

# Population-Based Surveillance of Neonatal Herpes Simplex Virus Infection in Australia, 1997–2011

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**Background.** Neonatal herpes simplex virus (HSV) infection is uncommon, but mortality after disseminated disease and morbidity after encephalitis are high. For the last decade, increased dose and duration of acyclovir has been advised to prevent disease progression and recurrence. We sought to determine prospectively the epidemiologic, clinical, and secular trends of this condition in Australia.

**Methods.** This was prospective national active surveillance for neonatal HSV disease through the Australian Paediatric Surveillance Unit from 1997 to 2011. Case notification triggered a questionnaire requesting de-identified data from the pediatric clinician.

**Results.** We identified 131 confirmed cases of neonatal HSV disease in 15 years from 261 notifications (95% response). The reported incidence (3.27 cases per 100 000 live births overall; 95% confidence interval [CI], 2.73–3.86) was stable. Overall mortality was 18.8% (95% CI, 12.1–25.5); the mortality rate was significantly lower in the latter part of the study period, 2005–2011, compared with 1997–2004 ( $P = .04$ ). There were significantly more young mothers (<20 years of age) compared with Australian birth record data (18.5% vs 4.8%;  $P < .001$ ). HSV-1 infection was more common than HSV-2 (62.7% vs 37.3%;  $P < .001$ ), and the rate of HSV-1 infections increased significantly over the surveillance period ( $P < .05$ ). From 2002, most infants received high-dose acyclovir. The time from symptom onset to initiation of therapy in survivors did not change over time.

**Conclusions.** Mortality from neonatal HSV infection has fallen but remains high. HSV-1 is the major serotype causing neonatal disease in Australia. Young mothers represent an important target group for prevention.

**Keywords.** neonatal herpes simplex virus infection; herpes simplex virus; adolescent mothers; genital herpes; vertical transmission.

Neonatal herpes simplex virus (HSV) infection is a rare but serious condition that can present with disease localized to the skin, eyes, and/or mouth (SEM), encephalitis, or disseminated infection [1]. Without antiviral therapy, death or handicap is almost inevitable after

disseminated or central nervous system (CNS) disease [2, 3]. Neonatal HSV infection is usually acquired during delivery following maternal genital HSV infection, but can also be acquired postnatally from an infected contact. Rarely, neonatal HSV disease can follow intrauterine infection [4]. The risk of mother-to-child transmission is greatest after primary maternal genital HSV infection [5, 6]. Early studies from the United States suggested that most neonatal infection was due to HSV-2 [7]. However, in many parts of the world, including the United Kingdom and Canada, HSV-1 now predominates as the cause of neonatal HSV disease [8, 9]. Two single-center case series from more than a decade ago reported HSV-1 as the dominant serotype

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causing neonatal disease in Australia [10, 11], but the national epidemiology is poorly described.

Early diagnosis and treatment with acyclovir are vital for a favorable outcome [12, 13]. Over the last 10 years, the recommended management of neonatal HSV disease changed to use larger doses of acyclovir for longer durations [12]. The use of molecular techniques in preference to antigen detection and culture has improved detection of neonatal HSV disease, neonatal HSV encephalitis in particular [14]. In view of these changes, our objectives were to utilize a national, active surveillance mechanism to determine prospectively the incidence, mortality, and morbidity of neonatal HSV infection in Australia; to describe the clinical presentation; and to document changes in the diagnosis and management of neonatal HSV infection over the last 15 years.

## METHODS

Approval for this study was obtained from the Royal Alexandra Hospital for Children (Children's Hospital at Westmead) Human Research Ethics Committee. The study protocol and questionnaire are available at: <http://www.apsu.org.au>.

### Case Definition

Pediatricians working in Australia were asked to report any neonate (age  $\leq 28$  days regardless of gestation) seen in the previous month with clinical HSV infection and laboratory confirmation. Laboratory confirmation was defined as isolation of HSV from the neonate by viral culture and/or detection of HSV DNA by polymerase chain reaction (PCR) or immunofluorescence and/or detection of HSV-specific immunoglobulin M (IgM) in neonatal serum, and/or isolation of HSV or detection of HSV DNA from peripartum maternal samples. Clinical evidence was defined as one or more of: typical herpetic SEM lesions, evidence of disseminated infection (bleeding, bruising or coagulopathy, jaundice or elevated serum bilirubin, hepatosplenomegaly or elevated liver transaminases), pneumonitis (respiratory distress or chest radiography) or encephalitis (lethargy, seizures, abnormalities on neuroimaging or electroencephalography).

