An audit of neonatal and infant hepatitis B immunisation and serological testing in two counties of England, 2007–12

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Abstract

We audited adherence to national hepatitis B virus (HBV) immunisation policy for neonates and infants born to HBV positive mothers in two counties of England during 2007/08 to 2011/12 ($n=112$ in County X, $n=190$ in County Y). Over the five year period, 29.9% of at risk neonates in County X and 23.5% in County Y required hepatitis B immunoglobulin (HBIG) at birth. The annual median age of HBIG administration was 0.0–0.5 days. The annual median coverage and timeliness of the first (coverage range 92.3–100.0%; age of administration range 0.0–0.0 days), second (83.8–100.0%; 32.0–42.0 days), third (81.1–100.0%; 62.0–81.0 days) and fourth dose HBV immunisations (44.4–91.9%; 378.0–443.0 days) and serological testing (8.6–81.0%; 450.0–707.0 days) were calculated. Statistically significant variation was found in the coverage of third and fourth dose immunisations in County Y, age of fourth dose immunisation in County X, and the coverage and timeliness of serological testing in both counties ($p < 0.05$). HBIG and the first three HBV immunisations were commonly administered according to the national schedule. Fourth dose immunisations and serological tests showed poor adherence. We advocate public health interventions to improve immunisation programme outcomes and hepatitis B surface antigen testing.

Introduction

Hepatitis B virus (HBV) is a bloodborne vaccine preventable virus that causes significant morbidity and mortality worldwide. Recent infections may be asymptomatic or present as influenza-like illness,

whereas malaise, fatigue, jaundice, abnormal liver function tests, and serological markers are indicative of active HBV infection. Individuals who become chronic carriers are at elevated risk of liver disease including cirrhosis, carcinoma and death (Public Health England, 2013; World Health Organization, 2013). The World Health Organization (WHO) suggest that more than two billion people worldwide have been infected with HBV and approximately 360 million are chronic carriers (WHO, 2009). The relative endemicity of HBV infection varies across countries, and prevalence of chronic infection peaks between 5–10% of adults in sub-Saharan Africa and East Asia, and less than 1% in Western Europe and North America (WHO, 2013).

Epidemiological investigations have shown that perinatal exposure and horizontal transmission between young children accounts for the majority of HBV infections in high prevalence countries (Goldstein et al, 2005; Public Health England, 2013). Unprotected sexual contact, sharing contaminated needles and injection equipment, occupational or custodial exposure, tattooing and body piercing account for the predominance of HBV infections in low prevalence countries (Goldstein et al, 2002). However, exposure events during the perinatal period and early childhood still account for around one-third of transmissions in low prevalence countries, and HBV detection rates are higher among immigrants born in high prevalence countries (Margolis et al, 1995; Aweis et al, 2001).

WHO recommend universal HBV immunisation of all children and the development of control strategies relevant to the epidemiological context of each region and country (WHO, 2009). In England, antenatal screening for hepatitis B surface antigen (HBsAg) status and a targeted accelerated immunisation course has been available across the National Health Service (NHS) for all babies born to infected mothers since 2000 (NHS Executive, 1998; Department of Health – Immunisation

Maternal hepatitis status (babies born to term)

- HBsAg positive and HBeAg positive
- HBsAg positive, HBeAg negative and anti-HBe negative
- HBsAg positive where e-markers have not been determined
- HBsAg positive and HBV DNA level $\geq 1 \times 10^6$ IU/ml in an antenatal sample, where viral load testing has been performed to inform the management of the mother
- Acute hepatitis B during pregnancy

Pre-term babies

- Babies with a birth weight of 1500 g or less, born to mothers infected with HBV regardless of e-antigen status

Figure 1. Indications for neonatal administration of hepatitis B immunoglobulin (Public Health England, 2013)

Branch, 2011;). The course is administered at birth, one month, two months and one year of age (Public Health England, 2013). Children born to women identified as highly infectious also require administration of hyperimmune hepatitis B immunoglobulin (HBIG) within 24 hours of birth (Public Health England, 2013). Close adherence to the schedule is required because 90% of unimmunised perinatally exposed neonates born to hepatitis B e-antigen positive mothers will develop chronic HBV infection, and the risk remains elevated in young children exposed to HBV compared to healthy adults (Hyams, 1995; Public Health England, 2013). Serological testing for HBsAg at one year of age is important to identify post-exposure prophylaxis failures and arrange onward referral for clinical assessment and management. Robust service arrangements to identify the target population and ensure immunisation programme delivery are therefore critical to providing adequate protection against HBV infection (Department of Health - Immunisation Branch, 2011). Services must be flexible and responsive to local need.

