UK National Screening Committee

Newborn screening for cytomegalovirus

25th October 2017

Aim

1. To ask the UK National Screening Committee (UK NSC) to make a recommendation, based on the evidence presented in this document, whether or not screening for cytomegalovirus (CMV) infection in newborns meets the UK NSC criteria for a systematic population screening programme.

Current recommendation

2. The 2012 review of screening for CMV in the antenatal and/or the neonatal periods concluded that systematic screening CMV infections in such populations did not meet the UK NSC criteria and the Committee did not recommend its introduction.

3. The reasons for the 2012 recommendation were as follows;

    a) there was a lack of clarity about the risks to the fetus associated with primary infection
    b) the optimum screening and diagnostic testing strategy had not been identified
    c) there was a lack of interventions to prevent mother-to-child transmission or minimise the severity of infection

    In relation to newborn screening, the 2012 UK NSC review reported that studies using both newborn dried blood spots (DBS) and saliva swabs showed potential for Congenital CMV screening. However, at the time of the review, there was uncertainty about whether these approaches were sufficiently reliable for use in a large-scale newborn screening programme.

    At the time of the review only one treatment was available, six weeks of intravenous antiviral medication, ganciclovir, which was only suitable for use in symptomatic newborns

(such as those with neurological manifestations). At the time of the review a trial was underway investigating an oral formulation, valganciclovir, as an alternative. No treatment was available for asymptomatic infants or those with transient or non-specific symptoms.

The review also highlighted a need to better define risk in newborns and identify specific diagnostic signs or markers that could predict which newborns were likely to develop long-term sequelae. This would help limit overdetection and subsequent overtreatment.

Evidence Summary

4. The current evidence summary was undertaken by Bazian Ltd, in accordance with the triennial review process. https://legacyscreening.phe.org.uk/cytomegalovirus

5. In the 2017 evidence summary antenatal screening for CMV infection is only discussed as part of the introduction. This is because very little information was found in the literature search undertaken to update the previous review and, perhaps more importantly, the focus of attention relating to screening has shifted to the newborn period.

6. The 2017 evidence summary therefore aims to assess whether the volume and direction of the evidence produced since the 2012 review is sufficient to change the current UK NSC recommendation on newborn screening for Congenital CMV.

7. The conclusion of this evidence summary is to reaffirm the UK NSC recommendation that newborn screening for Congenital CMV infection should not be implemented. The reasons remain unchanged from the previous review:

    a. That more research is needed on screening test

    The review reported that a candidate for a newborn screening test is polymerase chain reaction (PCR) evaluation of saliva samples. This was mainly based on one large US cohort study including 73,239 newborns (reported by two publications). This reported high sensitivity and specificity values. The review, reported some concern about verification bias as the gold standard (saliva and urine re-testing) was not applied to the whole study population. Although, the reported test values were high, this performance cannot be known with certainty. In addition the studies also had the limitation that they did not consider the test as part of a diagnostic pathway and did not assess whether it could be used to change the management of newborns found to have Congenital CMV. A smaller Irish study was also considered in the review. **Criterion 4 not met**

b. The treatment to be offered to babies with screen detected Congenital CMV remains unclear.

   One small RCT assessed valganciclovir as an oral alternative to ganciclovir in symptomatic newborns, comparing six weeks with six months of treatment. The trial found that six months treatment with valganciclovir did not have a statistically significant effect on the primary outcome (best-ear hearing at six months) compared to six weeks treatment. The trial also reported that valganciclovir had a moderate, statistically significant effect on longer-term hearing (total-ear hearing) and neurodevelopmental outcomes at 12 to 24 months. However, the authors caution that this effect could be due to statistical artefacts, but they did not provide more information. The study was very small, and its relevance to a screen-detected population was uncertain. **Criterion 9 not met**

c. There is still a lack of clarity about how to identify newborns that will develop long-term sequelae, and therefore may benefit from medical intervention.

   One UK guideline, published in 2011, demonstrates that there is a limited evidence-base guiding the management of Congenital CMV prior to 2011. The recommendation to treat newborns with neurological involvement is drawn from a single RCT of intravenous ganciclovir combined with expert opinion. The guideline authors acknowledged the need for large studies of predictive markers.

   Three small cohort studies assessed the potential of specific central nervous system signs or viral load to predict the likelihood of long-term sequelae. However, type of symptoms varied widely across these studies and it is difficult to know how relevant or applicable these potential predictive markers may be to a population of newborns with Congenital CMV identified through universal screening.

   No studies have assessed treatment for asymptomatic newborns. **Criterion 10 not met**

d. There is lack of evidence on whether newborn screening is effective in reducing morbidity or mortality from Congenital CMV infection

   One study found that, among a group of symptomatic newborns diagnosed with Congenital CMV during the first weeks of life, those who were tested on clinical suspicion had poorer childhood outcomes (including sensorineural hearing loss

(SNHL)), than those who were tested as part of routine screening. However, no information was provided on the management strategy or its implementation in either group. Therefore, the study cannot provide evidence that the lower rate of adverse outcomes in the screening group is the direct effect of screening**. Criterion 11 not met**

Consultation

8. A three month consultation was hosted on the UK NSC website. Direct emails were sent to 16 stakeholder organisations. **Annex A**

9. Responses were received from the following 14 stakeholders;

    - Royal College of Obstetricians and Gynaecologists,
    - National Deaf Children's Society,
    - British Paediatric Allergy Immunity and Infection Group,
    - CMV Action,
    - Rosa Crunkhorn (Royal Bolton Hospital),
    - Ansar Uddin Ahmmed (Lancashire Teaching Hospitals NHS Foundation Trust),
    - Richard Stanton & Vincent (Cardiff & Swansea Universities),
    - British Infection Association,
    - Royal College of Paediatrics and Child Health (RCPCH),
    - Congenital CMV Research Interest Group,
    - British Association of Paediatricians in Audiology (BAPA),
    - The British Association of Audiovestibular Physicians (BAAP)
    - Simone Walter (St George's Hospital, St Helier Hospital, Croydon University Hospital)
    - British Maternal and Fetal Medicine Society.

    All comments are **in Annex B**, below. In instances where the same sets of comments have been sent by different individuals, they have not been duplicated in the comments below.

10. Some stakeholders agreed with the conclusion of the review that before a population screening programme for Congenital CMV could be introduced in the UK;
    - more information is needed about the performance of salivary PCR and/or extended blood spot testing,
    - it is necessary to understand the natural history of CMV and which babies are at higher risk of adverse outcomes, and
    - more needs to be known about possible harms from treatment with valganciclovir, as well as the optimum duration of treatment.

Recommendation

11. The Committee is asked to approve the following recommendation:
Systematic population screening of newborns for cytomegalovirus infections is not recommended as a population screening programme in the UK.

In addition the Committee is asked to note that the UK NSC Secretariat is in the process of organising a meeting with stakeholders to discuss the options for taking forward research on screening related issues and to identify the appropriate organisations to address the issues which are not within the Committee's remit.

Based on the 20 UK NSC criteria set to recommend a population screening programme, evidence was appraised against the following four criteria:

	Criteria	Met / Not met
The Test		
4	There should be a simple, safe, precise and validated screening test..	Not met ✗
The intervention		
9	There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme shouldn't be further considered	Not met ✗
10	There should be agreed evidence based policies covering which individuals should be offered interventions and the appropriate intervention to be offered.	Not met ✗
The screening programme		
11	There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (such as Down's syndrome or cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.	Not met ✗

Annex A

List of organisations contacted:

1. Association for Improvements in the Maternity Services
2. British Association of Perinatal Medicine
3. British Infection Association
4. British Maternal & Fetal Medicine Society
5. CMV Action
6. Eastern Region Audiology Interest Group
7. The Faculty of Public Health
8. Microbiology Society
9. MBRRACE-UK
10. Maternity Action
11. National Childbirth Trust
12. Royal College of General Practitioners
13. Royal College of Midwives
14. Royal College of Obstetricians and Gynaecologists
15. Royal College of Paediatrics and Child Health
16. Royal Society for Public Health

Annex B

Consultation comments

UK National Screening Committee

Newborn screening for cytomegalovirus –an evidence review

Consultation comments pro-forma

Name:	xxxx xxxx	**Email address:**	xxxx xxxx
Organisation (if appropriate):	Royal College of Obstetricians and Gynaecologists		
Role:	xxxx xxxx		

Do you consent to your name being published on the UK NSC website alongside your response? **Yes ☐ No ☒**		
Section and / or page number	**Text or issue to which comments relate**	**Comment** *Please use a new row for each comment and add extra rows as required.*
General		This document is focused and well written. It explains clearly the reasons for not introducing screening for CMV in the neonatal population.
General		Use fetus rather than foetus throughout the document please.
Page 3		It would be helpful to know how the remaining 70–80% of babies with congenital CMV infection manifest. Do they have any physical disabilities despite congenital infection? Please could the authors clarify this point here?
Page 3		Where it says: "An additional 10 to 15% are well at birth, but go onto develop long-term hearing or developmental problems." On and to are 2 separate words and these babies 'appear well', rather than 'are well'.
Page 3		"no reliable test to detect cytomegalovirus infection during pregnancy " Maternal serology and Amniotic fluid PCR can be used to detect fetal CMV infection during pregnancy so this is not entirely true. However xxxx xxxx think what the authors mean here is that there is no reliable screening test in pregnancy
Page 3		Paragraph under 'The review also found that: Item 2 has a typo error in the first sentence. Please correct.

Page 4		Formatting of references page 4 [1-6]. Please correct
Page 4		“The previous review also highlighted a need to better define risk in newborns and identify specific diagnostic signs or markers that could predict which newborns were likely to develop long-term sequelae.” Grammar correction (split infinitive).

