

REVIEW



# New estimates of the prevalence of neurological and sensory sequelae and mortality associated with congenital cytomegalovirus infection<sup>†</sup>

Sheila C. Dollard,<sup>1\*</sup> Scott D. Grosse<sup>2</sup> and Danielle S. Ross<sup>2</sup>

<sup>1</sup>National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

<sup>2</sup>National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

## SUMMARY

Congenital CMV is a major cause of neurological and sensory impairment in children. Reliable estimates of the prevalence of permanent sequelae and mortality associated with congenital CMV are needed to guide development of education and prevention programmes and to gauge the financial costs associated with this disease. To calculate such estimates, this review used data solely from studies in which children with congenital CMV were identified through universal screening. Based on 15 studies with a total of 117 986 infants screened, the overall CMV birth prevalence estimate was 0.7%. The percentage of infected children with CMV-specific symptoms at birth was 12.7%. The percentage of symptomatic children with permanent sequelae was 40–58%. The percentage of children without symptoms at birth who developed permanent sequelae was estimated to be 13.5%. The true burden of congenital CMV infection is unclear because data on important outcomes, such as visual impairment, are lacking and follow-up of infected children has been too short to fully identify late-onset sequelae. Therefore, the estimates of permanent sequelae associated with congenital CMV presented here are likely underestimates. Future studies should extend follow-up of CMV-infected children identified through universal screening and include the evaluation of visual impairment. Copyright © 2007 John Wiley & Sons, Ltd.

Received: 19 March 2007; Revised: 19 April 2007; Accepted: 20 April 2007

## INTRODUCTION

Human cytomegalovirus is a widely distributed herpesvirus spread through close interpersonal contact with infected bodily fluids, usually saliva, urine, blood or genital secretions. CMV can be transmitted from mother to fetus anytime during gestation and is most likely to cause serious harm to the fetus when the mother experiences a primary CMV infection during pregnancy. Congenital CMV can cause permanent physical sequelae

or impairments that result in disabilities such as hearing loss (HL), visual impairment, and mental retardation; it also raises the risk of infant mortality [1,2]. According to a recent review, between 20 000 and 40 000 children are born with congenital CMV infections in the United States each year; 100–200 die as a consequence of symptomatic infections, and 4000–8000 develop permanent neurological complications that often lead to permanent disabilities [3]. Higher estimates of the burden of congenital CMV in terms of death and disability have also been published [4,5].

Sensorineural hearing loss (SNHL) is the most common symptom of CMV infection among the 10–15% of children with symptoms of infection at birth [6,7]. HL occurs at a lower rate among the 85–90% of infected infants who are asymptomatic at birth; however, because there are many more asymptomatic infants, the majority of cases of SNHL caused by CMV occur in this group.

\*Corresponding author: S. C. Dollard, Centers for Disease Control and Prevention, 1600 Clifton Road NE, Mailstop G-18, Atlanta, GA 30333, USA. E-mail: sgd5@cdc.gov

<sup>†</sup>The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

### Abbreviations used

CD, cognitive deficit; CID, cytomegalovirus inclusion disease; HL, Hearing Loss; MD, motor deficit; SES, socioeconomic status; SNHL, sensorineural hearing loss.

The frequencies of visual impairment, mental retardation or milder cognitive impairment are less well established and are concentrated among the minority who are symptomatic at birth [8]. Infant mortality has been reported in 10% or more of children who are symptomatic at birth [4,5]; however, one recent review suggested that the mortality rate from symptomatic CMV could be less than 5% [3].

Although several studies have estimated the burden of congenital CMV, the current study is the first systematic review of neurological and sensory sequelae associated with congenital CMV infection. It is also the first review of congenital CMV sequelae to include data from only studies that performed universal screening of all infants born at a given centre or centres. The review does not include studies in which any of the children with CMV were referred to the study based on clinical symptoms, nor does it include reports based on screening subsets of infants at elevated risk for congenital CMV infection. Our purpose is to provide an unbiased estimate of the frequency of permanent sequelae associated with congenital CMV infection to more accurately measure the preventable burden of this disease. To that end, this review presents estimates of the birth prevalence of symptomatic and asymptomatic congenital CMV infections and the probabilities of neurological sequelae in each of these groups.