The mode of presentation was categorized as disease localized to the SEM or the central nervous system (CNS), or as disseminated HSV infection (involvement of multiple viscera including liver, lungs, adrenal glands, and/or disseminated intravascular coagulation with or without CNS or SEM diseases).

### Case Ascertainment

The Australian Paediatric Surveillance Unit (APSU) performs active ascertainment of uncommon childhood conditions in Australia, and for the previous 20 years has a monthly response rate  $>90\%$ , and up to  $98\%$  in later years [15, 16]. Cases of neonatal HSV disease from 1 January 1997 through

31 December 2011 were ascertained prospectively by sending a monthly report card by email or reply post to all practicing pediatricians in Australia (general and subspecialists,  $n = 1350$ ) requesting new cases of neonatal HSV from the previous month. A study questionnaire and paid reply envelope were sent to any pediatrician who notified a case of neonatal HSV disease.

Study questionnaires requested de-identified demographic data on mother (age, country of birth, Australian Indigenous status, parity) and infant (age, birth weight, gestation), details of delivery (mode, use of scalp electrode, duration of rupture of membranes), age and clinical signs at presentation, antiviral therapy (whether used, drug given, duration, dose), any laboratory-proven HSV relapse, survival (at time of notification), source of infection (mother or father: genital or nongenital HSV; other contact; hospital-acquired infection), and results and dates of imaging and laboratory investigations (viral isolation, HSV serotype, CSF cell count, PCR result, CSF antibodies, acute and convalescent HSV-specific serology on mother and infant).

### Data Analysis

We calculated incidence rates per 100 000 births as the number of reported cases over the sum of the reported number of live births for each year (1997–2011), and mortality rates as the number of deaths over the sum of the reported numbers of live births for each year [17, 18]. We performed 1-sample binomial tests to compare proportions in demographic variables between cases with the Australian birth record data from the approximate midyear in the study period [17, 18]. Univariate logistic regression reported as odds ratios (ORs) with 95% confidence intervals (CIs) was performed to examine temporal trends of variables including incidence, serotype, mortality, and between HSV-1 and HSV-2 infections over time. Univariate linear regression was used to assess mean time between onset of symptoms and commencement of therapy. The  $\chi^2$  test was used to compare number of deaths between 2 time periods of the study (1997–2004 and 2005–2011). We calculated the OR for mortality for sex, gestational age, birth weight, antiviral dose, and HSV serotype [19].  $P$  values  $<.05$  were considered statistically significant. All analyses were conducted in SPSS for Windows, version 21.0 (SPSS Inc, Chicago, Illinois).

## RESULTS

### Reporting Rates and Case Classification

There were 261 APSU notifications of neonatal HSV disease in the 15-year period. Clinical data were provided for 247 reports (95%); after exclusion of duplicate reports and errors, 131 met the criteria for confirmed neonatal HSV infection. Five infants

