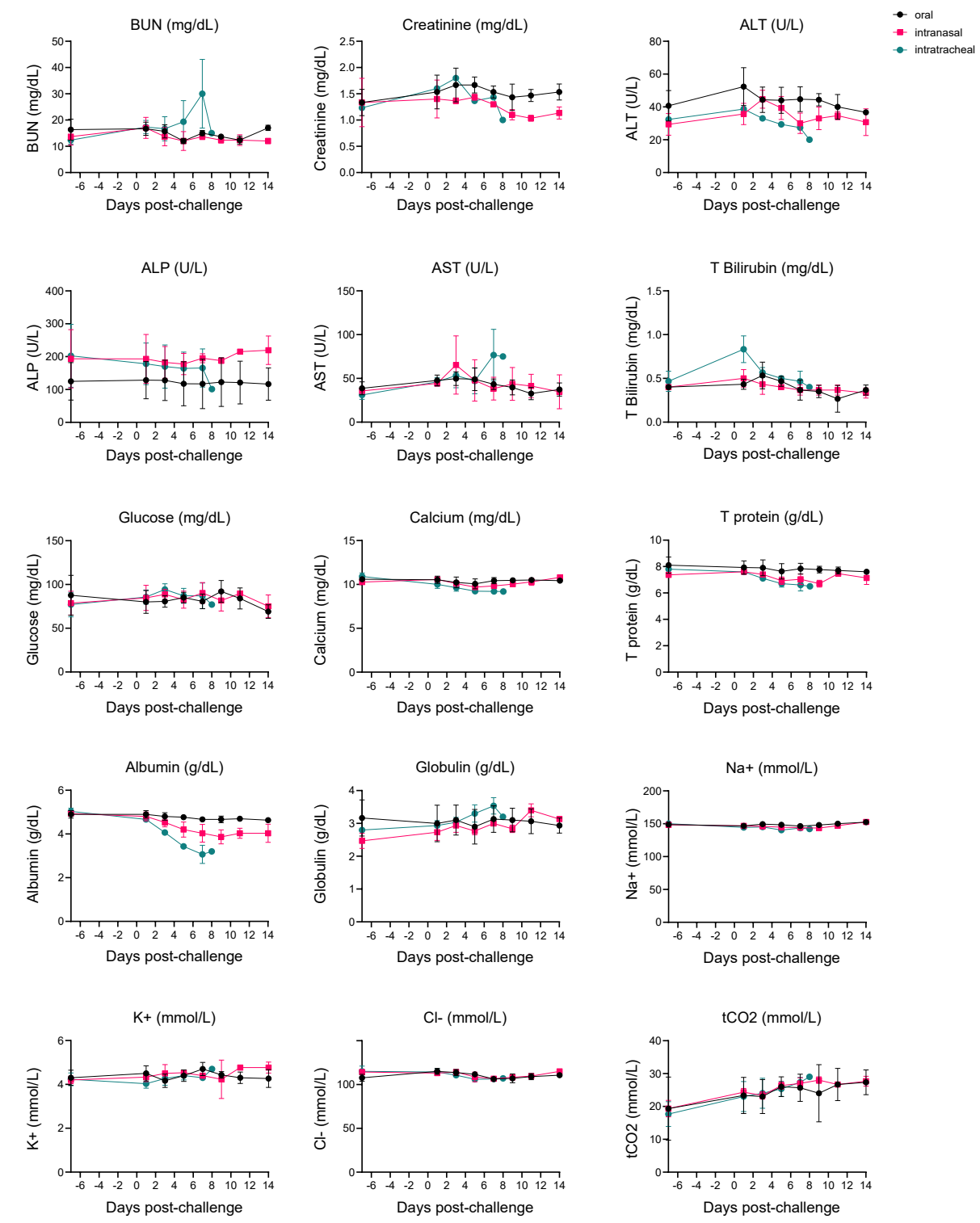


Animal		Day 1 & 2	Day 3 & 4	Day 5 & 6	Day 7 & 8	Day 9 & 10	Day 11 & 12	Day 13 & 14
Orogastric 1	Appearance	Normal	Normal	Normal	Normal	Normal	Normal	Normal
	Appetite	slightly decreased appetite	decreased appetite, no/decreased stool	slightly decreased appetite, dry stool	slightly decreased appetite, decreased/normal stool	decreased appetite	slightly decreased appetite, decreased/normal stool	slightly decreased appetite, decreased/normal stool
	Respiration	Normal	Normal	Normal	Normal	Normal	Normal	Normal
	Score	3/5	10/7	3/5	5/3	3/5	3/5	5/3
Orogastric 2	Appearance	Normal	Normal	Normal	Normal	Normal	Normal	Normal
	Appetite	decreased appetite, no stool	decreased appetite, decreased stool	slightly decreased appetite	slightly decreased appetite, decreased/normal stool	slightly decreased appetite, decreased/normal stool	slightly decreased appetite, decreased/normal stool	
	Respiration	Normal	Normal	Normal	Normal	Normal	Normal	Normal
	Score	3/10	10/7	3/5	5/3	5/3	5/3	0/0
Orogastric 3	Appearance	Normal	Normal	Normal	Normal	Normal	Normal	Normal
	Appetite	decreased appetite, decreased stool	decreased appetite, no/decreased stool	slightly decreased appetite, dry stool	decreased appetite	slightly decreased appetite	slightly decreased appetite	slightly decreased appetite
	Respiration	Normal	Normal	Normal	Normal	Normal	Normal	Normal
	Score	5/7	10/7	5/5	5/3	3/3	3/3	3/3
Animal		Day 1 & 2	Day 3 & 4	Day 5 & 6	Day 7 & 8	Day 9 & 10	Day 11 & 12	Day 13 & 14
Intranasal 1	Appearance	Normal	Possible rectal bleeding*	Normal	Normal	Normal	Normal	Normal
	Appetite	decreased appetite, decreased stool	decreased appetite, no stool	decreased appetite, decreased stool	decreased appetite, decreased stool	decreased appetite, decreased stool	decreased appetite, decreased stool	decreased appetite, decreased stool
	Respiration	Normal	Normal	Normal	Normal	Increased	Increased	Normal
	Score	5/7	10/22	7/7	7/7	7/12	7/7	5/5
Intranasal 2	Appearance	Normal	Normal	Normal	Normal	Normal	Normal	Normal