## METHODS

We searched the Medline/OVID database for English-language papers published from 1966 through December 2006 using the subject headings 'CMV' or 'cytomegalovirus' with the keywords 'congenital' or 'newborn.' Papers were then restricted to those with any of the following key words: 'sequelae', 'symptoms', 'symptomatic', 'abnormalities', 'impairment', 'outcome', or 'prognosis'. This search resulted in approximately 450 papers, which we reviewed for the following inclusion criteria: (1) original peer-reviewed papers; (2) study populations from high-income countries, based on *per capita* income during the study period; (3) sample of 800 or more children; (4) identification of congenital CMV through universal screening in a defined population and (5) detection of CMV based on culture of urine or saliva collected within 3 weeks of birth. In the case of multiple reports from the same authors with overlapping

study dates, we chose the most recent or most comprehensive report to avoid counting the same study subjects more than once. Eighteen unique studies met our search criteria for universal screening of a birth cohort. Of these, 15 reported the prevalence of symptoms at birth and 3 studies reported infected children only.

Our criteria were defined to exclude reports likely to over-represent infants with severe sequelae. These include: (1) studies that selected women who experienced primary CMV infection during pregnancy or that identified CMV-infected infants based on elevated umbilical cord blood IgM, which mainly detects primary CMV infection [9]; and (2) reports limited to adolescent maternal populations who, being younger and therefore having a lower CMV seroprevalence, are more likely to experience a primary CMV infection. Reports on primarily populations with low socioeconomic status (SES) were included and identified as such. Reports from studies that screened fewer than 800 infants were excluded because of the instability in estimates of birth prevalence and sequelae.

We use the term 'symptom' to describe clinical indications of CMV infection in newborns known as cytomegalovirus inclusion disease (CID), defined as the presence of one or more of the following symptoms: petechiae, jaundice with associated hyperbilirubinemia, hepatosplenomegaly, thrombocytopenia, chorioretinitis, seizures, microcephaly, intracranial calcifications or fetal hydrops. The less severe symptoms are usually transient in newborns. Studies that used alternative or undefined criteria for defining symptomatic infection were not included. Intrauterine growth retardation (IUGR; also referred to as 'small for gestational age') has been observed in association with congenital CMV infection but was infrequently reported in the literature and not included as a symptom of infection for this review. It should be noted that many of the signs listed are not specific to CMV or readily apparent and hence symptomatic CMV often goes unrecognised in the absence of systematic attempts to identify it.

We use the term 'sequelae' to describe CMV-associated developmental delays or differences in sensory function that appear in infected children over time. The clinical terms used to describe sequelae in the literature and the methods used to measure sequelae were not clearly defined or

standardised across studies. Therefore, we grouped and simplified sequelae as follows: HL includes both unilateral and bilateral SNHL, but not conductive HL because the latter is usually temporary. Cognitive deficit (CD) includes what was variably referred to as mental retardation, neurological impairment and developmental delay. Many children reported as being mentally retarded were, in fact, too young to have been properly evaluated for mental retardation using standardised tests of cognitive ability. Motor deficit (MD) includes any limitation regarding bodily movement and includes cerebral palsy. Because the congenital CMV literature has rarely employed standardised measures of disability associated with neurological or sensory sequelae, we were not able to calculate the frequencies of developmental disabilities.

## RESULTS

Our inclusion criteria, which emphasised studies most likely to have unbiased sampling, excluded the majority of published reports on congenital CMV infection. Table 1 summarises data on symptomatic and asymptomatic CMV infection at birth. Table 2 summarises data on CMV-associated sequelae. Among the 117 986 infants in the 15 studies shown in Table 1 [10–24], 810 (0.7%) were infected with CMV. Five of the studies targeted low-SES populations and had an average infection rate of 1.2% (range 0.9–1.3%). The other 10 studies had populations that were unselected by SES (primarily middle SES) and had a markedly lower average infection rate of 0.39% (range 0.3–0.5%).

Among the 810 CMV-infected infants, 103 (12.7%, range 0.0–25.0%) had symptoms of CMV infection, or CID (Table 1). The percentage of infants with congenital CMV who had symptoms at birth did not vary significantly by average SES.

