RESEARCH ARTICLE

Childcare attendance and risk of infectious mononucleosis: A population-based Danish cohort study

Klaus Rostgaard¹,² *, Lone Graff Stensballe³, Signe Holst Søegaard¹, Mads Kamper-Jørgensen⁴, Henrik Hjalgrim¹,²,⁵,⁶

1 Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark, 2 Danish Cancer Society Research Center, Danish Cancer Society, Copenhagen, Denmark, 3 Department of Pediatrics and Adolescent Medicine, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark, 4 Department of Public Health, University of Copenhagen, Copenhagen, Denmark, 5 Department of Hematology, Copenhagen University Hospital, Copenhagen, Denmark, 6 Department of Clinical Medicine, Copenhagen University, Copenhagen, Denmark

* klar@cancer.dk

Abstract

Background

The risk of infectious mononucleosis (IM) is affected both by crowding and by sibship structure, i.e., number and signed age difference between an index child and a sibling. Siblings provide protection against IM by pre-empting delayed primary Epstein-Barr virus infection with its associated high risk of IM. The association between childcare attendance and risk of IM, on the other hand, has never been studied in a large, well-characterized cohort.

Methods

Danish children born in July 1992 through 2016 with a completely known simple childcare attendance history before age 1.5 years (n = 908,866) were followed up for a hospital contact with an IM diagnosis at ages 1.5–26 years. Hazard ratios (HRs) of IM for an additional year of exposure were obtained from stratified Cox regression analyses, stratified by sex and year of birth, with age as the underlying time scale, adjusted for sibship structure, and sociodemographic variables including parental ethnicity and maternal age.

Results

An additional year of exclusively attending a daycare home (max 5 children) yielded HR = 0.90 (95% confidence interval 0.81–1.00), and similarly, each year of exclusively attending a childcare institution (e.g., crèche) yielded HR = 0.94 (0.84–1.06).

Conclusions

Forwarding enrollment in childcare by a year lowers the risk of IM later in life much less than having an additional sibling of comparable age and has no practical public health implications. We find our results suggestive of a random threshold for successful Epstein-Barr virus
Introduction

Infection with human herpes virus 4, Epstein-Barr virus (EBV) is ubiquitous, and by adulthood the vast majority of the population is infected [1, 2]. Primary infection with EBV in childhood is usually asymptomatic or accompanied by only mild symptoms. Primary EBV infection in adolescence or adulthood, however, is often accompanied by infectious mononucleosis (IM), the estimated proportions in Danish teenagers ranging from 12% to 70% [2]. IM is typically characterized by fever, tonsilitis, lymphadenopathy and fatigue. Primary infection is followed by lifelong, mostly asymptomatic, latent infection of B lymphocytes [3], which occasionally reactivates lytically [4]. Thus, EBV persistence is characterized by the presence of latently infected cells in the blood and the periodical shedding of virus into saliva [5].

The consequences of IM in terms of educational and work-related absence and more rarely neurological, malignant, bone marrow or liver disease are substantial and underappreciated [6]. Together, this has suggested that reducing the IM-associated sequelae through vaccination targeting EBV would be beneficial in some populations and has prompted development of such vaccines [6].

Investigation of the impact of childcare attendance on age-specific IM risk is lacking and may provide useful information for our understanding of the roles of age, mechanism and “dose” of EBV exposure upon IM risk [2, 7, 8]. This information may help inform the design of an EBV vaccination program and guide policy decisions and parental decisions about when and where children should be enrolled in childcare.

Recently, it has been demonstrated that each additional sibling, especially younger siblings, was associated with lower risk of presenting with IM as a teenager [1, 9]. A similar pattern of sibling-induced protection has been observed for EBV- and IM-related diseases like Hodgkin lymphoma [10] and multiple sclerosis [11]. The study by Rostgaard et al. [1] also revealed 1) that the smaller the age difference between the sibling and the index child the lower the IM risk, interpreted as an indirect effect of early pre-emptive EBV infection, and 2) that having siblings age less than four years increased the IM risk acutely, interpreted as a direct effect of EBV transmission at the time. In line with this, follow-up of families with children as IM index cases [9, 12–15] and EBV serotype studies within families [16] both reveal intra-family contagion as an important source of EBV infection.

