

496 NHPs. Significant pair wise association between different experiments and models was  
497 tested based on a chi squared test and phi coefficient.

498

499 **Online supplements.**

500

501 **Online supplement 1. *Mycobacterium tuberculosis* transposon (Tn) mutants found to**  
502 **be attenuated for survival in the NHP aerosol model**

503 <sup>a</sup>, Present in two different pools; <sup>b</sup>, The two mutants with identical JHU ID are indeed  
504 genotypically identical (= derived from same parental strain and have the same himar1  
505 Tn inserted at the same site. However, the two strains were made and isolated at two  
506 different experiments) [14]; <sup>c</sup>, Positive control average value of pools 1 and 2 but not  
507 found in pool 3; <sup>d</sup>, By random chance, in a few cases, the transposon point of insertion  
508 can land in the different site; <sup>†</sup>, validated by real time PCR.

509

510 **Online supplement 2. Clinical measures of disease progression.**

511 (A) Temporal changes of body temperature (°C) following exposure to infectious aerosol  
512 of *Mtb* mutants. (B) % Loss of body weight. (C) Whole blood IFN- $\gamma$  release assay  
513 (Primagam, A<sub>450</sub>) at the time of necropsy. The results are shown as mean  $\pm$  SD of  
514 triplicate experiment. The line perpendicular to X-axis and closer to Y-axis indicates a  
515 very likely presence of *Mtb* infection. A second line perpendicular to X-axis and farther  
516 from the Y-axis indicates the acceptance range of mean absorbance of the primate IFN- $\gamma$   
517 positive control. (D) Elevated serum C-reactive protein level (mg/L). (E) Confocal laser  
518 microscopy images show the lung sections of (i) animals belonging to the input pool

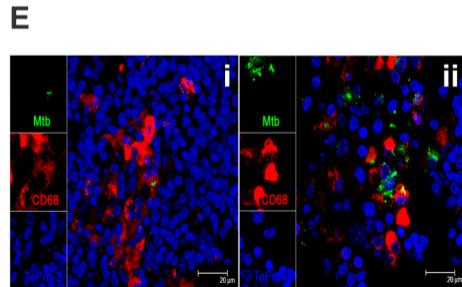
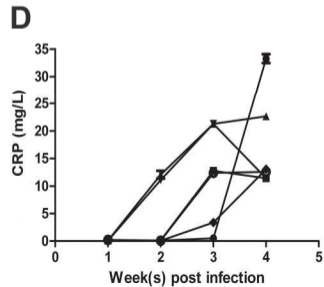
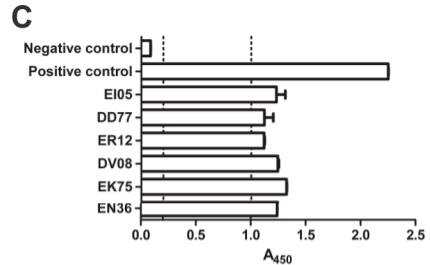
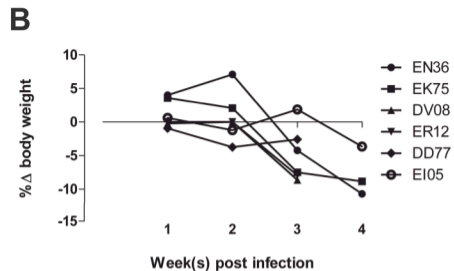
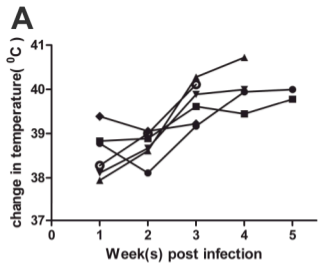
519 (DE81) and (ii) animals belonging to the output pool (DV08) respectively, stained with  
520 *Mtb* (green) and macrophage (red) markers.

