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#### ORIGINAL ARTICLE

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# Antenatal CMV screening, testing, and treatment strategies in Europe: a 2024 survey

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#### **ABSTRACT**

**Objective:** Congenital cytomegalovirus (cCMV) is the most common congenital infection globally, affecting approximately 0.5% of all live births in high income settings, with long-term sequelae affecting around a fifth of infected infants. Recently, interest in antenatal CMV screening has increased but current practices and impact are unclear. Our objective was to describe policy and practice around antenatal CMV screening, testing, and treatment in Europe, including the use of universal antenatal screening, in the context of the emerging evidence base for use of valaciclovir to reduce CMV vertical transmission (VT).

**Methods:** A web-based survey was distributed to healthcare professionals within antenatal services with knowledge of CMV testing/treatment practices, from 29 April 2024 to 24 July 2024. Responses from Europe were analyzed. Where multiple responses were submitted from the same healthcare service, the most complete response was kept for the analysis.

Results: We received responses from 73 centers in 21 countries in Europe, mostly 76% (55/72) from tertiary centers. Overall, 52% (38/73) had a CMV testing policy and 61% (23/38) reported that this had been introduced or significantly updated in the last 2 years. Half of respondents (53%, 39/73, from 11/21 countries) reported routine offer of CMV testing to pregnant woman at their center (universal antenatal screening), sometimes with gestational age limits, and mostly (67%, 26/39) on an "opt-out" basis. Universal antenatal CMV screening was more common among centers with formalized testing policies than those without (84% (32/38) vs. 20% (7/35) respectively,  $\chi^2 = 30.19$ , p < .01). For all sites, screening tests included CMV IgM and IgG, with 36% (14/39) offering IgG avidity, and 8% (3/39) using PCR. Of the 39 centers offering universal screening, the coverage was estimated to be >95% of pregnant women at half (18/39) of centers. Fifty-nine percent (23/39) of centers reported routinely offering repeat testing. Of 39 centers routinely offering testing, only 69% (27/39) gave advice on reducing CMV acquisition risk routinely to pregnant women. Medication was offered for prevention of CMV VT or tertiary prevention of cCMV disease at 82% (60/73) and 78% (56/72) of centers, respectively. Of 59 sites offering treatment for secondary and/or tertiary prevention and responding to a question on frequency of treatment monitoring, 93% (55/59) reported monitoring blood tests at least monthly. Forty-three percent of centers offering treatment lacked a formal procedure for reporting adverse drug reactions. Overall, 83% (58/70) respondents supported CMV testing (49 strongly, nine moderately), but 59% (41/70) identified at least one concern/risk.

**Conclusions:** This survey of antenatal CMV policies and practice at 73 centers in Europe highlights substantial variation in policies and practice, reflecting variation in national screening guidelines and the evolving evidence base around valaciclovir to reduce CMV VT risk. A recent opinion paper and statement have called for consideration of universal screening but also highlighted important evidence gaps around its implementation, risks, benefits, and cost-effectiveness. Responses to this survey suggested that valaciclovir is already quite widely used for prophylaxis of CMV VT in the context of maternal primary infection in early pregnancy, at participating sites. Our findings suggest that

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Cytomegalovirus; pregnancy; valaciclovir; screening; testing; Europe

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research to inform safe and equitable decisions around implementation of CMV testing and universal screening is urgently needed, in addition to epidemiological research to underpin screening decisions tailored to specific settings. Shared research priorities are needed to ensure testing and treatment are carried out in an evidence-based and equitable way.

## Introduction

Congenital cytomegalovirus (cCMV) is the most common congenital infection globally, affecting approximately 0.5% of all live births in high income settings [1]. It is associated with long-term sequelae including sensorineural hearing loss and/or neurodevelopmental impairment in 17–20% of infected infants [2]. cCMV can result from both primary maternal infection during pregnancy, which carries a vertical transmission (VT) risk of approximately 32%, and non-primary maternal infection, which has a lower VT risk estimated at  $\leq$ 3.5% [3,4], albeit difficult to ascertain due to challenges diagnosing non-primary CMV infection. Once congenital infection occurs, risk and severity of cCMV disease appears to be similar irrespective of maternal infection type [5].