Childcare attendance might have the same effect on IM risk as having a large sibship, i.e. lowering the risk of IM in teenage years. However, the incidence of hospitalized IM in Denmark was remarkably stable over a long time period during which childcare attendance became the norm [1, 2], suggesting that EBV transmission through exposure to other children in childcare facilities is less effectual or less frequent than through exposure to siblings. The importance of the source of contagion for disease risk has been well-characterized for other diseases [17–21], but has not been established for EBV/IM. Presumably EBV is transmitted through saliva (including sneezing [22]) to the pre-adolescents infected, because most other suggested routes of transmission (transfusion, sex, deep kissing) would seem less relevant for children, while transmission routes of particular relevance to children (breast milk, in utero infection) appear to play a minor role [7, 8, 23–26].
To qualify and quantify the above pre-conceptions we undertook the present study to investigate the impact of childcare attendance and timing of childcare enrollment on the age-specific risk of IM at ages 1.5–26 years, using a Danish childcare database with nation-wide coverage from around the turn of the century [27].

Materials and methods

The nation-wide Danish Civil Registration System (CRS) was implemented on April 1, 1968. All Danish citizens have since been assigned unique identification numbers (the CRS number), by which the CRS continuously monitors individual vital status, emigration status, identity of parents, and residence. The CRS number also allows for identity-secure linkage between health registers [28].

Children born in Denmark in July 1992 through 2016 formed our study base. Using the CRS, we identified their siblings and obtained dates of birth for all these children in order to allow the construction of variables such as age difference between a proband and an exposing sibling.

We collected information about individual childcare attendance at ages 0–6 years from the Childcare Database [27]. This database includes childcare attendance data on children aged 0–6 years living in one of the 98 Danish municipalities (originally 271), with data dating back to 1989. Recently, we updated the database to include childcare attendance data up to and including 2016. The childcare data are collected routinely by the Danish municipalities to organize payment and distribution of places in childcare facilities. We obtained the childcare attendance data from three Danish data management companies: KMD, IST-software, and GK-consult. In addition, archived data were obtained from the Danish National Archives and a local archive at the municipality of Hørsholm.

For each combination of calendar year and municipality we assessed whether childcare registration was complete based on the percentage of children aged 3–5 years enrolled in childcare on January 1st of that year. In the vast majority of municipalities with the highest coverage, the coverage was remarkably similar in any given calendar period, leading to the following criterion. If the registration percentage was below 72 and the calendar year before 2007 or the registration percentage was below 84 and the calendar year after 2006 the municipality was deemed to have incomplete registration for that year. This enabled censoring upon incomplete exposure information. 2007 was the year of the reorganization of the municipalities from 271 into 98.

From the Childcare Database we collected exact dates of enrollment and withdrawal from childcare facilities, and type of childcare facility. The four main types of childcare facilities registered were: daycare home, crèche, kindergarten, and age-integrated. Daycare homes are for max 5 children of the same age, while the other facilities included a mean number of children above 40 [27, 29, 30].

The Danish National Patient Register was established in 1977 and has since recorded 99.9% of all discharges from Danish non-psychiatric hospitals [31]. For each hospitalization, the register contains information on dates of admission and discharge, and discharge diagnoses. In the register, we identified all hospital contacts including outpatient visits containing a discharge diagnosis code B27* (ICD-10) or 075 (ICD-8). ICD-8 codes were used in the register before 1994, ICD-10 codes from 1994 onward.

The study was approved by SSI QA & Compliance (journal no. 20/13012). According to Danish law, no ethical approval nor consent is needed for a purely register-based study such as this.
Statistical analysis

The cohort of children born in Denmark from July 1992 through 2016 who were available for childcare attendance assessment from time of birth to age 1.5 years was followed for hospitalization for IM from age 1.5 years, until the date of diagnosis of IM, death, emigration, censoring due to unknown exposure status or December 31, 2018, whichever came first. Censoring due to unknown childcare attendance status occurred on the first occasion where the child was living in a municipality with incomplete childcare registration at the time and the child was less than 1.5 years old (end of exposure ascertainment).

Cox regression stratified by sex and year of birth with age as the underlying time-scale was used to model hazard ratios (HRs) and thereby assess the effects of childcare attendance. All analyses were adjusted for time-varying sibship characteristics (number of siblings of a certain age (0,1,2,3 years) and number of siblings with a certain age differential to the index child as in [1]. We also adjusted for some readily available potential socio-demographic confounders: maternal age [32], parental ethnicity [33–37], socio-economic index of the municipality of birth in year of birth [38] and the fraction of childcare exposure time before age 1.5 due to daycare in the municipality of birth in year of birth. In order to capture both genetic and socio-demographic effects of ethnicity in the most effective way we assessed for each parent whether they were born in a Western country, operationalized/approximated as being born outside Europe (excluding Turkey and including USA and Canada). The socio-economic index is a weighted basket of 14 indicators of municipal financial needs and tax incomes, used for redistribution of tax incomes between Danish municipalities in any given fiscal year, and as such is recalculated annually. The socio-economic index is designed to have an average value of 1, and higher values correspond to poorer municipalities. We observed that densely populated/more urban municipalities tended to have the largest part of childcare executed in institutions. The fraction of daycare out of all childcare at age below 1.5 years was designed to remove confounding that would otherwise occur as a consequence of correlation between urbanicity and both outcome and exposure when trying to assess a possible differential effect of exposure in institutions and daycare facilities.

