

## Seroprevalence of cytomegalovirus infection in France in 2010

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### SUMMARY

Cytomegalovirus (CMV) infection remains the leading cause of congenital virus infection in developed countries. Measuring the national prevalence of this infection, especially among women of childbearing age, is of great value to estimate the risk of congenital CMV infection, as well as to identify risk groups that should be targeted for behavioural interventions and/or vaccination once a CMV vaccine finally becomes available. In order to fulfil these objectives, a seroprevalence survey was conducted in 2010, using a nationally representative, population-based sample of 2536 people aged between 15 and 49 years, living in metropolitan France and attending private microbiological laboratories for blood testing. All blood samples were analysed in the same laboratory and screened for CMV-specific IgG using an enzyme-linked immunoassay technique (Elisa PKS Medac Enzyme immunoassay). The overall point estimate of CMV infection seroprevalence for individuals aged 15–49 years was 41.9%. The estimates were higher in women than in men (respectively 45.6% and 39.3%), and people born in a non-Western country were more likely to be CMV seropositive than those born in France or in another Western country (93.7% vs. 37.7%). Our results showed that a substantial percentage of women of childbearing age in France are CMV seronegative and therefore at risk of primary CMV infection during pregnancy. Educational measures and future vaccine are key issues to prevent infection in pregnant women and congenital CMV disease.

**Key words:** Cytomegalovirus, France, seroprevalence.

### INTRODUCTION

The human cytomegalovirus (CMV) belongs to the Herpesviridae family and is endemic worldwide [1]. It is transmitted through intimate contact with CMV-infected body fluids of individuals with symptomatic or asymptomatic CMV infection and replicates only in human cells [1–4]. Most CMV

infections are mild or asymptomatic in immunocompetent individuals although a mononucleosis syndrome is observed in 10% of infected cases [5]. However, CMV can produce severe disease in immunocompromised individuals and foetuses. As observed with other herpesviruses, CMV may become latent after primary infection, leading to later reactivation and disease, particularly in a context of immune suppression. Individuals with a higher incidence of primary infection include breastfed infants [6], toddlers, care providers in pre-school day-care settings [7, 8] and sexually active adolescents [9, 10].

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From a public health perspective, the most important medical impact of CMV is the damage caused to a foetus when infection occurs *in utero*. In Western countries, CMV remains the leading cause of congenital infection among new-borns, which may lead to permanent disabilities, such as hearing loss, intellectual disability, psychomotor delay, speech and language disabilities, behavioural disorders, visual impairment and cerebral palsy [11, 12]. A foetus is at great risk of CMV infection when a mother has a primary infection during pregnancy [1, 13]. But due to possible maternal CMV reactivation or reinfection with a different CMV strain, the risk of foetal infection still remains in women who were CMV seropositive before pregnancy, although the transmission risk is much smaller than for primary infection (0.2%–2% vs 30%–50%) [1, 14]. Furthermore, recent studies [15–17] showed that symptomatic infection might occur with similar frequency in children born to CMV seroimmune women. Surprisingly, the highest birth prevalence rates of congenital CMV infection are found in populations with nearly 100% seroprevalence, ranging from 0.3% in population with 30% seroprevalence to about 2% in populations with 98% seroprevalence [1, 17]. This paradox may be explained by a higher force of infection in highly seroimmune populations, with a risk of re-infection possibly outweighing the protective effect of maternal immunity on transplacental transmission and severe disease [18].

Measuring national prevalence, especially among women of childbearing age, is important in order to establish accurate estimates of the risk of congenital CMV infection, as well as to identify risk groups that should be targeted for behavioural interventions and/or vaccination once a CMV vaccine finally becomes available [19, 20]. After primary infection, CMV-IgG seropositivity remains for life; therefore, CMV-IgG seroprevalence reflects the primary infections cumulated over time. In 2010, we conducted a national cross-sectional sero-epidemiological survey in metropolitan France, targeted at ten diseases including CMV infection (five vaccine-preventable diseases: measles, rubella, mumps, varicella and hepatitis A, and five other infectious diseases: toxoplasmosis, CMV, herpes simplex virus types 1 and 2, and hepatitis E infections) [21]. Few seroprevalence surveys on CMV infection had previously been conducted in France, and were targeted to specific population subgroups including pregnant women [22, 23] and hospital employees [24], surveyed in a limited number of university hospitals.

## METHODS

The present study's objectives were to provide current estimates of CMV seroprevalence in France and describe individual characteristics associated with seropositive status.

### Population of interest

The population of interest was restricted to people aged between 15 and 49 years, living in metropolitan France and attending private microbiological laboratories for blood testing.