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Type of file: table

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Filename: Online\_supplement\_table.doc

**Online Supplement-1. *Mycobacterium tuberculosis* transposon (Tn) mutants found to be attenuated for survival in the NHP aerosol model**

MT/RV#	Symbol	Functional class	Description	Fold change Mean $\pm$ SD	p Value
MT1025.3		10	Hypothetical protein	3.59 $\pm$ 0.49	1.45E-07
MT1622.1		10	Conserved hypothetical protein	6.09 $\pm$ 5.10	0.005
MT1650.1		10	Hypothetical protein	1.99 $\pm$ 0.77	8.08E-05
MT2316		10	Hypothetical protein	1.79 $\pm$ 0.83	0.0002
MT2375		10	Hypothetical protein	2.03 $\pm$ 1.13	0.0005
MT2960 <sup>a†</sup>		10	Hypothetical protein	7.76 $\pm$ 3.20	0.0006
MT2960 <sup>a†</sup>		10	Hypothetical protein	7.13 $\pm$ 4.36	0.001
MT3037		10	Hypothetical protein	7.82 $\pm$ 5.05	0.001
MT3536 <sup>a</sup>		10	Hypothetical protein	2.88 $\pm$ 0.71	4.55E-06
MT3536 <sup>a</sup>		10	Hypothetical protein	5.68 $\pm$ 3.21	0.0007
Rv0068		7	Oxidoreductase	4.57 $\pm$ 1.84	0.0001
Rv0079		10	Hypothetical protein	2.38 $\pm$ 0.88	5.66E-05
Rv0084 <sup>†</sup>	<i>hycD</i>	7	Formate hydrogenlyase, subunit 4	7.31 $\pm$ 4.95	0.002
Rv0157A <sup>b</sup>		10	Hypothetical protein	4.24 $\pm$ 4.14	0.01
Rv0157A <sup>b</sup>		10	Hypothetical protein	4.92 $\pm$ 4.11	0.005
Rv0163		10	Conserved hypothetical protein	2.17 $\pm$ 0.70	2.69E-05
Rv0173	<i>mce1E</i>	3	Virulence factor mce family protein	6.60 $\pm$ 1.44	1.92E-06
Rv0179c	<i>lprO</i>	3	Hypothetical protein	3.63 $\pm$ 0.99	8.53E-06
Rv0213c		7	Methyltransferase, putative	6.45 $\pm$ 2.89	0.0002
Rv0240		0	Hypothetical protein	3.03 $\pm$ 2.25	0.003
Rv0250c		10	Conserved hypothetical protein	2.55 $\pm$ 0.74	0.0001
Rv0336		5	insertion seqs and phages	7.35 $\pm$ 5.19	0.002
Rv0381c		3	Hypothetical protein	5.20 $\pm$ 0.17	8.46E-12
Rv0393 <sup>†</sup>		5	Conserved protein	1.46 $\pm$ 0.14	7.62E-09
Rv0404	<i>fadD30</i>	1	Acyl-CoA synthase	5.19 $\pm$ 3.79	0.003
Rv0466 <sup>†</sup>		10	Hypothetical protein	3.70 $\pm$ 0.51	8.25E-08
Rv0491	<i>regX3</i>	9	DNA-binding response regulator	5.61 $\pm$ 4.50	0.004
Rv0502		10	Acyltransferase family protein	2.95 $\pm$ 1.62	0.0006
Rv0576 <sup>†</sup>		9	Transcriptional regulator	3.09 $\pm$ 0.41	6.47E-08
Rv0580c <sup>†</sup>		10	Hypothetical protein	3.36 $\pm$ 1.09	2.72E-05
Rv0595c <sup>†</sup>		0	Conserved hypothetical protein	7.76 $\pm$ 4.42	0.0008
Rv0654		7	Dioxygenase, putative	8.08 $\pm$ 4.39	0.0006
Rv0671	<i>lpqP</i>	3	Hydrolase/esterase, lpqP	4.52 $\pm$ 1.39	1.88E-05
Rv0687	<i>fabG</i>	7	Oxidoreductase	6.23 $\pm$ 0.60	7.07E-09
Rv0872c	<i>PE_PGRS15</i>	6	PE_PGRS family protein	6.23 $\pm$ 0.71	2.24E-08
Rv0910		10	Conserved hypothetical protein	4.64 $\pm$ 1.73	6.49E-05

