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Primary school-age children vaccinated after perinatal exposure maintain antibodies against Hepatitis B Surface Antigen without a pre-school booster

Tom A. Yates [1], Karthikeyan Paranthaman [1], Ly-Mee Yu [2], Elizabeth Davis [1], Sarah Lang [3], Scott J. Hackett [4], Steven B. Welch [4], Andrew J. Pollard [1], Matthew D. Snape [1]

[1] Oxford Vaccine Group, Department of Paediatrics, University of Oxford, [2] Centre for Statistics in Medicine, University of Oxford, [3] Thames Valley Health Protection Unit, Centre for Radiation, Chemical and Environmental Hazards, Chilton, near Didcot, Oxon, and [4] Department of Paediatrics, Birmingham Heartlands Hospital, Birmingham, United Kingdom

Since 2006, the UK has recommended a pre-school Hepatitis B (HBV) booster for children immunised in infancy after perinatal exposure. We studied persistence of antibodies induced by the UK 4-dose infant HBV vaccine schedule and the response to a 'pre-school' dose of HBV vaccine in 28 such children (mean age 6.2 years). Pre-booster titres of antibody against HBV surface antigen were >10mIU/mL in 84.6% (n=26; 95% C.I. 65.1-95.6%). All children (n = 25, 95% C.I. 86.3-100%) had titres >100mIU/mL after the booster. These data suggest primary school children in the UK retain immunity against HBV without a pre-school booster.

Key Words – Hepatitis B Virus, Vertical Transmission, Post Exposure Prophylaxis, Vaccine, Booster, Immune Memory, Seroepidemiology

Children born to women with detectable Hepatitis B Surface antigen (HBsAg) are at considerable risk of becoming chronic Hepatitis B (HBV) carriers [1]. An accelerated course of HBV vaccine initiated at birth is effective at reducing transmission [2, 3] and universally recommended for infants of HBsAg positive mothers [1, 4].

Most data on childhood persistence of anti-HBsAg IgG (anti-HBs) and the incidence of 'breakthrough' HBV infections following an accelerated course of HBV immunisation are from high-prevalence countries [5], where boosting of anti-HBs titres through natural challenge [6] may be more frequent. With lower rates of natural boosting in low prevalence countries, such as the UK, anti-HBs may decline more rapidly. However, children born to HBsAg positive mothers in this setting may remain at ongoing risk of infection from household exposure.

Immunisation against HBV in the UK is targeted to 'at-risk' groups rather than being universal. Children born to carrier mothers are immunised at 0, 1, 2, and 12 months of age. In 2006, partly in response to a paper [7] showing only 50% of adolescents previously immunised at 0, 1, 2 and 6 months of age still had anti-HBs titres ≥10mIU/mL, a 'pre-school' booster dose was added to this schedule [4 – pp178]. Internationally, there is consensus that booster doses are not needed in immunocompetent children vaccinated following perinatal exposure [1, 8]. We believe no other countries recommend HBV boosters in such children.

To investigate the need for this 'pre-school' booster we studied anti-HBs IgG titres in children immunised with the current (0, 1, 2, 12 month) UK infant schedule before and after a booster dose of HBV vaccine in mid-childhood.

POPULATION, MATERIALS AND METHODS

Study Population.

Letters were sent by clinicians with duty of care to parents of children who had commenced a course of HBV vaccination at birth. Children were identified from local records at three Primary Care Trusts in the Thames Valley and at the Departments of Paediatrics at the John Radcliffe Hospital, Oxford, and Heartlands Hospital, Birmingham. The letters informed parents of the recommendation for a pre-school HBV booster, offering them the option of it being administered through this clinical trial.

To be eligible for the study, children had to be aged between 3 years 4 months and ten years (inclusive), to have received a dose of HBV vaccine in the first week of life but not within the preceding two years and to remain potentially exposed to HBV within the household. Children with significant renal or hepatic impairment, life-limiting illness or evidence of HBV infection on a previous blood test were excluded. Children were enrolled between April 2009 and January 2011.

Study Design

Approvals were obtained from Oxfordshire Research Ethics Committee C (OxREC08/H0606/136), the Medicines and Healthcare Regulatory Agency and relevant NHS bodies.

