Astrocytes, Neurons, and Enteroviruses

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19 June 2020

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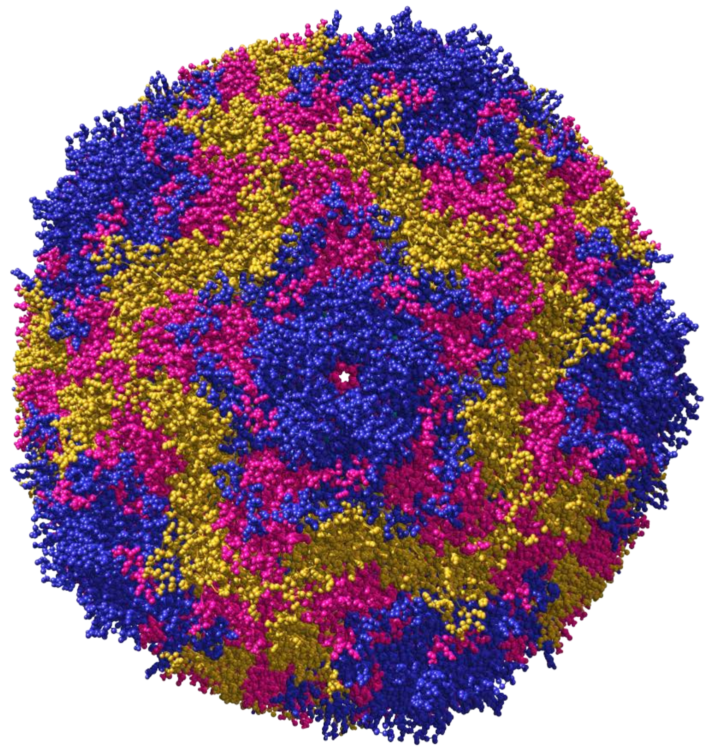
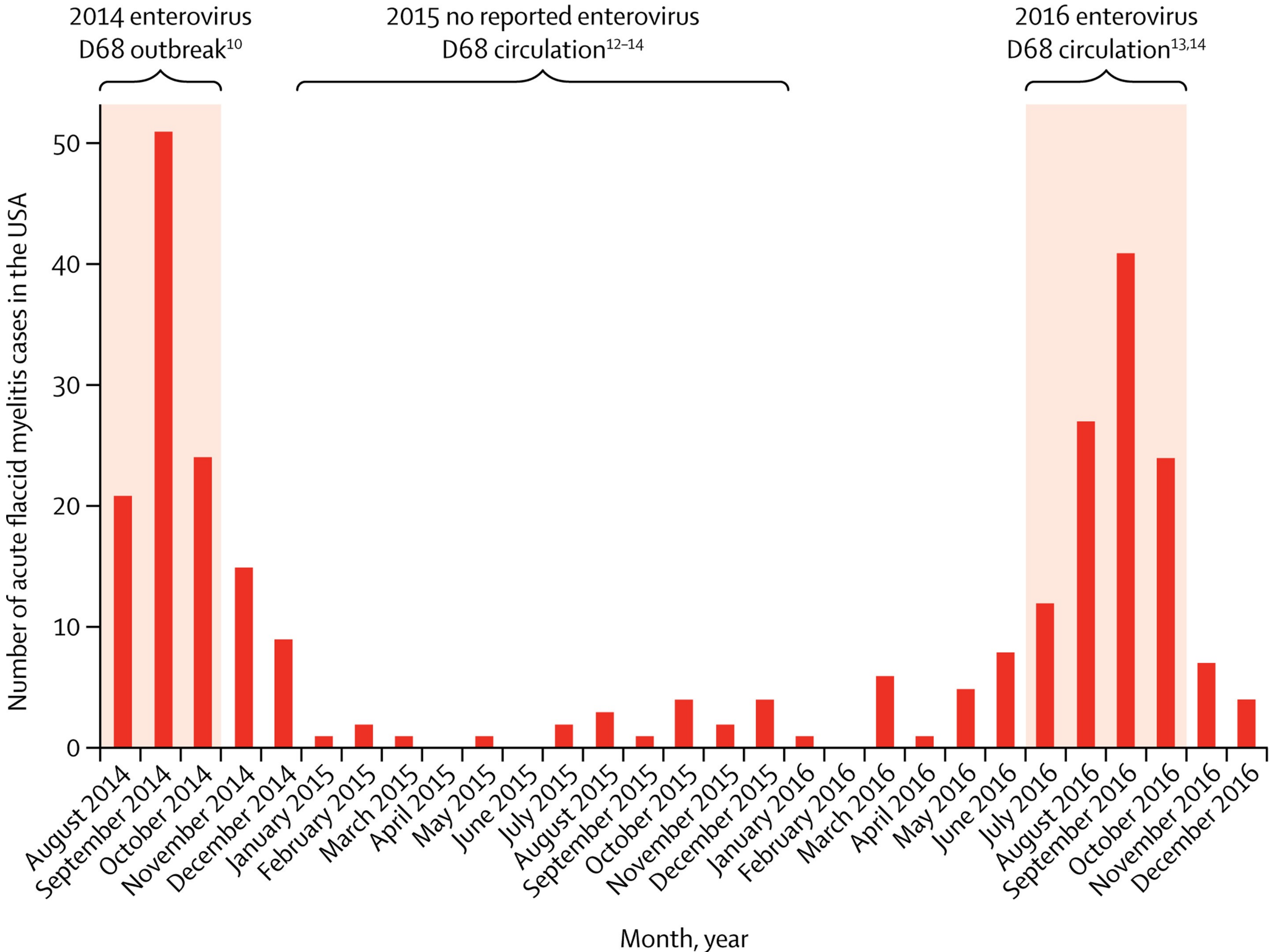
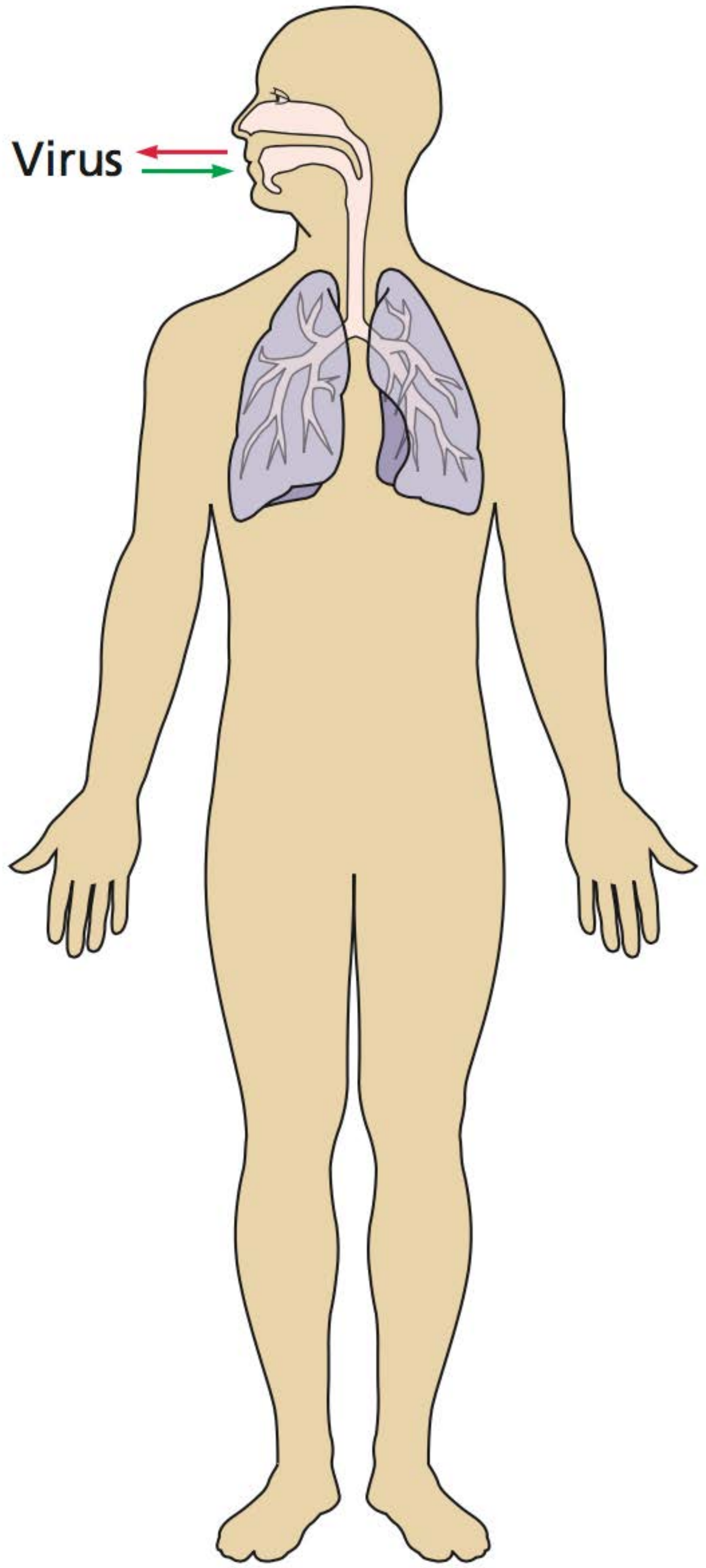
Enterovirus D68 (EV-D68)



