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

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Summary

Background Congenital viral infections cause substantial long-term morbidity but population-based data about diagnosis rates are scarce. The aim of this study was to assess the long-term trends in congenital viral infections in England and to report on how the rates of these infections might have changed with improved methods for detection, the introduction of the two-dose measles–mumps–rubella (MMR) vaccine in 1996, and the implementation of the Newborn Hearing Screening Programme (NHSP) in 2006.

Methods For this population-based, observational cohort study, we used national and regional hospitalisation data from 1968 to 2016 in England (Hospital In-Patient Enquiry, Hospital Episode Statistics, and Oxford Record Linkage Study) to calculate annual rates of hospital discharges coded with—and individuals aged younger than 1 month diagnosed with—congenital cytomegalovirus, herpes simplex virus (HSV), varicella zoster virus (VZV), and rubella. We investigated associations of congenital cytomegalovirus, HSV, and VZV with perinatal and maternal factors (sex, mother's ethnicity, mode of delivery, gestational age, birthweight, mother's age, mother's index of multiple deprivation, and number of previous pregnancies).

Findings In 2016, discharge rates per 100 000 infant population were 22·3 (95% CI 18·8–26·1) for congenital cytomegalovirus, 17·6 (14·6–21·1) for HSV, 32·6 (28·4–37·2) for VZV, and 0·15 (0·0–0·8) for rubella. Compared with earlier years of the study, the discharge rate in 2016 was higher for congenital cytomegalovirus, HSV, and VZV, whereas it was lower for rubella. For congenital cytomegalovirus, there was a significant step-increase between 2006 and 2007 following implementation of the NHSP (rate ratio comparing the trend line post-NHSP with that pre-NHSP 1·55 [95% CI 1·12–2·14], p=0·0072). Congenital cytomegalovirus infection was associated with birthweight less than 1 kg, maternal age younger than 25 years, socioeconomically deprived households, casearean section, and mothers of black ethnicity. Congenital HSV infection was associated with maternal age younger than 20 years, gestational age less than 32 weeks, and vaginal and emergency caesarean section deliveries, while VZV infection was associated with increased parity and black and south Asian ethnicities.

Interpretation The increase in hospital discharges coded with congenital cytomegalovirus is most likely due to the introduction of sensitive diagnostic techniques and retrospective diagnoses made in infants after implementation of the NHSP. Public health strategies to improve prevention and treatment of congenital viral infections are urgently warranted. The decrease in discharges for rubella is most likely due to the MMR vaccine.

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Introduction

The introduction of routine maternal screening for HIV, hepatitis B, and syphilis in England has greatly reduced the overall burden of infection in pregnancy and minimised adverse outcomes in neonates.[1–3] However, congenital viral infections still cause substantial morbidity and mortality. Few therapeutic interventions are available to manage cytomegalovirus, herpes simplex virus (HSV), varicella zoster virus (VZV), and rubella in neonates. This scarcity is in part due to an absence 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 cytomegalovirus infection is the most common non-genetic cause of sensorineural hearing loss and causes adverse neurodevelopmental outcomes in 20% of affected infants.[4] The National Hearing Screening Programme (NHSP) was implemented in the UK in 2006 to detect early hearing loss. However, screening is not routinely undertaken for congenital cytomegalovirus and so the majority of infants with sensorineural hearing loss related to cytomegalovirus infection are only diagnosed after the first month of life. Antiviral treatment for the infection has only been shown to be effective if started in the first month of life.[5]

Neonatal HSV can cause disease localised to the skin, eye, and mouth, disseminated infection with multiple organ involvement, or central nervous system (CNS) disease. CNS disease has a case-fatality rate of 70% in untreated patients and up to 30% in treated patients.[6] The incidence of primary genital herpes in women in

For more on the **National Hearing Screening Programme** see https://www.gov.uk/topic/population-screening-programmes/newborn-hearing

Research in context

Evidence before this study

We searched PubMed from inception up until March 1, 2019, for studies reporting on disease trends of congenital viral infections. We used the search terms "cytomegalovirus", "herpes simplex virus", "varicella zoster virus", or "rubella" in combination with "congenital" and "hospital", "incidence", "prevalence", or "epidemiology", without language restrictions. We also reviewed the reference lists of the identified studies.

We reviewed studies reporting disease incidence calculated from microbiological surveillance or hospital statistics in the UK and other countries with a similar disease burden to the UK.

We found only one national prospective surveillance study of congenital cytomegalovirus in the UK. The study was done in 2001–02 and included only 86 confirmed cases. A seroprevalence study done in a single centre in London in 1991 identifed nine neonates with cytomegalovirus infection. In the UK, the most recent published prospective study of herpes simplex virus (HSV) in neonates was done between 1986 and 1991 and showed an incidence of 0·5 per 100 000 livebirths. In 2013, a UK study of laboratory-confirmed HSV meningoencephalitis cases showed an apparent increased incidence of 2·2 per 100 000 livebirths, 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 varicella zoster virus (VZV) meningo-encephalitis in infants younger than 3 months was 1·68 per 100 000 in 2013. However, we could find no robust studies that restricted VZV disease to cases in neonates younger than 1 month. The most recent UK surveillance study, which interrogated Hospital Episode Statistics (HES) and the National Congenital Rubella Surveillance Programme, identified 12 cases of congenital rubella syndrome and three further cases of congenital rubella infection between 2003 and 2016.

