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INTRAFAMILIAL CMV TRANSMISSION IN THE FIRST TWO YEARS POSTPARTUM

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BACKGROUND

- A CMV vaccine is not yet available but an improved understanding of how CMV infection, and re-infection, occurs can help inform strategies to develop a successful vaccine
- The natural history of CMV infection is complex, with high levels of sustained viral shedding following infection of children (→ major source of transmission to adults)
  - Many individuals within a household can be shedding virus from various bodily fluids
- CMV is highly genetically diverse, even within an individual, which can help us discriminate the source of a virus and which allows for reinfection to occur within an individual
- Determining the characteristics of transmitted/founder CMV genotypes and the viral load required for transmission will provide insight into how to narrow the virologic bottleneck that CMV faces, and make transmission even more inefficient to a point of unsustainability

OBJECTIVE

To precisely define intrafamilial CMV transmission in order to characterize determinants of transmission including likely route, viral load, and genotypic factors in a high seroprevalence setting.

METHODS

- Prospective cohort of women in Nairobi, Kenya (50% living with HIV) and their children
- Recruitment in the third trimester of pregnancy with follow up to 2 years postpartum (clinic and home visits)
- Study enrolment began in Dec 2018 with the last follow up visit completed in May 2022
- Samples are collected from the enrolled woman, her infant from the pregnancy at enrollment, and other children aged <5 in the home

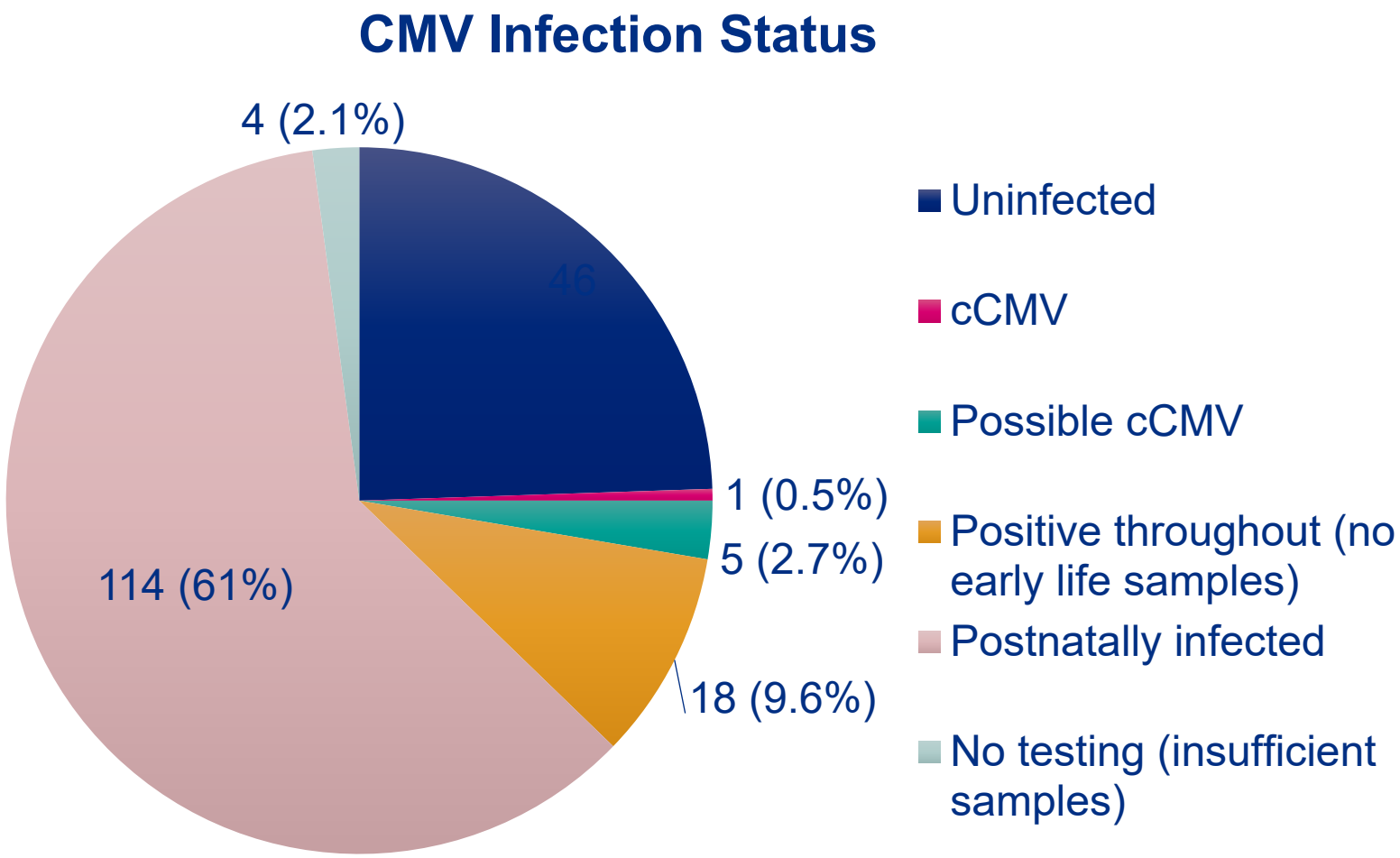
	Quantity or Volume per Sample	Enrollment	Delivery	Day 4	Year 1 Clinic Visits: Weeks 6, 10 & Months 6-12	Year 1 Home Visits: Weekly for first year	Years 2-4 Clinic Visits: Months 12-48
Maternal Samples							
Vaginal swab	2 swabs	X					
Breast swab	2 swabs				X (Week 6 only)		
Breast milk	5-10 mL from each breast			X	X	X	X
Blood	7-14 mL	X	X		X		X
Stool	N/A	X		X	X		X
Saliva	2 swabs	X		X	X	X	X
Nasal swab	2 swabs	X		X	X	X	X
Infant Samples							
Blood[1]	0.5-3 mL		Cord blood		X		X
Stool	N/A			X	X		X
Saliva	2 swabs			X	X	X	X
Urine	≥5 mL			X		X	
Nasal swab	2 swabs			X	X	X	X
Sibling Samples							
DBS[1]				X		X (at 48 weeks only)	
Saliva	2 swabs			X		X	
Urine	≥5 mL			X		X	

