



**HAL**  
open science

# Hygiene promotion might be better than serological screening to deal with Cytomegalovirus infection during pregnancy: a methodological appraisal and decision analysis

Agathe Billette de Villemeur, Pierre Tattevin, Louis-Rachid Salmi

## ► To cite this version:

Agathe Billette de Villemeur, Pierre Tattevin, Louis-Rachid Salmi. Hygiene promotion might be better than serological screening to deal with Cytomegalovirus infection during pregnancy: a methodological appraisal and decision analysis. *BMC Infectious Diseases*, 2020, 20 (1), pp.418. 10.1186/s12879-020-05139-8 . inserm-02967708

**HAL Id: inserm-02967708**

**<https://inserm.hal.science/inserm-02967708>**

Submitted on 15 Oct 2020

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

RESEARCH ARTICLE

Open Access



# Hygiene promotion might be better than serological screening to deal with Cytomegalovirus infection during pregnancy: a methodological appraisal and decision analysis

Agathe Billette de Villemeur<sup>1</sup>, Pierre Tattevin<sup>2</sup>, Louis-Rachid Salmi<sup>3,4,5\*</sup>  and the French Haut Conseil de la santé publique Working Group

## Abstract

**Background:** Cytomegalovirus infection is the most frequent viral congenital infection, with possible consequences such as deafness, or psychomotor retardation. In 2016, the French High Council of Public Health was mandated to update recommendations regarding prevention of cytomegalovirus infection in pregnant women. We summarize a critical appraisal of knowledge and deterministic decision analysis comparing the current no-screening situation to serological screening during pregnancy, and to hygiene promotion.

**Methods:** Screening was defined as systematic serological testing, during the first trimester, with repeated tests as needed, to all pregnant women. Outcomes were: 1) severe sequela: intellectual deficiency with  $IQ \leq 50$  or hearing impairment  $< 70$  dB or sight impairment ( $\leq 3/10$  at best eye); 2) moderate sequela: any level of intellectual, hearing or sight deficiency; and 3) death or termination of pregnancy. We simulated the one-year course of cytomegalovirus infection in a cohort of 800,000 pregnant women. We developed a deterministic decision model, using best and min-max estimates, extracted from systematic reviews or original studies.

(Continued on next page)

\* Correspondence: [louis-rachid.salmi@u-bordeaux.fr](mailto:louis-rachid.salmi@u-bordeaux.fr)

<sup>3</sup>CHU de Bordeaux, Pôle de santé publique, Service d'Information Médicale, F-33000 Bordeaux, France

<sup>4</sup>Univ. Bordeaux, ISPED, Centre INSERM U1219-Bordeaux Population Health, F-33000 Bordeaux, France

Full list of author information is available at the end of the article



© The Author(s). 2020 **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

(Continued from previous page)

**Results:** Relevant data were scarce or imprecise. We estimated that 4352 maternal primary infections would result in 1741 foetal infections, and an unknown number of maternal reinfections would result in 1699 foetal infections. There would be 788 cytomegalovirus-related consequences, including 316 foetal deaths or terminations of pregnancy, and 424 moderate and 48 severe sequelae. Screening would result in a 1.66-fold increase of poor outcomes, mostly related to a 2.93-fold increase in deaths and terminations of pregnancy, not compensated by the decrease in severe symptomatic newborns. The promotion of hygiene would result in a 0.75-fold decrease of poor outcomes, related to both a decrease in severe sequelae among symptomatic newborns ( $RR = 0.75$ ; min-max: 1.00–0.68), and in deaths and terminations of pregnancy ( $RR = 0.75$ ; min-max: 0.97–0.68).

**Conclusions:** Prevention of cytomegalovirus infection during pregnancy should promote hygiene; serological screening should not be recommended.

**Keywords:** Cytomegalovirus infection, Pregnancy, Mass screening, Hygiene, Decision support techniques

## Background

With a prevalence in live births from 0.6 to 6.1% in low-income countries [1] and 0.4 to 0.7% in industrialized countries [2], cytomegalovirus infection is the most frequent viral congenital infection worldwide [3]. Around 87% infected fetuses will not have any sequelae, even among those with severe symptoms at birth [4]; sequelae, however can occur in asymptomatic newborns, and late sequelae can occur up to 7 years after birth [4]. Accurate tools to predict the occurrence and consequences of congenital cytomegalovirus infection are lacking; imaging techniques do not accurately predict prognosis [5, 6]. Although cytomegalovirus infection is the first viral cause of deafness, which is the most frequent sequela [3, 7–11], severe sequelae, such as bilateral deafness, are rare (1–2%), occur in 40% of symptomatic infected newborns [4] and are rarer in asymptomatic infected newborns [4, 12]. The risk of sequelae related to congenital cytomegalovirus infection is similar to that of congenital toxoplasmosis or spina bifida [7, 13].

In the absence of a vaccine against cytomegalovirus [6, 14], some authors have suggested that screening during pregnancy or at birth could be good options to decrease the frequency of poor outcomes [15–17], but the possible benefits of screening has been debated [6, 15, 18–29]. Diagnosis of a primary infection relies on the appearance of IgG, or a significant increase in IgG or presence of IgM; a test of IgG avidity can confirm the date of infection, with an uncertainty of 3 months [30–33]. For optimal screening during pregnancy, tests should ideally be done during the first trimester, because the risk of transmission to the foetus is highest around conception and the performance of tests decreases later during pregnancy [34, 35]. One limit of screening for cytomegalovirus is related to the lack of reliable tests to identify reinfections or reactivations of previously acquired infections [6, 36]. In a population with 50% seroprevalence, the risk of transmission to the foetus and severity of consequences seem similar after reinfections or reactivations than after primary infections [37–43], but the frequency of reinfection remains unknown [6, 44–47].

To our knowledge, no national or international public health authorities have ever recommended screening as a strategy to decrease foetal transmission and its consequences, mostly because there is no effective treatment to propose to infected mothers. Still, some professional organizations have recommended screening during pregnancy or in healthcare professionals in a few countries [6, 18, 21, 22, 28, 48, 49]. Case-finding testing [50] by general practitioners or gynaecologists, as part of routine testing during pregnancy, has also been observed in Belgium, Portugal, Israel and France [15].

In France, two public bodies have considered, in 2002 [51] and 2004 [52], that screening could not be justified, given the absence of an effective treatment. They also argued that the World Health Organisation (WHO) criteria for the implementation of screening programs [53] were not respected. Both recommendations further underscored the need to put more efforts on prevention of cytomegalovirus infection, by focusing on known risk factors, and promoting hygiene [51, 52]. In 2016, the French General Direction of Health (DGS) mandated the French High Council of Public Health (HCPH) to update the latest 2004 recommendations regarding prevention of cytomegalovirus infection in pregnant women.

This paper summarizes the recommendations of the Working Group set by the HCPH to answer the French authorities' mandate. More specifically, we report the methods and results of a systematic critical appraisal of knowledge regarding cytomegalovirus infection and a deterministic decision analysis which compares the current no-screening situation to two strategies, namely screening during pregnancy and reinforcing hygienic measures, to identify the best strategy to decrease the burden of poor outcomes associated with congenital cytomegalovirus infection.

## Methods

### Scope and general process

The HCPH has constituted a Working Group including a core group of public health specialists, epidemiologists

and infectiologists, completed by representatives of stakeholders, including Public Health Agencies, virologists, infectiologists, paediatricians, ethicists, obstetricians, a paediatric nurse, an occupational physician, and a midwife. All members declared they had no potential conflict of interest related to this topic. The Working Group met 14 times to: i) formulate the targeted population, intervention, comparisons and outcomes (PICO) [54], ii) develop the decision model from a representation of the course of the infection, iii) review WHO screening criteria [53] and their adaptation [55], and iv) review the evidence. The Working Group also interviewed other stakeholders, including promoters of screening and patient associations. The last sessions were devoted to discussing conclusions and recommendations, which were approved by a formal vote, following HCPH rules [56]. This report is presented according to a combination of PRISMA for systematic reviews [57] and CHEERS for medico-economic evaluations [58]. The scope of the decision analysis, however, did not cover economic aspects, as there was no clear evidence on the effectiveness of the interventions compared (screening and hygiene promotion) when the work was initiated [59]. The protocol was not registered, but validated by the HCPH.

When building the decision analysis and reviewing evidence regarding screening, the Working Group considered that a recommendation should consider [53, 55]: the public health importance of the problem; the length of the preclinical phase; the reliability and accuracy of tests during the preclinical phase; the availability and effectiveness of a treatment during the preclinical phase; the risk-effectiveness balance associated with systematic serological screening.

#### Definition of compared interventions

We compared the current French situation, including one visit each month, at least four serology tests (toxoplasmosis; rubella; syphilis; hepatitis B virus) between 10 and 15 weeks of amenorrhoea, and three echography exams around 9–11, 20–25 and 30–35 weeks of amenorrhoea [60], with two strategies that would either introduce cytomegalovirus screening during pregnancy, or promote hygiene. The current situation was defined as recommended in 2004, i.e. no cytomegalovirus screening [52], neither during pregnancy nor at birth; there is however, since 2014, a national program promoting screening of hearing deficiency at birth [61]. The screening strategy would offer all pregnant women a systematic cytomegalovirus serology, during the first trimester, with possible repeated tests as needed. The hygiene strategy would consist in reinforcing hygiene measures through a strong and repeated promotion among pregnant women, the public and health professionals, as previously shown

as effective in several countries [17, 62–64]. Specific modalities were not defined, but we assumed that hygiene would be applied vigilantly [65].

#### Search strategy and selection criteria

Literature review started by identifying references assessed in the 2002 and 2004 reports [51, 52], and reviews published since [1, 2, 4–7, 10, 12, 14–16, 19, 23, 25, 29, 30, 34, 39, 49, 66–96]. Then, each member of the Working Group provided the literature regarding the topic they were in charge of. Relevant references were sought in Pubmed/Medline, Cochrane database, Google Scholar, and “banque de données en santé publique”, until 2017. Inclusion criteria covered articles published in French or English since 2002, completed with the evidence covered in the previous recommendations. Keywords or free-text expressions used were “congenital cytomegalovirus infection”, “congenital infection”, “TORCH”, “cytomegalovirus”, and “stillbirth”, “mortality”, “case fatality”, “termination of pregnancy”, “miscarriage”, “sensory neuro hearing loss”; complementary searches also included “transmission”, “vertical transmission”, “immunity”, “immune defence”, “day care centres”, “variability”, “contamination route”, “primary infection”, “reactivation-reinfection”, “recommendations”, “program”, “pregnancy”, “foetus”, “newborns”, “prevention”, “epidemiology”, “prevalence”, “incidence”, “symptomatology”, “low-birth weight”, “small size for gestational age”, “prognosis”, “follow up”, “outcome”, “sequelae”, “microcephaly”, “mental deficiency”, “mental disorder”, “visual disorder”, “sensorineural hearing loss”, “autism”, “screening”, “testing”, “assay”, “serology”, “diagnosis”, “predictive value”, “sensitivity and specificity”, “diagnostic accuracy”, “avidity”, “PCR”, “hygiene”. Whenever identified from reference lists of previously selected articles, articles and guidelines in other languages (Portuguese, German, and Hebrew) were translated. The search started with systematic reviews and meta-analyses, but all articles based on randomized controlled trials, case-control studies or other observational studies were used as needed, including opinion papers, to identify potential relevant evidence. We also completed our search by interviewing experts, and reading conferences abstracts. Data were also asked from Public Health agencies (Santé Publique France; Agence de la Biomédecine), registries of children with handicaps, National Reference Centres for the control of transmissible diseases and Pluridisciplinary Centres for Prenatal Diagnostic. Level of evidence was graded using SIGN checklists (available at <https://www.sign.ac.uk/checklists-and-notes.html>; accessed February 24, 2020).