Added value of this study

To our knowledge, this study is the first to describe long-term trends in diagnoses of congenital viral infections using national population-based data. Our study demonstrates a notable rise in diagnosis rates for congenital cytomegalovirus, HSV, and VZV during the past five decades in England, which most likely reflects improved case ascertainment following the introduction of molecular-based diagnostics. Specifically, our study highlights the effect of the Newborn Hearing Screening Programme (NHSP), after its implementation nationally in 2006, in revealing a burden of sensorineural hearing loss related to congenital cytomegalovirus, which has not been shown previously. Analysis of perinatal factors on a national scale revealed a nearly 90-times increase in the likelihood of a neonate weighing less than 1 kg having congenital cytomegalovirus infection compared with a neonate weighing 2·5 kg or more at birth. Between 1989 and 2016, there was an almost four-times 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-times increase in VZV-related hospital discharges for neonates. We also noted an association between congenital VZV and parity. Our study shows a sustained reduction in congenital rubella since the introduction of two doses of the measles–mumps–rubella (MMR) vaccine in 1996.

Implications of all the available evidence

The higher rate of neonatally diagnosed cytomegalovirus, HSV, and VZV infections in England in recent decades has probably increased the health service burden associated with these infections. Public health measures, such as promoting antenatal hygiene behaviours to prevent acquisition and transplacental transmission of infection, should be prioritised. The implementation of routine screening for congenital cytomegalovirus should be considered. Preventive measures through vaccination (eg, development of a cytomegalovirus vaccine, considering introduction of a routine varicella vaccine, and ensuring continued high uptake of the MMR vaccine) are warranted.

England increased by 22% between 2008 and 2017, but the effect of this increase on the incidence of neonatal HSV is unknown.[7]

Fetal infection with VZV due to maternal varicella during the first trimester or early in the second trimester of pregnancy occasionally results in death or varicella embryopathy. In the UK, immunisation against varicella is not part of the routine vaccination schedule and the burden of varicella in neonates is unknown.

Congenital rubella syndrome is rarely found in settings with comprehensive immunisation programmes. The clinical manifestations of congenital rubella syndrome 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 following the introduction of two doses of the measles–mumps–rubella (MMR) vaccine in 1996.[8]

The current epidemiology of cytomegalovirus, HSV, VZV, and rubella in neonates remains poorly understood, and few therapeutic options are available to manage these infections. Since the mid-2000s, highly sensitive diagnostic tools, such as multiplex PCR assays, have replaced cell culture methods in hospital laboratories.[9–13] During the past decade, the development of specific quantitative PCR assays to test for cytomegalovirus, HSV, and VZV has made it possible to measure viral load (enabling response during antiviral therapy to be monitored), and these assays are approaching 100% sensitivity and specificity when detecting these viruses in blood, cerebrospinal fluid, and saliva.[14–17] However, the effect of PCR assays on the recorded incidence of congenital viral infections in the population of England is unknown.

Understanding the epidemiology and health service burden of congenital viral infections is important to

	Cytomegalovirus, diagnosed at age ≤28 days	Cytomegalovirus, congenital	HSV, diagnosed at age ≤28 days	HSV, congenital	VZV, diagnosed at age ≤28 days	Rubella, diagnosed at age ≤28 days	Rubella, congenital
ICD 8 (1968–78)	079·5	..	054	..	052	056	..
ICD 9 (1979–94)	078·5	771·1	054·0, 054·2–054·9	..	052	056	771·0
ICD 10 (1994–2016)	B25·9	P35·1	B00	P35·2	B01	B06	P35·0

ICD=International Classification of Diseases. HSV=herpes simplex virus. VZV=varicella zoster virus. Some cells are empty because no congenital-specific ICD codes existed for these viral infections during the relevant periods. There were no specific ICD codes for congenital VZV throughout, so only the general code for varicella was used in conjunction with age.

Table 1: **ICD codes used to identify congenital viral infections from 1968 to 2016**

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 hospitals in England in the past five decades, and to report on how these trends might have changed with improved methods for detection, the introduction of the MMR vaccine, and the implementation of the NSHP. A secondary objective was to investigate associations of congenital viral infections with perinatal and maternal factors.

Methods

Datasets

We analysed de-identified patient records from two large datasets, both comprising hospital inpatient and day-case episodes in England: an English national dataset (Hospital Episode Statistics and equivalent predecessor data from the Hospital In-Patient Enquiry) and an English regional dataset (the Oxford Record Linkage Study [ORLS]). The regional and national datasets are described in detail elsewhere.[12] In brief, the ORLS dataset (1968–2016) comprises summary records of all National Health Service (NHS) day-case and inpatient episodes occurring in what was formerly the Oxford NHS regional health authority area (infant population 39 100 in 2016).[18] The Hospital In-Patient Enquiry (1979–85) was a representative sample of all NHS hospital discharge records in England (one in ten records were randomly selected), 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 Hospital Episode Statistics.

Diagnostic information in these datasets was coded using the International Classification for Diseases (ICD) Revisions 8 (1968–78), 9 (1979–94), and 10 (1995 onwards). The ICD codes used to identify congenital viral infections (table 1) comprised congenital-specific codes and 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 dataset before 1989, congenital VZV and congenital HSV could only be identified in the national dataset from 1989 onwards, and congenital cytomegalovirus and congenital rubella from 1979 onwards (when ICD9 was introduced; table 1). In the ORLS dataset, 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.

