. However, the roll-out highlighted several issues which challenge a clear interpretation of the data across countries.

Firstly, the application of the revised EU case definition which captures both acute and chronic cases was problematic for some countries. Whilst many countries were able to use the new definition, other countries reported cases as defined by their own national case definition or one of the previous EU case definitions which only capture acute cases. This heterogeneity is a challenge to the comparison of data between countries, but this should improve over time as more countries can adapt their surveillance systems to the new case definitions. Furthermore, it underlines the importance of having a good understanding of national surveillance systems to be able to interpret the data at EU level. In addition to the information obtained from the previous surveys of surveillance and prevention programmes across Europe [10], more detailed information on national surveillance practices would help understanding these differences. The classification of cases by disease status was also problematic for some countries, and many cases were classified as ‘unknown’. The reliance on sequential data to classify cases as acute or chronic is a particular issue. A further issue is that in some countries national legislation supports the reporting of acute cases only, so data are incomplete.

Another limitation was the incompleteness of data provided. In particular, many of the epidemiological variables (e.g. HIV status, HBV vaccination status, transmission route, country of birth) were poorly reported, and this restricts the analysis of the data and a clear understanding of hepatitis B epidemiology. Although data completeness improved over the reporting period, further work is necessary to address this issue.

The results indicate high numbers of reported cases of hepatitis B across Europe and variation in the distribution of reported cases of acute and chronic hepatitis B between countries. Although several countries were unable to provide data on chronic cases, the majority of all notified cases were chronic. Many of the countries with the greatest burden of chronic cases, for example UK, are those known to have comprehensive screening and diagnostic testing for key risk groups, which suggests that the chronic data are strongly influenced by testing practice.

The numbers and rates of acute infections show great variation between countries. Some of this variation may be explained by differences in the case definitions used and underreporting that is a problem in many countries, with France estimating this to be as high as 85% for acute hepatitis B cases in 2010 [14]. A further factor which may also account for some of the variation seen between countries may be the use of anti-HBc IgM to differentiate cases as acute or chronic. It has been estimated that acute exacerbations or ‘flare-ups’ of chronic hepatitis constitute between 15% and 50% of cases diagnosed as acute infections depending upon the underlying endemicity of the country [15,16]. Indeed, although anti-HBc IgM is commonly used for the diagnosis of acute hepatitis B infection, it may also be present in individuals with chronic infection during these ‘flare-ups’.

The geographical trends in chronic infections are the inverse of what may be expected based on findings from prevalence surveys. Indeed, the results of prevalence surveys indicate that countries in the south and east of Europe have a higher prevalence of chronic HBV than those in the north-west [17–19]. The observed mismatch between notifications and prevalence data highlights the problem of interpreting routine surveillance data for chronic hepatitis B which is largely asymptomatic until a late stage of disease, so notifications are mostly driven by national testing policies. The surveillance data should
therefore be interpreted with caution and considered carefully alongside available information on local testing practices. ECDC is working closely with Member States to explore the differences in reporting in order to better understand the observed incongruity with the data. It is hoped that this work will inform future improvements in the surveillance of this infection.

Acute hepatitis B infections correlate more closely with what may be expected based on the results from prevalence surveys, with the rates of reported cases highest among the eastern European countries [17]. The closer alignment of acute infections with prevalence data is likely to be related to the fact that most reported acute hepatitis B cases were among adults, in whom infection is frequently symptomatic and who are therefore expected to present clinically.

Despite the limitations, the surveillance data still provide valuable information on temporal trends. The data suggest an overall decrease in acute cases and a rise in newly reported chronic infections. The former is likely to be related to high coverage of national vaccination programmes [20]. A fall in the prevalence of HBsAg has been noted in many countries in Central Europe, Central Sub-Saharan Africa, Central America and South-East Asia, and this is probably due to the effective implementation of vaccination programmes [21]. The rise in chronic hepatitis B cases may be due to increased diagnostic testing, but another explanation for this rise, and for some of the variation between countries, could be the inward migration of chronic cases from countries with a high prevalence of hepatitis B. Migration has been reported to have an impact on HBV prevalence in several European countries [22]. Indeed, the data on importation status for chronic cases in the Netherlands, Norway and Sweden, that were fairly complete, indicate that a high proportion of chronic cases was classified as being ‘imported’ and it is likely that many of these cases were migrants.