	Appetite	decreased appetite, decreased stool	decreased appetite, no stool	decreased appetite, decreased stool	decreased appetite, no/decreased stool	severely decreased appetite, decreased/mucoid stool	decreased appetite, decreased stool	slightly decreased appetite, no/normal stool
	Respiration	Normal	Normal	Normal	Increased	Increased	Increased	Normal
	Score	5/7	10/10	7/7	10/12	12/17	12/12	8/3
Intranasal 3	Appearance	Normal	Normal	Normal	Normal	Normal	Normal	Normal
	Appetite	decreased appetite, decreased stool	decreased appetite, no stool	decreased appetite, decreased stool	decreased appetite, decreased/normal stool	decreased appetite	slightly decreased appetite, normal/decreased stool	slightly decreased/normal appetite
	Respiration	Normal	Normal	Normal	Normal	Normal	Normal	Normal
	Score	3/7	8/7	3/5	5/5	5/3	3/5	3/0
Animal		Day 1 & 2	Day 3 & 4	Day 5 & 6	Day 7 & 8	Day 9 & 10	Day 11 & 12	Day 13 & 14
Intratracheal 1	Appearance	Normal,	Normal	Normal	Weak, using cage for support	N/A	N/A	N/A
	Appetite	decreased appetite, normal/no stool	severely decreased appetite, decreased urine, no stool	severely decreased appetite, decreased urine, no stool	severely decreased, no stool	N/A	N/A	N/A
	Respiration	Normal	Increased	Increased	Open mouth breathing	N/A	N/A	N/A
	Score	5/10	10/22	17/15	45/euthanized	N/A	N/A	N/A
Intratracheal 2	Appearance	Normal	Normal	Normal	Severely hunched posture	N/A	N/A	N/A
	Appetite	decreased appetite, decreased stool	decreased appetite, no stool	severely decreased appetite, no stool	severely decreased appetite, no stool	N/A	N/A	N/A
	Respiration	Normal	Normal	Increased	Open mouth breathing	N/A	N/A	N/A
	Score	Score 3/7	Score 10/10	Score 10/15	Score 25/euthanized*	N/A	N/A	N/A
Intratracheal 3	Appearance	Normal	Blood around nares	Blood around nares	Bloody nose	N/A	N/A	N/A
	Appetite	decreased appetite, no stool	decreased stool, severely decreased appetite	decreased/no stool, severely decreased appetite	open mouth breathing, decreased appetite, no stool	N/A	N/A	N/A
	Respiration	Normal	Increased	Increased	open mouth breathing	N/A	N/A	N/A
	Score	Score 5/10	Score 10/22	Score 17/20	Score 45/euthanized	N/A	N/A	N/A