Ethical approval to study the datasets was obtained from the Central and South Bristol Multi-Centre Research Ethics Committee (04/Q2006/176). The committee determined that individual patient consent was not required on the basis that the patient records were pseudonymised through encryption of personal identifiers. The ORLS data have been curated by the Unit of Health-Care Epidemiology, University of Oxford, Oxford, UK, 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.

Time trends in congenital viral infections

For each calendar year, the recorded incidence of each congenital viral infection was calculated per 100 000 infants in the population. The ORLS dataset is fully record-linked, meaning that several 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 incidence for each disease from 1968 to 2016. In the national dataset, the records only became linkable from 1999 onwards, meaning that before 1999 there was no way of identifying multiple discharges per person. Therefore, for the national dataset, annual discharge rates for each infection are reported for the period up to 1999, expressed per 100 000 infant population. From 1999 onwards, 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 changes were modelled using Poisson regression, assuming a constant rate of change, with scaling adjustment to correct for overdispersion (to overcome the assumption of the Poisson distribution that

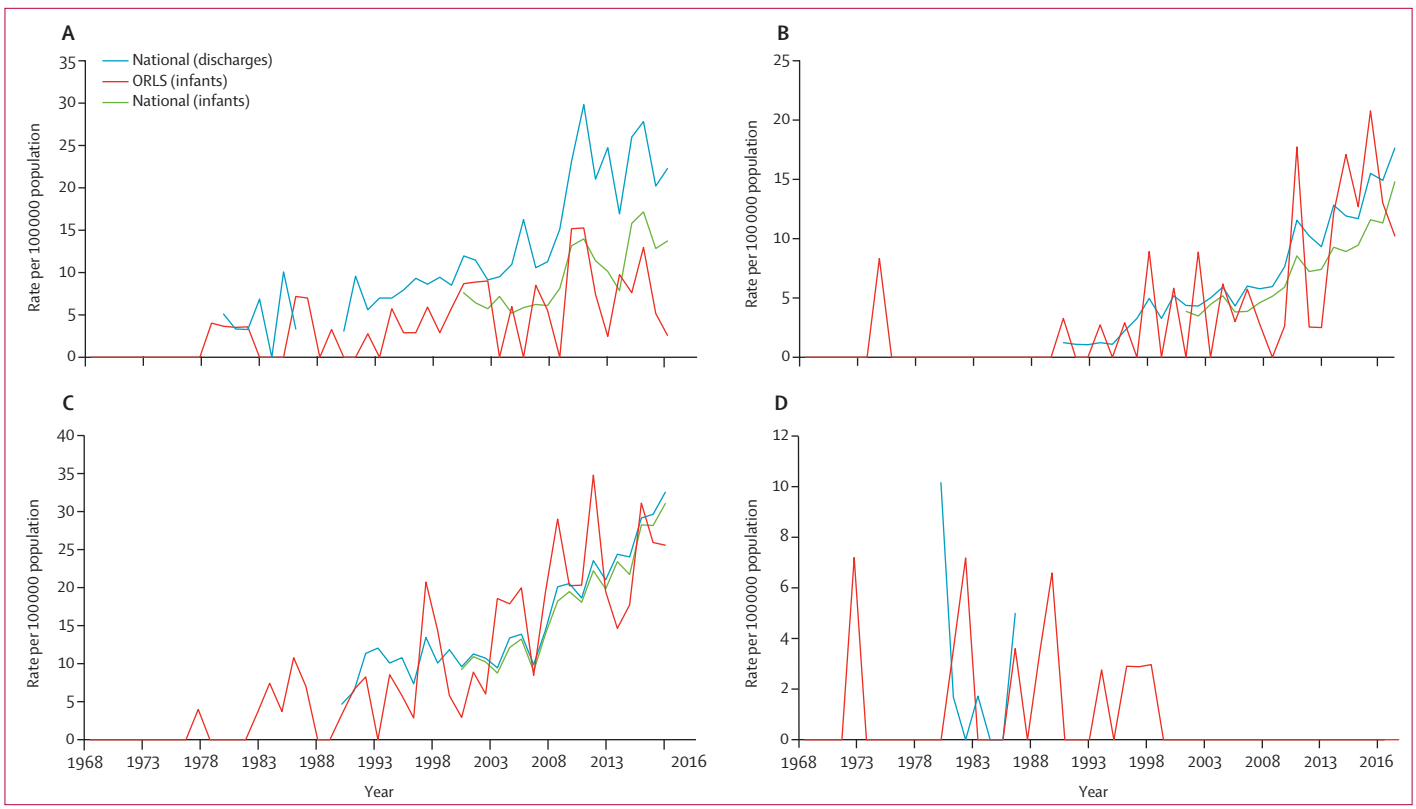

Figure 1: **Annual rate per 100 000 infant population of hospital discharges coded with, and individual infants diagnosed with, congenital viruses in England, nationally and in the ORLS region, 1968–2016**

(A) Cytomegalovirus. (B) Herpes simplex virus. (C) Varicella zoster virus. (D) Rubella. Congenital cytomegalovirus and congenital rubella became identifiable in the national data from 1979, and congenital herpes simplex virus and congenital varicella zoster virus from 1989. ORLS=Oxford Record Linkage Study.