Rv0924c	<i>mntH</i>	3	Transport protein, NRAMP family	8.68±2.73	1.69E-05
Rv0948c		10	Hypothetical protein	7.15±0.30	2.11E-11
Rv0954 <sup>†</sup>		3	Antigen 34 kDa	1.44±0.07	1.30E-10
Rv0976c		10	Conserved hypothetical protein	3.56±2.50	0.002
Rv1001	<i>arcA</i>	7	Arginine deiminase	7.07±0.42	2.70E-10
Rv1076	<i>lipU</i>	7	Esterase	5.42±0.14	8.50E-12
Rv1176c <sup>†</sup>		10	Hypothetical protein	5.07±3.95	0.004
Rv1181	<i>pks4</i>	1	Mycocerosic acid synthase	4.92±3.90	0.004
Rv1185c <sup>†</sup>	<i>fad21</i>	1	Acyl-CoA synthase	8.12±3.72	0.0002
Rv1200		3	Sugar transporter family protein	3.63±0.05	0.003
Rv1234		3	cell wall and cell processes	10.02±2.87	1.02E-05
Rv1264		7	Adenylate cyclase, putative	6.49±4.71	0.002
Rv1371 <sup>†</sup>		3	Desaturase-related protein	2.65±0.32	3.41E-08
Rv1433		3	Conserved hypothetical protein	5.73±3.31	0.0008
Rv1448c	<i>tal</i>	7	Transaldolase	2.68± 1.25	0.0002
Rv1489		10	Hypothetical protein	2.46±0.76	1.92E-05
Rv1633	<i>uvrB</i>	2	Excinuclease ABC, subunit B	8.18±4.17	0.0004
Rv1704c <sup>†</sup>	<i>cycA</i>	3	Amino acid permease	4.12±0.18	2.79E-11
Rv1769		10	Conserved hypothetical protein	4.90 ±3.92	0.004
Rv1799	<i>lppT</i>	3	Hypothetical protein	3.71±2.34	0.001
Rv1804c		10	Hypothetical protein	7.52±4.83	0.001
Rv1810		10	Hypothetical protein	2.94±1.17	9.73E-05
Rv1864c <sup>c†</sup>		10	Conserved hypothetical protein	3.09± 1.50	0.03
Rv1879		10	Conserved hypothetical protein	3.35±0.26	1.57E-09
Rv1894c		10	Hypothetical protein	4.32±2.82	0.001
Rv1965	<i>yrbE3B</i>	0	Conserved hypothetical protein	7.21±3.39	0.0002
Rv1966	<i>Mce1A</i>	0	Virulence factor	1.76±0.83	0.0001
Rv1978 <sup>†</sup>		10	Hypothetical protein	9.02±5.50	0.001
Rv2041c		3	Sugar ABC-transporter	2.80± 1.22	0.0001
Rv2046	<i>lppI</i>	3	Hypothetical protein	6.45±3.85	0.001
Rv2072c <sup>†</sup>	<i>cobL</i>	7	Methyltransferase	4.77±0.33	5.58E-10
Rv2077c		3	Hypothetical protein	3.17±1.74	0.0006
Rv2091c		10	Conserved hypothetical protein	2.64±0.57	2.30E-06
Rv2309A		16	Hypothetical protein	3.90±1.33	3.63E-05
Rv2385	<i>lipK</i>	1	Esterase, putative	5.60±2.79	0.0002
Rv2387 <sup>d†</sup>		10	Hypothetical protein	4.19±2.41	0.0008
Rv2387 <sup>d†</sup>		10	Hypothetical protein	10.28±1.17	2.22E-08
Rv2459 <sup>†</sup>		3	Drug transporter	7.04±3.78	0.0005
Rv2478c		10	Hypothetical protein	7.62±5.21	0.002
Rv2485c	<i>lipQ</i>	7	Carboxylesterase family protein	3.04±1.84	0.001
Rv2588c	<i>yajC</i>	3	Protein-export membrane protein	4.11±4.22	0.01
Rv2597		3	Hypothetical protein	7.48±0.20	1.14E-12
Rv2641	<i>cadI</i>	10	Conserved hypothetical protein	2.82±0.39	8.84E-08

