

# Recurrent maternal CMV infection associated with symptomatic congenital infection: results from a questionnaire study in Portugal

Paulo Paixão,<sup>1</sup> Maria João Brito,<sup>2</sup> Daniel Virella,<sup>3,4</sup> Maria Teresa Neto<sup>1,3</sup>

**To cite:** Paixão P, Brito MJ, Virella D, *et al.* Recurrent maternal CMV infection associated with symptomatic congenital infection: results from a questionnaire study in Portugal. *BMJ Paediatrics Open* 2019;**3**:e000455. doi:10.1136/bmjpo-2019-000455

► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/bmjpo-2019-000455>).

Received 6 February 2019  
Revised 1 April 2019  
Accepted 14 April 2019



© Author(s) (or their employer(s)) 2019. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

<sup>1</sup>Faculdade de Ciências Médicas, Universidade Nova de Lisboa, Lisboa, Portugal

<sup>2</sup>Infectious Diseases Unit, Hospital Dona Estefânia, Centro Hospitalar de Lisboa Central, Lisbon, Portugal

<sup>3</sup>Neonatal Intensive Care Unit, Hospital Dona Estefânia, Centro Hospitalar de Lisboa Central, Lisbon, Portugal

<sup>4</sup>Portuguese Paediatric Surveillance Unit, Sociedade Portuguesa de Pediatria, Lisbon, Portugal

## Correspondence to

Dr Paulo Paixão; paulo.paixao@nms.unl.pt

## ABSTRACT

**Objective** Human cytomegalovirus (CMV) is the most widespread agent of congenital infection in humans and is still a challenging issue. Despite lower rates of vertical transmission being associated with recurrent infection when compared with primary infection, the first still represents the majority of congenital infections worldwide. Based on data from active reporting, we explored the influence of maternal primary/non-primary infection both on the presentation and outcome of congenital CMV infection in early childhood.

**Design** Infants with positive viruria during the first 3 weeks of life were reported through the Portuguese Paediatric Surveillance Unit.

**Patients** Infants born between 2006 and 2011 with confirmed congenital CMV infection.

**Methods** Maternal infection was considered primary if CMV IgG seroconversion occurred during pregnancy or low avidity IgG was documented; it was considered non-primary if positive IgG was documented before pregnancy or high avidity CMV IgG was present early in pregnancy. Follow-up questionnaires were sent up to 6 years of age.

**Results** Forty confirmed cases of congenital CMV infection were reported (6.6:10<sup>5</sup> live births, 95% CI 4.81 to 8.92); 22 out of 40 were asymptomatic. The odds for non-primary maternal infection if the offspring was symptomatic at birth were 6.2 (95% CI 1.2 to 32.27).

**Conclusion** The reported number of confirmed cases of congenital CMV infection was much lower than expected. Under-reporting and missed diagnosis were considered possible reasons. Non-primary maternal infections were associated with symptomatic congenital CMV infection in the offspring. Maternal recurrent infections can have a significant impact on the total number of symptomatic infections in Portugal.

## INTRODUCTION

Human cytomegalovirus (CMV) is the most widespread agent of congenital infection in humans. About 0.7% of all newborn infants around the world are congenitally infected by CMV, with rates varying from 0.2% to 2.2%, and of these 10%–15% will be born with symptoms. Among the infants who are born asymptomatic, about 10%–15% will develop

## What is known about the subject?

- Maternal recurrent infections can have an important role in the occurrence of symptomatic infections.
- The registry of congenital cytomegalovirus (CMV) infections has been below those estimated by epidemiological studies.

## What this study adds?

- The probability of congenital CMV infection being symptomatic at birth may be significantly higher for non-primary maternal infection in Portugal.
- Surveillance through European paediatric surveillance units gave similar under-reporting results (in the current study, the prevalence rate was 6.6:10<sup>5</sup> live births).
- There is a need for new strategies to improve the adherence of clinicians to the registry.

late sequelae, such as neurological impairment or neurosensory hearing loss.<sup>1</sup>

