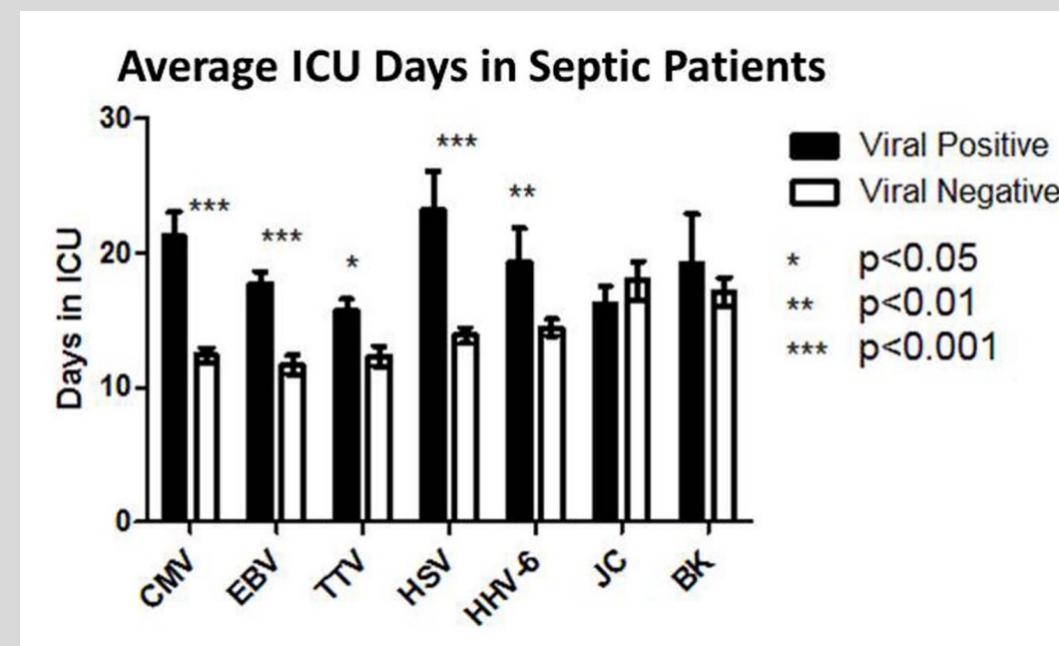


Background

- Sepsis remains a leading cause of pediatric mortality worldwide
- Surviving sepsis campaigns improved early mortality
- Ongoing contributors to mortality are unknown
 - Nosocomial infection
 - Genetic predisposition
 - Immune dysregulation
 - Viral reactivation?**
- Viral reactivation in adult patients:



Walton et al. PLOS. 2014.