Pages 7 to 11		The evidence presented here suggests that none of the strategies to monitor fetuses in pregnant women who test positive for primary infection or for non-primary infection actually works. No intervention in the antenatal period seems to be effective in preventing maternal infection or reducing the risk of transmission to the fetus. It also appears that there is no advantage in identifying a fetus who may be at higher risk by way of showing antenatal ultrasound features which may or may not be associated with congenital CMV infection, i.e. ventriculomegaly, echogenic bowel, fetal growth restriction, microcephaly etc. Therefore, it would be very useful to provide clear guidance in the situations described below as well as to have clear directions on what the obstetrician must do in those situations: 1. In the presence of the above high-risk findings on antenatal ultrasound examination, should tests for CMV antibodies be undertaken at all? 2. If we do indeed undertake maternal CMV antibody testing in the above circumstances do we then need to undertake antenatal fetal surveillance of any form in women with evidence of primary or non-primary CMV infection? 3. If fetal surveillance is necessary in women found to be 'positive' for CMV infection then what investigations or tests should be undertaken, how frequently and for what length of time during the antenatal period? At present, most fetal medicine departments would follow-up mothers with primary or non-primary CMV infection with serial ultrasound surveillance and occasionally amniocentesis to detect CMV DNA in amniotic fluid. This usually involves expensive healthcare resources, produces a risk of pregnancy loss due to amniocentesis, heightens uncertainties and anxiety and yet, according to current evidence, we do not achieve any concrete end point. Is there any benefit in doing such antenatal tests on mother or baby to detect CMV infection? It would be helpful if the document could provide more definitive guidance in this matter.

Pg 11		Extra comma after can at bottom of page
Pg 20		Similar to the Boppana et al. **study (typo)**
Pg 27		However, as this study assessed the predictive the ability of a tool, rather than specific signs or symptoms, this study was also of limited relevance. This sentence does not make grammatical sense.
Page 33		Down syndrome is the more appropriate terminology applied to this anomaly (not Down's syndrome)

UK National Screening Committee

Newborn screening for cytomegalovirus –an evidence review

Consultation comments pro-forma

Name:	xxxx xxxx	**Email address:**	xxxx xxxx
Organisation (if appropriate):	National Deaf Children's Society		
Role:	xxxx xxxx		
Do you consent to your name being published on the UK NSC website alongside your response? **Yes ☐X No ~~☐~~**			

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*

Other comments:

NDCS is the leading charity working with children and young people with all types and levels of deafness, their families, and the professionals who support them. We believe that deaf children can do anything other children do given the right support from the start and offer a range of family support to our members including a Helpline, information leaflets, specialist advice services and a family weekend programme. Through our work with families we know that parents of babies who have been diagnosed with congenital CMV are frequently devastated to know that their child's hearing loss may have been avoidable.

NDCS welcomes current research in this area into vaccines, screening, and treatments. NDCS firmly believes in informed choice and therefore welcomes research that will hopefully lead to a routine non-invasive test being available giving parents an opportunity to find out whether their baby is at risk of developing deafness and along with their medical team make choices that are best for them and their baby.

Having read the consultation document we understand the UKNSC's reasons for not recommending screening at this time. We would urge the Committee to consider timely review of the evidence as it becomes available. Thank you for giving us the opportunity to respond at this time.

Please return to the Evidence Team at screening.evidence@nhs.net **by Wednesday 13th September 2017.**

UK National Screening Committee

Newborn screening for cytomegalovirus –an evidence review

Consultation comments pro-forma

Name:	xxxx xxxx	**Email address:**	xxxx xxxx
Organisation (if appropriate):	British Infection Association		
Role:	xxxx xxxx		
Do you consent to your name being published on the UK NSC website alongside your response? **Yes** ☐ **No x** ☐			

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*

General	Recommendations	We agree with the recommendation not to introduce maternal or neonatal screening at this stage and support further research in this area.
General	Vaccines	We support further funding and support for a vaccine in this important area.

Please return to the Evidence Team at screening.evidence@nhs.net **by Wednesday 13th September 2017.**

UK National Screening Committee

Newborn screening for cytomegalovirus –an evidence review

Consultation comments pro-forma

Organisation (if appropriate):	Royal College of Paediatrics and Child Health (RCPCH)	**Email address:**	xxxx xxxx
Name:	Submitted by Clinical Standards at RCPCH. With thanks to the following for commenting: • Dr Martin Peter Ward Platt – Consultant Paediatrician • Dr Helen Mactier - Consultant Neonatologist (Honorary Secretary BAPM)		
Role:			

Do you consent to your name being published on the UK NSC website alongside your response?

Yes X☐ No ☐

Section and / or	**Text or issue to which**	**Comment**

page number	comments relate	*Please use a new row for each comment and add extra rows as required.*
General	General	We agree with the UK NSCs decision. In ten years' time we probably will do newborn screening for CMV, but right now the data is simply not there. Several studies need to be done: • We need to know more about the performance of salivary PCR and/or extended blood spot testing • We need to understand the natural history of CMV when detected in asymptomatic babies, and in particular if there is any threshold above which the risk of adverse outcomes such as hearing loss greatly increases • Much more needs to be known about possible harms from treatment with valganciclovir, as well as the optimum duration of treatment • Once the above information is known, and if it suggests that it would be a good idea, there needs to be a single region pilot of salivary screening linked to an RCT of treatment.
General	General	The UK NSC have produced a useful review which should stimulate the necessary research. We feel this is a very good document. We are supportive of the conclusion that there is no evidence for newborn screening for congenital CMV infection.

Please return to the Evidence Team at screening.evidence@nhs.net **by Wednesday 13th September 2017.**

UK National Screening Committee

Newborn screening for cytomegalovirus –an evidence review

Consultation comments pro-forma

Name:	XXXX XXXX	**Email address:**	XXXX XXXX
Organisation (if appropriate):	British Paediatric Allergy Immunity and Infection Group		
Role:	XXXX XXXX		

Do you consent to your name being published on the UK NSC website alongside your response?

Yes ☐ **No** ☒

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*
Summary page		Point 1; There is no evidence that the saliva studies cited (Boppana et al 2011, Waters et al 2014) cited are subject to verification bias. The findings from these studies have already been adopted into routine clinical practice and integral to national and international evidence based management guidelines (Shah T et al 2016, Rawlinson WD et al 2017) Point 2. This is not entirely true. Symptomatic and asymptomatic infants follow up published evidence based clinical care pathways (Shah T et al 2016). Affected infants are followed up in audiology clinic till the age of 6. There are no biomarkers to predict disease severity. However, this is the case with other conditions being screened for other conditions screened in newborns e.g. PKU, congenital hypothyroidism. Point 3: We take issue with this point too. A double blind controlled RCT of 6 months v 6 weeks valganciclovir shoed that 20% of infants who had 6 months of valganciclovir had severe neuropaenia compared to 27% who received placebo (Kimberlin et al 2015). Infants who received 6 months valganciclovir had statistically better hearing outcomes than those who received 6 weeks. These findings have been adopted into UK clinical practice (Shah T et al 2016). Most UK paediatricians now use oral valganciclovir and not IV ganciclovir if treating congenital CMV. there is no evidence this is inferior to IV treatment.
Page 8.	"There are no current figures on CMV seroprevalence among pregnant	Pembrey 2013 reports a pregnant cohort from Bradford. (Pembrey L, Raynor P, Griffiths P, Chaytor S, Wright J, Hall AJ. Seroprevalence of cytomegalovirus, Epstein Barr virus and varicella zoster virus among pregnant women in Bradford: a cohort study. PloS one. 2013;8(11):e81881. PubMed PMID: 24312372. Pubmed Central PMCID: 3842274.)

	women in the UK".	
Page 10.	“The updated search did not identify new evidence related to primary prevention methods”.	At least one RCT addresses this issue. (Revello MG, Tibaldi C, Masuelli G, Frisina V, Sacchi A, Furione M, et al. Prevention of Primary Cytomegalovirus Infection in Pregnancy. EBioMedicine. 2015 Sep;2(9):1205-10. PubMed PMID: 26501119. Pubmed Central PMCID: 4588434.) ? also French study
Page 11.		Potentially favourable results obtained of treating women antenatally with valaciclovir (but not RCT). (Leruez-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. American journal of obstetrics and gynecology. 2016 Oct;215(4):462 e1- e10. PubMed PMID: 27083761.)
Page 11.	“This group of babies is most likely to be the potential target and beneficiary of newborn screening.”	Cannon 2014 reviews estimates of the number of cases in the USA who would benefit from a screening programme because they are not detected clinically at birth and yet develop SHNL. Evidence for potential need (and effectiveness) of a screening programme. (Cannon MJ, Griffiths PD, Aston V, Rawlinson WD. Universal newborn screening for congenital CMV infection: what is the evidence of potential benefit? Reviews in medical virology. 2014 Sep;24(5):291-307. PubMed PMID: WOS:000344544900002.)
Page 11		Neurodevelopmental problems may only present in late infancy when the clinical picture and neuroimaging might have CMV on the list of differentials. Similarly hearing is often not made till weeks/months after 3 weeks of age. In both these instances, the Guthrie card will be retrieved. However, only a third of cases will be identified through this method due to its insensitive nature (Boppana et al JAMA 2010) and so the family and clinical team cannot know if CMV is the cause of the child’s problems.

