Hepatitis B vaccination coverage and risk factors associated with incomplete vaccination of children born to hepatitis B surface antigen-positive mothers, Denmark, 2006 to 2010

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In Denmark, universal screening of pregnant women for hepatitis B has been in place since November 2005, with the first two years as a trial period with enhanced surveillance. It is unknown what the change to universal screening without enhanced surveillance has meant for vaccination coverage among children born to hepatitis B surface antigen (HBsAg)-positive mothers and what risk factors exist for incomplete vaccination. This retrospective cohort study included 699 children of mothers positive for HBsAg. Information on vaccination and risk factors was collected from central registers. In total, 93% (651/699) of the children were vaccinated within 48 hours of birth, with considerable variation between birthplaces. Only 64% (306/475) of the children had received all four vaccinations through their general practitioner (GP) at the age of two years, and 10% (47/475) of the children had received no hepatitis B vaccinations at all. Enhanced surveillance was correlated positively with coverage of birth vaccination but not with coverage at the GP. No or few prenatal examinations were a risk factor for incomplete vaccination at the GP. Maternity wards and GPs are encouraged to revise their vaccination procedures and routines for pregnant women, mothers with chronic HBV infection and their children.

Introduction

Hepatitis B virus (HBV) infection is a worldwide health problem with more than 350 million people estimated to have chronic liver infections caused by HBV [1]. If hepatitis B surface antigen (HBsAg) is detected in the blood for more than six months, the HBV-infection has become chronic [2]. For infants (up to 1 year old) and children (1–10 years) the two primary sources of HBV infection are perinatal transmission from infected mothers and horizontal transmission from infected household contacts [2]. Mother-to-child transmission of HBV can be effectively (95%) prevented by vaccination [1,2]. The risk of becoming chronically infected with HBV is inversely related to the age of the patient at the time of infection [3]. Chronic infection occurs in ca 90% of infected infants, in 30% of infected children younger than five years and in less than 5% of those infected when they are five years or older [2].

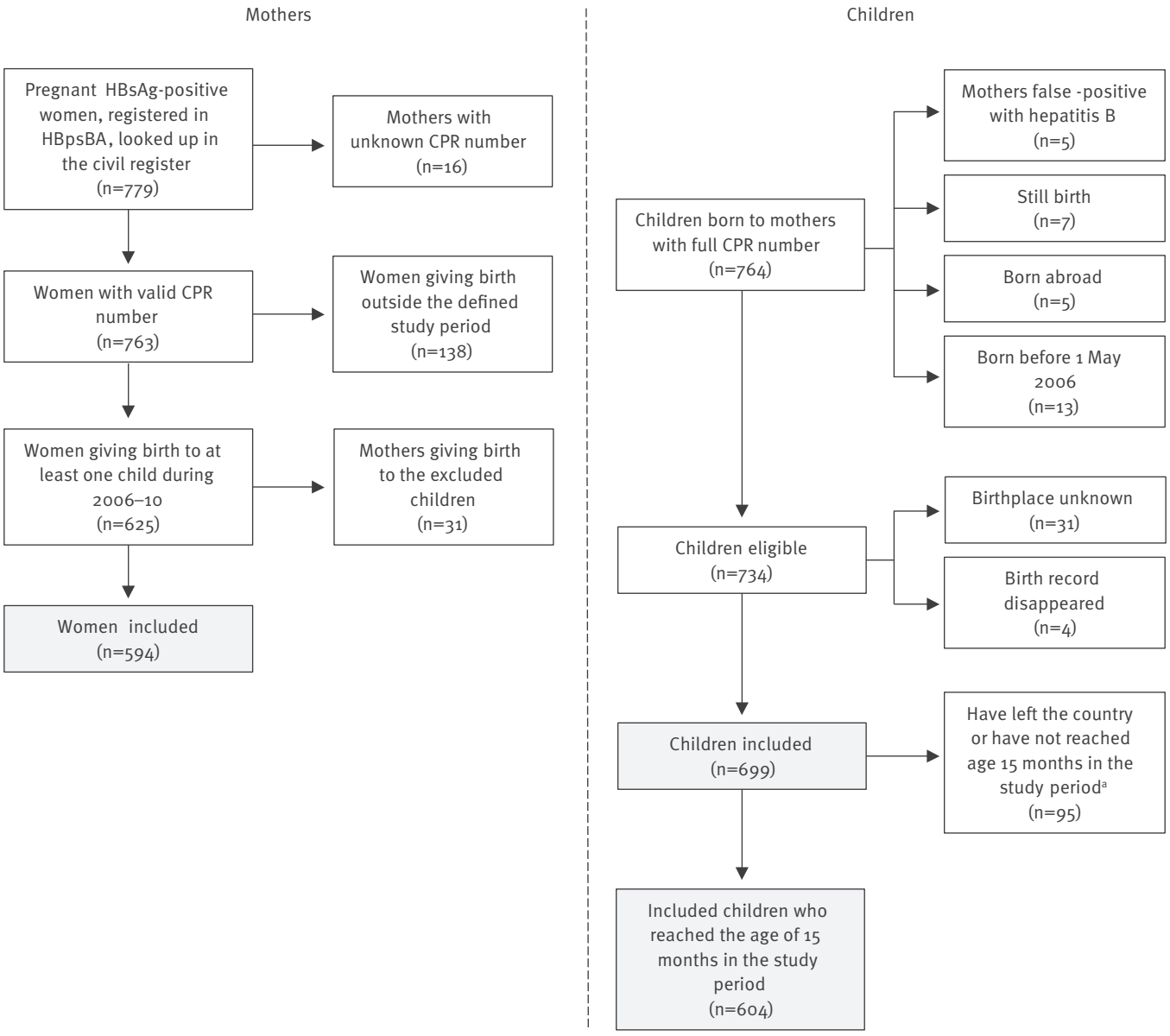
In Denmark, mother-to-child infection is the primary cause (72%) of chronic HBV-infection [4]. Universal screening of pregnant women for hepatitis B has been in place since November 2005 and was made permanent in November 2007 [5,6]. The first two years (1 November 2005 until 31 October 2007) were a trial period with enhanced surveillance. The enhanced surveillance comprised blood banks, maternity wards and general practitioners (GP), for example contacting the maternity wards to secure vaccination of the individual infants and informing the GP about further vaccination of the infants and screening of family members [7,8]. Approximately 180 cases of HBV infection were observed annually between 2006 and 2010, primarily among women from areas highly endemic for hepatitis B [9]. During the trial period, 0.26% of pregnant women were found to be chronically infected with HBV [7].