#### Construction and analysis of decision model

Outcomes were defined as follows: 1) severe sequelae: intellectual deficiency with Intelligence Quotient (IQ) ≤

50 or severe hearing impairment < 70 dB or severe visual impairment ( $\leq 3/10$  for the best eye); 2) moderate sequelae: any level of intellectual deficiency, hearing or sight impairment; and 3) death or termination of pregnancy.

We simulated the course of cytomegalovirus infection in a virtual cohort of 800,000 pregnant women, which is the estimated number of pregnancies in France in 2010, based on the number of live births. The time horizon was 1 year.

All parameters were extracted, wherever available, either from meta-analyses, or other systematic reviews, observational studies based on representative samples, prospective or historical cohorts or randomized trials. Studies with recruitment bias, major losses to follow up, or poor case definitions were used only if a parameter could not be found elsewhere. Case reports or case series were excluded. As no single study adequately described the course of the infection, from a healthy seronegative woman to the observation of sequelae in children, we used data from studies describing one stage of the course of the infection. Probability of an event at a given stage was multiplied by the probability of the next event.

We developed a deterministic decision model, using best and min-max estimates (Table 1). Whenever the literature provided several estimates for a given parameter, we used the mean of available values as best estimate. For min-max models, we used the lowest and highest limits of reported confidence intervals, or the minimum and maximum of all available estimates. When the expert group considered that an extreme value was either not coherent with the French context or considered unrealistic or incompatible with calculation (for instance a test specificity of 100%), we used minimum or maximum point estimates reported in a meta-analysis.

Because some key data were lacking, we made the following choices or hypotheses. 1) Prevalence of maternal Cytomegalovirus infection was taken from a French representative survey [97], rather than from a meta-analysis including non-representative studies [2]. Because this prevalence also varied dramatically across countries and French regions, we used age-specific prevalence to compute the minimum and maximum prevalence. 2) Because the number of reinfections or reactivations in women with preconception immunity is unknown [46, 144, 145], we hypothesized that the number of newborns infected would be the same in women with preconception immunity, after a reinfection or reactivation, and after a primary infection, in line with literature data [2, 6, 19, 33, 37–39, 42, 43, 87, 88, 102, 144–146]. 3) To estimate the potential impact of cytomegalovirus serological screening, we applied sensitivity and specificity estimates for the main tests used in France. 4) To consider the fact that infections occurring just before a pregnancy can have consequences for the foetus [39, 88, 98, 101], varying transmission rates by pregnancy trimesters, and the fact that seroconversion late

during pregnancy would not leave enough time to carry all exams, and the relatively moderate or low severity of late infections, we estimated the overall rate by dividing the time of transmission in four trimesters (prior to conception, and three pregnancy trimesters), and hypothesized that no intervention would be done during the last trimester. 5) To estimate the potential impact of hygiene, we used a conservative rate reduction found in a French study [64], considering that studies carried elsewhere lacked a control group and thus were overoptimistic and unrepresentative of the compliance expected in France.

## Results

### Decision model

The PICO and decision models were formulated from a public health perspective, to assess whether screening during pregnancy (intervention 1) or promotion of hygiene through information campaigns targeting the public and healthcare professionals (intervention 2) would decrease the frequency of children infected by cytomegalovirus and having sequelae, decrease the frequency of infected fetuses resulting in termination of pregnancy, and decrease the number of deaths in newborns and toddlers (outcomes), compared to care usually provided, which does not include screening (comparator).

### Data source

The Working Group reviewed 572 references, including 90 systematic reviews (Fig. 1). In general, data were scarce and often very imprecise (Table 1). Min-max estimates were used in the model only for sero-prevalence, incidence of maternal primary infection, transmission rate from mother to foetus, prevalence of infection at birth, and sensitivity and specificity of IgM tests; for the proportion of infected newborns free of symptoms, we only used the best and minimal estimate. For the screening scenario, the transmission rate from mother to foetus had to be estimated separately, depending on the time of transmission, as the rate during the first and second trimester are different, and a transmission during the third trimester was deemed too late to allow any early intervention. Best estimates for these transmission rates were based on expert consensus, as were the estimates for the effectiveness of hygiene promotion.

### Course of cytomegalovirus infection during pregnancy

In France, for a typical cohort of 800,000 pregnancies, we estimated there would be 4352 maternal primary infection, that would result in 1741 fetuses being affected by cytomegalovirus and an unknown number of maternal reinfections, that would result in 1699 fetus being affected by cytomegalovirus (Fig. 2). These foetal infections would result in a total of 788 cytomegalovirus-related consequences, including 316 foetal deaths or

**Table 1** Data sources and parameters regarding cytomegalovirus infection during pregnancy, potential screening tests and hygiene measures

Parameter	Sources	Best estimate	Min-Max	Comments
Sero-prevalence in 15–49 years-old women	[97]	45.6%	25.2–61.0%	Robust French representative survey
Incidence of MPI		1.0%	0.2–1.4%	Mean incidence and mean of CI lower and higher limits (expert consensus)
Transmission rate from mother to foetus	[19, 36, 53, 84, 87, 98–100]	40.0%	5.0–72.2%	Mean transmission rates and CI lower and higher limits from studies reporting rates by trimester of pregnancy
Transmission rate from mother to foetus (1st trimester)	[39, 88, 98, 101]	19%	NA	Mean incidence (expert consensus); screening scenario only
Transmission rate from mother to foetus (2nd trimester)	[39, 88, 98, 101]	36%	NA	Mean incidence (expert consensus); screening scenario only
Transmission rate after reinfection <sup>b</sup>	[42, 102–104]			Unknown; assumed equal to transmission after MPI
Proportion of infected newborns who are symptom free	[2, 4, 105, 106]	87.3%	Min: 75.0%	Stable across studies
Proportion of medical TOP among MPI or infected foetus	[2, 4, 20, 23, 25, 39, 41, 43, 74, 88, 89, 105, 107–120]	9.2%	NA	Data from National Reference Laboratory and literature
Proportion of medical TOP after screening	[85, 103]	95.0%	NA	Foetal infections confirmed by amniocentesis, positive or not at echography
Prevalence of infection at birth	[1, 2, 4, 38, 42, 68, 69, 97, 98, 112, 121]	0.43%	0.20–0.61%	Min-max from European studies, vary with selection and tests
Proportion of infected newborns who are symptomatic	[2, 4, 88, 105, 106]	12.7%	NA	Do not include TOP, part of whom would have died <sup>c</sup>
Proportion of infected newborns who are symptomatic born from mothers with immunity prior to pregnancy	[38, 39, 42, 105, 122]	12.7%	NA	Stable across studies
Incidence of hearing impairment between birth and 5 years among asymptomatic newborns with sequelae	[9]	53.0%	NA	
Frequency of any sequelae in asymptomatic newborns	[4, 11, 12, 43, 98, 106, 123, 124]	13.3%	NA	
Frequency of any severe sequelae in severe symptomatic newborns	[4, 9, 10, 19, 42, 43, 162, 163, 173]	47.0%	NA	Middle of value range
Frequency of any moderate sequela in severe symptomatic newborns	[4, 9, 19, 42, 43, 105, 106, 124]	25.0%	NA	Middle of value range
Frequency of any moderate sequela in moderately symptomatic newborns	[4, 9, 19, 42, 43, 105, 106, 124]	16.0%	NA	Middle of value range
Proportion of any severe symptomatic newborns without sequela	[105]	28.0%	NA	Middle of value range
Proportion of any moderately symptomatic newborns without sequela	[105]	51.0%	NA	Middle of value range
Frequency of any severe sequelae in moderately symptomatic newborns	[105]	33.0%	NA	Middle of value range
Proportion of any late sequelae among symptomatic newborns with sequelae	[105, 106, 125]	43.0%	NA	
Sensitivity IgG	[126–128]	99.7%		Diasorin test; false negative women considered negatives, but MPI and consequences considered in truly infected women

**Table 1** Data sources and parameters regarding cytomegalovirus infection during pregnancy, potential screening tests and hygiene measures (Continued)

Parameter	Sources	Best estimate	Min-Max	Comments
Specificity IgG	[126–128]	99.4%		Abbott test; false positive women considered positives, but MPI and consequences considered in truly infected women
Sensitivity IgM	[128–131]	94.0%	79.4–95.9% <sup>a</sup>	Vidas, Beckman-Coulter, Diasorin, Roche, Siemen HC tests
Specificity IgM	[128–132]	99.3%	96.4–100% <sup>a</sup>	
Sensitivity avidity of IgG	[23, 34, 36, 109, 131, 133–142]	83.0%		During first 12 weeks of pregnancy; applied when IgM positive
Specificity avidity of IgG	[23, 34, 133–143]	82.0%		During first 12 weeks of pregnancy; applied when IgM positive
Absolute reduction with hygiene	[63]	–50%		Group consensus on most plausible result

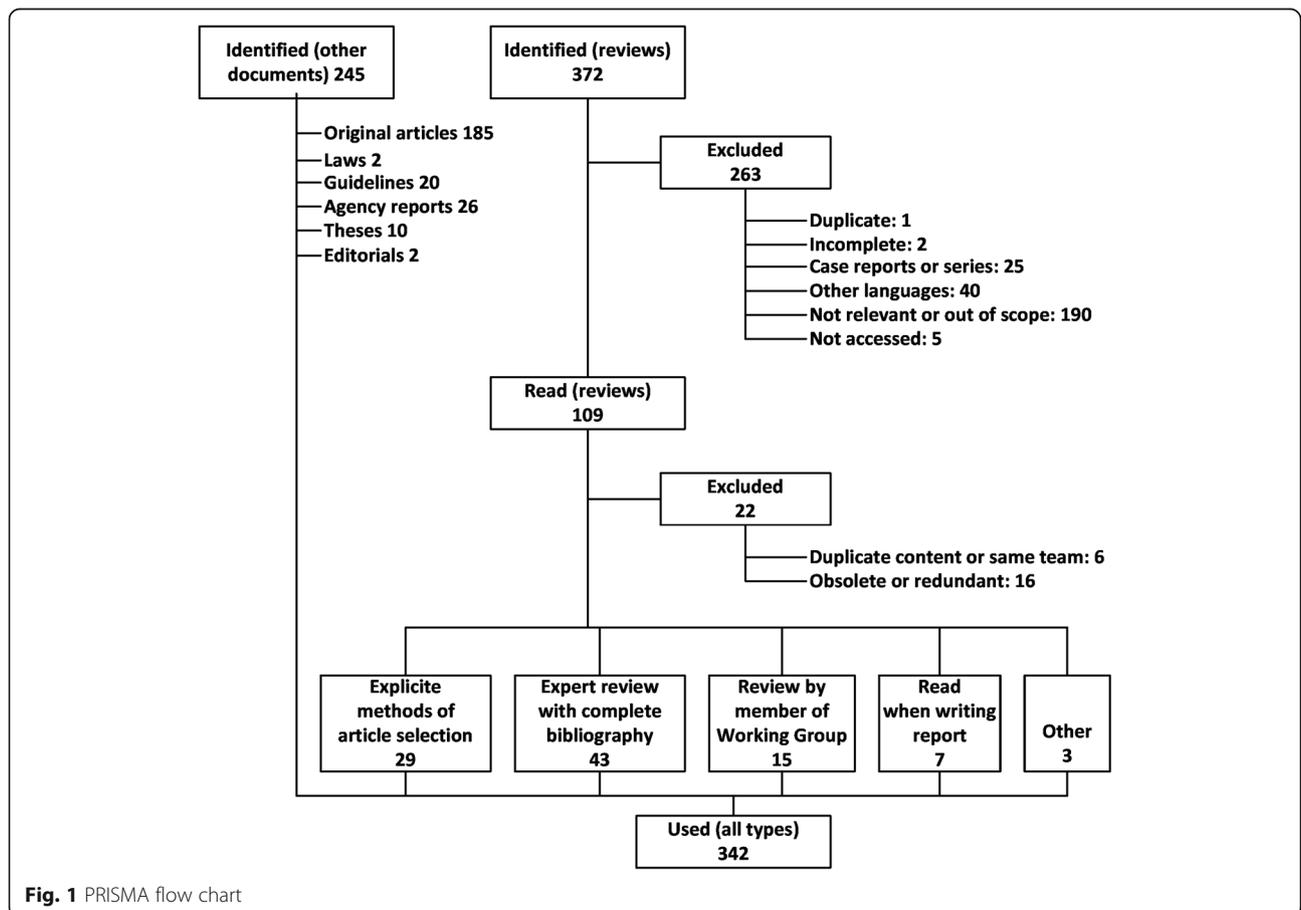
MPI maternal primary infection; TOP termination of pregnancy; <sup>a</sup> Maximum values are point estimates from studies not providing confidence intervals; <sup>b</sup>, unknown, considered equal to previous line; NA: min-max not considered in robustness analyses; <sup>c</sup> Min = 0 from [4] disregarded by group as not plausible

terminations of pregnancy, 424 moderate sequelae, and 48 severe sequelae.