The first 10 reports listed in Table 2 [10–13,18,20,22,25–27] present the results of evaluations of CMV-infected children for both cognitive and physical impairments to determine the frequency of long-term sequelae. Three of those studies [25–27] were not included in Table 1 because they only reported data on CMV-infected children.

Long-term sequelae in the symptomatic group were typically severe, and children were often affected by both HL and cognitive impairments, although the studies showed marked heterogeneity. Four studies in Table 2 [10,18,22,26] assessed

both general development and HL among a total of 19 children with symptomatic CMV infection. Eleven of the 19 children (57.9%) in these studies had long-term sequelae, including one child who subsequently died. The largest study was from Sweden [10] in which 4 of 11 (36.4%) children symptomatic at birth had long-term sequelae. In contrast, three studies that each followed only two or three symptomatic children [18,22,26], found that seven out of eight (87.5%) had long-term sequelae.

Four studies in Table 2 examined either HL only [28,29] or cognitive deficit only [16,23]. Fowler *et al.* [28] followed 53 surviving children with CID, of whom 19 (35.8%) had measurable HL. This finding is similar to that of Ahlfors *et al.* [10], who reported that 27.2% of children had HL. The reports by Griffiths *et al.* [16] and Starr *et al.* [23] followed a total of three children with CID, two of whom (66.7%) had cognitive deficits.

Mortality among children with CID was not specifically assessed in most reports. Fowler *et al.* [28] report that among a total of 407 children born with congenital CMV at a Birmingham, Alabama, hospital between 1980 and 1996, two were known to have died in the first few years of life and hence were not included in audiologic follow-up. If both deaths occurred among the children with CID, as appears to have been the case, the death rate in that cohort would be 3.6%.

As expected, the frequency of sequelae among children with asymptomatic infections is lower than that among symptomatic children. The 10 studies in Table 2 that followed CMV-infected children for hearing, cognitive and MDs included a total of 252 children who were asymptomatic at birth, 34 of whom (13.5%) developed long-term sequelae. The percentage of asymptomatic children with one or more sequela ranged from 0.0 to 23.5%, with a majority of studies reporting long-term sequelae among 8.5–17.9% of asymptomatic infants (Table 2). The sequelae were relatively less severe for the majority of the asymptomatic children; 23 of 34 asymptomatic children with sequelae (67.6%) were evaluated as having isolated HL without other impairment.

The two studies in Table 2 that evaluated HL alone reported this outcome among 47 of 394 (11.9%) children with asymptomatic infections. Among the 10 studies with comprehensive evaluations, 24 of 252 asymptomatic children (9.5%) were

**Table 1. Reported frequencies of infants with congenital CMV\* and the number of infected infants who had symptoms at birth**

First author/ Publ. year	> 50% Low SES	Maternal Seroprev**	Location/ time period	# Infants tested	# Infec. at birth	Infect. %	# Symp. at birth	Symp. %
Ahlfors <i>et al.</i> 1999 [10]		72%	Sweden, 1977–1986	16 474	76	0.5	14	18.4
Andersen <i>et al.</i> 1979 [11]		57%	Denmark 1974–1977	3060	12	0.4	3	25.0
Barbi <i>et al.</i> 1998 [12]		85%	Italy 1994–1995	1268	6	0.5	0	0.0
Boppana <i>et al.</i> 1999 [13]	X	80–85%	Alabama 1991–997	20 885	246	1.2	47	19.1
Casteels <i>et al.</i> 1999 [14]		na	Belgium 1996–1998	3075	15	0.5	3	20.0
Fowler <i>et al.</i> 1993 [15]	X	82–87%	Alabama 1980–1990	17 163	215	1.3	16	7.4
Griffiths <i>et al.</i> 1991 [16]		60%	London 1983–1985	2737	9	0.3	1	11.1
Kamada <i>et al.</i> 1983 [17]		94%	Japan 1980	2070	11	0.5	0	0.0
Melish and Hanshaw 1973 [18]	X	na	New York 1968–1970	1963	20	1.0	2	10.0
Montgomery <i>et al.</i> 1980 [19]	X	na	Texas 1972–1975	954	9	0.9	2	22.2
Numazaki and Fujikawa 2004 [20]		85% in 1988 68% in 2000	Japan 1977–2002	11 938	37	0.3	5	13.5
Peckham <i>et al.</i> 1983 [21]		56%	London 1979–1982	14 200	42	0.3	2	4.8
Saigal <i>et al.</i> 1982 [22]		44%	Canada 1973–1976	15 212	64	0.4	4	6.3
Starr <i>et al.</i> 1970 [23]	X	na	Ohio 1968	2147	26	1.2	2	7.7
Yow <i>et al.</i> 1988 [24]		52%	Texas 1981–1986	4840	22	0.5	2	9.1
			Total <i>n</i> = 15	117 986	810	0.7	103	12.7
			≥ 50% low SES <i>n</i> = 5	43 112	516	1.2	69	13.4
			Minus low SES <i>n</i> = 10	74 874	294	0.4	34	11.6