METHODS

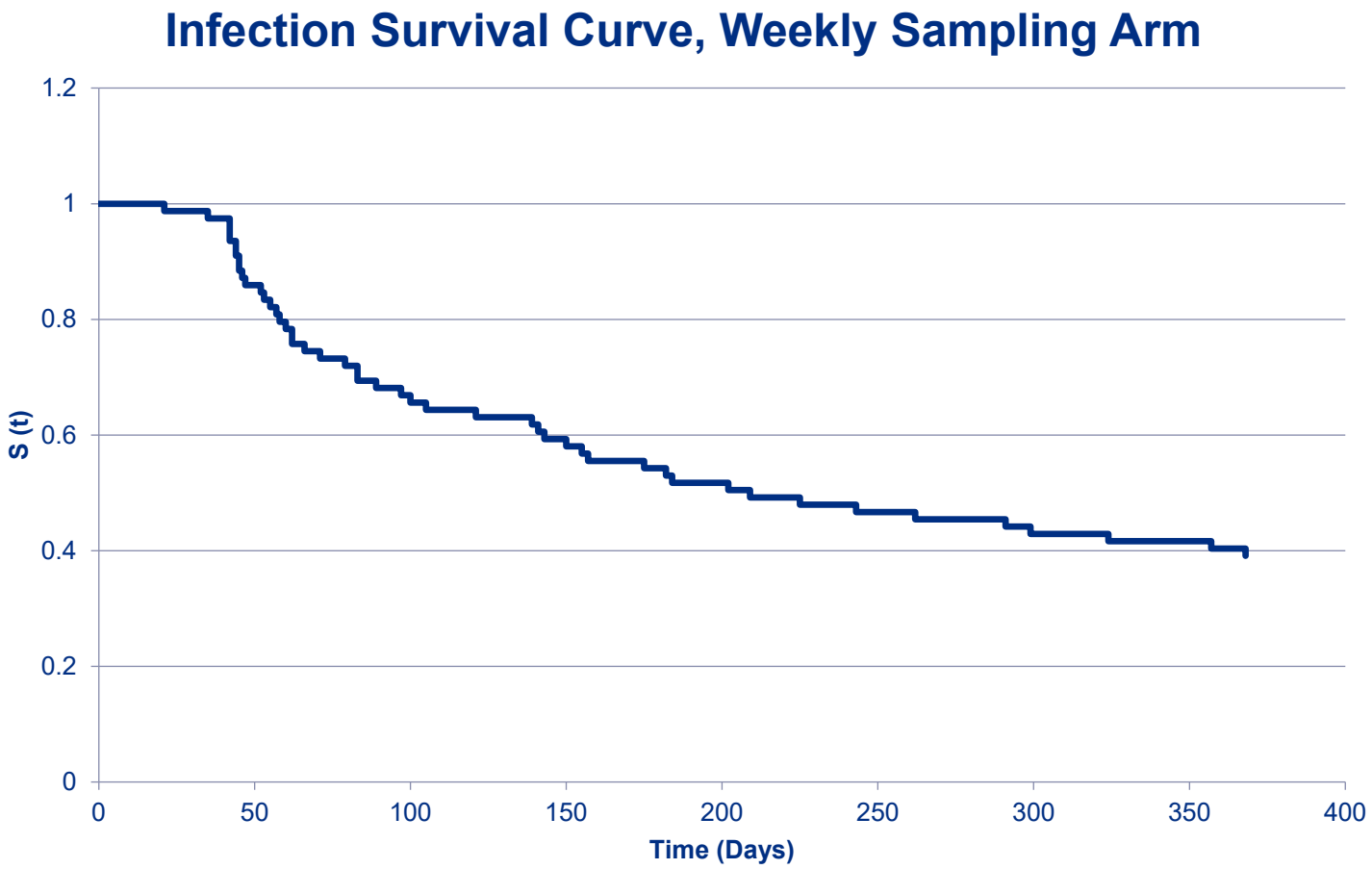
- Congenital CMV infection was identified by qPCR on infant day 4 urine samples
- Postnatal CMV infection was identified by qPCR on infant urine samples, narrowing down to find timing of infection
- Contact samples (maternal saliva & breast milk and sibling saliva & urine) were tested by CMV qPCR in the weeks preceding infection to identify exposures
  - Completed for infection cases and uninfected controls
- PCR of all remaining weekly samples from infants, mothers, and siblings is underway