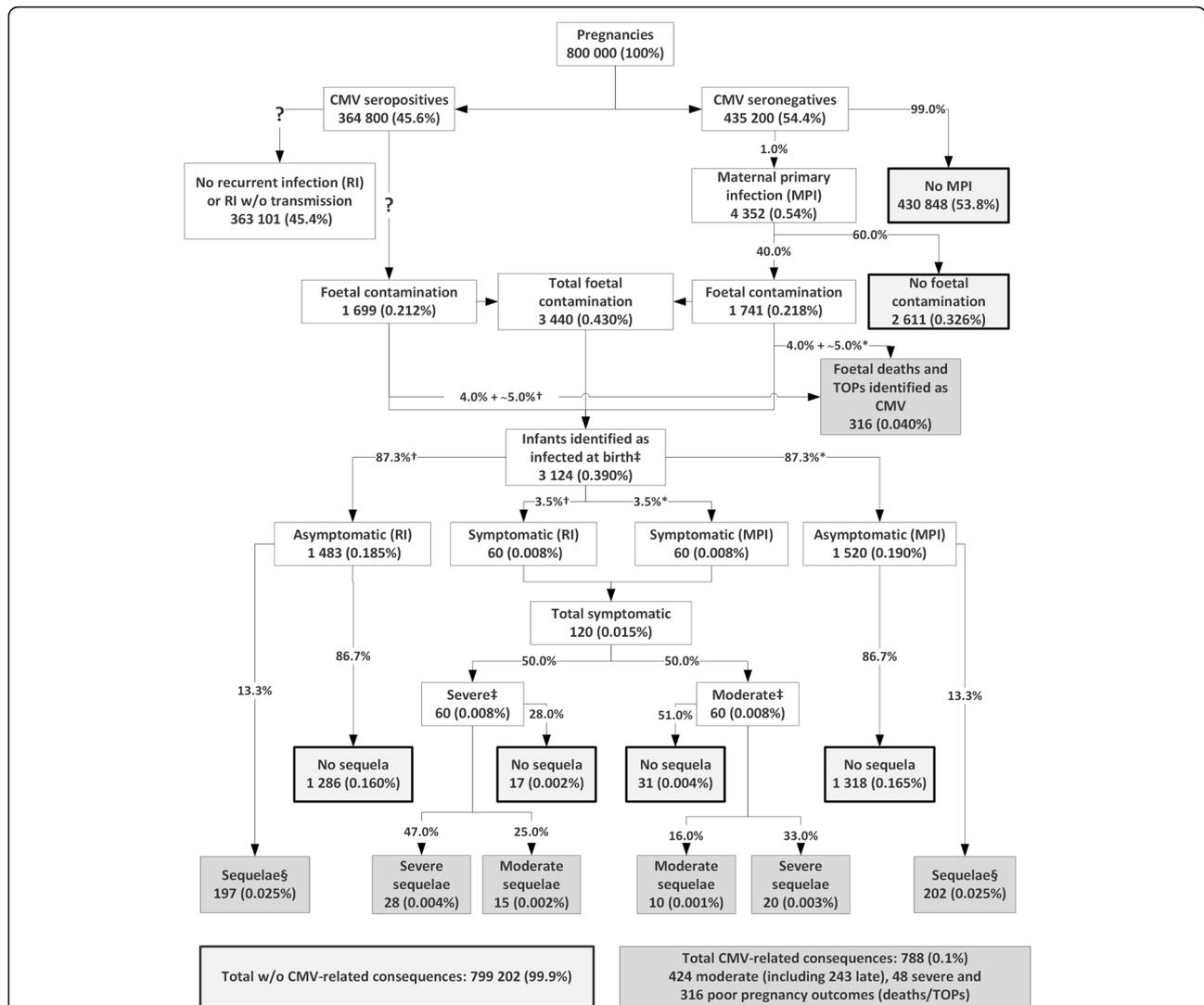
**Potential impact of systematic serological screening and hygiene promotion**

Compared to the current French situation, with the introduction of IgG, IgM and avidity of IgG in negative

in the first trimester and, in the second trimester, of IgG for women previously negative, serological screening would correctly identify 2780 MPIs and result in 484 false negatives and 238 false positives, and a total of 3018 women would be considered MPIs. Screening would result in a 1.66-fold increase (min: 1.13; max: 2.16) of poor outcomes, from 788/800000 to 1307/



**Fig. 1** PRISMA flow chart



800000 (Table 2). This increase would be mostly related to a 2.93-fold increase (min: 1.9; max: 4.38) in deaths and terminations of pregnancy, which would not be out-balanced by a decrease in severe symptomatic newborns ( $RR = 0.83$ ; min-max: 0.96–0.71) and severe sequelae in symptomatic newborns (Relative Risk ( $RR$ ) = 0.83; min-max: 1.00–0.71).

Compared to the current French situation, the promotion of hygiene would result in a 0.75-fold decrease (min: 0.97; max: 0.68) of poor outcomes, from 788/800000 to 588/800000 (Table 2). This would be related to both a decrease in severe sequelae among symptomatic newborns ( $RR = 0.75$ ; min-max: 1.00–0.68), and in

deaths and terminations of pregnancy ( $RR = 0.75$ ; min-max: 0.97–0.68).

## Discussion

### Main findings

To our knowledge, this is the first attempt to compare promotion of hygiene and systematic serological screening as interventions to deal with cytomegalovirus infection during pregnancy. Our review of the evidence and model suggest that screening of cytomegalovirus infection during pregnancy would actually increase the risk of poor outcomes. Compared to the current French situation, promotion of hygiene would result, each year, in 12 less children with severe sequelae, around a hundred

**Table 2** Cytomegalovirus infection during pregnancy, and potential impact of screening or a prevention program promoting hygiene. Figures are numbers (%) for the best and minimal and maximum; % are provided with one decimal when > 1%, two decimals when ≤ 1% but > 0.1%, and three decimals when ≤ 0.1%.

State	Current situation			Screening			Promotion of hygiene		
	Best (%)	Minimum (%)	Maximum (%)	Best (%)	Minimum (%)	Maximum (%)	Best (%)	Minimum (%)	Maximum (%)
CMV seronegative	435,200 (54.4)	598,400 (74.8)	312,000 (39.0)	433,683 (54.2)	595,414 (74.4)	310,128 (38.8)	435,200 (54.4)	598,400 (74.8)	312,000 (39.0)
MPI	4352 (0.54)	1197 (0.15)	4368 (0.55)	3018 (0.38)	1270 (0.16)	3069 (0.38)	2176 (0.27)	598 (0.07)	2184 (0.27)
Foetal infection in CMV-	1741 (0.22)	60 (0.0008)	3154 (0.39)	1741 (0.22)	60 (0.0008)	3154 (0.39)	870 (0.11)	30 (0.004)	1577 (0.20)
CMV seropositive	364,800 (49.6)	201,600 (25.2)	488,000 (61.0)	366,317 (45.8)	204,586 (25.6)	488,408 (61.1)	364,800 (45.6)	201,600 (25.2)	488,000 (61.0)
Foetal infection after RI	1699 (0.21)	1540 (0.19)	1726 (0.22)	1699 (0.21)	1540 (0.19)	1726 (0.22)	1699 (0.21)	1540 (0.19)	1726 (0.22)
Total foetal infections	3440 (0.43)	1600 (0.20)	4880 (0.61)	3440 (0.43)	1600 (0.20)	4880 (0.61)	2569 (0.32)	1570 (0.20)	3303 (0.41)
Deaths & TOP	316 (0.040)	147 (0.018)	449 (0.056)	919 (0.12)	183 (0.023)	1968 (0.25)	236 (0.030)	144 (0.018)	304 (0.038)
Total congenital infections	3123 (0.39)	1453 (0.18)	4431 (0.55)	2522 (0.32)	1417 (0.18)	2913 (0.36)	2333 (0.29)	1425 (0.18)	2999 (0.37)
Symptomatic in RI	60 (0.008)	54 (0.007)	60 (0.008)	60 (0.008)	54 (0.007)	60 (0.008)	60 (0.008)	54 (0.007)	60 (0.008)
Symptomatic in MPI	60 (0.008)	2 (< 0.001)	110 (0.014)	41 (0.005)	1 (< 0.001)	61 (0.008)	30 (0.004)	1 (< 0.001)	55 (0.007)
Severe symptomatic	60 (0.008)	28 (0.004)	85 (0.011)	50 (0.006)	27 (0.003)	60 (0.008)	45 (0.006)	27 (0.003)	58 (0.007)
Moderate symptomatic	60 (0.008)	28 (0.004)	85 (0.011)	50 (0.006)	27 (0.003)	60 (0.008)	45 (0.006)	27 (0.003)	58 (0.007)
Sequelae asymptom. RI	197 (0.025)	179 (0.022)	200 (0.025)	197 (0.025)	179 (0.022)	200 (0.025)	197 (0.025)	179 (0.022)	200 (0.025)
Sequelae asymptom. MPI	202 (0.025)	7 (< 0.001)	366 (0.05)	125 (0.016)	2 (< 0.001)	171 (0.022)	101 (0.013)	3 (< 0.001)	183 (0.023)
Severe sequela (symptom)	48 (0.006)	22 (0.003)	68 (0.009)	40 (0.005)	22 (0.003)	48 (0.006)	36 (0.005)	22 (0.003)	46 (0.006)
Mod. sequelae (symptom)	35 (0.004)	11 (0.001)	35 (0.004)	21 (0.003)	11 (0.001)	25 (0.003)	18 (0.002)	11 (0.001)	24 (0.003)
Total poor outcomes	788 (0.099)	367 (0.046)	1119 (0.14)	1301 (0.16)	397 (0.050)	2413 (0.30)	588 (0.074)	356 (0.045)	757 (0.095)

CMV cytomegalovirus; RI recurrent infection in CMV seropositive mothers; MPI maternal primary infection; CMV- mothers who are CMV seronegative before pregnancy; TOP termination of pregnancy; asymptom.: if asymptomatic at birth; Mod.: moderate; symptom: if symptomatic at birth

less children with moderate sequelae, and would avoid a quarter of cytomegalovirus-related foetal deaths and medical terminations of pregnancy.