Exposure was defined as the time enrolled in a childcare institution (crèche, kindergarten or age-integrated institution) or a daycare home before age 1.5 years, assuming that the former comprised a more infectious environment than the latter. The age interval of 0–17 months both contained most of the variation in childcare attendance as well as being the period in childhood with the most EBV sero-conversions [2]. The parameter on log-scale corresponding to these predictors is the hazard rate of seroconverting during the first 18 months due to the exposure (and thus be removed from risk of getting IM at a later age).

We only followed up children who had been attending exclusively daycare homes or institution care. Thus, the followed up cohort could be viewed as the observational equivalent of a randomized trial where each child was exposed a random strictly positive amount of time to either daycare home or institution care (childcare in a crèche, kindergarten, or similar) before age 1.5 years, but not both.

All analyses were performed using the SAS statistical software package (version 9.4 SAS Institute, Cary, NC, USA). Ninety-five percent confidence intervals (CIs) were based on Wald tests. Fig 1 was prepared using the forestplot package in R, to visually augment Table 1.

Results

Our sampling frame consisted of the 1,567,388 children born in Denmark in July 1992 through 2016 with a known mother. In total, 1,152,329 of these children had complete childcare exposure information from birth to age 1.5 years and could be followed afterward. Among these,
980,011 individuals had been exposed to childcare before age 1.5 years, of whom 908,866 had been exclusively exposed to either daycare homes or childcare institutions before age 1.5 years. Thus, our study base modelled the 908,866/1,152,329 = 79% of a contemporary Danish birth cohort who were exclusively exposed to either daycare home or childcare institution within the first 1.5 years of life. The distribution of events, follow-up time and contributing persons in

### Predictor | HR
--- | ---
**Exposure per year**
Daycare homes only | 0.90
Institutions only | 0.94

**Per sib by age interval**
- 9+ years younger | 0.78
- 6-8 years younger | 0.88
- 3-5 years younger | 0.84
- 0-2 years younger | 0.78
- 0-2 years older | 0.88
- 3-5 years older | 0.95
- 6-8 years older | 1.01
- 9+ years older | 1.01

**Per sib aged 0-3 years**
- Age 0 | 1.34
- Age 1 | 1.72
- Age 2 | 1.61
- Age 3 | 1.26

**Sociodemographics**
- Maternal age per year | 0.99
- Daycare fraction | 0.80
- SEI of municipality | 0.93
- non-Western mother | 0.75
- non-Western father | 0.84

---

Fig 1. HRs from model M2B (Table 1) with abbreviated predictor descriptions.

https://doi.org/10.1371/journal.pone.0261665.g001
various strata is illustrated in Table 1. Onset of exposure occurred mainly in a narrow time interval. The 5, 25, 50, 75 and 95% quantiles for the exposure time in years was as follows: exclusively enrollment in daycare home (0.20, 0.53, 0.67, 0.86, 1.04), exclusively enrollment in childcare institution (0.17, 0.47, 0.62, 0.75, 1.00), and any of these two (0.18, 0.50, 0.64, 0.81, 1.03).

The effect of sibship structure (sibling age differentials and having 0-3-year-old sibs) was broadly as expected; i.e., more protection the smaller the difference in age, younger sibs being generally more protective than older sibs and a marked instantaneous effect of having 0-3-year-old sibs on IM risk (see [1]) (Table 1, Fig 1). The estimates were very stable between models, indicating that sibship structure is not confounding the estimation of childcare effects (Table 1).
One additional year of enrollment in a daycare home before age 1.5 years implied a 10% relative reduction in IM risk, while gaining one year in a childcare institution lowered the IM risk by 6% (Table 1). The difference in IM risk due to exposure in daycare homes and exposure in childcare institutions was small and statistically insignificant (Table 1). A one-year increase in exposure time is a lot compared to e.g. an interquartile distance of around 0.3 years for all three types of exposure time. Hence the variation in IM risk explained by childcare exposure would be even smaller.

**Discussion**

Childcare attendance has consistently been found to entail a short-term increased risk of childhood infections, all well as affecting the risk of some long-term outcomes, e.g. acute lymphoblastic leukemia, see [29, 30] and references therein. However, the effect sizes we found regarding a phenomenon mainly caused by EBV infection are so small as to have no public health implications. Nevertheless, our study may be informative about how and when infants are infected with EBV—an open and important question in basic IM/EBV epidemiology [7].