Population coverage of neonatal and infant HBV immunisations is monitored in England through the Cover of Vaccination Evaluated Rapidly (COVER) programme. However, collated statistical releases have been published by the NHS Information Centre since 2010/11 only and remain in experimental form due to concerns regarding data quality (Health and Social Care Information Centre Screening and Immunisations Team, 2011, 2012). Data have been incompletely reported by primary care organisations and do not describe HBIG, dose-specific immunisation or serological testing coverage. Owing to these weaknesses, we used local data to audit adherence to HBV immunisation policy for neonates and infants born to HBV positive mothers from two counties of England.

Methods

This retrospective audit was conducted using individual patient data maintained by the East Midlands Centre of Public Health England (PHE). We identified neonates and infants born to HBV positive mothers during 2007/08 to 2011/12 (April to March) reported to the local Health Protection Team. We categorised individuals according to the case definition used by COVER, which included those registered with a general practitioner and unregistered persons who lived within the geographical boundaries of the two counties (Health Protection Agency, 2013). All neonates and infants born to HBV positive mothers were eligible for inclusion if any part of the accelerated immunisation course for post-exposure prophylaxis against hepatitis B was indicated. The standards and definitions used for this audit conformed to those specified by national immunisation policy, which included that all babies born to HBV positive mothers should (Public Health England, 2013):

1. Complete the accelerated HBV immunisation course (first dose within 48 hours of birth and second, third and fourth doses at 1, 2 and 12 months after birth respectively)

2. Receive HBIG within 24 hours of birth, if the mother is highly infectious (see Figure 1)
3. Undergo a blood HBsAg test at one year of age to ascertain infection status following immunisation

Variables extracted included socio-demographic characteristics, maternal hepatitis B infection status, requirement for neonatal HBIG, dates of HBIG and immunisation administration, HBV infection status testing and associated results. For the purpose of this audit, we included venous or dried blood spot HBsAg testing and plasma hepatitis B surface antibody (anti-HBs) testing at one year of age as in the majority of cases this was the only result available (Craine et al. 2009; Mohamed et al. 2013). The inclusion of anti-HBs testing reflects local testing practice and does not suggest or imply equivalence to HBsAg testing for clinical purposes.

Individual patient data were cleaned for analysis using Microsoft® Excel 2010 software version 14.0 (Microsoft Corporation, Richmond, VA, USA). All patient identifiable information was removed from the audit sample and the identity of each county and all cases were link anonymised. Analyses were conducted for each county separately to account for known variation in processes used to follow up neonates and infants requiring hepatitis B immunisations. Descriptive statistics were used to summarise the baseline characteristics of the audit sample and coverage of each immunisation dose and the HBsAg or anti-HBs test. Data were analysed for each annual birth cohort. Binomial exact 95% confidence intervals (95% CIs) were calculated around these estimates. Binomial interpolated 95% CIs were determined around the median age of administration for each intervention. Fisher's exact test was used to explore whether a statistical variation existed in the coverage of each immunisation dose and the HBsAg or anti-HBs test across each annual birth cohort. The Kruskal-Wallis one-way test and χ^2 test adjusted for ties were used to explore the equality in median age of intervention administration. We excluded cases that transferred out of the area where no data were available to confirm administration of each immunisation or serological test. All statistical analyses were carried out using Stata software version 12.1 (StataCorp, College Station, TX, USA) and we assumed $\alpha = 0.05$. Ethical approval was not required because we audited the performance of an existing immunisation service using routine data held for public health activities.

Results

A total of 302 infants (112 in County X; 190 in County Y) including one set of twins met the criteria for inclusion. Table 1 shows the neonatal and maternal baseline characteristics. Maternal ethnic origin was reported with varying completeness (96/112 (85.7%) in County X; 58/190 (30.5%) in County Y). The most frequently reported ethnic origin was Chinese (43/96 (44.8%) in County X; 18/58 (31.0%) in County Y). None of the mothers identified themselves as white British.