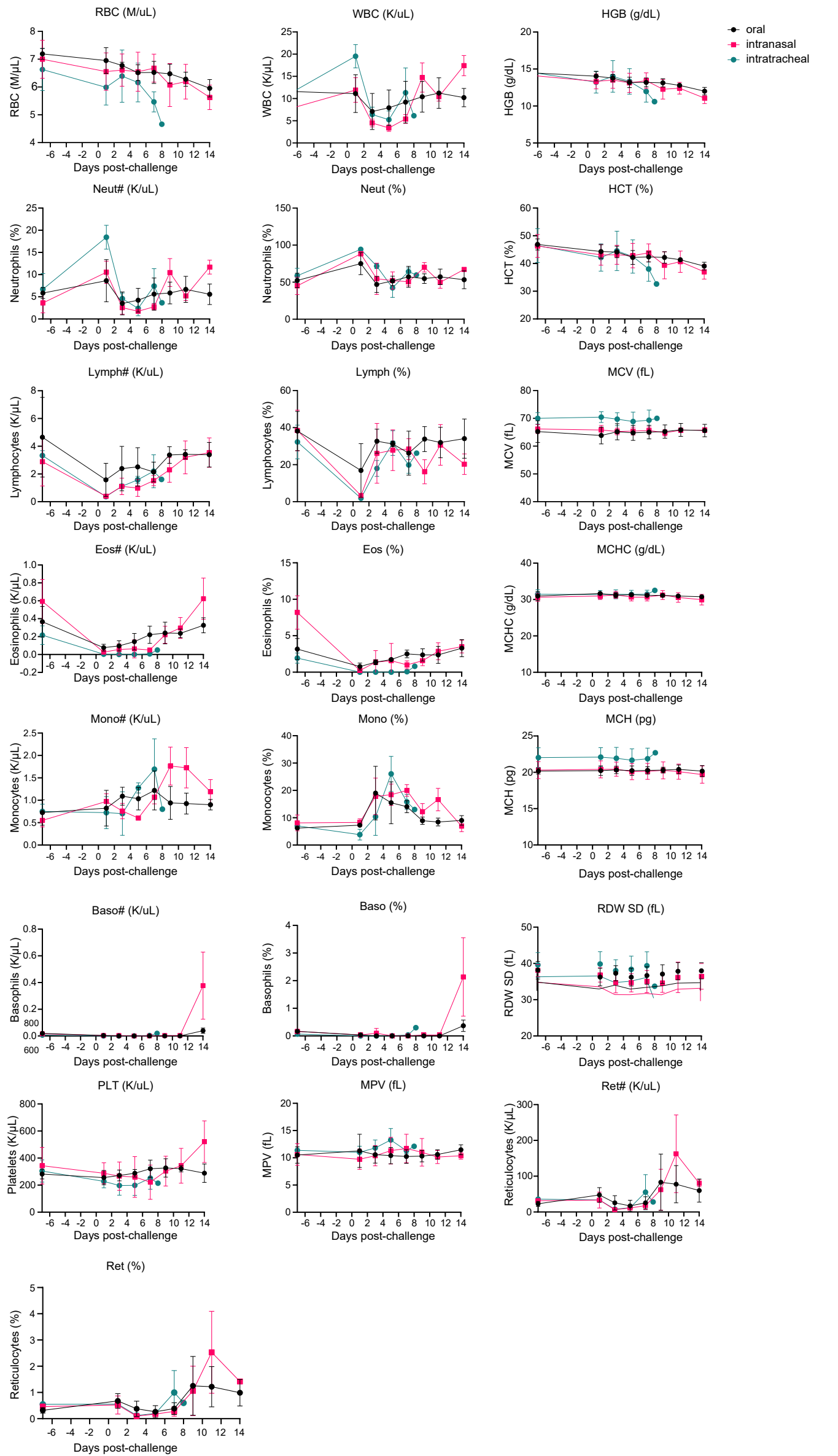
Supplemental Figure 1



Supplemental Figure 1: Blood Chemistries in cynomolgus macaques inoculated with HPAIV H5N1.

Serum was collected at each clinical exam and at the time of euthanasia and blood chemistry analysis was performed to assess organ function over the course of the study. Data represent 3 animals per inoculation route.