The true lasting effect of childcare exposure must be caused by early seroconversion and hence be protective against IM [2, 37]. In our study most children were enrolled in childcare at age 6 to 16 months, where most childhood sero-conversion occurs [2], so that age at enrollment in childcare could make a noticeable lasting difference in IM risk. Taking the observed estimates at face value the effect of bringing forward childcare attendance one year (from age 1.5 to 0.5 years) was much less than the effect of having an additional sibling of roughly the same age, as observed here and in an overlapping study [1]. And there was no suggestion of a trend in the direction of exposure to many children in an institution being more protective against IM than exposure to few children in a daycare facility.

In other childhood infections it has been found that acquiring the infection from a sibling makes the disease course more severe, presumably due to both intensity and duration of exposure diseases [17–21]. This would suggest that “dose” of EBV matters for EBV to succeed in invading and establishing a persistent infection in the host. On the other hand the summary of the few studies on the related topic of EBV infection being accompanied by IM in [2] is that “dose” of EBV does not matter. We also found effect sizes for sibship exposures to be the same whether the outcome was a hospital contact with IM as here, or self-reported IM [1]. Seemingly the simplest way to reconcile these two sets of observations would be to assume the existence of a random threshold for successful EBV infection, such that once this threshold is reached there is no longer correlation between IM outcome and EBV dose; and on the other hand, low dose EBV exposures as expectedly experienced in childcare would typically not suffice to reach the threshold. By implication some children must be exposed repeatedly to EBV before the infection becomes persistent, i.e. each individual has a certain susceptibility to EBV infection [37, 39, 40], and the EBV infection may be eliminated as demonstrated in vitro [41].

From the sibship parameters presented here and in [1] it can be inferred that especially 0–3 year old sibs and those with the smallest difference in age to the index child are the most contagious. Considering the modest effect of childcare attendance in the first 1.5 years of life observed in this study, the question becomes a conundrum: How do (one of) your sibs become infected in the first place at a young age? Three out of 7 families studied in [16] included examples of the same EBV strain in a parent and a child, indicative of transmission from parent to child. In one of the families 4 of 8 children carried the same EBV strain as the mother; presumably some of the children could have become infected through a sibling. Other available studies of EBV-transmission are by design not so informative on this point [12–15]. We also note that apparently parents and other adult contacts of a household increase the shedding of EBV in

---

**Childcare and infectious mononucleosis**

One additional year of enrollment in a daycare home before age 1.5 years implied a 10% relative reduction in IM risk, while gaining one year in a childcare institution lowered the IM risk by 6% (Table 1). The difference in IM risk due to exposure in daycare homes and exposure in childcare institutions was small and statistically insignificant (Table 1). A one-year increase in exposure time is a lot compared to e.g. an interquartile distance of around 0.3 years for all three types of exposure time. Hence the variation in IM risk explained by childcare exposure would be even smaller.

**Discussion**

Childcare attendance has consistently been found to entail a short-term increased risk of childhood infections, all well as affecting the risk of some long-term outcomes, e.g. acute lymphoblastic leukemia, see [29, 30] and references therein. However, the effect sizes we found regarding a phenomenon mainly caused by EBV infection are so small as to have no public health implications. Nevertheless, our study may be informative about how and when infants are infected with EBV—an open and important question in basic IM/EBV epidemiology [7].

The true lasting effect of childcare exposure must be caused by early seroconversion and hence be protective against IM [2, 37]. In our study most children were enrolled in childcare at age 6 to 16 months, where most childhood sero-conversion occurs [2], so that age at enrollment in childcare could make a noticeable lasting difference in IM risk. Taking the observed estimates at face value the effect of bringing forward childcare attendance one year (from age 1.5 to 0.5 years) was much less than the effect of having an additional sibling of roughly the same age, as observed here and in an overlapping study [1]. And there was no suggestion of a trend in the direction of exposure to many children in an institution being more protective against IM than exposure to few children in a daycare facility.

In other childhood infections it has been found that acquiring the infection from a sibling makes the disease course more severe, presumably due to both intensity and duration of exposure diseases [17–21]. This would suggest that “dose” of EBV matters for EBV to succeed in invading and establishing a persistent infection in the host. On the other hand the summary of the few studies on the related topic of EBV infection being accompanied by IM in [2] is that “dose” of EBV does not matter. We also found effect sizes for sibship exposures to be the same whether the outcome was a hospital contact with IM as here, or self-reported IM [1]. Seemingly the simplest way to reconcile these two sets of observations would be to assume the existence of a random threshold for successful EBV infection, such that once this threshold is reached there is no longer correlation between IM outcome and EBV dose; and on the other hand, low dose EBV exposures as expectedly experienced in childcare would typically not suffice to reach the threshold. By implication some children must be exposed repeatedly to EBV before the infection becomes persistent, i.e. each individual has a certain susceptibility to EBV infection [37, 39, 40], and the EBV infection may be eliminated as demonstrated in vitro [41].