RESULTS

188 infants

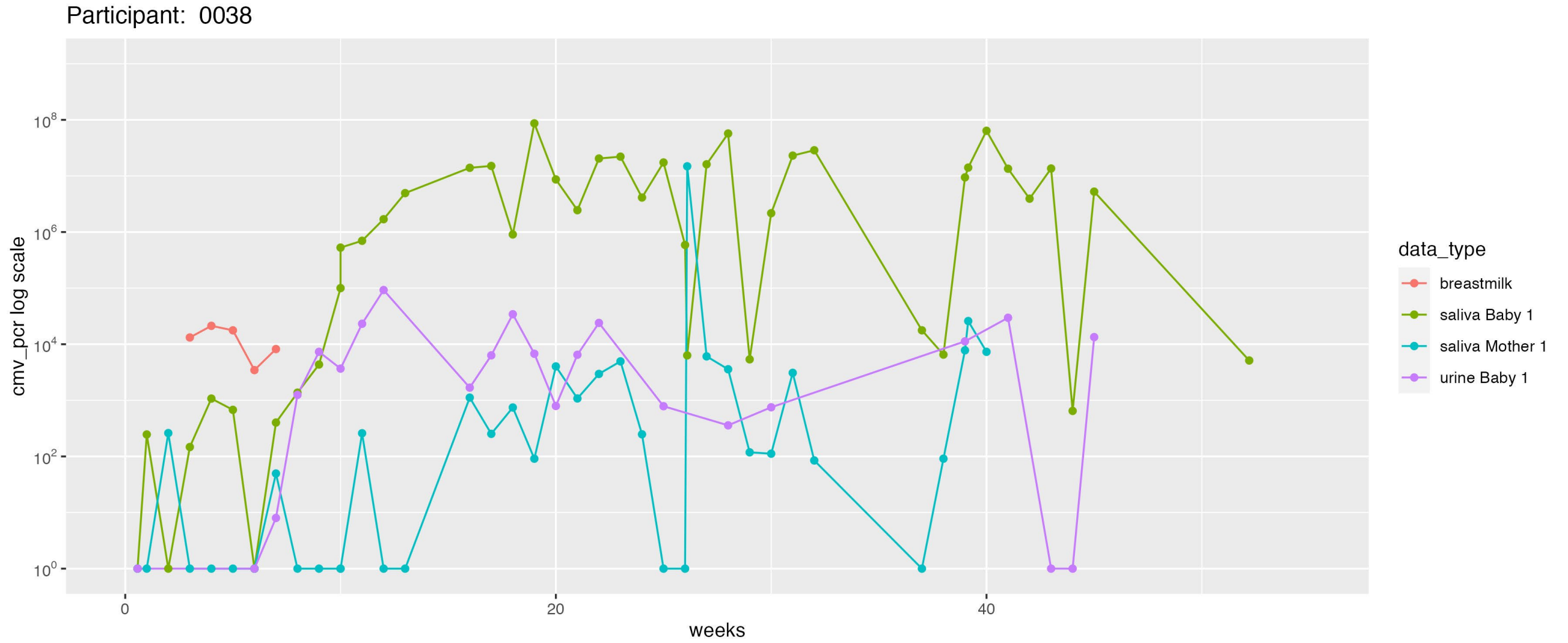


RESULTS: INFECTION DYNAMICS



Time frame	Cumulative incidence (including cCMV)
Week 10	29.17%
Month 6	52.78%
Year 1	66.67%

RESULTS: INFECTION DYNAMICS



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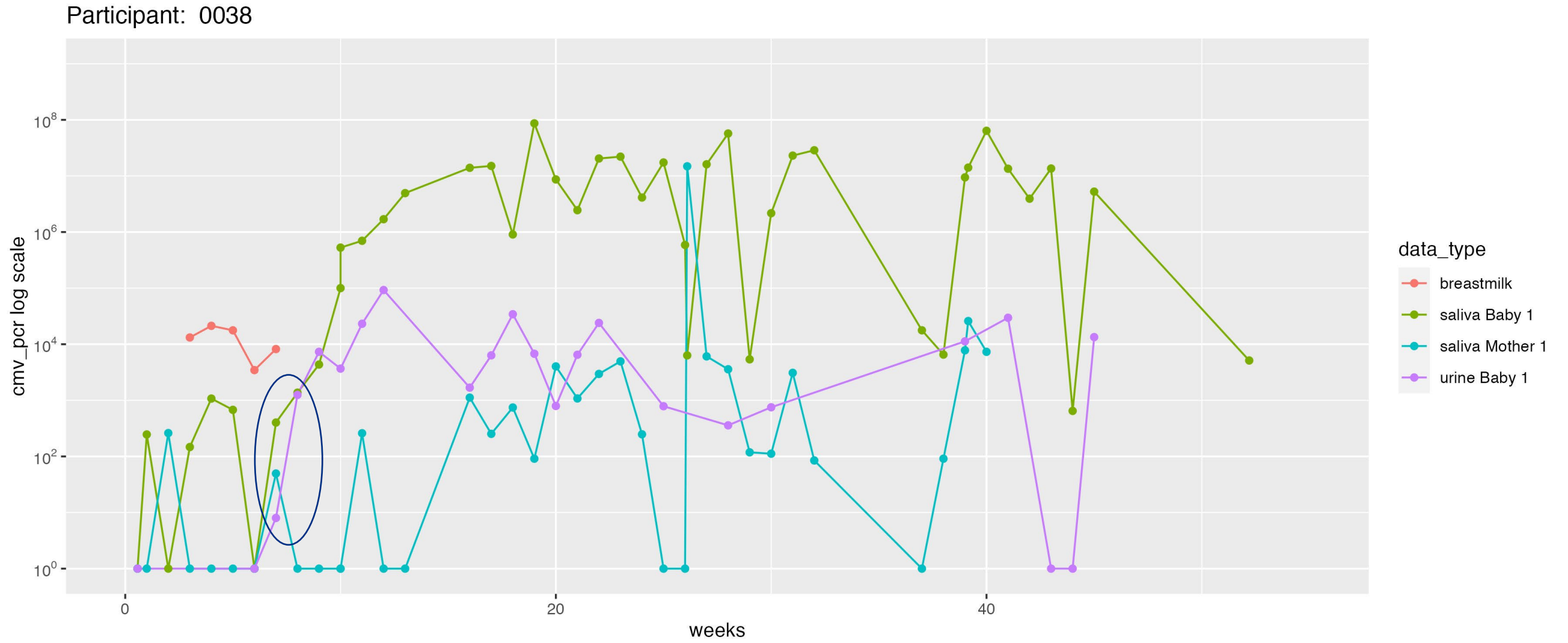