After maternal primary infection, transmission to the fetus occurs in 30%–35% of cases, and clinical disease will be present in around 10%–15% of those born with congenital infection. In women who are already seropositive, reactivation may cause fetal infection, at a rate of about 1.2%.<sup>2</sup> Although transmission in recurrent infection is much lower than in primary infection, it is the main contributor to the total number of congenital infections (and disease) worldwide. In addition, an increased number of observations demonstrates that the risk for symptomatic infection at birth and sequelae after primary and non-primary maternal CMV infections, especially hearing loss, is not as different as previously assumed.<sup>3</sup>

Population surveillance systems for congenital CMV infection, intended to register all confirmed cases, are crucial to evaluate the impact of this infection. Different approaches

for the registry of cases have been used, including national programmes and the search of databases on hospital records.<sup>4-7</sup> Although under-reporting is common in these surveillance systems, valuable information can be obtained from the registry of congenital infections.

Between 2006 and 2011, an experimental surveillance of infants with congenital CMV infection was carried on through the Portuguese Paediatric Surveillance Unit (PPSU)<sup>8</sup> in order to estimate the number of cases of congenital CMV infection in Portugal, the proportion of maternal primary/non-primary infections responsible for these cases, and the outcome of these children in early childhood.

## MATERIALS AND METHODS

Between 2006 and 2011, infants born in Portugal with confirmed congenital CMV infection (positive viruria during the first 3 weeks of life, detected by commercial PCR techniques or shell vial culture) were reported through the PPSU, a national surveillance programme ran through the Portuguese Paediatric Society. Clinicians were asked to complete questionnaires about clinical and laboratory presentations at birth, at 6, 12 and 18 months, and at 2, 3, 4, 5 and 6 years of age. Follow-up for the last reported children ended in 2017 (protocol available at <http://www.spp.pt/conteudos/default.asp?ID=143>). The questionnaire at presentation (questionnaire in English in online supplementary file 1) included identification of the notifier and a coded identification of the patient; data on gestational age, birth weight and exams during gestation (serology, ultrasound scan and amniocentesis result, if performed); viruria for CMV in the first 3 weeks of age; clinical symptoms (fever, sepsis-like syndrome, weight below the 10th percentile for gestational age and/or postnatal age, pneumonia, hepatosplenomegaly, microcephaly, and seizures); laboratory blood and cerebrospinal fluid findings (hepatitis, cholestasis, anaemia (haemoglobin <140 g/L in the first week or <12 mg/dL in the first month of life), thrombocytopenia (<150x10<sup>9</sup>/L), leucopenia (<5.0x10<sup>9</sup>/L) and/or neutropenia (<1.5x10<sup>9</sup>/L)); intracranial calcifications, chorioretinitis, deafness (diagnosed by otoacoustic emissions or auditory evoked potentials of the brainstem); antiviral therapy (drug and duration, if performed); length of hospital stay (if admitted) and immediate outcome; and family data (maternal age and job; number and age of siblings and their frequency of kindergarten or school) were also included in this questionnaire.

Cases (those with positive viruria for CMV in the first 3 weeks of age) were classified as either symptomatic infection (also known as symptomatic disease) or asymptomatic infection at diagnosis,<sup>9</sup> based on the reported presence of any of the symptoms or signs listed above.

Maternal infection was considered primary if there was either reported positive IgM with low avidity IgG or documented IgG seroconversion during pregnancy, and classified as non-primary (meaning recurrent or reinfection)

if there was reported documented positive IgG before pregnancy or positive IgM with high avidity CMV IgG in the early pregnancy samples.

The questionnaires at 6, 12 and 18 months and at 2, 3, 4, 5 and 6 years of age consisted of questions regarding the clinical follow-up: physical examination, laboratory tests, cranial ultrasound scan findings, and audiological and ophthalmological assessment.

Cumulative birth prevalence rate was estimated with 95% CI.

As a post-hoc analysis, the association between symptomatic or asymptomatic presentation at diagnosis and type of maternal infection (primary or non-primary) was assessed. After assessing the heterogeneity of the possibility for non-reported or for a reported unknown time of maternal infection if the offspring was symptomatic or asymptomatic at diagnosis, the odds for the type of maternal infection were estimated as ORs with 95% CI. OpenEpi was used for estimations.<sup>10</sup>

## Patient involvement

Patients were not directly involved in the design of this study and the questionnaires were not sent to the parents.