From the sibship parameters presented here and in [1] it can be inferred that especially 0–3 year old sibs and those with the smallest difference in age to the index child are the most contagious. Considering the modest effect of childcare attendance in the first 1.5 years of life observed in this study, the question becomes a conundrum: How do (one of) your sibs become infected in the first place at a young age? Three out of 7 families studied in [16] included examples of the same EBV strain in a parent and a child, indicative of transmission from parent to child. In one of the families 4 of 8 children carried the same EBV strain as the mother; presumably some of the children could have become infected through a sibling. Other available studies of EBV-transmission are by design not so informative on this point [12–15]. We also note that apparently parents and other adult contacts of a household increase the shedding of EBV in
the presence of a child with IM [12], raising the perspective that the protective effect of having siblings may actually to some extent be transmitted or mediated by parents and other adults. The stability of the IM occurrence by calendar year [1] also favors parents as main contributors of EBV infection in their children.

A theoretical partial explanation for the predominance of family members as sources of successful EBV infection could be that the EBV they are shedding contain mutant EBV clones specifically suited to escape immune surveillance by the index child’s immune system, which to a large extent is shared with other family members. For e.g. HIV it is commonplace [42]. The theoretical possibility has been raised, and intra-host genomic diversity of the EBV is well established, but the extent to which genomic diversification and adaptation occurs in the population of EBV-infected cells in a human host is not currently known [42–44].

It is noteworthy that the difference in effect of exposure to institutional childcare and day-care homes was very small if at all present; and if anything, we would have expected the opposite sign of this difference. Maybe daycare homes resemble a family home more closely in some important way.

**Strengths and weaknesses**

The present study has several strengths and weaknesses to consider. We performed a purely register-based study, thus by design avoiding biases regarding recall, participation, outcome and follow-up. Secular trends were tightly adjusted for by using Cox regression stratified by sex and year of birth with age as underlying time scale. Analyses were adjusted thoroughly for sibship structure, which we believe mediates much of the effect of other socio-demographic factors [1]. Analyses were also adjusted for some readily available strong predictors of IM risk: parental ethnicity and maternal age at birth (Table 1). We also adjusted for two predictors characterizing the municipality of the followed up persons at birth: a socio-economic index and the balance between daycare and institution utilization. The former seemed of little importance, the latter turned out to be a strong predictor of IM risk, by being correlated with urbanicity (Table 1). It is not obvious that the ignored socio-demographic factors should be noticeably correlated with age at childcare enrollment/childcare exposure as this is mainly a question about capacity or supply in the municipalities. Effect sizes with hospitalized IM and self-reported IM as outcomes are remarkably similar when considering exposure to other children [1]. Despite accruing more than 5000 outcome events from essentially following up an entire National birth cohort (Table 1), the study ultimately lacks statistical precision. The main cause for this is a combination of small effect sizes (as expected) and little variation in exposure. We do however gain enough information to confidently rank the effect size as numerically smaller than the effect of having a sibling of roughly the same age as the index person. The small effect sizes identified provides a convincing argument why the incidence of IM has remained so stable in Denmark from 1977 to 2008 [1, 2]. Finally, as far as we know, this is the first study ever having childcare as the only or main exposure of interest for an EBV/IM outcome. The variation in context, exposure, design and measurement makes it very difficult to compare and synthesize relevant previous study findings, see [32, 33, 37] for the most recent studies.

We believe that parents’ choice between a daycare home and a childcare institution is mainly a matter of what is available and convenient. When children are kept out of childcare for long, we believe this would usually be due to a combination of a stay at home parent and a somehow fragile child,—not primarily a matter of socio-demographic confounding. By design these children were excluded from follow-up after age 1.5 years, and therefore did not influence our results. Children who are weak and have many infections may preferentially attend
daycare homes rather than childcare in an institution, but how this should affect our results is unclear to us. An unknown, but probably small fraction of the followed up children would have attended a daycare home in the informal economy or private childcare or some unregistered type of childcare prior to enrollment in public childcare [27, 29, 30]. If anything, this would bias our results toward the null.

**Conclusion**

The risk of IM is affected much less by age at enrollment in childcare within the first 1.5 years of life than by an additional sibling of a comparable age. Biologically, we interpret our results as suggestive of a random threshold for successful EBV infection, that is more easily reached by a sibling than the collective of playmates in a daycare home or a childcare institution.

