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Review

Desirability and feasibility of a vaccine against cytomegalovirus

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ABSTRACT

Publication of a report from the Institute of Medicine in 2000 showing that a vaccine against cytomegalovirus (CMV) would likely be cost saving was very influential and encouraged the clinical evaluation of candidate vaccines. The major objective of a CMV vaccination program would be to reduce disease caused by congenital CMV infection, which is the leading viral cause of sensorineural hearing loss and neurodevelopmental delay.

CMV has challenges as a vaccine target because it is a herpesvirus, it persists lifelong despite host immunity, infected individuals can be reinfected with new strains, overt disease occurs in those with immature or impaired immune systems and persons with this infection do not usually report symptoms. Nevertheless, natural immunity against CMV provides some protection against infection and disease, natural history studies have defined the serological and molecular biological techniques needed for end-points in future clinical trials of vaccines and CMV is not highly communicable, suggesting that it may not be necessary to achieve very high levels of population immunity through vaccination in order to affect transmission. Three phase 2 CMV vaccine studies have been completed in the last 3 years and all report encouraging outcomes.

A key international meeting was organized by the Food and Drug Administration in January 2012 at which interested parties from regulatory bodies, industry and academia discussed and prioritised designs for phase 2 and phase 3 clinical trials. Vaccines able to prevent primary infection with CMV and to boost the immune response of those already infected are desirable. The major target populations for a CMV vaccine include women of childbearing age and adolescents. Toddlers represent another potential population, since an effect of vaccine in this age group could potentially decrease transmission to adults. In addition, prospective recipients of transplants and patients with AIDS would be expected to benefit.

Contents

Abbreviations: CMV, cytomegalovirus; SNHL, sensorineural hearing loss; EOD, end organ disease; Gb, glycoprotein B; WHO, World Health Organisation.

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1. Epidemiology and natural history

CMV is transmitted through mucosal contact with infected body fluids, including saliva, urine, semen and cervical secretions [1–3]. After primary infection (the first infection in life), CMV establishes latency. An infected individual can experience reactivation of the latent strain or reinfection by another strain of CMV. CMV infection detected within 2 weeks of birth is termed congenital infection, and is the result of a maternal infection that first involves the placenta and then the fetus [4]. In developed countries, many women enter the childbearing years susceptible to primary infection whereas, in developing countries, virtually 100% of antenatal women are seropositive (that is, they have IgG antibodies specific for CMV antigens) [5,6]. Seropositive pregnant women can reactivate latent CMV or be reinfected with a new strain; both types of infection can transmit virus across the placenta to the developing fetus [4,7,8]. However, there is evidence that preconception maternal immunity does provide some protection against intrauterine transmission with one study showing a 69% reduction in risk for seropositive women of having a baby with congenital CMV compared to seronegative women from the same community [9].

Primary infection, reinfection and reactivation also occur in immunocompromised persons, including transplant patients. A seropositive solid organ donor can transmit CMV to cause primary infection in a seronegative recipient or reinfection in a seropositive recipient [10]. One study showed that natural immunity provides an 84% reduction in viral load parameters compared to those in seronegative recipients [11]. In haematopoietic stem cell transplantation, most infections are reactivations and seropositive donors may adoptively transfer immunity to recipients [12,13]. Adoptive transfer of CMV immunity has been achieved using isolated CMV antigen-specific T cell immunotherapy [14,15].

2. Burden of disease

CMV infection results in substantial burden of disease in congenitally infected infants and post-transplant patients. CMV is an occasional cause of heterophile negative mononucleosis in otherwise immunocompetent adults [16,17]. This virus has also been linked with other conditions, briefly mentioned below, where the associations have not been proven to be causal [18].

2.1. Congenital infection

Although congenital CMV infection results in significant burden of disease globally, the best population-based estimates come from the USA. Based on reviews of the published literature, it is estimated that 0.4–0.7% of babies, (about 28,000) are born each year with congenital CMV infection in the United States; 12.7% are estimated to have symptoms at birth (termed "symptomatic"); and 13.5% of those asymptomatic at birth develop symptoms when followed-up [19,20]. The prevalence of congenital CMV infection in Europe is thought to be similar to that of the USA. Reliable data on the birth prevalence of congenital CMV infection from developing countries is lacking. In a review of studies from 11 developing countries, the average birth prevalence of congenital CMV infection was 1.6%. The classical symptoms of cytomegalic inclusion disease at birth include hepatosplenomegaly, thrombocytopenic purpura, microcephaly and sensorineural hearing loss (SNHL). The symptoms on follow-up include SNHL and/or neurodevelopmental delay [4,20]. The hearing loss is progressive (Fig. 1), so that less than half of the children destined to develop SNHL have done so by birth [21].

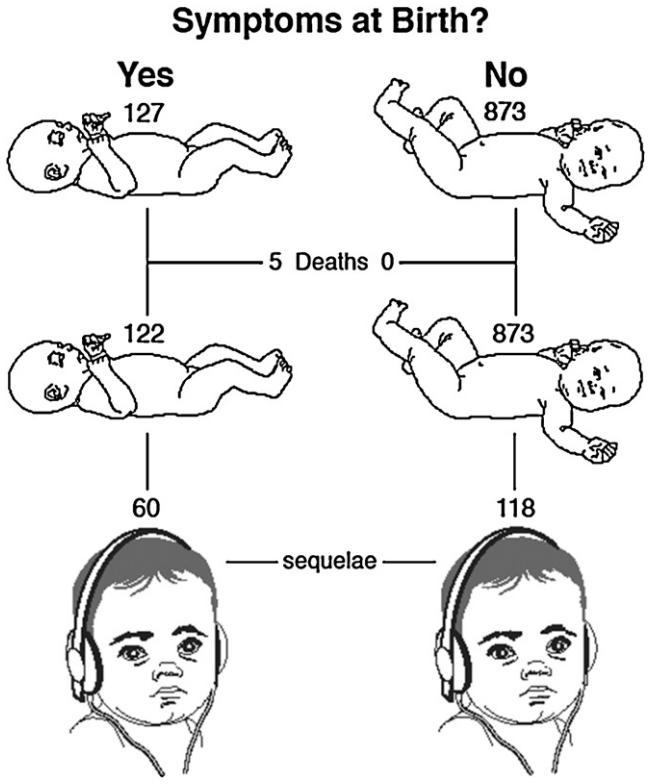

Fig. 1. Disease outcome per 1000 babies with congenital CMV [20]. The major long-term effects are sensorineural hearing loss (represented by a child wearing earphones) and neurodevelopmental delay.

Overall, approximately 5000 babies are born in the United States each year who are estimated to develop disease caused by congenital CMV infection, making it the most common viral cause of SNHL (Fig. 2) and of neurodevelopmental delay in that country [22,23]. Congenital infection is linked to socioeconomic and racial/ethnic differences within the USA and so is linked to health disparities within a country [24].

It has been established that transmission and disease do occur in babies born to seropositive mothers in developing countries, but the full burden of congenital CMV in those countries remains to be defined [25]. Since the incidence of congenital infection is directly correlated with the seroprevalence of CMV antibodies in the population, congenital CMV infection may indeed exert its greatest burden in developing countries with high birth rates and high seroprevalence.