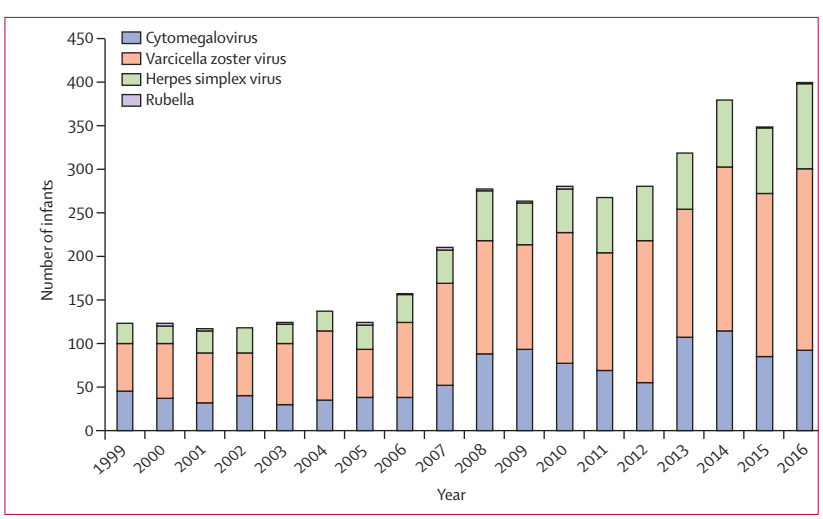

Figure 2: **Number of infants diagnosed in hospital with congenital virus infections in England, 1999–2016**

Data are from the linked Hospital Episode Statistics dataset.

See Online for appendix

the variance should be equal to the expected count). We also did an interrupted time-series analysis to identify any step changes in the rates of congenital cytomegalovirus recorded in hospital after implementation of the NHSP in 2006, by comparing the period 1999–2006 with the period 2007–16.[19]

Associations of congenital viral infections with perinatal and maternal factors

For the period April 1, 1998, to March 31, 2012, perinatal and maternal variables in the national dataset were available.[20] 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 p 1), were linked using methods described elsewhere.[21] In brief, matching mother–infant pairs was achieved using a mixture of deterministic and probabilistic methods. Deterministic matching was used to create provisional pairs based on encrypted date of birth, encrypted postcode, encrypted mother's date of birth, birthweight, hospital provider code, and family doctor practice. Probabilistic matching (which was based on a much larger range of variables) was conducted to break provisional pairs and to identify the best pair in circumstances where deterministic methods caused a conflict. We compared the perinatal and maternal

	Cytomegalovirus		Herpes simplex virus		Varicella zoster virus		Rubella	
	Discharges	Individuals	Discharges	Individuals	Discharges	Individuals	Discharges	Individuals
1979–85	4·6 (2·7–7·1)	..	..	..	..	..	2·6 (1·3–4·7)	..
1989–98	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)
2007–16	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)

Data are rates per 100 000 infant population (95% CI). 2007–16 is the most recently available 10-year period covered by national linked Hospital Episode Statistics (HES) database and represents the period after implementation of the National Hearing Screening Programme. 1999–2006 is the earliest period covered by linkable HES data. 1989–98 is the period covered by unlinkable HES data and 1979–85 is the period covered by the unlinkable Hospital In-Patient Enquiry dataset. National hospitalisation data were not collected between 1986 and 1988.

Table 2: **Average annual rate of discharge diagnoses for, or of individuals with, congenital viral infections, expressed per 100 000 infant population, by calendar period (national dataset)**

characteristics of infants diagnosed with congenital viral infection with those of all other infants in the dataset. The perinatal and maternal factors investigated were gestational age, birthweight, mode of delivery (vaginal, elective caesarean, or emergency caesarean), mother's age, mother's ethnicity, mother's area-level deprivation status (according to index of multiple deprivation), and parity.[22] For the investigation of associations with perinatal and maternal factors, logistic regression was used to calculate odds ratios after multivariable adjustment. The confidence intervals were calculated as the exponentiated lower and upper confidence interval limits of the beta estimates. To account for multiple testing, Bonferroni corrections were applied.

All analyses were done using Stata version 14.0.

Role of the funding source

This study had no funding source. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The national dataset and the regional ORLS dataset both demonstrated a substantial rise in discharge rates for congenital cytomegalovirus, VZV, and HSV, and a significant decline in the rate for congenital rubella in recent years compared with the previous decades (figures 1, 2; table 2).

In the national dataset, in 2016, there were 149 congenital cytomegalovirus discharges for 92 infants in a corresponding national population of 669 100 infants, giving a discharge rate of 22·3 (95% CI 18·8–26·1) per 100 000 infant population and a person-based rate of 13·7 (11·1–16·9) per 100 000 infant population. This result represented a substantial increase compared with the earlier years of the study: for example, between 1979 and 1985 (unlinked Hospital In-Patient Enquiry period), the average annual rate of congenital cytomegalovirus discharges in the national dataset was 4·6 (95% CI 2·7–7·1) per 100 000 infant population (figure 1A; table 2). Logistic regression analysis showed that, although the modelled