**Author Contributions**

**Data curation:** Signe Holst Søegaard, Mads Kamper-Jørgensen, Henrik Hjalgrim.

**Formal analysis:** Klaus Rostgaard.

**Funding acquisition:** Klaus Rostgaard, Henrik Hjalgrim.

**Investigation:** Klaus Rostgaard, Lone Graff Stensballe, Henrik Hjalgrim.

**Methodology:** Klaus Rostgaard.

**Resources:** Signe Holst Søegaard, Mads Kamper-Jørgensen, Henrik Hjalgrim.

**Writing – original draft:** Klaus Rostgaard, Henrik Hjalgrim.

**Writing – review & editing:** Klaus Rostgaard, Lone Graff Stensballe, Signe Holst Søegaard, Mads Kamper-Jørgensen.

**References**

1. Rostgaard K, Nielsen TR, Wohlfahrt J, Ullum H, Pedersen O, Erikstrup C, et al. Sibship structure and risk of infectious mononucleosis: a population-based cohort study. Int J Epidemiol. 2014; 43: 1607–1614. [https://doi.org/10.1093/ije/dyu118 PMID: 25436250]

2. Rostgaard K, Balfour HH, Jarrett RF, Erikstrup C, Pedersen O, Ullum H, et al. Primary Epstein-Barr virus infection with and without infectious mononucleosis. Khan G, editor. PLoS One. 2019; 14: e0226436. [https://doi.org/10.1371/journal.pone.0226436 PMID: 31846480]

3. Niedobitek G, Agathangelou A, Steven N, Yongu L. Epstein-Barr virus (EBV) in infectious mononucleosis: detection of the virus in tonsillar B lymphocytes but not in desquamated oropharyngeal epithelial cells. Mol Pathol. 2000; 53: 37–42. [https://doi.org/10.1136/mp.53.1.37 PMID: 10884920]

4. Tamoto N, Nagata K, Hara S, Nakayama Y, Kuwamoto S, Matsuhashita M, et al. Subclinical Epstein-Barr Virus Primary Infection and Lytic Reactivation Induce Thyrotropin Receptor Autoantibodies. Viral Immunol. 2019; 32: 362–369. [https://doi.org/10.1089/vim.2019.0086 PMID: 31580214]

5. Hadinoto V, Shapiro M, Sun CC, Thorley-Lawson DA. The Dynamics of EBV Shedding Implicate a Central Role for Epithelial Cells in Amplifying Viral Output. Speck SH, editor. PLoS Pathog. 2009; 5: e1000496. [https://doi.org/10.1371/journal.ppat.1000496 PMID: 19578433]

6. Ainsworth C. Building a better lymphoma vaccine. Nature. 2018; 563: S52–S54. [https://doi.org/10.1038/d41586-018-07366-1 PMID: 30429570]

7. Balfour HH, Dunmire SK, Hogquist KA. Infectious mononucleosis. Clin Transl Immunol. 2015; 4: e33. [https://doi.org/10.1038/cti.2015.1 PMID: 25774295]

8. Crawford DH, Macsween KF, Higgins CD, Thomas R, McAulay K, Williams H, et al. A cohort study among university students: identification of risk factors for Epstein-Barr virus seroconversion and infectious mononucleosis. Clin Infect Dis. 2006; 43: 276–82. [https://doi.org/10.1086/505400 PMID: 16804839]
9. Liu Z, Fang F, Chang ET, Adami H-O, Ye W. Sibship size, birth order and risk of nasopharyngeal carcinoma and infectious mononucleosis: a nationwide study in Sweden. Int J Epidemiol. 2016; 45: 825–34. https://doi.org/10.1093/ije/dyu038 PMID: 25925268

10. Hjalgrim H, Smedby KE, Røstgaard K, Molin D, Hamilton-Dutoit S, Chang ET, et al. Infectious mononucleosis, childhood social environment, and risk of Hodgkin lymphoma. Cancer Res. 2007; 67: 2382–8. https://doi.org/10.1158/0008-5472.CAN-06-3566 PMID: 17332371

11. Bager P, Nielsen NM, Bihrmann K, Frisch M, Wohlfart J, Koch-Henriksen N, et al. Sibship characteristics and risk of multiple sclerosis: A nationwide cohort study in Denmark. Am J Epidemiol. 2006; 163: 1112–1117. https://doi.org/10.1093/aje/kwj148 PMID: 16675539

12. Sumaya CV, Ench Y. Epstein-Barr virus infections in families: the role of children with infectious mononucleosis. J Infect Dis. 1986; 154: 842–850. https://doi.org/10.1093/infdis/154.5.842 PMID: 3021867

13. Joncas J, Miltyan C. Serologic response of the EBV antibodies in pediatric cases of infectious mononucleosis and in their contacts. Can Med Assoc J. 1970; 102: 1260–1263. PMID: 4315636