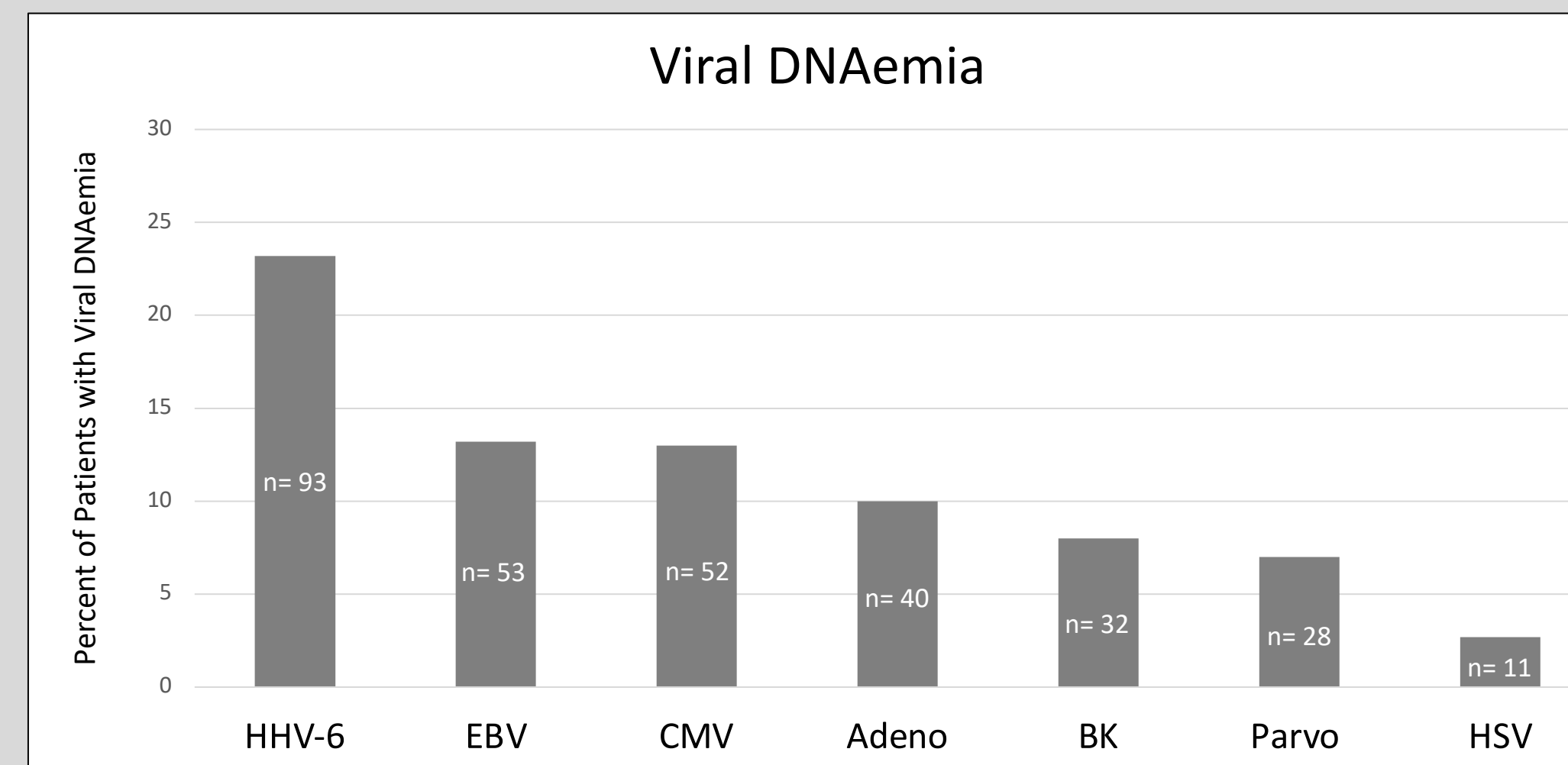
Methods

- Subjects: 401 pediatric patients from 9 PICUs in the Eunice Kennedy Shriver National Institutes of Child Health and Human Development Collaborative Pediatric Critical Care Research Network
- Blood samples collected twice weekly for 28 days or until ICU discharge or death
- Plasma samples tested for:

Virus	Quantitative PCR	Serology (IgG)*
CMV	✓	✓
EBV	✓	✓
HSV	✓	✓
HHV-6	✓	✓
Adenovirus	✓	✓
Parvovirus B19	✓	✓
BK	✓	✓
TTV	✓	✓

*Serology only performed on one sample per patient (1st or 2nd sample as available). Patients excluded from serology analysis if <18 months of age OR received IVIG prior to sample collection

- Viral DNAemia defined as qPCR detection of virus in one or more plasma samples excluding TTV



