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CONCISE ARTICLE

Occupational risk of human *Cytomegalovirus* and *Parvovirus* B19 infection in female day care personnel in the Netherlands; a study based on seroprevalence

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Abstract *Cytomegalovirus* (CMV) and *Parvovirus* B19 infections acquired during pregnancy may result in developmental disabilities of the foetus. This study evaluates the occupational risk of these infections in female day care personnel. IgG seroprevalence was determined in 310 Dutch day care workers and 158 nursing school students. CMV seroprevalence was age-related, starting at 21% in those <20 years and reaching 65% in those >35 years. Between the ages of 20 and 24 years the CMV prevalence was higher in day care personnel than in controls, 50% versus 31% (p=0.03). In the first 2 years of employment the risk of attracting CMV was significantly increased (OR_{adj}=3.80; p<0.001) and the occupational risk was also increased (OR_{adj} 2.19; p<0.001). *Parvovirus* seropositivity (71–77%) was not related to age or working at a day care centre. In conclusion, an occupational risk was observed for CMV, but not for *Parvovirus* infection in female day care personnel.

The fieldwork was performed at the Department of Infectious Diseases, South Limburg Public Health Service. Analyses and editing were finalised at the Department of Medical Microbiology, University Hospital Maastricht.

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Introduction

Infections with *Parvovirus* B19—the causative agent of erythema infectiosum or fifth disease—and *Cytomegalovirus* (CMV) are global and common. Both infections have a benign or asymptomatic course in the immunocompetent host, while in the immunocompromised patient the viruses can severely affect health. Another important risk group for CMV and *Parvovirus* infections are pregnant women, with a reported incidence that varies between 0.09 and 2% and 1 and 5% respectively [1, 2]. Since few newborns are screened for CMV and *Parvovirus*, the true impact of congenital CMV and *Parvovirus* infection is unknown. Intrauterine transmission of CMV occurs in approximately 40% of the primary CMV infections [3, 4]. Ten percent of these infected infants present at birth with symptoms of irreversible central nervous system involvement including microcephaly, encephalitis, seizures, deafness, upper motor neuron disease and mental retardation. In addition, 10–17% of the infants that are asymptomatic at birth develop sensorineural hearing loss or neurodevelopmental sequelae months to years afterwards [5, 6]. Transplacental transmission rates of *Parvovirus* have been estimated to be between 25 and 33%. Fetal infection with *Parvovirus* may lead to severe anemia, generalised edema, congestive heart failure and myocarditis, leading to fetal death in 5–9% of the cases, with the greatest risk in the second trimester of pregnancy.

Approximately 60 and 30% of the women of childbearing age in developed western European countries, such as the Netherlands, are still susceptible to developing either a primary CMV or *Parvovirus* infection [7, 8]. Nevertheless, there are great variations in seroprevalence according to geographical region, socioeconomic status and ethnic composition [5]. Therefore, it is important to establish local sero-epidemiology data to offer preventive strategies in a

given country, as CMV and *Parvovirus* infections cannot yet be prevented by immunisation and therapeutic options are questionable. In the Netherlands, in a recent prospective study, an unusually low incidence of congenital CMV infection of 0.09% was reported [7]. The authors concluded that preventive measures for CMV were thus not justified, and that antenatal and perinatal counselling should be reserved for (upcoming) *Parvovirus* epidemics. However, this incidence is based on calculations in the general population and small, potentially high-risk groups such as day care workers will not be identified. Young children are an important source of CMV or *Parvovirus* infection due to poor hygiene. Up to 71% of children attending day care centres may carry CMV in saliva or urine [9]. Direct and indirect exposure of day care personnel by touching, diapering, washing, feeding and contact with environmental surfaces put them at a higher risk of acquiring a viral infection [9, 10]. The aim of our study was to assess the occupational risk of CMV and *Parvovirus* B19 infection in female day care personnel in the Netherlands to determine whether or not preventive measures (for instance, serological testing followed by alternative work during pregnancy being offered to women who test CMV-seronegative) should be offered or not.