**Table 1. Description of Herpes Simplex Virus–Infected Infants and Their Mothers**

Variable <sup>a</sup>	Infants With HSV <sup>a</sup> , No. % (n = 131)	Australian Birth Record Data <sup>b</sup> (%)	P Value
<b>Maternal characteristics (n = 130)<sup>c</sup></b>			
Maternal age, y (n = 99)			
Median	27.3	30.0	
Minimum, maximum	16, 44	13, 55	
<20 y	18 (18.2)	(4.8)	<.001
Country of birth (n = 118)			
Australia (not ATSI)	101 (85.6)	(76.9)	.25
Australia ATSI	5 (4.2)	(3.8)	.44
Other <sup>d</sup>	12 (11.3)	(23.1)	.98
Parity (n = 107)			
Primipara	49 (45.8)	(41.6)	.33
Multipara	58 (54.2)		
Mode of delivery (n = 123)			
Vaginal	73 (55.7)	(61.0)	.69
Instrumental	12 (9.2)	(11.2)	.67
Cesarean	38 (29.0)	(28.5)	.47
ROM (hours) (n = 77)			
Median (SD)	9 (80.6)		
Minimum, maximum	0–528		
Intact or ROM <4			
All cases	25 (32.5)		
Cesarean, (n = 29)	10 (34.5)		
Fetal electrode use (n = 80)	6 (7.5)		
<b>Infant characteristics (n = 131)<sup>c</sup></b>			
Sex (n = 123)			
Male	54 (43.9)	51.0%	.77
Female	67 (56.1)		
Birth weight, g (n = 112)			
Mean	2856	3646	
Minimum, maximum	734, 4700	(6.2)	
<2500 g	32 (28.6)	(1.3)	<.001
<1500 g	12 (10.7)	(1.0)	<.001
Gestational age, wk (n = 119)			
Mean	36.6	38.9	.60
Minimum, maximum	24, 42		
<37 wk	37 (31.1)	(8.2)	<.001
<28 wk	5 (4.2)	(1.0)	.08
Category of disease (n = 129)			
Skin, eye, mouth	60 (46.5)		
CNS	29 (22.5)		
With skin lesions	14		
Disseminated	40 (31.0)		
With skin lesions	16		
With CNS disease	17		
With pneumonitis	10		
Intrauterine	4		

Table 1 continued.

Variable <sup>a</sup>	Infants With HSV <sup>a</sup> , No. % (n = 131)	Australian Birth Record Data <sup>b</sup> (%)	P Value
<b>HSV serotype (n = 118)</b>			
HSV-1	74 (62.7)		
HSV-2	44 (37.3)		

Abbreviations: ATSI, Aboriginal or Torres Strait Islander; CNS, central nervous system; HSV, herpes simplex virus; ROM, rupture of membranes; SD, standard deviation.

<sup>a</sup> n = Number with data available.

<sup>b</sup> Source: [17].

<sup>c</sup> One hundred thirty mothers to 131 infants.

<sup>d</sup> New Zealand/South Pacific (2), Europe (7), Africa (1), Asia (1), Middle East (1).

with laboratory-confirmed HSV infection occurring outside the neonatal period (age 29–50 days) were excluded. The reported incidence of neonatal herpes in Australia over the 15 years was 3.27 (95% CI, 2.71–3.84) per 100 000 live births. The annual incidence was stable over the study period, and there was no significant geographic variation (data not shown).