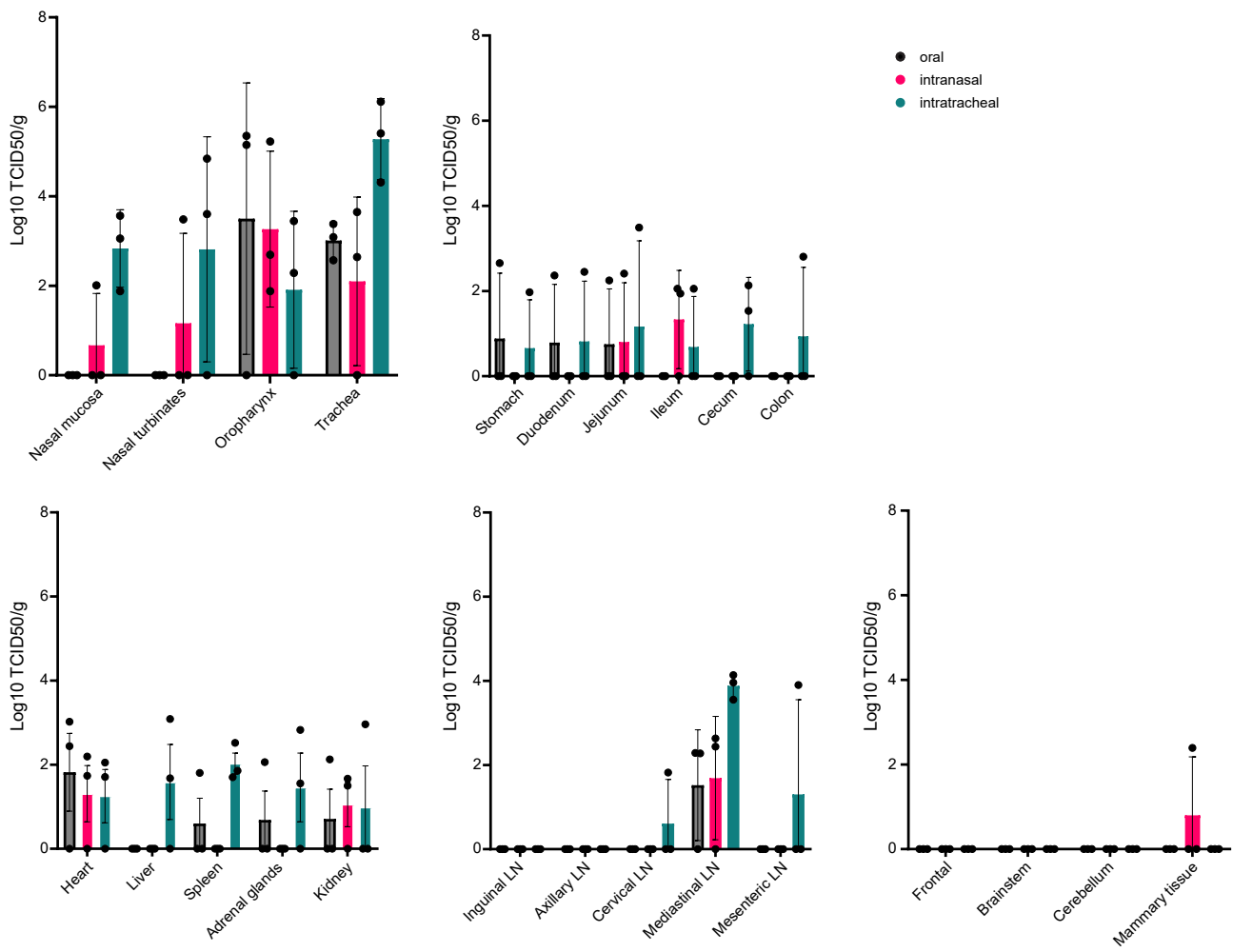
Supplemental Figure 2



Supplemental Figure 2: Hematological changes in cynomolgus macaques inoculated with HPAIV

