

REVIEW



# Implementing neonatal screening for congenital cytomegalovirus: addressing the deafness of policy makers

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## SUMMARY

Congenital cytomegalovirus (CMV) infection is an important public health problem with approximately 7 in 1,000 newborns infected and consequently at risk for hearing impairment. Newborn hearing screening will fail to detect this hearing impairment in approximately half of the cases because late onset hearing loss is frequent. Hearing impairment has profound impact on cognitive and social development of children and their families, determining most of the disease burden of congenital CMV infection. The potential value of newborn screening for congenital CMV is increasingly discussed. To date, many experts acknowledge the benefit of antiviral treatment in the prevention of hearing deterioration in newborns with neurological symptoms, and the benefit of early identification of late-onset hearing impairment by means of extensive audiological follow up of infected infants. These opinions imply that the potential of newborn screening for CMV would lie in the identification of the large proportion of asymptomatic congenitally infected newborns at risk for developing late-onset hearing loss. Experience with postnatal antiviral treatment of symptomatic newborns is encouraging, but has not been studied in asymptomatic congenitally infected newborns. A large-scale study on the safety and effectiveness of combined screening and antiviral therapy for congenital CMV infection is the necessary next step to take and should not be delayed. Copyright © 2011 John Wiley & Sons, Ltd.

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## INTRODUCTION

Despite the appeals for preventive measures for congenital cytomegalovirus (CMV) infection by Yow and Demmler in 1992 "Congenital CMV disease—20 years is long enough" [1] and the statement by Adler that, in 2005, "there is considerable rationale for implementing neonatal screening now" [2], newborn screening for congenital CMV has only recently begun to be explored. Indeed, in the last year, several original articles, editorials and reviews have been published on this subject [3–11]. In a recent review,

Dollard *et al.* [8] showed that, after many years of research, congenital CMV infection now satisfies most screening criteria of Wilson and Jungner [12]. There is growing support [3,6,8,9,11] for two primary conceptions: the benefit of prevention of hearing deterioration in symptomatic newborns by means of antiviral treatment, and the benefit of early identification of late-onset hearing impairment by means of extensive audiological follow-up in congenitally infected infants. So now, after again almost 20 years, the stage appears to be set for neonatal screening.

## THE WILSON AND JUNGNER CRITERIA AND NEWBORN SCREENING ON CONGENITAL CMV

The Wilson and Jungner [12] criteria for newborn screening include the requirements that the disease has to be an important public health problem with a well understood history, that an early diagnosis

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### Abbreviations used:

DBS, dried blood spots; EU-27, 27 countries of the European Union; SNHL, sensorineural hearing loss.

can be made with a suitable screening test, and that the benefits outweigh the risks and costs of early intervention. The overall birth prevalence of congenital CMV is approximately 0.7%, and an estimated 18% of the congenitally infected newborns will develop permanent neurological sequelae [13–16]. Hence, congenital CMV is responsible for affecting approximately 126 in 100,000 newborns causing permanent neurologic sequelae, most prominently sensorineural hearing loss (SNHL), but also neurodevelopmental disabilities. In the 27 countries of the European Union (EU-27), every year 37,800 congenital CMV-infected babies are born, of which 6807 will eventually suffer from permanent sequelae (Figure 1). Among children with bilateral profound SNHL, the hearing disability is attributable to congenital CMV infection in one in five patients, making CMV the leading cause of non-genetic congenital hearing impairment [14,17]. Due to the frequently occurring late-onset character of the hearing loss caused by congenital CMV, approximately half of the patients will pass the newborn hearing screening [18].

Compared to several other diseases for which newborn screening has already been implemented, the prevalence of congenital CMV infections is

notably high (Table 1). For example, sequelae caused by congenital CMV are more than 100 times more prevalent than homocystinuria, a partially untreatable disorder for which postnatal screening is standard care in most developed countries nowadays [19].