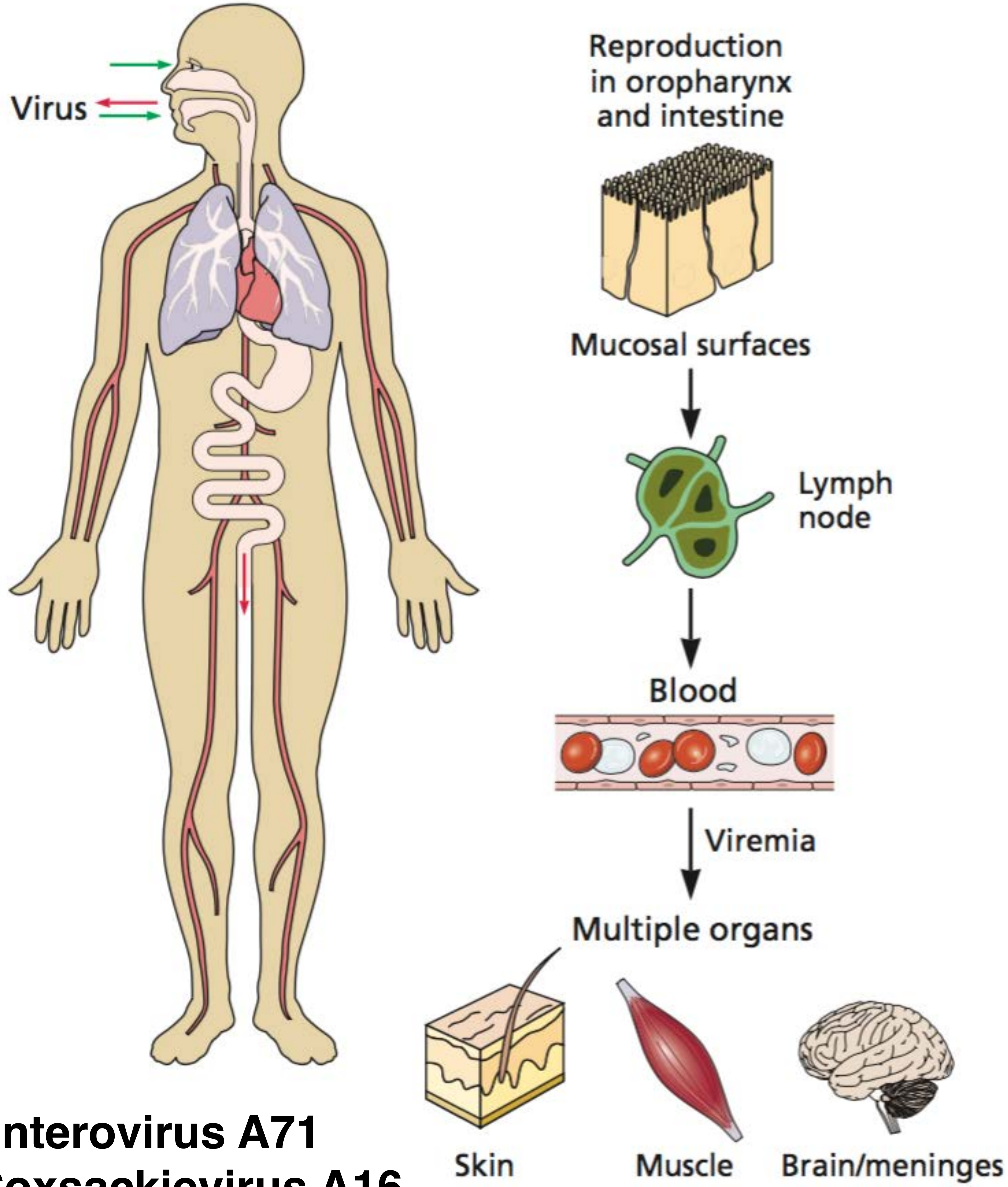
- First identified in California during the 1960s
- Infection results in “common cold-like” symptoms
- Outbreaks in the United States occurred during summers of 2014, 2016 and 2018
- Associated with “a polio-like” flaccid myelitis-626 CDC confirmed cases



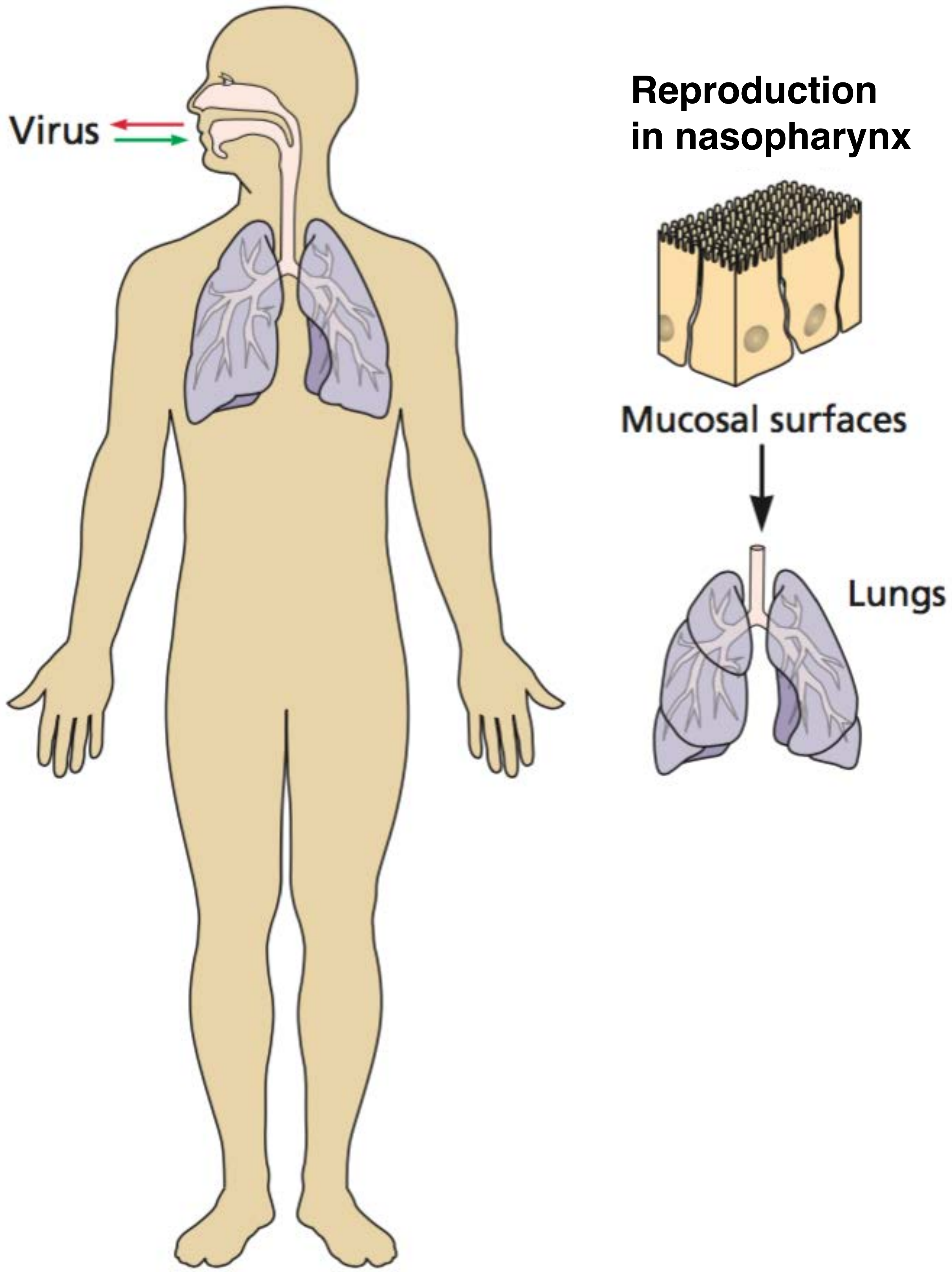
EV-D68 pathogenesis



- Virus infection initiates in nasopharyngeal cavity
- Infection results in respiratory disease
- No respiratory epithelium damage
- No virus isolated from blood or stool of patients, pH instability
- Virus in CSF in 4/626 cases
- Immunoreactivity to EV-D68 VP1 peptides in CSF of 43% and sera of 73% AFM patients (Mishra *et al.*, mBio. **2019**)
- Motor cortex lesions similar to those of poliovirus



Enterovirus A71
Coxsackievirus A16
Poliovirus 1, 2, 3



Enterovirus D-68

Neurotropism, neurovirulence and neuroinvasion

- **Neurotropism**- the production of infectious progeny resulting from infection of cells within the central nervous system

- **Neurovirulence-** disease that results from infection of cells within the central nervous system

