PREVALENCE AND CORRELATES OF CYTOMEGALOVIRUS VIREMIA IN KENYAN CHILDREN AT HOSPITAL DISCHARGE

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Abstract

Prevalence and correlates of cytomegalovirus viremia in Kenyan children at hospital discharge

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Background

CMV viremia is common in immunocompetent adults admitted to intensive care units, and individuals with detectable CMV viremia are at a higher risk for death and other poor outcomes. Given the high prevalence and early acquisition of CMV in Sub-Saharan Africa, hospitalized African children may also be at high risk for CMV viremia. However, while CMV has been well-studied in severely immunosuppressed populations including those with congenital infection or organ transplant, no studies have examined the association between CMV viremia and mortality in post-discharge children in sub-Saharan Africa; nor, documented the prevalence of CMV viremia in children admitted or discharged from the hospital. This cross-sectional study utilizes baseline clinical, demographic, and CMV DNA data from Kenyan children aged 1 to 59 months enrolled in a randomized controlled trial in Western Kenya, to determine the prevalence and correlates of CMV viremia at hospital discharge. Utilizing quantitative CMV PCR, it also determines the relationship between clinical and laboratory risk factors and the quantity of CMV DNA in blood.

Methods

To determine the prevalence of CMV viremia, quantitative real-time CMV PCR was used to measure CMV viral loads in stored plasma specimens from 1024 children aged 1-59 months at hospital discharge (with a detection limit of 50 copies/ml of plasma). CMV viral loads were compared among children by HIV exposure and HIV-infection status using the 2-sample Wilcoxon rank-sum (Mann-Whitney). Among HIV-uninfected children, the general linear model with Poisson distribution was used to calculate prevalence ratios for hypothesized correlates of CMV viremia and correlates of high CMV viral load (≥1000 copies/ml). Prevalence ratios were adjusted for age and HIV exposure status.

Results

The study population consisted of 1024 children 1 to 59 months old who were enrolled at hospital discharge into an ongoing randomized controlled trial of azithromycin to prevent post-discharge morbidity and mortality. The median age was 18 months, and over half of children were under the age of 2 years old. Malnutrition was common; 24% were stunted, 6% wasted and 12% underweight. Most children were HIV unexposed (HUU) (85%), while a number were HIV-exposed uninfected (HEU)

(9%) and HIV-infected (HIV+) (2%). CMV viremia was detected in 32% of children at enrollment; 30% in HUU children, 40% in HEU children, and 40% in HIV+ children. The median viral load for all included children was 2.4 $\log_{10}$ copies/mL (IQR: 2.0 to 2.9); it was 2.4 $\log_{10}$ copies/mL (95% CI: 2.0 to 2.9) in HIV-unexposed children, 2.3 $\log_{10}$ copies/mL (95% CI: 2.0 to 2.8; p-val.=0.8) in HEU, and 3.3 $\log_{10}$ copies/mL (95% CI: 2.6 to 5.4) HIV+ children. HIV+ children had significantly higher $\log_{10}$ copies/mL CMV viral load than HEU (p=0.01) or HUU children (p=0.02). Among all HIV-uninfected children (HEU and HUU), age younger than 2 years was associated with a 40% (PR=0.6; 95% CI: 0.5 to 0.8) increased prevalence of CMV viremia at discharge adjusting for HIV-exposure. Adjusting for age, children who were HEU had a 30% (PR=1.3; 95% CI=1.0 to 1.9) higher prevalence of CMV viremia. Among 314 children with detectable CMV, potential correlates including length of hospital stay, discharge diagnosis, and anthropometric indices were not associated with CMV prevalence. Study site and age were the only predictors of high CMV viral load in adjusted models.

Conclusions

Among children being discharged from hospitals in western Kenya, detectable CMV viremia was common, with a prevalence of CMV viremia similar to that previously reported in adults admitted to ICU in high income settings. Geographical region and young age were correlates of viremia in this population of children. Understanding the potential clinical implications of CMV viremia in these recovering children may offer opportunity for targeted interventions to reduce CMV viral load and improve outcomes.

Keywords

CMV reactivation, Cytomegalovirus, human herpesvirus, immunosuppressed, hospitalized children, Kenya

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I also want to thank my colleagues and peers at the University of Washington's School of Public Health for the constant encouragement and comradery. I could not be more excited to cross paths with each and everyone one of you in our careers in public service.

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Background

Cytomegalovirus

Despite dramatic reductions in child mortality observed globally in the past several decades, under-5 mortality remains 15 to 30 times higher in Sub-Saharan Africa than in western countries.[1,2] These deaths are largely attributable to infectious diseases such as HIV/AIDS, malaria, cholera, tuberculosis, and diarrhea and likely reflect differences in geographic, demographic, and socio-economic factors (e.g., crowded living conditions, poor nutrition and sanitation).[1,3] While global efforts to reduce under-5 mortality in low-to-middle income countries have primarily focused on improved access to quality care and preventative services, the burden of morbidity and mortality following hospitalization for acute illness has been underappreciated.[3–5] In many settings, rates of pediatric post-discharge death are often as high as rates of in-hospital deaths. However, the underlying risk factors and mechanisms driving post-discharge death remain unclear.[4–6]

Cytomegalovirus (CMV) is a ubiquitous human herpesvirus, infecting 80-100% of the world's population, which emerges in human hosts through primary infection, reinfection, and reactivation.[7–9] It is one of several members of the human herpesvirus family (which include, Epstein-Barr virus (EBV), human herpesviruses (HHV)-6 and 8, herpes simplex virus (HSV), and varicella zoster virus) that infect a large proportion of the world's population. In East Africa, most children acquire CMV, EBV and HHV-6 before their second birthday.[10–15]CMV establishes lifelong persistent latent infection in the host. The majority of immunocompetent individuals remain asymptomatic with lifelong infection. However, CMV can be life-threatening for immunosuppressed populations, including newborns with congenital infection, organ transplant recipients, critically-ill adults, and those with HIV infection.[11,12,16–18] CMV can disrupt cell-mediated immunity, augment inflammatory responses, and appears to predispose infected individuals to other bacterial, fungal, and viral infections.[19–21] There is emerging evidence that CMV reactivation occurs frequently during critical illness in otherwise immunocompetent adults, and is associated with an increased risk of mortality, longer duration of hospitalization, increased duration of mechanical ventilation and increased susceptibility to new infections in these individuals.[11,21–24]

Review of Literature

Reliable estimates of prevalence, outcomes, and correlates of CMV viremia in hospitalized children, and in low-resource settings are limited.[9] To date, 13 studies have investigated the prevalence and consequences of CMV in immunocompetent critically-ill adult patients in ICUs across the United States and Europe.[21,25,26] One study on infants in Zambia found that, while there was no significant effect of CMV viremia on developmental growth from 6 to 18 months of age, there was evidence of interaction between CMV viremia and maternal HIV on stunting.[27] Given the early acquisition of CMV in African children, it is important to assess 1) whether CMV is also highly prevalent in hospitalized children, 2) whether it is associated with poor outcomes, and 3) whether reducing CMV viremia could be a novel target for interventions.