Page 18.		Note that an international standard is now available. (Fryer JF, Standardization WHOECoB. Collaborative study to evaluate the proposed 1st WHO international standard for human cytomegalovirus (HCMV) for nucleic acid amplification (NAT)-based assays 2010.)
Page 18.	"None of the 15 included studies came from the UK."	Not in review cited but in primary literature there are UK refs including Atkinson et al 2014 whose report discusses the development of a single tube nested PCR. The sensitivity for detecting CMV DNA from dried blood spots in known cases of congenital CMV infection was 81%. Importantly, the cases that were missed did not develop SNHL on follow-up. There is a difference, therefore, between sensitivity for detecting cases of infection and sensitivity for detecting cases at risk of developing disease in the future (which is what is required of a screening test). Caution in using studies reporting on outcomes of DBS testing if evidence for good sensitivity and specificity compared to external quality control panels are not presented. (Atkinson C, Emery VC, Griffiths PD. Development of a novel single tube nested PCR for enhanced detection of cytomegalovirus DNA from dried blood spots. JVirolMethods. 2014;196:40-4.)
Page 19		Point b validity as a diagnostic test and impact of test on management are separate questions that might not be expected to be answered by the study in question. this does not make the diagnostic validity any less important. Point d While manifestations of viruses may differ between different people and populations the natural history of viral replication is very similar in all human hosts so the use of different racial groups in the study mentioned does not significantly affect the validity of the results. Studies have also been done in UK populations with similar results
Page 20.	"None of the studies reviewed here have yet reported longer term disease outcomes."	A large study from the USA has now reported the audiological follow-up of 100,000 cases diagnosed by testing saliva for CMV DNA. Audiology tests done in those with positive saliva results revealed cases of SNHL which had not been detected by the routine national hearing screening programme, whose sensitivity was estimated at 57% for detecting SNHL caused by CMV. (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 Feb;139(2). PubMed PMID: 28049114. Pubmed Central PMCID: 5260148.)

Table 5.	The RCT of Kimberlin is listed as coming from the USA.	Although the majority of cases were from the USA, the UK (including members of BPAIIG) also contributed cases. (Kimberlin DW, Jester PM, Sanchez PJ, Ahmed A, Arav-Boger R, Michaels MG, et al. Valganciclovir for symptomatic congenital cytomegalovirus disease. The New England journal of medicine. 2015 Mar 5;372(10):933-43. PubMed PMID: 25738669. Pubmed Central PMCID: 4401811.)
Page 24.	"47% of the participants in the six month treatment group and 61% of the participants in the six weeks treatment group, entered the study at 15 days of age or older. Diagnosis of CCMV requires a sample to be collected within the first 2 weeks of life."	The second sentence is incorrect. The conventional cut-off time used in the published literature is 3 weeks. The figures relating to date of trial entry are not the same as the date of diagnosis!

Page 24.	"Nevertheless neutropenia remains a safety concern with valganciclovir."	Neutropenia seems less with oral valgan compared to intravenous ganciclovir and at the dose used in the RCT of 6 weeks vs 6 months there was no significant difference in neutropenia between recipients of drug or placebo. (Kimberlin DW, Jester PM, Sanchez PJ, Ahmed A, Arav-Boger R, Michaels MG, et al. Valganciclovir for symptomatic congenital cytomegalovirus disease. The New England journal of medicine. 2015 Mar 5;372(10):933-43. PubMed PMID: 25738669. Pubmed Central PMCID: 4401811.) Note that congenital CMV infection itself causes neutropenia. What is important is the difference in neutropenia between those receiving drug and placebo. (Kimberlin DW, Lin CY, Sanchez PJ, Demmler GJ, Dankner W, Shelton M, et al. Effect of ganciclovir therapy on hearing in symptomatic congenital cytomegalovirus disease involving the central nervous system: a randomized, controlled trial. JPediatr. 2003;143(1):16-25.)
Page 35.	"There remains a lack of clarity over how to identify which newborns are at risk of long-term neurodevelopmental sequelae."	Is this relevant? Introduction of screening for congenital CMV would identify cases who could all be offered treatment with a drug (or enhanced follow-up +/- educational/audiological support). Is it not true that all cases are given the same medical advice after screening for other conditions such as PKU/Downs/hypothyroidism with no requirement to identify subsets of patients? Is this criterion being applied equally to all conditions that may be screened for? It is clearly desirable to identify subsets of cases with a high risk of progression, if this is possible, but that is surely a research objective? Bullet points on page 36, this research concept is selected as one of 2 bullet points that must be met before screening can begin. The second bullet point also seems contentious (see comment above).
Page 36.	"The review was performed using a search strategy that would identify all evidence of relevance to maternal or antenatal screening for CMV… All evidence of	We have provided relevant references above that were published within the February 2016 cut-off and disagree that this review captures all relevant new data. It seems that a search has been made for publications specifically targeted at screening for CMV. This seems inappropriate, because important evidence of value to the screening committee will come from other areas of science or medicine such as diagnosis. It is also felt unlikely that further evidence will come regarding treatment in 'screened' group directly without large scale screening studies since in the absence of defined screening clinicians are treating these children with disease that seems modifiable from existing evidence. We are in a Catch 22.

	relevance to newborn screening, treatment and outcomes was then reviewed."	
Page 36.	"No studies were available to inform whether long-term outcomes, such as hearing, differ in screened vs. non-screened populations."	This is not correct since two studies (from the same cohort) report that outcomes are, indeed, worse in non-screened populations but that hearing deterioration still occurs in all groups. This does not mean therefore that interventions studies are NOT applicable to this group but merely that any implementation needs close monitoring to ensure overall benefit. (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. The Journal of pediatrics. 2014 Apr;164(4):855-9. PubMed PMID: 24433826. Pubmed Central PMCID: 39829; Pinninti SG, Rodgers MD, Novak Z, Britt WJ, Fowler KB, Boppana SB, et al. Clinical Predictors of Sensorineural Hearing Loss and Cognitive Outcome in Infants with Symptomatic Congenital Cytomegalovirus Infection. The Pediatric infectious disease journal. 2016 Aug;35(8):924-6. PubMed PMID: 27195603. Pubmed Central PMCID: 4979986.)
Page 37.	Implications for Research include to "identify an effective intervention that could be beneficial to a screen detected population".	Surely such effective interventions have been shown when establishing the case for the newborn hearing screening programme. In identifying babies with CCMV a group is identified that are at high risk of SNHL and providing interventions for children with SNHL underpins the already approved NHSP.

Page 45.	"Though uncertain what method of diagnostic confirmation would be used here."	This is incorrect. The natural history of congenital CMV infection has been described consistently over decades and multiple laboratory methods already exist to readily confirm or reject cases identified by universal screening. (Grosse SD, Dollard S, Ross DS, Cannon M. Newborn screening for congenital cytomegalovirus: Options for hospital-based and public health programs. Journal of Clinical Virology. 2009 Dec;46:S32-S6. PubMed PMID: WOS:000273109500007.)
Whole report		No comment anywhere in document about considering linking CMV screening to national hearing screening programme which many of us have proposed i.e. dont screen every infant but at least develop pathways to allow screening with failed hearing screens early in neonatal period (Williams EJ et al 2014, Williams EJ 2015, kadambari S et al 2015). These studies highlight that targeted screening for c CMV through the Newborn Hearing Screening Programme is acceptable, feasible and cost effective. However, this UK based programme of work which is based on enhancing existing NHS care pathways has not been included by the NSC review. Children with hearing loss have been shown in multiple studies to have poorer quality of outcomes compared to their peers. Salivary testing is sensitive (Boppana et al 2011) and valganciclovir is an effective therapy (Kimberlin et al 2015). Different regions across north America have started screening for c CMV as part of routine clinical care. We are keen to work with the NSC to fill the gaps identified in this review. In the last 8 months there have been significant advances in furthering our understanding of screening for c CMV (Fowler KB et al 2017 and Gantt et al 2017). We believe that the next NSC review should be conducted in the next 18 months to include these compelling data and evaluate the outcomes of routine screening for cCMV in several regions across North America.

Please return to the Evidence Team at screening.evidence@nhs.net **by Wednesday 13th September 2017.**

UK National Screening Committee

Newborn screening for cytomegalovirus –an evidence review

Consultation comments pro-forma

Name:	Caroline Star	**Email address:**	xxxx xxxx
Organisation (if appropriate):	CMV Action		
Role:	**Chair**		

Do you consent to your name being published on the UK NSC website alongside your response?

Yes √ **No** ☐

Section and / or page number	**Text or issue to which comments relate**	**Comment** *Please use a new row for each comment and add extra rows as required.*
p3	Cytomegalovirus is a	'Very rare' is a subjective term and can be misleading. CMV is the most common infection passed

	common viral infection in children and adults but very rare in newborn babies	from mother to unborn baby. Even using conservative estimates it affects hundreds of babies a year in the UK which is a greater number than many other conditions that can affect new-born babies.
P10	Primary prevention – the updated search did not identify new evidence related to primary prevention methods	A controlled study published in 2015 provided new evidence that an intervention based on the identification and hygiene counselling of CMV-seronegative pregnant women significantly prevents maternal infection: Revello et al. Prevention of Primary Cytomegalovirus in Pregnancy. EBioMedicine 2 (2015) 1205–1210 This report has highlighted a number of research gaps that need to be filled in order to advance a feasible and effective model for CMV diagnostics and treatment. This will realistically take many years. In the meantime hundreds of babies per year will continue to be born with disabilities caused by congenital CMV at significant cost to the NHS. There is international evidence that low cost / low risk education interventions can be effective. Given the very low public and professional knowledge of CMV transmission and the appetite for more information it is important to prioritise improving professional and public education in the UK. The NSC can help to support this through its education programmes for professionals on non-screened for conditions. CMV Action would like to work further with the NCS to highlight intervention that can and should currently be done without universal screening e.g. targeted diagnostics and educating pregnant women and health professionals about the risk of infection and how this can be managed., especially as the feasibility study to access an educational intervention to prevent CMV infection in pregnancy "Reducing Acquisition of CMV through AnteNatal Education (RACE-FIT)" progresses. Congenital CMV is a significant public health burden in the UK and it is important to progress understanding of how low cost/risk education interventions can be delivered most effectively in the UK. (http://www.hra.nhs.ukj/news/research-summaries/race-fit-phase-i/)
P11	Babies with severe	Feedback from families we support suggests that this is an optimistic statement and that knowledge