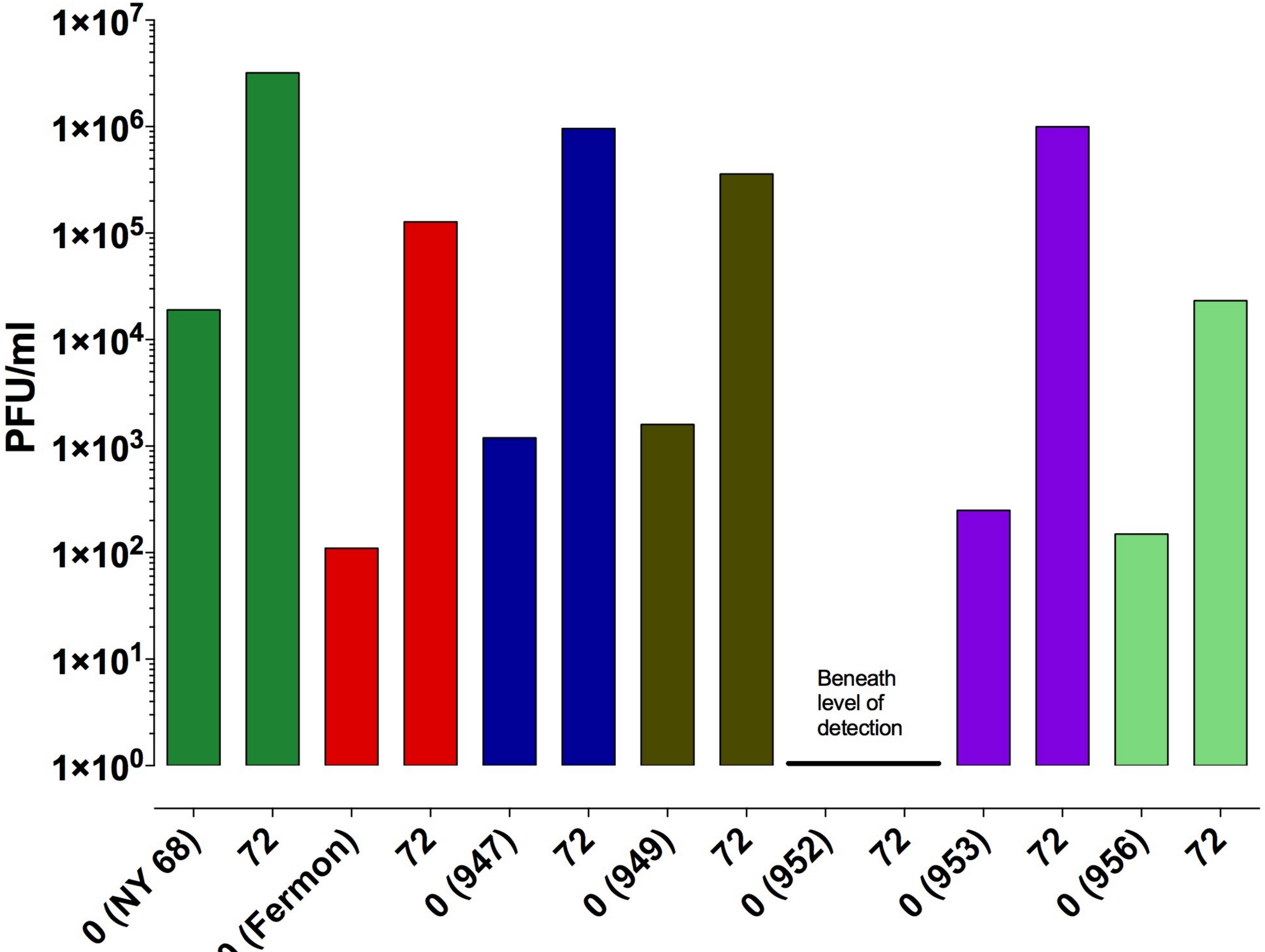
- **Neuroinvasion**- entry into the central nervous system from the periphery

EV-D68 isolates

- Fermon (California, 1962)
- Rhyne (California, 1962)
- New York (NYC, 2009)
- 947 (MO, 2014)
- 949 (MO, 2014)
- 952 (IL, 2014)
- 953 (KY, 2014)
- 956 (IL, 2014)
- 23087 (US, 2018)
- 23088 (US, 2018)
- 23089 (US, 2018)

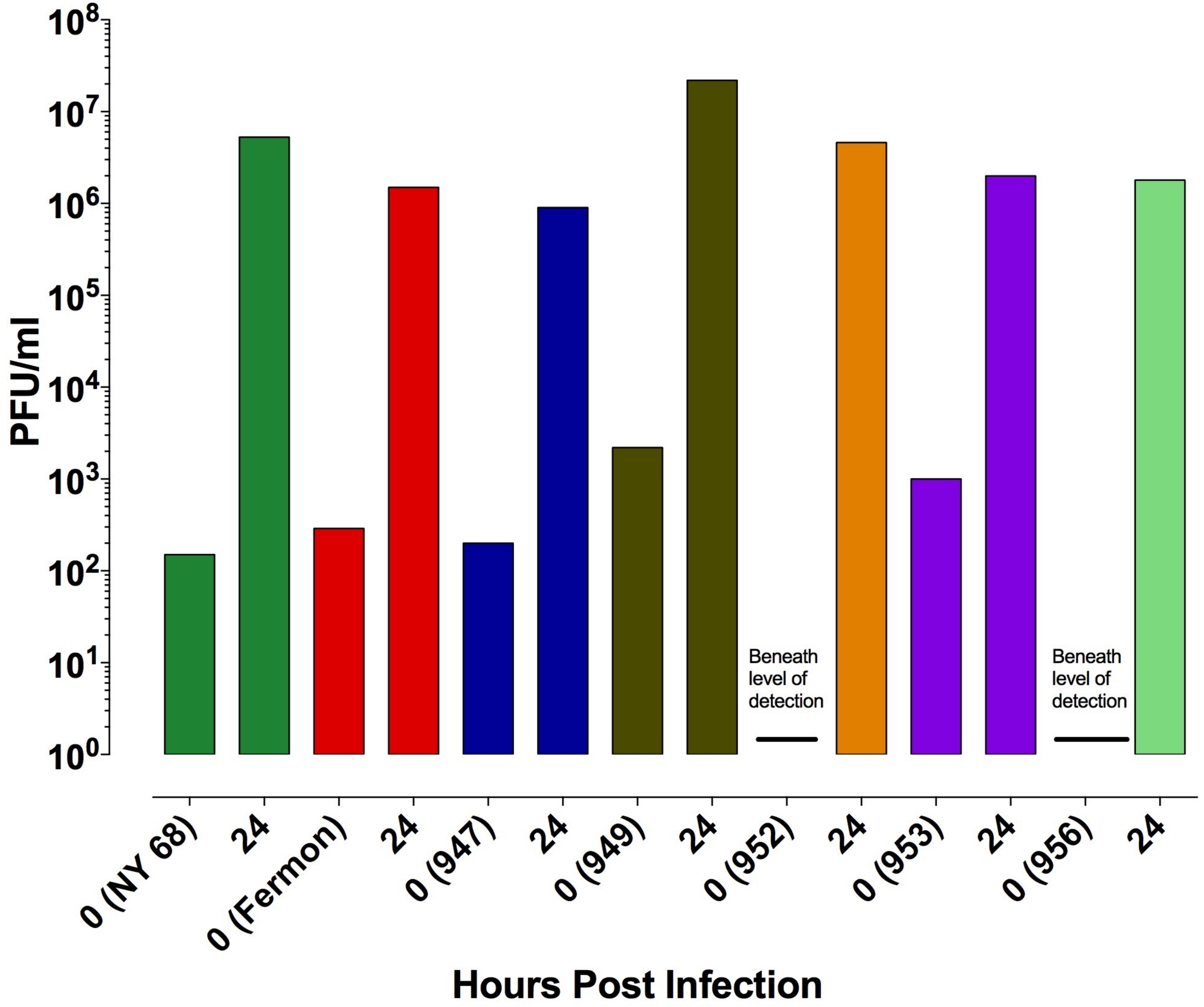
Is EV-D68 neurotropic?