## RESULTS

Sixteen notifiers reported 40 cases of confirmed congenital CMV infection. The median gestational age was 37 weeks (29–40) and birth weight was 2912 g (790–4120 g). No twins were reported.

The reported cumulative birth prevalence in Portugal between 2006 and 2011 was 40 out of 610 263 live births or a prevalence rate of 6.6/10<sup>5</sup> live births (95% CI 4.81 to 8.92).

Eighteen newborn infants (45%) were symptomatic and 22 (55%) were asymptomatic at birth. From the 40 mothers, 21 (52.5%) were classified as having had primary infection and 10 as non-primary infection (25%); the mother's previous serological status was not known in 9 cases (one woman with a positive IgM without IgG assessment during pregnancy was included in this group) (table 1). The odds for a non-reported or for a reported unknown time of maternal infection if the offspring was symptomatic at birth were 2.64 (95% CI 0.531 to 13.11; p=0.263).

From the 18 symptomatic newborn infants, 6 (33%) were born to mothers with primary infection and 9 (50%) to mothers with secondary infection. The other three symptomatic patients were born from mothers whose serology was unknown (table 1). The odds for a reported non-primary maternal infection if the offspring was symptomatic at birth were 6.2 (OR 6.2; 95% CI 1.2 to 32.27; p=0.033).

Follow-up information was received for 11 cases at 6 months, for 8 cases at 1 year, for 6 cases at 3 years and for 2 cases after 4 years. Asymptomatic cases at birth remained symptomless at 6 months (6 children), 3 years (4 children) and 4 years (2 children). Regarding the

**Table 1** Distribution of the 40 reported cases of congenital cytomegalovirus infection according to their clinical presentation at birth (symptomatic or asymptomatic) and reported maternal previous serological status

	Primary infection	Non-primary infection	Unknown time of infection	Total
Symptomatic at birth	6 (1)	7 (1)	5 (2)	18 (4)
Asymptomatic at birth	16 (3)	3 (1)	3 (2)	22 (6)
Total	22 (4)	10 (2)	8 (4)	40 (10)

In brackets are the number of children included in the follow-up. The odds for non-primary maternal infection were higher if the offspring was symptomatic at birth (OR 6.2; 95% CI 1.2 to 32.27;  $p=0.0033$ ).

symptomatic cases, two were followed up for 6 months, one became asymptomatic, but the other one had severe neurological sequelae. The third child was asymptomatic at 1 year of age and the fourth had severe neurological impairment at 3 years of age (table 2). The two patients with the most severe sequelae at 6 months and 3 years were born, respectively, to mothers with primary and non-primary infection.

## DISCUSSION

This study reports the first national registry of congenital CMV infection in Portugal. Out of 610 263 live births, there were 40 new confirmed cases of congenital CMV infection reported between 2006 and 2011. Therefore, the reported cumulative birth prevalence rate was 6.6:10<sup>5</sup> live births (95% CI 4.81 to 8.92). The British Paediatric Surveillance Unit was used to perform a similar study in 2001 and 2002 in the UK and Ireland.<sup>5</sup> Eighty-six confirmed cases were registered in those 2 years, from circa 1.3 million live births. The estimated prevalence of congenital CMV in the two studies was similar and quite far from the expected 0.3%–0.5% (about 0.03%–0.05% for symptomatic cases) for the UK<sup>11</sup> and 0.8%–1.5% (0.08%–0.15% for symptomatic cases) for Portugal.<sup>12</sup> The estimates of both PPSU strongly suggest under-reporting. However, other surveillance reports do not seem to be more effective. The Canadian Paediatric Surveillance Program, between the years of 2005 and 2008, reported a birth prevalence of 4.5:10<sup>5</sup> live births,<sup>13</sup> and a report from the five university hospitals in Finland detected 26 symptomatic cases in 12 years.<sup>6</sup> The National Congenital Cytomegalovirus Disease Registry of the USA detected 285 cases in 4 years,<sup>4</sup> in a country where more than 10 000 cases/year would be expected if both symptomatic and asymptomatic infections were to be included. A recently published paper with data from the Australian Paediatric Surveillance Unit also refers the under-reporting and under-recognition of congenital CMV despite the increasing use of antiviral therapy.<sup>14</sup> Therefore, either the estimates based on clinical pathology data are over-estimated or the available surveillance systems based on clinicians underestimate the number of congenital CMV infection.