Purpose

The present study has measured the prevalence of CMV in hospitalized children 1-to-59 months-old in Kenya and identified the correlates of viremia and viral load, focusing on variables which have been identified in adult ICU studies. We also evaluated factors that may impact CMV reactivation. Breastfeeding (CMV transmission via breast milk), and living in crowded households (CMV transmission via close contact) are associated with a risk of acquiring CMV earlier in life.[23,28] Geographic and sociodemographic conditions also relate to prevalence of CMV viremia as prior studies have suggested that populations with lower education and income experience a higher risk of seropositivity as well as a longer period of time spent with CMV infection; while definitive reasons for seroprevalence in poor-resource communities are still unclear, crowded living conditions may play a primary role.[29,30] Additionally, malnutrition is common among children in Kenya due to lack of food availability and diversity, frequent exposure to pathogens, and frequent infectious illness.[31–33] Malnutrition is associated with immunosuppression and, like HIV infection, may be an important risk factor for both presence and quantity of CMV in children.[34,35] Additional correlates include exposure to other infections including HIV and malaria.[22,36,37]

Innovation

Limited data exist regarding CMV prevalence and correlates in hospitalized children at discharge in sub-Saharan Africa. These study findings will provide rationale for future interventions to improve the care of hospitalized children.

Methods

Parent Study Research Design & Study Setting

This cross-sectional study uses specimens and data from its parent study, the Toto Bora Randomized Clinical Trial: "Azithromycin to Prevent Post-discharge Morbidity and Mortality in Kenyan Children" [NCT02414399]. Toto Bora is a randomized double-blind, placebo-controlled trial in Western Kenya among 1400 children aged 1-59 months who were recently hospitalized at hospitals in the Nyanza province of Kenya and ready for discharge.[6] Caregivers provided informed consent and agreed to participate in the study. Exclusion criteria was identified as children who were prescribed macrolide antibiotics during the index hospitalization, had a twin of the same sex enrolled in the trial on the same day, was admitted for trauma, had an injury or a birth defect, had a legal guardian not providing consent, or had plans to move out of the region within the 6 month period after being enrolled. At enrollment in the study, staff abstracted information from the medical record of the recent hospitalization, collected sociodemographic information and medical history information utilizing a standard questionnaire, and performed a physical exam and took height, length, weight, and mid-upper-arm circumference (MUAC) measurements from the child. Blood samples were collected from all enrolled children, centrifuged to separate plasma and buffy coat, and placed at −80°C within 1 hour of collection. Plasma samples were then shipped to the University of Washington (maintained at -80°C) for CMV analysis.[6]

CMV Assays

Stored plasma samples were used for quantitative real-time CMV PCR to measure CMV viral load at enrollment, as previously described.[38,39] CMV viral loads were measured in all specimens for each child, and the limit of detection of the assay was one copy per reaction (equivalent to 50 copies/ml of plasma). In the future, infants with no detection of CMV DNA will undergo serologic testing of their last-collected plasma specimen to determine final status.[40]

Data Analyses

STATA version IC 15.1 (College Station, TX) was used for all statistical analyses. All tests were 2-sided with an α=0.05. Because the Toto Bora trial is ongoing and the investigators are blind to treatment allocation, this analysis focused on prevalence and correlates of CMV viremia; a follow-up study will assess the association between CMV viremia and mortality/rehospitalization once the parent trial is complete.

The general linear model with Poisson distribution was used to calculate prevalence ratios for hypothesized correlates of CMV viremia, and correlates of high CMV viral load (≥1000 copies/ml). When detecting CMV viral load values of <1000 copies/ml, changes of <5-fold (0.7 $\log_{10}$) will rarely reflect clinically important changes in viral replication; subsequently, for values >1000 copies/ml, 3-fold (0.5 $\log_{10}$) changes in viral load may be significant.[41]
The prevalence of CMV viremia detection was calculated among all children recruited for the parent study with a confidence interval of 95% and assuming a binomial distribution. CMV prevalence was calculated separately for HIV-infected, HIV-exposed uninfected and HIV-unexposed children, given a wealth of data suggesting CMV viremia is common and often present at high concentrations in the plasma of HIV-infected and exposed uninfected children.[39] A list of potential correlates of CMV viremia was developed from the literature from adults in the ICU (disease severity, admission diagnosis), studies of CMV viremia in children with HIV (age, nursing), and additional variables hypothesized to be mechanistically related to immunosuppression and/or CMV reactivation (nutritional status).[38] For the evaluation of nutritional status, underweight, wasting, moderate acute malnutrition (MAM), severe acute malnutrition (SAM), stunting, and Mid-Upper Arm Circumference (MUAC) were examined. Prevalence ratios and associated 95% confidence intervals were calculated for all potential correlates. Because it is well established that CMV has a unique pathology in HIV-infected children, we excluded HIV-infected children and HIV-exposed children for whom HIV-infection status was unknown from the correlates analysis.[42] Among the 1004 uninfected children remaining in the analysis, we adjusted for HIV exposure and age.

Because CMV viral levels of >1000 copies/ml raise suspicion of active CMV disease in a clinical setting, we additionally assessed this as a second outcome of interest among the 314 HIV-uninfected children who were CMV viremic. To test for potential correlates of high level CMV viremia in this cohort, we classified children based on the quantity of CMV and created a dichotomous variable of high CMV viremia,

distinguishing children with high viral load (≥1000 copies/ml), and low viral load (<1000 copies/ml). The same variables as noted above as potential correlates of high-level CMV viremia were assessed for this outcome.

Ethical considerations

This study was approved by the ethics committees of the University of Washington, the Kenya Medical Research Institute (KEMRI), and the Kenyan Pharmacy and Poisons Board.

Results

Population characteristics

This study included 1024 children discharged from hospital in western Kenya. The median age of included participants was 18 months; approximately 65% of children were under the age of 2 years old and 61% were male (Table 1). Nearly a quarter of children (24%) were stunted, 6 % were wasted, and 12% underweight. A majority of children (85%) were HIV unexposed, while 9% were HIV-exposed uninfected, 2% were HIV-infected, and 46% were exclusively breastfed for the first six months of their life. Most children (85%) were in the hospital for less than 7 days prior to discharge and were most commonly hospitalized for lower respiratory tract infections (LRTI), malaria, and diarrhea. Accompanying caregivers were most commonly the biological mothers (91%). Nearly half (45%) of these caregiver and children dyads lived in crowded households and close to 80% lived in households earning less than 10,000 shillings, 60% of which earned less than the poverty line (less than 5,000 shillings (~$50USD) per month).