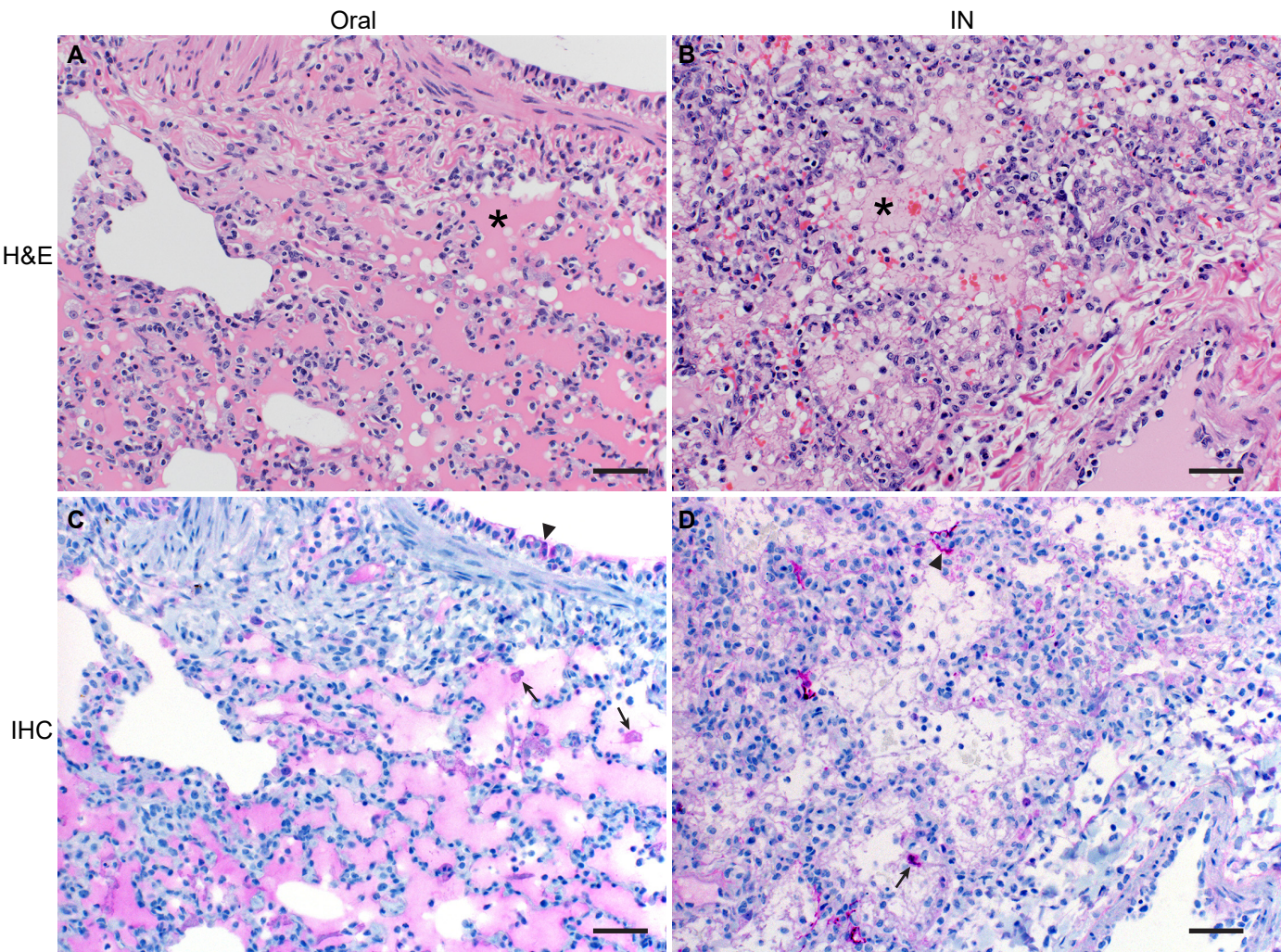
H5N1. Whole blood was collected at each clinical exam and at the time of euthanasia to assess the effects of inoculation over the course of the study. Data represent 3 animals per route.

