Editorial; making dollars and sense out of a screening programme

The ink was barely dry on my editorial for the previous issue of Reviews in Medical Virology than another piece of information was published relevant to screening for congenital CMV infection. Gantt and colleagues(1) have calculated the potential cost effectiveness of screening in the USA, divided into two major parts; selective testing of those neonates who fail national screening programmes for hearing loss; universal screening of all newborns.

To begin with, they estimated the costs associated with congenital CMV, based on the known natural history. A strength of their article is that they used the costs accepted by Medicare when reimbursing current expenditure. They allowed $10 per PCR test, one ophthalmology examination and cranial ultrasound in all neonates with congenital CMV with an estimate that 20% would require an MRI scan in addition. A course of valganciclovir would be given to those born with symptoms, so they included the cost of the drug plus monitoring for neutropenia. Audiology assessments would be performed every six months to the age of six years and they assumed that 50% of babies with bilateral, severe sensorineural hearing loss would need cochlear implants. They did not include administrative costs for running the programme, assuming that the current system could cope.(1)

They next looked at the monetary value of benefits that would accrue to society through screening, broken into two broad categories. First, it is well known that the young brain develops according to the stimuli it receives. This means that neonates who are profoundly deaf will have underdeveloped speech receptive areas so that, even if their perception of sound is subsequently improved through cochlear implantation, the brain will have impaired ability to process the signals received. Compensation for early diagnosis of hearing loss of any cause leads to a 24% improvement in scores for language, so this is the figure they used in the calculations of benefits for CMV.(2) For those children whose hearing is intact at birth but subsequently deteriorates, an estimate of a 12% improvement in language was used. Second, they estimated the benefits attributable to treatment with ganciclovir or its prodrug valganciclovir. Two randomised controlled trials provide evidence; six weeks of intravenous ganciclovir compared to controls randomised to no treatment which led to a six-week course of this drug being adopted as the standard of care.(3) A later study gave valganciclovir for six weeks to all followed by valganciclovir or placebo to complete six months of therapy.(4) The longer course provided a better clinical outcome with significantly improved hearing measured 12 months and 24 months after study entry and so is now the standard of care for neonates born with symptoms. Because the clinical progression of sensorineural hearing loss caused by CMV fluctuates with time, Gantt and colleagues subtracted the improvements seen in the control group to give an estimate that 50% of neonates will have hearing improvement after treatment for six months. The average degree of improvement was assumed to be one grade of hearing loss i.e. profound to severe, severe to moderate, moderate to mild or mild to normal.(1) Of note, both of these randomised clinical trials recruited babies born with symptoms; no study has recruited and randomised children born

with isolated sensorineural hearing loss caused by CMV, so clinical practice on treatment varies. To address this, the authors calculated benefits where screened children found to have congenital CMV infection were treated only if they had other stigmata of symptomatic congenital CMV (such as microcephaly or intracranial calcifications) and used separate calculations to estimate the benefits of treating those with isolated sensorineural hearing loss in addition. Although CMV also causes microcephaly, the authors did not claim a financial benefit for any improvement in intellectual function following early diagnosis and treatment because, although the results from clinical trials are encouraging, more data are required to allow a robust cost saving to be calculated. Savings were calculated to come from reduced educational needs such as speech therapy ($7,000 to $19,000 depending on age) and equipment needs (ranging from $1,400 for hearing aids to $100,000 for a cochlear implant). Finally, they calculated these direct benefits alone or together with estimates of social costs of impaired productivity caused by hearing loss. They used the figure of $926,000 for lost productivity where employees were profoundly deaf, but a figure of zero was used when the sensorineural hearing loss was only mild or moderate.(5)

Effectiveness and cost effectiveness can be presented in different ways. We would like to know how much of the clinic workload of dealing with children with severe or profound sensorineural hearing loss could be reduced by screening for congenital CMV. We would like to know how much it costs to diagnose a case of congenital CMV, to diagnose a case of sensorineural hearing loss caused by CMV and how much to prevent one cochlear implant needed because of the sensorineural hearing loss caused by congenital CMV.