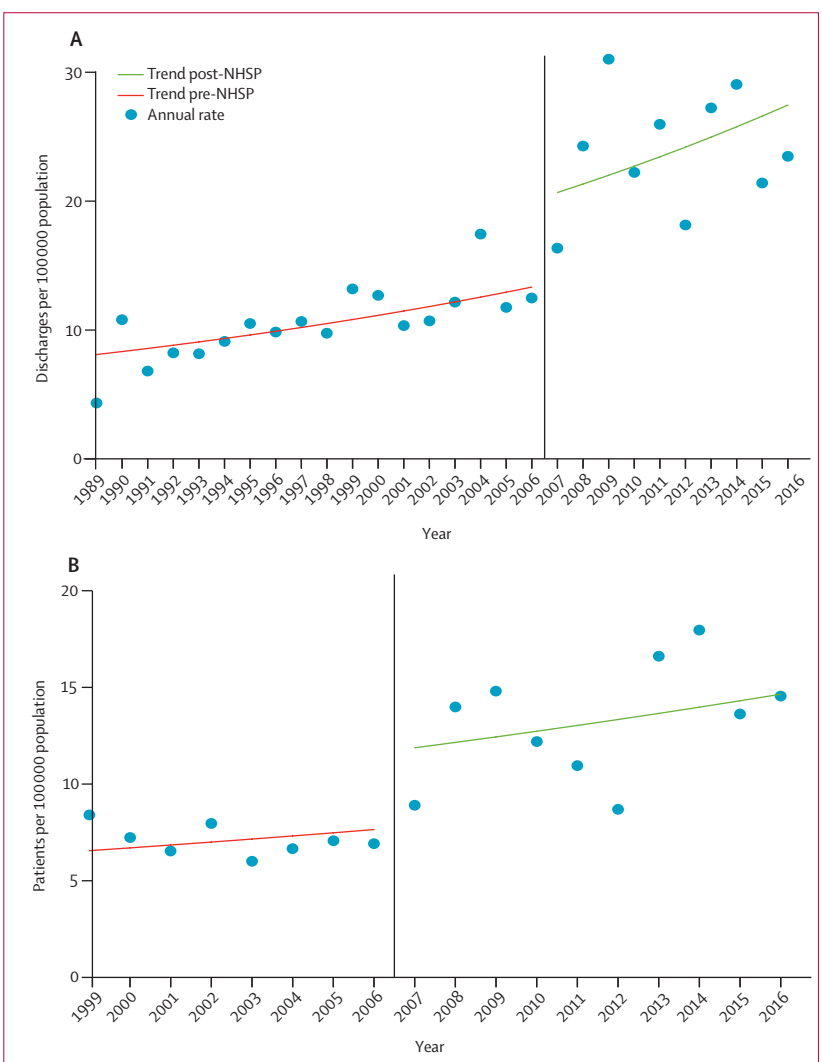

Figure 3: **Change in the rate of congenital cytomegalovirus infection diagnosed in hospital since 2007, after the NHSP was implemented in England**

(A) Annual rate of cytomegalovirus discharges in England, 1989–2016. (B) Annual rate of infants with cytomegalovirus infection in England, 1999–2016. NHSP=Newborn Hearing Screening Programme.

	Cytomegalovirus			Herpes simplex virus			Varicella zoster virus		
	Number (n=353)	Odds ratio (95% CI)	p value	Number (n=226)	Odds ratio (95% CI)	p value	Number (n=421)	Odds ratio (95% CI)	p value
Sex									
Female	175	Ref	..	115	Ref	..	219	Ref	..
Male	171	1·0 (0·8–1·3)	0·85	109	1·0 (0·8–1·3)	0·84	193	0·9 (0·8–1·1)	0·34
Ethnic category									
White	255	Ref	..	172	Ref	..	279	Ref	..
Black	41	2·1 (1·5–3·0)	<0·0001	17	1·5 (0·9–2·5)	0·13	33	1·8 (1·2–2·6)	0·0025
South Asian	36	1·2 (0·8–1·7)	0·32	10	0·5 (0·2–0·9)	0·031	59	1·8 (1·3–2·4)	<0·0001
Chinese or southeast Asian	17	0·9 (0·6–1·5)	0·74	15	0·5 (0·7–2·1)	0·94	25	1·2 (0·8–1·8)	0·48
Mode of delivery									
Elective caesarean section	36	2·0 (1·4–2·9)	0·00013	8	Ref	..	47	1·2 (0·9–1·6)	0·25
Emergency caesarean section	125	3·5 (2·8–4·5)	<0·0001	48	3·5 (1·6–7·3)	0·0012	45	0·7 (0·5–1·0)	0·028
Vaginal	192	Ref	..	170	2·2 (1·1–4·4)	0·034	329	Ref	..
Gestational age, weeks									
<32	91	34·5 (26·9–44·2)	<0·0001	14	7·0 (4·0–12·3)	<0·0001	1	0·3 (0·0–2·0)	0·21
≥32	262	Ref	..	212	Ref	..	420	Ref	..
Birthweight, g									
500–999	68	88·0 (42·8–180·8)	<0·0001	3	3·2 (0·8–12·2)	0·096	0	NA	NA
1000–1499	41	34·4 (19·1–61·8)	<0·0001	8	2·4 (0·6–9·4)	0·22	0	NA	NA
1500–2499	86	8·6 (6·3–11·9)	<0·0001	23	2·2 (0·5–9·8)	0·31	19	0·9 (0·6–1·6)	0·81
2500–5499	158	Ref	..	192	Ref	..	402	Ref	..
Mother's age, years									
<20	63	3·3 (2·3–4·6)	<0·0001	31	2·5 (1·6–3·9)	<0·0001	16	0·6 (0·4–1·0)	0·072
20–24	82	1·5 (1·1–2·0)	0·018	56	1·5 (1·0–2·1)	0·056	62	0·8 (0·6–1·1)	0·13
25–29	76	1·0 (0·7–1·3)	0·80	42	0·8 (0·5–1·2)	0·23	151	1·4 (1·1–1·7)	0·017
30–34	75	Ref	..	56	Ref	..	116	Ref	..
35–39	46	1·2 (0·8–1·7)	0·38	30	1·0 (0·6–1·6)	0·98	60	0·9 (0·7–1·3)	0·67
≥40	10	1·2 (0·6–2·3)	0·64	7	1·0 (0·5–2·3)	0·93	15	1·0 (0·6–1·8)	0·87
Index of Multiple Deprivation quintile									
5 (least deprived)	36	Ref	..	36	Ref	..	67	Ref	..
4	35	0·9 (0·6–1·5)	0·70	27	0·7 (0·4–1·1)	0·11	77	1·1 (0·8–1·5)	0·67
3	51	1·1 (0·7–1·7)	0·60	35	0·7 (0·4–1·1)	0·16	65	0·8 (0·6–1·1)	0·16
2	71	1·2 (0·8–1·8)	0·36	54	0·9 (0·6–1·4)	0·59	86	0·9 (0·6–1·2)	0·37
1 (most deprived)	149	1·8 (1·2–2·6)	0·0033	72	0·9 (0·6–1·3)	0·43	126	1·0 (0·7–1·3)	0·79
Number of previous pregnancies									
0	120	Ref	..	70	Ref	..	76	Ref	..
1	62	0·8 (0·5–1·0)	0·076	41	0·8 (0·6–1·2)	0·34	108	1·8 (1·4–2·5)	<0·0001
≥2	62	0·8 (0·6–1·2)	0·24	45	1·0 (0·7–1·5)	0·91	123	2·3 (1·7–3·1)	<0·0001