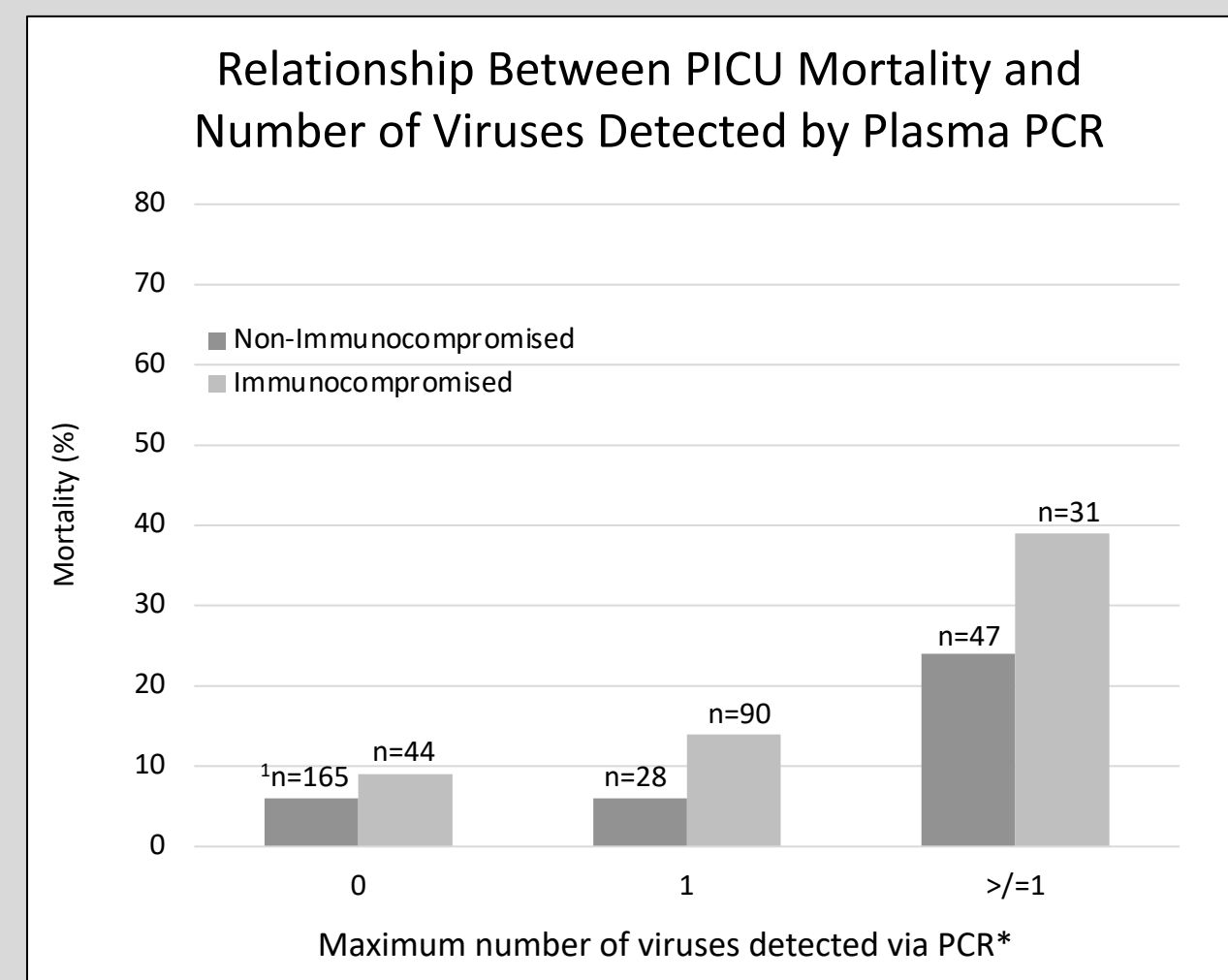
*TTV excluded from figure. Percent positive 96%.

Adjusted Mortality in Patients with Viral DNAemia ¹		Adjusted Mortality in Patients with Herpesvirus Seropositivity ¹	
	Odds Ratio (95% CI) ²		Odds Ratio (95% CI) ³
EBV	1.70 (0.69, 3.89)	EBV	9.10 (1.58, 172.80)
CMV	2.87 (1.23, 6.46)	CMV	1.22 (0.40, 3.90)
HHV-6	2.29 (0.89, 4.63)	HHV-6	1.42 (0.48, 4.37)
Adeno	3.03 (1.18, 7.39)		
Parvo	0.69 (0.15, 2.36)		
BK	2.63 (0.99, 6.53)		
TTV	2.11 (1.07, 4.08)		

