Sexual practices and oral and genital herpes simplex virus shedding patterns among a cohort with laboratory documented first episode genital HSV-1

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Aicuris (consulting)

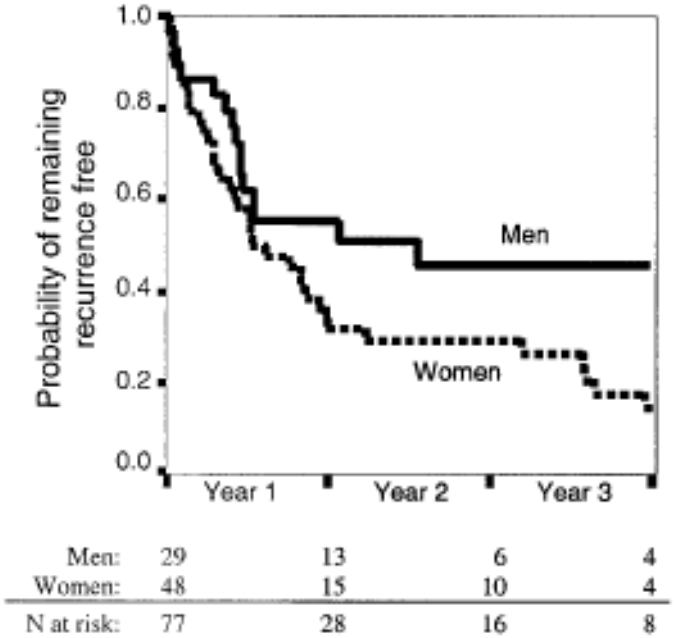
Genital HSV-1: a new epidemic

- Most common cause of first episode genital herpes in women and MSM<25 years old in high resource countries
  - 78% of cases in university setting in the USA
  - 76% of cases of symptomatic genital HSV in Herpevac vaccine trial
- Leading cause of neonatal herpes, may be more likely to be transmitted to neonate, if shedding present
- Epidemiologic change likely due to decreasing HSV-1 acquisition during childhood
  - First exposure to HSV-1 is at initiation of sexual activity
  - Possible changes in sexual behavior, increasing oral sex
- New estimates of burden of global burden of HSV-1 ages 0-49
  - 3709 million (67%)
  - 140 million genital HSV-1

Ryder et al , STI 2009
Xu et al, JAMA 2006
Kropp et al, Peds 2006
Belshe et al, NEJM 2012
Bernstein et al, JID 2013
Looker et al, PLOS One 2015

Genital HSV-1: Clinical aspects

- Primary infection can be severe and involve both genital and oral lesions
- Recurrences are less frequent than with HSV-2
- Less shedding than with HSV-2
  - HOWEVER, most available data only measured with culture rather than more sensitive PCR



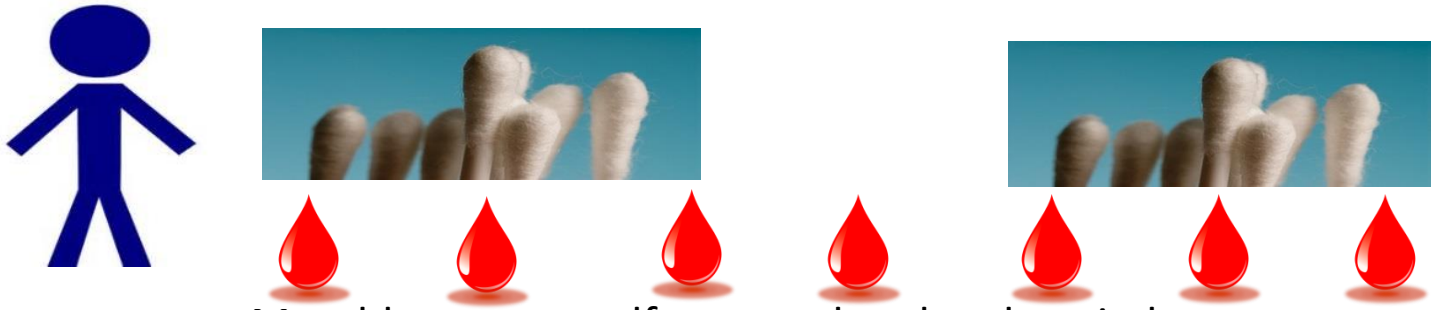
Time to first recurrence after healing of primary genital HSV-1, by gender

