Viral Infections: Contributions to Late Fetal Death, Stillbirth, and Infant Death

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Objective To determine the role of viral infections in causing fetal and infant death.

Study design We assessed a well-validated population database of fetal (≥20 weeks gestation) and infant death for infective deaths and deaths from viruses over a 21-year period (1988-2008). We analyzed by specific viral cause, timing (late fetal loss [20-23 weeks], stillbirth [≥24 weeks], neonatal death [0-27 days], and post-neonatal infant death [28-364 days]) and across time.

Results Of the 989 total infective deaths, 108 were attributable to viral causes (6.5% of late fetal losses, 14.5% of stillbirths, 6.5% of neonatal deaths, and 19.4% of postneonatal infant deaths). Global loss (combined fetal and infant losses per 100 000 registerable births) was 139.6 (95% CI, 130.9-148.3) for any infective cause and 15.2 (95% CI, 12.3-18.1) for viral infections. More than one-third (37%) of viral-attributed deaths were before live birth, from parvovirus (63%) or cytomegalovirus (33%). Parvovirus accounted for 26% (28 of 108) of all viral deaths. Cytomegalovirus was associated with a global loss rate of 3.1 (95% CI, 1.8-4.4) and an infant mortality rate of 1.3 (95% CI, 0.4-2.1) per 100 000 live births; 91% of cases were congenital infections. Herpes simplex virus caused death only after live births (infant mortality rate, 1.4; 95% CI, 0.5-2.3). No changes in rates were seen over time.

Conclusion We have identified a substantial contribution of viral infections to global fetal and infant losses. More than one-third of these losses occurred before live births. Considering our methodology, our estimates represent the minimum contribution of viral illness. Strategies to reduce this burden are needed. *(J Pediatr 2013;163:424-8)*.

Despite medical advances, infection remains a significant cause of perinatal and infant mortality, contributing to 10%-20% of infant deaths in the UK[1,2] and to 10%-25% of stillbirths in high-income countries.[3] Group B *Streptococcus* is the most commonly identified organism worldwide and as such has been the focus of national strategies aimed at reducing infection rates.[4-6] In contrast, the contribution of viral infections has been less well studied or described, despite their potential contribution to a significant proportion of deaths. The most widely recognized viral causes are cytomegalovirus (CMV), parvovirus, herpes simplex virus (HSV), and respiratory syncytial virus. Although there are some data on associated perinatal[7] and childhood mortality rates,[8,9] at present there are no population-based data on the total burden of death from viral infections, including deaths before birth.

Current data suggest that CMV is the most prevalent congenital viral infection, with significant public health consequences.[10] Infant mortality from congenital cytomegalovirus (cCMV) is reportedly 0.8/100 000 live births in the US[11] and between 0.7[8,9] and 0.8[12] per 100 000 live births in the UK; however, only live-born infants were included in those studies. Given the acknowledged impact of congenital viral infections as contributors to intrauterine demise or the decision to terminate pregnancy, data incorporating these fetal deaths are needed. Consequently, in the present study, we aimed to describe the burden and pattern of viral contributions to late fetal loss (at 20-23 weeks gestation), including loss from medical termination of pregnancy (TOP), stillbirth, and infant death, in a single large UK population cohort assessed over 2 decades.

Methods

We used the Perinatal Mortality Survey (PMS) database, which is coordinated by the Regional Maternity Survey Office in northern England.[13] This well-validated population-based survey captures the deaths of all fetuses at ≥20 weeks' gestation, including medical TOP, and all deaths in live-born infants within the first

cCMV	Congenital cytomegalovirus
CMV	Cytomegalovirus
HSV	Herpes simplex virus
IMR	Infant mortality rate
PMS	Perinatal Mortality Survey
TOP	Termination of pregnancy

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postnatal year, of mothers resident in the northeast and North Cumbria, including infants who were born or died outside the region. Deaths are classified at the time of death using a combination of clinical and postmortem data when available, using perinatal mortality meetings and confidential enquiries, and classified both by an obstetric classification (Aberdeen classification)[14] and a hierarchical clinicopathologic classification.[15] These classifications have been applied consistently since the start of the survey in 1981, and include infection as a category. Coexisting pathologies not directly causing death were recorded using relevant *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* codes. Any postmortem examinations were performed using virologic investigations according to the standards at the time.