Informed signed consent was obtained from parents of all participants.

Children in the study received a single 0.5mL dose of the paediatric formulation of Engerix B (GlaxoSmithKline, Brentford, UK), a recombinant vaccine (10μg of HBsAg adsorbed onto aluminium hydroxide). This was given as an intramuscular injection into the deltoid area via a 25mm 23 gauge needle.

Blood samples (up to 6ml) were obtained immediately before then 21-35 days following vaccination.

Laboratory Methods

Blood samples were stored at 2–8°C within 2 hours of sampling. Within 24 hours of sampling, they were centrifuged at 3000g for 10 minutes and sera stored at ≤-18°C. Sera were tested by Enzyme-Linked Immunosorbent assay (ELISA) at the microbiology laboratory, John Radcliffe Hospital, Oxford, for anti-HBs IgG, IgG against HBV Core Antigen (anti-HBc) and, as needed, HBsAg concentrations.

Statistical Methods

Two analyses were undertaken, an 'intention to treat' (ITT) analysis including all children and a 'per protocol' (PP) analysis including only children who had received four doses of vaccine with no significant delays to their schedule (i.e. three doses by six months of age and four doses by age 18 months).

95% binomial proportion confidence intervals were calculated using STATA, version 11 (StataCorp, College Station, USA). Calculation of Geometric Mean Concentrations of anti-HBs IgG was not performed as exact concentration of anti-HBs were not determined where >1000mIU/mL.