### Sample size

The sample size was calculated according to an expected CMV seroprevalence of 50%, derived from previous surveys [21–24], with a precision set at 5% and a type I error of 0.05. A design effect equal to 1.5 was chosen, based on the value observed in a similar seroprevalence survey conducted in 1998 [25]. The necessary sample size was estimated therefore at 2500 individuals.

### Sampling design

We used a two-stage stratified sampling design. First, we built a national sampling frame of private outpatient microbiology laboratories, stratified by geographical regions and laboratory activity (number of patients and ratio of children/adults tested annually). At the first stage, we randomly selected laboratories using simple random sampling in each of the strata obtained (31 in total). At the second stage, patients coming to the laboratory for a blood test and eligible for the survey were consecutively selected and included, after signing an informed consent form (signature of legal representatives for those under 18). A dedicated laboratory staff member conducted questionnaire-based interviews, and proposed collecting a supplementary blood sample. Patients having had a blood transfusion in the previous 3 months, those immunocompromised, those on immunosuppressive therapy and pregnant women coming for follow-up after having been found seronegative for one of the antigens of interest were not included in our study [21].

### Measures

Variables of interest included sex, age, birthplace (country), household education level (elementary/middle school, high school diploma or third-level college/university diploma/degree), employment status, household socio-professional category, insurance

status (covered or not covered by complementary health insurance) and place of residence.

### Statistical analysis

A sampling weight was associated with each individual, calculated as the inverse of inclusion. All statistical analyses were performed using Stata version 12.0 (StataCorp, College Station, Texas, USA) taking into account the sampling design. We improved the estimates by post-stratification on age groups, sex and geographical regions according to the 2008 French census data.

Variables which had a *P*-value of <0.20 in univariate analysis were retained for multivariate analysis (except the variable ‘socio-professional category’, which was forced into the model). We used a Poisson regression model to assess the association between CMV seropositivity and demographic factors while adjusting for multiple covariates and estimated adjusted prevalence ratios [26]. We studied first-order interactions for statistical significance, epidemiologic plausibility and the impact of their inclusion on the other model parameters. We used the *F* test to assess the statistical significance of variables and interactions in the model and the model fit. Variables with a *P*-value <0.05 were retained in the final model.

### Serological testing

All samples were tested in the same laboratory (Biomnis, Lyon). Serum samples were screened for CMV-specific IgG antibodies with the CMV IgG Elisa PKS Medac enzyme immunoassay, using a BEP III Dade Behring robot, with the following testing method characteristics: sensitivity 100%, specificity 97% and a positive threshold >0.8 universal arbitrary units per millilitre (UA/ml).

### Ethical and financial aspects

The survey protocol was reviewed and approved by a national institutional and ethical review board (Comité consultatif de traitement de l’information en matière de recherche dans la santé) on 18 December 2008 (N°08–582). The field survey and the serological analysis were funded exclusively by Santé publique France (the French National Public Health agency).

## RESULTS

A total of 2536 individuals aged 15–49 years were included in the survey; the male/female sex ratio was 0.94 (1230/1306), and median age was 27 years.

The overall point estimate of CMV infection seroprevalence for individuals aged 15–49 years was 41.9% (95% CI 38.4–45.5) (Table 1).

In a univariate analysis, CMV seropositivity was significantly associated with female sex, older age, non-Western birthplace, lower education level and residence in the Paris or South-East regions (Table 1).

The CMV prevalence estimates were 45.6% (95% CI 40.9–60.3) in women compared with 39.3% (95% CI 34.9–43.8) in men (*P* = 0.03). The estimates ranged from 28.8% (95% CI 25.1–32.8) to 44.4% (95% CI 39.0–49.8) and 47.6% (95% CI 43.2–52.1), respectively, in the 15–24, 25–34 and 35–49 age groups (*P* = 0.000).

People born in a non-Western country were more likely to be CMV seropositive compared with those born in France or in another Western country, with an estimated seroprevalence of 93.7% (95% CI 83.5–97.8) compared with 37.7% (95% CI 34.8–40.8) (*P* = 0.000). Among individuals born in a Western country, the prevalence estimates according to age ranged from 27.4% to 39.5% in men vs 27.6% to 48.6% in women. For individuals born in a non-Western country, these figures ranged from 69.1% to 99.3% in men vs 96.6% to 99.5% in women (Fig. 1).