\*CMV infection was determined by culture of urine or saliva; sampling was unbiased.

\*\*Maternal seroprevalence estimates were based on the study subjects, a representative subset of subjects, or a comparable population as defined by the authors. Numazaki and Fujikawa [36] reported a substantial drop in maternal CMV seroprevalence in Japan from 1988 to 2000 due to improved socioeconomic conditions. na, data not available.

identified with HL. Among the four studies with follow-up of at least 3 years [10,20,22,25], a total of 14 of 131 children asymptomatic at birth (10.7%) were diagnosed with HL.

The two studies in Table 2 that examined only cognitive outcomes reported some degree of cognitive deficit among 2 of 31 (6.5%) children with asymptomatic infections. Among the 10 studies

Table 2. Frequency and nature of long-term sequelae associated with congenital CMV\*

First author Publ. year	Location/ time period	# Infec. at birth	Symp./ asympt. followed; duration	Evaluation: HL, CD, MD or All	Symp. at birth later sequel	Symp. w/ Sequel (%)	Asymp. at Birth later sequel	Asymp. w/ sequel (%)
Ahlfors <i>et al.</i> 1999 [10]	Sweden 1977–1986	76	11/49 4–7 yrs	All	2 HL + CD 1 HL, 1 CD	4/11 (36)	1 CD + MD 2 HL, 5 CD	8/49 (16.3)
Andersen <i>et al.</i> 1979 [11]	Denmark 1974–1977	12	0/12 2 years	All	None with symp.		1 CD 1 CD + MD	2/12 (16.7)
Barbi <i>et al.</i> 1998 [12]	Italy 1994–1995	6	0/5 2 years	All	None with symp.		0	0
Casteels <i>et al.</i> 1999 [14]	Belgium 1996–1998	15	0/12 1 yr	All	None with symp.		2 HL	2/12 (16.7)
Kumar <i>et al.</i> 1984 [25]	Ohio 1968–1974	17	0/17 4.5–10 yr	All	None with symp.		4 HL	4/17 (23.5)
Melish and Hanshaw 1973 [18]	New York 1968–1970	20	2/17 1.5–3 yrs	All	1 HL + MD 1 CD	2/2 (100)	0	0
Numazaki and Fujikawa 2004 [20]	Japan 1977–2002	37	0/21 7 yr	All	None with symp.		2 HL	2/21 (9.5)
Preece <i>et al.</i> 1984 [26]	London 1980–1983	50	3/47 6 mo–3 yr	All	2 CD + MD 1 HL	3/3 (100)	1 HL + CD 3 HL	4/47 (8.5)
Saigal <i>et al.</i> 1982 [22]	Canada 1973–1976	64	3/44 3–5 yr	All	1 HL 1 CD	2/3 (67)	6 HL 1 D	7/44 (15.9)
Williamson <i>et al.</i> 1990 [27]	Texas 1981–1988	na	na/28 8–12 mo	All	Not followed		4 HL 1 CD	5/28 (17.9)
					TOTAL	11/19 (57.9)		34/252 (13.5)
Fowler <i>et al.</i> 1999 [28]	Alabama 1980–1996	388	53/335 3 yr	HL only	19 HL	19/53 (36)	38 HL	38/335 (11.3)
Williamson <i>et al.</i> 1992 [29]	Texas 1983–1989	na	na/59 2–27 mo	HL only	Not followed		9 HL	9/59 (15.3)
Griffiths <i>et al.</i> 1991 [16]	London 1983–1985	9	1/7 3 yr	CD only	1 CD	1/1 (100)	1 CD	1/7 (14.3)
Starr <i>et al.</i> 1970 [23]	Ohio 1968	26	2/24 6–15 mo	CD only	1 CD 1 D	2/2 (100)	1 CD	1/24 (4.2)