HBV vaccination is not part of the Danish childhood vaccination programme (CVP) [10,11]. Efforts were instead put into the pregnancy screening programme and into risk group vaccination [12]. This paper presents an evaluation of the pregnancy screening and the subsequent hepatitis B vaccination of the children.

The objective of pregnancy screening is to ensure that all neonates born to HBsAg-positive women are vaccinated against HBV. Furthermore, it is important that GPs refer HBsAg-positive pregnant women to a department for infectious diseases for further information and

Figure 1

Population and samples included in the retrospective cohort study of hepatitis B surface antigen-positive mothers (n = 594) and their children (n = 699 born 2006–2010), Denmark, 2006–2010



CPR: unique identification number in the Danish civil register; HBsAg: Hepatitis B surface antigen; HBpsBA: The national hepatitis B pregnancy-screening database.

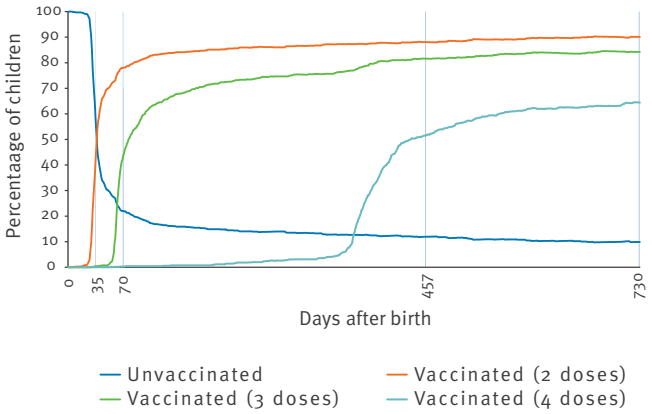
[a] Some children had not reached the age for the fourth vaccination or had left the country.

ongoing care for the newly diagnosed mother including eventually treatment during pregnancy [13]. Only half of the women were referred during the trial period (personal communication: Weiss N, Hvidovre Hospital, Denmark, June 2014, with permission). During the trial period with universal screening, 96% of the children received vaccination at birth [14]. The HBV vaccination coverage of the children born to HBsAg-positive mothers in Denmark during 2008 to 2010 is not known.

According to Danish national guidelines, the vaccination schedule for children born to HBsAg-positive mothers comprises four doses of vaccine, Engerix-B (10 µg): the first dose of vaccine and hepatitis B immunoglobulin (HBIG) at day 0 and three additional doses of vaccine at one, two and 12 months of age [13,15]. All the vaccinations are free of charge [16]. The maternity ward takes care of the first vaccination, including HBIG, and the GPs take care of the rest of the vaccinations.

