

Congenital viral infections in England over five decades: a population based observational study

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Summary

Background

Congenital viral infections cause significant long-term morbidity but there are limited population-based data on diagnosis rates. The aim of this study was to assess the long term trends in neonates diagnosed with congenital infections and report on how rates may have changed with improved detection, the introduction of MMR vaccine and implementation of the Newborn Hearing Screening Programme (NHSP).

Methods

Using national and regional hospitalisation data from 1968 to 2016 in England (Hospital In-Patient Enquiry, Hospital Episode Statistics and Oxford Record Linkage Study), we calculated annual rates of hospital discharges coded with, and unique individuals aged less than 1 month diagnosed with, congenital cytomegalovirus (cCMV), herpes simplex virus (HSV), varicella zoster virus (VZV) and rubella, and investigated associations with perinatal factors (sex, year of birth, ethnicity, mode of delivery, gestational age, birthweight, mothers age, index of multiple deprivation and number of previous pregnancies).

Findings

In 2016, in an infant population of 669,100 the numbers of discharge records in England specifying congenital CMV, HSV, VZV and rubella diagnoses were, respectively, 149, 118, 218, and 1, corresponding to discharge rates per 100,000 infant population of 22.3 (95% CI 18.8–26.1), 17.6 (14.6–21.1), 32.6 (28.4–37.2), and 0.15 (0.0–0.8). Compared with the discharge rates in the 1980s and 1990s, these represented a 5-fold increase for CMV; a 7-fold and 3-fold increase for HSV and VZV, respectively; and a 17-fold decrease for rubella. Additionally, for CMV, there was a significant step-increase between 2006 and 2007 when the NHSP was introduced (rate ratio, comparing the trend line post-NHSP with pre-NHSP, 1.55, 95% CI 1.12–2.14, $p=0.0072$). There was an 88-fold (95% CI 42.8–180.8, $p<0.0001$) higher odds of neonates <1kg being diagnosed with cCMV compared with those born ≥ 2.5 kg. cCMV and HSV were strongly associated with young maternal age and VZV with having older siblings.

Interpretation

The increases in discharges coded with cCMV are most likely due to the introduction of sensitive diagnostic techniques and retrospective diagnoses made among infants after implementation of the NHSP. Public health strategies to improve prevention and treatment of congenital viral infections are urgently warranted.

Funding

None.

Research in context

Evidence before this study

We searched Pubmed from inception up to March 1st 2019 for papers reporting on congenital viral infection disease trends. We used the search terms “cytomegalovirus”, “herpes simplex virus”, “varicella zoster virus” or “rubella” in combination with “congenital”, and additionally in combination with “hospital”, “incidence”, “prevalence” or “epidemiology” without language restrictions. We also reviewed references that were not identified in the original search. We reviewed studies reporting disease incidence from microbiological surveillance studies or hospital statistics in the UK and other countries with similar disease burden.

We found only one national prospective surveillance study of cCMV in the UK. The study was conducted in 2001-2 and included only 86 confirmed cases. A seroprevalence study conducted in a single centre in London in 1991 identified 9 neonates with CMV infection. In the UK, the last published prospective study of HSV in neonates was performed between 1986 -1991 and showed an incidence of 0.5/100,000 live births. In 2013, a UK study of laboratory confirmed HSV meningo-encephalitis cases showed an apparent increased incidence of 2.2 per 100,000 live births, which was attributed by the authors to the introduction of PCR leading to higher diagnostic rates. The same UK study showed that the incidence of VZV meningo-encephalitis in infants less than 3 months was 1.68 per 100,000 in 2013. However, we could find no robust studies that restricted VZV disease to cases less than 1 month of age. The most recent UK surveillance study, which interrogated Hospital Episode Statistics (HES) and the National Congenital

Rubella Surveillance Programme, identified 12 cases of CRS and 3 further cases of congenital rubella infection between 2003 and 2016.

Added value of this study

To our knowledge, this is the first study to describe long term trends in diagnoses of congenital viral infections using national population based data. Our study demonstrates a marked rise in diagnosis rates for congenital CMV, HSV and VZV over the last 5 decades in England which most likely reflects improved case ascertainment since the introduction of molecular-based diagnostics. Specifically, our study highlights the impact of the Newborn Hearing Screening Programme (NHSP) after its implementation nationally in 2006 in revealing a burden of CMV-related sensorineural hearing loss which has not been shown previously. Analysis of perinatal factors on a national scale revealed a nearly 90-fold increase in the likelihood of a neonate less than 1kg having cCMV compared with a neonate with birthweight greater than 2.5kg. Between 1989 and 2016, there was an almost four-fold increase in the rate of HSV-related hospital discharges for neonates. The burden of the disease was highest in the infants of the youngest mothers. Between 1989 and 2016, there was a three-fold increase in VZV-related hospital discharges for neonates. There was a strong association between congenital VZV and parity. Our study shows the sustained reduction in the rates of congenital rubella since the introduction of two doses of the MMR vaccine in 1996.

Implications of this study

The increasing emergence of neonatally diagnosed CMV, HSV and VZV in recent decades is likely to be associated with an increased health service burden. Public health measures such as promoting antenatal hygiene measures to prevent acquisition and transplacental transmission of infection should be prioritised. The implementation of routine screening for cCMV should be considered. Preventive measures through vaccination (e.g. developing a CMV vaccine, considering introduction of routine varicella vaccine and ensuring continued high uptake of MMR vaccine) are warranted.

Introduction

The introduction of routine maternal screening for HIV, hepatitis B and syphilis has significantly reduced the overall burden of infection in pregnancy and minimised adverse outcomes in neonates. However, congenital viral infections still cause significant morbidity and mortality. The therapeutic interventions available to manage cytomegalovirus (CMV), herpes simplex virus (HSV), varicella zoster virus (VZV) and rubella in neonates are limited. This is in part due to a lack of robust epidemiological data to inform which neonates are most susceptible to disease and how their management could be improved through optimising antenatal and postnatal care.