\*CMV infection was determined by culture of urine or saliva; sampling was unbiased. Sequelae: HL, hearing loss; CD, cognitive deficit; MD, motor deficit; D, death; na, data not available.

that examined a range of outcomes, a total of 10 of 252 (4.0%) surviving children were reported to have cognitive deficits. However, not all of the studies appear to have been equally thorough in ascertaining cognitive impairment. In particular, six studies, with a total of 116 children in the asymptomatic group, did not report a single child with cognitive deficits. Among the remaining four studies [10,11,26,27], 10 of 136 (7.4%) children were reported to have cognitive impairment. The latter percentage is consistent with the 6.5% rate from the two studies that assessed cognitive deficits only [16,23]. Only one study [10] included cases

of cognitive impairment and conducted follow-up for HL more than 3 years after birth. That study reported a prevalence of 16.3% of long-term sequelae among the asymptomatic group.

## DISCUSSION

This review estimated the frequency and nature of sequelae attributable to congenital CMV in order to calculate more precise estimates of the probabilities of sequelae of congenital CMV infection. These probabilities, when combined with a new estimate of the birth prevalence of congenital CMV infection, allow evidence-based estimates

of the preventable burden of congenital CMV infections. Reliable estimates of the magnitude of the impact in terms of disease, disability and mortality are necessary to calculate cost estimates for treatment and prevention strategies for congenital CMV infections.

This review found that the overall prevalence of congenital CMV infection in industrialised countries is likely to be 0.6–0.7%. This is consistent with a recent meta-analysis that employed less restrictive inclusion criteria resulting in a wider dispersion of estimates, which reported an average birth prevalence of 0.65% [30]. This is more precise than the range of 0.2–2.5% often cited in the literature [1,12,14]. It is also lower than commonly cited prevalence for the United States of 1.0% that is based on studies with predominantly low-SES subjects. Given that low-SES women are often overrepresented in the literature and were overrepresented in this review, the prevalence of congenital CMV infection in the general population is likely to be lower than the point estimate of 0.7% presented here. The exact prevalence of CMV infection cannot be determined without screening a large, representative sample of newborns using a reliable method of detection.

We found that approximately one in eight (12.7%) infants with congenital CMV infection had symptoms at birth identified as CID. This estimate is within the range of 10–15% that is typically cited. This percentage did not differ appreciably by SES or birth prevalence.

Follow-up of CMV-infected children identified by unselected screening supports the general understanding that infants who are symptomatic at birth are much more likely to experience sequelae and that their sequelae are more disabling. The reported prevalence of permanent sequelae among children with CID ranges from 35–100%, but the highest percentages come from studies that each followed only two or three children and reporting small numbers might be subject to negative publication bias (Table 2). Two studies (Ahlfors and Fowler) tracked more than 10 children with symptomatic infections and had similar outcomes. Ahlfors *et al.* [10] conducted thorough physical evaluations during 4 to 7 years of follow-up and reported that 4 of 11 symptomatic children (36.3%) had permanent sequelae, including two children with both HL and cognitive impairment. Fowler *et al.* [28] conducted audiologic examina-

tions and reported that 19 of 53 (35.8%) 3-year-old children with CID had HL; this finding compares with the 27.2% reported by Ahlfors *et al.* [10]. Fowler *et al.* did not assess cognitive impairment. If the same percentage of children in the Fowler *et al.* study had cognitive impairment as in the Ahlfors study, the total percentage with sequelae would have been 45%. Furthermore, the 3-year follow-up by Fowler *et al.* resulted in the under-ascertainment of cases of HL; another study from the same institution reported that among children with CID who were diagnosed with HL by age 15, only 88% had been diagnosed by age 3 [31].

Combining the observed prevalence of long-term sequelae in the larger and possibly more accurate Ahlfors *et al.* [10] and Fowler *et al.* [28] studies (36–45%) with the point estimate of 57.9% from Table 2 that considered all studies, we consider 40–58% to be a reasonable estimate of the prevalence of long-term sequelae among surviving children with symptomatic CMV infections.