HES=Hospital Episode Statistics. The total number of mother–infant pairs analysed was 4 666 265. All odds ratios presented in this table were adjusted for year of birth, maternal age, and deprivation a priori. Additionally, birthweight was adjusted for gestational age (in weeks) and sex. Numbers presented for each category are crude numbers (ie, before multivariable adjustment); the sum of cases in each category varied according to missing data (appendix pp 2–3). p values <0·0021 denote statistical significance after Bonferroni correction to account for chance findings when conducting 24 tests in relation to each disease.

Table 3: **Perinatal and maternal factors in the linked maternity HES dataset, England 1998–2012, and associations with congenital viral infections**

rate of discharges with congenital cytomegalovirus codes increased significantly each year nationally from 1989 to 2016 (annual percentage change 5·9% [95% CI 4·6–7·2], p<0·0001), the fit of the model improved significantly (likelihood ratio χ^2 (1 df) 31·6, p<0·0001) with the addition of a step-change parameter between 2006 and 2007 (when the NHSP was implemented nationally). This change corresponded to a notable step-increase in congenital cytomegalovirus-related discharges (rate ratio comparing the trend line post-NHSP with that pre-NHSP 1·55 [95% CI 1·12–2·14], p=0·0072; figure 3A). Similarly, analysis of the 18-year period of linked national data from 1999 to 2016 showed that, although the modelled person-based rate of congenital cytomegalovirus increased significantly each year from 1999 to 2016 (annual percentage change 6·1% [95% CI 3·7–8·6], p<0·0001), the fit of the model improved significantly (likelihood ratio χ^2 (1 df) 14·4, p<0·0001) with the addition of a step-change

parameter between 2006 and 2007, which corresponded to a substantial step increase (rate ratio comparing the trend line post-NHSP with that pre-NHSP 1·58 [95% CI 1·05–2·37], p=0·0274, figure 3B). In the ORLS dataset, the annual percentage change in the person-based rate of congenital cytomegalovirus across the 49-year period from 1968 to 2016 was 4·8% (95% CI 2·8–6·9, p<0·0001).

Analysis of the perinatal and maternal variables in linked Hospital Episode Statistics (April 1, 1998–March 31, 2012) showed a significantly higher odds of a neonate weighing less than 2·5 kg being diagnosed with congenital cytomegalovirus infection than a neonate with birthweight 2·5 kg or greater, with particularly high odds for a neonate weighing less than 1 kg (odds ratio 88·0 [95% CI 42·8–180·8], p<0·0001; table 3). The analysis also showed evidence for associations of congenital cytomegalovirus infection with either elective or emergency caesarean section and young gestational age (<32 weeks' gestation; table 3). Younger maternal age (<25 years) was associated with congenital cytomegalovirus; infants born to mothers aged younger than 20 years had an increased odds of being diagnosed with congenital cytomegalovirus (odds ratio 3·3 [95% CI 2·3–4·6], p<0·0001) compared with infants born to mothers aged 30–34 years. Mothers in the most socioeconomically deprived quintile were more likely to have an infant diagnosed with congenital cytomegalovirus than mothers in the least deprived quintile (odds ratio 1·8 [95% CI 1·2–2·6], p=0·0033). Congenital cytomegalovirus was more strongly associated with black ethnicity than other coded ethnic groups (table 3).

In the national 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 (95% CI 14·6–21·1) per 100 000 infant population and a person-based rate of 14·8 (12·0–18·0) per 100 000 infant population. This rate represents a significant increase compared with the earlier years of the study (figure 1B): the annual person-based rate in the national dataset was 3·9 (2·5–5·8) per 100 000 infants in 1999, corresponding to an annual percentage change of 8·5% (95% CI 7·1–9·9, p<0·0001). In the longer-running linked ORLS dataset, only ten individuals were diagnosed with congenital HSV in hospital from 1968 to 1998, corresponding to an average annual person-based rate of 0·9 (95% CI 0·4–1·6) per 100 000 infant population.