Engelberg et al, STD 2003
Reeves et al, NEJM 1991
Benedetti et al, Ann Int Med 1999
Kim et al, JID 2006

Genital HSV-1: Research Questions

- Transmission
  - Frequency of shedding from the genital tract
    - How does shedding rate change over the first year?
    - Significant decline may suggest rapid immunologic control
  - Are people who acquire HSV-1 genitally also at risk for oral acquisition?
- Risk factors for genital HSV-1 acquisition
  - Oral vs. genital exposure?

First episode genital HSV-1 study design: completed data on 59 persons with 2 shedding sessions



Daily oral and genital swabs for HSV PCR

Blood for serologic and immune assays

Monthly survey: self-reported oral and genital recurrences

Time 0 | 2-3 month "Session 1" | 6 months | 11-12 months "Session 2"

Entry criteria for first episode genital herpes:

*no prior history of genital herpes
*culture or PCR swab from genital tract lesion positive for HSV-1
*Both HSV-1 seronegative (primary) and seropositive (nonprimary)
*HIV-1 seronegative

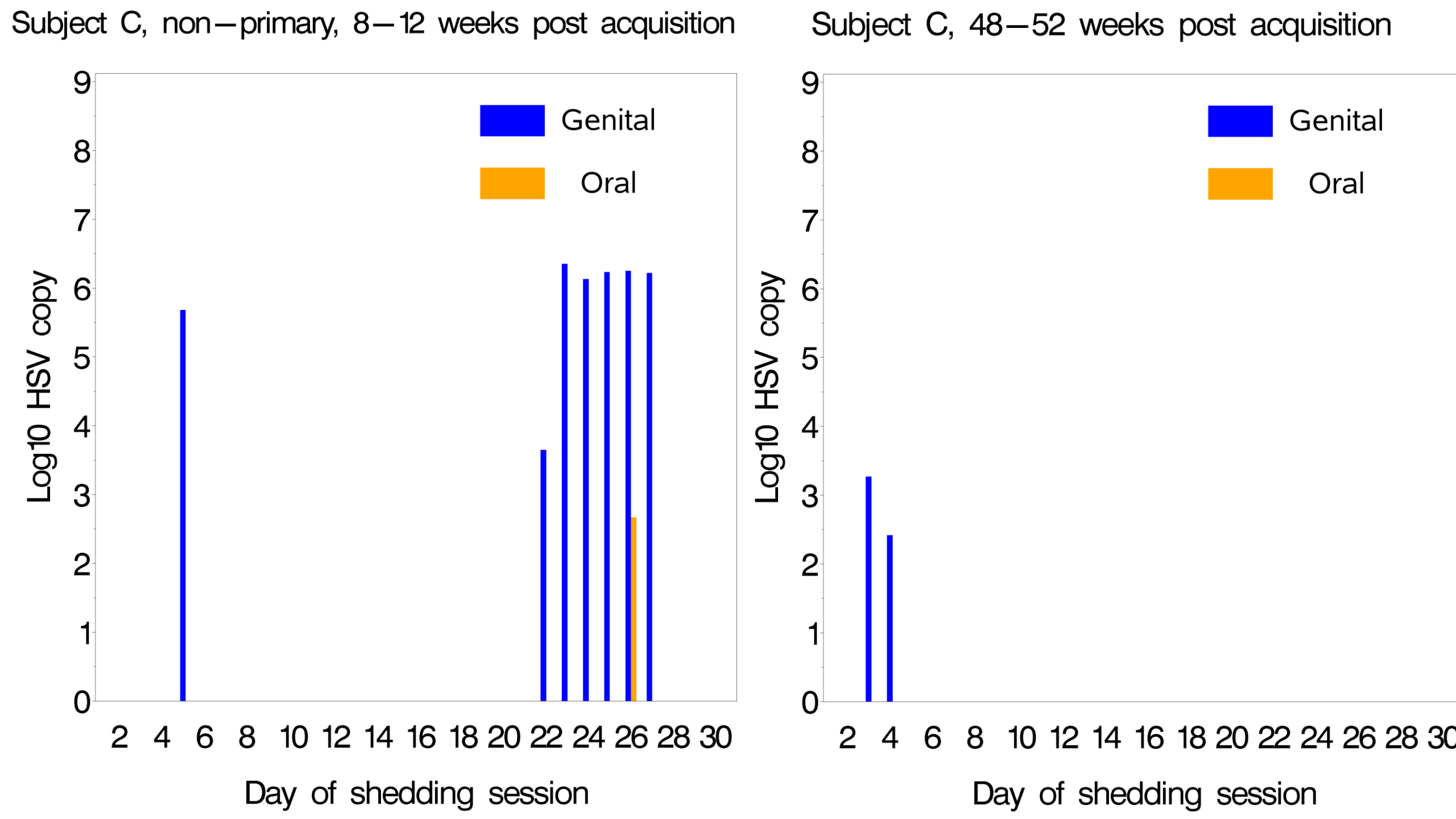
Baseline Demographic and Romance Data

	N=59
Age (Median, range)	26 (16-64)
Women	42 (69%)
White race	49 (83%)
Laboratory documented primary genital HSV-1 infection	36 (61%)
Number partners in past 4 weeks	
0	8 (14%)
1	41 (69%)
Partnership*	
Male-Female	40 (78%)
Male-Male	6 (12%)
Other	5 (10%)
Length of sexual partnership, (Median, range)	150 days (7 days – 3 years)

*8 persons who did not report any sexual partners

Relationship and behaviors (n=59)

	N=59
Talked about oral herpes with partner	48%
Partner said she/he had oral herpes	13%
Received oral sex	83%
Given oral sex	90%
Never used a barrier method for oral sex	93%


Subject C, non−primary, 8−12 weeks post acquisition
Subject C, 48−52 weeks post acquisition
Genital
Oral
Log10 HSV copy
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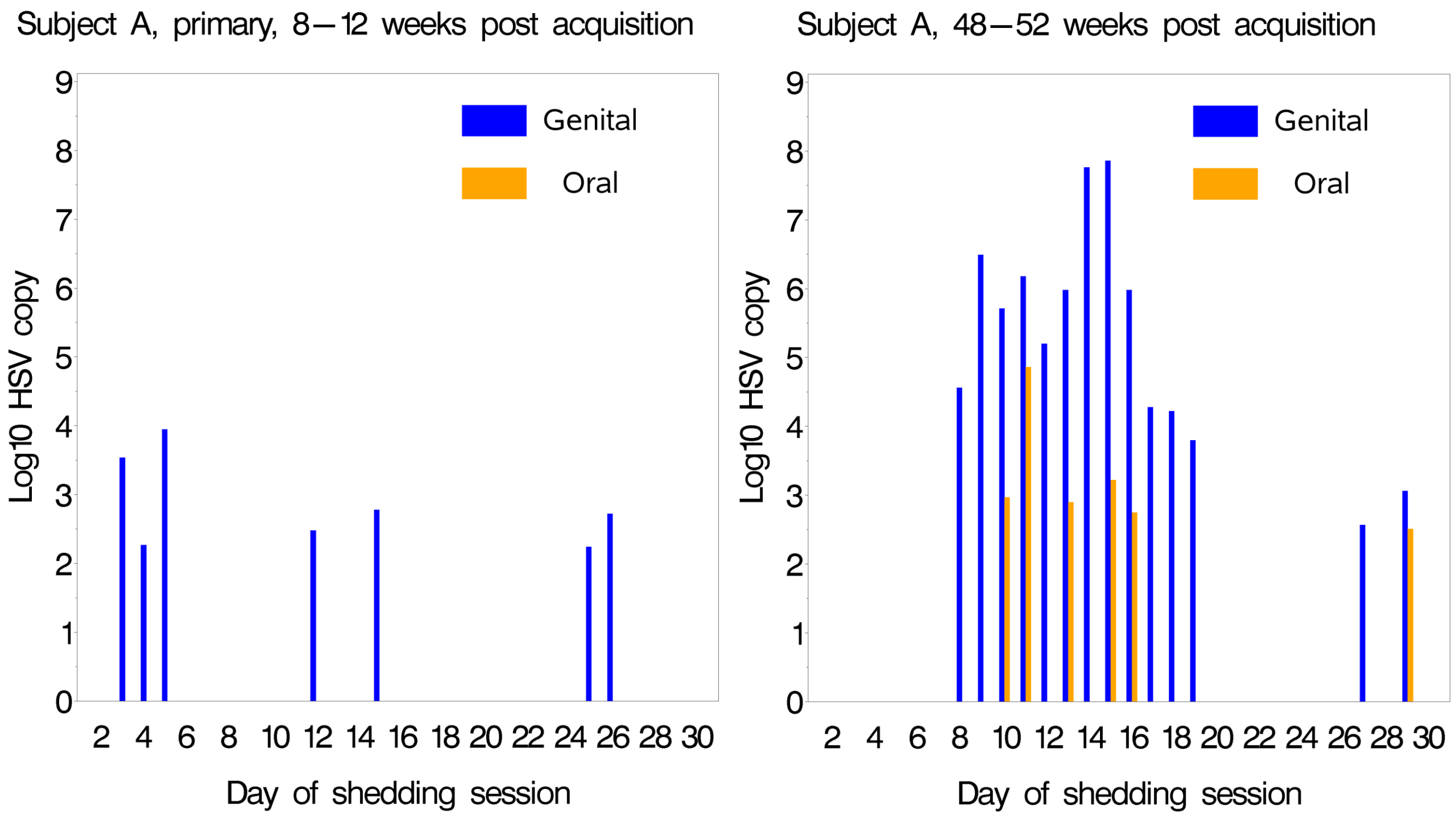
2 4 6 8 10 12 14 16 18 20 22 24 26 28 30
Day of shedding session