Figure 2

Cumulative Kaplan–Meier survival curves showing the proportion of children vaccinated for hepatitis B by their general practitioner and unvaccinated children, by days after birth, Denmark, 2006–2010 (n = 699)



The small drop in the beginning of the Unvaccinated curve, is explained by the number of children (n = 48) not having received the birth dose.

Table 1

Country of origin of hepatitis B surface antigen-positive mothers, retrospective cohort study, Denmark, 2006–2010 (n = 594)

Geographical area	Women included in the study	
	n	%
South-east Asia	252	42
The Middle East, northern African countries, including Israel and Turkey	107	18
Sub-Saharan Africa	91	15
Eastern Europe	71	12
Indian subcontinent, including India, Pakistan and Bangladesh	40	7
Denmark	20	3
Greenland	5	< 1
Oceania (Tonga and New Zeeland)	2	< 1
South America (Chile and Brazil)	2	< 1
Western Europe (France (n = 1), Spain (n = 2), Sweden (n = 1))	4	< 1

The aim of this study was to describe the vaccination coverage among children of HBsAg-positive mothers born during the trial period of universal screening with enhanced surveillance (2006–2007) or born in the following three years with universal screening without enhanced surveillance (2008–2010), to identify risk factors for incomplete vaccination and to discuss possibilities for additional prevention. This article is a proof of concept.

Methods

The study was a retrospective cohort study of pregnant HBsAg-positive women and their live-born children in Denmark from 2006 to 2010. The first two years of the universal screening constituted a trial period with enhanced surveillance.

All Danish residents are registered with a unique identification number (CPR number) [17]. From the national hepatitis B pregnancy screening database (HBpsBA), we know that around 2% of the pregnant women notified with hepatitis B do not have a CPR number. Since they are not listed in the civil register, they were not a part of this study.

Data sources and registers

The national hepatitis B pregnancy-screening database

Statens Serum Institute cooperates with the blood banks on monitoring the pregnancy screening in Denmark [15]. The database includes data on all HBsAg-positive women screened since 2005. From this database we extracted all women screened in the defined study period. Data on name, CPR number and date of screening were pulled from the database.

The civil register

This register was established in 1968. Danish residents are registered with a CPR number [17]. From this register, we obtained the CPR numbers of children born in Denmark to mothers known to be infected with HBV and still residing in Denmark. Further, we extracted data on country of origin and immigration/emigration data of the mothers of these women.

The service code register (in Danish: Sygesikringsregisteret)

This is a database containing all services given by primary healthcare practitioners. Each service has a code and each code is registered by CPR number. The database is updated monthly. We extracted service codes for HBV vaccinations of children born to HBsAg-positive mothers (code: 8314–8316), service codes for the prenatal visits (code: 8110–8130) and health examinations of the mothers eight weeks after giving birth (code: 8140).

The national birth register

This register was established in 1973. From this register we identified the hospitals where the HBsAg-positive mothers gave birth.

The maternity wards in Denmark

Data on HBV vaccination and HBIG at birth are registered at the hospitals. All maternity wards were contacted. Data collected were: time of birth, HBV vaccine given (yes/no), HBIG given (yes/no) and if yes for any of these, date and time.

The general practitioners

If data on vaccination were missing in the service code register, the GPs were contacted by phone.

Table 2

Children vaccinated against hepatitis B at birth and at the general practitioner's, by birth year, Denmark, 2006–2010 (n = 699)

Birth year	Live births	Birth vaccine				Vaccinations at the general practitioner's						All vaccinations	
		Vaccinated within 24 hours[a]		Vaccinated within 48 hours[b]		Second dose received within 5 weeks		Third dose received within 10 weeks		Fourth dose received within 15 months		All four doses received within 15 months	
		n	%	n	%	n	%	n	%	n	%	n	%
2006	100	89/100	89	93/100	93	47/100	47	48/100	48	59/99[c]	60	57/99[c]	58
2007	155	146/155	94	153/155	99	78/155	50	73/155	47	82/152[c]	54	80/152[c]	53
2008	161	133/161	83	139/161	86	66/161	41	66/161	41	78/160[c]	49	74/160[c]	46
2009	158	148/158	94	149/158	94	55/158	35	55/158	35	78/156[d]	50	78/156[d]	50
2010	125	112/125	90	117/125	94	59/125	48	62/125	50	15/37[d]	41	15/37[d]	41
Total	**699**	**628/699**	**90**	**651/699**	**93**	**305/699**	**44**	**304/699**	**43**	**312/604[d]**	**52**	**304/604[d]**	**50**

Vaccination schedule in Denmark: At birth (within 48 hours), and at age 1, 2 and 12 months.

The table is divided in columns of birth vaccines and columns of vaccinations at the general practitioner. Within these groups the numbers are summed up. For instance, when looking at the third dose received, these numbers include both second and third dose received, when the child is 10 weeks-old and so forth. The last column shows those children who have received all four doses of vaccine.