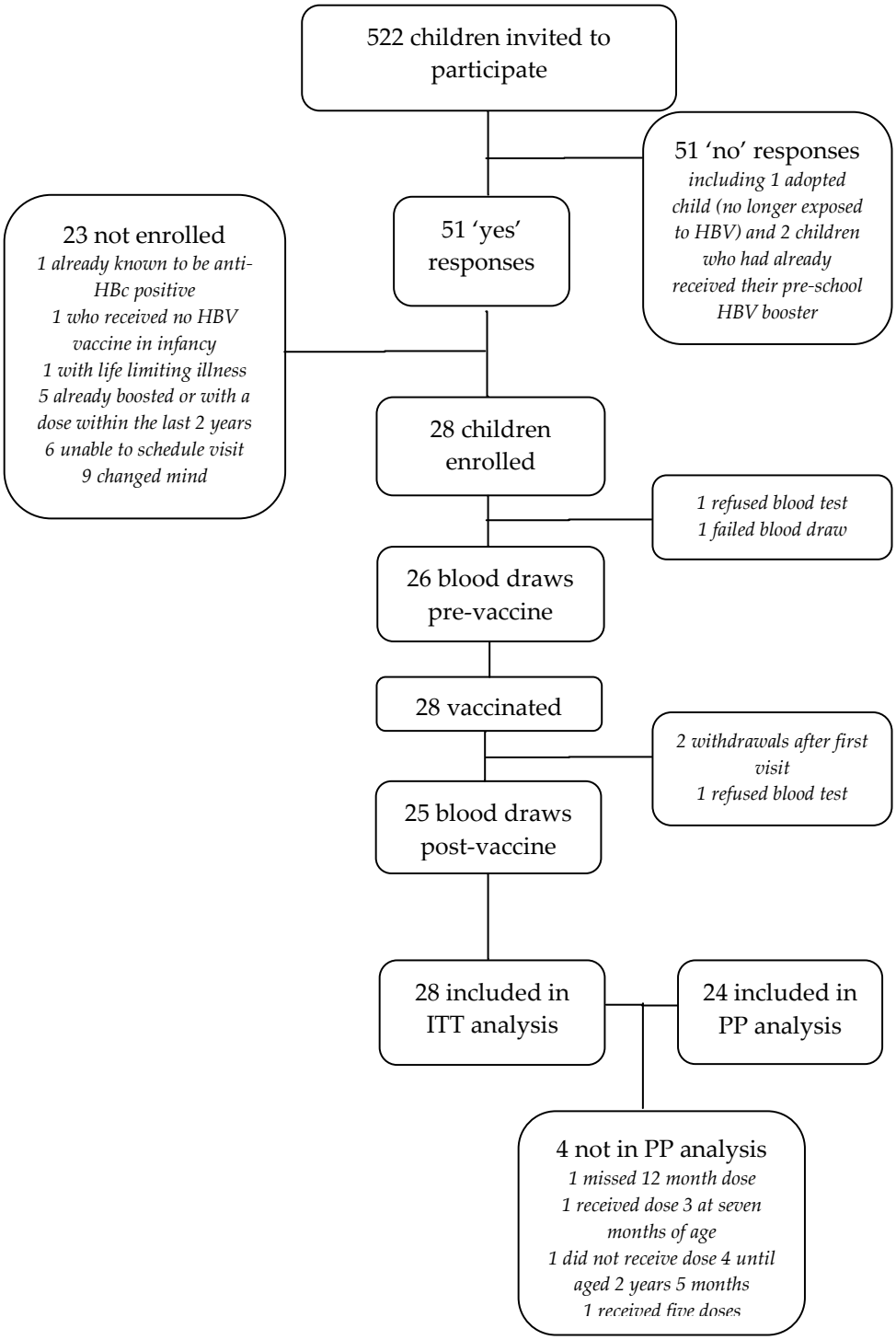

Figure 1. *Summary of the recruitment process.*

RESULTS

Participant Characteristics

Twenty-eight children with mean age 6.2 years (range 3.4 to 10.5 years) were enrolled. Fourteen (50%) were male. There were 15 Asian, 5 Black and 2 Caucasian children plus 6 children of other or mixed ethnicity. The cohort included one set of three siblings and eight sets of two siblings. Twenty-four children (86%) had received a four dose infant schedule with no significant delays so were included in the PP analysis. The ITT analysis included all 28 children (Figure 1).

Protocol Deviations

Four blood samples were documented to have been separated up to 16 hours later than allowed in the protocol. It was considered unlikely this would have significantly affected the assay. The data were therefore included in the analysis.

High Dose Hook Effect

Falls in anti-HBs titres between pre and post-booster samples in two participants raised concern that the assay might be influenced by a 'high dose hook' effect resulting in spuriously low antibody measurements. Repeat assays following dilution, performed by both the John Radcliffe microbiology laboratory and the assay manufacturer (Siemens Healthcare Diagnostics, Deerfield, USA), revealed, in these children, comparable baseline titres and elevated post-booster titres (both >1000mIU/mL).

Siemens repeated 45 of the 51 anti-HBs assays finding no difference in the proportion of assays >10mIU/mL pre-booster or >100mIU/mL post-booster. Here we present the John Radcliffe results with the two spuriously low measurements corrected to >1000mIU/mL.

Baseline anti-HBs Concentrations.

ITT analysis found 22 of the 26 children with samples had anti-HBs antibody concentrations >10mIU/mL prior to their pre-school booster dose of HBV vaccine (84.6%; 95% CI 65.1-95.6%). For the PP analysis the proportion was 86.4% (n=22; 95% CI 65.1-97.1%). No child had undetectable anti-HBs concentrations before the booster, the lowest level being 3.24mIU/mL (Figure 2).

Response to Booster.

In an ITT analysis, all 25 children with post-booster samples had anti-HBs concentrations >100mIU/mL (95% CI 86.3-100%) (Figure 2). The 95% confidence interval for the PP analysis was 83.9-100% (n=21).

Evidence of Infection.

One child was positive for anti-HBc at low levels with negative assays for both HBsAg and antibody against HBV e-Antigen (HBeAg). Enquiries revealed this child had had equivocal anti-HBc antibody levels aged one year, suggesting transient infection occurred within the first year of life. Anti-HBs titres from this child were included in the analysis.

