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# CMV vaccine trial endpoints

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ABSTRACT

**Background**: Despite some significant challenges, there are several reasons for being optimistic about the prospect of developing vaccines against cytomegalovirus (CMV). The aim of this paper is to anticipate how positive results might be interpreted by those charged with making recommendations about universal immunisation, given that vaccines are normally expected to be highly cost-effective.

**Perspective**: The cost effectiveness of a CMV vaccine will be assessed by means of quality adjusted life years gained, so we should design Phase III trials to capture the required evidence directly. Given a vaccine which is equally effective in all age groups at preventing primary CMV infection, immunisation of teenagers will be more cost-effective than immunisation of toddlers, because benefits which accrue in the future are discounted financially. Protection of women of childbearing age against primary infection is important, but may fail to convince sceptics because of the need to extrapolate to protection against transmission of virus to the fetus. The preference of this author is therefore to select congenital CMV infection as the primary endpoint of a Phase III study. We should also ensure that the primary endpoint of a study immunising seronegative women is congenital CMV infection in babies born to those women, not to women in general, because of the large number of babies born to seropositives.



## 1. Introduction

The Institute of Medicine identified CMV as a major target for vaccine development, primarily because of its long term effects on those neonates born with congenital CMV, but also because of its impact on allograft recipients.[1] They suggested that a vaccine against CMV could be cost saving (not just cost effective) when a series of assumptions were made about the costs and application of a licensed CMV vaccine. Specifically, they assumed that a development programme for CMV vaccine would cost $360 million, three doses would be required, each at $50, the efficacy for preventing primary infection would be 75% and the uptake would be only 50% when given to both boys and girls around age 12. These costs would be offset against the annual expenditure of approximately $4000 million in the USA for the current medical and educational care of congenital CMV and medical care of transplant recipients.[1] This report from the Institute of Medicine was highly influential in identifying a need for CMV vaccine but, at the time, there were no candidate vaccines which had proceeded to Phase II clinical trials and many sceptics were unconvinced that it would ever be possible to make a CMV vaccine. Some were so pessimistic that they advised that it was futile to even take candidate CMV vaccines into clinical trials because of the ability of this virus to persist in the face of humoral and cell mediated immunity, to reactivate and to reinfect with different strains.

This pessimism ignored the fact that a pioneering clinical trial of the CMV Towne strain live attenuated vaccine had significantly reduced the clinical severity of cases of CMV disease in allograft recipients,[2] which we would nowadays interpret as a reduced peak viral load post-transplant.[3] The pessimism was abolished when the first study of a modern vaccine with a potent adjuvant reported that immunisation of seronegative women of child bearing age could reduce significantly their risk of acquiring primary CMV infection.[4] Further studies are required to define the duration of this protection, to optimise the immunisation schedule and to determine if even better results are produced when additional immunogens are included in the vaccine. However, the level of efficacy provided (approximately 50–60%) is already sufficient to allow interruption of CMV transmission in a middle class community by means of herd immunity.[5,6] This means that protection of women of child bearing age through universal immunisation is now a real prospect and we should be considering and debating how Phase III studies should be designed and conducted in order to facilitate licensing of safe and effective vaccines.

## 2. The review process

In this brief article, I will take the perspective of a public body reviewing whether CMV vaccines should be recommended for universal immunisation, having made the assumptions that at least

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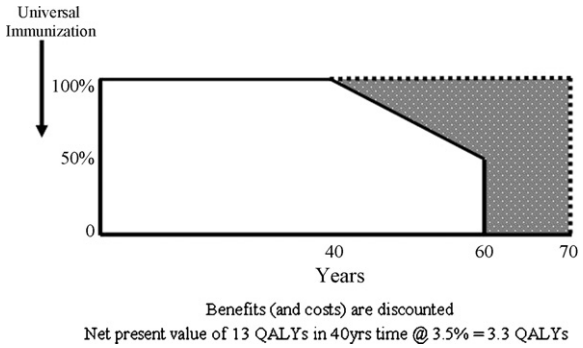


**Fig. 1.** Quality adjusted life years in a hypothetical case of hepatitis B discussed in the text.

one vaccine has been identified in seronegatives which is safe and immunogenic, that Phase III studies have been completed and the data submitted for licensure and that it is agreed that the burden of disease warrants protection by universal immunisation. Under these circumstances, the review will focus on the cost effectiveness of the vaccine. The costs include the cost of the vaccine itself (currently unknown, but a constant throughout these discussions), the programme of administration and its compatibility with existing immunisation programmes. For example, when the Institute of Medicine issued their report.[1] There was no immunisation schedule for giving vaccine to boys and girls aged 12 years. However, the new human papillomavirus vaccines[7,8] are now given to girls of this age and so the incremental costs of delivering a CMV vaccine to girls and to boys would be less than that required for setting up a new programme especially for CMV. The benefits will be assessed as QALYs in populations assumed to have a type-1 mortality; that is people who live with 100% of normal health until their seventieth birthday when they die instantaneously, having never incurred any expenditure for their healthcare. From the perspective of governments which provide subsidised healthcare, or that of health maintenance organisations, these citizens are perfect consumers and an intervention for them which would cost up to $50,000 per QALY is generally considered to be cost effective.