[a] Both hepatitis B immunoglobulin (HBIG) and hepatitis B vaccine received, except in 10 children who had only received the vaccine.

[b] Both HBIG and hepatitis B vaccine received, except in 11 children who had only received the vaccine. Four children were vaccinated at the delivery site, but after 48 hours, and are regarded as unvaccinated (and not included in the column).

[c] Some children had left the country.

[d] Some children had not reached the age for the fourth vaccination or had left the country.

Study population

We included all HBsAg-positive mothers registered in HBpsBA from 1 November 2005 until 10 January 2011 and the children they gave birth to from 1 May 2006 onwards (Figure 1).

Definition of 'vaccinated in time'

Scheduled vaccination of children born to HBsAg-positive mothers according to the national vaccination schedule is immediately/within 48 hours after birth, and at the age of one, two and 12 months. We used the following limits for timely vaccination:

- First vaccination: immediate vaccination after birth/ within 48 hours
- Second vaccination: 5 weeks after birth (nationally scheduled at 4 weeks)
- Third vaccination: 10 weeks after birth (nationally scheduled at 8 weeks)
- Fourth vaccination: 15 months after birth (nationally scheduled at 12 months)

Risk factors for missing vaccination

We analysed risk factors for incomplete vaccination. The following risk factors were included: the mothers' country of origin, year of delivery, number of pregnancy examinations, mother's age when giving birth and length of time in Denmark before giving birth. We were able to extract all risk factors from the registers.

Statistical analyses

Kaplan–Meier survival curves were used to estimate the probability for vaccination and how many days after birth the children were vaccinated. The regression model used in this study was logistic regression estimating odds ratios (OR) of included risk factors. The risk factor analyses had three steps: (i) univariate analysis for each risk factor separately, (ii) multivariate analysis with all risk factors included, and (iii) multivariate analysis, final model, with backward elimination with a threshold at 10%. When discussing changes in risk we used a binary regression (Poisson regression without exposure) to estimate risk ratios (RR). We used a significance level of 5%. All data were analysed in STATA version 10.0.

Results

After exclusion of mothers with unknown CPR number, mothers who had given birth outside the defined study period, mothers who had given birth to excluded children and children having left the country, the final cohort comprised 699 children and 594 mothers (Figure 1).

Characteristics of the mothers

The median age at delivery was 31 years (range: 17–44 years). Of the 594 mothers, 267 (45%) had previously given birth in Denmark. Thirty-five (6%) of the mothers were adopted as children from high-endemic countries for hepatitis B, and 252 mothers (42%) originated from south-east Asia, a high-endemic area (Table 1).

Vaccination of the children

Of the 699 children, 651 (93%) were vaccinated within 48 hours after birth, 628 (90%) within 24 hours. A total of 305 (44%) of the 699 children had received the second dose of vaccine from their GP at five weeks of age and 304 (43%) had received the third dose 10 weeks after birth. Of the 604 children who had reached the age of 15 months during the study period, 312 (52%)

Table 3

Factors associated with not receiving hepatitis B vaccination within 48 hours of birth, Denmark, 2006–2010 (n = 699)

Factor	Level	Liveborn children n = 699		Newborns not receiving vaccination[a] n = 48		Single factor analysis		Multivariate analysis (all factors)		Multivariate analysis (final model)[d]	
		n	%	n	%	OR (95%CI)	p [e]	OR (95% CI)	p [e]	OR (95% CI)	p [e]
Country of origin[b]	Danish Not Danish	23 676	3 97	8 40	17 83	1 (ref) 0.12 (0.05–0.29)	<0.01	1 (ref) 0.07(0.02–0.21)	<0.01	1 (ref) 0.11 (0.041–0.27)	<0.01
Year of delivery	2006 2007 2008 2009 2010	100 155 161 158 125	14 22 23 23 18	7 2 22 9 8	15 4 46 19 17	5.76 (1.17–28.34) 1 (ref) 12.11 (2.79–52.49) 4.62 (0.98–21.77) 5.23 (1.09–25.12)	<0.01	6.67 (1.21–36.90) 1 (ref) 15.80 (3.36–74.25) 5.30 (1.05–26.71) 5.66 (1.11–28.85)	<0.01	5.85 (1.10–31.04) 1 (ref) 13.06 (2.85–59.90) 5.02 (1.02–24.80) 5.51 (1.10–27.67)	<0.01
Pregnancy examinations	None 1 2 3	17 97 125 460	2 14 18 66	1 8 8 31	2 17 17 65	1 (ref) 1.44 (0.17–12.32) 1.09 (0.13–9.35) 1.16 (0.15–9.02)	0.95	1 (ref) 1.80 (0.28–11.47) 1.21 (0.19–7.73) 1.21 (0.20–7.18)	0.80	NA	NA
Age group (mothers age when giving birth)	17–24 years 25–29 years 30–34 years 35–44 years	66 217 255 161	9 31 36 23	4 11 22 11	8 23 46 23	1 (ref) 0.83 (0.25–2.69) 1.46 (0.47–4.41) 1.14 (0.35–3.71)	0.50	1 (ref) 1.26 (0.37–4.29) 2.84 (0.88–9.20) 1.62 (0.49–5.40)	0.12	NA	NA
Total time in Denmark before giving birth[c]	<1 year 1–5 years >5 years	n = 676 45 113 518	7 17 77	n = 40 5 5 30	13 13 75	1 (ref) 0.37 (0.10–1.35) 0.49 (0.18–1.34)	0.28	1 (ref) 0.27 (0.08–0.98) 0.35 (0.12–1.00)	0.11[e]	NA	NA