One of the Wilson and Jungner criteria for newborn screening concerns the availability of an acceptable screening test, suitable for diagnosis in an early stage of the disease. Newborn screening for congenital CMV infection would indeed identify newborns at risk for developing late-onset hearing loss at an early stage. Dollard *et al.* [8] have reviewed several laboratory aspects of newborn screening for congenital CMV. In view of the existing routes of national metabolic screening programmes, dried blood spots (DBS) would be the most practical specimen of choice. CMV DNA detection in DBS is technically feasible and has become routine practice in an increasing number of clinical microbiological laboratories [20]. Experience with DNA detection in newborn screening laboratories is accumulating, in particular in the postnatal screening for cystic fibrosis [19]. Specificity of CMV PCR assays on DBS has been reported to range between 99.3% and 100% [21–23], with a

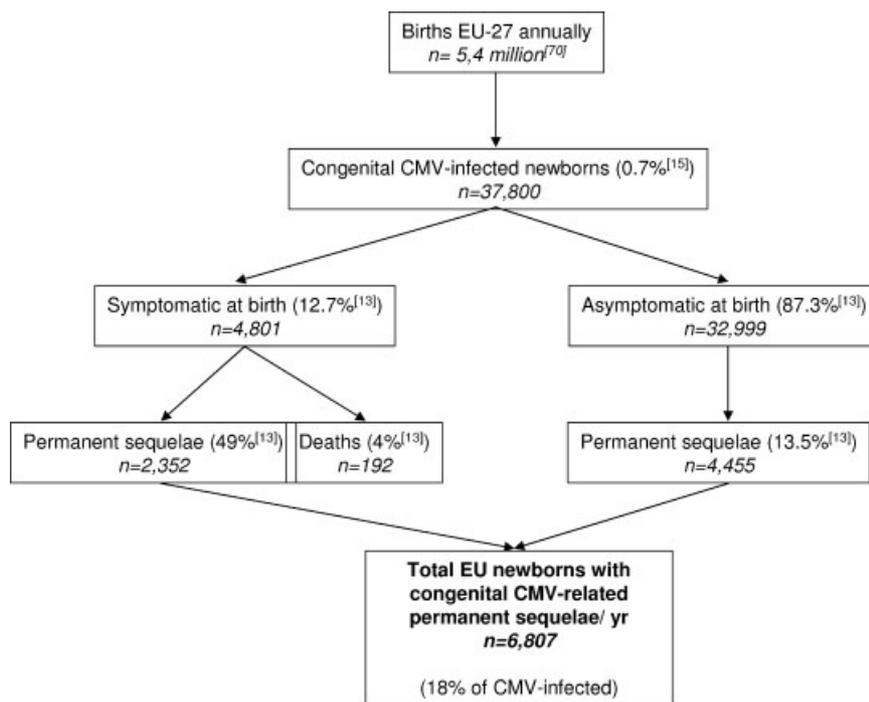


Figure 1. Congenital CMV disease burden in the EU-27.

**Table 1. Several disorders included in newborn screening in EU countries with their prevalences, clinical outcome if untreated and efficacy of early intervention.**

Several disorders included in newborn screening	Rate per 100,000 newborns (EU)	Clinical outcome if untreated	Efficacy of early intervention	References
Congenital CMV (proposed)	700	From asymptomatic to severe neurological damage (18%, $n = 126/700$ )	Partially treatable: prevention of deterioration of hearing with ganciclovir	[13–15]
Congenital hypothyroidism	45	From asymptomatic to severe mental retardation	Treatable: thyroxine prevents mental retardation	[71]
Cystic fibrosis	30	COPD, pancreas—and liver fibrosis	Mainly untreatable: limited to improved feeding status and genetic counselling of parents	[72]
Homocystinuria	1	From mild to severe, including thromboembolism, mental retardation and ectopia lentis	Partially treatable: vitamin B <sub>6</sub> responsive and non-responsive form	[73]

EU, European Union; CMV, cytomegalovirus.

specificity approaching 100% as a prerequisite for an acceptable positive predictive value. Additional confirmatory testing of newborns with CMV positive DBS, using urine sampled within the first 2–3 weeks after birth, the current gold standard, would increase specificity to 100% (positive predictive value of 100%).