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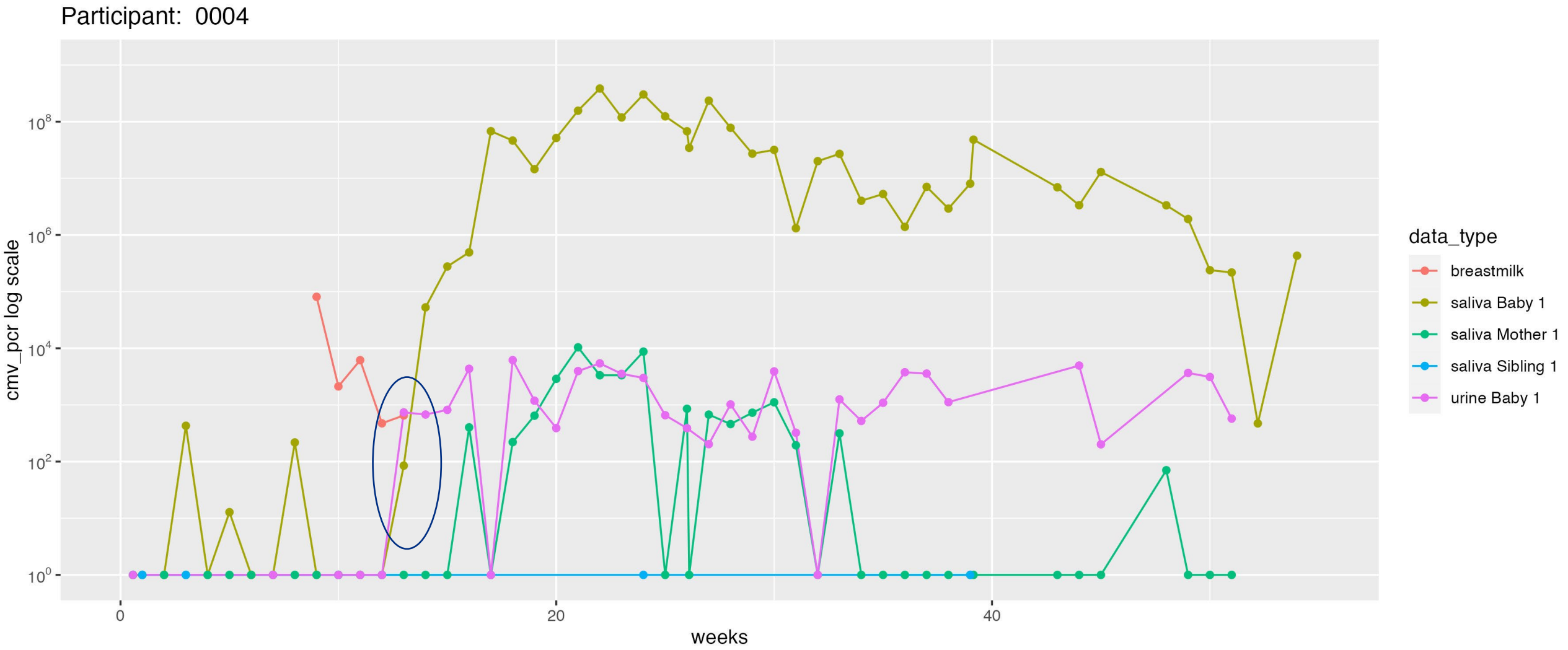

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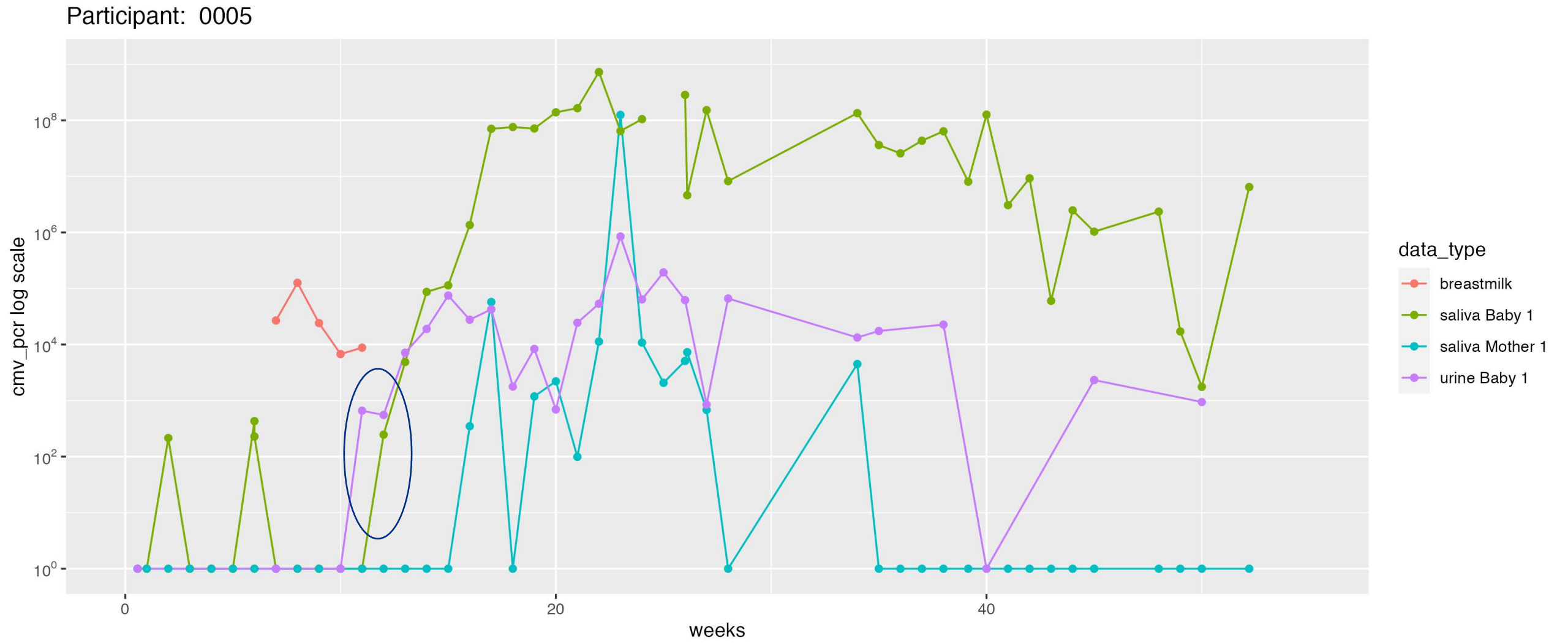
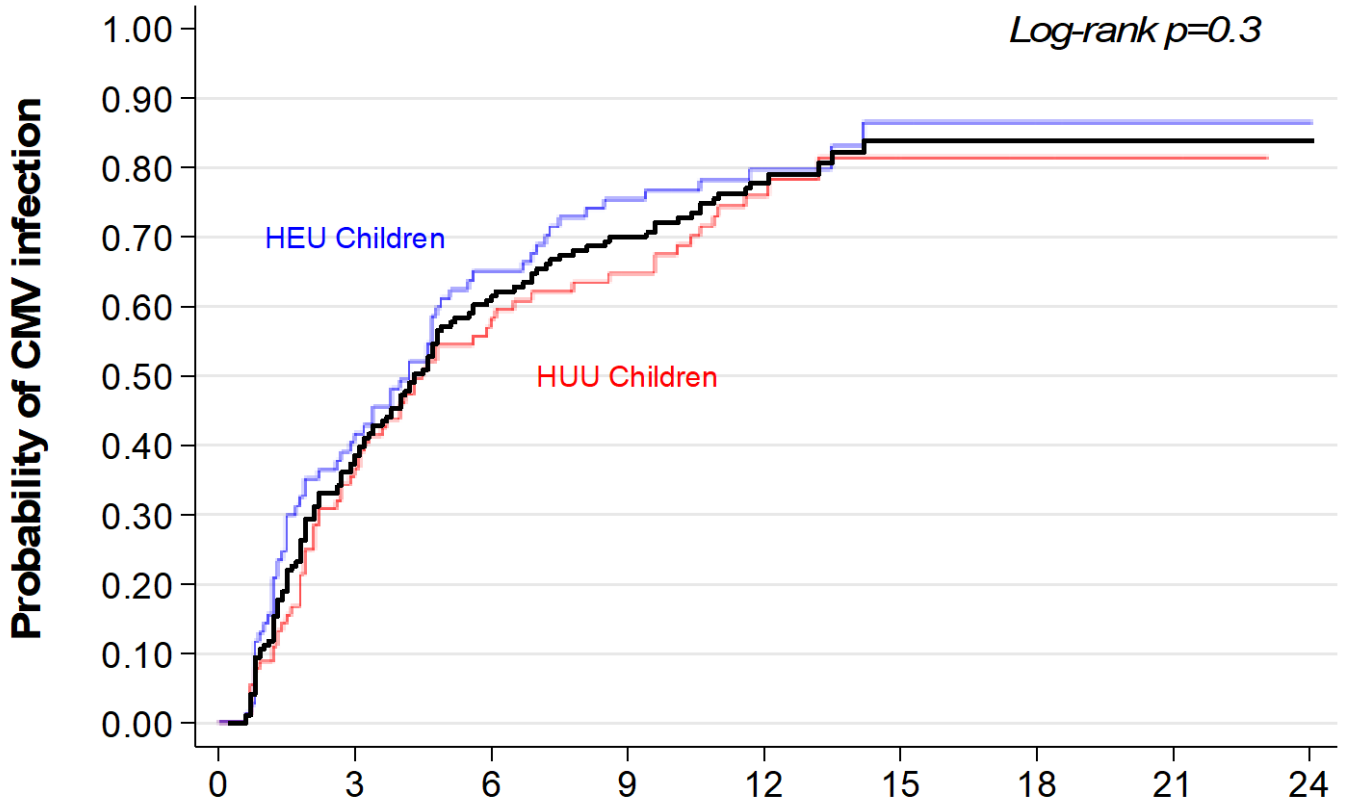