Subject A, primary, 8–12 weeks post acquisition
Subject A, 48–52 weeks post acquisition
Genital
Oral
Log10 HSV copy
Day of shedding session
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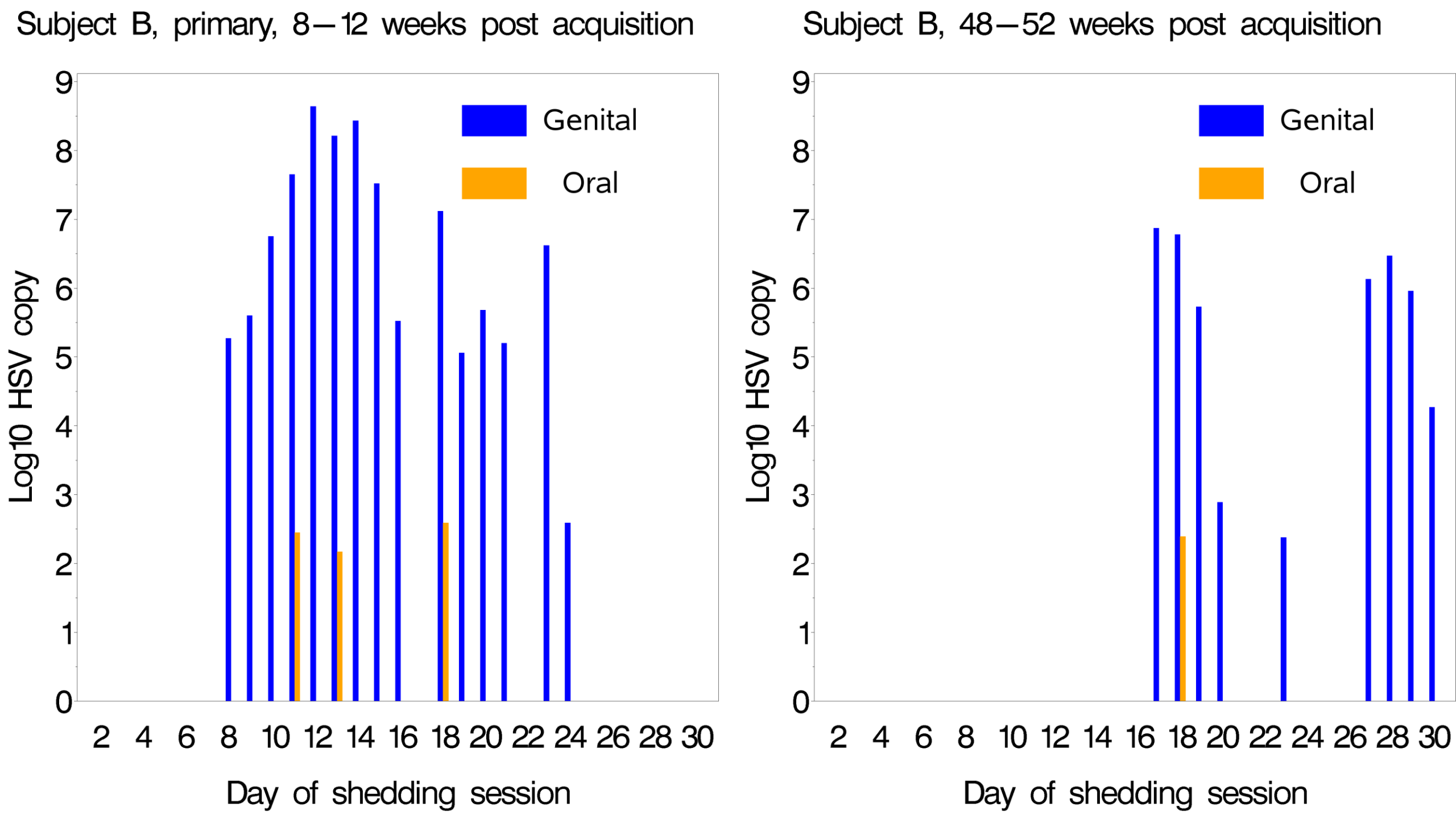
Subject B, primary, 8–12 weeks post acquisition
Subject B, 48–52 weeks post acquisition
Genital
Oral
Log10 HSV copy
Day of shedding session
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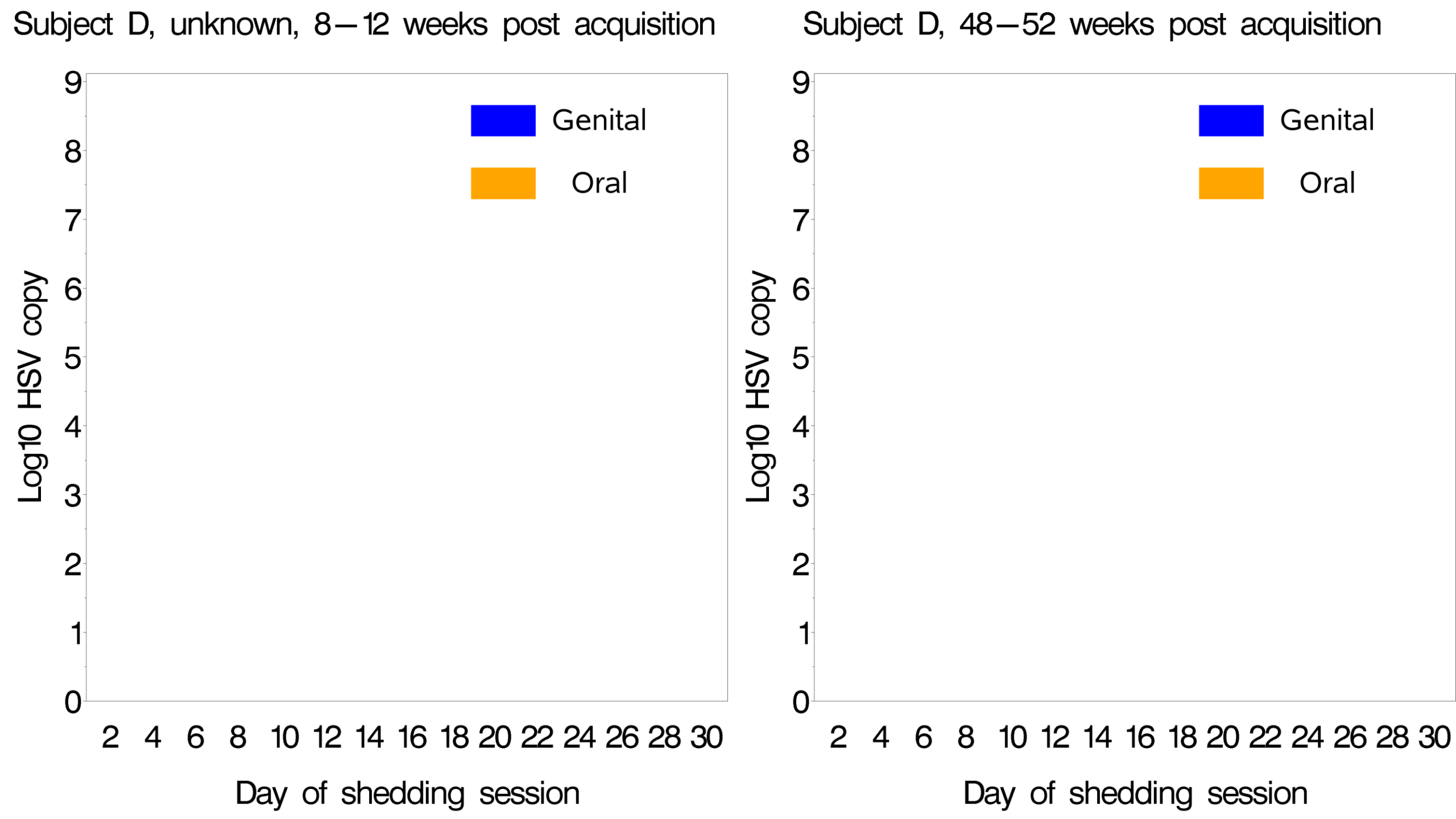
Subject D, unknown, 8—12 weeks post acquisition
Genital
Oral
Log10 HSV copy
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2 4 6 8 10 12 14 16 18 20 22 24 26 28 30
Day of shedding session
Subject D, 48—52 weeks post acquisition
Genital
Oral
Log10 HSV copy
0
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2 4 6 8 10 12 14 16 18 20 22 24 26 28 30
Day of shedding session