EV-D68 replication in iCell human Neurons

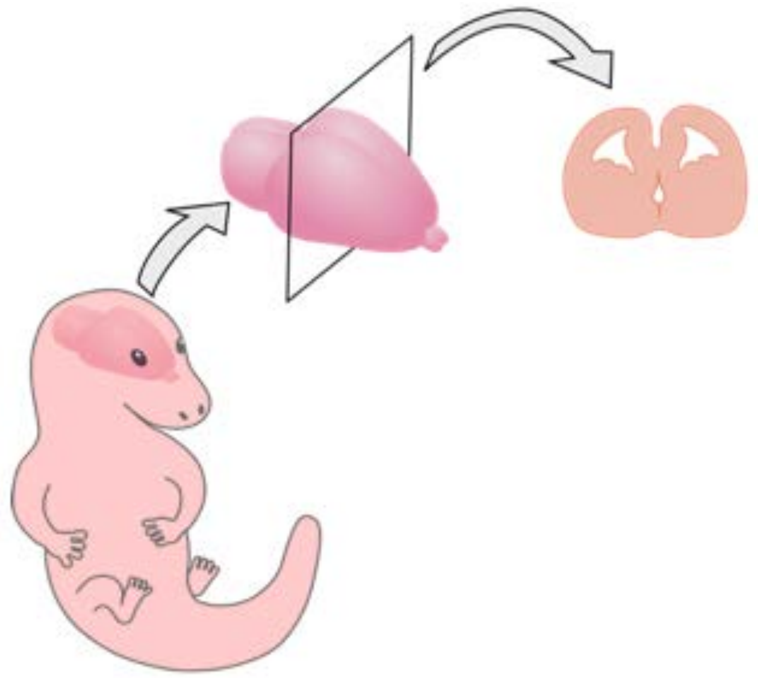


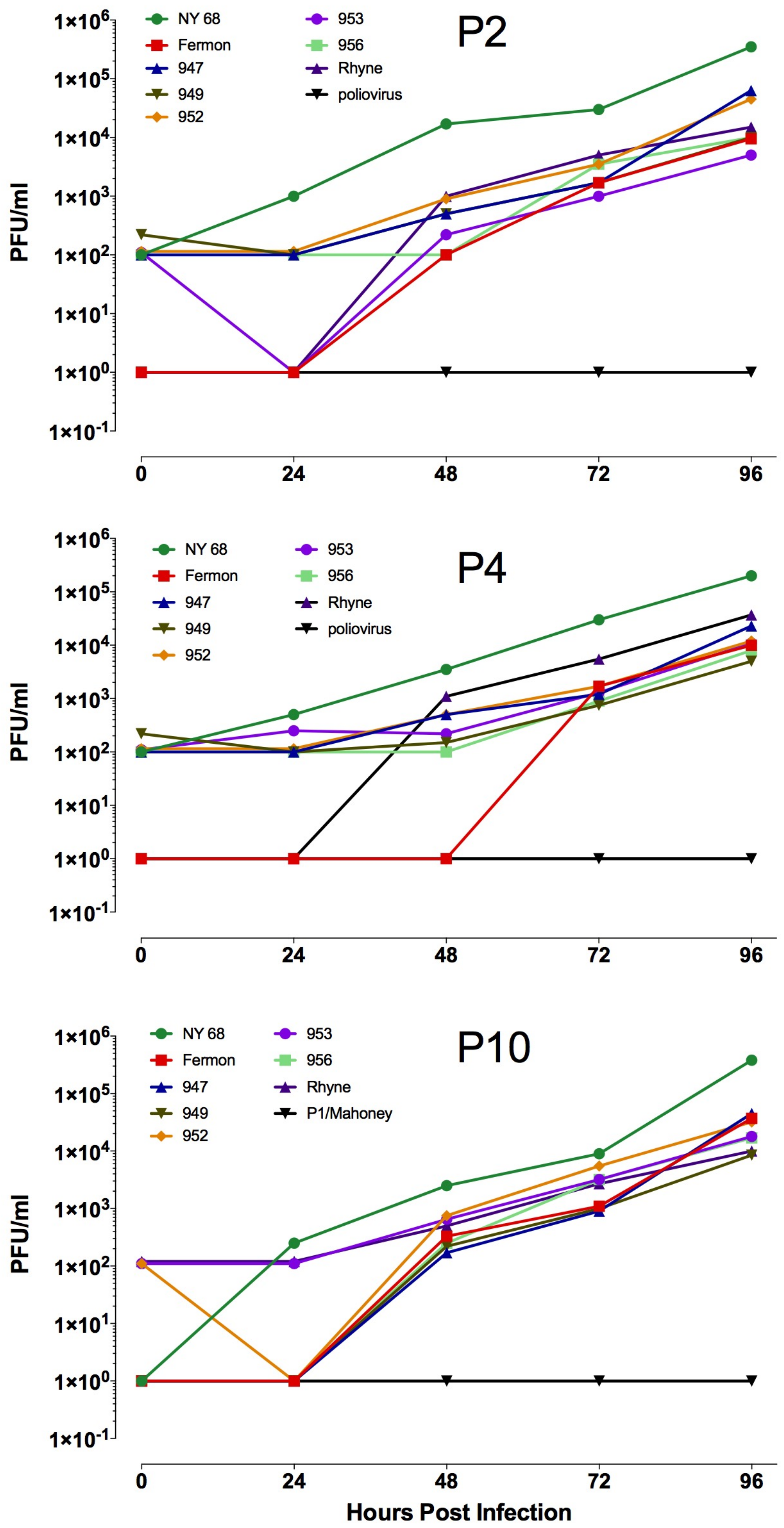

GFAP positive human astrocytes

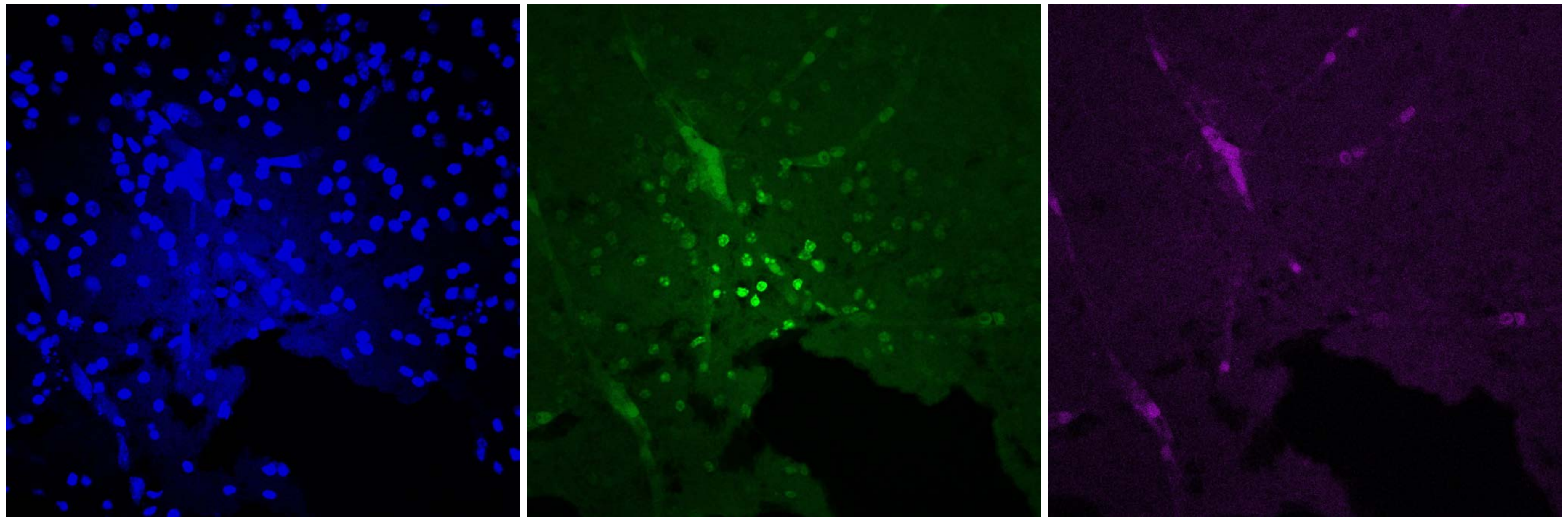
EV-D68 replication in human iAstrocytes



EV D-68 replication in mouse postnatal brain slices