Table 1. Baseline characteristics of the audit sample (n=302), 2007/08 to 2011/12

Characteristic	County X (n=112)	County Y (n=190)
<i>Neonatal characteristics</i>		
Sex (male)	58/101 (57.4%)	89/190 (46.8%)
Proportion HBIG required at birth	29/97 (29.9%)	38/162 (23.5%)
Proportion transferred out of area	12/100 (10.7%)	39/151 (20.5%)
<i>Maternal characteristics</i>		
Mean age at delivery $\pm$ SD (years)	28.8 $\pm$ 5.4	29.6 $\pm$ 5.2
Proportion HBeAg positive	18/92 (19.6%)	18/103 (17.5%)
Proportion anti-HBe negative	21/91 (23.1%)	9/78 (11.5%)
Mean IMD 2010 score $\pm$ SD	No data	34.4 $\pm$ 16.9

HBIG = hepatitis B immunoglobulin; SD = standard deviation; HBeAg = hepatitis B e-antigen; anti-HBe = hepatitis B e-antibody; IMD = index of multiple deprivation

In our audit sample of neonates requiring HBV immunisation, 29.9% in County X and 23.5% in County Y had been identified clinically as requiring the administration of HBIG at birth (see Table 1). The annual median age of HBIG administration for both counties was 0.0 to 0.5 days with associated upper 95% confidence interval (CI) limits not extending greater than 1.0 days, with the exception of that for County Y in 2010/11 which reached 5.0 days. No statistically significant differences were found when comparing the annual coverage of HBIG or the age of HBIG administration between 2007/08 to 2011/12. However, there was insufficient data available to confirm if or when HBIG had been administered to 34.5% (10/29) neonates in County X and 13.2% (5/38) in County Y. A post-hoc analysis showed 76.2% (16/21) neonates in County X and 75.0% (15/20) in County Y who required HBIG at birth were born to mothers who were also HBeAg positive (signifying that the mother was highly infectious; Public Health England, 2013). No data were available to confirm that HBIG was administered to five of these neonates in County X and two neonates in County Y.

Table 2 presents the coverage and median age of hepatitis B immunisations administered to neonates and infants in each county between 2007/08 and 2011/12. The annual first dose immunisation coverage ranged between 89.7% and 100.0%, falling to between 44.4% and 91.9% at the fourth dose. The identified reduction in the dose-specific rate of immunisations administered was observed consistently each year for both counties. Statistically significant differences were found across the annual proportion of infants in County Y receiving the third (Fisher's exact test; $p=0.041$) and fourth dose immunisations (Fisher's exact test; $p<0.001$). The median age of immunisation described for each year approximated the target age well for each dose, although 95% CIs were often wide. Statistically significant variation was identified in the age of fourth dose immunisations administered to infants in County X (Kruskal-Wallis test; χ^2 statistic = 12.6; degrees of freedom=4; $p=0.014$).

The coverage of HBsAg or anti-HBs tests between 2007/08 and 2011/12 was generally poor across both counties (see Table 1). These data were statistically significantly different for both counties (Fisher's exact test; $p=0.016$ and $p<0.001$, respectively). The median age of HBsAg or anti-HBs test administration showed frequent and occasionally large departures from the target age of one year. Statistically significant variation in the age of HBsAg or anti-HBs test administration was found in the audit sample from County X (Kruskal-Wallis test; χ^2 statistic = 9.7; degrees of freedom=4; $p=0.045$) and County Y (Kruskal-Wallis test; χ^2 statistic=13.0; degrees of freedom=4; $p=0.011$). We identified that 29.7% (30/101) infants in County X and 26.3% (42/160) infants in County Y underwent an HBsAg test.

Despite having appropriately received prophylaxis with HBV immunisation $\pm$ HBIG according to maternal status, 3.7% of infants (5/136) either became HBsAg positive or failed to seroconvert.

Discussion

This audit provides a contemporary analysis of dose-specific HBV immunisation and serological testing coverage and age of administration in at risk neonates and infants from two counties of England. Our data suggest that administration of HBIG and the first three immunisation doses commonly adhere to national policy requirements. However, reduced point estimates and wide 95% CIs calculated around the fourth dose immunisation and serological tests are concerning, and indicate underperformance. A potential explanation is loss to follow up due to migration. Delayed HBsAg or anti-HBs testing and reduced coverage is consistently observed in both counties when compared to those variables for the fourth dose immunisation despite national policy recommending the co-administration of these interventions. This is partially due to the fact that many infants are referred to secondary care to have venous blood samples taken, which introduced a delay between administration of the fourth dose immunisation and HBV serological test. The statistically significant differences we identified in coverage and age of intervention administration suggests variation in annual immunisation programme performance is present across the audit timeframe. Although the apparent low coverage in fourth dose immunisation and HBsAg or anti-HBs testing in 2011/12 may partially explain these findings, investigations are required to elucidate potential reasons for the reduced point estimates identified that year.

The low rate of HBsAg testing at one year of age across both counties highlights the need for local action to increase the use of this serological test in accordance with national clinical guidelines (Public Health England, 2013). Anti-HBs testing alone is unable to differentiate between recovery from HBV infection or seroconversion following prior exposure to immunisation, and cannot diagnose acute or chronic HBV infection. Use of this serological test following immunisation in babies born to HBV positive mothers should be actively discouraged in favour of HBsAg testing.