	and moderate symptoms in the first two weeks of life are likely to be identified without screening	amongst paediatricians is highly variable. It may be the case in hospitals with an infectious disease specialist on site but not in others. In such cases diagnosis is significantly delayed causing distress amongst families or never made at all. Diagnostic delays potentially mean that infants do not have the opportunity to receive Valganciclovir within the 30 days of life and therefore do not have the potential to benefit from a treatment which is widely recommended. Further data collection is needed to verify the assumption that such babies are identified early in life, for example through an updated BPSU surveillance study on CMV or a CMV registry that captures all babies diagnosed with CMV and compares rates in different regions with expected prevalence. This could help to ensure that all babies with severe and moderate symptoms really are diagnosed without universal screening.
Criterion 4	There should be a simple, safe, precise and validated screening test	We welcome the conclusion that saliva swabs are a practicable option and would endorse the view that at this point in time it is the best and most sensitive method of collecting and testing in a large new-born screening programme. Research now needs to be prioritised and funded to further evaluate this approach in a universal screening scenario. It is worth the NSC noting that NIHR funded research is underway to develop a new point-of-care diagnostic device that could reduce cost and increase practicality of other screening approaches. There are a number of developments in CMV research underway at the moment that warrant more regular review of screening recommendations in this area.
Citerion 9	There should be an effective intervention for patients identified through screening and this criterion has not been met	We would challenge the strength of the statements used in some parts of the report. For example p8 states that 'there is no clear evidence of benefit from the available intravenous or oral antiviral therapies'. But as p24 states, a recent study has reported some evidence that 6 months of treatment has a moderate and statistically significant effect on longer-term hearing (total-ear hearing) and neurodevelopmental outcomes at 12 to 24 months. *Only* pharmaceutical interventions have been considered in the review but the role of screening to monitor the 50% of babies who will eventually have CMV-related hearing loss who will pass the newborn hearing screen should also be considered. These are the cases most likely to be missed through existing diagnostic pathways and screening programmes where poor outcomes could be

		reduced through universal screening. The effectiveness of other interventions such as speech therapy, cochlear implants etc. and the impact of delayed diagnosis should be included.
Criterion 10	There should be agreed evidence-based policies covering which individuals should be offered treatment and the appropriate treatment to be offered	More recent evidence-based guidelines have now been published: Shah, T., Luck, S., Sharland, M., Kadambari, S., Heath, P., & Lyall, H. (2016). Fifteen-minute consultation: diagnosis and management of congenital CMV. Archives of Disease in Childhood - Education & Practice Edition, 101(5), 232–235. http://doi.org/10.1136/archdischild-2015-309656
Criterions 9, 10 & 11 & Page 36	Clear evidence based predictive, diagnostic and treatment pathways/Implications for research	Much of this report involves critique of the methodology of individual studies and highlights the lack of a joined up and strategic policy approach to tackle congenital CMV in the UK. We would therefore additionally call for a unified and multidisciplinary strategy for future research and evaluation to fill the research gaps highlighted in this document and would be happy to work with NSC and PHE on this.
Conclusion	The issues identified in this review are unlikely to be resolved without further research	We welcome the conclusion that further research is needed to advance specific details of how universal new-born screening for cCMV could be carried out effectively. We would welcome the opportunity for discussion with the NSC about how such research could be prioritised in the UK.
Conclusion	The current recommendation not to screen for this infection in the UK should be maintained at this current time	We recognise that not all criteria for screening have been met. However congenital CMV is a significant public health burden in the UK and there are a number of practical steps that can be taken to reduce its impact whilst research is underway to address evidence gaps. These include: - Health professionals working in neonatal care need to know the signs of symptomatic infection so that more babies can be diagnosed - Local diagnostic pathways need to improved so that diagnosis is possible within the window to start treatment for those babies that would benefit - Antenatal education needs to include information about CMV risk reduction. Other infections

		are included that affect far fewer babies, without any better evidence base on the impact of education. - Health professionals working in antenatal care need to know how CMV is transmitted, how risks can be reduced and what they should do if infection is suspected, in line with RCOG's shortly to be published scientific impact paper.

Please return to the Evidence Team at screening.evidence@nhs.net **by Wednesday 13th September 2017.**

UK National Screening Committee

Newborn screening for cytomegalovirus –an evidence review

Consultation comments pro-forma

Name:	Rosa Crunkhorn	**Email address:**	xxxx xxxx
Organisation (if appropriate):	Royal Bolton Hospital		
Role:	Speciality Registrar Audiovestibular Medicine		

Do you consent to your name being published on the UK NSC website alongside your response?

Yes ☒ **No** ☐

Section and / or page number	**Text or issue to which comments relate**	**Comment** *Please use a new row for each comment and add extra rows as required.*
P3 no 2	'There is still no reliable	Identifying newborn babies with congenital CMV is of huge importance from an audiological point of

p5 b p25	way of knowing which babies will go on to develop long term health problems from CMV infection' p3 AND 'There is still lack of clarity about how to identify newborns that will develop long-term sequelae and therefore benefit from medical intervention' AND 'Criterion 9: There should be an effective intervention for patients identified through screening and this criterion has not been met'	view. Whilst many of these babies thankfully may well go on to have no long-term problems, a significant proportion (10-15%) of the asymptomatic congenital CMV babies will go on to develop hearing loss for which early identification and treatment with hearing aids and audiological rehabilitation can make an enormous difference to outcome. This seems to have been overlooked by the review. Identification of those babies at risk, even with normal hearing initially, means targeted audiological follow up can be arranged and appropriate treatment commenced at an early stage which is likely to improve outcome. Additionally, asymptomatic children who are found to have hearing loss via the newborn hearing screen in areas where CMV is not tested, are currently subject to delays as CMV testing is then performed, meaning they may miss out on treatment by a matter of days or weeks. Given that there is a simple non-invasive test (saliva) with high sensitivity and an evidence based treatment available to prevent progression of hearing loss, this is an unacceptable variation in practice and a significant potential medico-legal risk. Whilst not all families may opt for the treatment, it should be available for all. Hence if a universal newborn screen for CMV is not undertaken, a targeted screen for patients identified as having SNHL through newborn hearing screen, should be properly assessed.

Please return to the Evidence Team at screening.evidence@nhs.net **by Wednesday 13th September 2017.**

UK National Screening Committee

Newborn screening for cytomegalovirus –an evidence review

Consultation comments pro-forma

Name:	Ansar Uddin Ahmmed	**Email address:**	xxxx xxxx
Organisation (if appropriate):	Lancashire Teaching Hospitals NHS Foundation Trust		
Role:	**Consultant Audio-vestibular Physician**		

Do you consent to your name being published on the UK NSC website alongside your response?

Yes ☒ **No** ☐

Section and / or page number	**Text or issue to which comments relate**	**Comment** *Please use a new row for each comment and add extra rows as required.*

Plain English summary; Page 3	Best treatment for congenital CMV	The statement “the best treatment for congenital CMV (cCMV) is still not clear” has been interpreted by some colleagues that current treatment for cCMV is not evidence based even in the presence of central nervous system involvement including Sensorineural hearing loss. Therefore, it needs to be clarified in this section if the National Screening Committee is suggesting that the current practice of treating symptomatic cCMV should continue or should stop due to lack of evidence.
Plain English summary; Page 3	Best treatment for congenital CMV	The consultation report mentions that the research was not clear if oral valganciclovir was better than the intravenous ganciclovir. The trial reported by Kimberlin et al (2003) showed that intravenous ganciclovir was significantly better than no treatment in neonates with Hearing loss due to cCMV. Statistical analyses can surely be done to compare the number or percentage of neonates with cCMV in the Kimberlin et al (2003) report who had worsening of hearing in the no treatment group with that in the Kimberlin et al (2015) report who had oral valganciclovir. My impression is that in such statistical comparison may show that the percentage of worsening hearing with oral valganciclovir, 6 weeks or 6 months, will be significantly less than the untreated cCMV group in Kimberlin et al. 2003. I feel that while we are awaiting further research to identify better treatment for cCMV the main question is if there is some evidence to give parents an informed choice to treat neonates with cCMV and CNS symptoms including Sensorineural hearing loss (SNHL). The intravenous or oral options and the complications can be discussed with parents before initiating treatment.
Plain English summary; Page 3	2011 UK NSC recommendation against screening for CMV	Universal screening for CMV is definitely a big undertaking and needs a rigorous approach. I agree with the consultation document that currently there is no clarity if children with CMV infection without any symptoms (majority of cases) will benefit from universal screening. However, this does not mean that a minority group of neonates with cCMV and CNS symptoms including SNHL should be denied treatment, which has some evidence to influence the prognosis. Therefore, the screening committee may not recommend universal screening, but there is no reason for the committee not to

		recommend timely testing for cCMV in neonates who are symptomatic of cCMV infection. Currently testing for CMV is part of the aetiological investigation for neonates identified with SNHL following the newborn hearing screening (NHSP). However, treatment for c CMV according to current evidence is effective if initiated within 4 weeks of birth. The current guideline for the NHSP suggests diagnostic ABR within 4 weeks of a no clear response in the newborn hearing screening. If a diagnostic ABR is carried out at 4 weeks or later and the baby turns out to have cCMV time window for treatment may be lost. Therefore, it would be ideal for diagnostic ABR to be carried out preferably within 2 weeks of birth in babies with no clear response in the hearing screening. I wondered if UK NSC could address such issues in the document.
Page 4; executive summary	Whether newborn screening for CCMV should be offered.	Although the aim is to consider universal screening for CMV, the way information is presented in the document may give the impression that the UK NSC does not recommend treating symptomatic CCMV. The consultation document has already been used as a evidence not to invest in resources so that neonates with possible signs and symptoms of CCMV are confirmed in a timely fashion so that they can be treated if CCMV is confirmed.
Page 4; executive summary	Considers literature published between 2011 and 2016	Statistical comparison of proportion of neonates with deteriorating hearing with CCMV who are not treated (Kimberlin et al 2003) and those treated with oral valganciclovir (Kimberlin et al 2015) may be helpful to show if treating with oral valganciclovir is effective in comparison to not treating neonates with symptomatic CCMV.
Page 5 &6; executive summary	The treatment offered to babies with screen detected CCMV remains unclear	This section needs more clarity if UK NCS is suggesting to stop giving patients informed choice and stop treating neonates with symptomatic CCMV with CNS involvement including SHNL.
		A distinction needs to be made between asymptomatic CMV and symptomatic CMV. Universal Screening for CCMV is different to testing for CCMV
		A distinction needs to be made between Universal Screening for CCMV and testing for CCMV in neonates with signs and symptoms of CCMV