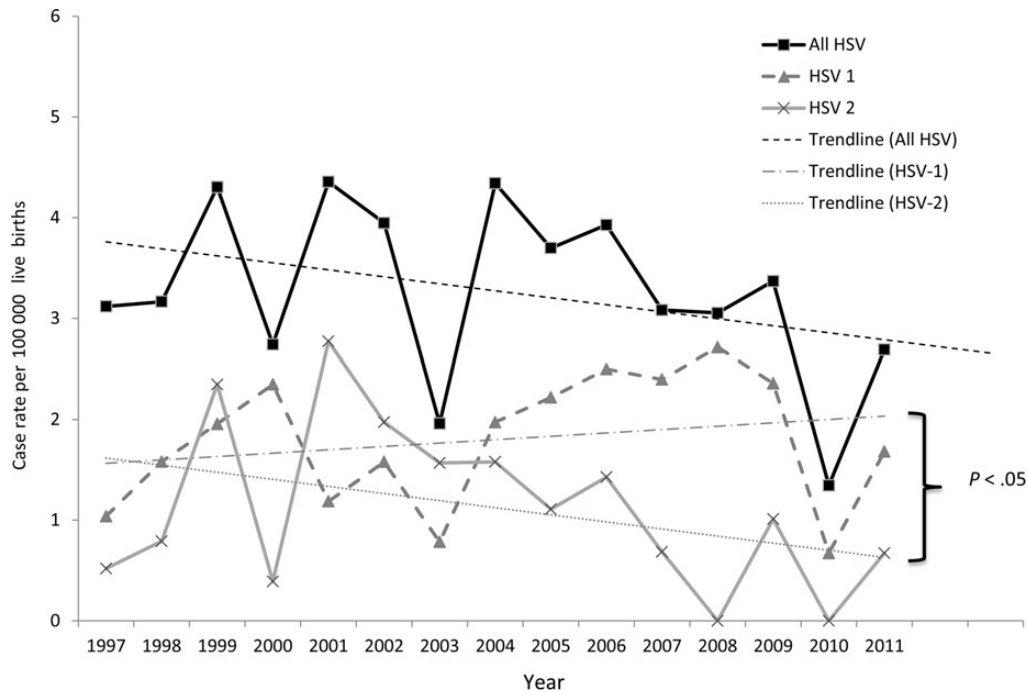
### Demographic Details

Demographic details of mothers of HSV-infected infants are compared with the Australian birth record data in Table 1. The median maternal age, parity, and mode of delivery were similar to the Australian birth record data, but mothers of HSV-infected infants were significantly more likely to be <20 years of age (18.4% vs 4.0%;  $P < .001$ ). Most mothers of HSV-infected neonates were born in Australia (89.8%), including 5 Indigenous (Aboriginal or Torres Strait Islander) mothers. Time between membrane rupture and birth was reported for 77 (58.7%) infants. Ten of 29 (34.5%) infants delivered by caesarean section had membranes that were intact or ruptured <4 hours at delivery.

Sex, mean gestation, and mean birth weight of the HSV-infected neonates were not significantly different from the Australian birth record data [17, 18] (Table 1). However, significantly more cases were low birth weight (<2500 g), very low birth weight (<1500 g), preterm (<37 weeks), or very preterm (<28 weeks) compared with the Australian birth record data (Table 1). Twin deliveries were reported in 4 cases, including 1 pair of infected twins.

### Clinical Characteristics at Presentation

The classification of neonatal disease according to clinical presentation remained stable over the study period (not shown). Almost half (46.5%) presented with SEM disease,



**Figure 1.** Rates of neonatal herpes simplex virus (HSV) disease by serotype in Australia per 100 000 births per year, 1997–2011, with trends over time for all HSV and each serotype. *P* value shows significant difference in trend over time between HSV-1 and HSV-2.

31% with disseminated infection, and 22.5% with CNS disease, half of whom also had cutaneous disease (Table 1). Of the 40 infants with disseminated infection, 17 infants also had encephalitis and 10 had pneumonitis. Four infants (3.0%) had features at birth consistent with intrauterine infection. The proportion of infants with each disease category did not vary with HSV serotype (not shown). The majority of infants presented with signs of HSV infection in the first 2 weeks of life (86.9%); 52.5% had signs of infection within 7 days of birth.

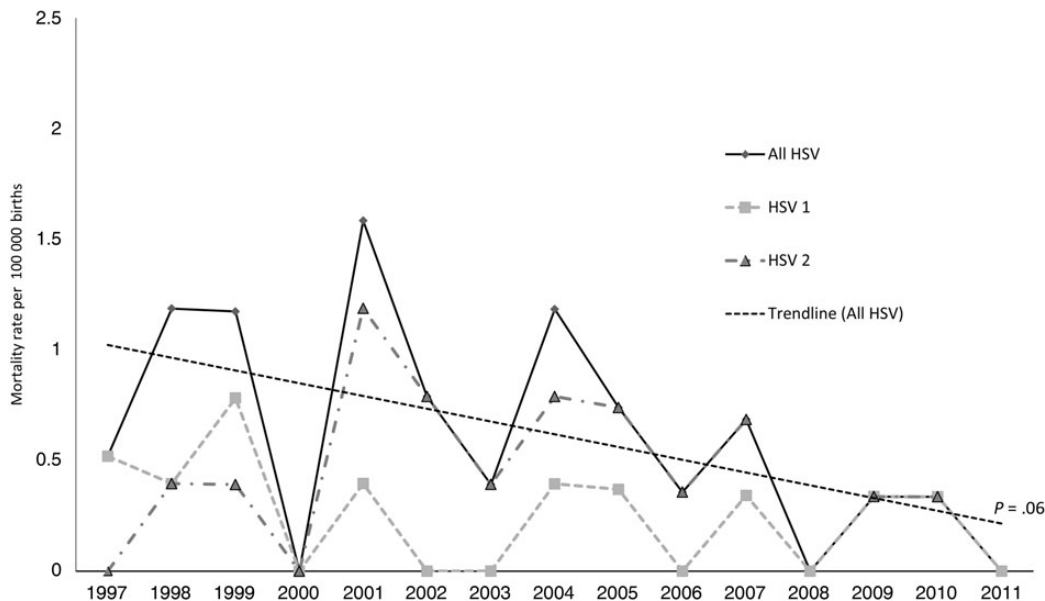
#### Laboratory Investigations and Imaging