CMV prevalence and levels by HIV exposure

Three hundred and twenty-two children (31%) had CMV detected in their plasma at hospital discharge. The prevalence of CMV among all HIV-unexposed children was 28%, in HEU was 39.6%, and HIV-infected was 40%. The median viral load among all children was 2.4 $\log_{10}$ copies/mL (IQR: 2.0 to 2.9); disaggregated by HIV status, 2.4 $\log_{10}$ copies/mL (IQR: 2.0 to 2.9) for HIV-unexposed children, 2.4 $\log_{10}$ copies/mL (IQR: 2.0 to 2.8) in HIV exposed uninfected children, and 3.3 $\log_{10}$ copies/mL (IQR: 2.6 to 5.4) in HIV-infected children. Among the 322 CMV viremic children, 66 (21%) had a high CMV viral load as defined by a viral load of ≥1000 copies/ml.

Correlates of CMV viremia in hospitalized HIV-uninfected children

We assessed sociodemographic and clinical correlates of CMV viremia at hospital discharge among the 1004 children confirmed to be HIV-uninfected. Table 2 shows adjusted and unadjusted prevalence ratios for each covariate examined. Presenting to Homa Bay County Hospital, younger age and current breastfeeding were associated with CMV viremia in the univariate analyses. When adjusting for age and HIV exposure, only presentation to Homa Bay (PR= 1.9; 95% CI: 1.5 to 2.4) remained significantly associated with CMV viremia. Children over 2 years of age had a 60% (95% CI: 0.5-0.8) decreased prevalence of CMV after adjustment of HIV-exposure. None of the other admission diagnoses, clinical

variables, or sociodemographic factors assessed were significantly associated with CMV viremia in the adjusted models.

Correlates of High CMV Viral Load

Table 3 shows unadjusted and adjusted prevalence ratios for high (≥1000 copies/ml) versus low (<1000 copies/ml) CMV viral load among 314 children who were confirmed to be HIV-uninfected and were CMV viremic. After adjusting for age and HIV-exposure, presentation to the Homa Bay County Hospital (PR=2.2; 95% CI: 1.3 to 3.7) was associated with a 2 times higher prevalence of high CMV viral load. Older age (> 2 years) also appeared protective against high-CMV viral load, with a 20% decreased prevalence of high-CMV viral load in this age group (PR=0.2; 95% CI: 0.1 to 0.5).

Discussion

In this study of 1024 children being discharged from hospital in western Kenya, CMV viremia was detected in over a third of the children. Among those with detectable CMV, viral loads were high (≥1000 copies/ml) in more than 20%. CMV viremia was associated with younger age, presentation to Homa Bay County Hospital, and HIV-exposure. To our knowledge, this is the first report of CMV viremia in hospitalized children without severe immune compromise due to HIV in Africa and these data suggest that interventions to reduce CMV viremia during hospitalization may warrant consideration in this population.

CMV viremia is rarely detected among immunocompetent individuals; the virus establishes a persistent latent infection that is well-contained by the host immune system, and reactivation is typically observed only in the most immunosuppressed individuals.[11,39] The prevalence of CMV viremia reported among immunocompetent children in this study is high, but is also consistent with rates of CMV reactivation in immunocompetent adults admitted to ICUs in the US and Europe (0 to 36%).[18,25] The similarity of these estimates is surprising, given that the children in our study were well enough to be discharged from the hospital, whereas patients in ICUs are acutely ill. Existing literature of ICU patients suggest that CMV viremia often precedes or coincides with clinical decline; given the high prevalence rate in this post-discharge population, further studies are needed to examine the directional relationship between CMV viremia and survival outcomes.[11,43]

Young age and current breastfeeding were associated with a higher rate of CMV viremia in our study, with the association between nursing and CMV going away after age and HIV-exposure adjustment. Breastfeeding is as an effective mechanism for postnatal transmission of CMV, with other transmission sources being other body fluids such as saliva and urine.[10,44] As stated previously, a majority of children growing up in sub-Saharan Africa acquire several human herpes virus infections before their first birthday, the earliest being CMV and HHV-6B; while other HHVs may not be routinely detected in breast milk, prior studies have found that rapid acquisition of CMV can be detected from the time of birth both among HIV-1-unexposed and HIV-1-exposed children with a strong associated with

breastfeeding.[11] Because accounting for age removed the association between breastfeeding and CMV, it is possible that most of the population was exposed to CMV, given that nearly all children were either exclusively breastfed for their first 6 months of life, or partially breastfed. The association of CMV viremia with age <2 years old may thus suggest that the occurrence of illness during recent primary CMV infection may result in either extended viremia during primary infection or CMV reactivation. Longitudinal data would be needed to confirm this hypothesis. It is unclear why the association between nursing and CMV was not evident in the present and select prior studies.[45]

As expected, HIV-infected children had a higher prevalence of CMV viremia and higher CMV levels than uninfected children, consistent with earlier research demonstrating viremia as a marker of advanced immunosuppression related to HIV infection as well as predicting the development of CMV disease.[46,47] Interestingly, children presenting to the Homa Bay hospital experienced a 2-fold increase in CMV prevalence compared to Kisii. While the reason for this is not clear, we note that these regions differ remarkably in terms of malaria prevalence, socioeconomic factors, water and sanitation conditions, child and maternal malnutrition, HIV prevalence and HIV stigma; all or any one of these factors or related unstudied variables could contribute to population differences in immune activation, undiagnosed or late-treated HIV infection.[48]

While we did not find child nutritional status to be associated with CMV viremia in our univariate or adjusted models, malnutrition is highly inflammatory and immunosuppressive.[35,49] This mechanism may enable ongoing CMV replication or reactivation, and should be explored as a potential predictor of survival and rehospitalization outcomes in the ongoing parent trial. Prior studies examining CMV viremia in hospitalized African children have noted significant associations between being underweight and CMV viremia, as well as poor growth.[11,19]

This study has several strengths and some important limitations. Strengths include the large sample size and detailed clinical characterization of the cohort. The study is limited by its cross-sectional design, and causal inference is limited in determining associations between covariates and CMV viremia. Because children were enrolled at discharge, we did not have adequate ascertainment of some clinical variables that have been associated with iatrogenic reactivation of CMV in adults, including blood transfusion and administration of corticosteroids. Based on existing literature, our current analysis assumes nearly 100% of children would have acquired CMV before hospital admission, but with the inclusion of children < 1 year old a subset of these is likely to be CMV uninfected; to accurately determine the prevalence of viremia among CMV infected children we will thus need to complete CMV serology on all of the CMV-aviremic children (ongoing). For our assessment of potential correlates including final diagnosis at discharge, we acknowledge the statistical limitation of performing multiple comparisons that may decrease the stringency of significance values; however, we did not identify any potential correlates that predicted CMV viremia and were affected by our multiple testing. Additionally, the study is also limited by the geographic location of Kenya, a region with high prevalence of malaria, malnutrition, and poverty, and so results may not be generalizable across other immunocompetent populations.