The issue has been raised whether the sensitivity of DBS testing for CMV DNA is adequate for screening purposes [4,5,7,9]. Previously reported analytical and clinical sensitivities of CMV DNA detection using DBS vary within a wide range from 34% by Boppana *et al.* [4] up to 100% [10,20,23–31]. The wide range in reported sensitivities can be explained by the population of newborns tested (proportion of asymptomatic and symptomatic cases), and the testing method used. A small number of prospective studies have tested sensitivity of CMV DNA detection in DBS in a large population of unselected newborns in comparison with the gold standard, i.e. urine CMV culture or PCR at 2–3 weeks after birth. Soetens *et al.* [30] reported sensitivities up to 83% testing DBS from 55 CMV-infected newborns detected with a large

urine screening program in an unselected population. Yamamoto *et al.* [32] reported a sensitivity of 71% testing 332 DBS from urine screened unselected newborns of whom seven with congenital CMV infection. Johansson *et al.* [28] described a sensitivity of 81% testing DBS from 16 congenitally infected newborns identified by means of urine screening. In contrast, the annotated [5,7] study by Boppana *et al.* [4] reported a sensitivity as low as 34% of the DBS assay used to screen 20,448 newborns compared to saliva testing. However, the most recent report on sensitivity of DBS testing by Kharrazi *et al.*, [10] screening 3972 newborns using DBS, measured a prevalence similar to reports using established methods for diagnosing congenital CMV infection, suggesting an adequate sensitivity. The major factor responsible for these considerable differences in reported sensitivities of DBS assays, even when assessing an unselected population of newborns in comparison with the gold standard, is the testing method used [5,7]. Widely different DBS test protocols have been used, including variations in DNA extraction methods. It has been demonstrated that these

differences in DBS test protocols result in major divergences in sensitivity [25]. Thus, sensitivity results obtained using one specific DBS testing protocol cannot be generalised to other DBS testing methods. Optimising DNA extraction protocols, PCRs, and testing algorithms, e.g. by means of performing independent triplicate testing, have been shown to increase analytical sensitivity significantly [25,27,30]. Recently, Gohring *et al.* [27] calculated a detection limit as low as 200 copies CMV-DNA per millilitre using a highly sensitive protocol. More important than the sensitivity when evaluating screening assays is the negative predictive value. Considering an international birth prevalence of 0.64%, a screening test with a sensitivity of 75% would still result in a negative predictive value as high as 99.84%. It appears that a perceived lack of analytical sensitivity need not be a diagnostic limitation. Furthermore, the previously demonstrated association between viral load and clinical outcome [33–36] suggests that any cases missed would be those with the lowest viral loads and probably the lowest chance of developing severe permanent sequelae. Thus, as Dollard *et al.* also mentioned, the clinical sensitivity, based on the detection of children that will eventually develop sequelae, may well be acceptable [5,7,8]. Obviously, high-throughput testing should be optimised before implementing universal neonatal screening [25]. It appears that with optimal quality assurance, a high specificity and a sufficient clinical sensitivity can be achieved, enabling exploratory regional trials for large-scale newborn screening.

#### POSTNATAL INTERVENTIONAL OPTIONS

As described by Wilson and Jungner [12], the benefits of newborn screening and intervention should outweigh potential physical and psychological disadvantages. The major benefit of newborn screening for congenital CMV would be early identification of newborns at risk for developing late-onset hearing loss. The current universal newborn hearing screening fails to detect approximately half of all SNHL caused by congenital CMV infection [18] and presently, the median age of detection of hearing impairment caused by congenital CMV infection is approximately 2 years [37]. Hearing impairment in the first 3 years of life has detrimental effects on speech and language development [38,39]. Correction of hearing impairment with hearing aids or cochlear implantation is

most effective prior to the age of 6 months [38,39]. At that early stage, correction of hearing can result in communicative and linguistic skills very similar to those of their normally hearing peers [38,39]. Newborn screening for congenital CMV would enable the identification of the 0.7% of newborns at risk for developing hearing impairment due to congenital CMV, potentially followed by intensive follow-up of audiological performance in this selected group. Audiological follow-up of up of all newborns without screening for congenital CMV is not an attractive alternative due the enormous numbers of newborns involved with the logistic, psychological, and financial consequences attached.