Historically, routine antenatal CMV screening has not been widely implemented due to the lack of effective interventions to mitigate VT or prevent fetal disease [6,7]. However, recent evidence has demonstrated that valaciclovir can reduce VT rates when started promptly after a primary maternal CMV infection in the periconception period or first trimester [8–10] and that the risk of infant cCMV-related sequelae is much higher when maternal infection occurs early in pregnancy [11]. This has prompted renewed interest in antenatal screening strategies; a recent consensus statement from the European Congenital Cytomegalovirus Initiative suggests consideration of universal screening depending on local CMV epidemiology, and recommends off-label use of valaciclovir for prevention of VT, where a maternal CMV infection is identified in early pregnancy [3]. Findings from an observational study also suggest the potential for valaciclovir to improve outcomes when given during pregnancy to treat moderately cCMV-symptomatic fetuses [12].

Although serological screening can only be used to identify primary maternal CMV infections, up to half of women of reproductive age in Europe are susceptible to primary CMV [13–16] and up to 1–2% may acquire CMV shortly before or during the first trimester [13,17], potentially making antenatal CMV screening for the purposes of reducing VT particularly relevant in this setting. However, there are important unanswered questions about its implementation and potential impact, including a lack of data so far on its potential to reduce severe cCMV-related sequelae in infants and children [18].

This survey aimed to investigate current antenatal CMV testing and treatment policies and practices, including the use of universal antenatal screening, in the context of evolving evidence supporting the use of valaciclovir for secondary and tertiary prevention of adverse cCMV-related outcomes.

## Methodology

To understand current antenatal CMV testing and treatment practices, we conducted a survey as part of the ACES (Antenatal CMV Evaluation of Screening) research project – a collaboration jointly led by University College London (UCL) and University College London Hospitals (UCLH). The web-based survey was created using REDCap (Research Electronic Data Capture) [19,20] and distributed among healthcare professionals via professional networks in maternal and fetal medicine, as well as to attendees of the 21st World Congress in Fetal Medicine in Lisbon, Portugal. The introductory text to the survey stated that it was for completion by healthcare professionals within antenatal services with knowledge of CMV testing or treatment practices. We did not apply any inclusion criteria based on number of deliveries at the respondents' healthcare center, but collected estimates of this, to describe the included sites. The survey was open between 29 April 2024 and 24 July 2024.

Statistical software STATA 17.0 (Stata Corp. LP, College station, TX) was used for the analysis. Duplicate responses were removed as well as responses that did not include information on the

healthcare center and professional role of the person completing the form, and/or information in at least one of the sections (testing or treatment approaches). Where multiple responses were submitted from the same healthcare service, the most complete response was kept for the analysis. We estimated the proportion of responses received from private healthcare providers using publicly available information online, as this information was not collected in the survey. No individual patient data were collected, and as the survey met the UK Health Research Authority definition for service evaluation (rather than research), ethics approval was not required.

Given the potential for differing uses of the term "screening" in the context of antenatal CMV testing, we did not use this term in the survey but instead asked respondents to state whether CMV testing was (1) offered routinely to everyone in pregnancy, with or without gestational age restrictions, or (2) in particular circumstances only (including to women perceived to be at high risk of CMV acquisition, or due to clinical concerns such as symptoms in the mother, or fetal anomalies on a scan). In the "Results" and "Discussion" sections, we refer to the first of these as universal antenatal CMV screening.

In this paper, we present analyses of responses received from healthcare professionals in Europe only. The maternal seroprevalence is lower in Europe than in some other regions [21], making the questions around antenatal screening particularly pertinent, and responses to our survey from outside of Europe were sparse and therefore difficult to interpret in context.