Conclusion

To our knowledge, this is the first evaluation of CMV viremia in African children without severe immunocompromise at hospital discharge. We found a prevalence of CMV viremia that was similar to that reported in adults admitted to the ICU and we identified geographical region and young age as correlates of viremia. Limited data exist regarding CMV prevalence and correlates in hospitalized children at discharge in sub-Saharan Africa and these study findings can provide rationale for future research to evaluate interventions to reduce CMV viremia in this population. While we are currently blinded to mortality outcomes in the main Toto Bora trial, the study will finish in March 2020, after which we will assess the association between CMV viremia and clinical outcome.

Tables & Figures

Figure 1. Number enrolled and included study participants

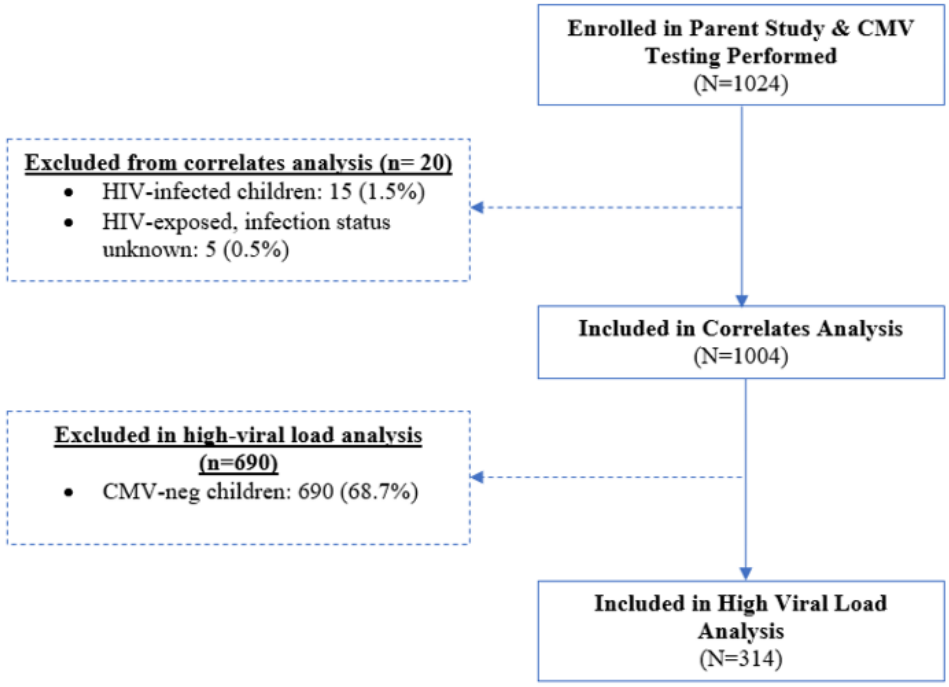

Figure 1. Exclusion criteria for analysis, resulting in N=1004

Figure 2. CMV DNA viral loads in HIV Unexposed, HIV Exposed Uninfected, and HIV- Infected children with CMV viremia

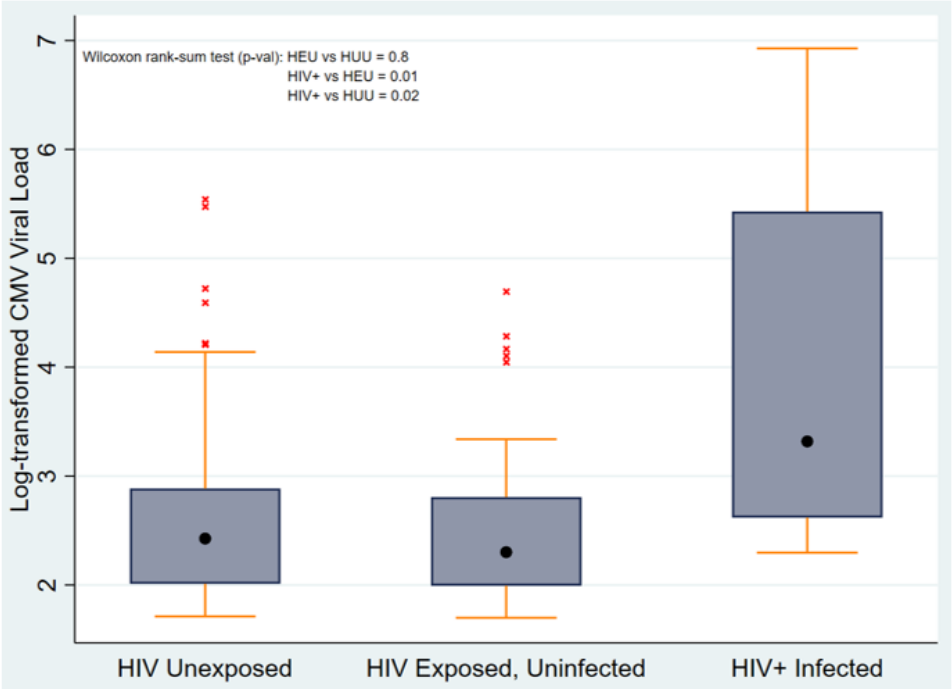

Figure 2. CMV viral load (log-transformed) in children, by HIV Unexposed, HIV Exposed Uninfected, and HIV+ Infected status (from left to right). Median values are shown by a black dot, IQR is shown within the blue box, outlier whiskers are shown by orange lines, and outlier values are indicated as red x-marks.

Table 1. Characteristics of enrolled children (N=1,024)

Characteristic	n Median	(%) (IQR)
Site		
Kisii	628	(61.3)
Homa Bay/ St. Paul[i]	396	(38.7)
Household		
Crowding	462	(45.1)
Household Income		
None[ii]	307	(30.0)
< 10,000 ksh	490	(47.8)
≥ 10,000 ksh	168	(16.5)
Caregiver Characteristics		
Biological Mother	927	(90.5)
Biological Father	32	(3.1)
Other	65	(6.4)
Child Characteristics[iii]		
Male	621	(60.8)
Female	401	(39.2)
Age (months)		
1 to > 6 mo	137	(13.4)
6 to < 12 mo	199	(19.4)
≥ 12 to 24 mo	328	(32.0)
≥ 24 mo	360	(35.2)
Nutritional Status		
Median WAZ	-0.5	(-1.3 to 0.3)
Underweight (WAZ < -2)	127	(12.4)
Median WHZ	0.0	(-0.8 to 0.9)
Wasted (WHZ < -2)	57	(5.6)
Severe Acute Malnutrition (WHZ < -3)	17	(1.7)
Median HAZ	-0.9	(-0.9 to 0.0)
Stunted (HAZ < -2)	248	(24.3)
MUAC (cm)[iv]	14.3	(13.2 to 15.2)
< 12.5	127	(12.4)
≥ 12.5	897	(87.6)
Length of Hospitalization (days)		
< 7	841	(85.1)
≥ 7	183	(17.9)
HIV Status		
HIV Unexposed	871	(85.1)
HIV Exposed, Uninfected	96	(9.4)
HIV Infected	15	(1.5)
Uninfected, Exposure Status Unknown	37	(3.6)
HIV Exposed, Infection Status Unknown	5	(0.5)
Breastfeeding Status[v]		
Never Breastfed	18	(1.8)
Exclusively Breastfed	467	(45.9)
Currently Nursing[vi]	483	(75.6)
Final Diagnosis		
Anemia	133	(13.0)
Lower Respiratory Tract Infection	350	(34.2)
Gastroenteritis/ diarrhea	187	(18.3)
Malaria	276	(27.0)
Malnutrition	58	(5.7)
Meningitis	53	(5.2)
Sepsis	30	(2.9)
Sickle Cell	70	(6.8)
Tuberculosis	15	(1.5)
Other	257	25.1