NA: not applicable; OR: odds ratio CI: confidence interval; ref: reference value.

[a] Vaccination means both hepatitis B immunoglobulin and vaccine received within 48 hours, except in 10 children who only received the vaccine.

[b] Country of origin is divided into only two levels, Danish and not Danish, since the single variable analysis showed no difference (p = 0.98) between any other ethnic groups compared with the Danish group. The other ethnic groups came from: Greenland, Indian subcontinent (including India, Pakistan and Bangladesh), the Middle East and Africa north of Sahara (including Turkey and Israel), Oceania, Africa south of Sahara, South America, south-east Asia, western and eastern Europe.

[c] Total time in Denmark is the accumulated time in the country for one person. If a person was travelling in and out of the country, the time not in Denmark was subtracted from the total time. Only mothers with non-Danish ethnicity were included in this variable. Only one pregnant woman arrived in Denmark less than six months before delivery.

[d] Final model: stepwise backward elimination at 10% level.

[e] The p values for total time in Denmark before giving birth refer to the joint effect/the overall significance of the factor, although the individual levels in the factor were significant.

had received three doses of vaccine at the GP. Half of the 604 children (n = 304) had received all four doses (one at birth and three doses at the GP's) (Table 2). At the time of the study, 95 of the total 699 children had not reached the age for the fourth dose of vaccine or had left the country (Figure 1) and could therefore not be followed up at age 15 months.

HBV vaccinations were under-reported to the service code register. For 325 of the 699 children (46%), the second dose of HBV vaccine (the first given by the GP) had not been recorded in the register by the GP. However, contact to the GPs revealed that of these 325 children, 251 (77%) had in fact received the second dose. For the third and fourth dose, the corresponding proportions were 64% (208/327) and 36% (166/457), respectively.

Experience from the collection of data in several cases showed that the reason for a disrupted vaccination schedule was that the mother changed GP.

Table 4

Factors associated with an incomplete course of hepatitis B vaccine (less than four doses) at 15 months of age, Denmark, 2006–2010 (n = 604)

Factor	Level	Liveborn children n = 604		Children with incomplete vaccination n = 300		Single factor analysis		Multivariate analysis (all factors)		Multivariate analysis (final model)[d]	
		n	%	n	%	OR (95%CI)	p	OR (95% CI)	p	OR (95% CI)	p
Received vaccination at birth[a]	Yes No	565 39	94 6	261 39	87 13	[a] 1 (ref)	<0.01*	NA	NA	NA	NA
Country of origin[b]	Danish Not Danish	20 584	3 97	12 288	4 96	1 (ref) 0.64 (0.26–1.61)	0.35	1 (ref) 1.08 (0.34–3.36)	0.90	NA	NA
Year of delivery	2006 2007 2008 2009 2010	99 152 160 156 37	16 25 26 26 6	42 72 86 78 22	14 24 29 26 7	0.82 (0.49–1.36) 1 (ref) 1.29 (0.82–2.02) 1.11 (0.71–1.74) 1.63 (0.79–3.38)	0.30	0.68 (0.39–1.17) 1 (ref) 1.03 (0.64–1.65) 1.02 (0.64–1.64) 1.58 (0.71–3.53)	0.34	NA	NA
Pregnancy examination	None 1 2 3	15 84 104 401	2 14 17 66	10 52 55 183	3 17 18 61	1 (ref) 0.81 (0.25–2.60) 0.56 (0.18–1.76) 0.42 (0.14–1.25)	0.02	1 (ref) 0.73 (0.20–2.63) 0.53 (0.15–1.84) 0.40 (0.12–1.36)	0.07	1 (ref) 0.45 (0.24–0.86) 0.56 (0.29–1.05) 0.76 (0.39–1.48)	0.03
Post-pregnancy examination	Yes No	364 240	60 40	167 133	56 44	0.68 (0.71–0.97) 1 (ref)	0.02	0.73 (0.51–1.04) 1 (ref)	0.08	NA	NA
Age group (mothers' age when giving birth)	17–24 years 25–29 years 30–34 years 35–44 years	58 196 215 135	10 32 36 22	36 84 106 74	12 28 35 25	1 (ref) 0.45 (0.25–0.84) 0.59 (0.33–1.08) 0.74 (0.39–1.39)	0.04	1 (ref) 0.46 (0.23–0.89) 0.55 (0.29–1.06) 0.76 (0.39–1.51)	0.05	1 (ref) 0.75 (0.21–2.62) 0.54 (0.16–1.85) 0.39 (0.12–1.29)	0.03
Total time in Denmark before giving birth[c]	<1 year 1–5 years >5 years	n = 584 37 91 456	6 16 78	n = 288 20 48 220	7 17 76	1 (ref) 0.95 (0.44–2.04) 0.79 (0.40–1.55)	0.62	1 (ref) 1.44 (0.60–3.43) 1.18 (0.54–2.56)	0.64	NA	NA