#### Results

Responses were received from respondents based at 73 healthcare centers across 21 European countries: UK (n = 12), Spain (n = 11), Italy (n = 11), Germany (n = 6), Greece (n = 5), Portugal (n = 5), Belgium (n = 3), Bulgaria (n = 3), Denmark (n = 2), Poland (n = 2), Romania (n = 2), Turkey (n = 2), and one response each from Austria, Czech Republic, France, Hungary, Latvia, the Netherlands, Norway, Serbia, and Switzerland. Overall, 76% (55/72) of responses were from tertiary centers, and an estimated 10% (7/73) were from private healthcare centers. Respondents were mainly consultants in Fetal Medicine (44%, 32/73) and Obstetrics/Gynaecology (27%, 20/73); 10% (7/73) were consultants in another specialty, 11% (8/73) were trainees, and 8% (6/73) were in another or unstated healthcare professional group. The estimated median annual births per site was 3000 (available for 57/73).

Half (52%, 38/73) of health centers had formalized CMV testing policies (58% (32/55) of tertiary centers vs. 29% (5/17) of non-tertiary centers,  $\chi^2 = 4.302$ , p = .038) of whom 61% (23/38) had introduced or significantly updated their policy in the last 2 years. Half of sites overall (39/73) from 11 of 21 countries reported offering CMV testing routinely to every pregnant woman, i.e. followed a universal antenatal CMV screening approach, sometimes with gestational age limits (Table 1). This was more common among centers with formalized testing policies than those without (84% (32/38) vs. 20% (7/35) respectively,  $\chi^2 = 30.19$ , p < .01), and mostly offered on an "opt-out" basis (Table 1). There were significant differences by country; e.g. comparing the three countries with >10 responses each, universal screening was offered by none of 12 UK sites, 7/11 sites in Spain, and 11/11 sites in Italy. For all sites, screening tests included CMV IgM and IgG, with 36% (14/39) offering IgG avidity, and 8% (3/39) using PCR. Of the 39 centers offering universal screening, the coverage was estimated to be >95% of pregnant women at half (18/39) of centers, and 59% (23/39) routinely offered repeat testing.

In terms of primary prevention, 49% (36/73) of healthcare centers gave routine advice to pregnant women on reducing the risk of acquiring CMV infection. This proportion was similar at tertiary and non-tertiary centers (51% (28/55) vs. 41% (7/17), respectively,  $\chi^2 = 0.4924$ , p = .48) but higher at centers offering screening vs. those who did not (69% (27/39) vs. 26% (9/34),  $\chi^2 = 13.287$ , p < .01).

Secondary prevention - i.e. medication offered to women with evidence of CMV infection during pregnancy to prevent transmission to the fetus - was reported to be used at 82% (60/73) of the centers (11% (8/73) of respondents reported that this was not used, and 7% (5/73) answered "don't know"). Most respondents reported the use of valaciclovir and that treatment would be offered when maternal primary CMV infection was identified during the periconception period or first trimester,

Table 1. Antenatal CMV testing approaches.

Antenatal CMV testing approaches <sup>a</sup>	% (n) of centers
Testing is offered routinely to every pregnant woman	38% (28/73)
Opt in <sup>b</sup>	15% (11/73)
Opt out <sup>c</sup>	23% (17/73)
Testing is offered routinely to every pregnant woman starting antenatal care by a certain gestation	15% (11/73)
Up to end 1st trimester	10% (7/73)
Opt in	1.4% (1/73)
Opt out	8.2% (6/73)
Up to end 2nd trimester	5% (4/73)
Opt in	1.4% (1/73)
Opt out	4.1% (3/73)
Testing is offered in particular circumstances	99% (72/73)
Clinical concern	99% (72/73)
Maternal signs and symptoms flu-like symptoms, fever, sore throat, myalgia, nausea, rash, lymphadenopathy	71% (52/73)
Derangement of maternal blood tests	42% (31/73)
Fetal anomalies such as small for gestation, cerebral abnormalities, echogenic bowel etc. detected on ultrasound	92% (67/73)
If the woman is thought to be at higher risk	16% (12/73)
Occupational exposure	15% (11/73)
Having a nursery-going child at home	13% (10/73)
Maternal CMV seronegativity prior to pregnancy	3% (2/73)
Younger maternal age	1% (1/73)
At woman's request	21% (15/73)

<sup>&</sup>lt;sup>a</sup>Of the 39 respondents reporting that their center offered routine testing to all women or to all those starting antenatal care by a certain gestation, 38 also reported that testing was offered in particular circumstances (responses not mutually exclusive).