[i] Due to proximity and sociodemographic similarity, Homa Bay and St. Paul have been combined

[ii] The 1/3 of respondents who responded "none" to income are most likely subsistence farmers who have other sources of income in the form of bartering and trade

[iii] There are 2 observations in the data with missing sex data

[iv] MUAC of between 11.0cm and 12.5cm indicates Moderate Acute Malnutrition. MUAC of less than 11.0cm indicates Severe Acute Malnutrition, and the child should seek care immediately.

[v] Exclusive breastfeeding is defined by an infant receiving only breast milk in its first 6 months or up until the child's current age at recent hospitalization. Currently nursing is defined as a child who is breastfeeding at the time of recent hospitalization, and not mutually exclusive of those in the exclusively breastfed groups. Children's whose breastfeeding status was unknown or who only partially breastfed are not displayed

[vi] Among those less than 24 months old

Table 2. Socio-demographic and clinical characteristics of CMV DNA-negative and DNA-positive children (1,004)

Characteristic	CMV Negative n	%	CMV Positive n	%	Prev Ratio PR	(95% CI)	P > |z|	Age & HIV-Adjusted PR[i] PR	(95%CI)	P > |z|
Site										
Kisii	474	(76.6)	145	(23.4)	[REF]					
Homa Bay/ St. Paul	216	(56.1)	166	(43.1)	1.8	(1.5 to 2.3)	<0.001	1.9	(1.5 to 2.4)	<0.001
Child Characteristics										
Male	428	(70.0)	183	(30.0)	[REF]					
Female	261	(66.8)	130	(33.2)	1.1	(0.9 to 1.4)	0.4	1.1	(0.9 to 1.4)	0.4
Age (months)										
< 24 mo	399	(63.3)	231	(36.7)	[REF]					
≥ 24 mo	291	(77.8)	83	(22.2)	0.6	(0.5 to 0.8)	<0.001	0.6	(0.5 to 0.8)	<0.001
Nutritional Status										
Not Underweight	606	(68.7)	276	(31.3)	[REF]					
Underweight (WAZ < -2)	84	(68.9)	38	(31.1)	1.0	(0.7 to 1.4)	1.0	0.9	(0.6 to 1.2)	0.4
Not Wasted	647	(68.5)	298	(31.5)	[REF]					
Moderate Acute Malnutrition (WHZ ≥ -3)	28	(75.7)	9	(24.3)	0.7	(0.4 to 1.5)	0.4	0.7	(0.4 to 1.4)	0.4
Severe Acute Malnutrition (WHZ < -3)	10	(58.8)	7	(41.1)	1.3	(0.6 to 2.8)	0.5	0.9	(0.4 to 2.0)	0.8
Not Stunted	519	(68.0)	244	(32.0)	[REF]					
Stunted (HAZ < -2)	169	(70.7)	70	(29.3)	0.9	(0.7 to 1.2)	0.5	0.9	(0.7 to 1.2)	0.4
MUAC										
> 12.5 cm	615	(69.4)	271	(30.6)	[REF]					
< 12.5 cm	75	(63.6)	43	(36.4)	1.2	(0.9 to 1.6)	0.3	0.9	(0.6 to 1.2)	0.5
Length of Hospitalization (days)										
< 7	571	(68.7)	260	(31.3)	[REF]					
> 7	119	(68.8)	54	(31.2)	1.0	(0.7 to 1.4)	1.0	0.9	(0.7 to 1.2)	0.5
HIV Status[ii]										
HIV Unexposed	614	(70.5)	257	(29.5)	[REF]					
HIV Exposed, Uninfected	58	(60.4)	38	(39.5)	1.3	(1.0 to 1.9)	0.1	1.4	(1.0 to 2.0)	0.04
Not Currently Nursing	376	(74.3)	130	(35.7)	[REF]					
Currently	312	(62.9)	184	(37.1)	1.4	(1.2 to 1.8)	<0.001	1.1	(0.8 to 1.5)	0.5
Never Breastfed	13	(72.2)	5	(27.8)	[REF]					
Exclusively	300	(65.4)	159	(34.6)	1.2	(0.5 to 3.0)	0.6	1.4	(0.6 to 2.4)	0.5
Final Diagnosis										
Anemia	78	(60.9)	50	(39.1)	1.3	(1.0 to 1.8)	0.1	1.4	(1.0 to 1.8)	0.05
Pneumonia	204	(65.8)	106	(34.2)	1.1	(0.9 to 1.4)	0.3	1.0	(0.8 to 1.3)	1.0
Gastroenteritis/diarrhea	126	(68.9)	57	(31.1)	1.0	(0.7 to 1.3)	1.0	0.9	(0.7 to 1.2)	0.5
Lower Respiratory Tract Infection	22	(59.5)	15	(40.5)	1.3	(0.8 to 2.2)	0.3	1.2	(0.7 to 2.0)	0.6
Malaria	182	(67.4)	88	(32.6)	1.1	(0.8 to 1.4)	0.7	1.2	(1.0 to 1.6)	0.1
Malnutrition	32	(58.1)	23	(41.8)	1.4	(0.9 to 2.1)	0.2	1.1	(0.7 to 1.7)	0.7
Meningitis	42	(79.2)	11	(20.8)	0.7	(0.4 to 1.2)	0.2	0.7	(0.4 to 1.3)	0.3
Sepsis	18	(60.0)	12	(40.0)	1.3	(0.7 to 2.3)	0.4	1.3	(0.7 to 2.3)	0.4
Sickle Cell	53	(75.7)	17	(24.3)	0.8	(0.5 to 1.2)	0.3	0.9	(0.6 to 1.5)	0.7
Tuberculosis	13	(92.9)	1	(7.1)	0.2	(0.0 to 1.6)	0.1	0.2	(0.0 to 1.3)	0.1

[i] The age and HIV-adjusted prevalence ratio treats age as a continuous variable and includes only HIV-unexposed and HIV-exposed groups
[ii] Includes children with known HIV exposure status

Table 3. Socio-demographic and clinical characteristics of CMV High Viral Load Among CMV+ children (N=314)