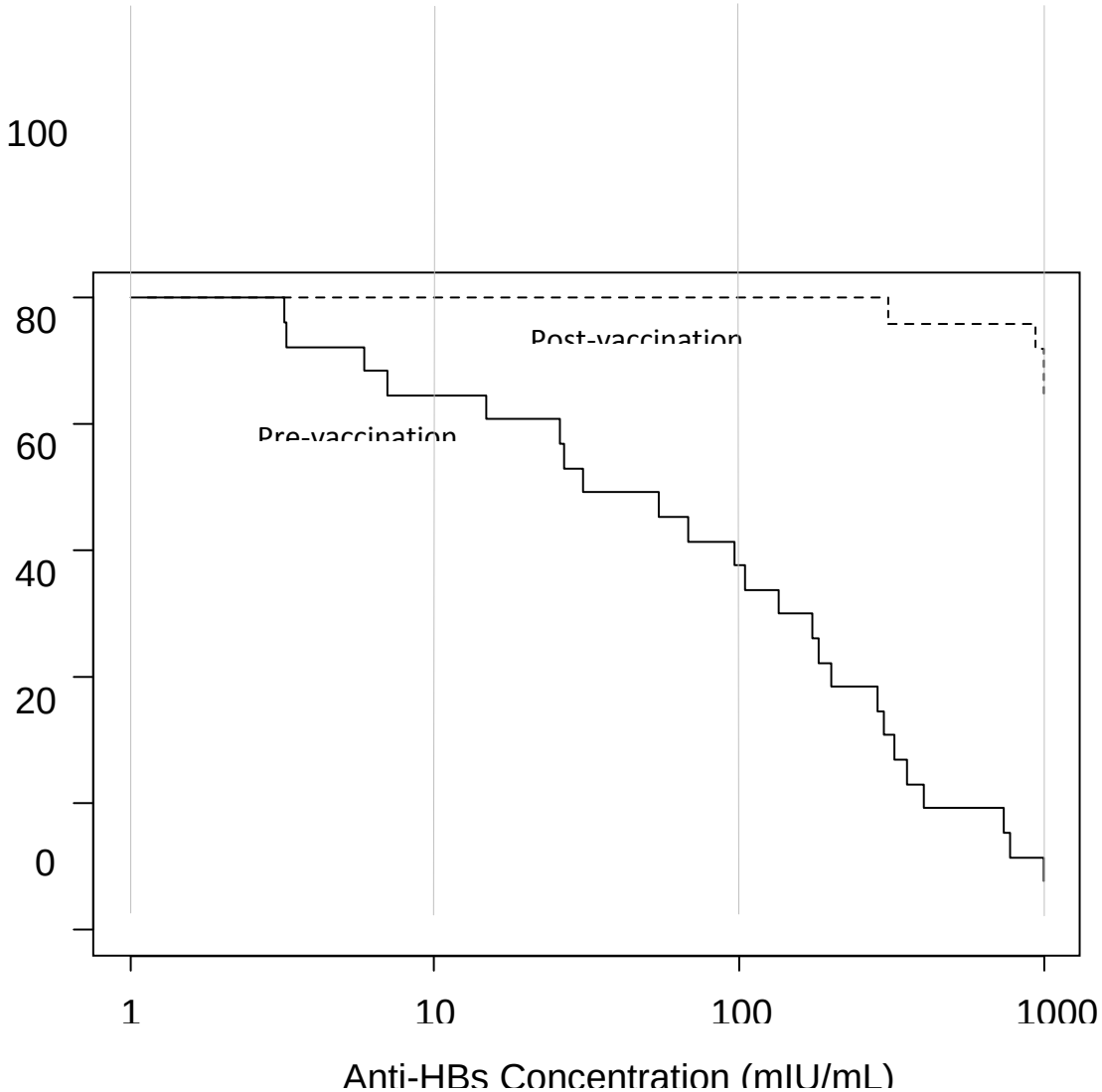

Figure 2. The data included in the intention to treat analysis, presented as a reverse cumulative distribution curve.

DISCUSSION

In this study, children immunised following perinatal exposure according to current UK recommendations were all shown to have immunity that had persisted to primary school-age. Most children retained anti-HBs concentrations >10mIU/mL. After a booster, all mounted strong anti-HBs responses (>100mIU/mL).