14. Nye FJ, Lambert HP. Epstein-Barr virus antibody in cases and contacts of infectious mononucleosis; a family study. J Hyg (Lond). 1973; 71: 151–161. https://doi.org/10.1017/s0022172400046325 PMID: 4348455

15. Fleisher GR, Pasquariello PS, Warren WS, Zavod WS, Korval AB, Turner HD, et al. Intrafamilial transmission of Epstein-Barr virus infections. J Pediatr. 1981; 98: 16–9. https://doi.org/10.1016/s0022-3476(81)80525-2 PMID: 7452392

16. Gratama JW, Oosterveer MA, Klein G, Ernberg I. EBNA size polymorphism can be used to trace Epstein-Barr virus spread within families. J Virol. 1990; 64: 4703–8. https://doi.org/10.1128/JVI.64.10.4703-4708.1990 PMID: 2168960

17. Aaby P. Malnutrition and overcrowding/intensive exposure in severe measles infection: review of community studies. Rev Infect Dis. 1988; 10: 478–91. https://doi.org/10.1093/clinids/10.2.478 PMID: 3287570

18. Paunio M, Peltola H, Valle M, Davidkin I, Heinonen OP. Explosive school-based measles outbreak: intense exposure may have resulted in high risk, even among revaccinates. Am J Epidemiol. 1998; 148: 1103–10. https://doi.org/10.1093/oxfordjournals.aje.a009588 PMID: 9850133

19. Sutter RW, Markowitz LE, Bennet JM, Morris W, Zell ER, Preblud SR. Measles among the Amish: a comparative study of measles severity in primary and secondary cases in households. J Infect Dis. 1991; 163: 12–6. https://doi.org/10.1093/infdis/163.1.12 PMID: 1984459

20. Salgame P, Geadas C, Collins L, Jones-López E, Ellner JJ. Latent tuberculosis infection—Revisiting and revising concepts. Tuberculosis (Edinb). 2015; 95: 373–84. https://doi.org/10.1016/j.tube.2015.04.003 PMID: 26038289

21. Nielsen NM, Hedegaard K, Aaby P. Intensity of exposure and severity of whooping cough. J Infect. 2001; 43: 177–81. https://doi.org/10.1053/jinf.2001.0907 PMID: 11798255

22. Abasszade JH, Tran J, Rama Raj P, Mahdi AA. Atypical transmission of Epstein-Barr virus to a medical practitioner—a case report. Ann Infect. 2021; 5: 4–4. https://doi.org/10.21037/aoi-21-5

23. Kusuhara K, Takabayashi A, Ueda K, Hidaka Y, Minamishima I, Take H, et al. Breast milk is not a significant source for early Epstein-Barr virus or human herpesvirus 6 infection in infants: a seroepidemiologic study in 2 endemic areas of T-cell lymphotropic virus type I in Japan. Microbiol Immunol. 1997; 41: 309–312. https://doi.org/10.1111/j.1348-0421.1997.tb01206.x PMID: 9159404

24. Junker AK, Thomas EE, Radcliffe A, Forsyth RB, Davidson AG, Rymo L. Epstein-Barr virus shedding in breast milk. Am J Med Sci. 1991; 302: 220–3. https://doi.org/10.1097/00000441-199110000-00005 PMID: 1656752

25. Avgil M, Ornoy A. Herpes simplex virus and Epstein-Barr virus infections in pregnancy: consequences of neonatal or intrauterine infection. Reprod Toxicol. 2006; 21: 436–445. https://doi.org/10.1016/j.reprotox.2004.11.014 PMID: 16580943

26. Perera R a PM, Samaranyake LP, Tsang CSP. Shedding dynamics of Epstein-Barr virus: A type 1 carcinogen. Arch Oral Biol. Elsevier Ltd; 2010; 55: 639–47. https://doi.org/10.1016/j.archoralbio.2010.06.009 PMID: 20627195

27. Kamper-Jørgensen M, Wohlfahrt J, Simonsen J, Benn CS. The Childcare Database: a valuable register linkage. Scand J Public Health. 2007; 35: 323–9. https://doi.org/10.1080/14034906010723356 PMID: 17530555

28. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. Eur J Epidemiol. 2014; 29: 541–549. https://doi.org/10.1007/s10654-014-9930-3 PMID: 24965263

29. Kamper-Jørgensen M. Disease in childhood and the impact of childcare. University of Copenhagen. 2007.
30. Kamper-Jørgensen M, Stabell Benn C, Wohlfahrt J. Childcare and health: A review of using linked national registers. Scand J Public Health. 2011; 39: 126–130. https://doi.org/10.1177/1403498109359826 PMID: 21775370

31. Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National patient registry: A review of content, data quality, and research potential. Clin Epidemiol. 2015; 7: 449–490. https://doi.org/10.2147/CLEP.S91125 PMID: 26604824

32. Carvalho-Queiroz C, Johansson MA, Persson J-O, Jörtsö E, Kjerstadius T, Nilsson C, et al. Associations between EBV and CMV Seropositivity, Early Exposures, and Gut Microbiota in a Prospective Birth Cohort: A 10-Year Follow-up. Front Pediatr. 2016; 4: 93. https://doi.org/10.3389/fped.2016.00093 PMID: 27630978

33. Pembrey L, Waißlinger D, Griffiths P, Patel M, Azad R, Wright J. Cytomegalovirus, Epstein-Barr virus and varicella zoster virus infection in the first two years of life: A cohort study in Bradford, UK. BMC Infect Dis. 2017; 17: 1–18. https://doi.org/10.1186/s12879-016-2122-x PMID: 28604444

34. Balfour HH, Odumade O a, Schmeling DO, Mullan BD, Ed JA, Knight JA, et al. Behavioral, virologic, and immunologic factors associated with acquisition and severity of primary Epstein-Barr virus infection in university students. J Infect Dis. 2013; 207: 80–6. https://doi.org/10.1093/infdis/jitsa11 PMID: 23100562

35. Condon LM, Cederberg LE, Rabinovitch MD, Liebo RV, Go JC, Delaney SA, et al. Age-Specific Prevalence of Epstein-Barr Virus Infection Among Minnesota Children: Effects of Race/Ethnicity and Family Environment. Clin Infect Dis. 2014; 59: 501–508. https://doi.org/10.1093/cid/ciu342 PMID: 24820696

36. Jansen MAE, Van Den Heuvel D, Bouthoorn SH, Jaddoe VWV, Hooijkaas H, Raat H, et al. Determinants of Ethnic Differences in Cytomegalovirus, Epstein-Barr Virus, and Herpes Simplex Virus Type 1 Seroprevalence in Childhood. J Pediatr. Elsevier Inc.; 2016; 170: 126–134.e6. https://doi.org/10.1016/j.jpeds.2015.11.014 PMID: 26707579

37. Winter JR, Jackson C, Lewis JE, Taylor GS, Stagg HR. Predictors of Epstein-Barr virus serostatus and implications for vaccine policy: A systematic review of the literature. J Glob Health. 2020; 10: 010404. https://doi.org/10.7189/jogh.10.010404 PMID: 32257152

38. Indenrigsm ministeriet. Kommunal udligning og generelle tilskud 2019. Copenhagen; 2018.

39. Helminen ME, Kilpinen S, Virta M, Hurme M. Susceptibility to primary Epstein-Barr virus infection is associated with interleukin-10 gene promoter polymorphism. J Infect Dis. 2001; 184: 777–80. https://doi.org/10.1086/322987 PMID: 11517440

40. Kenney AD, Dowdle JA, Bozzacco L, McMichael TM, St. Gelais C, Panfil AR, et al. Human Genetic Determinants of Viral Diseases. Annu Rev Genet. 2017; 51: 241–263. https://doi.org/10.1146/annurev-genet-120116-023425 PMID: 28853921

41. Wilson AD, Morgan AJ. Primary Immune Responses by Cord Blood CD4+ T Cells and NK Cells Inhibit Epstein-Barr Virus B-Cell Transformation In Vitro. J Virol. 2002; 76: 8504–8504. https://doi.org/10.1128/jvi.76.10.5071-5081.2002 PMID: 11967323

42. Midgley RS, Bell AJ, Yao QY, Croom-Carter D, Hislop AD, Whitney BM, et al. HLA-A11-restricted epitope polymorphism among Epstein-Barr virus strains in the highly HLA-A11-positive Chinese population: incidence and immunogenicity of variant epitope sequences. J Virol. 2003; 77: 11507–16. https://doi.org/10.1128/jvi.77.21.11507-11516.2003 PMID: 14557696

43. Palser AL, Grayson NE, White RE, Corton C, Correia S, Ba abdullah MM, et al. Genome Diversity of Epstein-Barr Virus from Multiple Tumor Types and Normal Infection. Longnecker RM, editor. J Virol. 2015; 89: 5222–5237. https://doi.org/10.1128/JVI.03614-14 PMID: 25787276

44. Weiss ER, Lamers SL, Henderson JL, Melnikov A, Somasundaran M, Garber M, et al. Early Epstein-Barr Virus Genomic Diversity and Convergence toward the B95.8 Genome in Primary Infection. Jung JU, editor. J Virol. 2017;92. https://doi.org/10.1128/JVI.01466-17 PMID: 29093087