Table 2. Use of medication for prophylaxis or treatment among 60 respondents who stated that at their center, medication would be offered to women with evidence of CMV infection during pregnancy, to prevent transmission to the fetus.

Question	Response	Ν	%
Under what circumstances is	Primary infection during periconception	56/60	93%
medication offered?a	period or in first trimester		
	Primary infection in second trimester	18/60	30%
	Primary infection in third trimester	8/60	13%
	Primary infection – unknown timing	12/60	20%
	Non-primary infection during periconception period or in first trimester	12/60	20%
	Non-primary infection in second trimester	4/60	7%
	Non-primary infection in third trimester	2/60	3%
	Non-primary infection – unknown timing	3/60	5%
	Don't know	3/60	5%
If medication is considered, who is the	Obstetric/fetal medicine specialist	47/60	78%
health professional that prescribes	Infectious disease specialist	14/60	23%
it?a	Virologist	6/60	10%
	All of these health professionals	1/60	2%
	Clinical geneticist	1/60	2%
What medication is offered prenatally	Valaciclovir	55/60	92%
with the aim of preventing CMV	Acyclovir	4/60	7%
transmission to the fetus?a	Valganciclovir	3/60	5%
	CMV specific Immunoglobulin	4/60	7%
If you decide to give women	Yes	54/60	90%
medication as above, would you	No	4/60	7%
offer an amniocentesis later in pregnancy?	Don't know/missing	2/60	3%
If yes, when would the amniocentesis	From 17 weeks	35/54	65%
be offered?	From 20 weeks	17/54	31%
	Other	2/54	4%

<sup>&</sup>lt;sup>a</sup>Multiple responses were accepted in this question.

with most also offering an amniocentesis in these circumstances. Despite valaciclovir being the most commonly used agent, use of acyclovir, valganciclovir and CMV specific immunoglobulin was also reported by 5-7% of respondents (Table 2). If treatment had been started for secondary prevention

bOpt in defined as "patients are offered testing and have to choose to take this up".

Opt out defined as "testing is done for all patients unless they request for it not to be done".

but an amniocentesis result was subsequently CMV DNA PCR positive, indicating that VT had occurred, then 79% (58/73) of respondents stated that the same treatment would be continued, with few opting to switch or stop treatment (5% 4/73 and 5% 4/73, respectively).

In managing pregnancies with evidence of fetal CMV infection, 78% (56/72) of respondents reported that at their center, maternal treatment would be offered, predominantly with valaciclovir (84%, 47/56), with the aim of reducing fetal CMV infection severity (i.e. tertiary prevention). Overall, among 64 respondents reporting that their center would offer medication for either secondary or tertiary prevention, 70% (45/64) considered an amniocentesis strongly indicated in these circumstances and 27% (17/64) that an amniocentesis would be useful (two responses: "don't know" or missing).

Of 59 sites offering treatment for secondary and/or tertiary prevention and responding to a question on frequency of treatment monitoring, 27% (16/59) monitored blood tests at least weekly, 46% (27/59) weekly to monthly, 20% (12/59) monthly, and 7% (4/59) less frequently than monthly. Adverse drug reaction reporting at centers offering treatment was inconsistent, with 43% (26/60) lacking a formal procedure, 38% (23/60) reporting to regional or national systems, and 25% (15/60) using local adverse event reporting systems.