Supplemental Figure 3



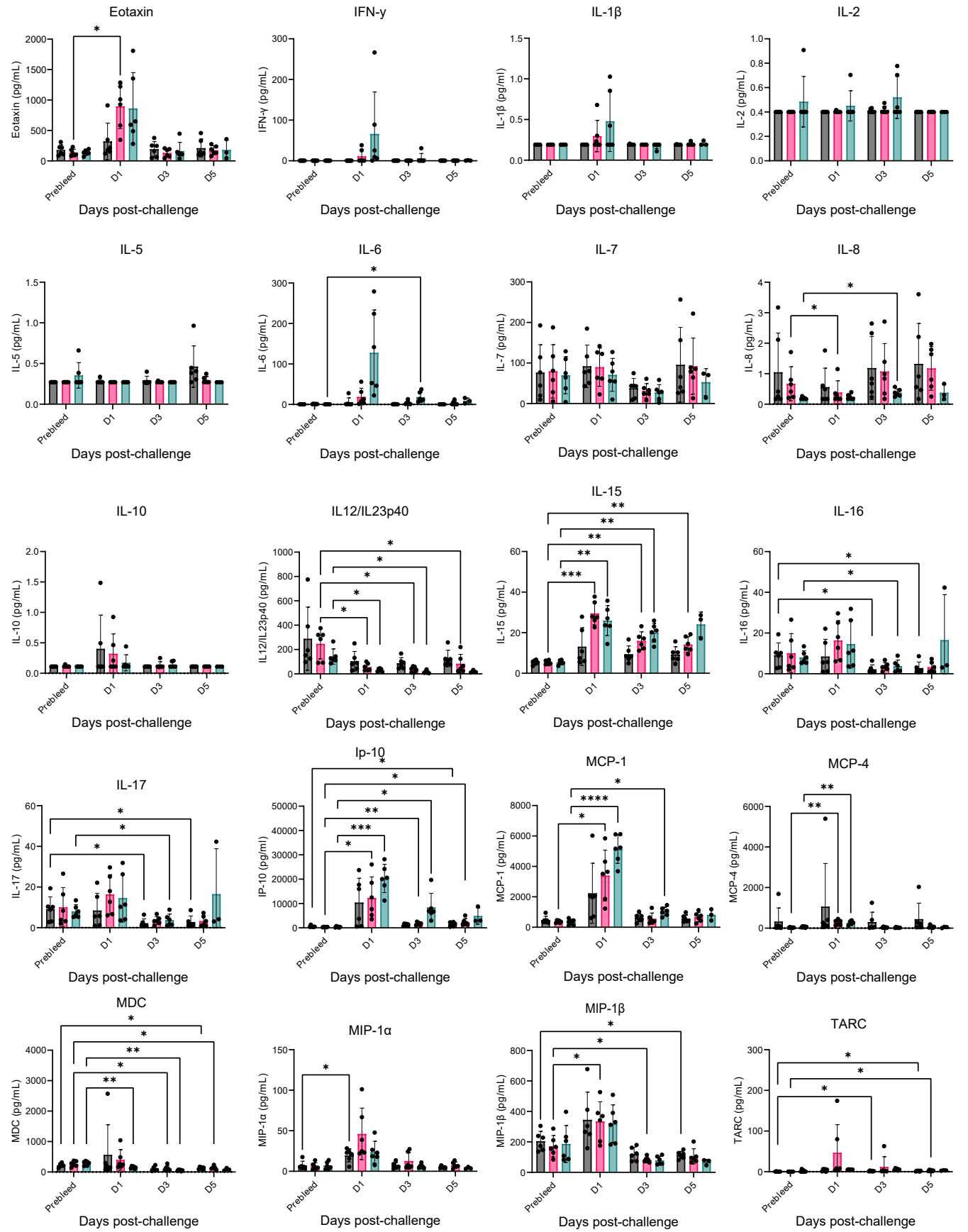
Supplemental Figure 3: Virus titers in tissues of cynomolgus macaques inoculated with HPAIV H5N1. Three animals per inoculation route were euthanized on D4/D5 and infectious virus was measured in tissues.

Supplemental Figure 4



Supplemental Figure 4: Rare histologic lesions in lungs of cynomolgus macaques inoculated with HPAIV via the orogastric or intranasal route during Acute Disease. Pulmonary lesions were observed in two lobes of one orogastric and one lobe in two intranasally inoculated animals euthanized on D5. Mild signs of pneumonia were observed with limited macrophage and neutrophil infiltration. HE: Asterisk = edema, IHC: Arrows = macrophages, arrowhead = bronchiolar epithelium. 200X; bar = 50 μ m.

Supplemental Figure 5



Supplemental Figure 5: Cytokine and Chemokine levels in the blood of cynomolgus macaques inoculated with HPAIV H5N1. Serum was collected from all animals (n=6 per inoculation route) during the first 5 days of the study to compare cytokine and chemokine levels across the three inoculation groups. Statistical analysis was performed with a mixed-effects model (Dunnett's multiple comparison test) with multiple comparisons. * = P-value <0.05, ** = P-value <0.01, *** = P-value <0.001, **** = P-value <0.0001