Page 6; executive summary	No evidence of Effectiveness of valganciclovir	Comparison of data in Kimberlin et al 2003 vs 2015 would show if the proportion of neonates with CCMV who had worsening of hearing in the group with no treatment is significantly higher than those treated with ganciclovir (Kimberlin et al 2003) and those treated with valganciclovir (Kimberlin et al 2015).
Page 6; executive summary	No evidence of safety	Complications like neutropenia and ways to manage this is well described by Kimberlin et al. Neutropenia is a known complication of many approved treatments for many different conditions. Therefore, not sure why Ganciclovir and Valganciclovir are singled out. No deaths have been reported from complications of these drugs.
Page 12 &13; Table 1	Effective intervention for patients identified through screening. Relevance of Key question 3	It is true that vast majority of neonates with CCMV will be asymptomatic and there is no evidence to treat neonates with asymptomatic CCMV. Therefore, a universal screening for CCMV may not be indicated. However, testing and treating neonates with signs of symptomatic CCMV is different to Universal screening. The consultation document to suggest that there are no studies to show the effectiveness of ganciclovir or valganciclovir is not clear. Integrating evidence from the 2011 NCS review (e.g. Kimberlin et al 2003, showing hearing worsen if symptomatic CCMV is not treated compared to those treated with ganciclovir) with research post 2011 (Kimberlin et al 2015 showing impact on hearing and development using valganciclovir) may show that treating with antiviral agents influences hearing in symptomatic CCMV than no treatment. Such medications are also currently used as CMV prophylaxis in transplant patients. The question of appropriateness of treatment of for asymptomatic CCMV identified through universal screening

		should not be mixed up with treatment choice for symptomatic CCMV with CNS involvement including SNHL.
Page 13; Table 1	Is there evidence that screening for CCMV impacts on morbidity outcomes? Clarity of Key question 5	Needs to distinguish between screening for asymptomatic CCMV and testing for CCMV in neonates with symptom and signs of CMV infection with CNS involvement including SNHL
Page 21	Description of previous UK NSC evidence	It is not clear if this new consultation document is reversing the conclusion about the recommend treatment for neonates with CCMV and neurological involvement in the previous UK NSC review.
Page 21	Description of previous UK NSC evidence	Some non-medical colleagues in the NHS are already citing this consultation document to suggest that tests for detecting CMV is not carried out in neonates with possible symptoms of CCMV with CNS involvement including SNHL, as there is no evidence based treatment. Therefore, clarity in this document is needed if the NSC is recommending that neonates with symptomatic CCMV with CNS symptoms including SNHL are not treated, neither with ganciclovir nor valganciclovir.
Page 24,	Diagnosis of CCMV requires a sample to be collected within two weeks of life.	This statement by the UK NSC is important which should help to integrate the Auditory brain stem response (ABR) diagnostic and the aetiological investigation protocols of the newborn hearing screening programme. Currently there is a contradiction between the two protocols. ABR diagnostic protocol is recommended within four weeks after no clear response in the newborn hearing screening tests. Therefore, if

		a baby has SNHL due to CCMV and the diagnostic test is carried out 4 weeks after the screening, the recommended aetiological investigation for CMV will not be able to establish easily if the infection was congenital or acquired after birth. Secondly the treatment option after 4 weeks would also not be evidence based. There is therefore a need to carryout ABR diagnostic test within 2 weeks, so that CMV testing would useful which may influence the prognosis of hearing loss, if CCMV is the underlying cause. Such a model is working in a number of NHSP sites.
Page 25; Summary: Criterion 9 not met	Applicability of therapy to babies with mildly symptomatic disease	It is not clear if NSC is suggesting that neonates with SNHL due to CCMV are not offered informed treatment choice. It needs to be clarified that universal CMV screening is not the same as CMV testing for neonates with symptoms and signs of symptomatic CCMV.
Page 35; conclusions	Item C in evidence	It is agreed that no evidence if outcome of treatment in applicable to the general screening population. Unfortunately, some colleagues are citing this consultation document to suggest that treatment are not effective in treating symptomatic CCMV with neurological symptoms including SNHL. It needs to be very clear in the document if NSC is suggesting withholding CMV testing in neonates with signs and symptoms of CCMV and if treatments choice should not be offered if CCMV is confirmed.

Please return to the Evidence Team at screening.evidence@nhs.net **by Wednesday 13th September 2017.**

UK National Screening Committee

Newborn screening for cytomegalovirus –an evidence review

Consultation comments pro-forma

Name:	Richard Stanton, Vincent Teng	**Email address:**	xxxx xxxx
Organisation (if appropriate):	Cardiff & Swansea Universities		
Role:	**Academic Researchers**		

Do you consent to your name being published on the UK NSC website alongside your response?

Yes ☒ **No** ☐

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*

Page 3	CMV is….rare in newborn babies	'Rare' does not seem accurate. Congenital infection with HCMV infection is more common than many congenital diseases for which screening is already performed, including down's syndrome & fetal alcohol syndrome. More generally throughout, it would seem sensible for a review of screening to comment on the significant cost of caring for CCMV children, which has been estimated in the USA, and the cost of screening vs the cost of care, in which screening comes out as economically favourable (e.g. PMID 26122458). Furthermore, although this document concerns itself primarily with population-based screening, it fails to consider the possibility for targeted screening (e.g. for children that fail the newborn hearing screen).
Page 3	'has the infection'	This term is somewhat inaccurate, since congenital infection can occur due to *de novo* infection, reinfection with another strain, or reactivation of a pre-existing infection.
Page 3	'no treatment that could prevent babies from developing health problems from cytomegalovirus infection'	This statement is inaccurate - 2 studies of anti-virals have demonstrated some improvement of symptoms (or delayed deterioration) following administration to newborns. These studies may not be sufficient to justify a screening program, but it is nevertheless incorrect to state that there is 'no treatment'.
Page 4	'These strategies include….'	If reviewing the current state of recommendations, it would seem sensible to comment on CMV screening programs that are already underway in the USA (e.g. Utah).
Page 5	'Should only be used'	This statement implies that antivirals have been proven to not work in other scenarios (e.g. non-neurological manifestations). That is not the case. It would be more accurate to state that currently, treatment has only been investigated in cases of neurological manifestations.
Page 5 (and elsewhere)	Regarding the problem of identifying those who will go on to develop symptoms.	Although the ideal scenario for a screening test would be that it would identify only those that will definitely go on to have problems, it is not the only consideration. For example, identifying children 'at risk' of developing symptoms could enable them to be monitored more closely, enabling interventions to be put in place more rapidly if/when symptoms do occur.
Page 11	'10%...can later develop hearing	Hearing loss is not the only symptom of CCMV. Studies of permanent sequalae show

	loss’	that these are far more common (numerically) in the asymptomatic than in the symptomatic (e.g. PMID 21246642). Thus there is a strong case that screening will identify cases that would not otherwise be identified.
Page 33	No studies were identified..	The study should not just consider CCMV-specific studies. Since CCMV causes hearing loss, evidence from the newborn hearing screening program are relevant. I.e. early behavioural inteventions, speech therapy, early use of cochlear implants etc, can lead to improved outcomes at school age. Since newborn screening would identify babies at risk of late-onset hearing loss, these benefits need to be taken into account.
Page 35	Point f	As above – newborn hearing screening should be taken into account.

Please return to the Evidence Team at screening.evidence@nhs.net **by Wednesday 13th September 2017.**

UK National Screening Committee

Newborn screening for cytomegalovirus –an evidence review

Consultation comments pro-forma

Name:	Prof P D Griffiths on behalf of Congenital CMV Research Interest Group	**Email address:**	xxxx xxxx
Organisation (if appropriate):	Congenital CMV Research Interest Group		
Role:	We are a "prominent research group" that has provided much of the literature in this area for the UK. Members include: Prof Paul Griffiths (UCL); Prof Paul Heath (St George's); Dr Chrissie Jones (Southampton); Dr Seilesh Kadambari (Oxford); Dr Asma Khalil (St George's); Dr Sue Luck (Kingston and St George's); Dr Elizabeth Whittaker (Imperial).		
Do you consent to your name being published on the UK NSC website alongside your response? **Yes** ☒ **No** ☐			