A number of limitations associated with our audit warrant discussion. Insufficient data were available to calculate immunisation or HBsAg or anti-HBs testing uptake and calculating coverage alone may introduce bias to the overall assessment of immunisation programme performance. Dose-specific immunisation and serological testing data have to be obtained proactively by PHE and a lack of time and resources to do this may have an impact on the completeness of the data. Point estimates for 2011/12 may therefore represent an

Table 2. Hepatitis B Immunisation delivery for neonates and infants in two counties of England, 2007/08 to 2011/12

Year	Sample size*	First dose immunisation (target age = two days)		Second dose immunisation (target age = 30 days)		Third dose immunisation (target age = 60 days)		Fourth dose immunisation (target age = 365 days)		HBsAg or anti-HBs test (target age = 365 days)	
		Coverage (%)	Median age of administration (days)	Coverage (%)	Median age of administration (days)	Coverage (%)	Median age of administration (days)	Coverage (%)	Median age of administration (days)	Coverage (%)	Median age of administration (days)
County X	2007/08	18	100.0 (80.5 to 100.0)◇	0.0 (0.0 to 0.0)	94.1 (71.3 to 99.9)	38.5 (32.5 to 51.6)	88.2 (63.6 to 98.5)	69.0 (61.2 to 110.9)	75.0 (47.6 to 92.7)	62.5 (35.4 to 84.8)	450.5 (364.3 to 642.2)
	2008/09	18	100.0 (79.4 to 100.0)◇	0.0 (0.0 to 0.0)	100.0 (79.4 to 100.0)◇	42.0 (31.0 to 55.3)	100.0 (79.4 to 100.0)◇	81.0 (64.5 to 87.5)	86.7 (59.5 to 98.3)	53.3 (26.6 to 78.7)	583.5 (405.6 to 899.9)
	2009/10	29	89.7 (72.6 to 97.8)	0.0 (0.0 to 0.0)	89.7 (72.6 to 97.8)	32.0 (31.0 to 42.1)	86.2 (68.3 to 96.1)	71.0 (61.4 to 96.9)	82.8 (64.2 to 94.2)	53.6 (33.9 to 72.4)	707.0 (471.5 to 891.6)
	2010/11	24	90.9 (70.8 to 98.9)	0.0 (0.0 to 0.0)	90.5 (69.6 to 98.8)	34.0 (29.0 to 39.8)	90.5 (69.6 to 98.8)	68.0 (62.0 to 74.9)	85.7 (63.7 to 97.0)	52.4 (29.8 to 74.3)	455.0 (442.0 to 640.9)
	2011/12	23	100.0 (83.9 to 100.0)◇	0.0 (0.0 to 0.0)	95.2 (76.2 to 99.9)	32.0 (31.1 to 40.1)	90.5 (69.6 to 98.8)	62.0 (61.0 to 68.8)	52.4 (29.8 to 74.3)	14.3 (3.0 to 36.3)	450.0 (448.0 to 542.0)
County Y	2007/08	31	96.7 (82.8 to 99.9)	0.0 (0.0 to 0.0)	92.9 (76.5 to 99.1)	36.0 (32.0 to 61.5)	92.9 (76.5 to 99.1)	70.0 (64.5 to 130.9)	88.9 (70.8 to 97.6)	81.0 (58.1 to 94.6)	683.0 (480.1 to 1019.7)
	2008/09	45	97.8 (88.2 to 99.9)	0.0 (0.0 to 1.0)	92.9 (80.5 to 98.5)	37.0 (32.9 to 44.1)	92.9 (80.5 to 98.5)	78.0 (68.0 to 98.2)	90.2 (76.9 to 97.3)	78.9 (62.7 to 90.4)	559.0 (458.9 to 651.0)
	2009/10	39	100.0 (91.0 to 100.0)◇	0.0 (0.0 to 1.0)	97.4 (86.2 to 99.9)	34.0 (31.0 to 40.0)	100.0 (90.7 to 100.0)◇	68.0 (62.4 to 92.7)	91.9 (78.1 to 98.3)	64.7 (46.5 to 80.3)	489.0 (450.9 to 536.1)
	2010/11	36	97.2 (85.5 to 99.9)	0.0 (0.0 to 1.0)	100.0 (90.0 to 100.0)◇	36.5 (31.8 to 44.9)	94.1 (80.3 to 99.3)	71.0 (66.5 to 78.0)	84.3 (67.2 to 94.7)	65.6 (46.8 to 81.4)	452.0 (415.4 to 501.0)
	2011/12	39	92.3 (79.1 to 98.4)	0.0 (0.0 to 0.0)	83.8 (68.0 to 93.8)	33.0 (32.0 to 39.5)	81.1 (64.8 to 92.0)	67.5 (62.1 to 74.0)	44.4 (27.9 to 61.9)	8.6 (1.8 to 23.1)	499.0 (412.0 to 690.0)