Congenital CMV (cCMV) is the most common non-genetic cause of sensorineural hearing loss (SNHL) and causes adverse neurodevelopmental outcomes in 20% of affected infants (1). The National Hearing Screening Programme (NHSP) was implemented in the UK in 2006 to detect early hearing loss (<https://www.gov.uk/topic/population-screening-programmes/newborn-hearing>). However, screening is not routinely undertaken for cCMV and so the great majority of infants with CMV-related SNHL are detected after the first month of life. Antiviral treatment for cCMV has only been shown to be effective if started in the first month of life (2). Neonatal HSV can cause disease localised to skin, eye and mouth (SEM), disseminated infection with multiple organ involvement or central nervous system disease (CNS), the latter with 70% case fatality in untreated patients and up to 30% fatality in treated patients (3). The rate of primary genital herpes in women in England increased by 22% between 2008 and 2017 but the impact of this on the incidence of neonatal HSV is unknown (4). Foetal infection after maternal varicella during the first or early second trimester of pregnancy occasionally results in death or varicella embryopathy. In the UK, immunisation against varicella is not part of the routine schedule and the burden of varicella in neonates is unknown. Congenital rubella syndrome (CRS) is rarely found in highly immunised settings. The clinical manifestations of CRS include ophthalmic disease, cardiac disease and

CNS disease. Routine screening for rubella in pregnancy was stopped in 2016 in the UK because infection in pregnancy had become very rare (5).

The current epidemiology of CMV, HSV, VZV and rubella in neonates remains poorly understood and therapeutic options to manage these infections remain limited. Since the mid 2000's, highly sensitive diagnostic tools such as multiplex polymerase chain reaction (PCR) assays have replaced cell culture methods in hospital laboratories (6–10). Over the last decade, specific quantitative PCR assays to test for CMV, HSV and VZV have made it possible to measure viral load (enabling response during antiviral therapy to be monitored) and are approaching 100% sensitivity and specificity when detecting these viruses in blood, CSF and saliva (11–14). However, the impact of PCR assays on recorded incidence of congenital viral infections in the population is unknown.

Understanding the epidemiology and health service burden of congenital viral infections is important to inform clinical practice (optimising care pathways and updating existing guidelines), public health education (promoting antenatal hygiene behaviours and immunisation), policy measures (utility of neonatal screening) and research (through vaccine development). The primary objective of this study was to analyse trends in congenital viral infections recorded in hospital over the last five decades, and report on how these trends have varied with the aforementioned phenomena and innovations. For example, we sought to determine whether the introduction of the NSHP in 2006 coincided with a noticeable change in rates of hospital-recorded cCMV. A secondary objective was to investigate associations with perinatal factors including mode of delivery, gestational age, birthweight, maternal age, deprivation and parity.

Methods

Datasets

We analysed de-identified patient records from two large datasets, both comprising hospital inpatient and daycase episodes in England: an English national dataset (Hospital Episode Statistics and equivalent

predecessor data from the Hospital Inpatient Enquiry), and an English regional dataset (the Oxford Record Linkage Study [ORLS]). The regional and national datasets are described more fully elsewhere (9). In brief, the ORLS dataset (1968-2016) comprises statistical abstracts of all NHS day case and inpatient episodes occurring in what was formerly the Oxford NHS regional health authority area (infant population 39,100 in 2016). HIPE (1979-1985) was a random 1 in 10 representative sample of all NHS hospital discharge records in England, collated nationally by the national Office of Population Censuses and Surveys. Hospital statistics were not collected nationally between 1986 and 1988. Since 1989, statistical abstracts of every inpatient and day case episode from every NHS hospital in England have been collected by NHS Digital (formerly the national Health and Social Care Information Centre) in the form of HES.

Diagnostic information in these datasets was coded using the International Classification for Diseases (ICD) Revision 8 (1968-78), 9 (1979-94) and 10 (1995 onwards). The ICD codes used to identify congenital viral infections, listed in Table 1, comprised congenital-specific codes as well as non-congenital-specific codes, the latter of which were used in conjunction with age in days at diagnosis (<28 days). Since age in days was not available in the national data before 1989, congenital VZV and congenital HSV could only be identified in the national data from 1989 onwards, and congenital CMV and congenital rubella from 1979 onwards (when ICD9 was introduced; Table 1). In ORLS, age in days was available throughout the study period 1968-2016. In our analyses, diagnoses were taken from any diagnostic position on the hospital discharge record.

Time trends

For each calendar year, rates of each congenital viral infection were calculated per 100,000 infants in the population. The ORLS dataset is fully record-linked, meaning that multiple records per person could be ascertained, such that each patient could be counted only once for each infection, thus providing a continuous run of “person-based” annual rates for each disease from 1968 to 2016. In the national data, the records only became linkable from 1999 onwards, meaning that, prior to 1999, in the national data

there was no way of identifying multiple discharges per person. Therefore, for the national data, annual “discharge rates” for each infection are reported for the period up to 1999, expressed per 100,000 infant population. From 1999 onwards nationally, we report both annual discharge rates (to provide continuity with the earlier era) and annual person-based rates (in which only the earliest known relevant discharge diagnosis per individual was counted). Time trends and annual percentage change (APC) were modelled using Poisson regression, assuming a constant rate of change, with scaling adjustment to correct for over-dispersion (to overcome the assumption of the Poisson distribution that the variance should be equal to the expected count). Interrupted time series analysis was undertaken to identify any step-change in cCMV rates after the implementation of NHSP in 2006, by comparing the period 1999-2006 with the period 2007-2016 (18).

Associations with perinatal factors

For the period 1 April 1998 to 31 March 2012, perinatal variables in the national data set were available (15). These data items relate to the characteristics of the mother and the child, as documented on the mother’s maternity record and the infant’s delivery record in hospital. The mother-infant pairs, of which there were 4,666,265 million in total (Appendix Figure 1 and Appendix Table 1), were linked using methods described elsewhere (16). We compared the perinatal characteristics of infants diagnosed with congenital viral infection with all other infants in the dataset. The perinatal factors investigated were gestational age, birthweight, mode of delivery, mother’s age, mother’s ethnicity, mother’s area-level deprivation status, and parity (17). For the investigation of associations with perinatal factors, logistic regression was used to calculate odds ratios after multivariable adjustment (see footnote to Table 3). To account for multiple testing, Bonferroni corrections were applied.