The prevalence of permanent sequelae from congenital CMV was much lower among children who were asymptomatic at birth. The primary type of sequela was isolated SNHL. This contrasts with children who had symptomatic infections, who tended to have multiple sequelae that included cognitive deficit/mental retardation. Breaking the numbers down by impairment, 11–12% of children with asymptomatic infections at birth were diagnosed with HL, and 6.5% were classified as having some type of cognitive or neurological impairment. Because children can have both HL and cognitive impairment, the two percentages cannot be added together. The one study that had relatively complete data on both HL and cognitive impairment reported that 16.3% of children with asymptomatic infections had one or both sequelae [10], which is in agreement with our overall finding of 13.5% prevalence of sequelae in the asymptomatic infection group (Table 2).

In the studies reviewed, data were insufficient to accurately estimate prevalence of visual impairment and mortality, two important outcomes of congenital CMV. Anderson *et al.* [32] reported that 58% of 113 symptomatic infants had visual impairments, and Coats *et al.* [33] reported that 22% of 42 symptomatic infants had visual impairments; both of these study populations, however, had an overrepresentation of

infants with severe sequelae. One study with a likely unbiased recruitment strategy [10] did not report any visual impairment among 60 infected infants. However, because the study findings made no reference to the outcome of visual exams performed on the children, it is not clear whether there was an absence of observed visual impairments or problems with the measurements or their interpretation.

The frequency of death among symptomatic infants is commonly reported to be 10–30%. A large cohort study from Alabama [3,28] reported a much lower death rate of approximately 4% among the symptomatic group, although it is possible that the true death rate was higher because of loss to follow-up among children who screened positive for CMV. The total rate of mortality among the Alabama cohort of children with congenital CMV detected through screening, including both symptomatic and asymptomatic infections, was 0.5% [28]. A large-scale screening study with complete follow-up would be needed to provide a more reliable estimate of the mortality rate in congenital CMV.

The strength of this review is that it reports findings from only studies that used universal screening, rather than studies that recruited from populations at high risk for congenital CMV. However, this review has two important limitations. First, the inclusion criteria used to eliminate unbiased populations resulted in a relatively small number of studies for review. One implication is that we are missing data on important outcomes. For example, as noted previously, very few studies reviewed included data about visual impairment, a known sequela of congenital CMV infection [32,34,35].

Second, the estimates for permanent sequelae among symptomatic children (40–58%) and asymptomatic children (13.5%) are almost certainly underestimate. Length of follow-up in many of the studies reviewed was 3 years or less. This length of time is insufficient to capture late-onset of HL [31] and results in under-ascertainment of long-term sequelae. Studies of 5–7 years follow-up are needed to gain more accurate estimates of long-term sequelae associated with congenital CMV infection.

It is important to note that, although long-term sequelae occur 3 to 4 times more often among infants with CID than among asymptomatic infants (40–58% vs. 13.5%), and sequelae among symptomatic children are often severe, more children with long-term sequelae from congenital CMV are asymptomatic at birth. In a given cohort of 1000 infants with congenital CMV, approximately 127 have CID. If the death rate among those children is 4%, there will be 5 deaths and 122 survivors with CID, 50–70 of whom will have long-term sequelae. Of the 873 with asymptomatic infections, 118 are projected to have long-term sequelae, constituting approximately two thirds of the total children with sequelae (Table 3).

This review supports previous assessments of the prevalence of permanent sequelae among children with asymptomatic sequelae but differs from previous estimates of long-term sequelae among children with symptomatic infections. In particular, the U.S. Institute of Medicine (2000) estimated that 10% of children with symptomatic infections die and that 100% of survivors experience sequelae, including 90% with severe MR, and the rest with mild MR, vision loss, HL or two or more limitations. In contrast, the report assumed that only

**Table 3. Estimates of long-term sequelae in infants with congenital CMV**

Type of infection	1000 infants with congenital CMV	
	Symptomatic	Asymptomatic
Number of Infants	127 (12.7%)	873 (87.3%)
Deaths	5	0
Survivors	122	873
Number with Permanent sequelae	50–70 (40–58%)	118 (13.5%)
Conclusion	17–20% of the 1000 infected infants will have permanent sequelae; 1/3 from the symptomatic group and 2/3 from the asymptomatic group	

15% of asymptomatic infants would have some deficit, mostly HL. Although the latter estimate is consistent with the evidence reviewed here, the former estimate is not. In particular, one large study with follow-up to age 7 years has assessed MR; Ahlfors *et al.* [10] diagnosed MR in 2 of 11 (18%) children with CID, only 1 of whom had severe MR (9%).