RESULTS

	N	Infant primary infection, N=49	No infant primary infection, N=23	P value
HIV-exposed, N (%)	29	20 (41%)	9 (39%)	0.89
Maternal saliva CMV VL, median (IQR)	71	242.5 (131-404.3)	295 (88.4-12,406.8)	0.10
Maternal breast milk CMV VL, median (IQR)	71	32,900 (7742.4-95,900)	7270 (817.3-27,325)	**<0.001**
Sibling saliva CMV VL, median (IQR)	22	20,000 (1606.1-98,675)	1040 (450.5-2650)	**0.001**
Sibling urine CMV VL, median (IQR)	22	3990 (385.5-25,500)	-	-

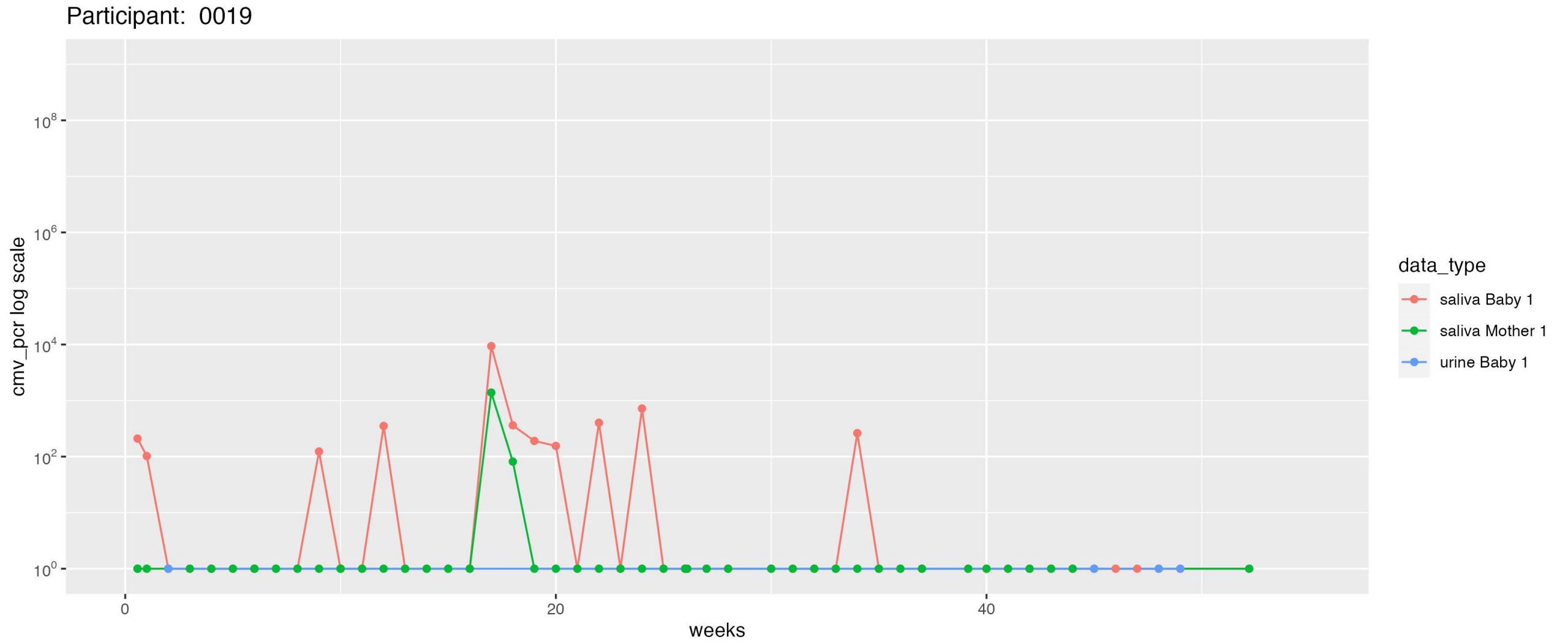
All CMV VLs are pre and peri-transmission values for positive samples only