Materials and methods

Participants

Cytomegalovirus and *Parvovirus* IgG seroprevalence was determined in 310 sera collected from 313 female day care personnel from 66 regional day care facilities for children in the southern part of the Netherlands between October 2000 and April 2003. Due to laboratory-related factors, 3 samples were not tested for CMV and *Parvovirus*. Written consent to participation was obtained from all participants. All women were asked to complete a questionnaire, including data regarding age, work seniority, infant ages of the care group, and the number and age of their own children at home. Data were entered into a codified database for analysis. One hundred and fifty-eight female students, aged between 17 and 26 years, attending a nurse school in the same region as the day care centres, served as a control group. Data on their age and own children at home were obtained.

Laboratory analysis

The outcome measure was seroprevalence for CMV and *Parvovirus* infection. Sera were frozen at −20°C until testing for CMV and *Parvovirus* IgG. CMV IgG was determined by an automated microparticle enzymatic immunoassay AxSym CMV IgG version (Abbott laboratories, Abbott Park, IL, USA) and *Parvovirus* IgG was assayed using a third generation *Parvovirus* IgG enzyme-linked immunoassay (Biotrin, Dublin, Ireland). Both assays were performed according to the manufacturer's instructions. A value of ≥15 U/ml for CMV IgG was considered positive, whereas a ratio of optical density sample to optical density cut-off (S/CO) of more than 1 was considered positive for *Parvovirus* IgG.

Statistical analysis

Proportions between the groups were compared using Chi-squared statistics. Associations were tested by univariate and multiple logistic regression analysis, the latter allowing adjustment for co-variables. The outcome variable of the regression models was CMV IgG seropositivity versus seronegativity. *Parvovirus* B19 was not considered in a regression model as no interesting age-related features and differences between groups were observed during the explorative Chi-squared analyses. Two different regression models were tested (Table 1). The first model tested the main effect "occupational risk," defined as being a day care worker or student (= control). The second model tested the main effect "work seniority" as defined by five categories reflecting the number of years of day care employment (0 years, 1–2 years, 3–4 years, 5–9 years, >9 years). Co-variables in both models were "age" in years, "having own children" as defined by parity (no children versus ≥1 child) and "having children who were in contact with other children" as defined by the presence of children at home attending school or a day care centre (yes versus no). All co-variables were simultaneously included in the logistic regression model.

Results and discussion

The main finding of this study was that female day care personnel have an increased risk of attracting a primo-infection with CMV (OR_{adj} 2.19, $p<0.001$; Table 1), especially during the first 2 years of day care employment (OR_{adj} 3.80, $p<0.001$; Table 1). Furthermore, an age-dependent increase in CMV IgG seropositivity was observed for both day care workers and controls (Fig. 1a). Of women younger than 19 years, 12.5% (1 out of 8) and 22% (23 out of 104) respectively were positive for CMV IgG. Fifty percent (40 out of 80) and 31% (16 out of 52; $p=0.03$) of women aged between 21 and 24 years and 53% (31 out of 58) and 50% (1 out of 2) of women aged between 25 and 29 years presented as CMV IgG-seropositive respectively. In day care personnel aged between 30 and 34 years, 59% (30 out of 51), and in the age group above 35 years, 65% (73 out of 113) were CMV IgG-seropositive. No women

Table 1 *Cytomegalovirus* (CMV) seroprevalence in female day care personnel (n=310) and controls (n=158) and odds ratios calculated by logistic regression analysis in female day care workers and controls