There were significantly more cases of neonatal infection with HSV-1 than with HSV-2 ( $P < .001$ ; Table 1), and there was a significant increase in trend over the 15-year study period of HSV-1 infections compared with HSV-2 (OR, 1.10 [95% CI, 1.00–1.21];  $P < .05$ ) (Figure 1). Laboratory confirmation was by virus isolation and/or detection of HSV DNA by PCR (86.3%) and/or positive immunofluorescence (33.6%) from mucocutaneous sites or vesicles, and/or positive CSF PCR (28.2%). CSF HSV serology was rarely performed (5/131), and only 1 case reported a positive result (CSF immunoglobulin G [IgG] and IgM). Measurement of HSV IgM in neonatal blood was not routinely performed (32/131), and where positive (3/32) was not the sole criterion for laboratory confirmation in this series.

#### Antiviral Therapy and Outcome

Information on antiviral therapy was reported for 128 infants: 117 received acyclovir, 10 died undiagnosed, and received no antiviral therapy, and 1 infant reported with SEM disease did not receive antiviral therapy but survived the infection. A change in the international standard of care for neonatal HSV disease arose after an open-label study published in 2001 suggested improved survival with high-dose intravenous acyclovir (60 mg/kg/day) for disseminated disease [12]. This was reflected in prescribing practice in Australia from 2002 whereby most infants received high-dose intravenous acyclovir (not shown). The mean time from the onset of symptoms to commencement of acyclovir was stable over time in survivors (1.9 days [minimum 0, maximum 18 days]).

Outcome at discharge was available for 128 infants. Twenty-four infants (18.8% [95% CI, 12.1%–25.5%]) had died at the time of notification, 23 from HSV infection. Of the 24 infants who died, 22 (92%) presented with disseminated HSV infection, and 1 who presented with CNS infection died at 85 days of age. The remaining infant presented with SEM disease responded to antiviral therapy, but died later from complications of prematurity. After excluding an infant who died in utero from intrauterine infection, the median age of death was 12 days. There were significantly fewer deaths in the latter period of the study compared with the earlier period (7/60 [11.7%] in 2005–2011 vs 17/68 [25.0%] in 1997–2004;  $P < .05$ ). This difference was



**Figure 2.** Rates of neonatal herpes simplex virus (HSV) deaths by serotype in Australia per 100 000 births per year, 1997–2011, and trend over time for mortality from all HSV. *P* value is for HSV mortality trend over time.

reflected in the mortality trend analysis for all HSV infection, where the decline in mortality approached significance (OR, 0.89 [95% CI, .80–1.00]; *P* = .06). The contribution of HSV-2 mortality to the overall trend is evident in the latter period of the study, where the HSV-2 mortality appeared to account for the majority of the overall trend (Figure 2). However, neither the HSV-1 or HSV-2 individual trends in mortality were significant (HSV-1: OR, 0.88 [95% CI, .74–1.04], *P* = .13; HSV-2: OR, 0.91 [95% CI, .75–1.10], *P* = .32).

The association between infant characteristics and mortality is shown in Table 2. Disseminated disease was approximately 70 times more likely to result in mortality; however, the confidence interval was very wide (OR, 70.9 [95% CI, 8.92–563.27]). Low birth weight (<2500 g) was also significantly associated with increased odds for mortality (OR, 3.45 [95% CI, 1.30–9.12]); there were no other significant associations with mortality. Mortality from neonatal infection with HSV-2 was more than twice that of HSV-1, but not significant (OR, 2.48 [95% CI, .97–6.36]; *P* = .06).