The prevalence point estimate in individuals with the lowest education level was 49.3% (95% CI 43.9–54.7) compared with 37.5% (95% CI 32.8–42.4) in people with a college/university diploma/degree (*P* = 0.001). People living in the North-West region had the lowest prevalence estimate (Table 1, Fig. 2: 30.1% (95% CI 24.9–35.8), whereas in the South-East and Paris regions prevalence estimates were 45.2% (95% CI 39.4–51.0) and 62.6% (95% CI 52.3–71.9), respectively. There were no statistical differences in prevalence estimates when looking at socio-professional categories, employment status or complementary health insurance cover (Table 1).

In the Poisson multivariate regression, we introduced the variables found to be significant in univariate analysis and forced the ‘socio-professional category’ variable into the model (redefined after collapsing the six-level variable into a four-level one). The multivariate model included age, sex, birthplace (country of origin), education level, complementary health insurance, region of residence and socio-professional category. We did not find any significant terms of interaction between variables, and only ‘complementary health insurance’ was not retained in the final model (*P*-value of 0.98). CMV seropositivity was found to be independently associated with a non-Western country birthplace, female sex, age  $\geq$  25

Table 1. *Estimated seroprevalence of CMV infection, univariate analysis, French metropolitan population aged 15–49 years, 2010*

	Sample size	Prevalence estimate (%)	95% CI	Prevalence ratio*	95% CI	P-value
Total	2536	41·9	38·4–45·5			
Sex	2536					
Male	1230	39·3	34·9–43·8	Ref	–	
Female	1306	45·6	40·9–60·3	1·2	1·0–1·3	0·03
Age (years)	2536					
15–24	1022	28·8	25·1–32·8	Ref	–	
25–34	751	44·4	39·0–49·8	1·5	1·3–1·8	0·000
35–49	763	47·6	43·2–52·1	1·7	1·5–1·9	0·000
Birth place	2534					
France or Western country	2400	37·7	34·8–40·8	Ref	–	
Non-Western country	134	93·7	83·5–97·8	2·5	2·3–2·7	0·000
Education†	2485					
≥2 years of higher education	1080	37·5	32·8–42·4	Ref	–	
High school	606	39·7	33·2–46·5	1·1	0·9–1·3	0·55
Elementary/middle school	799	49·3	43·9–54·7	1·3	1·1–1·5	0·001
Socio-professional category†	2517					
Managerial, intellectual occupations	332	36·6	28·6–45·3	Ref	–	
Intermediate occupations	455	35·4	30·5–40·6	1·0	0·8–1·2	0·79
Employees	760	45·6	40·8–50·3	1·3	1·0–1·6	0·06
Workers	288	46·0	38·3–53·9	1·3	1·0–1·6	0·08
Farmers–craftsmen	157	47·9	35·5–60·5	1·3	0·9–1·9	0·15
No professional qualification	525	40·6	33·4–48·3	1·1	0·8–1·5	0·45
Current employment status†	2534					
Employed	1756	41·5	37·6–45·4	Ref	–	
Inactive‡	606	42·2	35·6–49·0	1·0	0·9–1·2	0·85
Unemployed	172	47·4	36·5–58·6	1·1	0·9–1·5	0·29
Complementary health insurance	2490					
Yes	2224	40·4	36·9–44·1	Ref	–	
No	266	49·3	36·2–62·5	1·2	0·9–1·6	0·14
Region	2536					
North-West	501	30·1	24·9–35·8	Ref	–	
Paris & suburbs	316	62·6	52·3–71·9	2·1	1·6–2·7	0·000
North-East	775	35·5	29·5–42·0	1·2	0·9–1·5	0·17
South-East	624	45·2	39·4–51·0	1·5	1·2–1·9	0·000
South-West	320	34·9	26·7–44·0	1·2	0·9–1·6	0·34

\* Adjusted for age, sex and region of residence.

† Highest parents' education level and socio-professional category were used for people under 18 years of age.

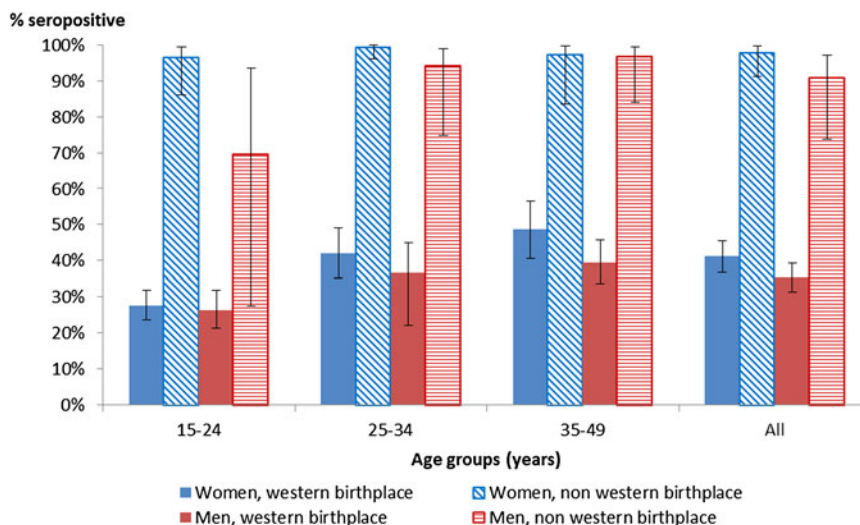
‡ Inactive people are defined as people who are neither in employment nor unemployed: students, retired people, people engaged in activities in the household, with an incapacity for employment, etc.