RESULTS



Number at risk									
HUU children	92	55	34	26	14	5	3	2	0
HEU children	79	46	27	19	11	4	3	1	1

RESULTS: TRANSIENT DETECTION IN UNINFECTED INFANTS



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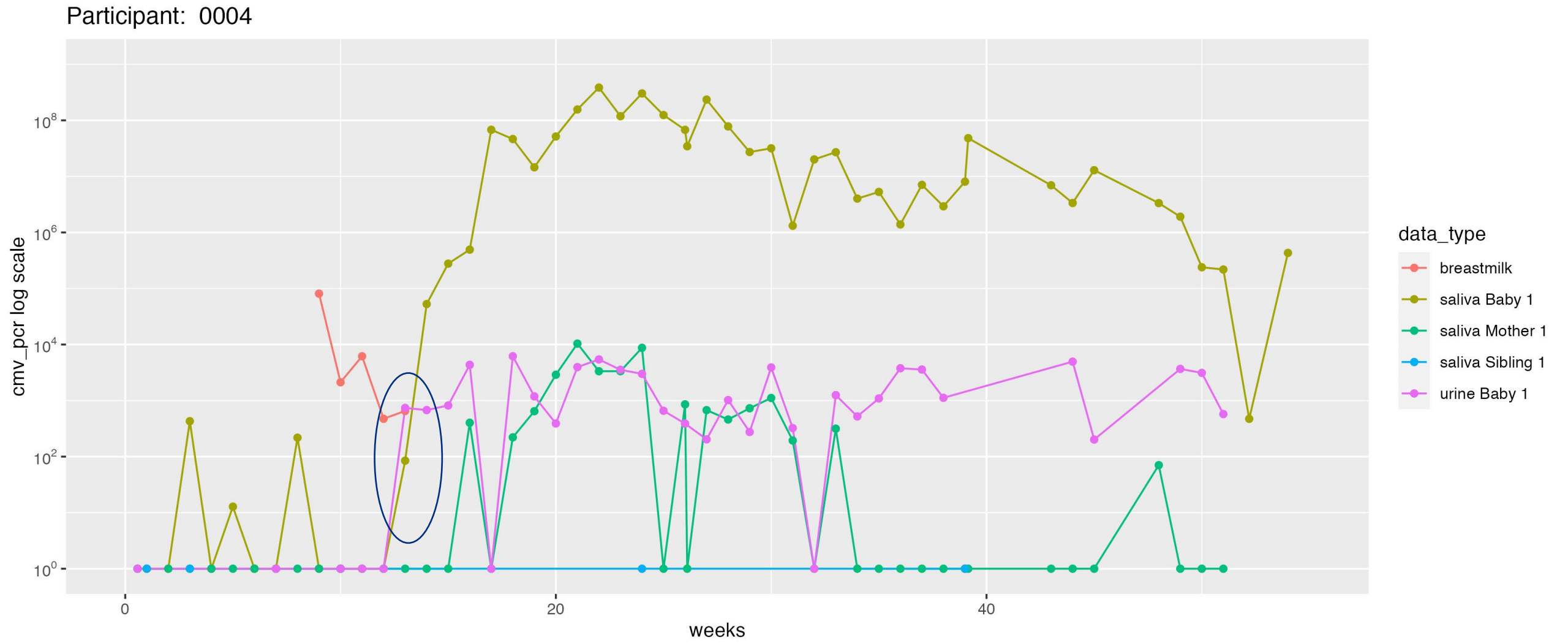


