



# Determinants of Ethnic Differences in Cytomegalovirus, Epstein-Barr Virus, and Herpes Simplex Virus Type 1 Seroprevalence in Childhood

Michelle A. E. Jansen, MD<sup>1,2,3</sup>, Diana van den Heuvel, PhD<sup>3</sup>, Selma H. Bouthoorn, MD, PhD<sup>1,4</sup>,  
Vincent W. V. Jaddoe, MD, PhD<sup>1,2,5</sup>, Herbert Hooijkaas, PhD<sup>3</sup>, Hein Raat, MD, PhD<sup>4</sup>,  
Pieter L. A. Fraaij, MD, PhD<sup>2,6</sup>, Menno C. van Zelm, PhD<sup>3,7</sup>, and Henriette A. Moll, MD, PhD<sup>2</sup>

**Objective** To identify whether there are ethnic differences in cytomegalovirus (CMV), Epstein-Barr virus (EBV), and herpes simplex virus type 1 (HSV-1) seroprevalence rates in children at 6 years of age, and when present, to evaluate how these differences can be explained by sociodemographic and environmental factors.

**Study design** This study was embedded within a multi-ethnic population-based prospective cohort study. Serum IgG levels against CMV, EBV, and HSV-1 were measured by enzyme-linked immunosorbent assay in 4464 children (median age 6.0 years). Information on demographics and characteristics were assessed by questionnaires. Herpesvirus seroprevalences between Surinamese-Creole, Surinamese-Hindustani, Turkish, Moroccan, Cape Verdean Antillean, and Native Dutch children were compared.

**Results** Non-Western ethnicity was an independent risk factor for CMV (aOR, 2.16; 95% CI 1.81-2.57), EBV (1.76; 1.48-2.09), and HSV-1 seropositivity (1.52; 1.39-1.66). Among the ethnic groups, CMV seroprevalences ranged between 29% and 65%, EBV between 43% and 69%, and HSV-1 between 13% and 39%. Low family net household income, low maternal educational level, crowding, and lifestyle factors explained up to 48% of the ethnic differences in HSV-1 seroprevalences, and up to 39% of the ethnic differences in EBV seroprevalences. These factors did not explain ethnic differences in CMV seroprevalences.

**Conclusions** Socioeconomic position and factors related to lifestyle explain only a part of the large ethnic differences in EBV and HSV-1 seroprevalences, whereas they do not explain ethnic differences in CMV seroprevalences in childhood. (*J Pediatr* 2016;170:126-34).

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Cytomegalovirus (CMV), Epstein-Barr virus (EBV), and herpes simplex virus type 1 (HSV-1) are ubiquitous herpesviruses, and often are acquired in childhood. These viruses usually are transmitted by contact with infected saliva (all 3 viruses), breastfeeding, placental transfer (CMV), or through contact with infectious skin lesions or secretions (HSV-1).<sup>1,2</sup> The viruses establish a lifelong latency after primary infection, and periodically can reactivate with shedding of the virus. Most primary infections are mild or asymptomatic in childhood, but they can cause serious complications in fetuses, immunocompromised individuals, or in elderly.<sup>3-9</sup> The incidence and severity of herpesvirus associated diseases vary geographically, and many studies link age at primary infection to the pathogenesis of herpesvirus associated diseases.<sup>10-14</sup>

CMV seroprevalences vary between 40% and 60% in children aged 4-12 years,<sup>8,15,16</sup> with exclusion of African countries where almost all children seroconvert by 3 years of age. Approximately 50% of children in the US and Europe are seropositive for EBV in the first years of life, but seroprevalences vary from 20%-80% depending on age, race/ethnicity, geographic location, and socioeconomic development of the country.<sup>9,12,17,18</sup> HSV-1 is widespread during the first few years of life in developing countries, whereas in some European countries primary infection occurs at an older age.<sup>19-22</sup> Besides geographical differences, ethnic differences also have been described in population subgroups.<sup>23</sup> Ethnic and geographical differences in CMV, EBV, and HSV-1 seroprevalences might be explained by differences in behavior that facilitate transmission, such as breastfeeding, daycare, family size, and socioeconomic position.<sup>17,22,24,25</sup> Because socioeconomic position and ethnicity are strongly related, it remains unclear to what extent socioeconomic factors explain ethnic differences in herpesvirus seroprevalences.<sup>26</sup> In addition, knowledge on other lifestyle-related determinants is based mainly on prevalence studies from the late 1990s,<sup>27-30</sup> but social conditions and lifestyles have changed over time.<sup>31,32</sup> Furthermore, the relative importance of

From the <sup>1</sup>The Generation R Study Group, Erasmus MC, University Medical Center; <sup>2</sup>Department of Pediatrics, Sophia Children's Hospital; Departments of <sup>3</sup>Immunology, <sup>4</sup>Public Health, <sup>5</sup>Epidemiology, and <sup>6</sup>Viroscience, Erasmus MC, University Medical Center, Rotterdam, The Netherlands; and <sup>7</sup>Department of Immunology and Pathology, Central Clinical School, Monash University, Melbourne, Victoria, Australia

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CMV	Cytomegalovirus
EBV	Epstein-Barr virus
HSV-1	Herpes simplex virus type 1

each risk factor needs to be assessed,<sup>26</sup> and many studies lack the assessment of multiple risk factors. Previously, it has been suggested that early life exposures, in particular breastfeeding, are more important for CMV infection than are adulthood exposures.<sup>33</sup> On the other hand, the Assessment of Lifestyle and Allergic Disease during Infancy birth cohort study found no strong influence of these early life risk factors.<sup>34</sup> Understanding transmission dynamics of herpesvirus infections within populations, and understanding how socioeconomic and ethnic groups are exposed differentially to these infections, can improve existing preventive policies and interventions, eventually including vaccination programs.<sup>35</sup>

The first aim of our study is to assess whether there are ethnic differences in acquisition of CMV, EBV, and HSV-1 in children by 6 years of age. The second aim is to evaluate how possible ethnic differences in acquisition of CMV, EBV, and HSV-1 can be explained by sociodemographic and environmental factors.