All analyses were undertaken using Stata/MP 14.0 (StataCorp, College Station, Texas).

Ethical approval

Ethical approval to study the datasets was obtained from the Central and South Bristol Multi-Centre Research Ethics Committee (04/Q2006/176). The ORLS data have been curated by the Unit of Health-Care Epidemiology, University of Oxford, over many decades. The national hospitalisation data were provided by NHS Digital or its predecessors, and the annual population statistics for England and ORLS were obtained from the Office for National Statistics. The patient records used in this study did not contain personally identifiable information.

Role of funding bodies

This study had no specific funding. The Big Data Institute has received funding from the Li Ka Shing Foundation and Robertson Foundations, the Medical Research Council, British Heart Foundation, and is supported by the NIHR Oxford Biomedical Research Centre. RG is part-funded by Public Health England. The corresponding author had full access to all data available in this study and had final responsibility to submit for publication.

Results

The all-England national dataset and the regional ORLS dataset both demonstrated a substantial rise in discharge rates for congenital CMV, VZV and HSV and a significant decline in the rate for congenital rubella in recent years compared with the previous decades (**Figures 1, 2 and Table 2**).

Congenital CMV

In the all-England dataset, in 2016, there were 149 cCMV discharges for 92 infants in a corresponding national population of 669,100 infants, giving a discharge rate of 22.3 per 100,000 infant population (95% CI, 18.8–26.1) and a person-based rate of 13.7 (95% CI, 11.1–16.9). This represented a substantial increase compared with the earlier years of the study (**Figure 1a**): for example, between 1979 and 1985 (unlinked HIPE period), the average annual rate of cCMV discharges in all-England was 4.6 (95% CI, 2.7 – 7.1) per 100,000 infant population (**Table 2**). Regression analysis demonstrated that, while modelled rates

of cCMV-related discharges increased significantly year-on-year from 1989 to 2016 (APC 5.9% (95% CI 4.6–7.2, $p < 0.0001$), the fit of the model improved significantly (likelihood ratio $\chi^2(1) = 31.6$, $p < 0.0001$) with the addition of a step-change parameter between 2006 and 2007 (when the NHSP was implemented nationally), which corresponded to a step-increase in cCMV-related discharges of 55% (rate ratio, comparing the trend line post-NHSP with pre-NHSP, 1.55, 95% CI 1.12 – 2.14, $p = 0.0072$) (**Figure 3**). Similarly, analysis of the 18-year period of linked national data from 1999 to 2016 demonstrated that, while modelled person-based rates of cCMV increased significantly year-on-year from 1999 to 2016 (APC 6.1% (95% CI 3.7–8.6, $p < 0.0001$), the fit of the model improved significantly (likelihood ratio $\chi^2(1) = 14.4$, $p < 0.0001$) with the addition of a step-change parameter between 2006 and 2007, which corresponded to a step-increase of 58% (rate ratio 1.58, 95% CI 1.05 – 2.37, $p = 0.0274$). In ORLS, the APC across the 49-year period of person-based rates from 1968 to 2016 was 4.8% (95% CI 2.8 – 6.9, $p < 0.0001$).

Analysis of the perinatal variables in linked HES (1 Apr 1998 to 31 March 2012) showed an 88-fold (95% CI 42.8–180.8, $p < 0.0001$) higher odds of a neonate less than 1kg being diagnosed with cCMV compared with a neonate with birthweight greater than 2.5kg. There was also evidence for associations with caesarean section and short gestational age (<32 weeks gestation). Infants born to mothers aged less than 20 years old had 3.3 times greater odds of being diagnosed with cCMV (95% CI 2.3–4.6, $p < 0.0001$) than infants born to mothers aged 30–34 years. Mothers in the most socioeconomically deprived quintile were 1.8 times more likely to have an infant diagnosed with cCMV than mothers in the least deprived quintile (OR 1.8, 1.2–2.6, $p = 0.0033$). Congenital CMV was more strongly associated with Black ethnicity than other coded ethnic groups. (**Table 3**)

Congenital HSV

In the all-England dataset, in 2016, there were 118 congenital HSV discharges for 99 infants in a corresponding national population of 669,100 infants, giving a discharge rate of 17.6 per 100,000 infant population (95% CI, 14.6–21.1) and a person-based rate of 14.8 (95% CI, 12.0–18.0). This represented a

significant increase compared with the earlier years of the study (**Figure 1b**) as the annual person-based rate in all-England increased from 3.9 in 1999 (95% CI, 2.5-5.8): APC 8.5 (95% CI, 7.1–9.9, $p<0.0001$). In the longer-running linked ORLS dataset, there were only ten individuals diagnosed with congenital HSV in hospital from 1968 to 1998, corresponding to an average annual person-based rate of 0.9 per 100,000 infant population (95% CI, 0.4–1.6).

Vaginal delivery and delivery by emergency caesarean section were both associated with increased odds of HSV diagnosis compared with elective caesarean section delivery (although only the former met the more stringent test of statistical significance after Bonferroni correction). Other factors associated with congenital HSV diagnosis were short gestational age (<32 weeks gestation) and young maternal age (<20 years old). (**Table 3**)

Congenital VZV

In the all-England dataset, in 2016, there were 218 congenital VZV discharges for 208 individuals aged under 1 year in a corresponding national population of 669,100 infants, giving a discharge rate of 32.6 per 100,000 infant population (95% CI, 28.4–37.2) and a person-based rate of 31.1 (95% CI, 27.0–35.6). This again represented a substantial increase compared with the earlier years of the study (**Figure 1c**); the APC in all-England across the 18-year period of person-based rates from 1999 to 2016 was 7.6 (95% CI, 6.3–8.9, $p<0.0001$). The longer-running linked ORLS dataset showed that annual person-based rates remained low from 1968 until the end of 1980s (average annual rate 2.2 per 100,000 (95% CI, 1.1-3.9)), and increased from 1990 onwards with an APC of 5.2 (95% CI 2.8–7.6, $p<0.0001$) to 2016, at which point the observed person-based rate was 25.6 (95% CI, 12.3-47.0).