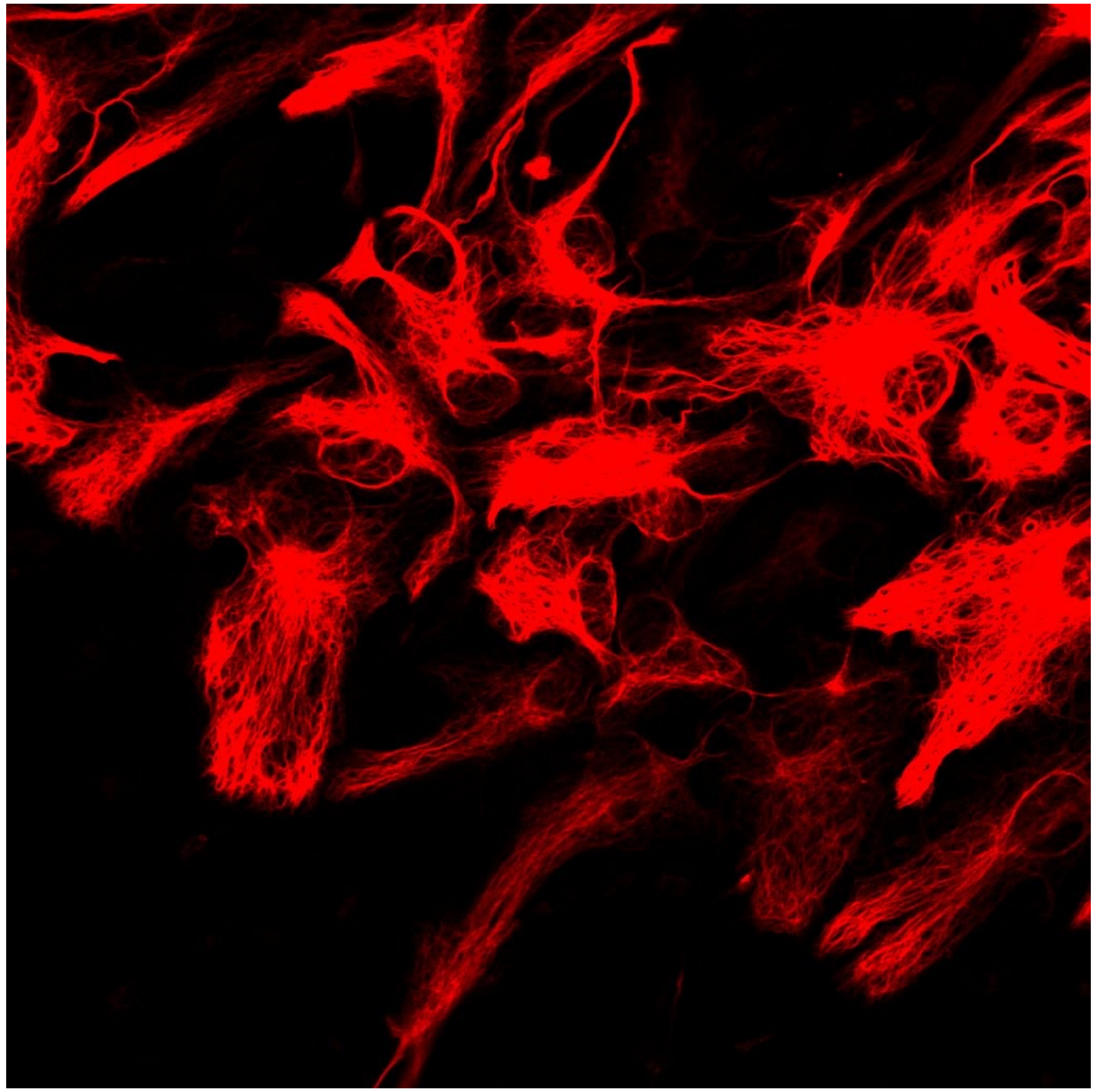


DAPI

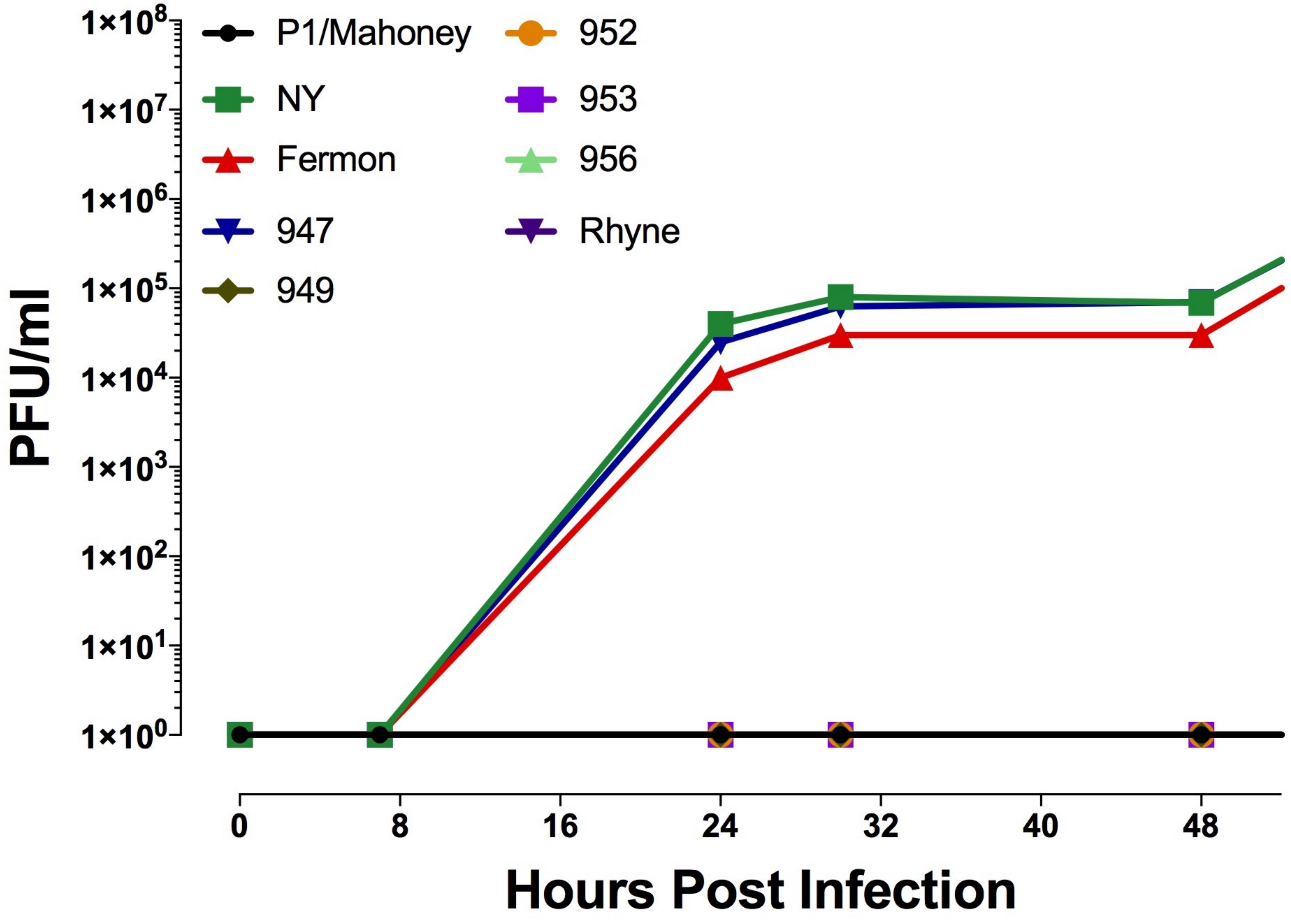
Anti-enterovirus

Nissl

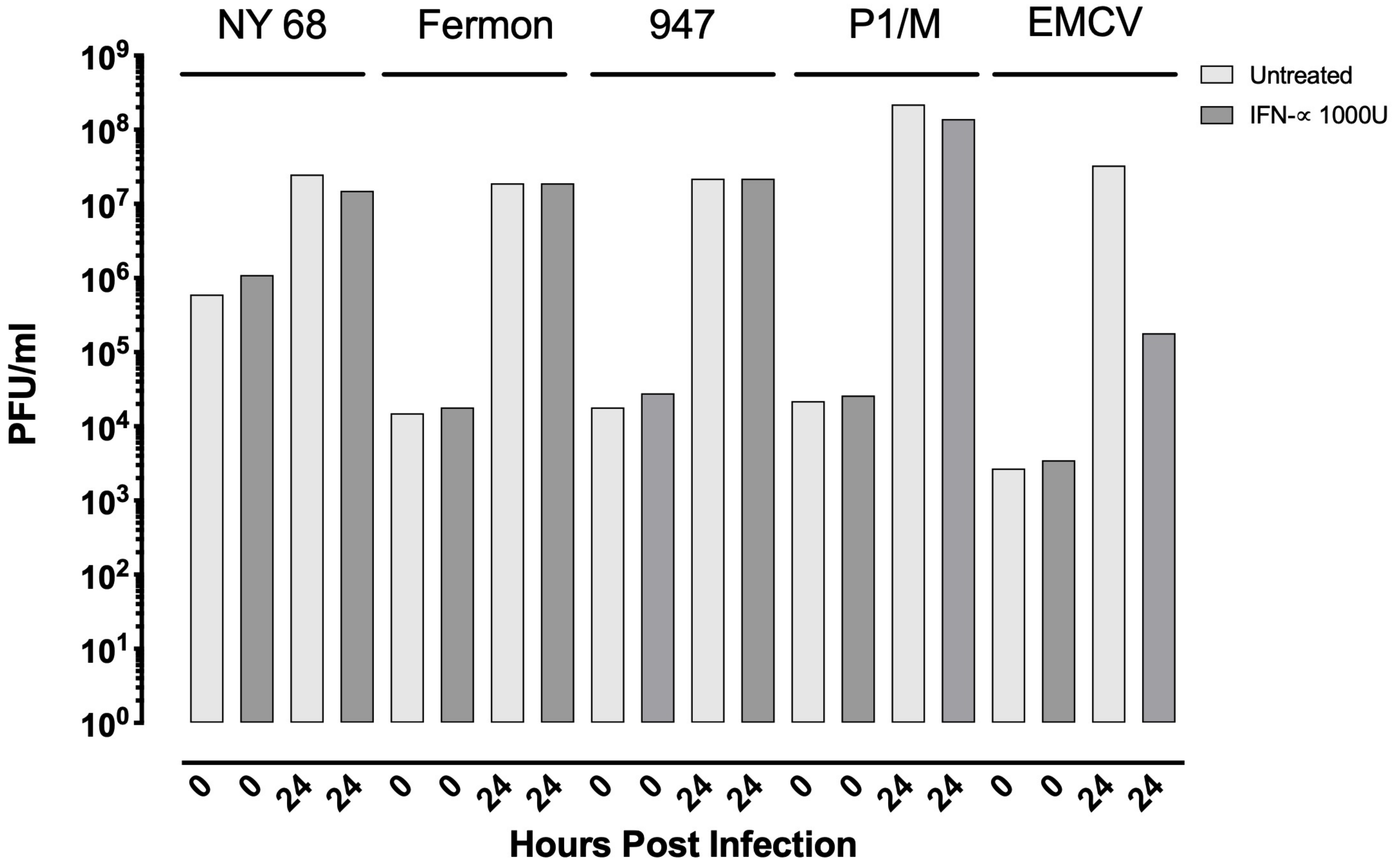
EV-D68 replication in isolated glial fibrillary acidic protein (GFAP) positive mouse astrocytes