The main limit of modelling the effect of screening during pregnancy on the course of cytomegalovirus infection is the absence of a treatment with proven effectiveness in this context. Thus, if cytomegalovirus infection is diagnosed during pregnancy, the only interventions to consider are termination of pregnancy and potentially harmful antiviral or immunoglobulin treatments, with unproven effectiveness [5, 79, 83, 86]. The only published evidence that valgancyclovir might be effective came from an uncontrolled trial [107], and no study, to our knowledge, has addressed side effects of available treatments, without any robust data on the tolerability of such regimen during pregnancy. Further, our model is based on available evidence which was often of low quality. Some authors have suggested that with serological tests to accurately date the maternal infection and safe foetal tests to accurately predict the occurrence of sequelae, screening could help better advise parents, who would, as autonomous adults, decide whether to terminate pregnancy or not [30, 147–149]. These ideal testing and prognostic conditions are currently unlikely to occur in any healthcare system [80]. Notably, most criteria set by the WHO to justify screening programs cannot be documented by appropriate evidence regarding 1) the availability and effectiveness of treatments [6, 150]; 2) the

actual magnitude of all dimensions of the problem, especially in women who are already seropositive and in children in the long term; 3) the reliability and validity of screening tests in a context of early infection and low prevalence; and 4) the lack of easily applicable prognostic markers to define women, fetuses, and children at risk of developing poor outcomes [6, 150]. Given that echography and magnetic resonance imaging still have numerous false negatives [77, 80], follow up and prognosis could be based on amniocentesis. An amniocentesis can confirm that a foetus is infected, and the likelihood of sequelae after a false negative is very low [151]. However, the predictive value of amniocentesis findings is poorly documented, as no follow-up study included systematic autopsy [103].

#### Strengths and limitations

One major limit, as was noted in previous systematic reviews [1, 2, 4–7, 10, 12, 14–16, 19, 23, 25, 29, 30, 34, 39, 49, 66–96], is the lack of high-grade evidence. No cohort study describes the full course of cytomegalovirus infection, from women of childbearing age, through conception, pregnancy, birth, to long-term follow up of children with sequelae. The only available cohort studies focused on one or a few steps of the course of the disease, providing only partial data [149]. Moreover, large studies are scarce, and a full cohort would require, given that cytomegalovirus congenital infection is rare, a huge number of women, which is probably not feasible.

Another limit is that our modelling of the course of the infection and the impact of hygiene promotion was based on average transmission frequencies. It has been shown that the frequency of MPIs increased from 5% around conception to 70% in the third trimester [88, 98, 101]. Because the frequency of transmission following reinfection remains undocumented throughout pregnancy, and the severity of infection decreases with late transmission, we believe the use of average transmission frequency provides a reasonable estimate of poor outcome frequency. Also, limiting the screening model to the impact on first-trimester transmissions and resulting outcome would not affect the overall result of the comparisons. Estimates of the potential impact of hygiene only came from studies conducted among women aware of their serological status; nevertheless, as it was shown that the main determinant of adherence to hygiene was the fact of being pregnant [152], we believe our estimated impact of hygiene is reasonable. Ideally, however, we would need confirmation of this effect in cohorts of pregnant women who are unaware of their serological status. Similarly, in the absence of studies focusing on the impact of hygiene on reinfections in seropositive women, we have not considered in our model the possibility of such an impact. Therefore, if messages promoting hygiene are well framed, the effects might even be larger than estimated, as already suggested for toxoplasmosis [65].

Another limit of the literature is the heterogeneity of the elements used by authors to define cases, regarding 1) number and types of symptoms considered at birth (clinical definition, including or not hypotrophy...) [2, 4, 9, 12, 81, 86]; 2) types of imaging or other tests used [5, 6, 29, 108, 147, 150, 153–161]; and 3) classification of intermediary avidity results (considered to be linked either with recent or past infection in different studies) [23, 24, 109, 162]. Losses to follow up were seldom considered, and many studies did not report foetal deaths in utero, stillbirths, or terminations of pregnancy [110]. No randomized trial ever evaluated screening; some observational studies did not include a comparison group, or only drew comparison with historical cohorts, some of which seem outdated [85]. Most studies of foetal death or post-neonatal fatalities did not include autopsies; the interpretation of autopsy findings is questionable, as there is no clear correlation between lesions found in cytomegalovirus-infected foetuses and the occurrence of sequelae [111, 147, 163, 164]. In addition, many comparative studies did not adjust for key confounding factors such as age, parity, occupation, or risk factors for infection.

Consequently, we sometimes had to use imprecise estimates and strong hypotheses. Still, the estimated number of severe sequelae for the course of infection is

consistent with the numbers observed locally by handicap registries, extrapolated to France, and with the results of a comprehensive survey [112], even though these estimates might be underestimated because a cytomegalovirus cause can be missed as tests based on the dried blood spots have a low sensitivity [30, 165]. We still believe our estimates of severe sequelae frequency are accurate enough to estimate the impact of screening, as screening would only detect MPIs [91]. We also modelled the course of disease and the potential impact of screening and hygiene using an incidence of MPI of 1%, as lower values reported in France [64] and in the Netherlands [166] were considered unrealistic by the Working group or likely linked to contexts where hygiene was much better than usual practices. One study reported much higher estimates, but was clearly overestimating the incidence of sequelae in infants, because the results of intermediate calculations were inappropriately rounded [19]. Another hypothesis was that the risk of foetal infection would be the same, whether women were already seropositive or not. Suggestions of higher risk following reinfections came from non-comparative case series of seropositive women [5, 68, 69, 72], or from studies where the risk of transmission was poorly documented in seropositive women [5, 72]. One of the strongest hypotheses concerns the frequency of pregnancy terminations related to the increased positive detection following screening [98, 103, 155]. This hypothesis, however, is coherent with European data, suggesting that pregnancy termination is more likely to be proposed than the option of welcoming a handicapped child [113]. One strength of the models is that we used a specific definition of moderate to severe sequelae. Some authors have suggested that intellectual deficiency can be observed in children with sensory neuro hearing loss, but this broader definition of possible sequelae came from non-comparative studies [4, 123, 167], and this disappeared in comparative studies, where asymptomatic newborns who have only an SNHL never have intellectual deficiency [12, 43]. Therefore, more evidence is clearly needed regarding the effectiveness of behavioural interventions to promote hygiene, the frequency of reinfection, and the information given to parents to make decisions, especially in relation to TOPs. Appropriate randomized controlled trial must also assess the effect of treatments, including on the severity of sequelae.

### Interpretation

To our knowledge, screening is not recommended by any national public health institution. Nevertheless, during interviews carried out by the Working Group, we identified practices of systematic prenatal screening at the level of one or several maternities, in France and in Israel [24, 110]. In the latter country, this practice is

associated with up to 50% voluntary or medical terminations of pregnancy [24, 110]. In Canada, a screening can be proposed to professionals who work with young children [49]; the same recommendation exists in Portugal but is poorly applied [28]. Beyond the results of our simulation, not recommending eviction from work (as applied for instance in Belgium [22, 48]) and screening in France is also justified by two facts [168]: 1) prevalence of infection is slightly higher in professionals than in families [78, 93, 168–171], though the difference disappears when hygienic measures are applied in professionals [170, 172–177]; and 2) when professionals are at home, they tend not to apply hygienic measures as consistently [7, 85, 168].

Until randomised trials demonstrate that a treatment is safe and effective to deal with cytomegalovirus congenital infection, the best strategy seems to be hygiene promotion, an educational intervention that would be relatively inexpensive and poses essentially no risk. Nevertheless, effective treatment should only be considered as a last resort, if infection occurs, and reinforcement of hygiene should always be promoted. Although the general principles of these measures are well known [6, 62, 84], we did not specify the nature of the promotion tools and organization. Hygiene measures are meant to decrease contact with urine, saliva, nasal and lachrymal fluid of young children [71]. They include handwashing and recommendations for young women, pregnant or with a project of pregnancy, and their partner to avoid sucking their child's spoons or teats, finishing their child's meals, sharing their toilet utensils, and kissing the face of a child who cries. Use of a condom is also recommended with a new or casual sex partner or when the partner is likely to be infected with cytomegalovirus [71]. Although some of these measures seem difficult to adopt in cultures where cuddling and consoling toddlers is usual, we found several studies documenting their effectiveness [25, 63, 178]. Our simulation, however, used a conservative estimate of halving MPI risk [25] whereas other studies that focused only on MPIs found reductions around 85% in that group [25, 63, 178]. These studies, however, were not randomized [84], compared with a non-comparable historical period [64] or another maternity where no information was provided [63].

The effectiveness could thus even be higher than simulated here, if recommendations were made to all women, regardless of the serology status, as hygiene would decrease both MPIs and reinfections [6, 73, 152, 179]. There are also too many uncertainties regarding the frequency of reinfections; studies dramatically fail to consider the raising anxiety related to screening, information on risk, stigmatization and the anxiety of parents who could have an infected child with sequelae [65, 180–182], especially if they have applied rigorous hygiene measures.

Professional and public health bodies should promote a better knowledge regarding cytomegalovirus in professionals and women. Knowledge regarding cytomegalovirus congenital infection is indeed insufficient in France and many other countries [6, 62, 65, 179, 181, 183–189]. The proportion of pregnant women who say they know about cytomegalovirus vary from 12.5 to 39.0% across countries [188]; this proportion goes up to 55.7 to 74.0% where reinforced information is associated to serology [184, 188], but this increase is more related to knowing that one is pregnant than to knowing the results of the serology [65, 178]. Moreover, women who are seropositive are likely to stop respecting hygiene measure consistently [65, 81], and are usually not followed as there is no test to identify reinfections outside of research projects [5, 36]. In most countries, cytomegalovirus is less known than diseases such as toxoplasmosis, human immunodeficiency virus, hepatitis B virus, rubella, autism, syphilis, sudden infant deaths, B streptococcus, Down syndrome, foetal alcohol syndrome, spina bifida, listeria, or parvovirus B19 [183–185, 187, 188]. One obstacle to an appropriate information of pregnant women, however, is that health professionals themselves have a poor knowledge regarding the modes of transmission, maternal symptoms, neonatal complications and effective preventive measures [180, 190–192].

## Conclusions

This review of the impact of hygiene promotion and systematic serological screening, as interventions to deal with cytomegalovirus infection during pregnancy, suggests that systematic screening would increase the risk of poor outcomes. Until randomised trials demonstrate that a treatment is safe and effective to deal with cytomegalovirus congenital infection, prevention of cytomegalovirus infection during pregnancy should primarily promote hygiene reinforcement. Serological screening should not be recommended.

## Abbreviations

CHEERS: Consolidated Health Economic Evaluation Reporting Standards; CMV: Cytomegalovirus; DGS: French General Direction of Health; HCPH: French High Council of Public Health; IQ: Intelligence Quotient; MPI: Maternal Primary Infection; PICO: Population Intervention Comparisons Outcome; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses; RI: Recurrent Infection; RR: Relative Risk; SIGN: Scottish Intercollegiate Guidelines Network; TOP: Termination of Pregnancy; TORCH: TOxoplasmosis Rubella Cytomegalovirus Herpes; WHO: World Health Organizations

## Acknowledgements

Members of the Working Group: Alain S, Limoges, virology; Antona D, Saint-Maurice, epidemiology; Aujard Y, Paris, paediatrics; Bégue A, Nice, ethics; Barjat T, Saint-Etienne, obstetrics; Billaud E, Nantes, infectiology; Billette de Villemeur A, Grenoble, public health; Colson S, Marseille, puericulture; Dufour V, Paris, paediatrics; Jean D, Grenoble, paediatrics; Gehanno JF, Rouen, occupational medicine; Halley des Fontaines V, Paris, public health; Mandelbrot L, Colombes, obstetrics; Matheron S, Paris, infectiology; Minodier P, Marseille, intensive care paediatrics; Roussey M, Rennes, paediatrics; Royère

D, reproductive medicine; Salmi LR, Bordeaux, public health; Scemama O, Saint-Denis, public health; Tattevin P, Rennes, infectiology; Teurnier F, Paris, midwifery; Trastour C, Nice, obstetrics; Vauloup-Fellous C, Villejuif, virology. A special acknowledgement to Marie-France d'Acremont, Scientific advisor to the General secretariat of the Haut Conseil de la santé publique.