There was strong evidence of an association between VZV diagnosed in the infant and increased number of previous pregnancies in the mother. VZV was associated with Black and South Asian ethnicities. (**Table 3**)

Congenital rubella

In the linked national dataset (1999-2016), a diagnosis of congenital rubella featured on only 48 discharge records for 24 individuals aged under 1 year, an average annual person-based rate of 0.2 per 100,000 infant population (95% CI, 0.1-0.3). This represented a decrease compared with earlier years (**Table 2**). Between 1979 (single dose rubella vaccine was introduced in 1970) and 1985 (single dose MMR replaced the rubella vaccine in 1988) there were 2.6 discharges with recorded congenital rubella per 100,000 infant population (95% CI 1.3-4.7). Between 1989 and 1996 (second dose of MMR was introduced in 1996) the average annual discharge rate dropped to 1.5 (95% CI 1.2-1.9). In twenty years following the introduction of the two dose MMR vaccine, the average annual discharge rate of congenital rubella was 0.5 (0.0-0.6) per 100,000 infant population.

Discussion

The introduction of acyclovir to treat HSV and VZV and ganciclovir to treat cCMV since the late 1990s, and more recently valganciclovir, have broadly remained the only therapeutic interventions available to manage affected neonates. Understanding the epidemiological trends and current burden of disease is necessary to inform future interventional trials. This population based study, which describes long-term (49 years) trends in hospital discharge diagnoses for congenital CMV, HSV, VZV and rubella in neonates, provides the most complete population-based data available for congenital viral infections in England over the last 5 decades.

In the last two decades of the study, from 1999 to 2016 in England, there has been a 3-fold rise in the rate of neonates diagnosed with CMV, HSV or VZV. This increase is most likely due to the introduction of highly sensitive PCR assays that replaced cell culture as the diagnostic tool of choice. PCR assays started becoming commonly integrated into NHS laboratories from the early 2000s (8). This corresponds with significant APC increases in the rates of neonates diagnosed with congenital CMV, HSV and VZV.

Data from HES also showed that there was a significant step-increase in the rate of infants diagnosed with cCMV between 2006 and 2007. This coincided with the introduction of the NHSP in England. The uptake of the NHSP, which screens neonates within 4 weeks of birth, has been above 90% across all NHS regions in England since its implementation. Neonates who do not pass their hearing screen are seen by an audiologist for confirmatory testing within 3 months of life. A panel of aetiological tests, including evaluation for cCMV, are performed at the point an infant has been diagnosed with SNHL. However, oral valganciclovir has only been shown to be effective in reducing SNHL and improving neurodevelopmental outcomes if started in the first month of life (2). Data from this study suggest that the high rates of cCMV since 2007 are likely to be partly driven by the success of the NHSP in identifying infants with SNHL.

In comparison with other national surveillance studies of cCMV, which note as limitations that preterm infants were not adequately evaluated (19,20), this study provides strong evidence to suggest that a significant burden of disease lies in preterm infants in neonatal intensive care units. The mother-infant pairs dataset showed strikingly strong associations between cCMV and preterm birth and very low birthweight adjusted for gestational age. Studies have shown that CMV infects the placenta and amniotic membranes, leading to vascular remodelling causing hypoxia, subsequent restriction in foetal growth and preterm delivery (21,22). Results from this study support investigating the feasibility of targeted screening for cCMV at the point a neonate fails their initial newborn hearing screen in order for valganciclovir to be started in the first month of life and early implementation of non-pharmacological interventions such as cochlear implants and speech therapies (23). Furthermore, universal screening for all preterm infants on the NICU who are less than 1kg should be considered.

Previous studies have suggested that pregnant mothers may be more likely to contract CMV via saliva from young children aged 1 – 2 years (through sharing food and kissing on the lips) and via urine (from children who are not yet toilet trained) (24,25). In the present study we did not find any evidence of an

association between mother's parity status and cCMV diagnosis. Regional studies conducted in North America (26,27) have shown that neonates born in more deprived households are at higher likelihood to develop cCMV, a finding also supported by this study. Surveys of paediatric healthcare practitioners in France and USA show that less than half of respondents had adequate knowledge of the disease to educate women during pregnancy (28,29). These data should encourage healthcare practitioners to reinforce important antenatal hygiene measures. Public health measures should include socioeconomically deprived households which are at highest risk.

The rate of neonates diagnosed in hospital with HSV increased nearly fourfold between 1999 – 2016. Whilst this increase could be due in part to increased coding of the condition in hospital, it also corresponds with a 22% increase in diagnosis of new episodes of genital HSV in England between 2008 – 2017 (4). In the largest trial to assess the influence of maternal infection on the likelihood of neonatal transmission, Brown and colleagues showed that 57% of infants born to women with first episode primary HSV infection developed neonatal HSV disease compared with 25% of infants born to women with first episode non-primary infection and 2% of women delivered to women with recurrent HSV (30). Neonates with HSV were 2.5 times more likely to be born to women less than the age of 20 years old, which is a similar finding to that published by Public Health England, which showed that the highest rate of anogenital herpes occurred in women between 20 – 24 years old (4). In England, sex and relationship education will be mandatory in all school children aged 11 years and older from September 2020 (31). Data from this study supports the importance of sex education for adolescents.

The rapid rise in the number of neonatal VZV diagnoses since 1999 is most likely due to increasing use of PCR-based testing amongst NHS laboratories for viral infections. Analysis of the mother-infant pairs dataset showed that there was a strong association between VZV diagnosed and maternal parity which has been well documented in studies in Germany, Greece and Switzerland (32–34). In the UK, pregnant women and neonates less than 7 days old had been offered varicella zoster immune globulin (VZIG) to

prevent severe infection. In 2018, Public Health England restricted the use of VZIG due to manufacturing problems which led to severe shortages. Pregnant women exposed to chickenpox after 20 weeks gestation are therefore offered acyclovir and not VZIG. The UK has also opted against universal vaccination for VZV. However, national data from post vaccine surveillance studies in Australia, Canada and USA showed over 78% reduction in the number of neonatal varicella cases after the introduction of the VZV vaccine (35–37). Data from this study highlight the potential for controlling this problem through introducing a VZV vaccination programme into the routine schedule in the UK.