years, education level up to middle-school, lower socio-professional categories and residing in Paris, the South-East or the North-East regions (Table 2).

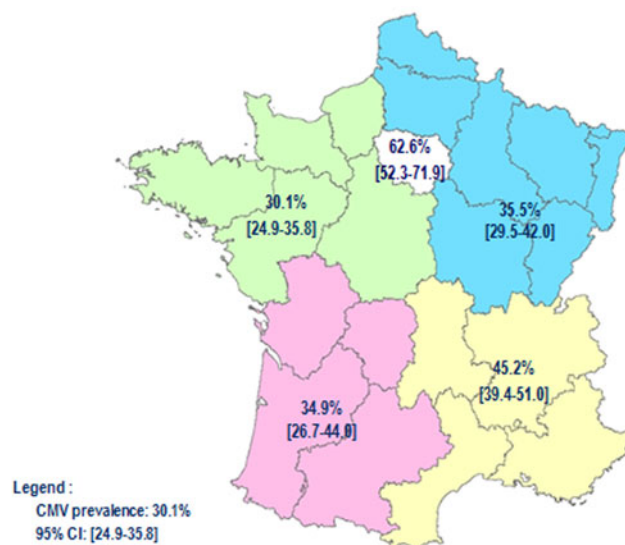
## DISCUSSION

This is the first study in France looking at CMV seroprevalence, using a nationally representative, population-based sample. It yielded national estimates of CMV seroprevalence in metropolitan France for

residents aged 15–49 years, with a national point estimate of 41·9%. Our main findings showed different rates between men and women, respectively, 39·3% and 45·6%. The highest prevalence rates (over 96%) were in women born in a non-Western country, irrespective of their age, and the lowest in individuals aged 15–24 years born in a Western country (27% for both men and women). The prevalence was higher in individuals living in the Paris region (62·6%) and in those with a lower educational level (49·3%).



**Fig. 1.** CMV infection seroprevalence by age-group, sex and birthplace, French metropolitan population aged 15–49 years, 2010.



**Fig. 2.** CMV infection seroprevalence according to region of residence, French metropolitan population aged 15–49 years, 2010.

Our findings reinforced prevalence results found in previous surveys conducted in France, targeted at specific sub-populations such as pregnant women or healthcare workers [22–24]. Furthermore, our prevalence estimates were comparable with those obtained in national surveys conducted in the general populations of other Western countries, such as the USA, the Netherlands and Australia [2, 27, 28]. Consistent with their findings, we identified sex, age, country of origin and educational level as factors independently associated with CMV seropositivity.

One limitation of our study was the survey setting (private medical laboratories), which prevented us from asking questions about more personal issues, such as home crowding and household income. These two factors have been previously described to be independently associated with CMV seropositivity in the literature [2, 27]. We had to use proxies for household income level such as socio-professional categories, current employment status and complementary health insurance, and we found an association between higher seropositivity and the absence of a



Table 2. Poisson regression final model of factors independently associated with CMV prevalence, French metropolitan population aged 15–49 years, 2010

	Sample size	Prevalence estimate (%)	95% CI	Adjusted prevalence ratio*	95% CI	P-value
Total	2536	41.9	38.4–45.5			
Sex	2536					
Male	1230	39.3	34.9–43.8	Ref	–	
Female	1306	45.6	40.9–60.3	1.2	1.0–1.3	0.03
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35–49	763	47.6	43.2–52.1	1.7	1.5–2.0	0.000
Birth place	2534					
France or Western country	2400	37.7	34.8–40.8	Ref	–	
Non-Western country	134	93.7	83.5–97.8	2.4	1.7–3.3	0.000
Education†	2485					
≥2 years higher education	1080	37.5	32.8–42.4	Ref	–	
High school	606	39.7	33.2–46.5	1.1	0.9–1.2	0.66
Elementary/middle school	799	49.3	43.9–54.7	1.2	1.0–1.4	0.001
Socio professional category	2517					
Managerial, intellectual and intermediate occupations	787	35.9	30.8–41.3	Ref	–	
Employees	760	45.6	40.8–50.3	1.2	1.0–1.4	0.05
Workers/farmers/craftsmen	445	46.8	39.8–53.8	1.3	1.0–1.6	0.02
No professional qualification	525	40.6	33.4–48.3	1.4	1.1–1.7	0.002
Region	2536					
North-West	501	30.1	24.9–35.8	Ref	–	
Paris & suburbs	316	62.6	52.3–71.9	1.9	1.6–2.3	0.000
North-East	775	35.5	29.5–42.0	1.2	1.0–1.5	0.06
South-East	624	45.2	39.4–51.0	1.6	1.3–1.9	0.000
South-West	320	34.9	26.7–44.0	1.2	0.9–1.6	0.19