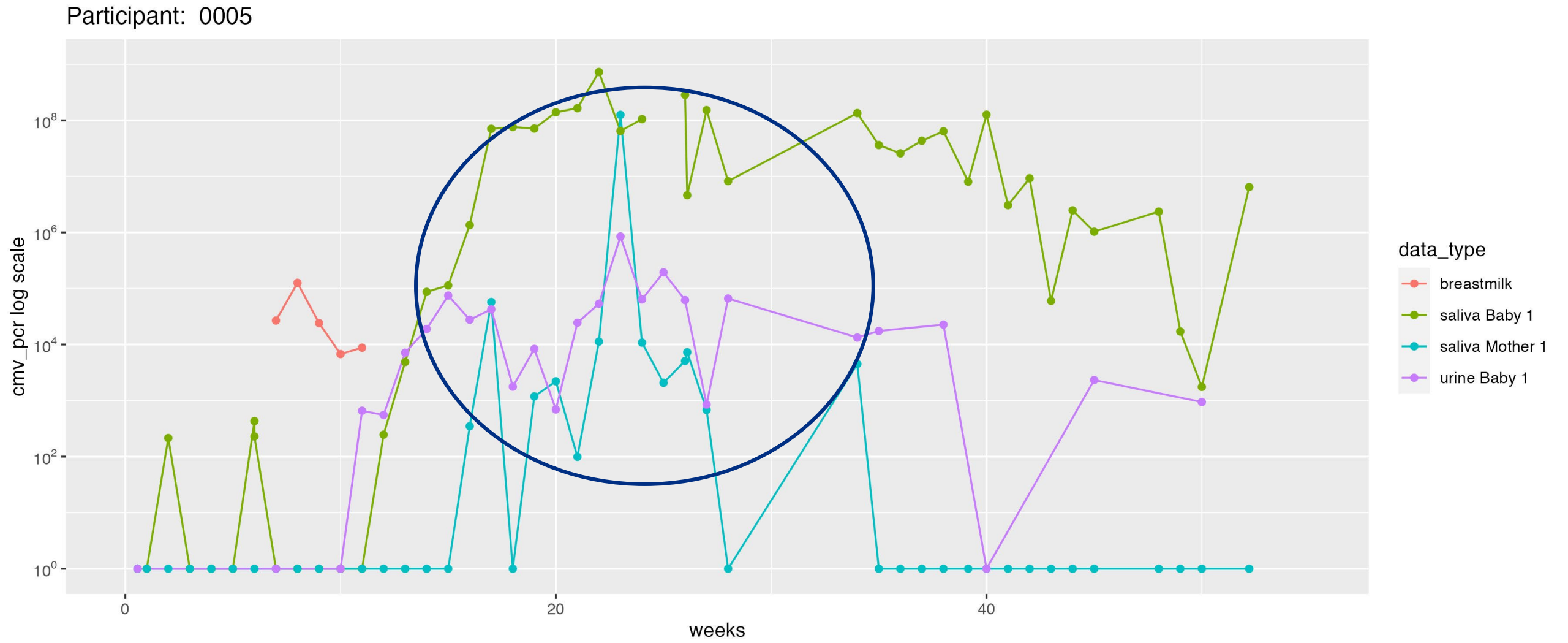
RESULTS: TRANSIENT DETECTION IN UNINFECTED INFANTS

- This has been previously described by Mayer et al., J Virol, 2017
  - Described as transient infection with unsuccessful establishment of latent infection
  - Consistent with the inefficiency of natural transmission of CMV
- Other studies have ruled out breast milk contamination based on transient saliva viral loads being higher than those in contemporaneously sampled milk
  - Additional breast milk data to come from this study
- We will also be assessing for seroconversion to ensure the transient nature of infection

RESULTS: MATERNAL NONPRIMARY INFECTION

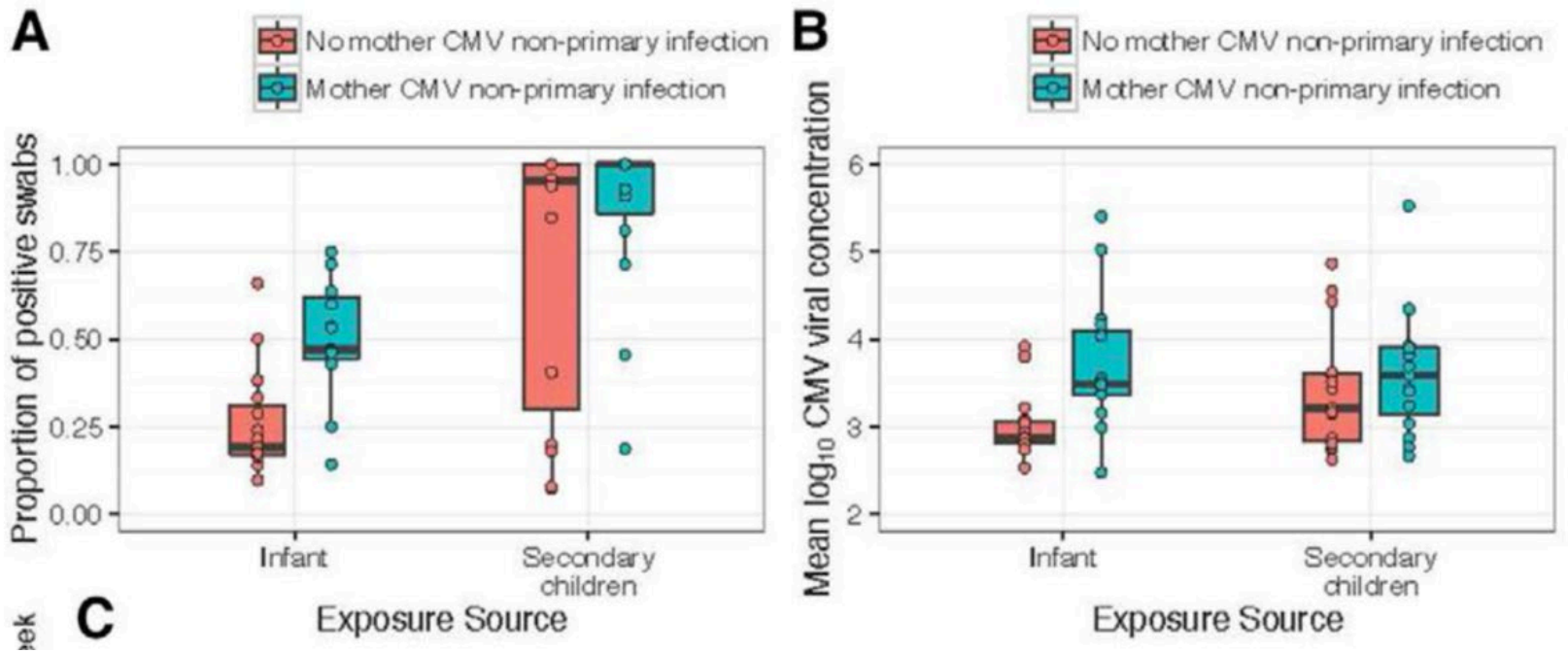
- Maternal non-primary infection = detection of ≥3 log copies/mL of CMV DNA in ≥2 consecutive weekly oral swabs
- Maternal oral swab sequencing not yet complete but we have already detected 21 non-primary infections during follow up