To move this abstract concept into the real world of virology, consider a patient in Fig. 1 who is infected perinatally with hepatitis B virus. Chronic infection continues asymptomatically until the age of 40 years when declining quality of health leads to a diagnosis of chronic hepatitis B infection. Despite interventions, this hypothetical patient dies at the age of 60 of having lost 13 QALYs in total; 10 between the years of 60 and 70 (where death is equated with zero quality of life) and three between the years of 40 and 60 (representing the area under the curve of the quality: time plot shown in Fig. 1). To those who trained in medical school, universal immunisation of all neonates to prevent such cases is clearly beneficial and would be expected to prevent most such

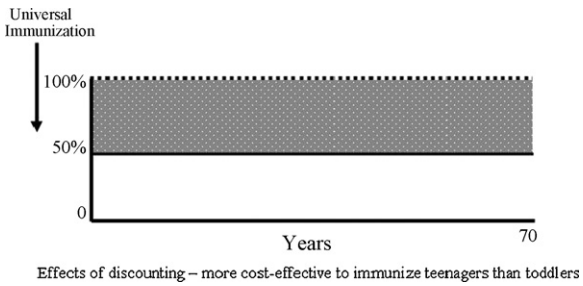


**Fig. 2.** Quality adjusted life years in a hypothetical case of symptomatic congenital CMV discussed in the text.

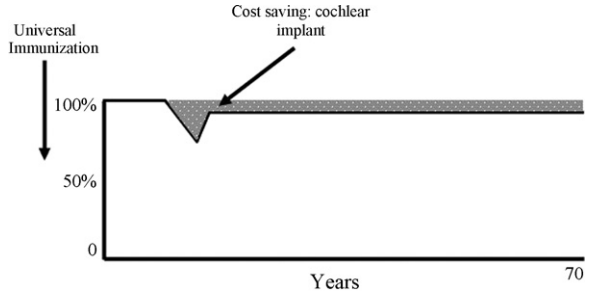


**Fig. 3.** Quality adjusted life years in a hypothetical case of asymptomatic congenital CMV discussed in the text.

cases. However, for those who trained in accountancy school, the picture is somewhat different because both benefits and costs are discounted, typically by 3.5% per annum. This procedure of discounting has nothing to do with inflation; it reflects the idea that the ideal consumer wishes to have their benefits delivered immediately following expenditure so that any which are delayed are worth less to the consumer the longer he or she has to wait for them. This process of discounting is used to make judgments about all investments in public services, despite the fact that its intellectual validity for interventions of a medical nature can be questioned.[9] The effect of discounting 30 QALYs to be gained in 40 years time at 3.5% per annum turns 13 QALYs into a net present value of only 3.3 QALYs. Thus, the expenditure of a universal immunisation campaign against hepatitis B would have to be set against a gain of only 3.3 QALYs not the 13 which are found in the real (non-discounted) world.

To apply this concept to congenital CMV we can use data on the epidemiology of this infection (for example, from systematic reviews[10,11]) and divide cases into those born with classical symptoms of CMV (Fig. 2) and those without symptoms but who nevertheless develop symptoms on follow up (Fig. 3). In Fig. 2, a hypothetical child born with symptoms of congenital CMV has its quality of life restricted to 50% of that expected and this disadvantage remains for the entire 70 years of its life. This patient has thus lost 35 QALYs and these could be gained if universal immunisation was introduced to prevent primary maternal infection transmitting to the fetus. As before, the effects of discounting are high here because the children to be immunised have to grow into the child bearing age before they are protected against primary CMV infection occurring during pregnancy. For this reason, it would be more effective to immunise teenagers than to immunise toddlers, even if clinical trials showed that the vaccine was equally efficacious in both of these age groups, because of the shorter time between incurring costs and delivering benefits that is associated with immunising teenagers. This conclusion assumes that the uptake of vaccine is equal in toddlers and teenagers. If uptake is significantly greater in toddlers, then it may compensate for the greater discounting applied to that age group.

In Fig. 3, a child is born with asymptomatic congenital CMV infection but develops hearing loss on follow up. Some of its impaired quality of life is repaired by a cochlear implant but this hypothetical child still loses the QALYs depicted in Fig. 3. In this case, universal immunisation would be expected to save the cost of the cochlear implant procedure which could be offset against the programmatic costs of introducing universal immunisation.

Turning to allograft recipients, a CMV vaccine administered pretransplant could be expected to produce direct cost savings in terms of hospitalisation for CMV disease, the drugs used for antiviral prophylaxis[12] or preemptive therapy[13] as well as other indirect effects such as reduced graft rejections.[14] In this case, the effects of discounting would be small because people would be given vaccine