		Total number[a]	Positive IgG CMV number (%)	OR_{crude}	95% CI	OR_{adj}	95% CI
Model 1	Occupational risk						
	Control	158	40 (25)	1		1	
	Day care personnel	310	175 (57)	3.82	2.51–5.84	2.19	1.28–3.74
	Parity; number of own children						
	0	302	111 (37)	1		1	
	≥1	160	99 (62)	2.79	1.88–4.15	0.76	0.34–1.66
	Children in day care or at school						
	No	371	152 (41)	1		1	
	Yes	97	63 (65)	2.67	1.68–4.25	1.70	0.86–3.36
	Age (years)			-		0.96	0.93–0.99
Model 2	Work seniority (years)						
	0	158	40 (25)	1		1	
	1–2	78	36 (46)	2.53	1.43–4.48	3.80	1.53–9.38
	3–4	69	32 (46)	2.55	1.41–4.62	2.06	0.93–4.58
	5–9	90	57 (63)	5.10	2.91–8.91	2.04	0.93–4.50
	>9	70	48 (69)	6.44	3.47–11.95	1.06	0.52–2.19
	Parity; number of own children						
	0	302	111 (37)	1		1	
	≥1	160	99 (62)	2.79	1.88–4.15	0.69	0.31–1.54
	Children in day care or at school						
	No	371	152 (41)	1		1	
	Yes	97	63 (65)	2.67	1.68–4.25	1.83	0.91–3.67
	Age (years)			–		0.97	0.94–1.01

OR = odds ratio; 95% CI = 95% confidence interval of odds ratio; OR_{crude} = crude odds ratio; OR_{adj} = adjusted odds ratio
[a] Total group N=468, discrepant numbers are due to missing values

older than 26 years were encountered in the control group. Therefore, CMV seroprevalence data above this age are not available in this group, which is a limitation of our study. Age-dependent CMV seroprevalence has been described before, with an annual seroconversion rate of 1% throughout adulthood [3]. Therefore, similar age groups to those of the day care personnel and the control group were compared. In both study populations, the expected age-dependent increase in CMV seroprevalence was observed; however, this increase was greater in day care personnel under 25 years of age than in the control population. The fact that day care personnel are more likely to be exposed to a CMV infection is additionally supported by the age-adjusted associations between CMV seropositivity and day care workers' seniority found in the present study.

Work seniority was positively associated with an increased risk of becoming CMV-seropositive (see also Table 1), but when adjusting for age, having children and children in day care or at school, only the first 2 years of day care employment showed any significant influence. In day care workers, CMV seroprevalence was associated with having children at home (OR 2.79, p<0.001; Table 1) and with having children attending a day care centre or a primary school (OR 2.67, p<0.001; Table 1). However,

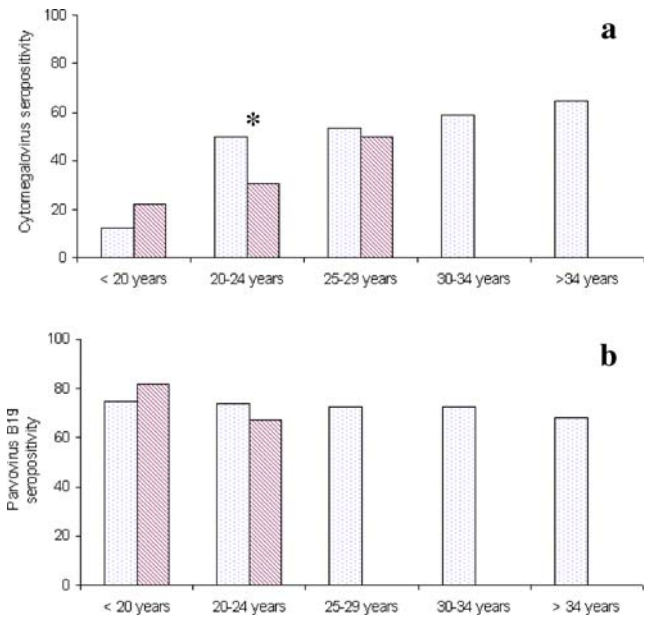

Fig. 1 **a** Age-related distribution of *Cytomegalovirus* seropositivity in female day care personnel and controls. In the age group 20–24 years the CMV seropositivity was significantly higher in day care personnel than in controls (50 versus 31%; p=0.03 *). **b** Age-related distribution of *Parvovirus* B12 seropositivity in female day care personnel and controls. No relation was seen with regard to age and no difference between day care personnel and controls was observed

when adjusting for co-variables, these associations were no longer significant (see Table 1).

