Epidemiological impact and disease burden of congenital cytomegalovirus infection in Europe

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In Europe, congenital cytomegalovirus (CMV) infection is the leading cause of neurological disabilities in children, causing severe sequelae such as sensorineural hearing loss, neurodevelopmental delay or blindness. The infection causes high disease burden and costs. Nevertheless, there is little awareness of CMV among medical officials and the general public. Although the individual risk of congenital CMV infection is greatest from a primary infection of the mother during pregnancy, maternal non-primary infections also account for a substantial disease burden associated with congenital CMV. Screening programmes for pregnant women and newborns are widely discussed, but have not been implemented by any public health authority in Europe so far. This article gives an overview about a variety of European and other relevant studies regarding CMV seroprevalence, congenital CMV infection and disease as well as screening strategies and preventive approaches.

Primary and non-primary maternal cytomegalovirus infection

Cytomegalovirus (CMV) is a beta-herpesvirus member of the family *Herpesviridae*. The virus spreads via excretion in nearly all body fluids, such as urine, saliva, vaginal secretions, semen or breast milk. Especially infants and toddlers shed high amounts of virus for months or even years and represent a substantial risk for transmitting the virus to pregnant women by saliva or urine [1]. Sexual transmission of the virus is a common way of infection in adults.

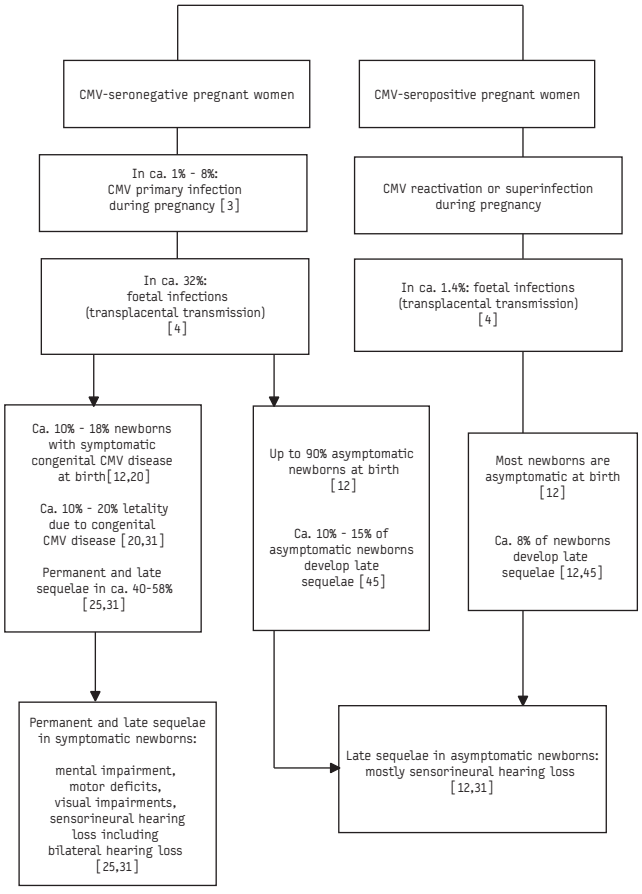
Because the infection in adult immunocompetent individuals is mostly mild or asymptomatic [2], primary CMV infection is rarely diagnosed during pregnancy. The risk of seronegative women to contract primary CMV infection during pregnancy has been reported to be between 1% and 8% [3,4] (see Figure). A force of CMV infection of ca. 0.03 per seronegative women per annum has been found in a British study by Griffiths *et al.* [5].

Viral transmission at the uterine-placental interface can result in congenital CMV infection [6,7] of the foetus or embryo, which can cause congenital CMV disease and permanent sequelae. The risk of CMV disease from intrauterine infection is highest in primary maternal infection. However, in non-primary maternal infections, which results from reactivation of latent CMV genomes or superinfection with new virus strains [8], permanent neurological disabilities or even death of the foetus have been observed [9-11]. In non-primary infection the foetus is thought to be partially protected by maternal immunity and transplacental transmission of immune IgG [12,13].