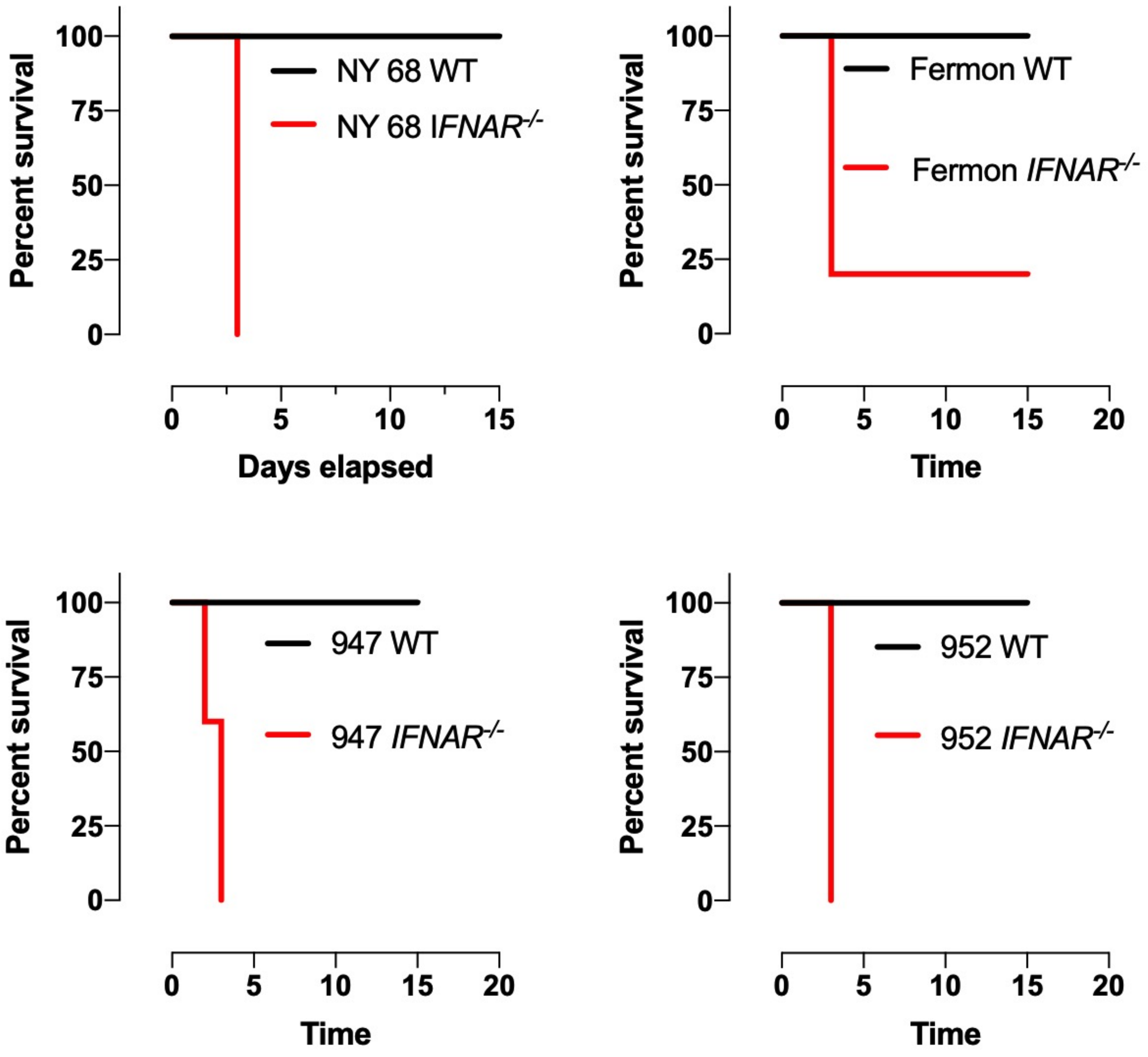
from P1-P3 mice



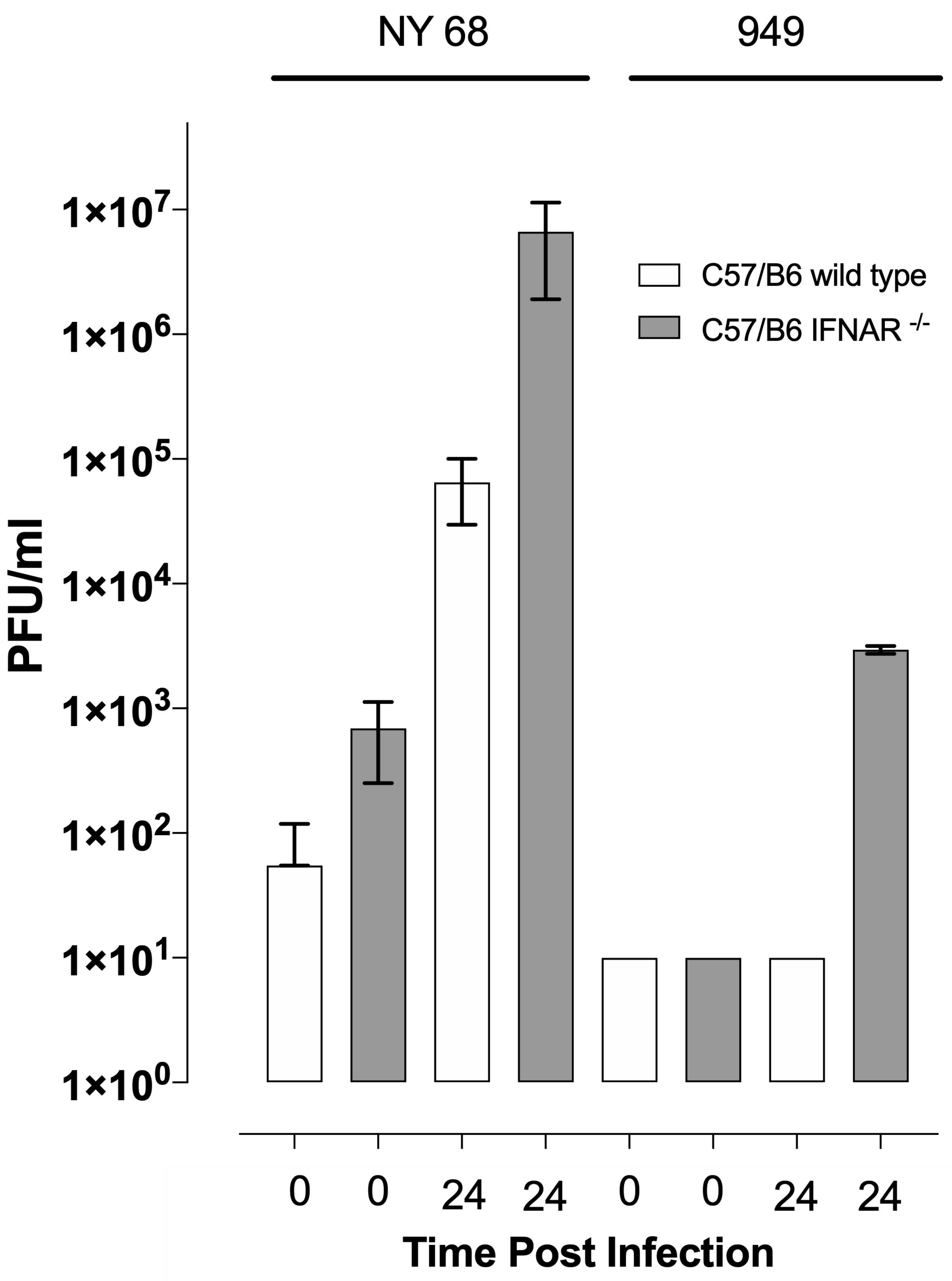
Does type I Interferon repress EV-D68 reproduction in Sk-N-Sh cell culture?



4 week old C57BL/6 mice lacking the IFN α/β receptor develop paralysis after EV-D68 intracranial inoculation