Gantt and colleagues estimate that a selective screening programme would reduce clinic workload by 4.2%, increasing to 9.7% if children with isolated sensorineural hearing loss were treated in addition. For universal screening, the corresponding figures were 7.5% and 13%. Assuming that only symptomatic cases at birth would be treated (to reflect current clinical practice), the costs to identify one case of congenital infection, one case of CMV-related hearing loss and to prevent one cochlear implant were $566, $975 and $39,401 respectively for selective screening. The corresponding costs for universal screening were $2,000, $27,460 and £4,064,157.

When these costs were compared to the savings in direct costs, there was a net saving of $0.90 per case through selective screening which increased to a saving of $10.66 when indirect costs were included. The corresponding figures for universal screening were a cost of $10.86 and a saving of $21.34. When treatment for those with isolated sensorineural hearing loss was included, there was a net saving of $4.95 for selective screening which improved to $27.31 when indirect costs were incorporated. The equivalent figures for universal screening were a cost of $6.83 and a saving of $37.97.

All of these costs are well within those generally accepted for a screening programme for other conditions and the combinations of parameters that lead to overall cost savings to society are clearly welcome.

So, where does this new research leave us? This paper will undoubtedly be influential, because screening committees have been waiting for information on cost-effectiveness before deciding what to do about congenital CMV infection. Some commentators may feel that the authors have been too optimistic (assuming no administration costs) or too pessimistic (assuming no financial benefits from improved intellectual function). Some will want to stick to conventional medical practice by treating only those with classical symptoms at birth, while others will want to get on and include treatment for cases with isolated hearing loss in addition, citing the evidence that valganciclovir predominantly reduces future hearing loss rather than repairing damage to hearing that has already occurred.(4) This genuine difference in clinical opinion and practice should not be a barrier to action; instead, it should stimulate members of steering committees to press for pilot studies to define the remaining uncertainties in more detail. They should be encouraged by the finding that any combination of the parameters reported for CMV will be more cost-effective than existing screening programmes they have supported in the past, so they are unlikely to make a mistake whatever decision they take. There are no bad decisions here, only a series of good decisions, and diversity of potential approaches should be welcomed. For example, different States in the USA could elect for universal screening where selective screening has already started as a way of identifying the incremental benefits of screening all births, including identification of late onset cases of sensorineural hearing loss caused by CMV. Alternatively, they could introduce universal screening de novo. In either case, screening could be based on testing saliva or testing dried blood spots using improved PCR methods. (6-8) Comparison of the results from these different States would help inform the type of screening programme that should be recommended throughout the USA and put robust values on the estimates of medical and financial benefits that can be delivered in practice.

What are the realistic prospects of this coming to pass? As the USA at last comes out of the decade-long recession, politicians are said to be short of "shovel ready" infrastructure projects to spend money on. Here is one project that is likely to be a great investment, because it is projected to be cost saving for society irrespective of what option is selected; so start shovelling dollars in the direction of CMV screening.

PD Griffiths

1. 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.

2. Kennedy CR, McCann DC, Campbell MJ, Law CM, Mullee M, Petrou S, et al. Language ability after early detection of permanent childhood hearing impairment. New Engl J Med. 2006 May 18;354(20):2131-41. PubMed PMID: WOS:000237575400007. English.
3. 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.
4. 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.
5. Mohr PE, Feldman JJ, Dunbar JL, McConkey-Robbins A, Niparko JK, Rittenhouse RK, et al. The societal costs of severe to profound hearing loss in the United States. Int J Technol Assess. 2000 Fal;16(4):1120-35. PubMed PMID: WOS:000165817300016. English.
6. Boppana SB, Ross SA, Shimamura M, Palmer AL, Ahmed A, Michaels MG, et al. Saliva polymerase-chain-reaction assay for cytomegalovirus screening in newborns. The New England journal of medicine. 2011;364(22):2111-8.
7. Boppana SB, Ross SA, Novak Z, Shimamura M, Tolan RW, Jr., Palmer AL, et al. Dried blood spot real-time polymerase chain reaction assays to screen newborns for congenital cytomegalovirus infection. JAMA. 2010;303(14):1375-82.
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.