Multiple studies have determined the rate of vertical transmission in primary and non-primary maternal CMV infection and the development of subsequent CMV disease of the child [9,14-16]. The results of the studies are hampered by difficulties to distinguish between primary and non-primary maternal CMV infection. A metaanalysis by Kenneson *et al.* revealed a transmission rate of 32% in primary maternal infection and a transmission rate of

Figure

Frequency of maternal and foetal cytomegalovirus infection and morbidity of infected children



CMV: cytomegalovirus

1.4% in recurrent maternal infection [4]. The Figure shows the frequency of maternal and foetal CMV infection and morbidity of infected children.

Foetal CMV infection and the progression to congenital disease in children

The gold-standard method for prenatal diagnosis of foetal CMV infection is the detection of CMV in amniotic fluid by virus culture or PCR, which is as accurate as and even more sensitive than viral culture [17,18]. False negative results can occur when the test is performed too early after foetal infection, before the foetus sheds virus via the urine [17]. According to the European Congenital Cytomegalovirus Initiative (ECCI), the sensitivity of PCR used to detect viral DNA is very good if amniotic fluid is collected at least six weeks after seroconversion and around the 22nd week of pregnancy [3].

Diagnosis of congenital CMV infection does not necessarily predict later development of congenital CMV disease [19]. Systematic ultrasound is not sensitive enough to detect signs of foetal CMV disease, and most CMV complications can be observed only in the last trimester of pregnancy [3], when interruption of pregnancy is not legally possible in most European countries. Congenital CMV infection during the first trimester is more likely to cause CMV disease, since organogenesis takes place in this period [20,21].

CMV-damage in the foetus may cause spontaneous abortion or prematurity. Cases of congenital CMV syndrome present with an involvement of multiple organs including splenomegaly, hepatomegaly, prolonged neonatal jaundice, pneumonitis, thrombocytopenia, growth retardation, microcephaly and cerebral calcifications. Organ damage is thought to be caused by CMV replication in target organs like the central nervous system of the foetus and indirectly by CMV-induced placental dysfunction [19]. Permanent impairments mostly affect the central nervous system and include progressive hearing loss, spastic tetraplegia, mental retardation and visual impairments [21]. Nearly 14% of children with congenital CMV infection suffer from sensorineural hearing loss (SNHL), and 3-5% of children with congenital CMV infection suffer from bilateral moderate to profound SNHL [22]. About 15-20% of children with moderate to profound permanent bilateral hearing loss were associated with CMV infection, according to a publication by Grosse et al. [22].

The majority of congenitally infected children appear asymptomatic at birth, but neurological sequelae may develop after months or even years [23]. Fowler *et al.* report that after a mean follow-up of 4.7 years, 25% of children of mothers with primary CMV infection during pregnancy and 8% of children of mothers with recurrent CMV infection exhibit one ore more sequelae [12]. Especially hearing loss may often not being present in the period immediately after birth [24,25]. In a longitudinal study by Dahle et al., 7.4% of 651 children with asymptomatic CMV infection developed SNHL, compared to 40.7% of 85 children born with symptomatic CMV infection [25]. The development of late sequelae accounts for substantial disease burden associated with congenital CMV infection. According to Caroppo *et al.* the costs for prosthesis per child with SNHL that accrued for the Italian public health system in 2005 add up to 260,000 Euro [26].

Although there is evidence for mental retardation in symptomatic children congenitally infected with CMV, the intellectual development of the much larger group of asymptomatic CMV-infected children does not seem to be impaired [27]. A Swedish study failed to detect evidence for intellectual impairment at the age of seven years in a group of children with congenital CMV infection who had shown normal neurological development at the age of 12 months [27].

Seroprevalence of CMV and prevalence of CMV infection at birth in Europe

Prevalence in the mother

The prevalence of CMV infection at birth is related to the CMV seroprevalence in women of childbearing age, with a reported increase of 10% in maternal seroprevalence correspondending to a 0.26% increase in CMV birth prevalence [4]. Multiple studies have shown that the overall CMV seroprevalence in women of childbearing age depends on age, parity, ethnicity and social status, and differs between countries and regions [28,29,30]. A low socioeconomic status is a risk factor for CMV seroprevalence and congenital CMV infection [31,32]. The Table lists studies from several European countries, indicating factors that were found to influence CMV seroprevalence.

