

Day	DV1				DV2				DV3				DV4			
	0	14	30	62	0	14	30	62	0	14	30	62	0	14	30	62
Animal																
4 (1427)	10	2560	640	640	10	10	2560	2560	10	160	640	2560	10	10	2560	10
5 (1272)	10	640	1280	160	10	160	1280	2560	10	2560	160	2560	10	160	2560	20
35 (1253)	10	120	2560	640	10	1280	2560	160	10	1280	2560	2560	10	10	1280	2560
42 (1407)	10	1260	1280	2560	10	320	10	640	10	10	2560	2560	10	2560	1280	640
WT-Tet GMT	10	705	1280	640	10	160	538	905	10	269	905	2560	10	80	1810	135
6 (1301)	10	10	640	1280	10	10	10	2560	10	320	2560	80	10	10	1280	2560
15 (1151)	10	10	40	1280	10	10	10	320	10	1280	1280	160	10	10	640	2560
25 (1095)	10	40	640	2560	10	80	160	10	10	1280	2560	320	10	10	80	160
30 (1115)	10	10	10	160	10	10	2560	2560	10	10	1280	640	10	640	2560	2560
1 (1405)	10	10	640	2560	10	80	160	2560	10	2560	10	320	10	10	2560	2560
10 (1463)	10	10	2560	640	10	10	320	10	10	80	10	10	10	10	640	160
16 (1157)	10	10	2560	10	10	10	320	2560	10	1280	2560	40	10	10	320	2560
18 (1178)	10	20	2560	1280	10	2560	2560	160	10	1280	160	20	10	10	1280	320
2 (1411)	10	10	80	1280	10	640	640	1280	10	20	10	640	10	10	320	640
22 (1083)	10	80	80	2560	10	640	10	320	10	2560	40	80	10	10	2560	40
29 (1114)	10	2560	10	160	10	2560	40	10	10	20	10	160	10	10	2560	160
40 (1420)	10	2560	1280	2560	10	2560	1280	10	10	640	320	10	10	10	2560	10
8 (1454)	10	2560	10	160	10	80	1280	640	10	10	10	320	10	10	1280	20
13 (1133)	10	2560	10	1280	10	10	2560	10	10	2560	1280	80	10	10	20	20
36 (1261)	10	2560	10	10	10	10	320	10	10	640	10	10	10	40	320	1280
39 (1225)	10	2560	20	1280	10	10	1280	10	10	10	40	160	10	10	20	10
HR-Tet GMT	10	104	123	538	10	100	269	129	10	252	123	91	10	21	742	247
9 (1456)	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
31 (1117)	10	10	10	10	10	10	10	10	10	80	10	10	10	10	10	10
37 (1152)	10	20	10	10	10	10	10	10	10	10	10	10	10	10	10	10
38 (1209)	10	40	80	10	10	10	20	10	10	10	1280	10	10	10	10	10
17 (1174)	10	10	640	10	10	80	10	10	10	10	10	10	10	10	10	10
24 (1091)	10	160	1280	10	10	10	160	10	10	10	10	10	10	10	10	10
41 (1381)	10	10	20	10	10	160	10	10	10	10	10	10	10	10	10	10
44 (1439)	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
7 (1452)	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
14 (1138)	10	10	10	160	10	10	10	10	10	10	10	10	10	10	10	10
26 (1096)	10	10	10	10	10	40	10	10	10	10	10	10	10	20	10	10
32 (1121)	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
3 (1426)	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
11 (1464)	10	10	10	10	320	10	10	10	10	10	10	10	10	10	10	10
12 (1466)	10	10	10	10	10	10	10	10	10	10	10	10	10	10	160	10
19 (1206)	10	10	10	1280	10	1280	10	10	10	10	10	10	10	10	10	10
Mock GMT	10	14	21	16	10	30	10	10	10	11	14	10	10	10	12	10
HR-Tet vs. Mock	NS	p<0.05	p<0.05	p<0.0001	NS	NS	p<0.0005	p<0.001	NS	p<0.005	p<0.005	p<0.005	NS	NS	p<0.0001	p<0.0001
WT-Tet vs. Mock	NS	p<0.02	p<0.005	p<0.02	NS	NS	NS	p<0.001	NS	NS	p<0.01	p<0.0001	NS	NS	p<0.0001	NS
HR-Tet vs. WT-Tet	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	p<0.0001	NS	NS	NS	NS

Supplemental Figure 1. Plaque reduction neutralization test (PRNT) to 50% of control wells for individual animals. Geometric mean titers (GMT) shown are identical to those seen in Table 3. To determine significant changes in titers between groups, Tukey HSD tests were done. For all groups, no significant difference was noted between the three groups on Day 0 for any of the serotypes. For DV1, both HR-TET and WT-Tet GMTs were significantly higher than Mock titers ( $p<0.05$  and  $p<0.02$  respectively) on Day 14, Day 30 ( $p<0.05$  and  $p<0.005$  respectively), and Day 62 ( $p<0.0001$  and  $p<0.02$  respectively). There was no difference between WT-Tet and HR-TET for DV1 for any of the days tested. For DV2, no significant difference in GMT was noted between the three test groups on D14. By D30, HR-TET GMT was significantly different from the Mock GMT ( $p<.0005$ ) while there was no statistical difference in GMT for WT-Tet vs Mock or for HR-TET vs WT. On Day 62, both HR-TET and WT-Tet had GMTs significantly different from those of Mock vaccinated animals ( $p<0.001$  for both). For DV3, HR-Tet vaccinated animals had significantly higher GMTs compared to Mock vaccinated animals on Days 14, 30, and 62 ( $p<0.005$  for all days) whereas WT-Tet GMTs were only significantly different from Mock vaccinated animals on D30 and 62 ( $p<0.01$  and  $p<0.0001$  respectively). For DV4, there was no significant difference in GMT between the three groups on D14. By D30, both HR-TET and WT-Tet had GMTs significantly greater than those of Mock vaccinated animals ( $p<0.0001$  for both). This trend

continued for HR-TET out to D62, where HR-TET had a significantly elevated GMT compared to Mock ( $p < 0.0001$ ). At no time point was there a significant difference in GMT between HR-TET and WT-Tet animals.