Vaginal delivery and delivery by emergency caesarean section were both associated with an 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; table 3). Other factors associated with congenital HSV diagnosis were young gestational age (<32 weeks' gestation) and young maternal age (<20 years old; table 3).

In the national dataset, in 2016, there were 218 congenital VZV discharges for 208 infants in a corresponding national population of 669 100 infants, giving a discharge rate of 32·6 (95% CI 28·4–37·2) per 100 000 infant population and a person-based rate of 31·1 (27·0–35·6) per 100 000 infant population. This change represented a substantial increase in congenital VZV infections compared with earlier years of the study (figure 1C); the annual percentage change in person-based rate of congenital VZV infections from 1999 to 2016 was 7·6% (95% CI 6·3–8·9, p<0·0001). The longer-running linked ORLS dataset showed that the annual person-based rate remained low from 1968 until the end of the 1980s (average annual rate 2·2 per 100 000 infants [95% CI 1·1–3·9]), and increased from 1990 onwards, with an annual percentage change 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).

Evidence suggested an association between congenital VZV infection and number of previous pregnancies in the mother. Congenital VZV infection was also associated with black and south Asian ethnicities (table 3).

In the linked national dataset (1999–2016), a diagnosis of congenital rubella featured on only 48 discharge records for 24 individuals, giving a discharge rate of 0·4 per 100 000 infant population (95% CI 0·0–0·6) and an average annual person-based rate of 0·2 (95% CI 0·1–0·3) per 100 000 infant population, which represented a decrease compared with earlier years (figure 1D, table 2). Between 1979 (the single-dose rubella vaccine was introduced in 1970) and 1985 (the single-dose MMR vaccine replaced the rubella vaccine in 1988), there were 2·6 (95% CI 1·3–4·7) discharges with recorded congenital rubella per 100 000 infant population. Between 1989 and 1996 (the second dose of the MMR vaccine was introduced in 1996) the average annual discharge rate decreased to 1·5 (95% CI 1·2–1·9) per 100 000 infant population. In the 20 years following the introduction of the two-dose MMR vaccine (ie, between 1997 and 2016), the average annual discharge rate of congenital rubella was 0·5 (95% CI 0·0–0·6) per 100 000 infant population, and in 2016 was 0·15 (0·0–0·8) per 100 000 infant population. For comparison, in the longer running ORLS dataset, the average annual rate of individuals diagnosed with congenital rubella from 1979 to 1996 was 2·0 (95% CI 1·0–3·5). There were no recorded cases of rubella in the ORLS dataset after the introduction of the two-dose MMR vaccine.

Discussion

Acyclovir to treat HSV and VZV and ganciclovir to treat congenital cytomegalovirus, introduced in the late 1990s, and valganciclovir, introduced in the mid-2000s to treat congenital cytomegalovirus, are the only therapeutic interventions widely available to manage congenital virus infections in neonates. An understanding of 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 cytomegalovirus, HSV, VZV, and rubella in neonates, provides the most complete population-based data available for congenital viral infections in England during the past five decades.

In the most recent two decades of the study, from 1999 to 2016, the rate of cytomegalovirus, HSV, and VZV diagnoses in infants in England increased by approximately three times. This increase is most likely due to the introduction of highly sensitive PCR assays that have replaced cell culture as the diagnostic tool of choice since the mid-2000s. PCR assays began to be commonly integrated into NHS laboratories from the early 2000s.[11] This period corresponds with significant annual percentage change increases in the numbers of neonates diagnosed with congenital cytomegalovirus, HSV, and VZV.

Data from HES showed a significant step-increase in the rate of congenital cytomegalovirus diagnoses in infants between 2006 and 2007. This increase coincided with the introduction of the NHSP in England in 2006. Uptake of the NHSP, which screens neonates within 4 weeks of birth, has been greater than 90% across all NHS regions in England since its implementation.[23] Neonates who do not pass their hearing screen are seen by an audiologist for confirmatory testing, which typically occurs within 3 months of birth. A panel of aetiological tests, including screening for congenital cytomegalovirus, is done at the point of diagnosis of an infant with sensorineural hearing loss. However, oral valganciclovir has been shown to be effective in reducing sensorineural hearing loss and improving neurodevelopmental outcomes only if treatment is started within the first month of life.[5] Data from this study suggest that the increased rate of congenital cytomegalovirus diagnoses since 2007 is likely to be partly driven by the success of the NHSP in identifying infants with sensorineural hearing loss.

Compared with other national surveillance studies of congenital cytomegalovirus, which note as a limitation that preterm infants were not adequately evaluated,[24,25] this study provides evidence to suggest that a substantial burden of disease lies in preterm infants in neonatal intensive care units. The mother–infant pairs dataset showed strong associations between congenital cytomegalovirus and preterm birth and very low birthweight adjusted for gestational age. Studies have shown that cytomegalovirus infects the placenta and amniotic membranes, leading to vascular remodelling, which causes hypoxia, subsequent restriction in fetal growth, and preterm delivery.[26,27] Results from the current study support investigating the feasibility of targeted screening for congenital cytomegalovirus at the point a neonate fails their initial newborn hearing screen to enable valganciclovir treatment to be started in the first month of life and to allow early implementation of non-pharmacological interventions such as cochlear implants and speech therapies.[28] Furthermore, universal screening of all preterm infants on the neonatal intensive care unit who weigh less than 1 kg should be considered.