Only 24 individuals with congenital rubella have been recorded in English hospital data since 1999 following the introduction of the two dose MMR schedule in 1996. A study of childhood encephalitis using the same datasets showed a 98% reduction in mumps and 97% decrease in hospital admission due to measles in England after the introduction of the two dose MMR (9). More recently in the U.K, a surveillance study using data from HES and a disease specific registry, identified 12 cases of CRS and 3 cases of congenital rubella infection between 2003 – 16 (38). However, the uptake of the MMR (measles mumps and rubella) vaccine in children in England reaching their 2nd birthday has fallen each year between 2014 – 2018 and was 91.2% in 2017-18. Data from this study support the continued efforts to encourage MMR uptake above the 95% target set by the World Health Organisation and ensure unvaccinated women from abroad and the U.K are given every opportunity to be fully immunised before pregnancy.

A strength of this study is the long span of hospitalisation data available to evaluate long term trends in diagnosis of congenital viral infections, with reference to both national and regional data sources that yield comparable findings. To our knowledge, clinical or laboratory reports of CMV, HSV or VZV in neonates are not routinely collected. These datasets therefore provide a unique opportunity to investigate this poorly understood group of infections.

There are limitations to this study. The integrity of the hospital statistics relies on the accuracy of recording clinical information from case notes and appropriate coding. The use of successive ICD revisions, with different disease nomenclature, could also affect the estimates. In the absence of routine screening, the vast majority of cCMV cases will be missed clinically in the neonatal period and not reported. Preterm infants and those with very low birthweight may be over-represented among those diagnosed with cCMV as they may be more likely to be diagnosed in hospital compared with term babies with milder disease who may only be seen in the outpatient setting. The limitations of the perinatal variables in the national data set have been discussed elsewhere (16). In brief, some hospitals were less thorough than others in supplying the full range of data items from the delivery episode. This meant that the number of mother–infant pairs used in the perinatal analysis was substantially reduced as there were relatively high numbers of missing values for variables such as birth status, parity, birthweight, gestational age and ethnic category (Appendix Figure 1; Appendix Table 1). This is unlikely to have caused bias in relation to the congenital diagnoses providing that the shortfall was random but it does reduce statistical power.

In conclusion, the rate of congenital viral infections diagnosed in hospital has increased three-fold since the introduction of highly sensitive molecular techniques to identify infection. However, the therapeutic interventions available to manage these cCMV, HSV and VZV remain limited. The increasing emergence of neonatally diagnosed CMV, HSV and VZV in recent decades is likely to be associated with an increased health service burden. Public health measures such as promoting antenatal behavioural and hygiene measures to prevent acquisition and transplacental transmission of infection should be prioritised. The implementation of routine screening for cCMV should be considered. Preventive measures through vaccination (e.g. developing a CMV vaccine, considering introduction of routine varicella vaccine and ensuring continued high uptake of MMR vaccine) are warranted.

Contributors

All authors had access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. S.K and A.J.P had the idea for the study. All authors designed the study. M.J.G curated the datasets. R.G designed and undertook the analyses. All authors contributed to data interpretation. S.K conducted the literature search and wrote the first draft of the paper. A.J.P, M.J.G and R.G contributed to subsequent drafts and approved the final report.

Declaration of interests

We declare that we have no conflicts of interest.

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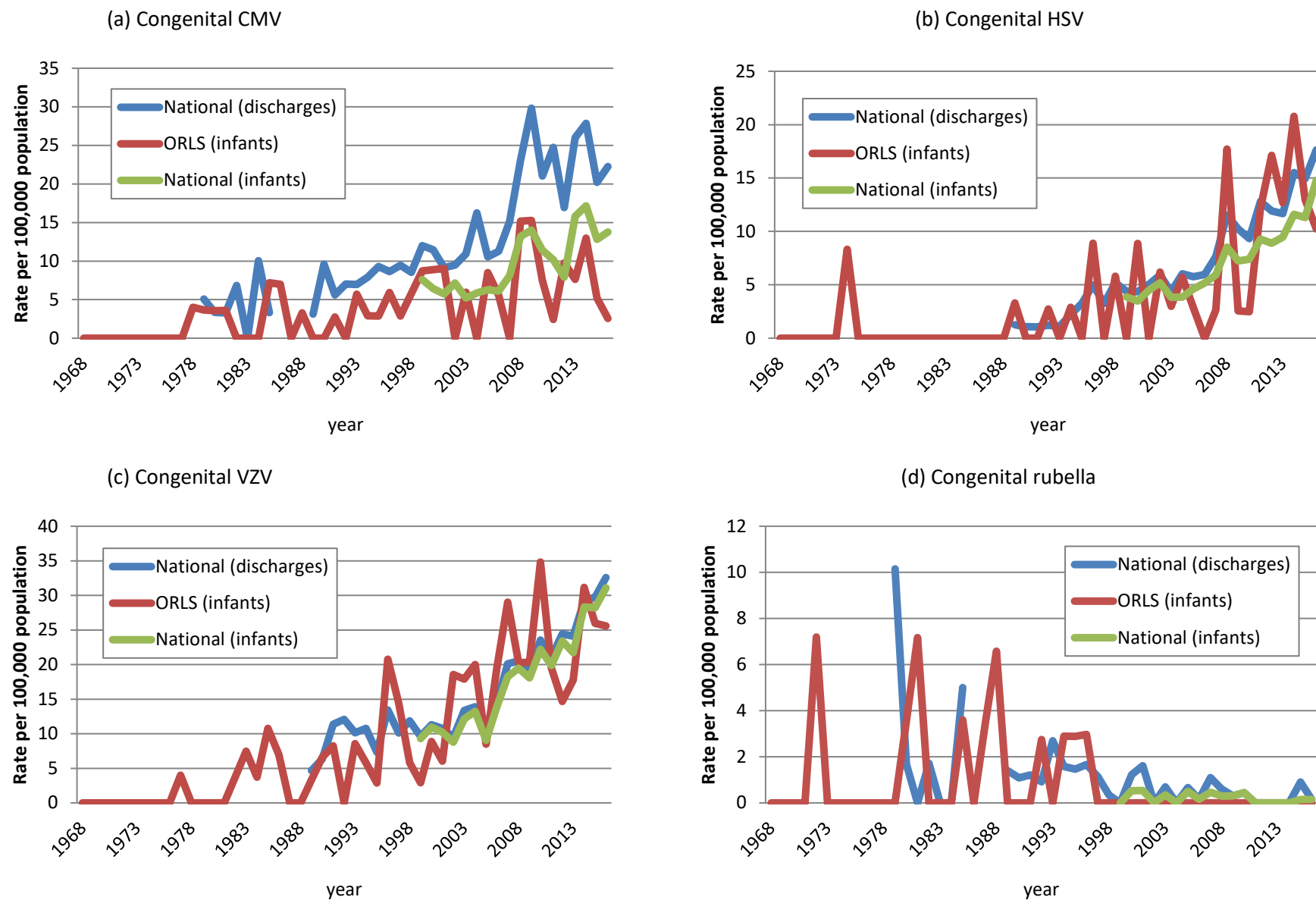
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Figure 1: Annual rates per 100,000 infant population of hospital discharges coded with, and individual infants diagnosed with, CMV, HSV, VZV and rubella in England nationally and in the Oxford Record Linkage Study (ORLS) region, 1968-2016