Congenital CMV does not fulfil the conditions to be included in the list of notifiable infectious diseases, which means that these cases are not mandatorily

registered. Therefore, alternative forms of surveillance are important for the knowledge of the epidemiology of this congenital infection, such as the universal neonatal screening. Of note, this screening has several important dilemmas, with the most frequent being that many true positives will be healthy babies without any complication or sequelae.<sup>15</sup> Following examples of countries where a CMV surveillance system exists,<sup>4 5 12</sup> the authors sought to use the PPSU as a source of national data on the occurrence of new cases and their evolution.<sup>8</sup>

Using the PPSU system as the primary source of data for this national registry, under-reporting and missed diagnosis must be taken into account, although the former is probably much more frequent. In fact, only 16 notifiers registered the 40 cases, which means that the majority of the Portuguese paediatricians and neonatologists did not register any case. In addition, the system involves paediatricians who are included voluntarily in the mailing. This represents a bias given in Portugal many children are followed up by their family practitioner, the majority of whom are not participants of the surveillance system. Without a screening programme, some symptomatic cases, particularly those included in the group of the so-called 'Mildly symptomatic congenital cytomegalovirus disease', might also have been lost due to the fact that symptoms can be mild and transient<sup>9</sup> and therefore easily missed.

On the other hand, the low return rate of the follow-up questionnaires was very disappointing and does not allow any generalisation. Those asymptomatic children at birth, from whom follow-up information was received, remained asymptomatic. Of note, none of them was followed up until 6 years of age. There is also a lack of information regarding the evolution of most symptomatic at birth cases. Of those where there is information, some seem to have come free of sequelae. Although the audiological evaluation was part of the initial evaluation (the Portuguese universal auditory screening programme started in 2007) and of the follow-up routine, all the notifiers confirmed that it was always performed, but it was surprising that no case of deafness is referred. A possible explanation could be the late appearance of this sequela,<sup>1</sup> which together with the low number of children followed would decrease the probability of detecting cases of deafness.

**Table 2** Summary of the available information of all the cases of congenital cytomegalovirus infection reported (maternal information, symptoms and neuroimaging findings at birth and on follow-up)

	Maternal infection	At birth	6 months	1 year	2 years	3 years	4 years
1	Primary	A	A	A	–	A	A
2	Recurrent	A	A	A	–	A	A
3	Primary	A	A	A	–	A	–
4	Primary	A	A	A	–	A	–
5	Unknown	A	–	–	–	–	–
6	Unknown	A	A	–	–	–	–
7	Recurrent	A	A	A	A	A	–
8	Unknown	IUGR, H	A	–	–	–	–
9	Primary	IUGR, VA	CP, DCD, M, S	–	–	–	–
10	Unknown	An, Cr, H, Hs, J, L, SBB, S, T	A	A	–	–	–
11	Recurrent	An, Ch, H, T, Hs	CH, VSV	AH	At, D	DS, DDFM, AMRI	–
12	Unknown	An, J, L, T	–	–	–	–	–
13	Unknown	A	–	–	–	–	–
14	Recurrent	J	–	–	–	–	–
15	Primary	AMRI	–	–	–	–	–
16	Primary	A	–	–	–	–	–
17	Primary	A	–	–	–	–	–
18	Primary	A	–	–	–	–	–
19	Primary	An, N, Vm	–	–	–	–	–
20	Recurrent	An, H, Hs, IC, SL, T	–	–	–	–	–
21	Primary	A	–	–	–	–	–
22	Primary	A	–	–	–	–	–
23	Unknown	A	–	–	–	–	–
24	Primary	A	–	–	–	–	–
25	Primary	A	–	–	–	–	–
26	Primary	A	–	–	–	–	–
27	Recurrent	An, Sp	–	–	–	–	–
28	Primary	A	–	–	–	–	–
29	Primary	IUGR	–	–	–	–	–
30	Recurrent	A	–	–	–	–	–
31	Recurrent	VSV	–	–	–	–	–
32	Primary	IC	–	–	–	–	–
33	Recurrent	IUGR, PCL	–	–	–	–	–
34	Recurrent	SL, L, T	–	–	–	–	–
35	Recurrent	SL, L, T, IUGR	–	–	–	–	–
36	Recurrent	IUGR	–	–	–	–	–
37	Primary	An, T, IC, D	–	–	–	–	–
38	Primary	A	–	–	–	–	–
39	Primary	A	–	–	–	–	–
40	Primary	A	–	–	–	–	–