Previous studies have suggested that pregnant mothers might be at risk of contracting cytomegalovirus 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) through exposure at home or work.[29,30] In this study, we did not find any evidence of an association between mother's parity status and congenital cytomegalovirus diagnosis. Regional studies done in North America[31,32] have shown that neonates born in more deprived households are at an increased risk of developing congenital cytomegalovirus than those in less deprived households—a finding that is also supported by the present study. Surveys of paediatric health-care practitioners in France and the USA found that less than half of respondents had adequate knowledge of the disease to educate women during pregnancy.[33,34] These data should encourage health-care practitioners to reinforce important antenatal hygiene measures. Public health advice should target young women and socioeconomically deprived households that are at highest risk.

The rate of neonates diagnosed in hospital with HSV increased nearly four times between 1999 and 2016. Although this increase could be partly attributable to increased coding of the condition in hospitals, it also corresponds to a 22% increase in diagnosis of new episodes of genital HSV in England between 2008 and 2017.[7] In the largest trial so far to assess the effect of maternal infection on the likelihood of neonatal transmission, Brown and colleagues[35] 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 infants born to women with recurrent HSV. Neonates with HSV were 2·5 times more likely to be born to women younger than the age of 20 years old, which is a similar finding to that published by Public Health England,[7] which showed that the highest rate of anogenital herpes occurred in women between 15 and 24 years. In England, sex and relationship education will be mandatory for all schoolchildren aged 11 years and older from September 2020.[36] 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 in NHS laboratories for viral infections. Analysis of the mother–infant pairs dataset showed that there was an association between VZV diagnosis and maternal parity, which has been previously documented in studies in Germany, Greece, and Switzerland.[37–39] In the UK, pregnant women and neonates younger than 7 days are offered varicella zoster immune globulin to prevent severe infection. However, in 2018, Public Health England restricted the use of varicella zoster immunoglobulin because of manufacturing problems, which led to severe shortages.[40] Since 2018, pregnant women exposed to chickenpox after 20 weeks' gestation are therefore offered

acyclovir and not varicella zoster immunoglobulin. The UK has also opted against universal vaccination against VZV. However, national data from post-vaccine surveillance studies in Australia, Canada, and the USA showed that the introduction of the VZV vaccine led to a greater than 78% reduction in the number of neonatal varicella cases.[41–43] Data from the current study highlight the potential for controlling this problem through the introduction of a VZV vaccination programme into the routine immunisation schedule in the UK.

Only 24 infants 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 admissions due to measles in England immediately after the introduction of the two-dose MMR.[12] A surveillance study in the UK using data from HES and a disease-specific registry (the National Congenital Rubella Surveillance Programme) identified 12 cases of congenital rubella syndrome and three cases of congenital rubella infection between 2003 and 2016.[44] However, uptake of the MMR vaccine in children in England reaching their 2nd birthday decreased each year between 2014 and 2018, and was 91·2% in 2017–18.[45] Data from the current study support the continued efforts to encourage MMR vaccine uptake above the 95% target set by WHO[46] and to ensure unvaccinated women from abroad and the UK are given every opportunity to be fully immunised before pregnancy.

A strength of this study is the long timespan 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 similar findings. To our knowledge, clinical or laboratory reports of cytomegalovirus, HSV, or VZV in neonates are not routinely collected. These datasets therefore provide a unique opportunity to investigate this poorly understood group of infections.

This study has some limitations. 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 congenital cytomegalovirus cases will be missed clinically in the neonatal period and not reported. Preterm infants and those with very low birthweight might be over-represented in those diagnosed with congenital cytomegalovirus because they might be more likely to be diagnosed in hospital than full-term babies with milder disease who might only be seen in the outpatient setting. The limitations of the perinatal and maternal variables in the national dataset have been discussed elsewhere.[21] In brief, some hospitals were less thorough than others in collecting and reporting the full range of data items from the delivery episode. This shortfall meant that the number of mother–infant pairs used in the perinatal analysis was substantially reduced because there were quite high numbers of missing values for variables such as birth status, parity, birthweight, gestational age, and ethnic category (appendix pp 2–3). These missing data are unlikely to have caused bias in relation to the congenital diagnoses providing that the shortfall was random, but it did reduce statistical power.

In conclusion, the rate of congenital viral infections diagnosed in hospital has increased approximately three times in England since the introduction of highly sensitive molecular techniques to identify infection. However, few therapeutic interventions are available to manage these infections. The rising rate of neonatally diagnosed cytomegalovirus, HSV, and VZV in recent decades has probably increased the health service burden associated with these infections. 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 congenital cytomegalovirus should also be considered. Preventive measures through vaccination (eg, development of a cytomegalovirus vaccine, considering the introduction of routine varicella vaccination, and ensuring continued high uptake of the MMR vaccine) are warranted.

Contributors

All authors had access to all 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. SK and AJP had the idea for the study. All authors designed the study. MJG curated the datasets. RG designed and undertook the analyses. All authors contributed to data interpretation. SK did the literature search and wrote the first draft of the paper. AJP, MJG, and RG contributed to subsequent drafts and approved the final report.

Declaration of interests

We declare no competing interests.

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