Note: Congenital CMV and congenital rubella became identifiable in the national data from 1979, and congenital HSV and congenital VZV from 1989.

Figure 2: Three-fold increase in the number of unique infants diagnosed in hospital with congenital infections in England: 1999-2016 using linked HES dataset, with colour-coded distribution of individual infections.

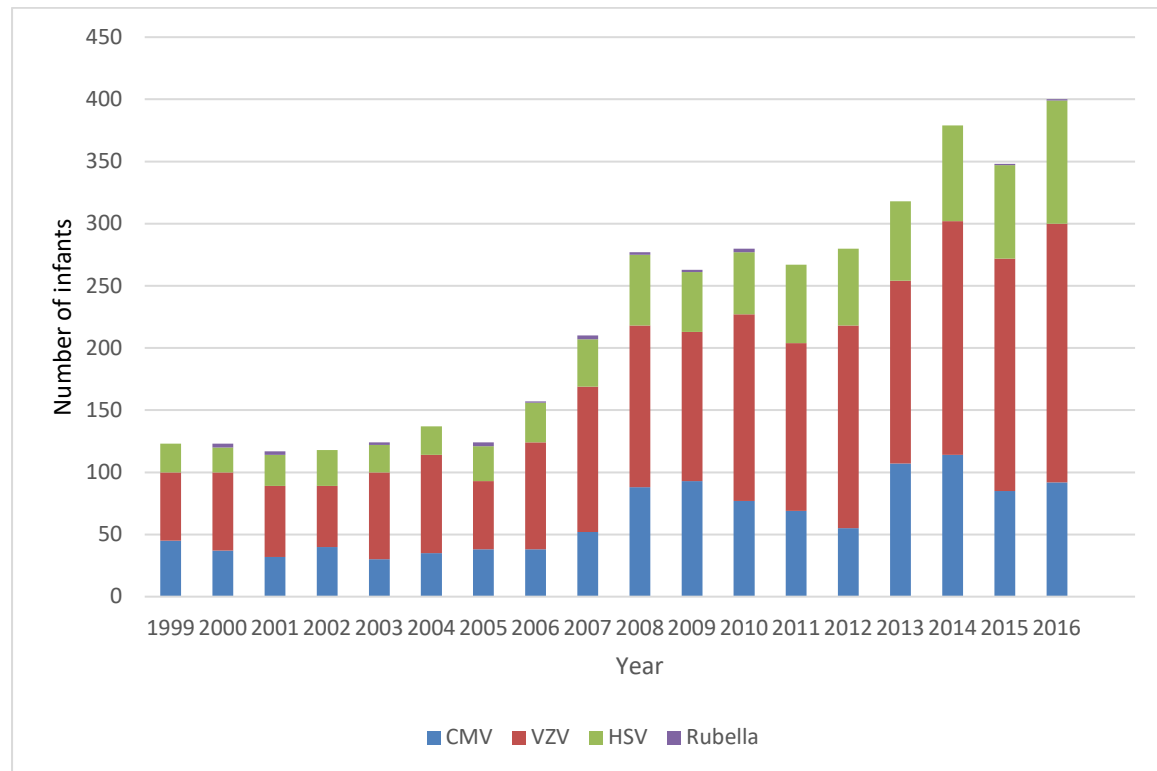


Figure 3: Significant step-change in the rates (per 100,000 infant population) of cCMV diagnosed in hospital since 2007 when the newborn hearing screening programme (NHSP) was implemented in England