Parvovirus serology was performed in both study groups. No clear age-related increase in positive serology was observed in either group (see Fig. 1b). Also, no overall significant difference was seen between the two groups, as the seroprevalence was 71% (n=319) and 77% (n=158) respectively (p=0.224; Fig. 1b). The mean *Parvovirus* seroprevalence of about 70% was comparable with the seroprevalence of 70% measured in the Netherlands [8]. *Parvovirus* B19 is a highly contagious viral disease causing erythema contagiosum, which is transmitted by droplets and aerosols. Due to the general mode of transmission, all young members of the general population are at increased risk of acquiring the infection. According to a recent study in the UK, antibody prevalence rose nonlinearly with age from 21% in children aged 1–4 years to >75% in adults aged ≥5 years, with the highest risk of acquiring infection being in those aged <15 years [11]. Therefore, it is not surprising that there is no occupational risk associated with *Parvovirus* B19.

The main limitation of our study was the fact that the control group is different from the day care workers; it had a limited age range (17–26 years) and the female students mainly had no own children or exposure to young children. The main purpose of the control group was therefore to establish the occupational risk of CMV and *Parvovirus* B19 infection adjusted for age.

Our data are important as CMV is not considered a public health problem in the Netherlands, whereas other countries, such as the US, recognise that women within certain professions like day care are more at risk of acquiring a primary CMV infection during pregnancy [9, 10]. The rate of CMV IgG seropositivity found in our control group mirrors the 35% observed in an earlier Dutch study performed by Gaytant and coworkers [7]. Sixty-five percent of Dutch women of childbearing age are thus still at risk of attracting a CMV primo-infection. Nevertheless, there appears to be little CMV-related morbidity in children in the Netherlands. In a recent Dutch study performed in the metropolitan agglomeration formed by the cities Amsterdam, Rotterdam and The Hague, CMV seropositive neonates were followed for 24 months. No significant symptoms of CMV infection were observed in these infants [7]. From studies outside the Netherlands it is known that about 7–15% of asymptomatic infants will eventually develop sensorineural hearing loss [5]. However, the CMV seroprevalence in the Netherlands is lower than that in the United States and other western European countries, ranging from 40 to 83% [5]. Studies from other countries have demonstrated that women working at child-care centres are at increased risk of acquiring primo-CMV infections [10], and our study confirms that this is also the case in the Netherlands.

Cytomegalovirus infection, is mediated through contact with infant saliva and urine, exposure mainly associated with caring for young infants. Children who attend day care centres are at a higher risk of acquiring infections due to close contact and the sharing of toys and food. In addition, infected children may excrete CMV for a prolonged time. According to different reports, up to 50% of children attending day care centres may excrete CMV [9].

Preconceptional maternal immunity (i.e., IgG seropositivity) has been demonstrated to protect against congenital CMV [12, 13]; however, several studies have also pointed out that recurrent CMV infections, as well as reactivation of latent infections, may cause congenital CMV [12]. Our data neglect the possibility of a recurrent CMV infection and the true occupational risk of CMV infections will therefore be even higher.

Hitherto, the only mode of prevention for congenital CMV disease has consisted of increasing population awareness and improvement of hygienic practices in those at increased risk. The availability of a licensed and effective CMV vaccine will probably take years and drug treatment for pregnant women has not yet been extensively studied because of concerns about toxicity. In a recent study, CMV hyperimmune globulins were administered to CMV-infected pregnant women [14]. Although the results suggested that passive immunisation could prevent congenital CMV infection, the results should be further substantiated in a randomised and controlled trial. As such, women in contact with small children, or those who are planning a pregnancy, at least deserve to be informed how to prevent CMV acquisition through improved personal hygiene [15]. Also, serological screening of pregnant women who are at increased risk, followed by offering alternative duties at work in those tested negative, should be considered.

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