Rv2686c		3	Hypothetical protein	3.83±2.33	0.001
Rv2690c		3	Amino acid permease, putative	5.85±4.68	0.004
Rv2694c		10	Conserved hypothetical protein	3.20±0.36	2.26E-08
Rv2725c	<i>hflX</i>	7	GTP-binding protein (hflX)	5.56±4.28	0.003
Rv2741	<i>PE_PGRS47</i>	6	PE_PGRS family protein	6.07±2.64	0.0001
Rv2796c <sup>†</sup>	<i>lppV</i>	3	Hypothetical protein	1.94±0.13	6.08E-10
Rv2819c		10	CRISPR-associated protein,	1.57±0.69	0.0001
Rv2820c		16	CRISPR-associated protein	7.19±5.05	0.002
Rv2850c		7	Magnesium chelatase, putative	7.05±4.34	0.001
Rv2879c		10	Conserved hypothetical protein	5.85± 3.66	0.001
Rv2911	<i>dacB1</i>	3	D-alanyl-D-alanine carboxypeptidase	3.27±0.69	1.15E-06
Rv2920c	<i>amt</i>	3	Ammonium transporter	5.58±3.26	0.0009
Rv2924c	<i>fpg (mutM)</i>	2	DNA glycosylase	3.46±0.66	5.28E-07
Rv2936 <sup>†</sup>	<i>drrA</i>	3	ABC transporter	9.01±5.52	0.001
Rv3094c		10	Phenol hydroxylase	4.20±4.45	0.01
Rv3111	<i>moaC1</i>	7	Molybdopterin biosynthesis protein	3.96± 2.69	0.002
Rv3117	<i>cysA3</i>	7	Thiosulfate sulfurtransferase	7.88±3.08	8.72E-05
Rv3159c	<i>PPE53</i>	6	PPE family protein	6.24±0.59	6.45E-09
Rv3197 <sup>†</sup>		3	ABC transporter	7.07±4.41	0.001
Rv3297 <sup>†</sup>	<i>nei</i>	2	Endonuclease	7.27±4.61	0.001
Rv3327 <sup>†</sup>		5	IS1547, transposase	6.35±4.96	0.004
Rv3430c		5	IS1540, transposase	3.52±0.18	9.66E-11
Rv3486		10	Conserved hypothetical protein	6.25±5.01	0.004
Rv3494c	<i>mce4F</i>	0	Virulence factor mce family protein	5.58±2.52	0.0001
Rv3495c	<i>lprN</i>	0	Virulence factor mce family protein	3.73±1.23	2.59E-05
Rv3683		10	Conserved hypothetical protein	3.99± 2.77	0.002
Rv3727		7	Hypothetical protein	0.80±0.04	1.01E-10
Rv3741c <sup>†</sup>		7	Hypothetical protein	7.23±5.55	0.008
Rv3775	<i>lipE</i>	7	Conserved hypothetical protein	6.51±5.04	0.004
Rv3787c <sup>†</sup>		10	Conserved hypothetical protein	6.70±3.57	0.01
Rv3793	<i>embC</i>	3	Arabinosyl transferase	6.77±0.39	1.96E-10
Rv3830c	<i>mce4E</i>	9	Transcriptional regulator	5.28±0.56	6.38E-09
Rv3871 <sup>†</sup>		3	FtsK/SpoIIIE family protein	9.32±4.91	0.002