Values in parentheses are 95% confidence intervals; * = infants requiring immunisation against hepatitis B in accordance with national policy; ◇ = one-sided 97.5% confidence interval

underestimation due to missing data. However, given the comparable sample sizes with previous years and similar first to third dose immunisation coverage estimates we anticipate the likely impact of this to be negligible. Limited information on maternal serological HBV markers was present to confirm the need for HBIG administration. For 15 neonates who required HBIG at birth but where confirmatory data of administration is not available, we cannot exclude the possibility this was provided but not reported to PHE or that the infants did not receive it. We cannot discount the potential for double counting if transfers occurred between the two counties or the inclusion of data where immunisations were given outside of these counties. Although we adopted the same case definition as COVER there was inadequate information to identify when transfers occurred, thereby potentially introducing measurement bias to our findings. However, the low proportion of transfers identified in both counties suggests this limitation may have a minimal impact on the validity of our results.

A limited number of published studies and audits have examined dose-specific coverage of neonatal and infant HBV immunisations in England (Smith et al., 1994; Dunn et al., 1999; Wallis and Boxall, 1999; Sloan et al., 2005; NHS Lincolnshire, 2013). Our data and these earlier works are comparable in their findings regarding a consistently observed decline in immunisation coverage from first to later doses and low rate of serological testing. Although this may suggest that HBV immunisation programme performance across Counties X and Y is not substantially different from other areas, it also implies that limited progress has been made to improve service delivery in recent years for which potential explanations are not forthcoming. Sloan et al (2005) constructed univariate and multivariate statistical models to identify factors associated with endpoints for successful HBV immunisation. The authors reported that year, HBV immunisation schedule, maternal HBeAg and anti-HBe status, and prior booking of the pregnancy were statistically significantly associated with neonates receiving HBIG and first vaccine dose on time following multivariate analysis. Infants with HBeAg seropositive and anti-HBe seronegative mothers were statistically significantly associated with receipt of an HBsAg serological test at one year of age. While the authors undertook an extensive analysis, the proportion of variance explained in their statistical models is not reported, maternal HBV DNA levels were not adjusted for and analyses were not conducted to explore factors associated with each HBV immunisation dose. Risk factors associated with poor dose-specific immunisation uptake and the study of interventions to increase uptake remain as important areas which urgently require further investigation.

Giraudon et al (2009) describe the importance of studying aspects relating to the configuration of health services, processes and patient pathways for neonatal and infant HBV immunisation to further explain the observed levels of coverage. Before the creation of PHE and NHS England in April 2013, non-mandatory best practice guidance from the National Institute of Health and Care Excellence (NICE) were produced to support commissioners to improve services and maximise immunisation uptake (NICE, 2009; Department of Health

– Immunisation Branch, 2011). Local experience suggests that to date health services have used different models of provision, which creates challenges especially when seeking to benchmark and quality assure health outcomes. However, an evidence-based national service specification for neonatal HBV immunisation services has recently been published by NHS England which places a clear expectation on local services to drive improvement on current levels of HBV immunisation coverage (Department of Health, 2012). County Y has been involved in a pilot of dried blood spot testing for HBsAg in primary care. This has the potential to increase coverage and timeliness of the serological test and a national roll-out is being considered. The timely provision of metrics to describe service activity and immunisation outcomes which enable regular audits of these services are critical to quality assure service delivery and protect vulnerable children from developing chronic HBV infection. Robust arrangements are therefore necessary to ensure the timely submission of data and failsafe mechanisms to safeguard the administration of hepatitis B prophylaxis according to national policy. The overall effectiveness of the newly commissioned services will partly depend on local areas successfully engaging with a typically ethnically diverse and socioeconomically deprived target group (Hahné et al, 2004; Giraudon et al, 2009).

Although our findings may generalise to other areas of England, further analyses are required to confirm this. Monitoring the recommendations made herein, re-auditing and conducting studies to develop and evaluate targeted public health interventions are important to drive improvements in HBV immunisation programme performance. Administration of a booster HBV immunisation along with other pre-school childhood immunisations remains important for children at continued risk of infection, including HBV prophylaxis for uninfected household members (Public Health England, 2013). HBsAg testing at one year remains critically important for clinical management of infants born to HBV positive mothers.

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