NA: not applicable; OR: odds ratio; CI: confidence interval; ref: reference value.

Only mothers who had not left Denmark at the 15-months examination are included in the Table.

[a] Vaccination means both hepatitis B immunoglobulin and vaccine received at the birth place any time before 48 h, except in 11 children who only received the vaccine. Because all live born children with no vaccination at birth (n = 39) were exactly the same as those with incomplete vaccination at 15 months of age, the OR could not be estimated for this group. Therefore, this group was excluded from the multivariate analysis; in the univariate analysis, a Fisher's exact test could calculate the significance of this factor.

[b] Country of origin is divided into only two levels, Danish and not Danish, since the single variable analysis showed no difference (p = 0.98) between any other ethnic groups compared with the Danish group. The other ethnic groups came from: Greenland, Indian subcontinent (Including India, Pakistan and Bangladesh), the Middle East and Africa north of the Sahara (including Turkey and Israel), Oceania, Africa south of the Sahara, South America, south-east Asia, western and eastern Europe.

[c] Total time in Denmark is the accumulated time in the country for one person. If a person was travelling in and out of the country, the time not in Denmark was subtracted from the total time. Only mothers with non-Danish ethnicity were included in this variable. Only one pregnant woman arrived in Denmark less than six months before delivery.

[d] Final model: stepwise backward elimination at 10% level.

*Statistically significant in Fischer's exact test.

Box

Lessons learned

- Vaccination procedures and routines at the sites of delivery with optimal organisation (best practice) should be a model to implement at all sites.
- The sites of delivery should be attentive to mothers of foreign origin but not forget mothers of Danish origin with chronic HBV infection as well as mothers who were themselves adopted.
- It is important that GPs are informed about vaccinations initiated at the hospital and know the plan for subsequent treatment.
- The GP should pay particular attention to ensure that pregnant women with chronic HBV infection attend all prenatal examinations.
- If it becomes known that a child has not received the vaccination series as recommended, the child should be called in for vaccination.
- If the child changes GP, it is important to communicate the HBV vaccination status to the new GP.
- It is important that the GP employ the special provider number for the vaccine, which forms the basis of any assessment of the vaccination coverage nationally.

In addition to how many children received the recommended number of doses of vaccine, we also analysed the timeliness of the vaccines given. Figure 2 shows the total number of unvaccinated children and when the children obtained the individual vaccines at the GP's. At the age of 10 weeks, 78% (545/699) of the children had received the second dose. At the age of two years, 64% (306/475) of the children had received all four vaccinations. At the age of 15 months (457 days), 12% (72/604) of the children had not received any HBV vaccinations at all; this figure had dropped to 10% (47/475) by the age of two years (Figure 2).

Risk factors associated with not receiving hepatitis B vaccination within 48 hours after birth

Year of delivery was significantly correlated with risk of not being vaccinated: Giving birth in 2008, just after the enhanced surveillance was terminated, had a 12 times higher risk (relative risk (RR) = 11.70; 95% confidence interval (CI): 2.80–48.80) of not being vaccinated than giving birth in 2007 (Table 3; odds ratio (OR) = 13.06; 95% CI: 2.85–59.90). This increased risk declined in the following years, but was still five times higher (RR = 4.84; 95% CI: 1.14–20.53) in 2009 and 2010 together than in 2007.

For children of HBsAg-positive non-Danish mothers, the risk of missing vaccination at the time of birth was 87% lower (RR = 0.13; 95% CI: 0.063–0.25) than for children of Danish HBsAg-positive mothers (Table 3).

