**Acute Infectious Hepatitis in Hospitalised Children: A BRITISH PAEDIATRIC SURVEILLANCE UNIT (BPSU) STUDY**

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Key words: hepatitis, child, British Paediatric Surveillance Unit (BPSU), vaccine

**Word count:** 2,495

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**ABSTRACT**

*Background.*

Hepatitis remains a key public health priority globally. Most childhood cases are caused by viruses, especially Hepatitis A (HAV) and B (HBV). This study aimed to estimate the burden of acute infectious hepatitis in hospitalised children, and to describe their clinical characteristics and outcomes.

*Methods.*

Paediatricians in the United Kingdom and Ireland reported cases in children aged 1 month to 14 years diagnosed between January 2014 and January 2015 (inclusive) through the British Paediatric Surveillance Unit (BPSU) and completed a detailed questionnaire. Additional HAV and HBV cases in England and Wales were identified through a national electronic database, LabBase2. All confirmed cases were followed-up at six months with a second questionnaire.

*Results.*

The BPSU survey identified 69 children (annual incidence, 0.52/100,000), including 27 HAV (39%), three HBV (4%), 16 other viruses (23%) and 23 with no aetiology identified (33%). LabBase2 identified an additional ten HAV and two HBV cases in England. Of the 37 hospitalised HAV cases, 70% had travelled abroad but only 8% had been vaccinated. Similarly, three of the five children with acute HBV had not been immunised, despite being a household contact of a known infectious individual. All patients with HAV recovered uneventfully. In contrast, three children with acute HBV developed liver failure and two required liver transplantation.

*Conclusions.*

Acute infectious hepatitis is a rare cause of hospital admission. Most children recovered without complications, but those with acute HBV had severe presentations. At least three of the five HBV cases could have been prevented through immunisation.

***Introduction***

Infectious hepatitis remains a key public health priority in industrialised countries. Acute infectious hepatitis (AIH) is characterised by an acute onset of discrete symptoms including fever, jaundice, abdominal pain, nausea, and vomiting. Occasionally, the condition may progress to fulminant hepatic failure and the need for liver transplantation. Most childhood cases are caused by viruses, with hepatitis A virus (HAV) and hepatitis B virus (HBV) being the main culprits. Other viruses (e.g. Hepatitis E, Epstein-Barr, cytomegalovirus) and non-viral infections (e.g. toxoplasma, leptospirosis) may also cause AIH in children. Countries with routine childhood immunisation programmes, such as the United States, have observed significant reductions in the incidence of acute HAV (92%) and HBV (82%) infections, respectively, across all age-groups.1 The UK and Ireland do not routinely immunise against HAV and, while HBV vaccination is included in the Irish infant immunisation schedule, the UK has adopted a selective policy of vaccinating high-risk individuals only.2

Little is known about the burden of childhood AIH in industrialised countries. In the UK, national surveillance systems are not set up to identify clinical syndromes such as AIH. Rates of laboratory-confirmed infections due to specific pathogens are readily available, but are not accompanied with clinical or outcome data. Consequently, current knowledge of syndromic conditions such as AIH is very limited.

This study aimed to estimate the burden of childhood AIH in the UK and Ireland, with particular emphasis on the vaccine-preventable (HAV and HBV) aetiologies. Here, we report the overall and pathogen-specific incidence, clinical features, investigations, aetiology, known risk factors, management and outcomes of hospitalised children with AIH.

***Methods***

This study was conducted by Public Health England (PHE) and St. George’s University of London through the British Paediatric Surveillance Unit (BPSU), a unique national clinical surveillance set up to study rare diseases.3 The BPSU functions by sending paediatric consultants across the United Kingdom and the Republic of Ireland a short electronic list of rare childhood conditions every month. All paediatricians have to respond to the electronic notification and either report a case with a condition in the electronic list (e.g. acute infectious hepatitis) or confirm that there were no cases to report. Reporting is not compulsory but strongly encouraged and the BPSU send monthly reminders if no response is received. The reporting paediatrician is then requested to complete a questionnaire on demographic, clinical and laboratory information for each case.

This study began on 01 January 2014 for 13 months and included hospitalised children from 1 month up to 14 years of age with raised levels of the liver enzyme, alanine transaminase (ALT), more than twice above the upper limit of normal, with or without jaundice, and any suspicion of an infective cause (with or without an identified causative agent) and excluding drug-induced, metabolic or auto-immune hepatitis. LabBase2, a national electronic reporting system used by NHS laboratories to notify clinically significant infections to Public Health England (PHE), was used as an alternative national data source for laboratory-confirmed HAV and HBV cases in England, Wales and Northern Ireland.4

The BPSU does not allow for the request of patient names, so other parameters such as month and year of birth, gender, NHS number, hospital, diagnosis date and partial post-code were used to cross-link and de-duplicate BPSU cases. GPs were initially contacted to confirm the diagnosis of acute HAV or HBV infection and whether the child was admitted to hospital. After confirmation, the responsible paediatric consultants were also sent the same questionnaire for completion.