Characteristic	Viral Load Copies (log-transformed) Median	(IQR)	≤ 1000 copies/ml n	%	> 1000 copies/ml n	%	Prev Ratio PR	(95% CI)	P > |z|	Age & HIV-Adjusted PR	(95%CI)	P > |z|
All	2.4	(2.0 to 2.9)	248	(79.0)	66	(21.0)						
Site												
Kisii	2.3	(2.0 to 2.7)	123	(84.8)	22	(15.2)	[REF]					
Homa Bay/ St. Paul	2.5	(2.0 to 3.0)	125	(74.0)	44	(29.0)	1.7	(1.0 to 2.9)	0.04	2.2	(1.3 to 3.7)	0.003
Child Characteristics												
Male	2.4	(2.0 to 2.8)	146	(79.8)	37	(20.2)	[REF]					
Female	2.4	(2.0 to 2.9)	101	(77.7)	29	(22.3)	1.1	(0.7 to 1.8)	0.7	1.0	(0.6 to 1.7)	0.9
Age (months)												
< 24 mo	2.5	(2.1 to 3.0)	169	(73.2)	62	(26.8)	[REF]					
≥ 24 mo	2.1	(1.9 to 2.5)	79	(95.2)	4	(2.8)	0.2	(0.1 to 0.5)	0.001	0.2	(0.1 to 0.5)	0.001
Nutritional Status												
Not Underweight	2.4	(2.0 to 2.8)	220	(79.7)	56	(20.3)	[REF]					
Underweight (WAZ < -2)	2.6	(2.2 to 3.3)	28	(73.7)	10	(26.3)	1.3	(0.7 to 2.5)	0.5	1.1	(0.5 to 2.1)	1.9
Not Wasted	2.4	(2.0 to 2.9)	237	(79.5)	61	(20.5)	[REF]					
Moderate Acute Malnutrition (WHZ ≥ -3)	2.3	(2.2 to 2.5)	8	(89.0)	1	(11.1)	0.5	(0.1 to 4.0)	0.5	0.4	(0.1 to 3.1)	0.4
Severe Acute Malnutrition (WHZ < -3)	3.6	(2.0 to 3.6)	3	(42.9)	4	(57.1)	2.7	(1.0 to 7.7)	0.05	2.4	(0.8 to 7.0)	0.1
Not Stunted	2.4	(2.0 to 2.9)	189	(77.5)	55	(22.5)	[REF]					
Stunted (HAZ < -2)	2.4	(2.0 to 2.8)	59	(84.3)	11	(15.7)	0.7	(0.4 to 1.3)	0.3	0.7	(0.4 to 1.4)	0.4
MUAC												
≥ 12.5 cm	2.4	(2.0 to 2.8)	219	(80.8)	52	(19.2)	[REF]					
< 12.5 cm	2.7	(2.2 to 3.3)	29	(67.4)	14	(32.6)	1.7	(0.9 to 3.1)	0.08	1.0	(0.6 to 1.9)	0.9
Length of Hospitalization (days)												
< 7	2.4	(2.0 to 2.8)	208	(80.0)	52	(20.0)	[REF]					
> 7	2.6	(2.0 to 3.0)	40	(74.1)	14	(25.9)	1.3	(0.7 to 2.3)	0.4	1.0	(0.5 to 1.8)	1.0
HIV Status												
HIV Unexposed	2.4	(2.0 to 2.9)	202	(78.6)	55	(21.4)	[REF]					
HIV Exposed, Uninfected	2.3	(2.0 to 2.8)	31	(81.6)	7	(18.4)	0.9	(0.4 to 1.9)	0.7	1.0	(0.5 to 2.2)	1.0
Not Currently Nursing	2,2	(1.9 to 2.7)	115	(88.5)	15	(11.5)	[REF]					
Currently	2.1	(2.1 to 3.0)	133	(72.3)	51	(27.7)	2.4	(1.4 to 4.3)	0.003	1.0	(0.5 to 2.1)	1.0
Never Breastfed	2.1	(2.0 to 2.1)	4	(80.0)	1	(20.0)	[REF]					
Exclusively Breastfed	2.4	(2.0 to 2.9)	124	(78.0)	35	(22.0)	1.1	(0.2 to 8.0)	1.0	1.0	(0.1 to 7.5)	1.0
Final Diagnosis												
Anemia	2.5	(2.0 to 2.7)	43	(86.0)	7	(14.0)	0.6	(0.3 to 1.4)	0.2	0.9	(0.4 to 2.0)	0.8
Pneumonia	2.5	(2.0 to 2.9)	82	(77.4)	24	(22.6)	1.1	(0.7 to 1.9)	0.7	0.7	(0.4 to 1.2)	0.2
Gastroenteritis/diarrhea	2.3	(2.0 to 3.0)	42	(73.7)	15	(26.3)	1.3	(0.7 to 2.4)	0.3	1.1	(0.6 to 2.0)	0.7
Lower Respiratory Tract Infection	2.5	(2.1 to 3.2)	9	(60.0)	6	(40.0)	2.0	(0.9 to 4.6)	0.1	1.3	(0.6 to 3.1)	0.5
Malaria	2.3	(2.0 to 2.7)	76	(86.4)	12	(13.6)	0.6	(0.3 to 1.1)	0.1	0.9	(0.5 to 1.8)	0.9
Malnutrition	2.3	(2.0 to 3.3)	16	(69.6)	7	(30.4)	1.5	(0.7 to 3.3)	0.3	1.3	(0.6 to 3.0)	0.5
Meningitis	2.7	(2.1 to 3.1)	8	(72.7)	3	(27.3)	1.3	(0.4 to 4.2)	0.7	1.2	(0.4 to 3.7)	0.8
Sepsis	2.6	(2.0 to 3.0)	8	(66.7)	4	(33.3)	1.6	(0.6 to 5.5)	0.3	1.7	(0.6 to 4.5)	0.3
Sickle Cell	2.0	(1.8 to 2.3)	16	(94.1)	1	(5.9)	0.3	(0.0 to 1.9)	0.2	0.4	(0.1 to 3.1)	0.4
Tuberculosis	1.8	(1.8 to 1.8)	1	(100)	0	(0)	0.0	(0.0 to 0.0)	1.0	0.0	(0.0 to 0.0)	1.0