Neither age of the mother when giving birth nor total time in Denmark before giving birth were significantly correlated with the risk of not being vaccinated. Likewise, the number of pregnancy examinations had no statistically significant influence on the risk of not being vaccinated at birth. Finally, it made no difference in which region of Denmark the birth had taken place, nor was there any difference in the risk of missed vaccination at birth between urban and rural hospitals.

Ten sites of delivery had vaccinated all children, while the remaining 19 sites each counted between one and seven cases of lacking vaccination at birth.

The multivariate models fit well. For the all-factors and final-model analysis in Table 3, the R2 coefficients were, respectively, 0.1349 and 0.1065.

Risk factors associated with less than four hepatitis B vaccinations by the age of 15 months

Newborns who had not received HBV vaccine at birth had a significantly higher risk of incomplete vaccination at 15 months (Table 4). The number of prenatal examinations was also significantly correlated with the completeness of vaccination, more prenatal examinations being associated with a lower risk of incomplete vaccination. Finally, the mothers' age was significantly correlated with the risk of incomplete vaccination at 15 months: the youngest (17–24 years) and the oldest (35–44 years) age groups of mothers had the highest risk of incomplete vaccination of their children.

Neither the mothers' country of origin nor their total time in Denmark were significantly correlated with the risk of incomplete vaccination. In contrast to vaccination at birth, the year of delivery had no effect on the risk of incomplete vaccination at the GP's (Table 4).

In the multivariate analysis, there was no effect of the enhanced surveillance in 2007 (Table 4). We even observed a slight, but not significant, increasing trend (p = 0.08) over the years in the risk of incomplete vaccination at 15 months of age. Whether or not the mother had had a post-pregnancy examination did not significantly influence the risk of incomplete vaccination at 15 months, although there was a tendency towards a higher risk for those not having received this examination, the RR being 0.87 (95% CI: 0.74–1.02) (p = 0.08).

The multivariate models fit well. For the all-factors and final-model analysis in Table 4, the R2 coefficients were respectively 0.0347 and 0.0237.

Discussion

This retrospective cohort study comprised a total of 699 children born to HBsAg-positive mothers. The participation in the study was 95.2% (four birth records had disappeared or birth site was unknown for 31 children) (Figure 1).

The overall vaccination coverage 48 hours after birth was 93% (651/699) (Table 2). Missing vaccination is considered an adverse event and is subject to internal auditing at the hospital. It is discouraging to find that such a high proportion of the children were not vaccinated according to schedule. Furthermore, 10% (47/475) of the children had not received a single vaccine at the age of two, a dire sign of missed opportunities (Figure 2).

Considerable under-reporting of hepatitis B vaccinations by the GPs to the service code register was revealed. Had we not contacted the GPs, the results would have been misleading.

Compared with other European countries, the percentage of vaccination at birth was lower in Denmark. In a study in London in 2006, 97% of the children received their birth vaccination and 49% of the children had received four vaccines by the age of 15 months [18]. In a Swiss study from 2010, 99% of newborns received their vaccination within 24 hours [19]. In the same study, the vaccination series was completed in 83% of the children in that they had received at least two doses besides the birth dose. In a study in Amsterdam in 2001, 96% of all newborns received HBIG within 24 hours and 91% of the children received their third vaccination dose on time (within seven months after the second vaccination) [20]. We expected the Danish birth vaccination percentage to be higher because the standard procedures for this group of women were supposed to be incorporated as routine after the two-year trial period with enhanced surveillance during which the midwives were obliged to fill in questionnaires regarding all children born to HBsAg-positive mothers. In the Netherlands, the Municipal Health Service played a major role in the organisation and follow-up of the children's vaccination status, in contrast to the Danish system.

Variation in birth vaccination coverage was observed between the time periods analysed. In the period with enhanced surveillance (1 November 2005 to 31 October 2007) [8], vaccination coverage at the sites of birth was considerably higher than after termination of the monitoring efforts. In 2007, when the routines had become standard procedure at the sites of birth, only 1% did not receive vaccination at birth (Table 2). Since 2009, the vaccination procedures and coverage have remained at the level they had without enhanced surveillance (94% vaccinated). No effect of the monitoring year was observed for vaccinations at the GPs. We did not find any other studies describing the difference between periods with and without enhanced surveillance.