Paediatricians who completed the clinical questionnaires for confirmed cases were contacted after 12 months with a follow-up questionnaire on long-term outcomes.

**Data Analysis**

Data were entered into Microsoft Excel™ and analysed using Stata v.13.0 (Statcorp, Tx). Results are mainly descriptive. Population estimates for 2014 were obtained from the Office for National Statistics (ONS) for United Kingdom and from Central Statistics Office (CSO) for Republic of Ireland and were used to calculate country-specific and overall incidence rates.

Annual age-specific population estimates were adjusted for the 13-month surveillance period. Continuous variables that did not follow a normal distribution were described as medians with interquartile ranges and compared using the Mann Whitney U test. Categorical data were compared using the chi-squared test or Fisher’s Exact tests as appropriate. Estimated cases and 95% confidence intervals (95% CI) for HAV/HBV infections in England and Wales were calculated using capture-recapture analysis according to Howitz and colleagues.5 This methodology is often applied to epidemiologic studies to estimate the true number of cases when two or more independent data sources are available for the same population.

***Results***

Of the 113 notifications received by BPSU during the 13-month surveillance period, 69 cases were included in the study (Figure 1); 27 were due to HAV and 3 due to HBV. Fifty five cases were reported from England (22 HAV, 4 HBV, 12 others, 18 no aetiology), 12 from Wales, Scotland and Northern Ireland (4 HAV, 0 HBV, 4 others, 4 no aetiology) and two from the Republic of Ireland (1 HAV, 1 no aetiology). During the same period, 268 HAV/HBV confirmed infections among <15 year-olds in England and Wales were reported in LabBase2 ([**Figure**](#Table2) **2**). The GPs of these children confirmed that the vast majority had mild HAV or known chronic HBV infection, but 12 (10 HAV, 2 HBV) hospitalised cases were identified that had not been notified through the BPSU ([**Figure 2**](#Figure2)). Including these cases increased the total cohort to 81 children: 37 (45.7%) HAV, 5 (6.2%) HBV, 16 (19.8%) other viruses and 23 (28.4%) with no pathogen identified.

**Estimated incidence** *(n=81)*

When analysing BPSU only cases, AIH incidence across the UK and Ireland was 0.52/100,000 children aged <14 years. In England and Wales, capture-recapture of the 39 HAV/HBV cases (0.38/100,000) identified through BPSU only (n=17), LabBase2 only (n=12) and both surveillance systems (n=10) estimated the total number of cases to be 1.5-fold higher at 59 (95% CI, 40-78) cases, with an estimated incidence of acute hepatitis A and B in hospitalised children in England and Wales of 0.58/100,000.

**HAV cases**

Of the 37 children hospitalised with confirmed HAV, ten were aged <5 years (27.0%), more than two-thirds (26/37, 70.3%) had travelled abroad in the previous six months, compared to 2/16 (12.5%) of those infected with other viruses, 1/23 (4.4%) with no aetiology and none of the HBV cases. More than half (18/26, 69.2%) had travelled to countries in the WHO Eastern Mediterranean Region (eleven to Pakistan, three to Afghanistan, one each to Iran, Morocco, Somalia and Yemen), three in the African region (Kenya, Mauritius and Uganda) and four in other regions (Bangladesh, Honduras, Albania and Romania). Only three HAV had received anti-HAV immunisation (8.1%), including two who were vaccinated one and two weeks prior to becoming unwell, following a case in the family and a school outbreak, respectively. Most presented with gastro-intestinal symptoms and half had fever. Bilirubin and alanine transaminase levels were significantly raised in nearly all children with HAV infection, while C-reactive protein levels were low or normal (Supplement Table 1). The children with HAV infection did not have any significant co-morbidities, had short in-patient hospital stays and recovered without complications (Table 1). One child (2.70%) had a positive bacterial culture (*Campylobacter jejuni* in stools) and 7 (18.9%) had abnormal liver imaging (USS mainly showing hepatomegaly, increased liver echogenicity and enlarged periportal lymph glands) (Supplement Table 2).