Our findings contrast with those of Boxall et al [7], who found anti-HBs IgG concentrations ≥10mIU/mL in only half of adolescents immunised in infancy with an accelerated course of HBV vaccine. The mean age of these participants was 14.5 years, compared to 6.2 years in our study, so it is possible that this difference reflects waning of antibody between these two ages. However, a younger cohort (mean age 11.7 years) were described in the same paper with similarly low pre-booster anti-HBs titres. The vaccine history of this younger cohort is not described, but these children are likely to have received a 3 dose infant schedule with their last dose at 6 months of age; i.e. fewer doses and finishing earlier than children in the current study.

It is also striking that, in the Boxall study, 16% of participants had both baseline titres <10mIU/mL then failed to mount a 'memory' response to a further dose of HBV vaccine (defined as a post-vaccination anti-HBs titre >100mIU/mL); again similar results were seen in the younger cohort and these contrast with our findings that all participants had IgG >100 mIU/mL after the booster dose. In high prevalence areas, loss of 'memory' response has been seen in some other cohorts of adolescents vaccinated, using various schedules, in infancy [5].

As well as being younger, children in the current study received their last dose of vaccine at 12 months of age or older (as per current UK guidelines), rather than 6 months of age (as in the Boxall study). It is possible the higher percentage of participants with anti-HBs levels <10mIU/mL and the apparent loss of immunological memory in the Boxall study is related to the relative immunological immaturity of these children when they received their last dose. The relative crowding of their vaccine doses may also have been important.

A recent Cochrane review found no high quality randomised clinical trials (RCTs) addressing the need for booster doses of HBV vaccine [9]. One study [10] of Senegalese children vaccinated in infancy – some who received a school-age HBV booster (n=41) and some who did not (n=51) – found that, aged 9-12 years, the booster significantly reduced the proportion of children with detectable anti-HBc with no impact on HBsAg positivity. The relevance of these data to a low incidence country is uncertain.

Correlates of Protection against HBV infection

Peak anti-HBs IgG concentration <10mIU/mL after a primary course of HBV vaccine predicts future vaccine failure [6, 11]. To what extent this is due to protection mediated by these antibodies rather than being simply a marker of the strength of vaccine response is not known.

In Gambian children, vaccinated in infancy then followed to age seven years, waning of anti-HBs was associated with increased risk of core antibody reversion, a marker of transient infection [11]. However, multiple studies of children vaccinated in infancy in high prevalence countries, some with more than 20 years follow-up, show children who initially respond to immunisation remain protected against HBV carriage even if anti-HBs falls below 10mIU/mL [5]. A growing literature suggests the same may be true in low prevalence countries [7, 12, 13, 14]. This protection is thought to be mediated either by cell-mediated immunity [8] or anamnestic antibody responses [6, 8].

Citing this observational data, the European Consensus Statement on Hepatitis B booster doses states that there is no evidence to support the use of boosters in immunocompetent children or adolescents [8].

Many studies have used a dose of HBV vaccine as a probe to assess immunological memory, defined as a rise in antiHBs concentrations from <10mIU/mL to either >10mIU/mL [6, 8, 9] or >100mIU/mL [7] post immunisation. It is believed that individuals able to mount a non-primary response to vaccine would mount such a response in the context of natural challenge. Given HBV's long latency period, it is argued that this should be sufficient to clear the infection [6, 8]. To our knowledge there have been no attempts to correlate memory defined in this manner with rates of subsequent breakthrough infection.

The contrast between the data in the current study and the Boxall study [7] is striking. Larger studies in low prevalence settings may explain the discrepancy. However, there is good evidence that protection against HBV carriage persists after antibody wanes and no data correlating loss of a 'memory response' following boosting with future susceptibility to chronic infection. Given the paucity of knowledge about correlates of long-term protection, active surveillance for breakthrough infections may be more informative. We support calls [9] for RCTs addressing the need for booster doses of HBV vaccine.

Limitations.

This study is small. The high number of sibling groups limits the genetic and environmental diversity of the participants, an effect not accounted for in our estimates of protection. It is possible our participants did not fully reflect the population of at-risk children, as invitations to participate were not translated into languages other than English. We did not have access to information on the HBeAg status of participants' mothers or whether children received HBV specific immunoglobulin at birth. Receipt of immunoglobulin appears to predict loss of 'memory' response to vaccine challenge in adolescence [7].

Conclusion. The data presented, along with previously published research, call into question the need for a pre-school HBV booster.