A, asymptomatic; AH, axial hypotonia; AMRI, abnormal MRI (unspecified); An, anaemia; At, ataxia; CH, cerebellar hypoplasia; CP, cerebral palsy; Ch, cholestasis; Cr, chorioretinitis; D, dystonia; DCD, diffuse cortical dysplasia; DDFM, delayed development of fine movements; DS, delayed speech; H, hepatitis; Hs, hepatosplenomegaly; IC, intracerebral calcifications; IUGR, intrauterine growth restriction; J, jaundice; L, leucopaenia; M, microcephaly; N, neutropaenia; PCL, periventricular cystic lesions; S, strabismus; SBB, subependymal bilateral bleeding; SL, sepsis-like; Sp, splenomegaly; T, thrombocytopenia; VA, ventricular asymmetry; VSV, ventriculostriated vasculopathy; Vm, ventriculomegaly.

The study also suggests that symptomatic congenital CMV infection at birth is significantly higher for non-primary maternal infection (OR 6.2; 95% CI 1.2 to 32.27).

In spite of the statistical significance of the association, the interpretation must take into account that data are based only on the reporting of newborns with confirmed

infection, as defined on the surveillance protocol (available at <http://www.spp.pt/conteudos/default.asp?ID=143>). There is the possibility of an identification bias due to the diagnostic process. It can be assumed that clinicians would proceed to confirm the diagnosis in case of prenatal suspicion or in newborns with symptoms or signs suggesting CMV infection. As such, there is potential for reporting bias given there would be less notification of asymptomatic infants from non-suspected pregnancies. A higher quality of the information on cases with prenatal suspicion of infection may also lead to reporting bias.

It is now widely accepted that mothers' recurrent infections are responsible for symptomatic, sometimes severe, congenital infections in newborns. Some studies confirm that the majority of congenital infections result from the mother's non-primary infection, particularly in countries with higher seroprevalence rates.<sup>16</sup> However, even in countries with low seroprevalence rates, the impact of non-primary infections can be significant.<sup>6</sup> Our data reinforce the relevance of maternal recurrent infection on the overall impact of symptomatic congenital CMV infections. This is a matter of major importance nowadays, since the discussion about the possible introduction of a CMV vaccine is very much focused on the observations that natural immunity is not completely protective against maternal reinfection and congenital transmission.<sup>17</sup> However, there is evidence that vaccination is associated with reduced transmission of CMV to the fetus in seronegative women, reason why some authors claim that in light of the substantial burden on society conferred by this infection, even a modest reduction in the occurrence is an important public health goal.<sup>18</sup>

## CONCLUSIONS

Maternal recurrent infections can have a significant impact on the occurrence of symptomatic infections in newborns. Similar to studies in other countries, the surveillance of congenital CMV infection in Portugal revealed the problem of under-reporting of cases. New strategies are necessary to improve the registration of this congenital infection by clinicians in order to improve knowledge of the epidemiology in each country.

**Collaborators** The clinical data from this study were sent by the following paediatricians/neonatologists: Elisabete Coelho (Hospital Póvoa de Varzim), José Gonçalves Marques (Hospital de Santa Maria), Ana Nunes (Hospital S Francisco Xavier), Luís Pinto (Maternidade Bissaya Barreto), José Luís Fonseca (Hospital Guimarães), Eduardo Gonçalves and Licinia Lima (Centro Hospitalar Alto Minho), DV (Hospital Dona Estefânia), MTN (Hospital Dona Estefânia), Cristina Godinho (Maternidade Júlio Dinis), Teresa Martins (Hospital Pedro Hispano), Isabel Malta (Maternidade Alfredo da Costa) and MJB (Hospital Fernando Fonseca).