**HBV cases**

All five UK-born patients with acute HBV infection were previously healthy and were close contacts of known chronically infected individuals (Table 2). Only two were immunised; one neonate received a dose at birth and became unwell before receiving the second dose, while the other patient was lost to follow-up and did not complete the recommended immunisation schedule. The patients with acute HBV infection did not have fever, diarrhoea or rash, but presented with various combinations of abdominal pain, jaundice, lethargy and drowsiness (Table 1). Three were severely unwell at presentation, including two who went on to require a liver transplant.

**Other Viruses**

Other viruses causing AIH included EBV (n=6), adenovirus (n=4), one case each of cytomegalovirus (CMV), HHV6, rotavirus and influenza A H1N1). Two additional cases were positive for EBV co-infection other viruses (adenovirus, cytomegalovirus). The patients with AIH caused by other viruses were born in the UK and had not travelled abroad; most were previously healthy; One premature twin had been born prematurely and contracted CMV-related hepatitis in the first few weeks of life while still in Neonatal Intensive Care Unit, while a young child with neurological malformation developed dual infection with EBV and adenovirus. More than half presented with jaundice. All patients were managed at their local hospital, had an uneventful course and recovered without complications (Table 1). All but one had liver imaging performed and, in five (31.25%), abdominal USS identified inflammatory changes of the liver and peri-hepatic structures. One also had an MRI scan which showed similar changes to the USS. Two patients (12.50%) had a liver biopsy, which revealed inflammation and hepato-necrosis. (Supplement Table 1). Two patients whose AIH resolved and liver functions returned to normal had complications at follow-up, including one with HHV6 infection who developed acute aplastic anaemia, another with multiple viruses who developed interstitial lung disease

**No Aetiology**

Children without an identifiable aetiological agent presented mainly with jaundice, fever, vomiting, abdominal pain and lethargy (Table 1). Five children had comorbidities, including sickle cell disease, metastatic malignancy, Charcot-Marie-Tooth, Pierre-Robin sequence and Cri-du-chat syndrome. The majority were appropriately investigated and all had an USS, which was normal in 10 (43.48%) and showed hepatomegaly with inflammatory changes in 13 (56.52%) (Supplement Table 2). Three children (13.04%) had a liver biopsy, which showed inflammation and necrosis of the hepatic parenchyma. One child who initially presented with grade 1 encephalopathy and progressive coagulopathy recovered initially, but then developed *Pneumocystis* jiroveci pneumonia and died. He was investigated for immunodeficiency but an underlying cause was not identified. Another boy recovered from AIH and developed enteropathy secondary to enterovirus infection with hypogammaglobulinaemia. The other children all had an uncomplicated course and recovered uneventfully (Table 1).

**Outcomes at follow-up**

Overall, none of the children – even those with acute HBV – developed chronic infection and, apart from the single fatal case, all recovered without long-term complications at 12 months follow-up.

**Discussion**

We report the first national prospective study on the epidemiology of acute infectious hepatitis in hospitalised children in the UK and Ireland. Our study confirms a low incidence and identified HBV as a rare but severe cause of AIH in hospitalised children. Of the 81 confirmed cases, 37 (46%) had self-limiting HAV infection and five had acute HBV infection, with three children being very unwell and two needing a liver transplant. A range of other viral infections were confirmed in 20% of children with AIH, while, in 28%, the aetiological agent was not identified despite extensive testing.

In this study, we particularly focused on acute HAV and HBV infections because they are both vaccine-preventable. Although the UK is one of very few countries in the world without a routine HBV vaccination, a very effective antenatal screening programme with high coverage is in place. This programme aims not only to identify HBV-positive pregnant women and prevent subsequent mother-to-child transmission, but also to screen household contacts and either protect them through immunization or refer them to specialist care for treatment. Additionally, HBV screening in each pregnancy helps identify mothers with newly acquired HBV infection as well as children infected in previous pregnancies or diagnosed cases that were subsequently lost to follow-up.

In our recent prospective follow-up of children with chronic hepatitis B in England, we identified only three children since 2001, who had become infected through horizontal transmission from household contacts.6 In the current study, three UK-born children developed acute HBV infection over a 13-month surveillance period who also acquired the infection from a household contact. These children could potentially have been protected through a routine infant HBV immunisation programme. In all three cases, however, opportunities were missed for screening and vaccinating contacts after an infected individual was diagnosed.

**Acute HAV**

We identified HAV as the most common cause of AIH in children, acquired mostly after travelling abroad. Follow-up of cases identified through LabBase2 in England and Wales revealed that the majority of children with acute HAV infection were managed in primary care without the need for hospital referral. Of those who were hospitalised, most were admitted for a very short duration, with a median length of stay of one day, and recovered without any complications.