#### Authors' contributions

ABD, PT and LRS have made substantial contributions to the design, analysis and interpretation of the study; LRS has drafted the work; ABD and PT have substantially revised it. All authors have read and approved the manuscript.

#### Funding

No funding was obtained for this study.

#### Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

#### Ethics approval and consent to participate

Not applicable.

#### Consent for publication

Not applicable.

#### Competing interests

The authors declare that they have no competing interests.

#### Author details

<sup>1</sup>Haut Conseil de Santé Publique, F-75000 Paris, France. <sup>2</sup>CHU de Rennes, Service de maladies infectieuses et médecine tropicale, F-35000 Rennes, France. <sup>3</sup>CHU de Bordeaux, Pôle de santé publique, Service d'Information Médicale, F-33000 Bordeaux, France. <sup>4</sup>Univ. Bordeaux, ISPED, Centre INSERM U1219-Bordeaux Population Health, F-33000 Bordeaux, France. <sup>5</sup>INSERM, ISPED, Centre INSERM U1219-Bordeaux Population Health, F-33000 Bordeaux, France.

Received: 12 December 2019 Accepted: 5 June 2020

Published online: 16 June 2020

#### References

- Lanzieri TM, Dollard SC, Bialek SR, Grosse SD. Systematic review of the birth prevalence of congenital cytomegalovirus infection in developing countries. *Int J Infect Dis*. 2014;22:44–8.
- Kenneson A, Cannon MJ. Review and meta-analysis of the epidemiology of congenital cytomegalovirus (CMV) infection. *Rev Med Virol*. 2007;17(4):253–76.
- Cohen BE, Durstenfeld A, Roehm PC. Viral causes of hearing loss: a review for hearing health professionals. *Trends Hear*. 2014;18:2331216514541361.
- Dollard SC, Grosse SD, Ross DS. New estimates of the prevalence of neurological and sensory sequelae and mortality associated with congenital cytomegalovirus infection. *Rev Med Virol*. 2007;17(5):355–63.
- Pass RF, Arav-Boger R. Maternal and fetal cytomegalovirus infection: diagnosis, management, and prevention. *F1000Res*. 2018;7:255.
- Rawlinson WD, Boppana SB, Fowler KB, Kimberlin DW, Lazzarotto T, Alain S, et al. Congenital cytomegalovirus infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis, and therapy. *Lancet Infect Dis*. 2017;17(6):e177–e88.
- Cannon MJ, Griffiths PD, Aston V, Rawlinson WD. Universal newborn screening for congenital CMV infection: what is the evidence of potential benefit? *Rev Med Virol*. 2014;24(5):291–307.
- Delobel-Ayoub M, Klapouszczak D, Cans C, Arnaud C, van Bakel ME. Données épidémiologiques sur les surdités bilatérales sévères et profondes en France pour les générations 1997 à 2005. *Bulletin Epidémiologique Hebdomadaire*. 2015;2015(42–43):781–8.
- Fowler KB, McCollister FP, Sabo DL, Shoup AG, Owen KE, Woodruff JL, et al. A Targeted Approach for Congenital Cytomegalovirus Screening Within Newborn Hearing Screening. *Pediatrics*. 2017;139(2):e20162128.
- Goderis J, De Leenheer E, Smets K, Van Hoecke H, Keymeulen A, Dhooge I. Hearing loss and congenital CMV infection: a systematic review. *Pediatrics*. 2014;134(5):972–82.
- Lanari M, Lazzarotto T, Venturi V, Papa I, Gabrielli L, Guerra B, et al. Neonatal cytomegalovirus blood load and risk of sequelae in symptomatic and asymptomatic congenitally infected newborns. *Pediatrics*. 2006;117(1):e76–83.
- Bartlett AW, McMullan B, Rawlinson WD, Palasanthiran P. Hearing and neurodevelopmental outcomes for children with asymptomatic congenital cytomegalovirus infection: a systematic review. *Rev Med Virol*. 2017. <https://doi.org/10.1002/rmv.1938>. Online ahead of print. on PubMed.
- Newborn screening: toward a uniform screening panel and system—executive summary. *Pediatrics*. 2006;117(5 Pt 2):S296–307.
- Itell HL, Nelson CS, Martinez DR, Permar SR. Maternal immune correlates of protection against placental transmission of cytomegalovirus. *Placenta*. 2017;60(Suppl 1):S73–s9.
- Khalil A, Jones C, Ville Y. Congenital cytomegalovirus infection: management update. *Curr Opin Infect Dis*. 2017;30(3):274–80.
- Leruez-Ville M, Ville Y. Fetal cytomegalovirus infection. *Best Pract Res Clin Obstet Gynaecol*. 2017;38:97–107.
- Reichman O, Miskin I, Sharoni L, Eldar-Geva T, Goldberg D, Tsafir A, et al. Preconception screening for cytomegalovirus: an effective preventive approach. *Biomed Res Int*. 2014;2014:135416.
- Adler SP. Screening for cytomegalovirus during pregnancy. *Infect Dis Obstet Gynecol*. 2011;2011:1–9.
- Buxmann H, Hamprecht K, Meyer-Wittkopf M, Friese K. Primary human Cytomegalovirus (HCMV) infection in pregnancy. *Deutsches Arzteblatt international*. 2017;114(4):45–52.
- Carrara J, N'Diaye DS, Azria E, Launay O, Rozenberg F, Yazpandanah Y, et al. Management of Cytomegalovirus Seroconversion during pregnancy in France. *Fetal Diagn Ther*. 2016;39(1):4–12.
- Gruppo multidisciplinare "Malattie infettive in ostetricia-ginecologia e neonatologia". Percorsi diagnostico-assistenziali in Ostetricia-Ginecologia e Neonatologia - Citomegalovirus. Milano: Società Italiana di Neonatologia; 2012.
- Gyselaers W, Jonckheer P, Ahmadzai N, Ansari MT, Carville S, Dworzynski K, et al. What are the recommended clinical assessment and screening tests during pregnancy? Bruxelles: Belgian Health Care Knowledge Centre; 2015. p. 125.
- Lazzarotto T, Guerra B, Gabrielli L, Lanari M, Landini MP. Update on the prevention, diagnosis and management of cytomegalovirus infection during pregnancy. *Clin Microbiol Infect*. 2011;17(9):1285–93.
- Rahav G. Congenital cytomegalovirus infection—a question of screening. *Isr Med Assoc J*. 2007;9(5):392–4.
- Revello MG, Fabbri E, Furione M, Zavattoni M, Lillieri D, Tassi B, et al. Role of prenatal diagnosis and counseling in the management of 735 pregnancies complicated by primary human cytomegalovirus infection: a 20-year experience. *J Clin Virol*. 2011;50(4):303–7.
- Schlesinger Y, Reich D, Eidelman AI, Schimmel MS, Hassanin J, Miron D. Congenital cytomegalovirus infection in Israel: screening in different subpopulations. *Isr Med Assoc J*. 2005;7(4):237–40.
- Seror J, Bordes P, Luton D. Dépistage systématique du CMV pendant la grossesse : évaluation des pratiques en Île-de-France. *Gynecol Obstet Fertil*. 2013;41(10):578–82.
- Sousa P, Madureira G, Moucho M, Rouxinol-Dias AL, Montenegro N. Periconceptional CMV infection prevention in Portugal: population subgroup study in a tertiary perinatal care center. *J Matern Fetal Neonatal Med*. 2018;31(15):1956–61.
- Walker SP, Palma-Dias R, Wood EM, Shekleton P, Giles ML. Cytomegalovirus in pregnancy: to screen or not to screen. *BMC Pregnancy Childbirth*. 2013; 13:96.
- Benoist G, Leruez-Ville M, Magny JF, Jacquemard F, Salomon LJ, Ville Y. Management of pregnancies with confirmed cytomegalovirus fetal infection. *Fetal Diagn Ther*. 2013;33(4):203–14.
- Furione M, Rognoni V, Sarasini A, Zavattoni M, Lillieri D, Gerna G, et al. Slow increase in IgG avidity correlates with prevention of human cytomegalovirus transmission to the fetus. *J Med Virol*. 2013;85(11):1960–7.
- Maidji E, Genbacev O, Chang HT, Pereira L. Developmental regulation of human cytomegalovirus receptors in cytotrophoblasts correlates with distinct replication sites in the placenta. *J Virol*. 2007;81(9):4701–12.
- Public Health England UK. UK standards for microbiology investigations. Cytomegalovirus Serology Virology. 2015;28(3):1–21.
- Grangeot-Keros L, Cointe D. Diagnosis and prognostic markers of HCMV infection. *J Clin Virol*. 2001;21(3):213–21.