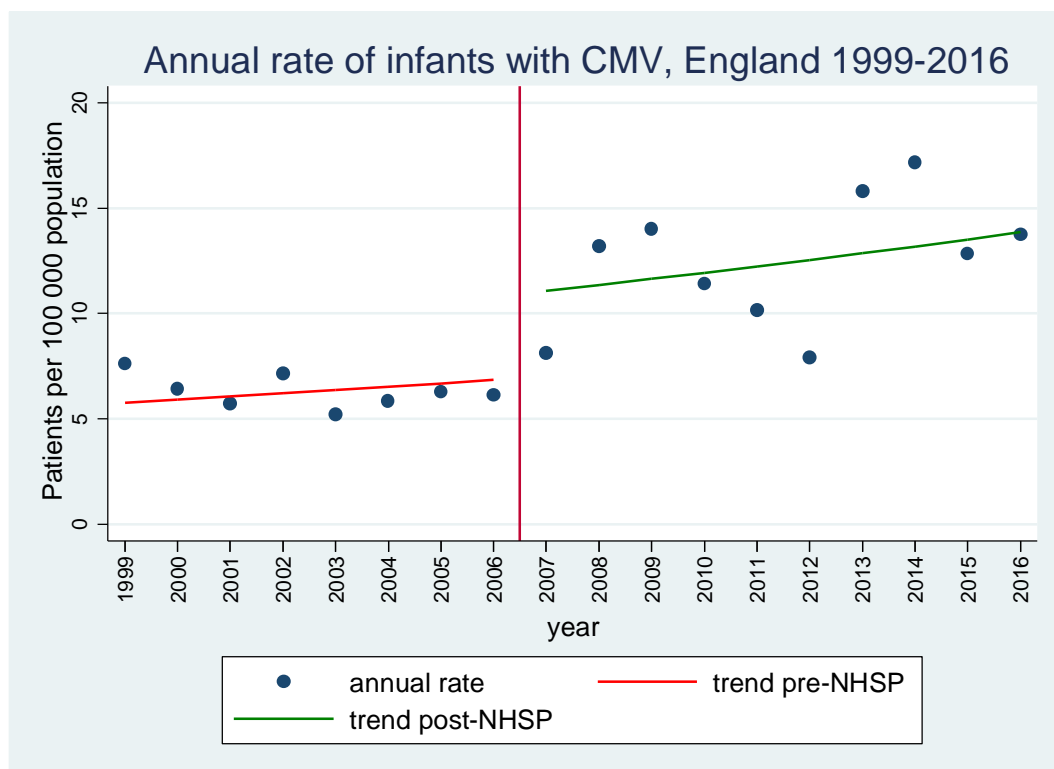
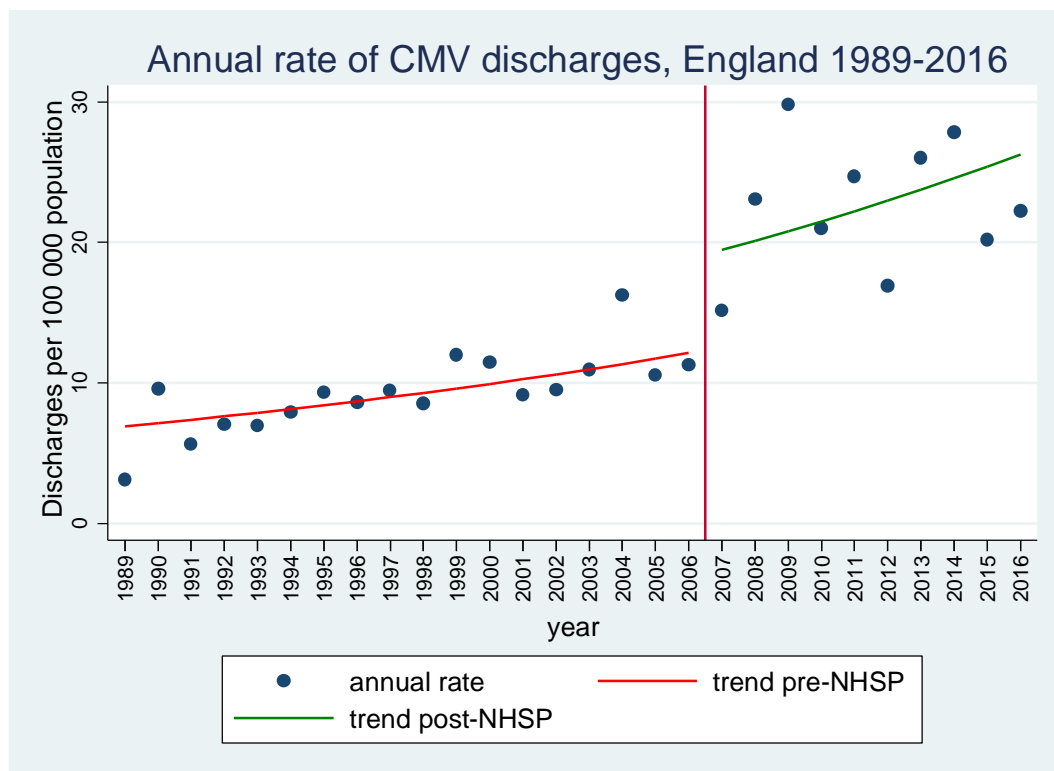


Table 1: International Classification of Diseases (ICD) codes used to identify the congenital viral infections from 1968 to 2016

Years		ICD disease classification and code						
		CMV, diagnosed ≤28 days	CMV, congenital	HSV, diagnosed ≤28 days	HSV, congenital	VZV, diagnosed ≤28 days	Rubella, diagnosed ≤28 days	Rubella, congenital
ICD 8	1968-78	079.5		054		052	056	
ICD 9	1979-94	078.5	771.1	054.0, 054.1-054.9		052	056	771.0
ICD 10	1994-2016	B25.9	P35.1	B00	P35.2	B01	B06	P35.0

Table 2: Numbers of neonatal hospital discharge records containing a diagnosis of each congenital viral infection, expressed per 100,000 infant population, and (where available) numbers of individuals discharged with the diagnoses, in the all-England data from 1979 to 2016 by calendar period

Calendar period	CMV		HSV		VZV		Rubella	
	Discharges	Individuals	Discharges	Individuals	Discharges	Individuals	Discharges	Individuals
1979 – 1985	4.6 (2.7, 7.1)	-	-	-	-	-	2.6 (1.3, 4.7)	-
1989 – 1998	7.6 (6.9, 8.3)	-	2.4 (2.0, 2.8)	-	9.8 (9.0, 10.6)	-	1.4 (1.1, 1.7)	-
1999 – 2006	11.4 (10.5, 12.4)	6.3 (5.6, 7.1)	5.2 (4.6, 5.9)	4.3 (3.7, 5.0)	11.6 (10.7, 12.6)	11.0 (10.0, 12.0)	0.5 (0.0, 0.8)	0.3 (0.0, 0.4)
2007 – 2016	22.7 (21.6, 23.9)	12.4 (11.6, 13.3)	12.3 (11.5, 13.2)	9.5 (8.7, 10.2)	24.4 (23.2, 25.6)	23.1 (21.9, 24.3)	0.3 (0.0, 0.5)	0.2 (0.0, 0.3)

Note: 2007-2016 is the latest available ten-year period covered by national linked HES and represents the period after implementation of the NHSP, while 1999-2006 is the earlier years covered by linkable HES; 1989-1998 is the period covered by unlinkable HES; 1979-1985 is the period covered by the unlinkable HIPE dataset; national hospitalisation data were not collected from 1986 to 1988.