**Other aetiologies**

We also identified other well-known hepatotropic viruses responsible for 20% of AIH cases, especially EBV (8/16, 50%) and adenovirus (5/16, 31%). The only CMV case was a preterm baby with intrauterine growth retardation, who developed AIH whilst in the neonatal intensive care unit. In a third of cases, however, the aetiology was not identified. It is reassuring to note that nearly all children in this group were screened for the common hepatitis viruses and they recovered without sequelae. In severe cases and for cases that do not resolve quickly, early liaison with paediatric specialists may help identify less common causes, such as Hepatitis E virus (HEV),7 and seronegative hepatitis.8

**Strengths and Limitations**

The BPSU provides a unique platform for national surveillance of rare syndromic illnesses with variable or unknown aetiology. Although, case ascertainment may not be complete, this methodology has provided a unique insight into the aetiology, clinical course and outcomes of childhood AIH in a country with low HAV/HBV prevalence. A limitation of the study is that we only had an alternative data source for HAV/HBV infections and, therefore, could not ascertain the completeness of AIH due to other viruses or unknown aetiology. Another limitation is the accuracy of the capture-recapture analysis, which assumes a closed population with 2 independent data sources where individuals have an equal probability of being captured by either source and can be matched adequately. Since paediatricians utilise the same laboratories for confirming the diagnosis as those that report through LabBase2, the two data sources may not be truly independent; this, however, would under-estimate rather than overestimate the total number of HAV/HBV cases.

**CONCLUSIONS**

Children with AIH generally had good outcomes, except for those with acute HBV infection. Although none went on develop chronic HBV, one neonate and three children were seriously unwell at presentation, and the latter two went on to require liver transplantation. The UK does not have a universal HBV immunisation programme; a recent economic analysis, however, indicated that infant HBV immunisation could be cost-effective if the vaccine could be procured at a low price, ideally as part of a multivalent combination vaccine. The infant HBV vaccination programme would have to be in addition to the current antenatal screening programme and could potentially reduce both acute and chronic HBV cases acquired through horizontal transmission but would not prevent cases in children born abroad. Like HIV or other serious chronic illnesses, clinicians should liaise early with paediatric specialists to ensure children with acute and chronic HBV infections receive the best possible specialist care and follow-up.

**Funding**

This investigator-led study was funded by GlaxoSmithKline SA(NCT number). GlaxoSmithKline Biologicals SA was provided the opportunity to review and comment on the study protocol and a preliminary version of this manuscript for factual accuracy but the authors are solely responsible for obtaining the appropriate approvals, conducting the study, collecting and analysing the data, as well as the final content and interpretation in the manuscript. The authors received no financial support or other form of compensation related to the development of the manuscript.

**Acknowledgements**

The authors would like to thank all the paediatricians and general practitioners who reported cases and competed the surveillance questionnaires. A special thanks to Sonia Ribeiro at PHE Colindale for developing and maintaining the surveillance questionnaire and database. The authors would also like to thank Richard Lynn and his team at the BPSU for their continued support throughout the study and for their critical review of the manuscript.

**What is known about this topic**

* Acute infectious hepatitis (AIH) is characterised by an acute onset of discrete symptoms including fever, jaundice, abdominal pain, nausea, and vomiting.
* Most childhood cases are caused by viruses, especially Hepatitis A (HAV) and B (HBV), although other viruses and non-viral infections may also be responsible.
* Little is known about the total burden, aetiology, clinical course, management or outcomes of childhood AIH in industrialised countries.

**What this study adds**

* 81 cases were identified over the 13-month surveillance period (annual incidence, 0.52/100,000 children aged <14 years) and most recovered without complications
* The aetiology included hepatitis A (n=27, 39%) cases, hepatitis B (n=5, 4%), and 16 other viruses (23%), while 23 (33%) with no pathogen identified.
* Of the 5 children with acute hepatitis B infection, 3 developed liver failure and two required liver transplantation.

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**Figure 1.** Notifications to BPSU of Acute Infectious Hepatitis in Hospitalised Children from January, 2014 to January, 2015.

**Figure 2.** Number of positive electronic reports to Public Health England for viral hepatitis among <15 year-olds in England and Wales.