35. Lazzarotto T, Varani S, Spezzacatena P, Gabrielli L, Pradelli P, Guerra B, et al. Maternal IgG avidity and IgM detected by blot as diagnostic tools to identify pregnant women at risk of transmitting cytomegalovirus. *Viral Immunol.* 2000;13(1):137–41.
36. Picone O, Grangeot-Keros L, Senat M, Fuchs F, Bouthry E, Ayoubi J, et al. Cytomegalovirus non-primary infection during pregnancy. Can serology help with diagnosis? *J Matern Fetal Neonatal Med.* 2017;30(2):224–7.
37. Giannattasio A, Di Costanzo P, De Matteis A, Milite P, De Martino D, Bucci L, et al. Outcomes of congenital cytomegalovirus disease following maternal primary and non-primary infection. *J Clin Virol.* 2017;96:32–6.
38. Lereuz-Ville M, Magny JF, Couderc S, Pichon C, Parodi M, Bussières L, et al. Risk factors for congenital Cytomegalovirus infection following primary and nonprimary maternal infection: a prospective neonatal Screening study using polymerase chain reaction in saliva. *Clin Infect Dis.* 2017;65(3):398–404.
39. Manicklal S, Emery VC, Lazzarotto T, Boppana SB, Gupta RK. The "silent" global burden of congenital cytomegalovirus. *Clin Microbiol Rev.* 2013;26(1):86–102.
40. Puhakka L, Renko M, Helminen M, Peltola V, Heiskanen-Kosma T, Lappalainen M, et al. Primary versus non-primary maternal cytomegalovirus infection as a cause of symptomatic congenital infection - register-based study from Finland. *Infect Dis.* 2017;49(6):445–53.
41. Rahav G, Gabbay R, Ornoy A, Shechtman S, Arnon J, Diav-Citrin O. Primary versus nonprimary cytomegalovirus infection during pregnancy, Israel. *Emerg Infect Dis.* 2007;13(11):1791–3.
42. Ross SA, Fowler KB, Ashrith G, Stagno S, Britt WJ, Pass RF, et al. Hearing loss in children with congenital cytomegalovirus infection born to mothers with preexisting immunity. *J Pediatr.* 2006;148(3):332–6.
43. Townsend CL, Forsgren M, Ahlfors K, Ivarsson SA, Tookey PA, Peckham CS. Long-term outcomes of congenital cytomegalovirus infection in Sweden and the United Kingdom. *Clin Infect Dis.* 2013;56(9):1232–9.
44. Boppana SB, Rivera LB, Fowler KB, Mach M, Britt WJ. Intrauterine transmission of cytomegalovirus to infants of women with preconceptional immunity. *N Engl J Med.* 2001;344(18):1366–71.
45. Nigro G, Mazzocco M, Anceschi MM, La Torre R, Antonelli G, Cosmi EV. Prenatal diagnosis of fetal cytomegalovirus infection after primary or recurrent maternal infection. *Obstet Gynecol.* 1999;94(6):909–14.
46. Ross SA, Arora N, Novak Z, Fowler KB, Britt WJ, Boppana SB. Cytomegalovirus reinfections in healthy seroimmune women. *J Infect Dis.* 2010;201(3):386–9.
47. Yamamoto AY, Mussi-Pinhata MM, Boppana SB, Novak Z, Wagatsuma VM, Oliveira Pde F, et al. Human cytomegalovirus reinfection is associated with intrauterine transmission in a highly cytomegalovirus-immune maternal population. *Am J OBSTET Gynecol.* 2010;202(3):297.e1–8.
48. Conseil supérieur de la santé. La problématique du cytomégalovirus chez la femme enceinte [AVIS DU CONSEIL SUPERIEUR DE LA SANTE N° 9262]. Bruxelles: Conseil supérieur de la santé; 2015.
49. Yinon Y, Farine D, Yudin MH. Screening, diagnosis, and management of cytomegalovirus infection in pregnancy. *Obstet Gynecol Surv.* 2010;65(11):736–43.
50. Haynes RB, Sackett DL, Guyatt GH, Tugwell P. Clinical epidemiology: how to do clinical practice research. Third ed. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 480.
51. Conseil Supérieur d'Hygiène Publique de France. Avis du Conseil Supérieur d'Hygiène Publique de France. Section des Maladies Transmissibles du 8 mars 2002 relatif aux recommandations pour la prévention de l'infection à cytomégalovirus chez les femmes enceintes. Paris: CSHP; 2002.
52. Agence nationale d'évaluation en santé. Évaluation de l'intérêt du dépistage de l'infection à cytomégalovirus chez la femme enceinte en France. Paris: ANAES; 2004.
53. Wilson JMG, Jungner G. The principles and practice of screening for disease. Geneva: World Health Organization; 1968.
54. Straus S, Richardson WS, Glasziou P, Haynes RB. Evidence-based medicine. How to practice and teach EBM. Edinburgh: Elsevier Churchill Livingstone; 2005. p. 299.
55. Salmi LR, Coureau G, Bailhache M, Mathoulin-Péllissier S. To screen or not to screen: reconciling individual and population perspectives on screening. *Mayo Clin Proc.* 2016;91(11):1594–605.
56. Ministre des solidarités et de la santé. Arrêté du 13 décembre 2018 portant approbation du règlement intérieur du Haut Conseil de la santé publique. *J Officiel de la République Française.* 2018;2018(294):30.
57. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev.* 2015;4(1).
58. Huserau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated Health economic evaluation reporting standards (CHEERS) statement. *BMJ.* 2013;346:f1049.
59. Drummond MF, Schulpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. Methods for the economic evaluation of health care programmes. 3rd ed. Oxford: Oxford Medical Publications; 2005. p. 182.
60. Haute Autorité de Santé. Suivi et orientation des femmes enceintes en fonction des situations à risque identifiées. Recommandation de bonne pratique. Saint-Denis: Haute Autorité de Santé; 2016.
61. Ministre du travail, de l'emploi et de la santé. Arrêté du 23 avril 2012 relatif à l'organisation du dépistage de la surdité permanente néonatale. *J Officiel de la République Française.* 2012;2012(105):7915.
62. Adler SP. Prevention of maternal-fetal transmission of Cytomegalovirus. *EBioMedicine.* 2015;2(9):1027–8.
63. Revello MG, Tibaldi C, Masuelli G, Frisina V, Sacchi A, Furione M, et al. Prevention of primary Cytomegalovirus infection in pregnancy. *EBioMedicine.* 2015;2(9):1205–10.
64. Vauloup-Fellous C, Picone O, Cordier AG, Parent-du-Chatelet I, Senat MV, Frydman R, et al. Does hygiene counseling have an impact on the rate of CMV primary infection during pregnancy? Results of a 3-year prospective study in a French hospital. *J Clin Virol.* 2009;46(Suppl 4):S49–53.
65. Thackeray R, Magnusson BM. Women's attitudes toward practicing cytomegalovirus prevention behaviors. *Prev Med Rep.* 2016;4:517–24.
66. Averill LW, Kandula W, Akyol Y, Epelman M. Fetal brain magnetic resonance imaging findings in congenital Cytomegalovirus infection with postnatal imaging correlation. *Semin Ultrasound CT MR.* 2015;36(6):476–86.
67. Bonalumi S, Trapanese A, Santamaria A, D'Emidio L, Mobili L. Cytomegalovirus infection in pregnancy: review of the literature. *J Prenat Med.* 2011;5(1):1–8.
68. Britt WJ. Congenital Human Cytomegalovirus Infection and the Enigma of Maternal Immunity. *J Virol.* 2017;91(15):e02392–16.
69. Britt W. Controversies in the natural history of congenital human cytomegalovirus infection: the paradox of infection and disease in offspring of women with immunity prior to pregnancy. *Med Microbiol Immunol.* 2015;204(3):263–71.
70. Cannon MJ, Schmid DS, Hyde TB. Review of cytomegalovirus seroprevalence and demographic characteristics associated with infection. *Rev Med Virol.* 2010;20(4):202–13.
71. Cannon MJ, Hyde TB, Schmid DS. Review of cytomegalovirus shedding in bodily fluids and relevance to congenital cytomegalovirus infection. *Rev Med Virol.* 2011;21(4):240–55.
72. Davis NL, King CC, Kourtis AP. Cytomegalovirus infection in pregnancy. *Birth Defects Res.* 2017;109(5):336–46.
73. de Vries JJ, van Zwet EW, Dekker FW, Kroes AC, Verkerk PH, Vossen AC. The apparent paradox of maternal seropositivity as a risk factor for congenital cytomegalovirus infection: a population-based prediction model. *Rev Med Virol.* 2013;23(4):241–9.
74. Emery VC, Lazzarotto T. Cytomegalovirus in pregnancy and the neonate. *F1000Res.* 2017;6:138.
75. Fowler KB, Boppana SB. Congenital cytomegalovirus (CMV) infection and hearing deficit. *J Clin Virol.* 2006;35(2):226–31.
76. Hamilton ST, van Zuylen W, Shand A, Scott GM, Naing Z, Hall B, et al. Prevention of congenital cytomegalovirus complications by maternal and neonatal treatments: a systematic review. *Rev Med Virol.* 2014;24(6):420–33.
77. Hughes BL, Gyamfi-Bannerman C. Diagnosis and antenatal management of congenital cytomegalovirus infection. *Am J Obstet Gynecol.* 2016;214(6):B5–b11.
78. Hyde TB, Schmid DS, Cannon MJ. Cytomegalovirus seroconversion rates and risk factors: implications for congenital CMV. *Rev Med Virol.* 2010;20(5):311–26.
79. James SH, Kimberlin DW. Advances in the prevention and treatment of congenital cytomegalovirus infection. *Curr Opin Pediatr.* 2016;28(1):81–5.
80. Jarvis D, Mooney C, Cohen J, Papaioannou D, Bradburn M, Sutton A, et al. A systematic review and meta-analysis to determine the contribution of mr imaging to the diagnosis of foetal brain abnormalities in utero. *Eur Radiol.* 2017;27(6):2367–80.
81. Luck SE, Wieringa JW, Blazquez-Gamero D, Henneke P, Schuster K, Butler K, et al. Congenital Cytomegalovirus: a European expert consensus statement on diagnosis and management. *Pediatr Infect Dis J.* 2017;36(12):1205–13.