## CONCLUSION

Although several previous studies have estimated the burden of congenital CMV, this report presents probabilities of CMV-associated infant mortality and neurological sequelae based on studies with minimal population bias. Overall, we project that 0.5% of children with congenital CMV die and that 17–20% of surviving children have one or more long-term sequelae. These estimates, which show that congenital CMV infection is associated with a substantial long-term burden and an elevated risk of infant mortality, can be used in the development and evaluation of prevention strategies for this important risk factor for death and developmental disability. To better understand the true burden of congenital CMV, future studies should focus on evaluation of visual impairment and extend follow-up of CMV-infected children, to capture sequelae with delayed onset.

## ACKNOWLEDGMENTS

We would like to thank members of the CDC congenital CMV working group for useful input and encouragement regarding this review, especially Michael Cannon, Owen Devine, Aileen Kenneson, Esther Sumartojo, Scott Schmid and the European Congenital Cytomegalovirus Initiative for inviting this review.

## REFERENCES

- Fowler KB, Stagno S, Pass RF, Britt WJ, Boll TJ, Alford CA. The outcome of congenital cytomegalovirus infection in relation to maternal antibody status. *N Engl J Med* 1992; **326**: 663–667.
- Pass RF, Fowler KB, Boppana SB, Britt WJ, Stagno S. Congenital cytomegalovirus infection following first trimester maternal infection: symptoms at birth and outcome. *J Clin Virol* 2006; **35**: 216–220.
- Ross SA, Boppana SB. Congenital cytomegalovirus infection: outcome and diagnosis. *Semin Pediatr Infect Dis* 2005; **16**: 44–49.
- U.S. Institute of Medicine. Committee to Study Priorities for Vaccine Development. *Vaccines for the 21st Century: A Tool for Decisionmaking*. National Academy Press: Washington, DC, 2000.
- Cannon MJ, Davis KF. Washing our hands of the congenital cytomegalovirus disease epidemic. *BMC Public Health* 2005; **5**: 70.
- Ross SA, Fowler KB, Ashrith G, *et al.* Hearing loss in children with congenital cytomegalovirus infection born to mothers with preexisting immunity. *J Pediatr* 2006; **148**: 332–336.
- Fowler KB, Boppana SB. Congenital cytomegalovirus (CMV) infection and hearing deficit. *J Clin Virol* 2006; **35**: 226–231.
- Pass RF. Cytomegalovirus infection. *Pediatr Rev* 2002; **23**: 163–170.
- Stagno S, Pass RF, Dworsky ME, *et al.* Congenital cytomegalovirus infection. *New Engl J Med* 1982; **306**: 945–949.
- Ahlfors K, Ivarsson S-A, Harris S. Report on a long-term study of maternal and congenital cytomegalovirus infection in Sweden. Review of prospective studies available in the literature. *Scand J Infect Dis* 1999; **31**: 443–457.
- Anderson HK, Brostrom K, Brogard Hansen K, *et al.* A prospective study on the incidence and significance of congenital cytomegalovirus infection. *Acta Paediatr Scand* 1979; **68**: 329–336.
- Barbi M, Binda S, Primache V, Clerici D. (For the NEOCMV Group). Congenital cytomegalovirus in a northern Italian region. *Europ J Epidemiol* 1998; **14**: 791–796.
- Boppana SB, Fowler KB, Britt WJ, *et al.* Symptomatic congenital cytomegalovirus infection in infants born to mothers with preexisting immunity to cytomegalovirus. *Pediatrics* 1999; **104**: 55–60.
- Casteels A, Naessens A, Gordts F, *et al.* Neonatal screening for congenital cytomegalovirus infections. *J Perinat Med* 1999; **27**: 116–121.
- Fowler KB, Stagno S, Pass RF. Maternal age and congenital cytomegalovirus infection: screening of two diverse newborn populations, 1980–1990. *JID* 1993; **168**: 552–556.
- Griffiths PD, Baboonian C, Rutter D, Peckham C. Congenital and maternal cytomegalovirus infections in a London population. *BJOG* 1991; **98**: 135–140.
- Kamada M, Komori A, Chiba S, Nakao T. A prospective study of congenital cytomegalovirus infection in Japan. *Scand J Infect Dis* 1983; **15**: 227–232.
- Melish ME, Hanshaw JB. Congenital cytomegalovirus infection. *Am J Dis Child* 1973; **126**: 190–194.
- Montgomery JR, Mason EO Jr, Williamson AP, *et al.* Prospective study of congenital cytomegalovirus infection. *South Med J* 1980; **73**(5): 590–593.