Hepatitis B is more common among males than females and among the younger age groups. There were gender differences between acute and chronic cases with relatively more male cases among acute cases than chronic cases. This variation may be partly explained by the antenatal screening programmes in many countries which identify many cases of chronic infection among women. There was a decline over time in the proportion of cases aged under 25, which is most likely to be related to the ongoing impact of vaccination programmes.

Heterosexual transmission, nosocomial transmission, nonoccupational injury, transmission among MSM and injecting drug use were the most commonly reported transmission routes for acute cases. Mother-to-child transmission was the most common route for chronic cases, and the

| Transmission category                        | Acute (n = 1120) % | Chronic (n = 1827) % | Unknown (n = 65) % | Total (n = 3012) % |
|----------------------------------------------|-------------------|--------------------|-------------------|-------------------|
| Heterosexual transmission                   | 31.1              | 6.7                | 11.9              | 15.9              |
| Nosocomial (includes hospital, nursing home, etc.) | 20.7              | 2.2                | 0.0               | 9.0               |
| Men who have sex with men (MSM)             | 11.1              | 2.5                | 9.0               | 5.8               |
| Nonoccupational injuries (needle stick, bites, tattoos, piercings) | 9.3               | 1.0                | 9.0               | 4.3               |
| Injecting drug use                          | 8.7               | 3.9                | 7.5               | 5.8               |
| Other†                                      | 6.6               | 9.0                | 3.0               | 7.9               |
| Sexual transmission (not specified)         | 5.1               | 1.7                | 14.9              | 3.2               |
| Household                                   | 4.7               | 3.3                | 23.9              | 4.3               |
| Blood and blood products                    | 1.1               | 2.4                | 6.0               | 2.0               |
| Mother-to-child transmission               | 0.7               | 66.9               | 13.4              | 41.1              |
| Haemodialysis                               | 0.5               | 0.1                | 0.0               | 0.2               |
| Needle stick and other occupational exposure | 0.4               | 0.3                | 1.5               | 0.4               |
| Organ and tissues                           | 0.0               | 0.0                | 0.0               | 0.0               |
| Total                                       | 100.0             | 100.0              | 100.0             | 100.0             |

Source: Country reports: Czech Republic, Denmark, Estonia, Finland, France‡, Germany, Hungary, Ireland, Italy, Latvia, Lithuania, Malta, Netherlands, Norway, Poland, Romania, Slovakia and Sweden.

*Analyses undertaken by disease status category for all cases where the transmission category was not classified as ‘unknown’.
†The route of transmission is known, but cannot be attributed to any of the specified transmission categories.
‡Underreporting was estimated to be 85% for acute hepatitis B cases in France in 2010.
limited data suggest that most of these infections were acquired in a country different from the reporting country.

In conclusion, robust, standardized epidemiological information is important to monitor disease distribution and to evaluate public health responses aimed at controlling the transmission of infections across Europe. The results from this first data collection suggest a high burden of disease and considerable differences in the epidemiology of these infections across the EU/EEA. Interpreting these differences has been a challenge. The downward trend in acute notifications has been noted elsewhere and reflects the widespread implementation of vaccination programmes across Europe. Geographical trends in acute infections are harder to interpret and are most likely to be related to the underlying epidemiology as well as differences in reporting and surveillance practices. The geographical trends in chronic case data are contrary to what may be expected based on results from prevalence surveys with reported data reflecting national testing practices. Improving the quality of the surveillance data and considering reported notifications alongside other data sources, such as local screening practices and vaccination policies, will improve the general utility of the data.

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Note

1Eurostat database: http://epp.eurostat.ec.europa.eu

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