¹ Mortality adjusted for: Age, PRISM, Immunosuppression, Previously healthy

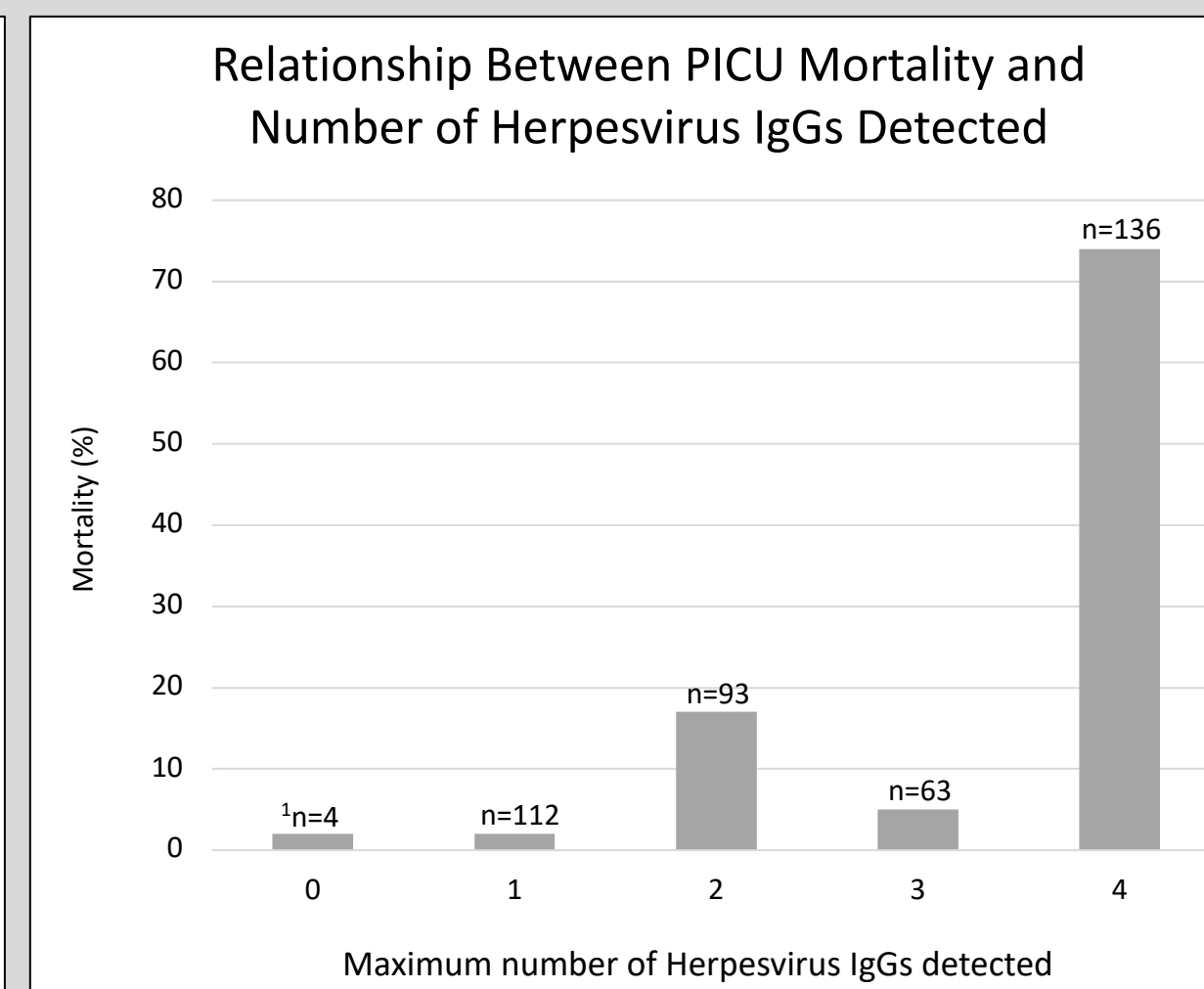
² HSV excluded as only 1/11 patients died in DNAemia group (p=1.00)

³ HSV excluded as no mortality observed in seropositive group



¹ Where n = total number of patients tested in each group

² Excludes TTV



¹ Where n = total number of patients tested in each group

Results

- Of 401 pediatric patients with severe sepsis, 55% were male, 39% previously healthy, and 27% immunocompromised. 44 subjects (11%) died in the PICU.
- 56% of subjects had documented infection(s) on enrollment (63% bacterial, 50% viral, and 2% fungal).
- Viral DNAemia, excluding TTV, was detected in 57% of immunocompromised patients and 44% of non-immunocompromised patients.
- Viral DNAemia was due to presumed reactivation in 91% of subjects with EBV DNAemia, 63% of those with CMV, and 100% of subjects with HSV and HHV-6.

Conclusions

- Viral DNAemia and viral seropositivity are common in pediatric patients with severe sepsis
- Multiple virus detection via plasma PCR is associated with mortality
- Viral seropositivity with EBV is strongly associated with ICU mortality
- Mortality risk is present in both immunocompromised and previously immunocompetent patients
- Future investigations will study mechanisms by which viral DNAemia and seropositivity contribute to pediatric sepsis mortality

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