References

1. Nemetchek B, English L, Kissoon N et al. Paediatric post discharge mortality in developing countries: a systematic review. *BMJ Open*. 2018;8. doi:10.1136/bmjopen-2018-023445
2. Institute of Health Metrics and Evaluation (IHME). GBD Compare. https://vizhub.healthdata.org/gbd-compare/. Published 2019.
3. Boutayeb A. The Burden of Communicable and Non-Communicable Diseases in Developing Countries. *Handb Dis Burdens Qual Life Meas*. 2010. doi:10.1007/978-0-387-78665-0_32
4. Wiens MO, Pawluk S, Kissoon N, Kumbakumba E, Ansermino JM, Singer J et al. Pediatric Post-Discharge Mortality in Resource Poor Countries: A Systematic Review. *PLoS One*. 2013;8(6). doi:10.1371/journal.pone.0066698
5. Chisti MJ, Graham SM, Duke T et al. Post-discharge mortality in children with severe malnutrition and pneumonia in Bangladesh. *PLoS One*. 2014;9(9). doi:10.1371/journal.pone.0107663
6. Pavlinac PB, Singa BO, John-Stewart GC et al. Azithromycin to prevent post-discharge morbidity and mortality in Kenyan children: a protocol for a randomised, double-blind, placebo-controlled trial (the Toto Bora trial). *BMJ Open*. 2017;7(12). doi:10.1136/bmjopen-2017-019170
7. Center for Disease Control and Prevention. Cytomegalovirus and CMV Infection. https://www.cdc.gov/cmv/. Published 2019.
8. Lachmann R, Loenenbach A, Waterboer T et al. Cytomegalovirus (CMV) seroprevalence in the adult population of Germany. *PLoS One*. 2018;13(7). doi:10.1371/journal.pone.0200267
9. Manicklal S, Emery VC, Lazzarotto T, Boppana SB GR. The “silent” global burden of congenital cytomegalovirus. *Clin Microbiol Rev*. 2013;26(1):86-102. doi:10.1128/CMR.00062-12
10. Cannon MJ, Schmid DS HT. Review of cytomegalovirus seroprevalence and demographic characteristics associated with infection. *Rev Med Virol*. 2010;20(4):202-2130. doi:10.1002/rmv.655.
11. Alyazidi R, Murthy S, Slyker JA GS. The Potential Harm of Cytomegalovirus Infection in Immunocompetent Critically Ill Children. *Front Pediatr*. 2018;6:96. doi:doi:10.3389/fped.2018.00096
12. Zerr DM , Meier AS SSs al. A population-based study of primary human herpesvirus 6 infection. *N Engl J Med*. 2005;352:768-776.
13. Smith JS RN. Age-specific prevalence of infection with herpes simplex virus types 2 and 1: a global review. *J Infect Dis*. 2002;186(1):3-28.
14. de-The G , Day NE GA al. Sero-epidemiology of the Epstein-Barr virus: preliminary analysis of an international study - a review. *IARC Sci Publ* . 1975;11(2):3-16.
15. Soren Gantt, Jackson Orem, Elizabeth M. Krantz, Rhoda Ashley Morrow, Stacy Selke, Meei-Li Huang, Joshua T. Schiffer, Keith R. Jerome, Annet Nakaganda, Anna Wald, Corey Casper LC. Prospective Characterization of the Risk Factors for Transmission and Symptoms of Primary Human Herpesvirus Infections Among Ugandan Infants. *J Infect Dis*. 2016;214(1):36-44. doi:10.1093/infdis/jiw076

16. Russel MY, Palmer A MM. Cytomegalovirus infection in pediatric immunocompromised hosts. *Infect Disord Drug Targets*. 2011;11(5):437-448.
17. Emery VC. Investigation of CMV disease in immunocompromised patients. *J Clin Pathol*. 2001;54(2):84-88. doi:10.1136/jcp.54.2.84
18. Lachance P, Chen J, Featherstone R SW. Association Between Cytomegalovirus Reactivation and Clinical Outcomes in Immunocompetent Critically Ill Patients: A Systematic Review and Meta-Analysis. *Open Forum Infect Dis*. 2017. doi:10.1093/ofid/ofx029
19. Garcia-Knight, Miguel A.a, b; Nduati, Euniceb; Hassan, Amin S.b, c; Nkumama, Ireneb; Etyang, Timothy J.b, c; Hajj, Naseem J.c; Gambo, Faithb; Odera, Denisb; Berkley, James A.b, c; Rowland-Jones, Sarah L.d,*; Urban B. Cytomegalovirus viraemia is associated with poor growth and T-cell activation with an increased burden in HIV-exposed uninfected infants. *AIDS*. 2017;31(13):1809–1818. doi:10.1097/QAD.0000000000001568
20. Gianella S LS. Cytomegalovirus and HIV: A Dangerous Pas de Deux. *J Infect Dis*. 2016. doi:10.1093/infdis/jiw217
21. Al-Omari A, Aljamaan F, Alhazzani W, Salih S AY. Cytomegalovirus infection in immunocompetent critically ill adults: literature review. *Ann Intensive Care*. 2016;6(1):110. doi:doi:10.1186/s13613-016-0207-8
22. Bates M BA. Human cytomegalovirus (CMV) in Africa: a neglected but important pathogen. *Virus Erad*. 2016;2(3):136-142.
23. Barbosa NG, Yamamoto AY, Duarte G et al. Cytomegalovirus Shedding in Seropositive Pregnant Women From a High-Seroprevalence Population: The Brazilian Cytomegalovirus Hearing and Maternal Secondary Infection Study. *Clin Infect Dis*. 2018;67(5):743-750. doi:doi:10.1093/cid/ciy166
24. Bourne R, Stevens G, White R, Smith J, Flaman S, Price H et al. Causes of vision loss worldwide, 1990-2010: a systematic analysis. *Lancet Glob Heal* . 2013. doi:10.1016/S2214-109X(13)70113-X
25. Osawa R SN. Cytomegalovirus infection in critically ill patients: a systematic review. 2019;13(3). doi:10.1186/cc7875
26. Limaye AP, Stapleton RD, Peng L et al. Effect of Ganciclovir on IL-6 Levels Among Cytomegalovirus-Seropositive Adults With Critical Illness: A Randomized Clinical Tria. *JAMA*. 2017;318(8):731-740. doi:10.1001/jama.2017.10569
27. Gompels UA, Larke N, Sanz-Ramos M et al. Human cytomegalovirus infant infection adversely affects growth and development in maternally HIV-exposed and unexposed infants in Zambia. *Clin Infect Dis*. 2012;54(3):434-442. doi:10.1093/cid/cir837
28. Stadler Laura, Berstein David, Callahan Todd, Ferrieira Jennifer, Simone Gina, Edwards Kathryn, Stanberry Lawrence RS. Seroprevalence and Risk Factors for Cytomegalovirus (CMV) Infection in Adolescent Males. *Clin Infect Dis*. 2010;51(10):76-81. doi:10.1086/656918
29. Wizman, Sarah, Lamarre, Valerie, Coic, Lena, Kakkarm, Fatima, Le Meur, Jean-Baptiste, Rouseau, Celine, Boucher, Marc, Tapiero B. Awareness of cytomegalovirus and risk factors for susceptibility among pregnant women, in Montreal, Canada. *BMC Pregnancy Childbirth*.