Table 3: Perinatal and maternal factors in the linked maternity HES dataset, England 1998-2012, and associations with congenital CMV, HSV, VZV

	CMV			HSV			VZV		
	Number (n=353)	Odds ratio	P value	Number (n=226)	Odds ratio	P value	Number (n=421)	Odds ratio	P value
Sex									
Females	175	Reference	-	115	Reference	-	219	Reference	-
Males	171	1.02 (0.82-1.26)	0.8508	109	0.97 (0.75-1.27)	0.8416	193	0.91 (0.75-1.11)	0.3426
Year of birth									
1998 – 2002	62	Reference	-	33	Reference	-	48	Reference	-
2003 – 2005	41	1.20 (0.80-1.80)	0.3754	25	1.32 (0.79-2.23)	0.2917	60	2.22 (1.52-3.25)	<0.0001
2006 - 2008	137	2.21 (1.62-3.01)	<0.0001	87	2.44 (1.63-3.65)	<0.0001	167	3.24 (2.35-4.47)	<0.0001
2009 - 2012	113	2.33 (1.69-3.21)	<0.0001	81	2.80 (1.86-4.21)	<0.0001	146	3.58 (2.58-4.96)	<0.0001
Ethnic category									
White	255	Reference	-	172	Reference	-	279	Reference	-
Black	41	2.12 (1.50-3.02)	<0.0001	17	1.49 (0.89-2.48)	0.1303	33	1.78 (1.22-2.59)	0.0025
S. Asian	36	1.20 (0.84-1.73)	0.3157	10	0.47 (0.24-0.93)	0.0312	59	1.80 (1.34-2.42)	0.0001

Chinese/SE Asian	17	0.92 (0.56-1.51)	0.7382	15	0.49 (0.71-2.05)	0.939	25	1.16 (0.77-1.76)	0.4750
Mode of delivery									
Elective C section	36	Reference	-	8	Reference	-	47	Reference	-
Emergency C section	125	1.75 (1.20-2.55)	0.0036	48	3.46 (1.64-7.34)	0.0012	45	0.59 (0.39-0.89)	0.0112
Vaginal	192	0.49 (0.34-0.71)	0.0001	170	2.17 (1.06-4.43)	0.0339	329	0.84 (0.61-1.14)	0.2549
Gestational age (weeks)									
<32	91	34.48 (26.89-44.22)	<0.0001	14	7.02 (4.00-12.31)	<0.0001	1	0.28 (0.04-2.00)	0.2055
>=32	262	Reference	-	212	Reference	-	420	Reference	-
Birthweight (gm)									
500 - 999	68	87.99 (42.83-180.77)	<0.0001	3	3.16 (0.82-12.2)	0.0958	0	n/a	n/a
1000 -1499	41	34.40 (19.13-61.84)	<0.0001	8	2.37 (0.60-9.43)	0.2199	0	n/a	n/a
1500 -2499	86	8.64 (6.26-11.91)	<0.0001	23	2.17 (0.48-9.83)	0.3142	19	0.94 (0.56-1.57)	0.8124
2500 - 5499	158	Reference	-	192	Reference	-	402	Reference	-
Mother's age (years)									
<20	63	3.28 (2.31-4.64)	<0.0001	31	2.47 (1.57-3.87)	<0.0001	16	0.62 (0.36-1.04)	0.0723
20 - 24	82	1.48 (1.07-2.04)	0.0177	56	1.45 (0.99-2.13)	0.0558	62	0.79 (0.58-1.08)	0.1348
25 - 29	76	0.96 (0.69-1.33)	0.8004	42	0.78 (0.52-1.17)	0.2317	151	1.35 (1.06-1.72)	0.0165
30 - 34	75	Reference	-	56	Reference	-	116	Reference	-

35 – 39	46	1.18 (0.81-1.72)	0.3796	30	0.99 (0.64-1.55)	0.9774	60	0.93 (0.68-1.28)	0.6710
40+	10	1.17 (0.60-2.27)	0.6427	7	1.04 (0.47-2.28)	0.9256	15	1.04 (0.61-1.79)	0.8730
Index Multiple Deprivation quintile									
5 (least deprived)	36	Reference	-	36	Reference	-	67	Reference	-
4	35	0.91 (0.57-1.46)	0.6993	27	0.66 (0.40-1.09)	0.1071	77	1.07 (0.77-1.49)	0.6739
3	51	1.12 (0.73-1.73)	0.6000	35	0.71 (0.44-1.14)	0.1577	65	0.78 (0.55-1.10)	0.1566
2	71	1.21 (0.80-1.82)	0.3619	54	0.89 (0.58-1.37)	0.5890	86	0.86 (0.62-1.19)	0.3683
1 (most deprived)	149	1.77 (1.21-2.58)	0.0033	72	0.85 (0.56-1.28)	0.4325	126	0.96 (0.71-1.30)	0.7913
No. of previous pregnancies									
0	120	Reference	-	70	Reference	-	76	Reference	-
1	62	0.75 (0.54-1.03)	0.0757	41	0.83 (0.56-1.22)	0.3382	108	1.84 (1.37-2.48)	<i>0.0001</i>
2+	62	0.82 (0.58-1.15)	0.2430	45	0.98 (0.65-1.46)	0.9076	123	2.28 (1.69-3.07)	<i><0.0001</i>

Note: All results presented in the Table were adjusted for year-group of birth, maternal age, and deprivation *a priori*. Additionally, birthweight was adjusted for gestational age (in individual weeks) and sex.

Italicised p-values denote statistical significance after Bonferroni correction (i.e. $p < 0.0021$) to account for chance findings when conducting 24 tests in relation to each disease.