Delaying this booster to early adolescence might extend protection into adult life. Abandoning it would free up resources.

Whilst there is doubt about the need for HBV boosters, there is none about the efficacy of the primary course. Improving poor uptake nationally of the infant doses [15] must take priority.

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Conflicts of Interest

AJP and MDS conduct clinical trials on behalf of Oxford University which are funded by manufacturers of hepatitis B vaccines. Oxford University receives unrestricted educational grants from vaccine manufacturers to support educational activities coordinated by AJP. AJP does not receive any personal payments from vaccine manufacturers. MDS has travel and accommodation costs paid to the University of Oxford by manufacturers of Hepatitis B vaccines to facilitate attendance at academic conferences.

1. World Health Organisation. Hepatitis B vaccines. Wkly Epidemiol Rec 2009; 84(40): 405-19.

2. André FE, Zuckerman AJ. Review: Protective Efficacy of Hepatitis B Vaccines in Neonates. Journal of Medical Virology 1994; 44: 144-151.

3. Lee C, Gong Y, Brok J, Boxall EH, Gluud C. Hepatitis B immunisation for newborn infants of hepatitis B surface antigen-positive mothers. Cochrane Database of Systematic Reviews 2006, Issue 2.

4. Salisbury D, Ramsay M, Noakes K, eds. 'Hepatitis B' in Immunisation against Infectious Diseases. London: The Stationary Office, 2006.

5. Leuridan E, Van Damme P. Hepatitis B and the Need for a Booster Dose. Clin Infect Dis 2011; 53(1): 68-75.

6. West DJ, Calandra GB. Vaccine induced immunologic memory for hepatitis B surface antigen: implications for policy on booster vaccination. Vaccine 1996; 14: 1019-1027.

7. Boxall EH, A Sira J, El-Shuhkri N, Kelly DA. Long-term persistence of immunity to hepatitis B after vaccination during infancy in a country where endemicity is low. J Infect Dis 2004; 190: 1264-9.

8. European Consensus Group on Hepatitis B Immunity. Are booster immunisations needed for lifelong hepatitis B immunity? Lancet 2000; 355: 561–65.
9. Poorolajal J, Mahmoodi M, Haghdoost A, Majdzadeh R, Nasseri-Moghaddam S, Ghalichi L, Fotouhi A. Booster dose vaccination for preventing hepatitis B. Cochrane Database Syst Rev. 2010 Nov 10;(11):CD008256.
10. Coursaget P, Leboulleux D, Soumare M, le Cann P, Yvonnet B, Chiron JP, Coll-Seck AM, Diop-Mar I. Twelve-year follow-up study of hepatitis B immunization of Senegalese infants. J Hepatol 1994; 21(2) :250-4.
11. Jack AD, Hall AJ, Maine N, Mendy M, Whittle HC. What Level of Hepatitis B Antibody Is Protective? J Infect Dis 1999; 179: 489-92.
12. Mele A, Tancredi F, Romanò L, Giuseppone A, Colucci M, Sangiuolo A, Lecce R, Adamo B, Tosti ME, Taliani G, Zanetti AR. Effectiveness of hepatitis B vaccination in babies born to hepatitis B surface antigen-positive mothers in Italy. J Infect Dis 2001; 184(7): 905-8.
13. Bracciale L, Fabbiani M, Sansoni A, Luzzi L, Bernini L, Zanelli G. Impact of hepatitis B vaccination in children born to HBsAg-positive mothers: a 20-year retrospective study. Infection 2009; 37(4): 340-3.
14. Roznovsky L, Orsagova I, Kloudova A, Tvrdik J, Kabieszova L, Lochman I, Mrazek J, Hozakova L, Zjevikova A, Pliskova L. Long-term protection against hepatitis B after newborn vaccination: 20-year follow-up. Infection 2010; 38(5): 395-400.
15. Health Protection Agency. Quarterly vaccination coverage statistics for children aged up to five years in the UK (COVER programme): April to June 2010. Quarterly vaccination coverage statistics for children aged up to five years in the UK (COVER programme): January to March 2011. Health Protection Report 20110; 54 (2538).