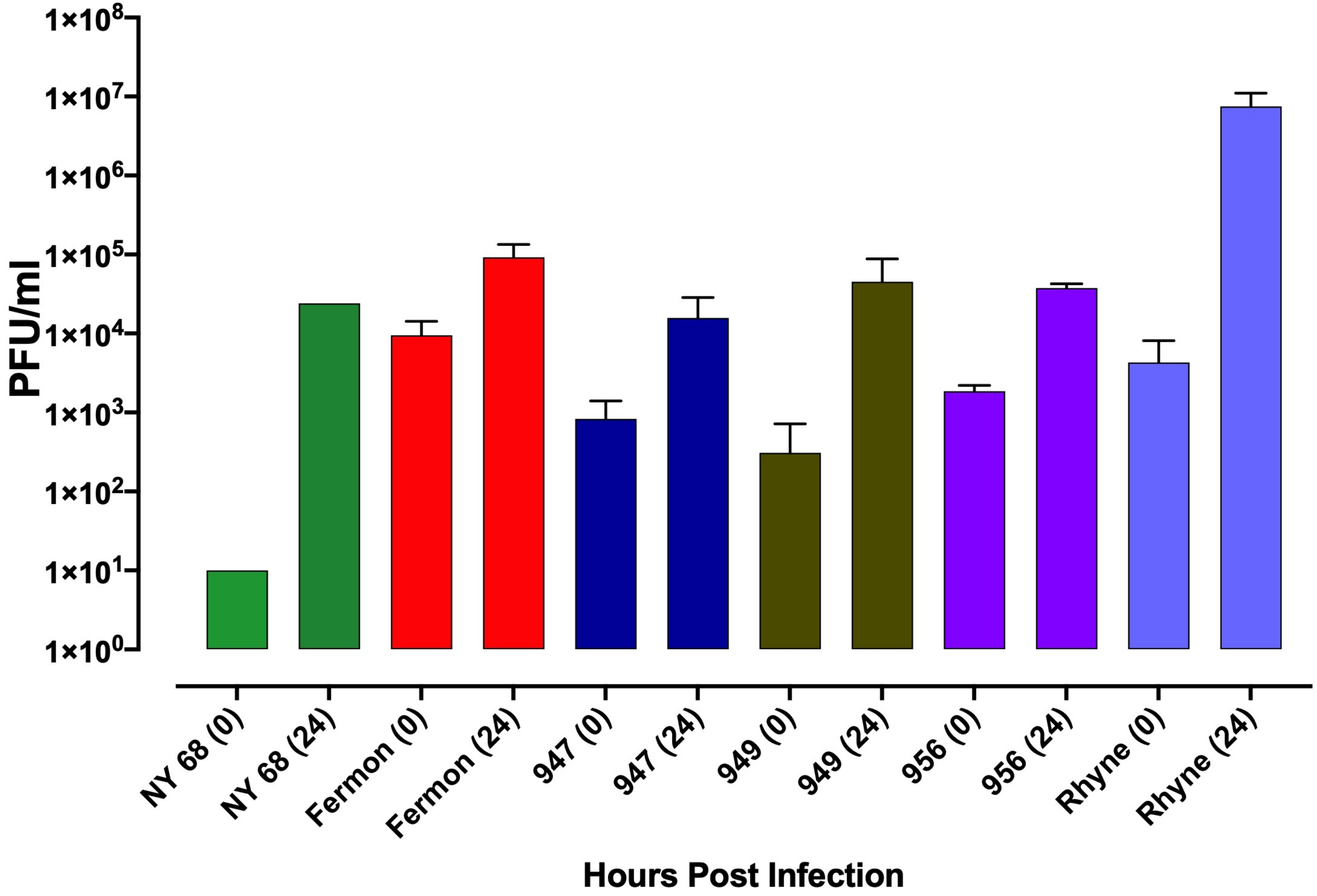
EV-D68 replication is enhanced in astrocytes isolated from IFNAR$^{-/-}$ mice C57/B6



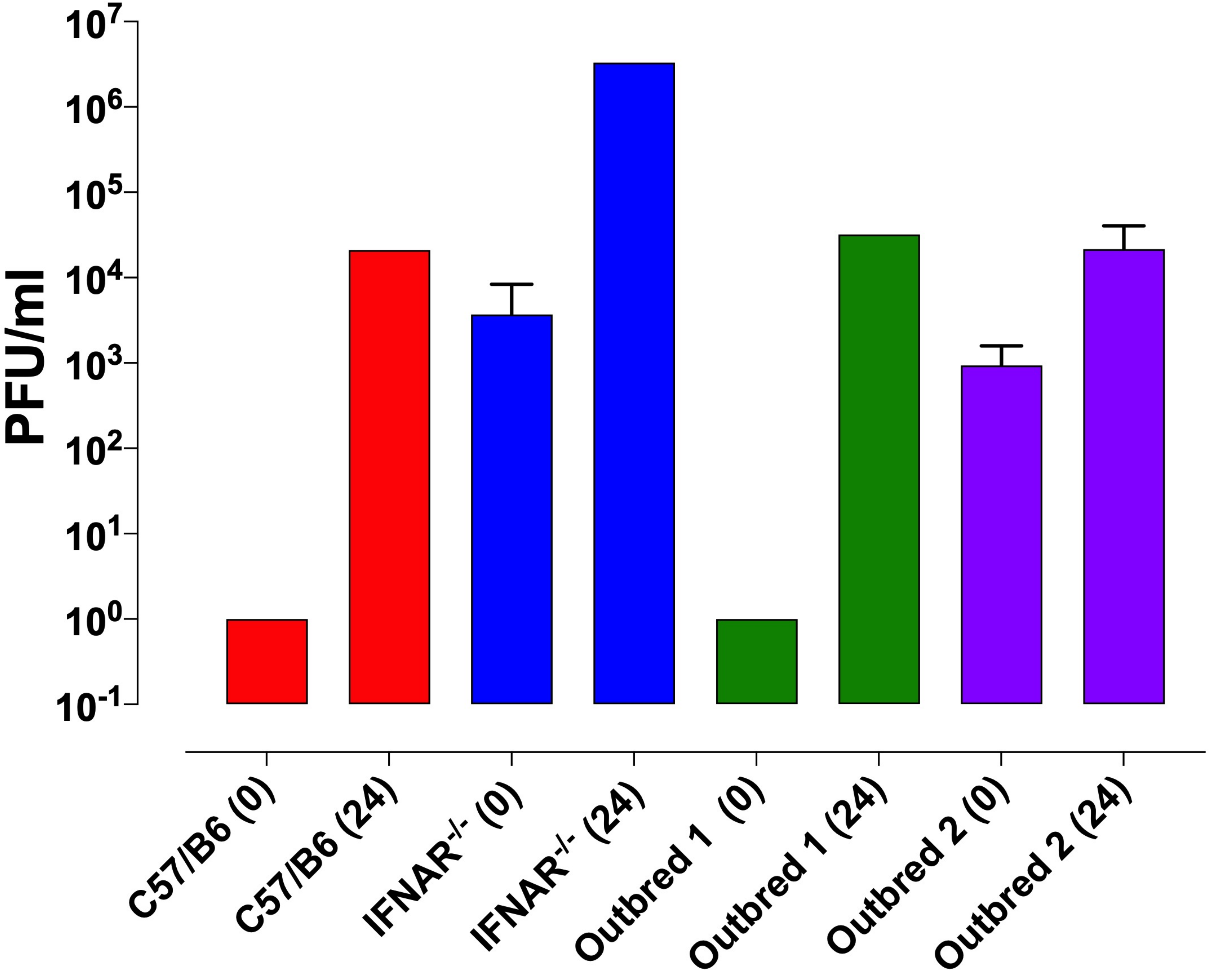
Type I IFN modulates EV-D68 neurotropism

IFNAR$^{-/-}$ mice are not sufficient to study to EV-D68 associated pathologies

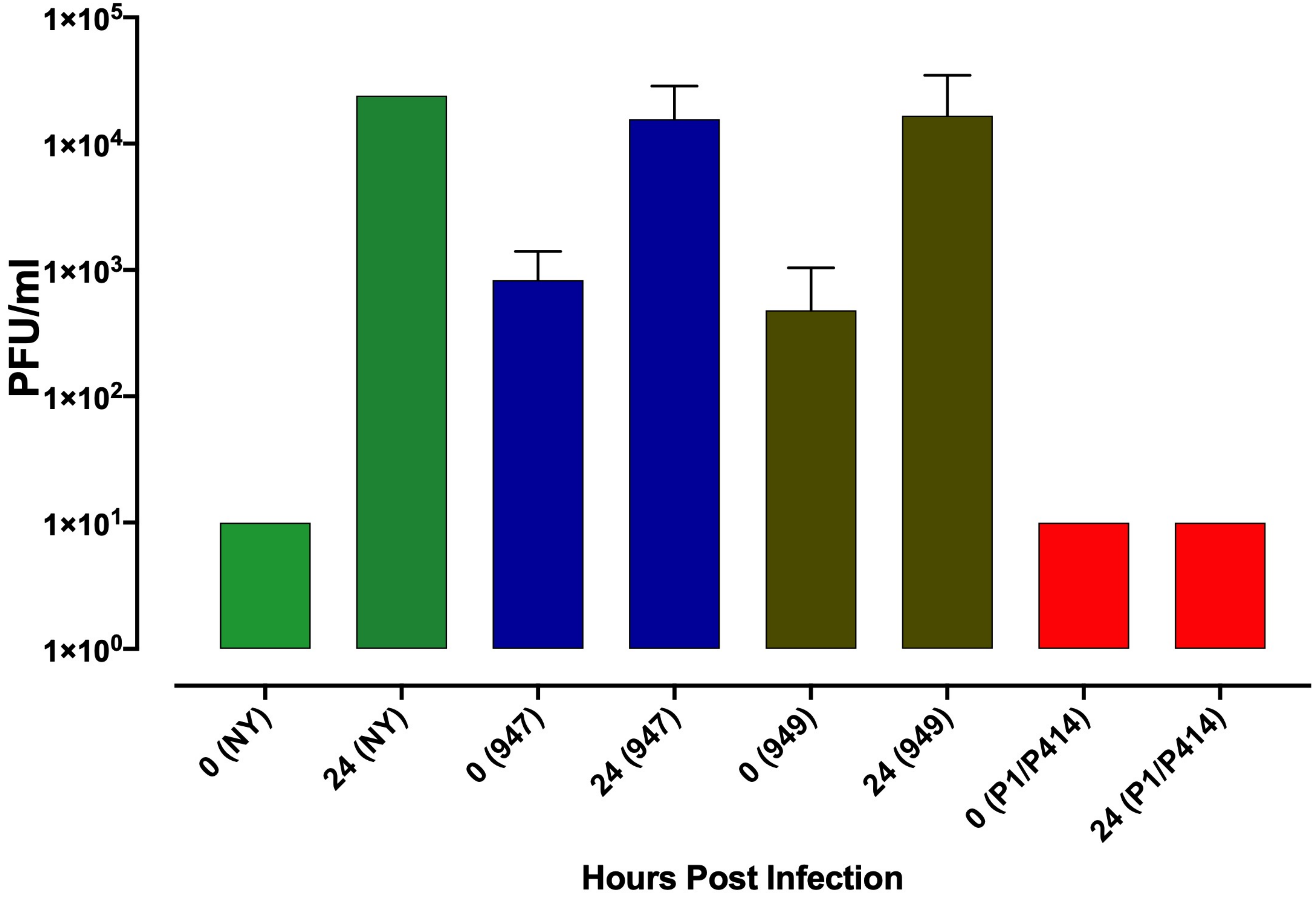
Reproduction of EV-D68 isolates in astrocytes purified from outbred mice