Rates of genital and oral shedding & lesions

	Session 1 2-3 months	Session 2 11-12 months
GENITAL		
Participants with genital shedding	36 (61%)	17 (29%)
Genital shedding rate	12.9%	5.6%
Median quantity of virus shed	2.79 $\log_{10}$ copies/ml	4.58 $\log_{10}$ copies/ml
Genital lesion rate	1.9%	4.1%
ORAL		
Number of participants with oral shedding	17 (29%)	13 (22%)
Oral shedding Rate	3.9%	3.7%
Median quantity of virus shed	3.15 $\log_{10}$ copies/ml	2.95 $\log_{10}$ copies/ml
Oral lesion rate	0.6%	0.6%

Relative risk of shedding & lesions

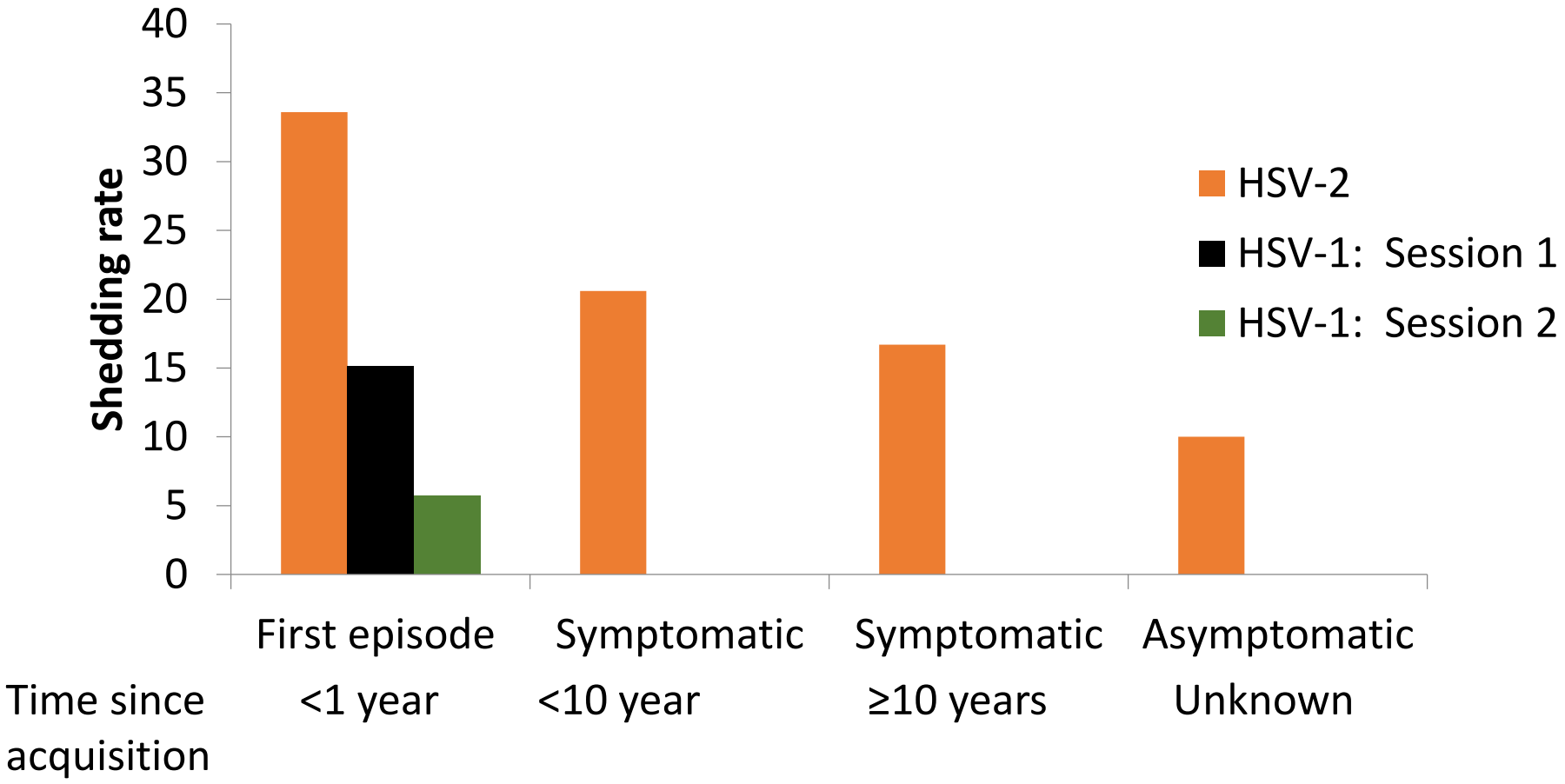
	Relative risk of shedding & lesions Session 2 vs. Session 1	95% CI	P-value
Genital shedding	0.44	0.23-0.83	0.013
Genital lesions	2.02	0.72-5.53	0.17
Oral shedding	0.96	0.45-2.02	0.91
Oral lesions	1.19	0.23-6.04	0.83

Methods: Poisson mixed model regression

Shedding rates at >2 years

		Genital			Oral		
Participant		8-12 wks	48-52 wks	**>2 years**	8-12 wks	48-52 wks	**>2 years**
1	Primary	62.5	33.3	0	12.5	3.7	0
2	Primary	3.5	51.7	0	0	0	0
3	Primary	15	6.6	0	0	0	0
4	Primary	17.3	33.3	0	0	38	19.2

Shedding Rate: Genital HSV-2 vs. HSV-1



Phipps *et al*, JID 2011
Tronstein *et al*, JAMA 2011

Remaining questions

- Can we estimate risk of genital HSV-1 transmission by number of clinical recurrences or shedding?

- How is control of HSV-1 replication achieved so quickly after first episode?
  - Decreased fitness for sacral ganglia compared to HSV-2?
  - Better immunologic response?
    - Studies to define development of cell mediated immune response are ongoing
    - Role of tissue resident memory CD4/CD8 cells?
    - Is there an association between virologic control and type of immune response elicited?

Conclusions

- Genital HSV-1 shedding and recurrences are relatively infrequent, and quantity of virus shed is low
  - Genital shedding: 5.6% at one year post infection
- Oral HSV-1 shedding and recurrences are rare among those who acquired HSV-1 genitally
- These data suggest that the risk of genital HSV-1 transmission to sexual partners is much lower than risk of HSV-2 transmission
- Genital HSV-1 has a very different natural history compared to HSV-2
  - HSV typing of first episode is critical to appropriately counsel patients

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