The ultimate benefit of newborn screening would come from the prevention of both early and late-onset hearing deterioration. Any reduction in the number of children with severe to profound hearing loss will have great impact on the burden of disease, influencing both the quality of life of the patients and the economic burden of disease. One randomised controlled trial with intravenous ganciclovir therapy for 6 weeks significantly reduced hearing deterioration in a selected group of symptomatic newborns with congenital CMV infection involving the central nervous system (microcephaly, intracranial calcifications, abnormal CSF, chorioretinitis, and/or hearing deficits) [40]. Sixty-eight % of the untreated infants in the trial had hearing deterioration at the age of  $\geq 1$  year versus 21% of the ganciclovir-treated infants, resulting in an efficacy of 69%. Additionally, ganciclovir had a beneficial effect on the neurological development (personal/social and motor development) of these infants [41]. Although this study had some major drawbacks, such as the high number of cases lost to follow-up and the lack of the usage of a placebo in the untreated group, these results have led to the general opinion that this subgroup of congenitally infected children with neurological symptoms should be treated with at least 6 weeks of (val)ganciclovir. Subsequent trials with this particular group of symptomatic children have actually not included a placebo-group ([www.clinicaltrials.gov](http://www.clinicaltrials.gov), accessed December 2010).

Despite the encouraging results in symptomatic children, the benefit of antiviral therapy in asymptomatic newborns with congenital CMV infection has not yet been proven to date. For this

reason, this intervention is not included in current guidelines [42,43]. To our knowledge, only one randomised controlled trial with asymptomatic congenitally infected newborns without hearing loss has been reported studying the effect of 3 weeks intravenous ganciclovir on hearing [44]. During 4 to 10 years of follow-up, none of 10 treated infants developed hearing loss, compared with two out of eight untreated infants. Unfortunately, this study lacked statistical power to draw firm conclusions about the efficacy of the antiviral treatment in this group. In addition, Yilmaz-Ciftdogan *et al.* [45] reported the improvement of bilateral hearing impairment in an otherwise asymptomatic congenitally infected newborn treated with intravenous ganciclovir for 1 week followed by oral valganciclovir for five additional weeks.

Valganciclovir, which can be administered as a convenient oral solution, is now considered an adequate and practical substitute of the previously applied intravenous formulation of ganciclovir [46–48]. In many other (pediatric) settings, both ganciclovir and valganciclovir have increasingly been tested and used, also for prolonged periods. (Val) ganciclovir has side-effects, with neutropenia being the most common one. A moderate to severe neutropenia is seen in approximately one out of five untreated newborns with congenital CMV infection and in an additional two out of five ganciclovir treated newborns [40,45]. This neutropenia is transient and reversible within a few days upon dose reduction or discontinuation of the drug. Human data on the potential long-term side effects of the active substance of valganciclovir, ganciclovir are lacking. The only data come from a small number of animal studies in which carcinogenic and aspermatogenic effects have been observed [49,50]. Ganciclovir was carcinogenic in mice at doses that produced concentrations of 0.1 and 1.4 times the mean drug exposure in humans [49]. Additionally, ganciclovir decreased fertility in mice at concentrations comparable to human usage, whereas embryotoxicity in pregnant rabbits and mice have only been observed at twice the drug concentrations obtained in humans [49]. It is unclear to what extent these limited data can be extrapolated to humans. Future data from a lifetime of human usage will position these long-term side effects in the proper perspective. To date, no reports have been published on documented or

suspected carcinogenic or teratogenic effects due to (val) ganciclovir, despite its extended usage in adults and its growing usage in the paediatric publication since the first publication on ganciclovir in 1982 [51].