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*
Page 3	"Cytomegalovirus is a common viral infection in children and adults but very rare in newborn babies."	A very rare condition would suggest that congenital CMV occurs at a rate of substantially less than 5 per 10,000 (NHS England definition of rare disease). This is not the case for all babies with congenital CMV, estimated to be 3 per 1,000 in the UK (Peckham CS, Chin KS, Coleman JC, et al. Cytomegalovirus infection in pregnancy: preliminary findings from a prospective study. Lancet 1983;1:1352–5.5. Griffiths PD, Baboonian C, Rutter D, et al. Congenital and maternal cytomegalovirus infections in a London population. Br J Obstet Gynaecol 1991;98:135–40.)
Page 8 and executive summary	"There are no current figures on CMV seroprevalence among pregnant women in the UK".	This is incorrect. The paper by Pembrey 2013 reports a pregnant cohort from Bradford with 49% seropositivity in white UK women, 89% among South asian women born in the UK and 98% among women born in South Asia. (Pembrey L, Raynor P, Griffiths P, Chaytor S, Wright J, Hall AJ. Seroprevalence of cytomegalovirus, Epstein Barr virus and varicella zoster virus among pregnant women in Bradford: a cohort study. PloS one. 2013;8(11):e81881. PubMed PMID: 24312372. Pubmed Central PMCID: 3842274.)
Page 10.	"The updated search did not identify new evidence related to primary prevention methods".	This is incorrect. There has been one RCT addressing this issue with statistically significant decrease in seroconversion in the intervention group. (Revello MG, Tibaldi C, Masuelli G, Frisina V, Sacchi A, Furione M, et al. Prevention of Primary Cytomegalovirus Infection in Pregnancy. EBioMedicine. 2015 Sep;2(9):1205-10. PubMed PMID: 26501119. Pubmed Central PMCID: 4588434.) A randomised controlled trial is currently underway in the UK (where one of us is the Principal Investigator). (http://www.hra.nhs.uk/news/research-summaries/race-fit-phase-i/)
Page 11.		Although not an RCT, there is no mention of the potentially favourable results obtained of treating women antenatally with valaciclovir. (Leruez-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. American journal of obstetrics and gynecology. 2016 Oct;215(4):462 e1- e10. PubMed PMID: 27083761.)
Page 11.	"This group of babies is most likely to be the potential target and beneficiary of newborn screening."	The review by Cannon 2014 provides estimates of the number of cases in the USA who would benefit from a screening programme because they are not detected clinically at birth and yet develop SHNL. These results speak to the potential effectiveness of a screening programme. (Cannon MJ, Griffiths PD, Aston V, Rawlinson WD. Universal newborn screening for congenital CMV infection: what is the evidence of potential benefit? Reviews in medical virology. 2014 Sep;24(5):291-307. PubMed PMID: WOS:000344544900002.)
Page 14 Also page 24	"…diagnosis of CCMV requires a sample to be collected within the first two weeks of life…."	A sample should be collected within the first three weeks of life to establish a diagnosis of CCMV because this is the conventional cut-off time used in the published literature.
Page 18.		Note that an international standard is now available so the results of testing dried blood spots for CMV DNA can now be calibrated in international units. (Fryer JF, Standardization WHOECoB. Collaborative study to evaluate the proposed 1st WHO international standard for human cytomegalovirus (HCMV) for nucleic acid amplification (NAT)-based assays 2010.)
Page 18.	"None of the 15 included studies came from the UK."	This may be true for the review article examined, but the primary literature contains important new information which has been missed. For example, Atkinson et al 2014 (from the UK laboratory of one of us) reported the development of a single tube nested PCR which provides the increased sensitivity of nesting without the need to open vials and add fresh reagents, which runs the risk of cross contamination. The sensitivity of this method was such that 100% of coded dried blood spot samples provided as part of external quality assurance were detected. The sensitivity for detecting CMV DNA from dried blood spots in known cases of congenital CMV infection was 81%. Importantly, the cases that were missed did not develop SNHL on follow-up. These results speak directly to the difference between sensitivity for detecting cases of infection and sensitivity for detecting cases at risk of developing disease in the future (which is what is required of a screening test). (Atkinson C, Emery VC, Griffiths PD. Development of a novel single tube nested PCR for enhanced detection of cytomegalovirus DNA from dried blood spots.

		JVirolMethods. 2014;196:40-4.)
Page 20.	"None of the studies reviewed here have yet reported longer term disease outcomes." “It is not known how screening test results correlate with the likelihood of adverse outcomes”	This was correct when the report was written, but a large study from the USA has now reported the audiological follow-up of 100,000 cases diagnosed by testing saliva for CMV DNA. Audiology tests done in those with positive saliva results revealed cases of SNHL which had not been detected by the routine national hearing screening programme, whose sensitivity was estimated at 57% for detecting SNHL caused by CMV. (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 Feb;139(2). PubMed PMID: 28049114. Pubmed Central PMCID: 5260148.)
Table 5.	The RCT of Kimberlin is listed as coming from the USA.	This is not correct. The majority of cases were from the USA, but the UK (including authors of this report) also contributed cases. (Kimberlin DW, Jester PM, Sanchez PJ, Ahmed A, Arav-Boger R, Michaels MG, et al. Valganciclovir for symptomatic congenital cytomegalovirus disease. The New England journal of medicine. 2015 Mar 5;372(10):933-43. PubMed PMID: 25738669. Pubmed Central PMCID: 4401811.)
Page 24.	"47% of the participants in the six month treatment group and 61% of the participants in the six weeks treatment group, entered the study at 15 days of age or older. Diagnosis of CCMV requires a sample to be collected within the first 2 weeks of life."	The second sentence is incorrect. The conventional cut-off time used in the published literature is 3 weeks. The first sentence reveals a misunderstanding. These figures relate to the age at which neonates were recruited into the study. Before that time, samples would have been collected to confirm the diagnosis, imaging studies and hearing tests would have been performed, the clinical trial would have been discussed with the parents, the parents would have signed a consent form and the drug would have been dispensed. Thus, the figures relating to date of trial entry are not the same as the date of diagnosis.
Page 24.	"Nevertheless neutropenia remains a safety concern with valganciclovir."	This is true for intravenous ganciclovir but not for valganciclovir at the dose used in the RCT where there was no significant difference in neutropenia between recipients of drug or placebo. (Kimberlin DW, Jester PM, Sanchez PJ, Ahmed A, Arav-Boger R, Michaels MG, et al. Valganciclovir for symptomatic congenital cytomegalovirus disease. The New England journal of medicine. 2015

		Mar 5;372(10):933-43. PubMed PMID: 25738669. Pubmed Central PMCID: 4401811.) Note that the earlier RCT from Kimberlin was the first to describe that congenital CMV infection itself causes neutropenia. What is important is the difference in neutropenia between those receiving drug and placebo. (Kimberlin DW, Lin CY, Sanchez PJ, Demmler GJ, Dankner W, Shelton M, et al. Effect of ganciclovir therapy on hearing in symptomatic congenital cytomegalovirus disease involving the central nervous system: a randomized, controlled trial. JPediatr. 2003;143(1):16-25.)
Page 25.	"The trial found no evidence that prolonged treatment with oral valganciclovir improves short-term hearing outcomes."	This statement is correct but gives an overly harsh impression, because the objective is to control long-term hearing loss caused by congenital CMV infection (which is addressed in the sentence that follows). In addition, the final sentence of this paragraph "however, there were some concerns on the safety of the drug" is misleading because the major known toxicity of valganciclovir (neutropenia) was not increased compared to children receiving placebo. (Kimberlin DW, Jester PM, Sanchez PJ, Ahmed A, Arav-Boger R, Michaels MG, et al. Valganciclovir for symptomatic congenital cytomegalovirus disease. The New England journal of medicine. 2015 Mar 5;372(10):933-43. PubMed PMID: 25738669. Pubmed Central PMCID: 4401811.) The overall effect of the way this paragraph is written is to play down the important contribution made by this publication. This impression of negativity is continued in the construction of the final sentence "finally, the population enrolled in the study was not enrolled through screening, limiting the applicability of the result to a screening programme." The conclusion could equally have been: "now that this drug has been shown to be safe and with moderate efficacy in congenital CMV infection, future studies should be conducted to see if the same conclusion applies to children identified through screening." The current unjustifiably negative interpretation is repeated in paragraph C of the conclusions on page 35 which contains the incorrect statement "oral valganciclovir caused severe neutropenia in about one in 5 infants." We repeat: what is important is the difference in neutropenia between those receiving drug and placebo. This concept was correctly identified in the second bullet point of page 56 but does not appear to have made it into the main body of the text.

		Despite there being just a single placebo-controlled trial of six months of treatment vs 6 weeks of treatment, this study has completely changed clinical practice in the UK, where infants with CCMV who meet pre-defined criteria are treated for 6 months in order to improve hearing and neurological outcomes
Page 28.	" A single, UK evidence-based guideline on the management of CCMV was identified (Kadambari et al 2011)	A more recent article has also been published which includes recommendations for 6 months of valganciclovir. Shah, T., Luck, S., Sharland, M., Kadambari, S., Heath, P., & Lyall, H. (2016). Fifteen-minute consultation: diagnosis and management of congenital CMV. Archives of Disease in Childhood - Education & Practice Edition, 101(5), 232–235. http://doi.org/10.1136/archdischild-2015-309656
Page 35.	"There remains a lack of clarity over how to identify which newborns are at risk of long-term neurodevelopmental sequelae."	This is a true statement, but it is not clear to us why this appears to be a prerequisite for screening for CMV. Introduction of screening for congenital CMV would identify cases who could all be offered treatment with a drug that has now been shown to be safe. Is it not true that all cases are given the same medical advice after screening for phenylketonuria or Down's syndrome, with no requirement to identify subsets of patients? What is the origin of this criterion and is it being applied equally to all conditions that may be screened for? It is clearly desirable to identify subsets of cases at birth with a high risk of progression, if this is possible, but that is surely a research objective. Furthermore, this research objective would be facilitated if cases were identified in the future by universal screening so they could be followed up. It seems perverse to us to be requiring a precondition (which may not even be possible medically or scientifically) for congenital CMV that is not being applied to other conditions that are screened for already. It is also not clear to us why, on page 36, this research concept is selected as one of 2 bullet points that must be met before screening can begin. The second bullet point also seems contentious to us (see comment above) since an effective intervention does exist that could be beneficial to a screen-detected population. Just because treatment studies to date have not examined populations detected through screening (largely because screening is not part of standardised care – a classical Catch 22) does not mean that the intervention is not effective.