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Hep A** | | **Hep B** | | **Other viruses** | | **No viruses** | | **Total** | | |
|  | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | | **%** |
| **Clinical presentation** | | | | | | | | | | | |
| Fever | 18 | 48.65% | 0 | - | 6 | 37.50% | 13 | 56.52% | 37 | | 45.68% |
| Lethargy | 15 | 40.54% | 2 | 40.00%- | 6 | 37.50% | 10 | 43.48% | 33 | | 40.74% |
| Abdominal pain | 23 | 62.16% | 3 | 60.00%- | 6 | 37.50% | 11 | 47.83% | 43 | | 53.09% |
| Jaundice | 29 | 78.38% | 2 | 40.00% | 9 | 56.25% | 14 | 60.87% | 54 | | 66.67% |
| Drowsiness | 5 | 13.51% | 2 | 40.00% | 0 | - | 2 | 8.70% | 9 | | 11.11% |
| Nausea | 11 | 29.73% | 0 | - | 0 | - | 6 | 26.09% | 17 | | 20.99% |
| Diarrhoea | 13 | 35.14% | 0 | - | 3 | 18.75% | 7 | 30.43% | 23 | | 28.40% |
| Vomiting | 20 | 54.05% | 3 | 60.00% | 5 | 31.25% | 13 | 56.52% | 41 | | 50.62% |
| Rash | 2 | 5.41% | 0 | - | 3 | 18.75% | 4 | 17.39% | 9 | | 11.11% |
| Other | 8 | 21.62% | 5 | 100.00% | 7 | 43.75% | 14 | 60.87% | 34 | | 41.98% |
| **Progression in hospital** | | | | | | | | | | | |
| Clinical deterioration | 0 | - | 3 | 60.00% | 0 | - | 1 | 4.35% | 4 | | 4.94% |
| Transfer | 0 | - | 3 | 60.00% | 0 | - | 0 | - | 3 | | 3.70% |
| On-going hepatitis | 0 | - | 5 | 100.00% | 0 | - | 0 | - | 5 | | 6.17% |
| Acute liver failure | 0 | - | 3 | 60.00% | 0 | - | 1 | 4.35% | 4 | | 4.94% |
| Liver transplant | 0 | - | 2 | 40.00% | 0 | - | 0 | 0.00% | 2 | | 2.47% |
| Deaths | 0 | - | 0 | - | 0 | - | 1 | 4.35% | 1 | | 1.23% |
| **Hospital length of stay (days)** | | | | | | | | | | | |
| Median (range) | 1 (0-7) | | 31 (0-35) | | 4.5 (0-79) | | 2 (0-26) | | | 2 (0-79) | |

**Table 1.** Signs and symptoms at presentation, clinical progression in hospital and post discharge outcome of paediatric patients with acute infectious hepatitis, divided by aetiological agent. Proportion where calculated using as denominator the number of participants to the study for the progression in hospital (Hepatitis A = 37, Hepatitis B = 5, Other viruses hepatitis = 16, No viruses hepatitis = 23, Total =81), and the number of participants with complete follow up questionnaires returned for the post-discharge outcome.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Hepatitis B cases | | | | |
|  | **1** | **2** | **3** | **4** | **5** |
| Age | 7years | 2 months | 3years | 9years | 10years |
| Ethnic background | Black African | Indian | Other Asian | Pakistani | White |
| Country of birth | U.K. | U.K. | U.K. | U.K. | Poland |
| Risk for hepatitis B | Mother tested HepB positive 2 years before pregnancy but was negative during pregnancy. Father was identified as positive when subject was 2 years old but no family screening was done | Mother known HepB positive in pregnancy but with absent viral load, HBeAg negative and on antivirals, therefore subject did not receive Hep B Ig at birth but anti-HepB vaccine only (1 dose). Scalp laceration during delivery was noted. Became unwell before receiving the second dose of vaccination. | Lived in household with grandfather who had Chronic Kidney Disease on dialysis, chronic HepB carrier and Diabetes Mellitus. Not identified as at increased risk. | Father known chronic HepB carrier (same genetics). Subject not screened. | Limited information |
| Vaccination | No | 1 dose | No | No | 1dose |
| Presentation | Acute liver failure (cardiocirculatory collapse) | Hypoglycaemia and generalised tonic-clonic seizures | Acute liver failure (hypoglycaemia and neurological deterioration) | Jaundice, vomiting, cough, coryzal | Long history (months) of abdominal pain and feeling unwell |
| Treatment | Liver transplant | Paediatric Intensive Care admission, antivirals, vitamin K and supportive treatment. | Liver transplant | No treatment | None |
| Complications | Well post-transplant | None | GvHD medically treated | None | None |
| Hospitalization | 35 days | 28 days | 34 days | 1 day | 0 days |

**Table 2.** Demographic, risk factors, clinical characteristics and outcomes of children with acute hepatitis B in the United Kingdom and Ireland, January 2014 to January 2015.