Though randomised controlled-trials should provide further evidence, there are data that support the hypothesis that antiviral therapy has a role in preventing hearing loss in asymptomatic newborns. Several findings suggest that ongoing viral replication is responsible for CMV-associated SNHL. First, CMV-induced labyrinthitis has been demonstrated in human cases and animal model studies [52–56]. Viral DNA has indeed been detected in the perilymph of children with congenital CMV infection at ages ranging from one to 19 years [57–60]. Finally, indirect evidence of a viral replication-associated pathogenesis can be found in the previously published relationship between CMV viral load in the newborn and the occurrence of SNHL [33–36,61–63], the late-onset character of the hearing loss [18,64] and the beneficial effect of antiviral treatment in reducing the development or deterioration of SNHL [40,41]. On the other hand it has been shown that treatment with intravenous ganciclovir or oral valganciclovir will reduce CMV viral load in a predictable pattern as shown by Emery *et al.* [65]. Since the majority of children with congenital CMV infection are asymptomatic at birth, studies are required to define their baseline viral load and determine if this can be efficiently reduced to an undetectable and safe level.

To initiate postnatal antiviral treatment in initial asymptomatic children is a difficult decision, due to the fact that about 82% of the children with congenital CMV infection will not develop any sequelae [13] but will be treated with an antiviral drug with potential side-effects. However, the potential lifelong benefit for those that will have severe hearing loss and possibly neurodevelopmental delay has to be balanced against this disadvantage of a preemptive strategy. To achieve a benefit ratio of 10 newborns needed to treat to obtain benefit for one child, the efficacy of antiviral treatment of approximately 70% is needed, based on the natural history of development of hearing loss as described by Fowler *et al.* [64]. To date, no data are available on the efficacy of antiviral therapy in initially asymptomatic newborns, and therefore, a well-considered appraisal cannot be made at this moment. Considering that potential harm would be mild and temporary whereas

potential benefit would be substantial and permanent, the preventive measure of combined neonatal screening and antiviral treatment is certainly worth to be studied in a randomised controlled trial. Ongoing research will lead to insight into the optimal treatment strategy and duration and should reveal both viral and host factors involved in clinical outcome, potentially leading to a defined risk group that would benefit most from antiviral treatment.

### COST-EFFECTIVENESS

No data are available published on the cost-effectiveness of newborn screening for congenital CMV infection followed by intervention as compared to refraining from any screening or intervention. However, reliable data exist on the disease burden due to congenital CMV infection and the number of children with permanent sequelae. On the EU-27 scale, implementing a congenital CMV newborn screening program would detect approximately 37,800 newborns (Figure 1) with congenital CMV. The current lack of efficacy data on early antiviral treatment is hampering a detailed cost-effectiveness analysis at this moment. However, data on lifetime costs of hearing impairment, irrespective of the etiology, are available [66–69].

Lifetime costs include assistive devices, medical costs, special education and lost productivity, and (in 2007) were estimated to be over € 700,000 per person with prelingual bilateral hearing loss [66–69]. The costs of prevention of hearing deterioration of partially unilateral and bilateral hearing impairment as caused by congenital CMV (cost-of-illness) are not exactly reported and differentiated. However, it would be worthwhile to weigh the costs and benefits of newborn screening followed by intervention when insight in efficacy of treatment of initially asymptomatic newborns is expanded. Given the enormous costs of hearing impairment contracted in early childhood, there is potential for substantial cost reduction.

### CONCLUSION

Now that an increasing number of the Wilson and Jungner criteria for newborn screening have been met, a large-scale study on the effectiveness of newborn screening for congenital CMV infection is the necessary next step to take. Further delay should be considered undesirable and unjustifiable. Policy makers in healthcare should take action now, as the infected infants deserve the benefit of the doubt.

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