		This statement also completely overlooks the benefit of early educational, audiological, and neurodevelopmental support which can be implemented in children with known cCMV and in whom audiovestibular or neurodevelopmental difficulties are detected.
Page 36.	"The review was performed using a search strategy that would identify all evidence of relevance to maternal or antenatal screening for CMV… All evidence of relevance to newborn screening, treatment and outcomes was then reviewed."	We dispute this point and have provided relevant references above that were published within the February 2016 cut-off. It seems that a search has been made for publications able to answer every last question about screening for CMV. This seems inappropriate, because important evidence of value to the screening committee will come from other areas of science or medicine, such as diagnosis.
Page 36.	"No studies were available to inform whether long-term outcomes, such as hearing, differ in screened vs. non-screened populations."	This is not correct since two studies (from the same cohort) report that outcomes are, indeed, worse in non-screened populations. However, there was no difference in the incidence of progressive or delayed-onset hearing loss between screened and referred infants. The presence of motor abnormalities and chorioretinitis was also not significantly different between the 2 groups. This would further support the potential benefit of screening for cCMV in babies without obvious manifestations of disease at birth (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. The Journal of pediatrics. 2014 Apr;164(4):855-9. PubMed PMID: 24433826. Pubmed Central PMCID: 39829; Pinninti SG, Rodgers MD, Novak Z, Britt WJ, Fowler KB, Boppana SB, et al. Clinical Predictors of Sensorineural Hearing Loss and Cognitive Outcome in Infants with Symptomatic Congenital Cytomegalovirus Infection. The Pediatric infectious disease journal. 2016 Aug;35(8):924-6. PubMed PMID: 27195603. Pubmed Central PMCID: 4979986.)
Page 37.	Implications for Research include to "identify an effective intervention that could be beneficial to a screen detected population".	Surely such effective interventions have been shown when establishing the case for the newborn hearing screening programme. In identifying babies with CCMV a group is identified that are at high risk of SNHL and providing interventions for children with SNHL underpins the already approved NHSP.
Page 45.	"Though uncertain what method of	This is incorrect. The natural history of congenital CMV infection has been described consistently over decades and multiple laboratory methods already exist to readily confirm or reject cases

	diagnostic confirmation would be used here."	identified by universal screening. This was accepted in the review from the USA Centers for Disease Control and Prevention screening group and it is surprising that this appears to be not well-known. In other words, the basis for making decisions about universal screening for CMV should not just be based on one review of the current literature, but on all the scientific and medical foundations that have gone before. (Grosse SD, Dollard S, Ross DS, Cannon M. Newborn screening for congenital cytomegalovirus: Options for hospital-based and public health programs. Journal of Clinical Virology. 2009 Dec;46:S32-S6. PubMed PMID: WOS:000273109500007.)
Page 56.		Add that the reported gonadal toxicity and carcinogenicity was observed in rodents, not humans.
Whole report		Finally, we have some thoughts on the way forward on universal screening for congenital CMV. Some important publications have been made recently. Their lack of inclusion is not a criticism of this consultation document whose cut-off date was February 2016. However, it does show how fast this subject is developing and suggest that maintaining a three-year review cycle before CMV is discussed again will not be sufficient. These articles address the cost effectiveness of universal screening in the USA and the screening of approximately 100,000 live births using saliva swabs and comparing the outcome of additional tests for hearing after standard tests for the national hearing screening programme had been performed. These major publications add to the evidence that universal screening is both desirable and likely to be highly cost-effective. (Gantt S, Dionne F, Kozak FK, Goshen O, Goldfarb DM, Park AH, et al. Cost-effectiveness of Universal and Targeted Newborn Screening for Congenital Cytomegalovirus Infection. Jama Pediatr. 2016 Dec 1;170(12):1173-80. PubMed PMID: WOS:000390256900017. English. ; 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 Feb;139(2). PubMed PMID: 28049114. Pubmed Central PMCID: 5260148.)
Whole report		Our specific comments made above also show that a multidisciplinary team effort will be required to critically evaluate how the possibility of universal CMV screening for neonates could

		be taken forward. We offer our services and collaboration to the national screening programme to work towards a feasible, practical and cost-effective way of evaluating universal screening in a region of the UK so that lessons can be learned and applied prior to a national roll-out. We accept that universal screening for congenital CMV will probably be introduced first in the USA, but we feel that the UK should not lag too far behind.

Please return to the Evidence Team at screening.evidence@nhs.net **by Wednesday 13th September 2017.**

NSC UK National Screening Committee

bapa BRITISH ASSOCIATION OF PAEDIATRICIANS IN AUDIOLOGY

12th September 2017

I would like as Chair of the British Association of Paediatricians in Audiology (BAPA) to acknowledge and support the comments raised by xxxx xxxx, xxxx xxxx, with respect to the consultation on Newborn Screening for cytomegalovirus. We have, with our colleagues in the British Association of Audiological Physicians (BAAP), been recommending that all children and young people with any degree of sensorineural hearing loss be offered testing for CMV as part of aetiological investigations.

We have been aware of current research and developments in identification and treatment in this field which have been and are currently being under taken. Indeed we felt it such an important and relevant topic that we hosted a specialist session at the RCPCH UK conference in Birmingham in May 2017 to further raise awareness.

Our members are involved in the management of babies referred from the newborn hearing screening programmes (NHSP) throughout the UK and are aware of the potential that identification of cCMV following referral from NHSP may take place out with the current recommended eligible treatment window. Screening would afford early identification and the opportunity to offer treatment in these cases. In the case of asymptomatic babies where cCMV is identified it would enable early referral to appropriate specialists, including for hearing surveillance, according to the existing national guidelines.

We would support the submitted comments in particular the comments as highlighted on the attached copy.

Yours sincerely

Dr Patricia Townsley on behalf of BAPA Executive committee

BAPA Chair

UK National Screening Committee

Newborn screening for cytomegalovirus –an evidence review

Consultation comments pro-forma

Name:	Dr Simone Walter	**Email address:**	xxxx xxxx
Organisation (if appropriate):	St George's Hospital, St Helier Hospital, Croydon University Hospital		
Role:	**Consultant Audiovestibular Physician**		
Do you consent to your name being published on the UK NSC website alongside your response? **Yes** x **No**			

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*

P3 no.1	Regarding saliva sample: ‘more research is needed to understand more about it’	The saliva swab was the method preferred by parents compared with urine in the paper Williams et al (1). The wet and dry saliva swab have been studied by Boppana et al 2011 (2) and found to be highly sensitive for CMV detection.
P3 no 2.	‘There is still no way of knowing which will on to develop long-term problems and need medical treatment’	A screening test needs to detect disease, but is not required to predict outcome. For example, the newborn hearing screen does not predict the severity of the hearing loss (many children are, in fact, found to have normal hearing), nor predict the auditory rehabilitation they will need. Even though approximately 85% of those born without obvious symptoms will remain asymptomatic, we do have a way to detect the SNHL and to treat it (hearing aids and audiological rehabilitation). There are also benefits of identifying and treating those with symptomatic disease which is not detected at birth e.g. those with intrauterine growth retardation or prematurity who are not investigated at birth for congenital CMV, but may later present with SNHL, prolonged jaundice, cerebral palsy or autism, at an age which is too late to be eligible for antiviral treatment, (according to the evidence currently available). The NHSP is identifying children with cCMV related SNHL, but not identifying CMV as the causative agent, in time for referral for treatment. A targeted approach, whereby newborns are tested for CMV at birth when found to have SNHL, to allow assessment for treatment in time, has not been considered (3). Currently children are just missing out on being offered treatment because of the delay in cCMV diagnosis by a matter of days/weeks. There is currently clinical variation, and geographical inequality, in the opportunities for investigation for cCMV in the UK. This has resulted in some children being offered treatment and some not, due to the delay in detection. There is ensuing risk of medicolegal litigation. It is now mandatory by law to offer CMV screening to infants with SNHL in some states of the USA.
P3 no.3	‘The best treatment for congenital cytomegalovirus infection is still not clear’	Valganciclovir has superceded ganciclovir for children well enough to absorb it. Valganciclovir has been adopted by paediatric infectious diseases specialists in the UK as standard of care. (4, 5).

P3 no.3	'The research was not clear if this was better than the intravenous drug that is in use'	This is misleading, as the oral drug, valganciclovir, is the prodrug for ganciclovir and therefore the therapeutic agent is the same. The evidence for benefit to hearing was, as good, if not slightly better with valganciclovir (6). It is 'better' than ganciclovir, because it is oral and avoids the morbidity associated with intravenous use.
P5 b.	'There is still lack of clarity about how to identify newborns that will develop long-term sequelae and therefore benefit from medical intervention'	See point regarding the NHSP as above. These babies are being identified, but they are identified just too late, (by a matter of days/weeks), to be offered medical treatment to try to prevent further loss of hearing. Effective screening is possible using the sensitive rapid PCR techniques.
P6.	'No evidence was identified to establish the safety and effectiveness of oral valganciclovir compared to intravenous ganciclovir in terms of severity of hearing impairment or other complications at birth'	It does not make sense to define safety or efficacy according to degree of hearing loss because the hearing loss can progress. The benefit of treatment is in preservation of hearing rather than improvement of hearing. For example, those with bilateral profound loss have little hearing to preserve whereas those with mild or unilateral loss have much more hearing to preserve.
P6.	'No studies have assessed the benefit of treatment for asymptomatic newborns'	The screening programme does not have to provide medical treatment for asymptomatics, but should provide audiological follow up to allow early identification and rehabilitation of hearing loss, which is well evidenced, has no 'adverse side effects', and is the intervention used by the Newborn Hearing Screening Programme. There are already systems in place for this as part of the Newborn Hearing Screening Programme ('targeted audiological follow-up').
P6	'identify an effective intervention that could be beneficial to a screen detected population'	Current RCT evidence supports antiviral therapy for those with central nervous system effects (CNS effects) – this is the standard of clinical care in the UK (5). Those without CNS effects would receive audiological follow up as described above.
P11	'Babies with severe and moderate symptoms in the first two weeks of life are likely to be identified without	This is not always the case. Premature and IUGR babies are not screened for CMV on neonatal units or postnatal wards. We diagnose cCMV retrospectively in children with SNHL who have not infrequently have had a history of signs which did not prompt