A Finnish study showed that the CMV seroprevalence was higher in Helsinki compared to a rural area in the southwest of the country (70.7% versus 56.3%, respectively) [33]. Often, the seroprevalence in immigrants differed from that of the native population: In a study in Ireland, a low seroprevalence of 30.4% was detected in 670 Irish woman, whereas 359 non-Irish woman living in Ireland showed a CMV seroprevalence of 89.7% [36]. The overall CMV seropositivity can also change over time. In Spain, 66.3% of 2,136 women were found to be seropositive for CMV in 1993, compared to 57.4 % of 2,198 women in 1999 [37,38]. Between 1993 and 1999, the decrease in CMV seroprevalence has been significant in the age group of 31-41 year-olds in this study [37,38]. In pregnant women in Turkey, very high seroprevalences of up to 94.9 % were reported [40,41]. In most European countries, a high socioeconomic status seemed to correlate with low CMV seroprevalence. The IgG antibody prevalence against CMV among pregnant women in Germany was highest among welfare recipients (93%), followed by those covered by statutory health insurance (56,2%), but was only 31,8% in the group of women with private health insurance [35].

Prevalence in the newborn

The prevalence of CMV infection in the newborn at birth depends on diagnostic criteria and the laboratory detection methods used. Some publications define CMV infection on the basis of a positive virus culture in urine or saliva [9,30,42]. In other studies, positive results of PCR assays are used for diagnosis of CMV infection at birth [16]. The sensitivity of CMV-IgM testing in the newborn as basis for birth prevalence estimates is about 25% and can not be recommended [4]. Diagnosis of CMV infection should be performed within two weeks after birth, since later diagnosis does not allow differentiation between congenital and sub- or postpartal CMV infection.

In a Dutch study, CMV infection was diagnosed by positive CMV PCR from throat samples or by CMV culture from urine samples. 7,793 newborns were tested, and the prevalence of CMV infection at birth was 0.9 per 1,000 newborns. None of seven congenitally infected children in this study showed any sequelae in a follow-up

period of 24 months [30]. However, a differentiation between primary and non-primary infection in the mothers of congenitally infected children was only available for two mothers, who suffered from a recurrent CMV infection during pregnancy. The overall CMV seroprevalence of mothers in this study was 41% [30].

A large Swedish study revealed 0.5% congenitally CMV-infected newborns by virus isolation testing. A total of 16,474 newborns were tested, and 29% of the infected children showed transient neonatal symptoms, whereas 18% of the infected children presented with neurological symptoms at the age of seven years [9].

In an Italian study, isolation of CMV from saliva led to diagnosis of congenital CMV infection [42]. Newborns were subdivided in two groups, a group of 185 children with suspected congenital CMV infection and a control group of 1,286 asymptomatic children. In the control group, overall prevalence of CMV in saliva was 0.47%, compared to 5% in the group of children with suspected CMV infection. Two of 15 neonates with congenital CMV infection developed sequelae in the two-year follow-up period and one further neonate died [42]. A meta-analysis by Kenneson et al. including 27 studies reported a birth prevalence of congenital CMV of 0.64% (95% confidence interval (CI): 0.60-0.69%) [4]. A further metaanalysis by Dollard *et al*. revealed a birth prevalence of 0.7% and a percentage of 12.7% symptomatic children at birth [31].

In an early African study from 1978, Schopfer *et al*. reported that 1.4 % of 2,032 newborns in Côte d'Ivoire had CMV viruria, when screened by viral culture [14]. Two studies recently performed in Gambia (West Africa), which defined CMV infection at birth on the basis of a sensitive nested PCR detection method and screening of urine samples within two weeks after birth, found prevalences of 5.4% and 3.9% [16,43]. Congenital CMV infection was associated with active placental malaria infection [16]. The prevalences of congenital CMV were higher in these studies compared to birth prevalences in industrialised countries [16,43]. Although these African studies may not be directly relevant for European societies in general, it is of interest that in populations with a presumably very high seroprevalence of CMV, about 1.4-5% of infants are shedding CMV at birth due to non-primary maternal infection. A considerable proportion of these children may develop late sequelae and thus contribute to the disease burden of congenital CMV infection. It is therefore important to consider vertical transmission of CMV due to non-primary maternal infection, and similar infection rates may be possible in immigrant communities living in Europe who originated in high-prevalence countries.