The salient point is to set a limit for 'vaccinated in time'. To calculate the vaccination coverage at exactly the date scheduled would give an underestimation of the coverage. Still, the date should reflect whether or not the child has been vaccinated according to the national programme and protected against HBV infection. The time limit for each of the vaccinations (doses two to four) in this study was set based upon the Summary of Product Characteristics (SPC) for Engerix-B [21], minimum/maximum intervals [22] and practicalities around the examination schedules for mother and child. According to the Danish national guidelines, the second dose of vaccine can be postponed until the child is five weeks old [15]. This is also the time for the first (of six) routine scheduled childhood examinations at the GP's. The London study from 2006 looking at risk factors used the limit of 15 months for the fourth dose of vaccine [18]. The same limit was used in our study, an extension of 25% compared with the national schedule that foresees this vaccination at 12 months. We also increased the two other vaccination times with 25% for our study, to respectively five and 10 weeks.

Other studies have focused on setting the limit for 'vaccinated in time' [2,19,23-25]. A study from Thailand found a 3.74 times (95% CI: 0.97–14.39) increased risk of the child being chronically infected with HBV if the interval between the first and second vaccine dose was more than 10 weeks [24]. It has been described that vaccination and HBIG at birth, at one and at six months, compared with at birth, at two and at six months, lead to the same protection from acute and chronic HBV infection in children born to HBsAg- and HBeAg-positive mothers [2]. A study form Switzerland did not find any evidence of age at vaccination (one instead of two months-old) having an influence on prevention of HBV infection [19].

The likelihood of having completed vaccinations at the age of 15 months (but not vaccinations at birth) was positively associated with the mother's number of prenatal examinations, as it was in a study in London from 2006 [18]. Although not significant (Table 3), there seemed to be a slightly lesser risk of not being vaccinated at all, if the mother had no prenatal examinations compared with having one, two or three examinations (Table 3 and 4). This is probably because women with no prenatal examinations are often seen in the maternity ward at birth without being registered before. Thus they have their blood sample taken just before giving birth and/or the newborns are vaccinated without knowledge of the mothers' hepatitis B status.

Ethnicity and total time in the country before giving birth were without significance both in our study and the London study [18]. We were not able to assess the mothers' level of integration into Danish society, nor their command of Danish. In the London study, more than basic command of English was correlated with completed vaccination status. Very few mothers in the study were of Danish origin. The children of these mothers had a significantly higher risk of not being vaccinated than children of mothers from high-prevalence countries. The low prevalence in Denmark could mean that attention was not paid to the small group of HBsAg-positive Danish women. In our study, 6% (35/594) of the mothers were themselves adopted. The

hepatitis B status of the adoptees was often unknown by the GP [7]. In Denmark, it is recommended to test adopted children of non-Danish origin for HBV upon arrival in the country [26]. An American study from 2008 found a 4% prevalence for HBV in internationally adopted children [27], which is also high compared to an estimated prevalence of chronic hepatitis B of 0.2–0.3% in the general population in Denmark [14].

Denmark is among the six European countries that have not yet adopted the World Health Organization (WHO) recommendation for inclusion of hepatitis B vaccine in all national vaccination programmes [10-12,28]. These six countries (Denmark, Finland, Iceland, Norway, Sweden and the UK) have adopted risk group-targeted hepatitis B vaccination only [29]. In Denmark, even with hepatitis B vaccination included in the CVP, it will still be necessary to maintain the general screening of pregnant women for HBV, with subsequent vaccination of their newborns against HBV. Including hepatitis B vaccination in the CVP would not save the children of hepatitis B-infected mothers from being infected at birth because the first childhood vaccination is not given before the age of three months.

Our study has some limitations. It has not been possible to investigate other potentially relevant risk factors for incomplete vaccination that could help target preventive measures, such as socioeconomic status, written information about hepatitis B given to the mother and whether the hospital record contains information from the GP.

Since no new national initiatives were implemented during the study period, we have no reason to believe that the coverage has improved or the risk factors have changed after the study period. Since January 2014, parts of the enhanced surveillance of the screening have been revived and since 15 May 2014, a national reminder system has been implemented [30]. The reminder concerning the hepatitis B vaccination of children born to mothers infected with HBV will be sent to the GP as soon as possible after birth. Following the results from this study, it is now recommended that GPs test the infants for protective antibody levels after completed vaccination schedule.

Conclusion

In Denmark, timely and complete HBV vaccination of children born to HBsAg-positive mothers need to be optimised. Sites of birth and GPs are encouraged to revise their vaccination procedures and routines for the group of all pregnant women, mothers with chronic HBV infection and their children. Future studies will show if the resumed national monitoring beginning in 2014 will lead to increased vaccination coverage.

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Conflict of interest

None declared.

Authors' contributions

Asja Kunoee: data collection, data management and analysis, writing the manuscript.

Jens Nielsen: data management and advanced data analysis, commenting the manuscript.

Susan Cowan: data analysis, manuscript co-writer, Danish hepatitis B pregnancy screening background knowledge.

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