2016;16:54. doi:10.1186/s12884-016-0844-9
30. Ibrahim, Saira, Siddiqui, Anwar, Siddiqui, Amna, Ahmed, Qaquaruddin, Moss Pal, Lalani E-N. Sociodemographic factors associated with IgG and IgM seroprevalence for human cytomegalovirus infection in adult populations of Pakistan: a seroprevalence survey. *BMC Public Health*. 2016;16:112. doi:10.1186/s12889-016-3772-8
31. De Vita, Maria, Scolfaro, Carlo, Santini, Bruna, Lezo, Antonella, Gobbi, Federico, Buonfrate, Dora, Kimani-Murage, Elizabeth, Macharia, Teresiah, Wanjohi, Milka, Rovarini, Jacopo, Morino G. Malnutrition, morbidity and infection in the informal settlements of Nairobi, Kenya: an epidemiological study. *Ital J Pediatr*. 2019;45:12. doi:10.1186/s13052-019-0607-0
32. Ndemwa Morris, Wanyua Sheru, Kaneko Satoshi, Karama Mohammed AM. Nutritional status and association of demographic characteristics with malnutrition among children less than 24 months in Kwale County, Kenya. *Pan Afr Med J*. 2017;28:265. doi:10.11604/pamj.2017.28.265.12703
33. Gewa, Constance, Yandell N. Undernutrition among Kenyan children: contribution of child, maternal and household factors. *Public Health Nutr*. 2012;15(6):1029-1038. doi:https://doi.org/10.1017/S136898001100245X
34. Rytter, Maren, Kolte, Lilian, Briend, Andre, Friis, Henrik, Christensen V. The Immune System in Children with Malnutrition—A Systematic Review. *PLoS One*. 2014;9(8). doi:10.1371/journal.pone.0105017
35. Schaible, Ulrich, Kaufmann S. Malnutrition and Infection: Complex Mechanisms and Global Impacts. *PLoS Med*. 2007;4(5):115. doi:10.1371/journal.pmed.0040115
36. Garcia-Knight M, Nduati E, Hassan A, Nkumama I, Etyang T, Hajj N, Gambo F, Odero D, Berkley J, Rowland-Jones S UB. Cytomegalovirus viraemia is associated with poor growth and T-cell activation with an increased burden in HIV-exposed uninfected infants. *AIDS*. 2017;31(13):1809-1818. doi:10.1097/QAD.0000000000001568
37. van der Sande, Marianne, Kaye, Steve, Miles, David, Waight, Pauline, Jeffries, David, Ojuola, Olubukola, Palmero, Melba, Pinder, Margaret, Ismaili, Jamila, Flanagan, Katie, Aveika, Zaman, Akram, Rowland-Jones, Sarah, McConkey, Samuel, Whittle, Hilton, Mar A. Risk Factors for and Clinical Outcome of Congenital Cytomegalovirus Infection in a Peri-Urban West-African Birth Cohort. *PLoS One*. 2007;2(6):492. doi:10.1371/journal.pone.0000492
38. Slyker Jennifer, Lohman-Payne Barbara, Rowland-Jones Sarah, Oteino Phelgona, Maleche-Obimbo Elizabeth, Richardson Barbra, Farquhar Carey, Mbori-Ngacha Dorothy, Emery Vincent J-SG. The detection of cytomegalovirus DNA in maternal plasma is associated with mortality in HIV-1 infected women and their infants. *AIDS*. 2010;23(1):117-124. doi:10.1097/QAD.0b013e32831c8abd
39. Slyker JA, Lohman-Payne BL, Rowland-Jones SL et al. The detection of cytomegalovirus. *AIDS*. 2009;23(1):117-124. doi:10.1097/QAD.0b013e32831c8abd
40. Richardson Barbra, John-Stewart Grace, Atkinson Claire, Nduati Ruth, Asbjornsdottir Kristjiana, Boeckh Michael, Overbaugh Julie, Emery Vincent SJ. Vertical Cytomegalovirus Transmission From HIV-Infected Women Randomized to Formula-Feed or Breastfeed Their Infants. *J Infect*

Dis. 2016;213(6):992-998. doi:10.1093/infdis/jiv515

41. Kraft Colleen, Armstrong Wendy CA. Interpreting Quantitative Cytomegalovirus DNA Testing: Understanding the Laboratory Perspective. *Clin Infect Dis*. 2012;54(12):1793-1797. doi:10.1093/cid/cis212
42. Kfutwah AK, Ngoupo PA, Sofeu CL et al. Cytomegalovirus infection in HIV-infected versus non-infected infants and HIV disease progression in Cytomegalovirus infected versus non infected infants early treated with cART in the ANRS 12140-Pediacam study in Cameroon. *BMC Infect Dis*. 2017;17(1):224. doi:10.1186/s12879-017-2308-x
43. Varani, Stefania, Landini MP. Cytomegalovirus-induced immunopathology and its clinical consequences. *Herpesciridae*. 2011;2:6. doi:10.1186/2042-4280-2-6
44. Stowell JD, Forlin-Passoni D, Radford K et al. Cytomegalovirus survival and transferability and the effectiveness of common hand-washing agents against cytomegalovirus on live human hands. *Appl Env Microbiol*. 2014;80(2):455-461. doi:10.1128/AEM.03262-13
45. Kumar, Mary, Nankervis, George, Jacobs, Irwin, Ernhart, Claire, Glasson, Chloe, McMillan, Pamella, Gold E. Congenital and postnatally acquired cytomegalovirus infections: Long-term follow-up. *J Pediatr*. 1984;104(5):674-679. doi:10.1016/S0022-3476(84)80942-7
46. Spector, Stephen, Hsia, Karen, Crager, Michael, Pilcher, Marshall, Cabral, Sheila, Stempien M. Cytomegalovirus (CMV) DNA Load Is an Independent Predictor of CMV Disease and Survival in Advanced AIDS. *J Virol*. 1999:7027-7030. https://jvi.asm.org/content/jvi/73/8/7027.full.pdf.
47. Ross SA, Novak Z, Pati S BS. Overview of the diagnosis of cytomegalovirus infection. *nfect Disord Drug Targets*. 2011;11(5):466-474.
48. Tom Achoki, Molly K Miller-Petrie, Scott D Glenn, Nikhila Kalra, Abaleng Lesego, Gladwell K Gathecha, Uzma Alam HWK, Isabella Wanjiku Maina, Ifedayo M O Adetifa, Hellen C Barsosio, Tizta Tilahun Degfie, Peter Njenga Keiyoro, Daniel N Kiirithio YK, Damaris K Kinyoki, James M Kisia, Varsha Sarah Krish, Abraham K Lagat, Meghan D Mooney WNM, Charles Richard James Newton, Josephine W Ngunjiri, Molly R Nixon, David O Soti, Steven Van De Vijver, Gerald Yonga SIH, Christopher J L Murray MN. Health disparities across the counties of Kenya and implications for policy makers, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Glob Heal*. 2018. doi:10.1016/ S2214-109X(18)30472-8
49. Bourke, Claire, Berkeley, James, Prendergast A. Immune Dysfunction as a Cause and Consequence of Malnutrition. *Trends Immunol*. 2016;37(6):386-398. doi:10.1016/j.it.2016.04.003