20. Numazaki K, Fujikawa T. Chronological changes of incidence and prognosis of children with asymptomatic congenital cytomegalovirus infection in Sapporo, Japan. *BMC Infect Dis* 2004; **4**: 22.
21. Peckham CS, Coleman JC, Hurley R, et al. Cytomegalovirus infection in pregnancy: preliminary findings from a prospective study. *Lancet* 1983; **1**(8338): 1352–1355.
22. Saigal S, Lunyk O, Bryce Lark RP, Chernesky MA. The outcome in children with congenital cytomegalovirus infection. *Am J Dis Child* 1982; **136**: 896–901.
23. Starr JG, Bart RD Jr, Gold E. Inapparent congenital cytomegalovirus infection. *N Engl J Med* 1970; **282**: 1075–1078.
24. Yow MD, Williamson DW, Leeds LJ, et al. Epidemiologic characteristics of cytomegalovirus infection in mothers and their infants. *J Obstet Gynecol* 1988; **158**: 1189–1195.
25. Kumar ML, George AN, Jacobs IB, et al. Congenital and postnatally acquired cytomegalovirus infections: long-term follow-up. *J Pediatr* 1984; **104**: 674–679.
26. Preece PM, Pearl KN, Peckham CS. Congenital cytomegalovirus infection. *Arch Dis Child* 1984; **59**: 1120–1126.
27. Williamson WD, Percy AK, Yow MD, et al. Asymptomatic congenital cytomegalovirus infection. *Am J Dis Child* 1990; **144**: 1365–1368.
28. Fowler KB, Dahle AJ, Boppana SB, Pass RF. Newborn hearing screening: will children with hearing loss caused by congenital cytomegalovirus infection be missed? *J Pediatr* 1999; **135**: 60–64.
29. Williamson WD, Demmler GJ, Percy AK, Catlin FI. Progressive hearing loss in infants with asymptomatic congenital cytomegalovirus infection. *Pediatrics* 1992; **90**: 862–866.
30. Kenneson A, Cannon MJ. Review and meta-analysis of the epidemiology of congenital cytomegalovirus (CMV) infection. *Rev Med Virol* (in press).
31. Dahle AJ, Fowler KB, Wright JD, Boppana SB, Britt WJ, Pass RF. Longitudinal investigation of hearing disorders in children with congenital cytomegalovirus. *J Am Acad Audiol* 2000; **11**: 283–290.
32. Anderson KS, Amos CS, Boppana S, Pass R. Ocular abnormalities in congenital cytomegalovirus infection. *J Am Optom Assoc* 1996; **67**: 273–278.
33. Coats DK, Demmler GJ, Paysse EA, Du LT, Libby C. Ophthalmologic findings in children with congenital cytomegalovirus infection. *J Amer Assoc Ped Ophthalmol Strab* 2000; **4**: 110–116.
34. Andriessse GI, Weersink AJ, de Boer J. Visual impairment and deafness in young children: consider the diagnosis of congenital infection with cytomegalovirus, even years after birth. *Arch Ophthalmol* 2006; **124**: 743.
35. Pass RF, Stagno S, Myers GJ, Alford CA. Outcome of symptomatic congenital infection: results of long-term longitudinal follow-up. *Pediatrics* 1980; **66**: 758–762.
36. Numazaki K, Fujikawa T. Prevalence of serum antibodies to cytomegalovirus in pregnant women in Sapporo, Japan. *Int J Infect Dis* 2002; **6**: 147–148.