### Source of Infection

Data on the source of HSV infection in the neonate were reported for 92 cases. A possible postnatal source of HSV was identified in 30 cases (32.6%), all of which were due to HSV-1 infection. There were 14 cases in which an active maternal non-genital source at delivery was identified (oral lesions, systemic HSV-1 disease, or maternal breast lesions), and 16 cases where exposure to another relative with active orolabial disease

or a possible hospital-acquired infection were reported. A history of maternal genital herpes at any time before, during or after delivery was reported in 37 cases (40.2%; 17 HSV-1, 18 HSV-2, 2 serotype not recorded), including a confirmed first episode of maternal genital herpes in 13 (6 HSV-1, 7 HSV-2). There was indirect evidence of a maternal genital source in a further 25 cases (27.1%) in the absence of reported maternal disease: neonatal HSV-2 and a history of genital herpes in the maternal sexual partner in 4 cases, intrauterine disease in 2 (1 due to HSV-1), and 19 infants with HSV-2 without identified postnatal or genital sources.

### DISCUSSION

We report a longitudinal population-based study of neonatal HSV disease in Australia, which is the largest and the only prospective series from the southern hemisphere. Although the reported incidence of neonatal HSV infection was stable, there was an increased rate of neonatal HSV-1, and a high incidence in younger mothers. We also observed significantly reduced mortality in the latter part of the study, temporally associated with larger antiviral doses.

The overall incidence of approximately 3 cases per 100 000 live births is similar to reports from the United Kingdom [8] and Canada [9], but lower than the United States, where rates up to 12.2 per 100 000 have been reported [20]. HSV is not a mandatory notifiable condition in Australia. From active surveillance, it is more common than neonatal or congenital varicella,



**Table 2. Odds Ratios for Mortality by Infant Characteristics (n = 128)**

Characteristic	Died, No. (%)	Survived, No. (%)	OR (95% CI)
Number	24 (18.75)	104 (81.3)	
Birth weight, g			
>2500 g	11 (13.8)	69 (86.3)	Referent
≤2500 g	11 (35.4)	20 (64.6)	3.45 (1.30–9.12) <sup>a</sup>
<1500 g	2 (22.2)	7 (77.8)	1.79 (.33–9.77)
Gestational age categories, wk			
≥37 wk	14 (17.1)	68 (82.9)	Referent
<37 wk	10 (27.0)	27 (73.0)	1.79 (.71–4.54)
<28 wk	1 (20.0)	4 (80.0)	1.21 (.13–11.70)
Sex			
Male	13 (24.1)	41 (75.9)	Referent
Female	9 (13.4)	58 (86.6)	0.49 (.19–1.25)
Category of disease			
Skin, eye, mouth	1 (1.7)	58 (98.3)	Referent
Disseminated	22 (55.0)	18 (45.0)	70.89 (8.92–563.27) <sup>a</sup>
Central nervous system	1 (1.7)	58 (98.3)	1.00 (.06–16.37)
Antiviral dose			
30 mg/kg/d	3 (13)	20 (87.0)	Referent
45 mg/kg/d	2 (28.6)	5 (71.4)	2.67 (.35–20.51)
60 mg/kg/d	8(10.8)	66 (89.2)	0.81 (.20–3.34)
HSV serotype			
HSV-1	10 (13.5)	64 (86.5)	Referent
HSV-2	12 (27.9)	31 (72.1)	2.48 (.96–6.36)

Abbreviations: CI, confidence interval; HSV, herpes simplex virus; OR, odds ratio.

<sup>a</sup> Statistically significant confidence interval.

but less common than congenital CMV [21, 22]. It is also more common than notifiable congenital infections (rubella, syphilis, human immunodeficiency virus) in Australia [23].