RESULTS: MATERNAL NONPRIMARY INFECTION



RESULTS: MATERNAL NONPRIMARY INFECTION

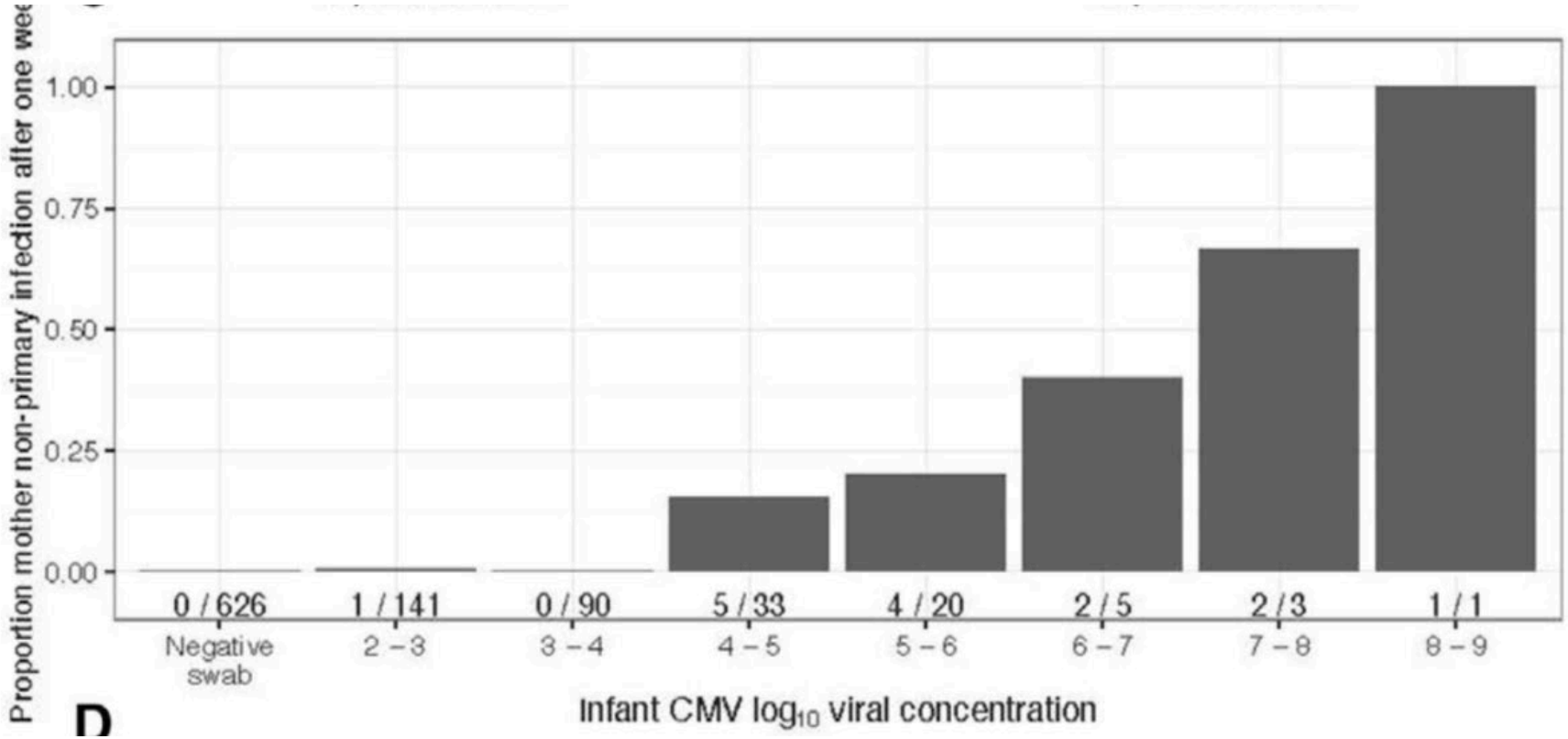
Median infant oral viral load in the preceding week was 11.9 million IU/mL (IQR: 5.9 million – 75.9 million)



Boucoiran et al. PIDJ 2018.

RESULTS: MATERNAL NONPRIMARY INFECTION

Higher infant saliva VL = higher proportion of moms reinfected



Boucoiran et al. PIDJ 2018.

RESULTS: MATERNAL NONPRIMARY INFECTION

TABLE 2. Risk Factors for Maternal CMV Nonprimary Infection: Results From Multivariate Analyses

Predictors	Hazard Ratio (95% CI)	
	Full Model	Final Model
Infant viral shedding the previous week (per $\log_{10}$ CMV DNA copies/swab)	2.42 (1.63–3.61)*	2.32 (1.63–3.31)*
Secondary child viral shedding the previous week (per $\log_{10}$ CMV DNA copies/swab)	1.11 (0.78–1.58)	—
Oral contact reported in the previous week	1.3 (0.14–12.45)	—
Maternal HIV infection	0.84 (0.26–2.69)	—

*Statistically significant ($P < 0.0001$).

CI indicates confidence interval.

Boucoiran et al. PIDJ 2018.

CONCLUSIONS TO DATE

Only 25% of infants remained CMV-uninfected by up to 2 years of life

Many postnatal CMV infections occurring between 40-100 days of life

Breast milk appears to be a common and high VL exposure source, as well as sibling saliva if a sibling is present

Only one (1/17) control family had no CMV exposure from contacts

We see early evidence of transient infection within infants that warrants further exploration

Maternal nonprimary infection is common and will also be further explored

NEXT STEPS

CMV qPCR of all remaining maternal, infant, and sibling samples

Serology to confirm seronegative status at study end of infants with transient detection

Examining likely transmission sources based on exposure viral loads and viral load thresholds of transmission

Identifying maternal re-infections and risk factors for these

Identifying sources of infections by NGS on contact exposures to compare CMV genotypes

Comparison of transmitted vs. non-transmitted strains in exposures

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Participants in the Linda Kizazi Study

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