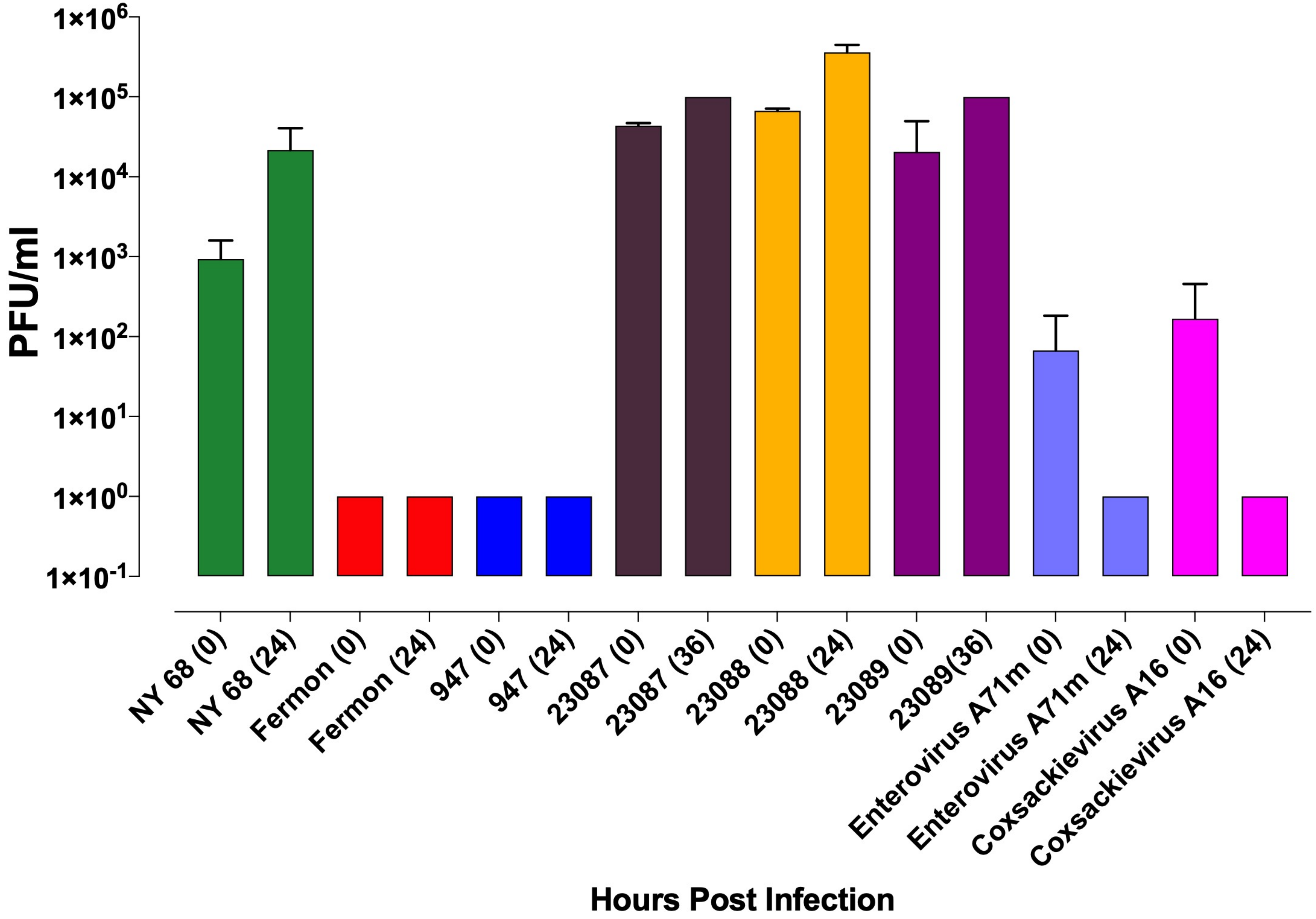
Not all genetic backgrounds are equal



EV-D68 and poliovirus are not the same



Enterovirus A71, enterovirus-D68 and Coxsackievirus A16 need different genetic background for reproduction

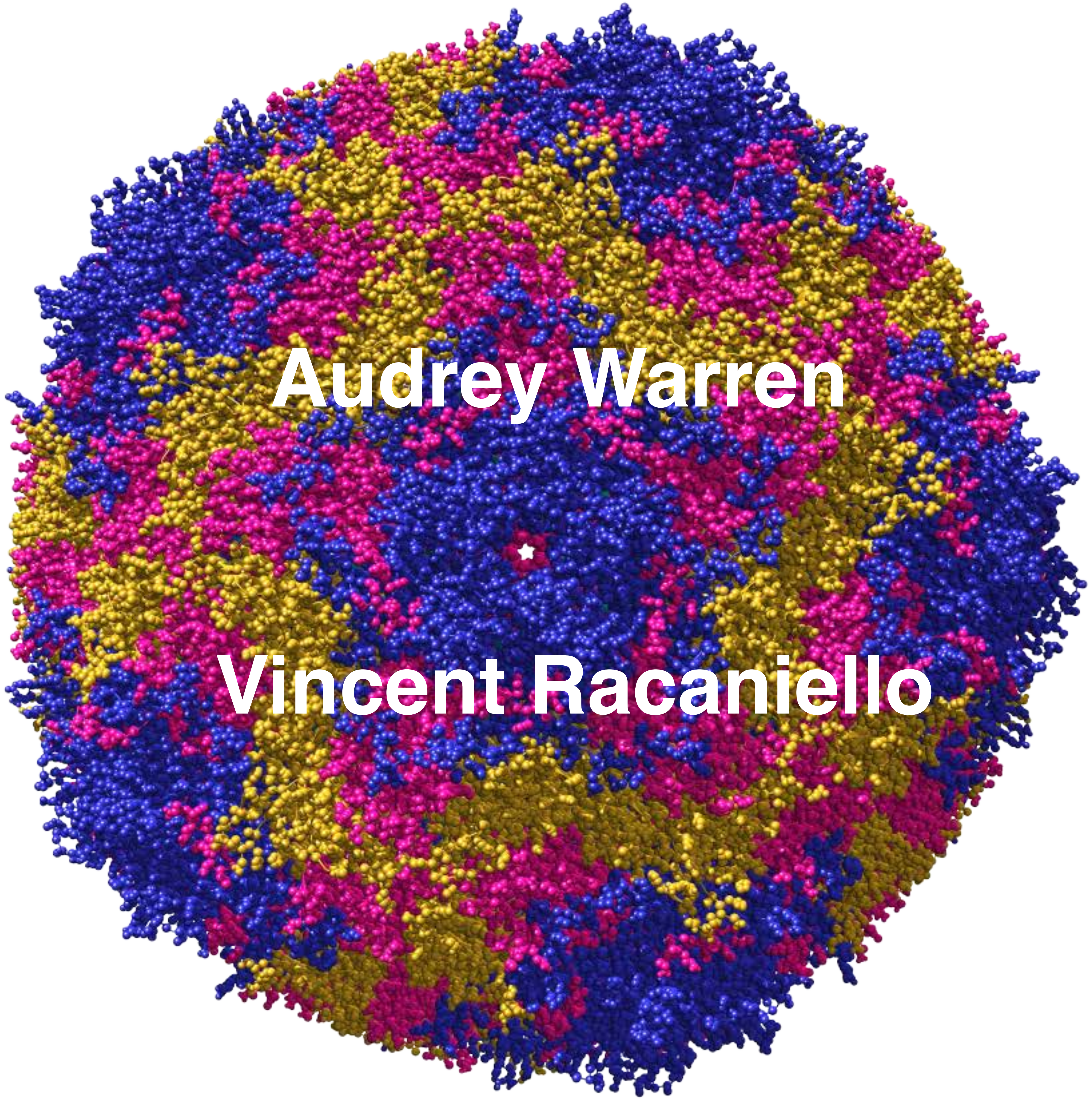


Summary

- EV-D68 infection is sensitive to the presence of type I Interferon
- Genetic requirements for neurotropism of EV-D68 are isolate specific
- Genetic requirements for neurotropism of EV-D68 differ from those necessary for poliovirus, enterovirus A71 and Coxsackievirus 16

Many pathways leads to neurotropism, a wrong turn for a respiratory virus

Viral infections of the CNS are less dependent on encounter with a potentially neuropathogenic agent than on some flaw in the usual barriers that normally exclude viruses from invading and infecting susceptible cells of the CNS- Richard T Johnson, 1982



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Animal models for studying AFM

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