82. Malm G, Engman ML. Congenital cytomegalovirus infections. *Semin Fetal Neonatal Med.* 2007;12(3):154–9.
83. Marsico C, Kimberlin DW. Congenital Cytomegalovirus infection: advances and challenges in diagnosis, prevention and treatment. *Ital J Pediatr.* 2017; 43(1):38.
84. McCarthy FP, Giles ML, Rowlands S, Purcell KJ, Jones CA. Antenatal interventions for preventing the transmission of cytomegalovirus (CMV) from the mother to fetus during pregnancy and adverse outcomes in the congenitally infected infant. *Cochrane Database Syst Rev.* 2011;16(3): Cd008371.
85. Peckham C, Tookey P, Logan S, Giaquinto C. Screening options for prevention of congenital cytomegalovirus infection. *J Med Screen.* 2001;8(3): 119–24.
86. Rawlinson WD, Hamilton ST, van Zuylen WJ. Update on treatment of cytomegalovirus infection in pregnancy and of the newborn with congenital cytomegalovirus. *Curr Opin Infect Dis.* 2016;29(6):615–24.
87. Revello MG, Gerna G. Pathogenesis and prenatal diagnosis of human cytomegalovirus infection. *J Clin Virol.* 2004;29(2):71–83.
88. Revello MG, Zavattoni M, Furione M, Lilleri D, Gorini G, Gerna G. Diagnosis and outcome of preconceptual and periconceptual primary human cytomegalovirus infections. *J Infect Dis.* 2002;186(4):553–7.
89. Revello MG, Gerna G. Diagnosis and management of human cytomegalovirus infection in the mother, fetus, and newborn infant. *Clin Microbiol Rev.* 2002;15(4):680–715.
90. Ross DS, Dollard SC, Victor M, Sumartojo E, Cannon MJ. The epidemiology and prevention of congenital cytomegalovirus infection and disease: activities of the Centers for Disease Control and Prevention Workgroup. *J Womens Health.* 2006;15(3):224–9.
91. Saldan A, Forner G, Mengoli C, Gussetti N, Palu G, Abate D. Testing for Cytomegalovirus in pregnancy. *J Clin Microbiol.* 2017;55(3):693–702.
92. Smit GSA, Padalko E, Van Acker J, Hens N, Dorny P, Speybroeck N, et al. Public Health impact of congenital toxoplasmosis and Cytomegalovirus infection in Belgium, 2013: a systematic review and data synthesis. *Clin Infect Dis.* 2017;65(4):661–8.
93. Stagno S, Cloud GA. Working parents: the impact of day care and breast-feeding on cytomegalovirus infections in offspring. *Proc Natl Acad Sci U S A.* 1994;91(7):2384–9.
94. Teissier N, Bernard S, Quesnel S, Van Den Abbeele T. Audiovestibular consequences of congenital cytomegalovirus infection. *Eur Ann Otorhinolaryngol Head Neck Dis.* 2016;133(6):413–8.
95. van Zuylen WJ, Hamilton ST, Naing Z, Hall B, Shand A, Rawlinson WD. Congenital cytomegalovirus infection: clinical presentation, epidemiology, diagnosis and prevention. *Obstet Med.* 2014;7(4):140–6.
96. Wang C, Zhang X, Bialek S, Cannon MJ. Attribution of congenital cytomegalovirus infection to primary versus non-primary maternal infection. *Clin Infect Dis.* 2011;52(2):e11–3.
97. Antona D, Lepoutre A, Fonteneau L, Baudon C, Halftermeyer-Zhou F, Y LES, et al. Seroprevalence of cytomegalovirus infection in France in 2010. *Epidemiol Infect.* 2017;145(7):1471–8.
98. Picone O, Vauloup-Fellous C, Cordier AG, Guitton S, Senat MV, Fuchs F, et al. A series of 238 cytomegalovirus primary infections during pregnancy: description and outcome. *Prenat Diagn.* 2013;33(8):751–8.
99. Enders G, Bader U, Lindemann L, Schallasta G, Daiminger A. Prenatal diagnosis of congenital cytomegalovirus infection in 189 pregnancies with known outcome. *Prenat Diagn.* 2001;21(5):362–77.
100. Gouarin S, Gault E, Vabret A, Cointe D, Rozenberg F, Grangeot-Keros L, et al. Real-time PCR quantification of human cytomegalovirus DNA in amniotic fluid samples from mothers with primary infection. *J Clin Microbiol.* 2002; 40(5):1767–72.
101. Enders G, Daiminger A, Bader U, Exler S, Enders M. Intrauterine transmission and clinical outcome of 248 pregnancies with primary cytomegalovirus infection in relation to gestational age. *J Clin Virol.* 2011;52(3):244–6.
102. Ahlfors K, Ivarsson SA, Harris S. Report on a long-term study of maternal and congenital cytomegalovirus infection in Sweden. Review of prospective studies available in the literature. *Scand J Infect Dis.* 1999;31(5):443–57.
103. Lereuz-Ville M, Stirnemann J, Sellier Y, Guilleminot T, Dejean A, Magny JF, et al. Feasibility of predicting the outcome of fetal infection with cytomegalovirus at the time of prenatal diagnosis. *Am J Obstet Gynecol.* 2016;215(3):342.e1–9.
104. Townsend CL, Peckham CS, Tookey PA. Surveillance of congenital cytomegalovirus in the UK and Ireland. *Arch Dis Child Fetal Neonatal Ed.* 2011;96(6):F398–403.
105. Dreher AM, Arora N, Fowler KB, Novak Z, Britt WJ, Boppana SB, et al. Spectrum of disease and outcome in children with symptomatic congenital cytomegalovirus infection. *J Pediatr.* 2014;164(4):855–9.
106. Fowler KB, Stagno S, Pass RF, Britt WJ, Boll TJ, Alford CA. The outcome of congenital cytomegalovirus infection in relation to maternal antibody status. *N Engl J Med.* 1992;326(10):663–7.
107. Lereuz-Ville M, Ghout I, Bussieres L, Stirnemann J, Magny JF, Couderc S, et al. In utero treatment of congenital cytomegalovirus infection with valacyclovir in a multicenter, open-label, phase II study. *Am J Obstet Gynecol.* 2016;215(4):462.e1–e10.
108. Lipitz S, Yinon Y, Malinger G, Yagel S, Levit L, Hoffman C, et al. Risk of cytomegalovirus-associated sequelae in relation to time of infection and findings on prenatal imaging. *Ultrasound Obstet Gynecol.* 2013;41(5):508–14.
109. Lereuz-Ville M, Sellier Y, Salomon LJ, Stirnemann JJ, Jacquemard F, Ville Y. Prediction of fetal infection in cases with cytomegalovirus immunoglobulin M in the first trimester of pregnancy: a retrospective cohort. *Clin Infect Dis.* 2013;56(10):1428–35.
110. Beloosesky R, Feldblum I, Shrim A, Kertes J, Segal J, Bachar R, et al. Trends in continuity of pregnancy in women with positive Cytomegalovirus IgM during the first trimester, 2008–2009. *Isr Med Assoc J.* 2017;19(8):484–8.
111. Iwasenko JM, Howard J, Arbuttle S, Graf N, Hall B, Craig ME, et al. Human cytomegalovirus infection is detected frequently in stillbirths and is associated with fetal thrombotic vasculopathy. *J Infect Dis.* 2011;203(11): 1526–33.
112. Parent du Châtelet I, Grangeot-Keros L, Le Strat Y, Leblond A, Six C, Lévy-Bruhl D. Enquête sur les infections maternofoetales à cytomégalovirus détectées pendant la grossesse ou à la naissance en France métropolitaine, novembre 2004-janvier 2005. *Bull Epidémiol Hebdomadaire.* 2008;2008(14–15):124–8.
113. EURO-PERISTAT. European Perinatal Health Report. The health and care of pregnant women and babies in Europe in 2010. Bruxelles: EURO-PERISTAT; 2013.
114. Benachi A, Picone O, Dumez Y. CMV infection: when should medical termination of pregnancy be discussed? *Gynecol Obstet Fertil.* 2003;31(6): 521–4.
115. Boppana SB, Ross SA, Fowler KB. Congenital cytomegalovirus infection: clinical outcome. *Clin Infect Dis.* 2013;57(Suppl 4):S178–81.
116. Delay F, Coste Burel M, Joubert M, Winer N. [Cytomegalovirus infection in pregnancy: a fourteen-year review in a pluridisciplinary prenatal center]. *J Gynecol Obstet. Biol Reprod.* 2016;45(9):1115–26.
117. Direction des études, de l'évaluation et des statistiques. 211900 interruptions volontaires de grossesse en 2016. Paris: Ministère des solidarités; 2017.
118. Goffinet F. CMV infection: when should medical termination of pregnancy be discussed? A. Benachi. *Gynecol Obstet Fertil.* 2003;31(11):993–4.
119. Ludwig A, Hengel H. Epidemiological impact and disease burden of congenital cytomegalovirus infection in Europe. *Euro Surveill.* 2009;14(9):26–32.
120. Williams EJ, Embleton ND, Clark JE, Bythell M, Ward Platt MP, Berrington JE. Viral infections: contributions to late fetal death, stillbirth, and infant death. *J Pediatr.* 2013;163(2):424–8.
121. Griffiths PD, Baboonian C, Rutter D, Peckham C. Congenital and maternal cytomegalovirus infections in a London population. *Br J Obstet Gynaecol.* 1991;98(2):135–40.
122. National Screening Committee UK. Newborn screening for cytomegalovirus. External review against programme appraisal criteria for the UK National Screening Committee. London: Public Health England; 2017.
123. Boppana SB, Fowler KB. Insight Into Long-term Neurodevelopmental Outcomes in Asymptomatic Congenital CMV Infection. *Pediatrics.* 2017; 140(5):e20172526.
124. Pass RF, Fowler KB, Boppana SB, Britt WJ, Stagno S. Congenital cytomegalovirus infection following first trimester maternal infection: symptoms at birth and outcome. *J Clin Virol.* 2006;35(2):216–20.
125. Fowler KB, Boppana SB. Congenital cytomegalovirus infection. *Semin Perinatol.* 2018;42(3):149–54.
126. Kotton CN, Kumar D, Caliendo AM, Asberg A, Chou S, Danziger-Isakov L, et al. Updated international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. *Transplantation.* 2013;96(4): 333–60.