We assessed the PMS database from 1988 to 2008 inclusive (21 years complete data) for deaths classified as being from any infective cause in the obstetric, clinicopathologic classification, or *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* coding systems. All available information was reviewed from these cases (E.W., all cases; N.E., some cases) to confirm whether infection was the likely primary cause of death, and whether a specific infectious cause was identifiable. Cases of primary immunodeficiency were excluded.

Mortality was attributed to a specific viral infection in cases with polymerase chain reaction, serologic, or histological confirmation and the clinical presentation was compatible. Deaths with clinical, microbiological, or histological features overwhelmingly suggestive of viral infection but with no specific virus identified were attributed to "unknown viral" causes. Deaths were categorized in 2 ways, by timing of death (ie, late fetal loss [20-23 weeks], stillbirth [≥24 weeks], neonatal death [<28 days], or postneonatal infant death [28-364 days) and by specific viral infection (**Table**).

Because techniques of viral identification have changed over time, we analyzed the data in three 7-year epochs: 1988-1994, 1995-2001, and 2002-2008. Denominator data were collected using the Northern Region yearly total live birth and stillbirth data provided by the Regional Maternity Survey Office. The stillbirth rate was calculated as the number of deaths occurring before delivery at ≥24 weeks gestation per 100 000 total births (liveborn and stillborn), and the infant mortality rate (IMR) was calculated as number of infant deaths occurring within the first year of life per 100 000 live births. Data collection for the PMS evolved over time, and the 1988-1991 data for late fetal loss (from 20 weeks) are not complete. The total burden of virus-attributed deaths, which we term "global loss," was calculated as the number of fetal losses occurring at 20-23 weeks gestation and stillbirths plus infant deaths using the denominator of total registerable births (ie, live births at any gestation and stillbirths after 24 weeks gestation).

The PMS was given ethical approval by the Ethics Committee of the Northern Regional Health Authority at its inception. Further approval from the National Information Governance Board to collect data under section 251 of the

Table. Etiology and timing of viral losses

Etiology	Late fetal loss, n, total (TOP)*	Stillbirth, n, total (TOP)	Stillbirth rate per 100 000 registerable births (95% CI)	Timing				Total loss, n	Global loss rate per 100 000 registerable births (95% CI)
				Neonatal, n	Neonatal mortality rate per 100 000 live births (95% CI)	Postneonatal, n	IMR per 100 000 live births (95% CI)		
All-cause deaths	2953 (1097)	3954 (243)	558.1 (540.7-575.4)	2796	396.9 (382.2-411.5)	1570	619.7 (601.4-638.0)	11 273	1591.1 (1562.0-1620.3)
All infection	247 (16)	165 (0)	23.3 (19.7-26.8)	340	48.3 (43.1-53.4)	237	81.9 (75.2-88.6)	989	139.6 (130.9-148.3)
All viral causes	16 (8)	24 (0)	3.4 (2.0-4.7)	22	3.1 (1.8-4.4)	46	9.7 (7.4-11.9)	108	15.2 (12.4-18.1)
Parvovirus	10 (4)	15	2.1 (1.1-3.20)	3	0.4 (0-0.9)	0	0.4 (0-0.9)	28	4.0 (2.5-5.4)
CMV	5 (3)	8	1.1 (0.4-1.9)	5	0.7 (0.1-1.3)	4	1.3 (0.4-2.1)	22	3.1 (1.8-4.4)
HSV	0	0	0	9	1.3 (0.4-2.1)	1	1.4 (0.5-2.3)	10	1.4 (0.5-2.3)
Respiratory viruses	0	0	0	1	0.1 (0-0.4)	19	2.8 (1.6-4.1)	20	2.8 (1.6-4.1)
Other viruses	1 (1)†	0	0	0	0	2‡	0.3 (0-0.7)	3	0.4 (0-0.9)
Unknown virus	0	1	1.1 (0-0.4)	4	0.6 (0-1.1)	20	3.41 (2.0-4.8)	25	3.5 (2.2-4.9)

*Data for late fetal loss (20-23 weeks) were not complete before 1991.
†One coxsackievirus.
‡One varicella zoster virus and 1 coxsackievirus.