Prevention and treatment strategies against congenital CMV infection

Prevention strategies are classified as primary, secondary and tertiary prevention. Primary prevention strategies try to avoid an infection and are mostly accomplished by precautions against exposition to the virus, i.e. hygiene measures and change of behaviour. Secondary prevention strategies allow identifying infected patients at an early stage, with the aim of stopping progression of infection and disease. In the case of symptomatic disease, tertiary

Table

Seroprevalence of cytomegalovirus infection in different European countries and influential factors

Country and region	Study	Seroprevalence	Number of study participants	Factors influencing seroprevalence
Finland, Helsinki	[29]	70.7%	1,088 pregnant women	Social environment, low impact of age
Finland, southwestern (rural) Finland	[33]	56.3%	558 parturient women	Parity
France	[34]	51.5%	1,018 pregnant women	Age, parity, place of birth (seroprevalence increasing from north to south)
Germany	[2]	64.4%	9,870 men and women (aged 1 to > 60 years)	Age
Germany	[35]	43.3% in pregnant women with testing initiated by gynaecologist; 47.5% in randomly selected pregnant women	11,572 pregnant women with testing initiated by gynaecologist; 1,033 randomly selected pregnant women	-
Ireland	[36]	30.4% in Irish women	670 Irish woman	Immigration
		89.7% in non-Irish women	359 non-Irish women	
The Netherlands	[30]	41%	7,524 pregnant women (aged 16-47 years)	Ethnicity, socio-economic status, metropolitan area (connected to ethnicity)
Spain	[37]	1993: 66.3%	1993: 2,136 women	Age
		1999: 57.4%	1999: 2,198 women (aged two to 60 years)	
Spain	[38]	1993-1994: 62.8%	2,030 men and women (aged two to 60 years)	Age
Sweden, southern Stockholm	[39]	72 %	1000 pregnant women	-
Turkey, South	[40]	94.9%	1,652 pregnant women	-
Turkey, West	[41]	96.4%	1,972 pregnant women	-
United Kingdom, London	[28]	45.9% in white women	20,000 women	Ethnic group, parity, age, social class
		88.2% in Asian women		
		77.2% in black women		

prevention strategies try to prevent the development of severe sequelae after infection. Prenatal primary and secondary screening strategies as well as postnatal secondary and tertiary screening strategies are widely discussed for congenital CMV disease, but have not yet been implemented by any European country [44,45]. The implementation of screening programmes is hampered by obstacles such as lack of awareness, financial costs and possible deficits in the availability of detection methods.

Prenatal prevention

As a strategy for primary prevention, all pregnant women should be provided with information about the risk of CMV infection and the possible consequences an infection can have for the child. According to a study in the United States (US), not many women are well informed about the risk of CMV infection and congenital CMV disease. Of 643 women surveyed, only 22% had heard of congenital CMV and among a list of common causes of birth defects, women were least aware of congenital CMV [46]. In a national mail survey of the US population, only 14% of female respondents had heard of CMV [47]. Pregnant women, especially those who work with children, should be educated about behaviours that are associated with a high risk of CMV transmission [48].

Close contact with young children is a particular risk factor for CMV transmission, because infected children shed high concentrations of the virus over a long period of time in urine and salivary secretions. In a recent molecular epidemiological study, children were identified as the source of infection for the majority of pregnant women with primary CMV infection [1]. Preventive hygienic measures such as handwashing and avoiding direct contact with potentially contaminated body fluids, are likely to be effective to prevent CMV seroconversion in pregnant women when dealing with infants or toddlers [49]. Nevertheless, unambiguous results from intervention studies showing reduced rates of congenital infections are still lacking.

Another important route of CMV infection in adults is sexual transmission of the virus. A recent onset of sexual activity has been identified as an independent risk factor for congenital CMV infection in the offspring of young women [50]. However, precise data on the relative risk of CMV transmission during pregnancy by a serodiscordant partner are not yet available.