**Contributors** PP designed the study, compiled the data and analysed them, drafted the manuscript and prepared the final version. MJB designed the study, contributed to data interpretation and reviewed the manuscript. DV contributed to data interpretation and reviewed the manuscript. MTN designed the study, contributed to data interpretation, reviewed the manuscript and prepared the final version.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

**Patient consent for publication** Not required.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** All data relevant to the study are included in the article or uploaded as supplementary information.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

## REFERENCES

1. Dreher AM, Arora N, Fowler KB, *et al.* Spectrum of disease and outcome in children with symptomatic congenital cytomegalovirus infection. *J Pediatr* 2014;164:855–9.
2. Emery VC, Lazzarotto T. Cytomegalovirus in pregnancy and the neonate. *F1000Res* 2017;6.
3. Giannattasio A, Di Costanzo P, De Matteis A, *et al.* Outcomes of congenital cytomegalovirus disease following maternal primary and non-primary infection. *J Clin Virol* 2017;96:32–6.
4. Istas AS, Demmler GJ, Dobbins JG, *et al.* Surveillance for congenital cytomegalovirus disease: a report from the National congenital cytomegalovirus disease registry. *Clin Infect Dis* 1995;20:665–70.
5. Townsend CL, Peckham CS, Tookey PA. Surveillance of congenital cytomegalovirus in the UK and Ireland. *Arch Dis Child Fetal Neonatal Ed* 2011;96:F398–F403.
6. Puhakka L, Renko M, Helminen M, *et al.* Primary versus non-primary maternal cytomegalovirus infection as a cause of symptomatic congenital infection – register-based study from Finland. *J Infect Dis* 2017;49:445–53.
7. Steurbaut K, De Backere F, Keymeulen A, *et al.* NEOREG: design and implementation of an online neonatal registration system to access, follow and analyse the data of newborns with congenital cytomegalovirus infection. *Informatics for Health and Social Care* 2013;38:223–35.
8. Comissão Executiva da Unidade de Vigilância Pediátrica da Sociedade Portuguesa de Pediatria (UVP-SPP/PPSU). Unidade de Vigilância Pediátrica da Sociedade Portuguesa de Pediatria: Balanço de 2008 E perspectivas para 2009. *Acta Pediatr Port* 2009;40:46–8.
9. Rawlinson WD, Boppana SB, Fowler KB, *et al.* Congenital cytomegalovirus infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis, and therapy. *Lancet Infect Dis* 2017;17:e177–88.
10. Dean AG, Sullivan KM, Soe MM. OpenEpi: open source epidemiologic statistics for public health, version. Available: [www.OpenEpi.com](http://www.OpenEpi.com) [Accessed 2018/08/19].
11. Manicklal S, Emery VC, Lazzarotto T, *et al.* The “Silent” Global Burden of Congenital Cytomegalovirus. *Clin Microbiol Rev* 2013;26:86–102.
12. Paixão P, Almeida S, Gouveia P, *et al.* Prevalence of human cytomegalovirus congenital infection in Portuguese newborns. *Euro Surveill* 2009;14:13–15.
13. Vaudry W, Lee BE, Rosychuk RJ. Congenital cytomegalovirus infection in Canada: active surveillance for cases diagnosed by paediatricians. *Paediatr Child Health* 2014;19:e1–5.
14. Bartlett AW, Hall BM, Palasanthiran P, *et al.* Recognition, treatment, and sequelae of congenital cytomegalovirus in Australia: an observational study. *J Clin Virol* 2018;108:121–5.
15. Fowler KB, Boppana SB. Congenital cytomegalovirus infection. *Semin Perinatol* 2018;42:149–54.
16. Yamamoto AY, Mussi-Pinhata MM, Isaac MdeL, *et al.* Congenital cytomegalovirus infection as a cause of sensorineural hearing loss in a highly immune population. *Pediatr Infect Dis J* 2011;30:1043–6.
17. Pass RF, Zhang C, Evans A, *et al.* Vaccine prevention of maternal cytomegalovirus infection. *N Engl J Med* 2009;360:1191–9.
18. Permar SR, Schleiss MR, Plotkin SA. Advancing our understanding of protective maternal immunity as a guide for development of vaccines to reduce congenital cytomegalovirus infections. *J Virol* 2018;14:92–7.