	screening'.	clinical CMV testing e.g. prematurity, IUGR, speech and language delay, cerebral palsy, autism.
P11	'However around 10% of babies who are asymptomatic at birth, or who have mild or unspecified symptoms, can, later develop hearing loss if they are not treated. This group of babies is likely to be the potential target and beneficiary of newborn screening'	This group can have hearing loss at, or shortly after, birth and would be eligible for assessment for medical treatment and audiological rehabilitation. This group also includes babies who are relatively well, or signs of infection are missed at birth, who may go on to develop cerebral palsy, autism, learning difficulties, epilepsy, (not just hearing loss).
P12	'There should be an effective intervention for patients identified through screening…'	The benefits of audiological follow up, to detect hearing loss and provide interventions early, have been overlooked.
P13 Criterion 9	'Is there evidence…For example children with bilateral or unilateral hearing impairment'	One could argue that there is a stronger argument to treat a child with unilateral hearing loss, as there is a normally hearing ear to preserve. Unilateral hearing loss can become bilateral in congenital CMV and the aim of treatment would be to try to prevent such worsening of hearing. A unilateral mild SNHL can rapidly become a bilateral profound in cCMV. The difference in socioeconomic cost of a unilateral loss compared with a bilateral loss is significant, For example a child managing without a hearing aid may go on to require bilateral hearing aids and then cochlear implants because of the progression of hearing loss.
P13 Criterion 10	'Has an evidence based pathway been identified which can distinguish babies that are likely to be adversely affected by cCMV and that may benefit from treatment?'	Current evidence from randomised controlled trials identifies children with central nervous system effects as being likely to benefit from treatment. Asymptomatic newborns would receive audiological follow up to detect hearing loss early.
P13 Criterion 11	'Is there evidence that screening of congenital CMV impacts on morbidity (e.g. hearing) outcomes?	Although small scale studies, both Williams et al and Kadambari et al (1, 7) identified cases of congenital CMV through pilot targeted screening programmes in the UK. Newborns with CMV related hearing loss were then offered treatment as part of clinical care to try to preserve hearing. Such a reduction in hearing loss is a reduction in

		morbidity. Children with congenital CMV and normal hearing went on to receive audiological follow up. Parents were in favour of the screen for CMV.
P18	'None of the 15 included studies came from the UK and it is unclear what method of CMV DNA PCR…would be preferentially be used here'	Atkinson et al 2014, from a UK laboratory, reported the development of a single tube nested PCR (8) CMVDNA PCR testing. It is available now across the UK, with rapid turn around**.**
P20	'It is therefore not known how the screening test results correlate with the likelihood of adverse outcomes'	The role of the screening test is to detect congenital CMV, not to predict outcome. Positive cases would be assessed for symptoms and offered medical treatment if there are CNS effects. They would also be followed up. 'Asymptomatic newborns at birth' would be provided with targeted audiological follow up.
P21	'There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes…'	There is benefit in audiological follow up because of the loss of the school hearing screen and the adverse effects of delayed detection. (See evidence for NHSP).
P24	'Nevertheless neutropenia remains a safety concern there were concerns on the safety of the drug with valganciclovir.'	For valganciclovir at the dose used in the RCT there was no significant difference in neutropenia between recipients of drug or placebo. (6)
P25	'There were concerns on the safety of the drug'	Oral valganciclovir for up to six months has been accepted as standard of care in the UK (4,5).

P25	Criterion 9 ’There should be an effective intervention for patients identified through screening and this criterion has not been met’	The benefits of early identification of hearing loss, and early rehabilitation and interventions for hearing loss have been overlooked. These valuable interventions underpin the Newborn Hearing Screening Programme. However, not all cases of CMV related SNHL in infancy are detected by the newborn hearing screen. (The newborn hearing screen can miss mild sensorineural hearing losses). Fowler et al (3) reports that 43% of the infants with CMV-related SNHL in the neonatal period were not identified by newborn hearing screen.
P35	Conclusions d. ‘differentially safe or effective in newborns according to severity of hearing impairment …	A unilateral loss can become bilateral. A mild or moderate loss can become severe or profound, so one could argue that there is more hearing to preserve when offering treatment to the children with mild to moderate loss. The risks/benefits of treatment are always discussed with parents.
P35	Conclusions e. ‘There remains a lack of clarity over how to identify those at risk of long term neurodevelopmental sequelae’	The NHSP is already identifying children with cCMV-related SNHL, which is at risk of progression. SNHL, and progressive SNHL are 'long-term neurodevelopmental sequelae’.
P35	Conclusions f. ‘No studies were available to inform whether long term outcomes, such as hearing, differed in screened v non screened populations’	The epidemiology is well known in both developed and less developed countries and we can predict the number of children eligible for treatment and audiological follow up. The CMV DNA PCR test is highly sensitive.

Additional comments:

- In the absence of a universal newborn screening in newborns for CMV, a targeted screen for newborns with SNHL should be piloted and evaluated, as an extension of the Newborn Hearing Screen.

- Cost benefit analyses of screening are detailed in papers 9 (USA) and 10 (UK) and are favourable towards screening.

- The cost and difficulty (owing to poorer sensitivity of the dried blood spot PCR, and destruction of dried blood spots during childhood) of investigating retrospectively for congenital CMV should also be considered. The British Association of Audiovestibular Physicians, the British Association of Paediatricians in Audiology, and the National Deaf Children Society recommend that all children and young people with any degree of SNHL are offered CMV tests (see BAAP /BAPA guideline, which is NICE approved, ref11).

References:

1**.** Williams EJ , Kadambari S, Berrington JE, Luck S, Atkinson C, Walter S, Embleton ND, James P, Griffiths P, Davis A, Sharland M, Clark JE. Feasibility and acceptability of targeted screening for congenital CMV-related hearing loss, Arch Dis Child Fetal Neonatal Ed 2014;0:F1–F7

2**.** Boppana SB, Ross SA, Shimamura M, Palmer AL, Ahmed A, Michaels MG, Sánchez PJ, Bernstein DI, Tolan RW Jr, Novak Z, Chowdhury N, Britt WJ, Fowler KB; National Institute on Deafness and Other Communication Disorders CHIMES Study.
Saliva polymerase-chain-reaction assay for cytomegalovirus screening in newborns. N Engl J Med. 2011 Jun 2;364(22):2111-8. doi: 10.1056/NEJMoa1006561.

3**.** 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 Feb;139(2). PubMed PMID: 28049114. Pubmed Central PMCID: 5260148 conflicts of interest to disclose.

4. Kadambari S, Luck, S, Griffiths, P, Sharland, M, Evidence based management guidelines for the detection and treatment of congenital CMV, Early Human Development 87 (2011) 723–728

5**.** Shah T, Luck S, Sharland,M, Kadambari S, Heath P, Lyall H. Fifteen-minute consultation: diagnosis and management of congenital CMV Arch Dis Child Educ Pract Ed doi:10.1136/archdischild-2015-309656

6. Kimberlin, D.W. et al.Valganciclovir for Symptomatic Congenital Cytomegalovirus Disease. New England Journal of Medicine, 2015. 372(10): p. 933-943.

7. Seilesh Kadambari & Suzanne Luck & Adrian Davis & Simone Walter & Charlotte Agrup & Claire Atkinson & Laura Stimson & Eleri Williams & Janet Berrington & Paul Griffiths & Mike Sharland. Evaluating the feasibility of integrating salivary testing for congenital CMV into the Newborn Hearing Screening Programme in the UK. Eur J Pediatr (2015) 174:1117–1121 DOI 10.1007/s00431-015-2506-8

8. Atkinson C, Emery VC, Griffiths PD. Development of a novel single tube nested PCR for enhanced detection of cytomegalovirus DNA from dried blood spots. JVirolMethods. 2014;196:40-4

9. Gantt S, Dionne F, Kozak FK, Goshen O, Goldfarb DM, Park AH, et al. Cost-effectiveness of Universal and Targeted Newborn Screening for Congenital Cytomegalovirus Infection. Jama Pediatr. 2016 Dec 1;170(12):1173-80. PubMed PMID: WOS:000390256900017. English.

10. Williams EJ, Gray J, Luck S, Atkinson C, Embleton ND, Kadambari S, Davis A, Griffiths P, Sharland M, Berrington JE, Clark JE.First estimates of the potential cost and cost saving of protecting childhood hearing from damage caused by congenital CMV infection.Arch Dis Child Fetal Neonatal Ed. 2015 Nov;100(6):F501-6. doi: 10.1136/archdischild-2014-306756. Epub 2015 Jun 29.

11. BAAP website:
http://www.baap.org.uk/Portals/0/Guidelines%20for%20aetiological%20investigation%20into%20mild%20to%20moderate%20bilateral%20permanent%20childhood%20hearing%20impairment%20(8).pdf

Please return to the Evidence Team at screening.evidence@nhs.net **by Wednesday 13th September 2017.**

From: xxxx xxxx >
Sent: 13 September 2017 21:01
To: EVIDENCE, Screening (PUBLIC HEALTH ENGLAND)
Cc xxxx xxxx; xxxx xxxx; xxxx xxxx
Subject: NSC review of screening for CMV

Dear xxxx xxxx

I write in my capacity as a consultant obstetrician and one of the fetal medicine representatives of the British Maternal and Fetal Medicine Society.

I was asked to review the Consultation document on newborn screening for Congenital CMV Infection, which I think provides a valuable overview of the evidence in relation to this problem.

My responses are therefore very much from the perspective of an obstetrician and fetal medicine specialist, and therefore do not relate to newborn screening, to which I would defer to my neonatal/paediatric colleagues.

Congenital CMV infection is the subject of a draft Royal College of Obstetricians & Gynaecologists Scientific Impact Paper “Congenital Cytomegalovirus Infection: Update on Treatment”, but this has not yet been approved at the time of writing:

“Congenital CMV infection is an important clinical problem in fetal-neonatal medicine. However, there remain significant hurdles in predicting the clinical outcome of the disease when CMV is suspected and the fetus does not have obvious structural anomalies identified on fetal ultrasound scans. Making a diagnosis of fetal CMV infection relies largely on invasive testing by amniocentesis or fetal blood sampling and as such carries a risk to the pregnancy of miscarriage or preterm delivery. For the severely affected fetus, termination of pregnancy may be discussed and considered.

While there is some evidence that fetal treatment _*may*_ be beneficial (ie in modifying the natural history of the disease) in some cases of confirmed fetal CMV infection, the evidence is limited, and therefore the criteria for offering universal or targeted screening do not appear to be met. Therefore maternal screening cannot be recommended currently”.

Dr Andrew Breeze, MD MRCOG

xxxx xxxx, xxxx xxxx

xxxx xxxx, xxxx xxxx

xxxx xxxx