127. Seed CR, Piscitelli LM, Maine GT, Lazzarotto T, Doherty K, Stricker R, et al. Validation of an automated immunoglobulin G-only cytomegalovirus (CMV) antibody screening assay and an assessment of the risk of transfusion transmitted CMV from seronegative blood. *Transfusion*. 2009;49(1):134–45.
128. Weber B, Fall EM, Berger A, Doerr HW. Screening of blood donors for human cytomegalovirus (HCMV) IgG antibody with an enzyme immunoassay using recombinant antigens. *J Clin Virol*. 1999;14(3):173–81.
129. Genser B, Truschning-Wilders M, Stunzner D, Landini MP, Halwachs-Baumann G. Evaluation of five commercial enzyme immunoassays for the detection of human cytomegalovirus-specific IgM antibodies in the absence of a commercially available gold standard. *Clin Chem Lab Med*. 2001;39(1):62–70.
130. Prince HE, Lape-Nixon M. Role of cytomegalovirus (CMV) IgG avidity testing in diagnosing primary CMV infection during pregnancy. *Clin Vaccine Immunol*. 2014;21(10):1377–84.
131. Revello MG, Vauloup-Fellous C, Grangeot-Keros L, van Helden J, Dickstein Y, Lipkin I, et al. Clinical evaluation of new automated cytomegalovirus IgM and IgG assays for the Elecsys(R) analyser platform. *Eur J Clin Microbiol Infect Dis*. 2012;31(12):3331–9.
132. Weber B, Prosser F, Munkwitz A, Doerr HW. Serological diagnosis of cytomegalovirus infection: comparison of 8 enzyme immunoassays for the detection of HCMV-specific IgM antibody. *Clin Diagn Virol*. 1994;2(4–5):245–59.
133. Bodeus M, Beulne D, Goubau P. Ability of three IgG-avidity assays to exclude recent cytomegalovirus infection. *Eur J Clinical Microbiol Infect Dis*. 2001;20(4):248–52.
134. Delforge ML, Desomberg L, Montesinos I. Evaluation of the new LIAISON(R) CMV IgG, IgM and IgG avidity II assays. *J Clin Virol*. 2015;72:42–5.
135. Grangeot-Keros L, Maysaux MJ, Lebon P, Freymuth F, Eugene G, Stricker R, et al. Value of cytomegalovirus (CMV) IgG avidity index for the diagnosis of primary CMV infection in pregnant women. *J Infect Dis*. 1997;175(4):944–6.
136. Guisasola ME, Ramos B, Sanz JC, Garcia-Bermejo I, De Ory Manchon F. Comparison of IgG avidity assays in the confirmation of the diagnosis of cytomegalovirus primary infection. *APMIS*. 2010;118(12):991–3.
137. Lagrou K, Bodeus M, Van Ranst M, Goubau P. Evaluation of the new architect cytomegalovirus immunoglobulin M (IgM), IgG, and IgG avidity assays. *J Clin Microbiol*. 2009;47(6):1695–9.
138. Lazzarotto T, Brojanac S, Maine GT, Landini MP. Search for cytomegalovirus-specific immunoglobulin M: comparison between a new western blot, conventional western blot, and nine commercially available assays. *Clin Diagn Lab Immunol*. 1997;4(4):483–6.
139. Lazzarotto T, Spezzacatena P, Varani S, Gabrielli L, Pradelli P, Guerra B, et al. Anticytomegalovirus (anti-CMV) immunoglobulin G avidity in identification of pregnant women at risk of transmitting congenital CMV infection. *Clin Diagn Lab Immunol*. 1999;6(1):127–9.
140. Revello MG, Genini E, Gorini G, Klersy C, Piralla A, Gerna G. Comparative evaluation of eight commercial human cytomegalovirus IgG avidity assays. *J Clin Virol*. 2010;48(4):255–9.
141. Vauloup-Fellous C, Berth M, Heskia F, Dugua JM, Grangeot-Keros L. Re-evaluation of the VIDAS(R) cytomegalovirus (CMV) IgG avidity assay: determination of new cut-off values based on the study of kinetics of CMV-IgG maturation. *J Clin Virol*. 2013;56(2):118–23.
142. Vauloup-Fellous C, Lazzarotto T, Revello MG, Grangeot-Keros L. Clinical evaluation of the Roche Elecsys CMV IgG avidity assay. *Eur J Clin Microbiol Infect Dis*. 2014;33(8):1365–9.
143. Revello MG, Gorini G, Gerna G. Clinical evaluation of a chemiluminescence immunoassay for determination of immunoglobulin g avidity to human cytomegalovirus. *Clin Diagn Lab Immunol*. 2004;11(4):801–5.
144. Yamamoto AY, Castellucci RA, Aragon DC, Mussi-Pinhata MM. Early high CMV seroprevalence in pregnant women from a population with a high rate of congenital infection. *Epidemiol Infect*. 2013;141(10):2187–91.
145. Yamamoto AY, Mussi-Pinhata MM, Isaac Mde L, Amaral FR, Carvalheiro CG, Aragon DC, et al. Congenital cytomegalovirus infection as a cause of sensorineural hearing loss in a highly immune population. *Pediatr Infect Dis J*. 2011;30(12):1043–6.
146. Munro SC, Trincado D, Hall B, Rawlinson WD. Symptomatic infant characteristics of congenital cytomegalovirus disease in Australia. *J Paediatr Child Health*. 2005;41(8):449–52.
147. Benoist G, Salomon LJ, Mohlo M, Suarez B, Jacquemard F, Ville Y. Cytomegalovirus-related fetal brain lesions: comparison between targeted ultrasound examination and magnetic resonance imaging. *Ultrasound Obstet Gynecol*. 2008;32(7):900–5.
148. Fabbri E, Revello MG, Furione M, Zavattoni M, Lilleri D, Tassis B, et al. Prognostic markers of symptomatic congenital human cytomegalovirus infection in fetal blood. *Bjog*. 2011;118(4):448–56.
149. Faure-Bardon V, Millischer AE, Deloison B, Sonigo P, Grevent D, Salomon L, et al. Refining the prognosis of fetuses infected with Cytomegalovirus in the first trimester of pregnancy by serial prenatal assessment: a single-Centre retrospective study. *BJOG*. 2020;127(3):355–62.
150. Coleman JL, Steele RW. Preventing congenital Cytomegalovirus infection. *Clin Pediatr (Phila)*. 2017;56(12):1085–94.
151. Bilavsky E, Pardo J, Attias J, Levy I, Magny JF, Ville Y, et al. Clinical implications for children born with congenital Cytomegalovirus infection following a negative amniocentesis. *Clin Infect Dis*. 2016;63(1):33–8.
152. Adler SP, Finney JW, Manganello AM, Best AM. Prevention of child-to-mother transmission of cytomegalovirus by changing behaviors: a randomized controlled trial. *Pediatr Infect Dis J*. 1996;15(3):240–6.
153. Avettand-Fenoel V, Marlin S, Vauloup-Fellous C, Loundon N, Francois M, Couloigner V, et al. Congenital cytomegalovirus is the second most frequent cause of bilateral hearing loss in young French children. *J Pediatr*. 2013;162(3):593–9.
154. Benoist G, Salomon LJ, Jacquemard F, Daffos F, Ville Y. The prognostic value of ultrasound abnormalities and biological parameters in blood of fetuses infected with cytomegalovirus. *Bjog*. 2008;115(7):823–9.
155. Carrara J, Delaveaucoupet J, Cordier AG, Vauloup-Fellous C, Senat MV, Ayoubi JM, et al. Detailed in utero ultrasound description of 34 cases of congenital cytomegalovirus infection. *J Gynecol Obstet Biol Reprod*. 2016;45(4):397–406.
156. Cheeran MC, Lokensgard JR, Schleiss MR. Neuropathogenesis of congenital cytomegalovirus infection: disease mechanisms and prospects for intervention. *Clin Microbiol Rev*. 2009;22(1):99–126 Table of Contents.
157. Daiminger A, Bader U, Enders G. Pre- and periconceptual primary cytomegalovirus infection: risk of vertical transmission and congenital disease. *Bjog*. 2005;112(2):166–72.
158. Farkas N, Hoffmann C, Ben-Sira L, Lev D, Schweiger A, Kidron D, et al. Does normal fetal brain ultrasound predict normal neurodevelopmental outcome in congenital cytomegalovirus infection? *Prenat Diagn*. 2011;31(4):360–6.
159. Lanari M, Capretti MG, Lazzarotto T, Gabrielli L, Rizzollo S, Mostert M, et al. Neuroimaging in CMV congenital infected neonates: how and when. *Early Hum Dev*. 2012;88(Suppl 2):S3–5.
160. Lipitz S, Hoffmann C, Feldman B, Tepperberg-Dikawa M, Schiff E, Weisz B. Value of prenatal ultrasound and magnetic resonance imaging in assessment of congenital primary cytomegalovirus infection. *Ultrasound Obstet Gynecol*. 2010;36(6):709–17.
161. Rolland M, Li X, Sellier Y, Martin H, Perez-Berezo T, Rauwel B, et al. PPARgamma is activated during congenital Cytomegalovirus infection and inhibits Neurogenesis from human neural stem cells. *PLoS Pathog*. 2016;12(4):e1005547.
162. Gandhi RS, Fernandez-Alvarez JR, Rabe H. Management of congenital cytomegalovirus infection: an evidence-based approach. *Acta Paediatr*. 2010;99(4):509–15.
163. Leyder M, Vorrsselmans A, Done E, Van Berkel K, Faron G, Foulon I, et al. Primary maternal cytomegalovirus infections: accuracy of fetal ultrasound for predicting sequelae in offspring. *Am J Obstet Gynecol*. 2016;215(5):638.e1–8.
164. Picone O, Mandelbrot L. Primary maternal cytomegalovirus infections: accuracy of fetal ultrasound to predict sequelae in offspring. *Am J Obstet Gynecol*. 2017;216(3):329–30.
165. Ross SA, Ahmed A, Palmer AL, Michaels MG, Sanchez PJ, Stewart A, et al. Newborn Dried Blood Spot Polymerase Chain Reaction to Identify Infants with Congenital Cytomegalovirus-Associated Sensorineural Hearing Loss. *J Pediatr*. 2017;184:57–61.e1.
166. Gaytant MA, Galama JM, Semmekrot BA, Melchers WJ, Sporken JM, Oosterbaan HP, et al. The incidence of congenital cytomegalovirus infections in the Netherlands. *J Med Virol*. 2005;76(1):71–5.
167. Fowler KB, McCollister FP, Dahle AJ, Boppa S, Britt WJ, Pass RF. Progressive and fluctuating sensorineural hearing loss in children with asymptomatic congenital cytomegalovirus infection. *J Pediatr*. 1997;130(4):624–30.
168. de Villemeur AB, Gratacap-Cavallier B, Casey R, Baccard-Longere M, Goirand L, Seigneurin JM, et al. Occupational risk for cytomegalovirus, but not for parvovirus B19 in child-care personnel in France. *J Inf Secur*. 2011;63(6):457–67.

169. Joseph SA, Beliveau C, Muecke CJ, Rahme E, Soto JC, Flowerdew G, et al. Risk factors for cytomegalovirus seropositivity in a population of day care educators in Montreal, Canada. *Occup Med (Lond)*. 2005;55(7):564–7.
170. Lepage N, Leroyer A, Cherot-Kornobis N, Lartigau I, Miczek S, Sobaszek A. Cytomegalovirus seroprevalence in exposed and unexposed populations of hospital employees. *Eur J Clin Microbiol Infect Dis*. 2011;30(1):65–70.
171. Stelma FF, Smismans A, Goossens VJ, Bruggeman CA, Hoebe CJ. Occupational risk of human Cytomegalovirus and parvovirus B19 infection in female day care personnel in the Netherlands; a study based on seroprevalence. *Eur J Clin Microbiol Infect Dis*. 2009;28(4):393–7.
172. Balcarek KB, Bagley R, Cloud GA, Pass RF. Cytomegalovirus infection among employees of a children's hospital. No evidence for increased risk associated with patient care. *Jama*. 1990;263(6):840–4.
173. Balfour CL, Balfour HH Jr. Cytomegalovirus is not an occupational risk for nurses in renal transplant and neonatal units. Results of a prospective surveillance study. *Jama*. 1986;256(14):1909–14.
174. Dworsky ME, Welch K, Cassidy G, Stagno S. Occupational risk for primary cytomegalovirus infection among pediatric health-care workers. *N Engl J Med*. 1983;309(16):950–3.
175. Hatherley LI. Is primary cytomegalovirus infection an occupational hazard for obstetric nurses? A serological study. *Infect Control*. 1986;7(9):452–5.
176. Lipscomb JA, Linnemann CC Jr, Hurst PF, Myers MG, Stringer W, Moore P, et al. Prevalence of cytomegalovirus antibody in nursing personnel. *Infect Control*. 1984;5(11):513–8.
177. Sobaszek A, Fantoni-Quinton S, Frimat P, Leroyer A, Laynat A, Edme JL. Prevalence of cytomegalovirus infection among health care workers in pediatric and immunosuppressed adult units. *J Occup Environ Med*. 2000;42(11):1109–14.
178. Adler SP, Finney JW, Manganello AM, Best AM. Prevention of child-to-mother transmission of cytomegalovirus among pregnant women. *J Pediatr*. 2004;145(4):485–91.
179. Pass RF, Anderson B. Mother-to-child transmission of Cytomegalovirus and prevention of congenital infection. *J Pediatric Infect Dis Soc*. 2014;3(Suppl 1):S2–6.
180. Knowledge and practices of obstetricians and gynecologists regarding cytomegalovirus infection during pregnancy--United States, 2007. *MMWR Morb Mortal Wkly Rep*. 2008;57(3):65–8.
181. Cannon MJ, Westbrook K, Levis D, Schleiss MR, Thackeray R, Pass RF. Awareness of and behaviors related to child-to-mother transmission of cytomegalovirus. *Prev Med*. 2012;54(5):351–7.
182. Price SM, Bonilla E, Zador P, Levis DM, Kilgo CL, Cannon MJ. Educating women about congenital cytomegalovirus: assessment of health education materials through a web-based survey. *BMC Womens Health*. 2014;14:144.
183. Binda S, Pellegrinelli L, Terraneo M, Caserini A, Primache V, Bubba L, et al. What people know about congenital CMV: an analysis of a large heterogeneous population through a web-based survey. *BMC Infect Dis*. 2016;16(1):513.
184. Cordier AG, Guitton S, Vauloup-Fellous C, Grangeot-Keros L, Ayoubi JM, Benachi A, et al. Awareness of cytomegalovirus infection among pregnant women in France. *J Clin Virol*. 2012;53(4):332–7.
185. Jeon J, Victor M, Adler SP, Arwady A, Demmler G, Fowler K, et al. Knowledge and awareness of congenital cytomegalovirus among women. *Infect Dis Obstet Gynecol*. 2006;2006:80383.
186. Mazzitelli M, Micieli M, Votino C, Visconti F, Quaresima P, Strazzulla A, et al. Knowledge of human Cytomegalovirus infection and prevention in pregnant women: a baseline, Operational Survey. *Infect Dis Obstet Gynecol*. 2017;2017:5495927.
187. Pereboom MT, Mannien J, Spelten ER, Schellevis FG, Hutton EK. Observational study to assess pregnant women's knowledge and behaviour to prevent toxoplasmosis, listeriosis and cytomegalovirus. *BMC Pregnancy Childbirth*. 2013;13:98.
188. Willame A, Blanchard-Rohner G, Combesure C, Irion O, Posfay-Barbe K, Martinez de Tejada B. awareness of Cytomegalovirus infection among pregnant women in Geneva, Switzerland: a cross-sectional study. *Int J Environ Res Public Health*. 2015;12(12):15285–97.
189. Wizman S, Lamarre V, Coic L, Kakkar F, Le Meur JB, Rousseau C, et al. Awareness of cytomegalovirus and risk factors for susceptibility among pregnant women, in Montreal, Canada. *BMC Pregnancy Childbirth*. 2016;16:54.
190. Cordier AG, Guitton S, Vauloup-Fellous C, Grangeot-Keros L, Benachi A, Picone O. Awareness and knowledge of congenital cytomegalovirus infection among health care providers in France. *J Clin Virol*. 2012;55(2):158–63.
191. Shand AW, Luk W, Nassar N, Hui L, Dyer K, Rawlinson W. Cytomegalovirus (CMV) infection and pregnancy-potential for improvements in Australasian maternity health providers' knowledge. *J Matern Fetal Neonatal Med*. 2018;31(19):2515–20.
192. von Gartzten A, Hollins Martin CJ. An email survey of midwives knowledge about CytoMegaVirus (CMV) in Hannover and a skeletal framework for a proposed teaching program. *Nurse Educ Pract*. 2013;13(5):481–6.

## Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

**Ready to submit your research? Choose BMC and benefit from:**

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

**At BMC, research is always in progress.**

Learn more [biomedcentral.com/submissions](https://www.biomedcentral.com/submissions)