## Methods

This study was embedded within the Generation R Study, a prospective population-based cohort study from fetal life onward.<sup>36,37</sup> All children were born between 2002 and 2006 in Rotterdam, the second largest city in The Netherlands. The study area covers more than one-half of the city's inhabitants, reflecting Rotterdam's multi-ethnic population.<sup>36</sup> The largest ethnic groups are of Dutch, Surinamese, Turkish, Moroccan, Dutch Antilles, and Cape Verdean origin.<sup>36</sup> In total, 8305 children participated in the postnatal phase of the study, of whom 81% (n = 6690) visited the research center (median age 6 years).<sup>37</sup> During this visit, blood samples were collected from 4593 children. Serologic data on EBV, CMV, and HSV-1 status were provided on 4464 children (**Figure 1**; available at [www.jpeds.com](http://www.jpeds.com)). The study was approved by the Medical Ethical Committee of Erasmus MC, University Medical Center Rotterdam. Parents of the children gave written informed consent.

### Herpesvirus Serology

Venous blood plasma samples were analyzed using enzyme immunoassays for IgG antibodies against CMV (purified native antigens strain "AD169"), EBV capsid antigen (native mixture of several viral capsid antigens), HSV-1 native glycoprotein C1, (all from EUROIMMUN, Lübeck, Germany).<sup>38</sup> The assays are specific for the particular viruses and discriminate between HSV-1 and HSV-2. Results were evaluated semiquantitatively relative to a manufacturer-provided reference threshold sample. Per manufacturer's instructions, an optical density in the patient sample >10% above the provided threshold sample was defined as positive.

### Ethnic Background

Ethnicity of the child was determined by country of birth of the parents. The child was of nonnative Dutch origin if one of the parents was born in a country other than

The Netherlands.<sup>39</sup> If both parents were born abroad, the country of birth of the mother was taken. To study whether ethnic background was related to herpesvirus infections, we constructed a dichotomous variable "Western/non-Western" ethnicity. Next, to study to what extent socioeconomic and lifestyle factors explained associations between ethnicity and herpesvirus infections, and to study the effect of cultural background of the mother (most often primary caregivers),<sup>40</sup> a distinction was made between mothers of Dutch, Turkish, Moroccan, Cape Verdean, Antillean, Surinamese Creole, and Surinamese Hindustani ethnic background. Maternal ethnic background was based on country of birth of mother's parents and was assessed by questionnaires at enrollment. Mothers were considered nonnative Dutch if one of her parents was born abroad.<sup>41</sup> If both parents were born abroad, country of birth of the mother's mother prevailed. Generational status of nonnative Dutch mothers was based on their own country of birth. Foreign-born mothers were classified as "first generation," and mothers born in The Netherlands were classified as "second generation."<sup>40</sup>

### Other Determinants

Other potential determinants of herpesvirus infections were selected based on existing literature.<sup>2,12,24,32,33,42-44</sup> These are: socioeconomic position, family size/parity, maternal lifestyle, breastfeeding, daycare, and sex. Data on sex, gestational age, birth weight, parity, and mode of delivery were obtained from obstetric records from hospitals and mid-wife practices. Data on sociodemographic and lifestyle factors were obtained by a combination of prenatal and postnatal questionnaires completed by both parents. Prenatal questionnaires included information on maternal lifestyle and maternal educational level. Information on family net household income was determined by questionnaires obtained at 6 years of age. Information on breastfeeding and daycare was obtained by postnatal questionnaires. All questionnaires were available in 3 languages (Dutch, English, and Turkish) and further support for verbal translation of questionnaires was available in Arabic, Portuguese, and French.

### Explanatory Variables

Most effects of ethnicity on herpesvirus infections are probably indirect ones, acting through more proximal determinants of CMV, EBV, and HSV-1. We considered the following factors to be potential explanatory variables: socioeconomic position, breastfeeding, parity as indicator for siblings/family size, and daycare attendance.<sup>2,12,24,32,33,43,45</sup> Information on household income<sup>46</sup> and educational level,<sup>47</sup> both indicators of socioeconomic position, were obtained using prenatal questionnaires. The Dutch Standard Classification of Education was used to categorize 4 subsequent levels of education: 1 = high, 2 = mid-high, 3 = mid-low, and 4 = low.<sup>47</sup> For additional analyses, income was subdivided into 3 categories: (1) below modal <€2000 per month (<US \$2511); (2) between €2000 and €3200 per month (US \$2511-\$4018); and (3) >€3200 per month (>US \$4018).<sup>48,49</sup> Child's age and sex were treated

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