A safe and effective CMV vaccine for seronegative women is not available so far and remains a major public health priority in countries with a high proportion of seronegative women of childbearing age [51,52].

Prenatal screening

Different secondary prenatal screening strategies exist that rely on early detection of primary CMV infection in pregnant women. Most prenatal strategies are based on serological testing during pregnancy. Primary CMV infection may not be diagnosed on clinical grounds, since symptoms such as fever or flu-like symptoms are often mild or misinterpreted, which makes it important to do serological tests for definitive diagnosis. Evidence for primary infection is based on seroconversion of the mother during pregnancy and the detection of low avidity anti-CMV-IgG antibodies which indicate a recent primary immune response.

In a study in Belgium, Naessens *et al.* used a serologic strategy based on testing for CMV-specific antibodies during the first prenatal visit and at birth. This approach identified 82% of newborns at risk for congenital infection and neurosensory sequelae [53]. Another screening strategy includes testing of maternal CMV antibodies at the beginning of pregnancy and at 20-22 weeks gestation to demonstrate seroconversion in pregnant women with primary infection. Screening during the first trimester allowes to determine the approximate date of primary infection by using CMV-IgG aviditiy tests [3].

In a pilot study undertaken in several Italian regions, routine screening used CMV avidity testing following positive detection of CMV-IgM to detect primary CMV infections. A low avidity of CMV-IgG antibodies suggested a recently acquired primary CMV infection [54]. Nevertheless, positive CMV-IgG testing and the presence of high avidity IgG antibodies do not exclude the possibility of congenital CMV infection of the unborn, since non-primary infection during pregnancy and CMV transmission to the foetus can occur. The serologic screening models may therefore not be appropriate for all pregnant women, especially in populations with high seroprevalence for CMV as seen in some European countries.

Prenatal management and treatment

The management of the pregnancy in cases of primary CMV infection is a matter of debate [23]. Suspected foetal CMV infection most often results in amniocentesis, an invasive test that causes spontaneous miscarriages in about 1% of the cases [44]. The danger of amniocentesis for the foetus needs to be taken into consideration when planning strategies for prenatal diagnosis [44]. When a foetal CMV infection is diagnosed, a decision for elective termination of pregnancy is possible, but difficult because a majority of infected foetuses remain unaffected, i.e. asymptomatic after birth [19]. Diagnosis of CMV infection in the unborn will severely worry most women, and obstetricians might not be able to refuse the request of pregnancy terminations due to the inability of excluding all possible severe sequelae [3].

At present, there is no recommended treatment for pregnant women with CMV infection. The effect of passive immunisation on prevention of congenital CMV infection in clinical trials has been investigated by Nigro *et al.* [55,56]. In a non-randomised prospective study, pregnant women with primary CMV infection received a preparation of human hyperimmune IgG against CMV (Cytotect®). Cytotect® infusion was reported to be associated with a significantly lower risk of congenital CMV infection and disease at birth [55]. These findings remain controversial as the study was lacking a strict randomised protocol [57,58]. The site of action of CMV hyperimmunoglobulin is presumably the placenta, as manifestations of congenital CMV at birth are probably caused in part by virus replication in placental tissue, leading to placental insufficiency [6,7,59].

Nigro et al. further reported a regression of foetal CMV-associated cerebral abnormalities following therapy with Cytotect® in individual cases [56]. The sensorial, mental and motor development of these children was normal when evaluated at the age of three to seven years [56]. However, a publication bias favouring those cases in which hyperimmunoglobuline treatment had a protective effect cannot be excluded. Independent controlled studies are needed to evaluate the safety, effectiveness and cost-effectiveness of passive immunisation in women with primary CMV infection during pregnancy. Possible side effects of CMV immune globulin are mainly anaphylactic reactions [51].