Overall, 83% (58/70) of respondents supported routine CMV testing for pregnant women (49 strongly, nine moderately), 6% (4/70) were neutral, and 11% (8/70) opposed it (seven moderately, one strongly). The majority of respondents (81%, 57/70) agreed with the statement that routine CMV testing enhances equitable access to prophylaxis, thereby reducing the risk of fetal infection, while 77% (54/70) agreed that prophylaxis or treatment could improve individual outcomes. About half (49%, 34/70) supported public health benefits and economic arguments for antenatal CMV screening, with 37% (26/70) citing patient reassurance as a benefit. Conversely, concerns included testing-induced anxiety (33%, 23/70), the potential for increased terminations (31%, 22/70), and insufficient safety data for prophylaxis in pregnancy (16%, 11/70). Notably, 41% (29/70) did not perceive any significant risks associated with routine testing.

#### **Discussion**

In this 2024 survey of healthcare professionals from 73 healthcare centers across 21 European countries, half reported that universal antenatal CMV screening is offered at their center (in some cases with gestational age limits). The substantial variation in antenatal screening, both within some countries with higher numbers of responses as well as between countries, reflect differences in national guidelines (e.g. antenatal CMV screening is not recommended in UK guidelines, but has been recommended in Italian guidelines since the end of 2023) [22,23], as well as the evolving evidence base around effectiveness of valaciclovir used off-label to reduce CMV VT risk [8,10].

Recently published studies from Canada [24] and France [25] have concluded that universal CMV serological screening in pregnancy would be cost-effective, while an analysis from the US concluded it would not, unless an additional 5% reduction in VT was achieved with valaciclovir over and above the 71% reported in the trial from Israel [26]. Meanwhile, an opinion paper and statement have called for consideration of universal screening, depending on local CMV epidemiology [3], but also highlighted important evidence gaps around its implementation, risks, benefits, and cost-effectiveness [18], bringing this debate to the fore. The majority of clinicians responding to this survey were strongly supportive of antenatal CMV screening, but significant proportions cited concerns around anxiety induced by testing and increased terminations and insufficient safety data for using antivirals in pregnancy to reduce the risk of VT. Of note, in both the valaciclovir trial [8] and in a recent screening pilot in Barcelona [27], some women chose to terminate their pregnancy based only on fetal infection status and not scan findings. However, terminations related to CMV may be reduced overall in a universal antenatal CMV screening scenario, due to prevention of cCMV infections and CMV-related anomalies (as predicted in a cost-effectiveness analysis from France [25] and reported in a meta-analysis [10]). Setting-specific data are therefore needed to understand real-world impact. Respondents also indicated substantial variation in criteria for conducting CMV tests in response to risk or symptoms, with only half of centers having formalized CMV testing policies overall.

A clear majority of respondents (77% overall) reported that antiviral medication is used at their center to reduce the risk of CMV VT in pregnant women identified as having an early maternal primary CMV infection, and a similar proportion reporting medication for tertiary prevention in pregnancies with evidence of fetal infection, with most offering amniocentesis in these circumstances. It seems clear, therefore, that the emerging evidence base for valaciclovir in reducing VT has already resulted in its quite widespread use in the context of maternal primary CMV infection in early pregnancy, at sites responding to this survey. Although 92% of respondents said that the medication offered would be valaciclovir, the varied responses including valganciclovir and CMV specific immunoglobulin highlight potential variability in management, including agents with no evidence of efficacy [3]. Safety data from CMV studies to date are reassuring regarding the short-term risk of severe adverse events from valaciclovir [8]; however, data on its overall safety profile in pregnancy remain limited, particularly at the high doses and long durations used for CMV, and longer term safety data are lacking.