In this study there were more infants with HSV-1 than HSV-2 disease, and the HSV-1 case rate increased over time. In the past, HSV-1 was typically associated with cold sores, whereas HSV-2 was the main cause of genital herpes. However, in recent years there has been an increase in genital herpes caused by HSV-1 in Australia, the United States, and elsewhere [24, 25]. This increase has been most marked in young women, and is consistent with our findings of an overrepresentation of adolescent mothers in this series. The reasons for this increase are unknown; however, preventive efforts should include increasing adolescent awareness of sexually transmitted infections like HSV.

One-third of our series of HSV-infected infants were born by cesarean delivery, some with intact membranes. Cesarean delivery has been reported to reduce rates of neonatal HSV infection among women shedding HSV during labor [6]; however, our

findings confirm other observations that it does not eliminate neonatal HSV disease [6, 9] and raises questions about the efficacy of this as a preventive intervention in a population with predominantly HSV-1 genital infection.

Since 1997, there have been changes in both diagnosis and treatment, and these are reflected in our data [12, 26]. These include the use of larger and longer doses of antiviral therapy to reduce disease progression in disseminated infection and reduce the likelihood of early neurologic recurrence. Diagnostic techniques have also changed to molecular methods, increasing sensitivity, particularly for neonatal HSV encephalitis. Measurement of HSV IgM in the blood is an insensitive and potentially nonspecific method for the diagnosis of neonatal infection, and is no longer recommended. Although this was included as a technique in our case definition, it was not the sole method used for confirmation of any case.

We observed significantly fewer deaths in the latter part of the study and a downward trend in mortality. Nearly all deaths were due to disseminated disease. Category of disease at presentation, which was similar to other large studies, did not change over the study period, so the downward trend was not due to less disseminated disease in recent years [8]. There was a temporal association with the use of increased doses of antiviral therapy in the latter study period, possibly because the sample size was too small and/or the study duration too short. As in a US series from 2001, we did not observe changes in gestational age, sex, or time between the onset of symptoms and the initiation of therapy [2]. However, as the time-to-treat interval was only calculated in survivors, it did not take into account the fact that there were no reports diagnosis of HSV at autopsy (and therefore not treated with antiviral therapy) after 2004, which suggests better recognition of disseminated disease [2]. The increased rate of neonatal HSV-1 infection in the latter study period is another possible explanation for the improved survival in recent years. Although we did not observe a significant difference in mortality between HSV serotype, there was a trend to suggest a more favorable outcome for HSV-1, suggesting that HSV serotype may in part account for the improved survival. Ongoing surveillance will be needed to confirm this.

Strengths of our study include its prospective nature and the population-based data, with good ascertainment. Although we cannot be certain that we have all cases, as there is no national reporting for this condition, it is likely that most eligible cases are included due to stringent methods of the APSU and concurrence with our validation study using International Classification for Diseases coding and mortality datasets (Khandaker, Raynes-Greenow, and Jones, unpublished observations). Our inclusion criteria were limited to neonates up to 28 days of age. There were at least 5 cases that were outside this age range, which otherwise fit the criteria but were excluded from data reported here. A recent prospective population-based

study from Canada extended reporting to 60 days of life so that late diagnoses were not missed [9]. There may also be neonates who died before HSV was identified, and fetal deaths were not routinely sought for this study. Our future study will include infants aged up to 12 months, and include long-term follow-up to better characterize recurrences and outcomes after suppressive antiviral therapy.

In summary, this is the first study to report the national incidence and secular trends of neonatal HSV disease in Australia. Over 15 years, we report a relatively stable rate of this condition, but identified important trends of increased HSV-1 disease, higher risk for young women, changes in therapy practices, and trends toward reduced mortality. Although neonatal HSV infection is rare, these findings highlight the importance of longitudinal studies. Young females are a target group for prevention of genital herpes, and knowledge of the role of HSV-1 in neonatal disease has implications for counseling and vaccine development. Gaps in our knowledge about the outcome of neonatal HSV infection remain important questions to be addressed.

## Notes

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**Author contributions.** D. I. conceived the study; C. A. J. conducted the study; C. A. J. and C. R.-G. analyzed the data; and C. A. J. and C. R.-G. wrote the manuscript.

**Potential conflicts of interest.** All authors: No potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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