Postnatal screening

Screening of all newborns for CMV infection is a postnatal tertiary screening approach. Universal hearing screening at birth by use of otoacoustic emission (OAE) is offered in most European countries and detects symptomatic hearing impairment at birth. However, more than two thirds of cases of hearing loss among children congenitally infected with CMV develop only months or years after birth and may therefore be missed by a hearing screening at birth [3,24]. Screening of all newborns for CMV shedding in the urine and monitoring of all congenitally CMV infected newborns in long-term audiologic follow-ups could improve the identification of children with progressive hearing loss which can become evident as late as at the age of five years or even later [24,60]. Early diagnosis and intervention such as speech therapy, sound amplification or cochlear implants are essential to improve the disease outcome in children with hearing loss. Newborns infected with CMV could also benefit from ophthalmological assessment and neuroimaging for documentation of central nervous system (CNS) disease in the neonatal period [48]. Postnatal screening strategies would allow the identification of risk factors for the development of severe sequelae and an assessment of the disease burden of congenital CMV disease.

The gold-standard to detect congenital CMV infection at birth is viral culture or PCR within the first two weeks of life from urine or saliva. Barbi *et al.* have implemented a nested-PCR test from neonatal dried blood spots on Guthrie cards as a convenient possibility for screening [42,61]. Most importantly, only this approach allows diagnosis of congenital CMV infection retrospectively. For this purpose, storage of Guthrie cards for a minimum of five years must be assured.

Postnatal treatment

Ganciclovir treatment of symptomatic newborns has been evaluated in several studies [62-65]. Kimberlin *et al.* investigated in a randomised controlled study the effect of a six-week therapy with intravenous ganciclovir in under 30 days-old neonates with symptomatic CMV disease involving the CNS [65]. At a follow-up hearing examination at the age of six months, 84% of the babies treated with ganciclovir had improved their hearing or maintained normal hearing between study entry and the age of six months, compared to 59% of controls. At the age of one year, the hearing had deteriorated in 21% of the treated children between study entry and the age of one year, compared to 68% in the control group [65]. According to Kimberlin *et al.* Ganciclovir therapy begun in the neonatal period in children with symptomatic CMV infection involving the CNS prevents hearing deterioration in the first six months of life and may prevent hearing deterioration in the first year of life [65]. Ganciclovir is toxic to the bone marrow, and two thirds of the treated infants in the study by Kimberlin *et al.* suffered from side effects such as significant neutropenia [65]. Recent studies in neonates with symptomatic congenital CMV infection reported that comparable plasma concentrations can be reached by oral administration of valganciclovir and intravenous administration of ganciclovir [66,67]. ECCI currently recommends the use of 6mg/kg intravenous ganciclovir twice daily for six weeks in babies born with CNS involvement and proven congenital CMV infection.

Disease burden and public health aspects

Based on the available data, congenital CMV infection is of major public health significance. Criteria for the prioritisation of infectious diseases in public health have been proposed, such as burden of disease, epidemiological dynamics, information need and health gain opportunity [68]. Despite the fact that considerable knowledge gaps still exist to date, CMV has been added to a list of infectious pathogens selected for further evaluation of prioritisation [68], particularly in the context of congenital disease.

CMV infection is the leading non-genetic cause of hearing impairment in children. In France, it has been estimated that a number of 480 infants per year experience severe sequelae and a number of approximately 675 infants per year present with hearing loss due to congenital CMV infection [44]. Around 8,000 children with neurological sequelae related to congenital CMV infection per year have been reported in the US [69].

The disease burden of congenital CMV infection is high and similar to that for congenital rubella before the introduction of rubella vaccination [52]. Since congenital CMV affects the very young, it results in long-term morbidity. In the 1990s, the estimated costs associated with CMV disease for the US health care system amounted to at least 1.86 billion US dollars annually, with more than 300,000 US dollars per child [52]. To assess the socio-economic costs of congenital CMV infection and its impact expressed as quality-adjusted life-years in Europe, complete epidemiological knowledge of the prevalence of this disease is mandatory. Further research on preventive measures, therapeutic options and screening methods for congenital CMV infection and subsequent health impairment are worthwhile. The availability of evidence-based preventive and therapeutic options should predetermine the implementation of general screening programmes for congenital CMV infection in European countries.

Given the low awareness of the infection in the general public, the need for information on congenital CMV infection is great. Up-to-date information about congenital CMV infection for both healthcare professionals and the public are provided by ECCI. The ECCI provides recommendations by international and European virologists, epidemiologists, immunologists, obstetricians and paediatricians whose aim is to promote awareness of congenital CMV and support research initiatives into this important infection.

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