Of the centers responding to our survey who offered treatment, 43% lacked a formal reporting procedure for adverse drug reactions, but 93% reported monitoring blood tests on treatment at least monthly. There is no consensus on optimal monitoring of valaciclovir in pregnancy, but during the valaciclovir secondary prevention trial [8], adherence, safety, and toxicity were assessed every four weeks, and this included a full blood count and biochemistry (which usually would include liver function tests, urea, creatinine, and electrolytes). Monitoring during treatment is important given that acyclovir/valaciclovir can cause acute kidney injury (AKI) and drug-related encephalopathy, while fetal health is typically assessed through obstetric ultrasounds every 2–4 weeks. The risk of miscarriage with amniocentesis, while small (estimated at one in 200 or below [28]) is also part of the overall balancing of risks and benefits for implementing CMV testing on a population level and for individual women and their families. The variation in practice around the use and monitoring of antiviral treatment creates an inconsistent and potentially unsafe environment for women facing dilemmas and making decisions about their pregnancies in the context of concerns around CMV infection.

Our findings suggest that research to inform safe and equitable decisions around implementation of CMV testing and universal screening is urgently needed, including outcome data from settings where universal CMV screening in pregnancy has been introduced. Epidemiological research to underpin screening decisions tailored to specific settings is also needed, for example, the proportion of pregnant women who are susceptible to primary CMV infection, and incidence of primary CMV in pregnancy. Shared agreement on approaches and research priorities within healthcare settings is likely to be important to ensure equitable access to CMV screening, testing and treatment, or advice around this, against a backdrop of significant inconsistencies in CMV knowledge and perceptions among the European healthcare professionals that has been highlighted by previous studies [6,7,29]. This includes provision of advice to pregnant women on primary prevention of CMV, which was routinely offered by only 49% of centers overall and 69% offering routine CMV testing, despite guidance and criteria for introduction of screening programs stating that other options such as primary prevention should be implemented as a pre-requisite [30,31].

The main limitations of our results are the non-representative nature of the sample for this service evaluation (both on a national and regional basis), with small numbers of responses from each country, and a convenience sample of respondents who were mostly from tertiary centers and may have a particular interest and expertise in CMV, whose responses may therefore not be generalizable to other sites within each country. Respondents were asked about policies/practice at their center, which may extend beyond their area of personal clinical practice.

In conclusion, this snapshot of antenatal CMV policies and practice at 73 centers in Europe high-lights substantial variation in policies and practice in this evolving area. Shared research priorities are urgently needed to ensure that testing and treatment are carried out in an evidence-based and equitable way.

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#### **Author contributions**

CRediT: Rifat Ara: Formal analysis, Methodology, Visualization, Writing - original draft, Writing - review & editing; Noa Mevorach Zussman: Investigation, Methodology, Writing - original draft, Writing - review & editing; Thomas Sammut: Conceptualization, Investigation, Methodology, Writing - review & editing; Sara Sorrenti: Methodology, Writing - review & editing; George Attilakos: Conceptualization, Investigation, Methodology, Writing - review & editing; Dan Stott: Conceptualization, Investigation, Methodology, Writing - review & editing; Surabhi Nanda: Investigation, Methodology, Writing - review & editing; Asma Khalil: Conceptualization, Methodology, Writing - review & editing; Eleni Nastouli: Conceptualization, Funding acquisition, Methodology, Supervision, Writing - original draft, Writing - review & editing; Heather Bailey: Conceptualization, Formal analysis, Funding acquisition, Methodology, Supervision, Writing - original draft, Writing - review & editing.

# **Ethical approval**

Not applicable.

#### **Consent form**

Not applicable.

#### **Disclosure statement**

AK is Vice President, Royal College of Obstetricians and Gynaecologists; member of the Advisory Group for the UK National Screening Committee review of evidence on CMV screening and member of the National Screening Committee Fetal, Maternal and Child Health Expert group. HB is a co-investigator of the European Pregnancy and Paediatric Infections Cohort Collaboration (EPPICC) which has received funding from ViiV Healthcare and Merck Sharp & Dohme via Penta Foundation and a member of the Advisory Group for the UK National Screening Committee review of evidence on CMV screening. EN is a member of the PENTA Working Group in infections in pregnancy and the Advisory Group for the UK National Screening Committee review of evidence on CMV screening. All other authors have no conflicts to disclose.

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#### Data availability statement

The participants of this survey did not give consent for their responses to be shared publicly, and so research supporting data are not available.

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