\* Adjusted for age, sex and region of residence.

† Highest parents' education level and socio-professional category were used for people under 18 years of age.

professional qualification and lowest possible educational level.

Due to the limitation in age groups included in our study, we could not document when seropositive individuals became infected with CMV during childhood. Although the cross-sectional nature of our study limits interpretation in terms of force of infection according to age, our data show an increase in seroprevalence during childbearing age for women born in France and other Western countries: <30% of them were CMV positive before 25 years of age, but nearly 50% above this age. Young seronegative women (>70%) are consequently at higher risk of primary CMV infection during pregnancy.

In 2010, Cannon *et al.* published an extensive review of literature on CMV seroprevalence surveys conducted between 1966 and 2008, most of them targeting special sub-groups of population [29]. The

authors highlighted that CMV seropositivity was relatively common among women of childbearing age, ranging from 45% to 100%. They confirmed the main risk factors associated with CMV seropositivity, including increased prevalence with age, female gender, belonging to a non-white ethnic group and lower socio-economic status. They pointed out substantial variations in CMV seroprevalence across continents, but also within them. The lowest prevalence rates were in Western Europe and USA, and the highest in South America, Africa and Asia. Within the USA, they showed prevalence discrepancies between different regions, as we did in our study in France.

As countries become more developed, one expects the level of hygiene and wealth to improve, and the CMV-IgG seroprevalence at the beginning of childbearing age to decrease [30, 31]. Regarding the risk of infection, unfortunately, both awareness and knowledge of

CMV infection are quite low in the general population, especially in pregnant women. This is mainly due to practitioners' lack of awareness and knowledge about CMV infection and its consequences, and in some maternities, to insufficient primary prevention through women's education programs about CMV transmission and basic hygiene preventive measures [19, 32]. The role of screening for CMV has been widely debated in recent years, but there is no consensus to date on the relevancy of screening pregnant women for CMV seronegativity [32–34]. Neither is there any current adequate treatment against CMV during pregnancy, nor an available vaccine [35]. Therefore, preventive measures against CMV infection during pregnancy are of crucial importance, and since the 2000s, national colleges of obstetricians and gynaecologists together with national public health authorities have encouraged counselling pregnant women on hygiene practices and providing information on CMV transmission routes, in order to reduce the risks linked to exposure to saliva and urine of toddlers [36]. These recommendations are targeted both at the mothers and their partners, as well as at pregnant women caring for children <3 years of age [37]. Furthermore, preconceptional immunity to CMV provides only incomplete protection against intrauterine transmission, as immune women may be infected with a new or different CMV strain [14]. In addition, using a population-based prediction model, de Vries *et al.* [18] showed that, paradoxically, maternal seropositivity might be a risk factor for congenital CMV infection, as they identified non primary maternal CMV infections responsible for the majority of congenital infections, for both high and low seroprevalent populations. Thus, to avoid any adverse outcomes that may occur in infected children born to women seropositive prior to pregnancy, counselling should be provided to all pregnant women. In France, CMV screening during pregnancy is therefore not recommended; but the importance of information on prevention of transmission has been stressed by the French National Agency for Accreditation and Evaluation in Healthcare (Haute Autorité de Santé) [38].

## CONCLUSION

Even if behavioural changes obtained through health counselling should lead to a decrease of congenital CMV infections, there is still an urgent need for improved treatments and vaccine development. CMV seroprevalence data could be used to power interventional studies for pregnant women with proven primary CMV infection and to plan strategies

against congenital CMV infection. Nevertheless, the best option remains an effective vaccine to be given to children and teenagers, and hopes are high that candidate vaccines currently in clinical evaluation, including live attenuated, protein subunit, DNA and viral-vectored approaches, will be successful [36, 39].

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## DECLARATION OF INTEREST

We report no conflicts of interest.

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