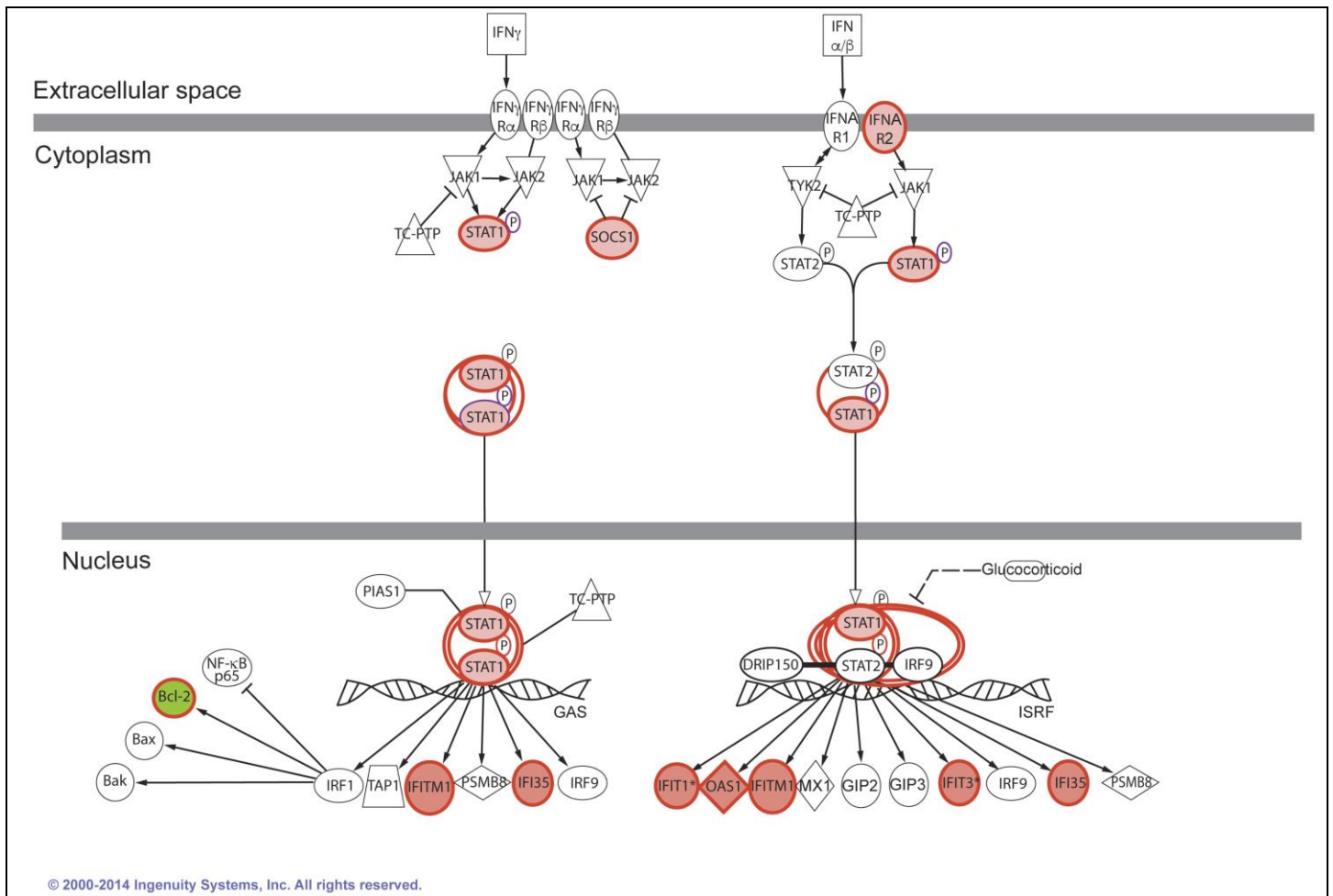
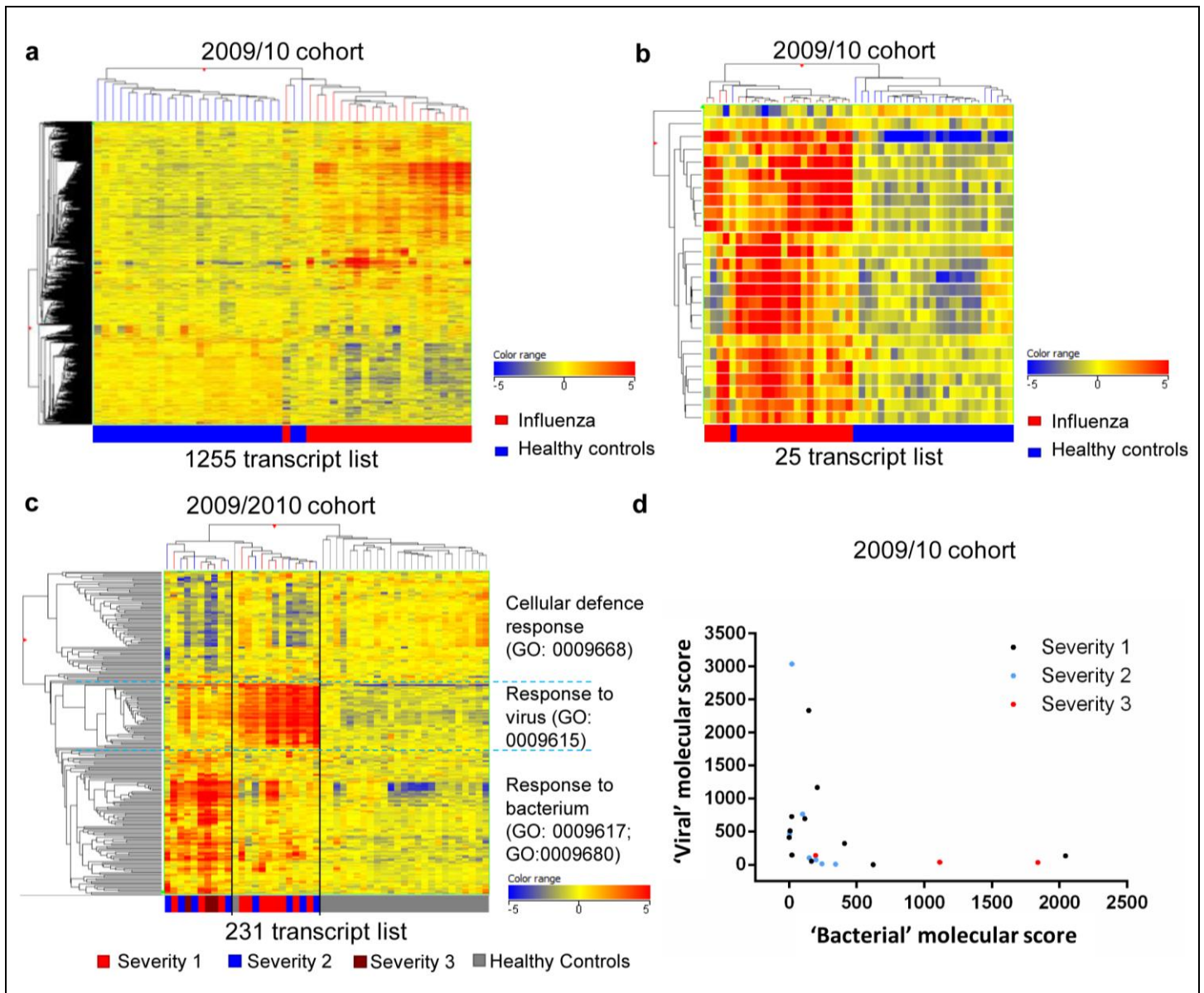




## Supplementary Figure 1

### Interferon signaling pathway

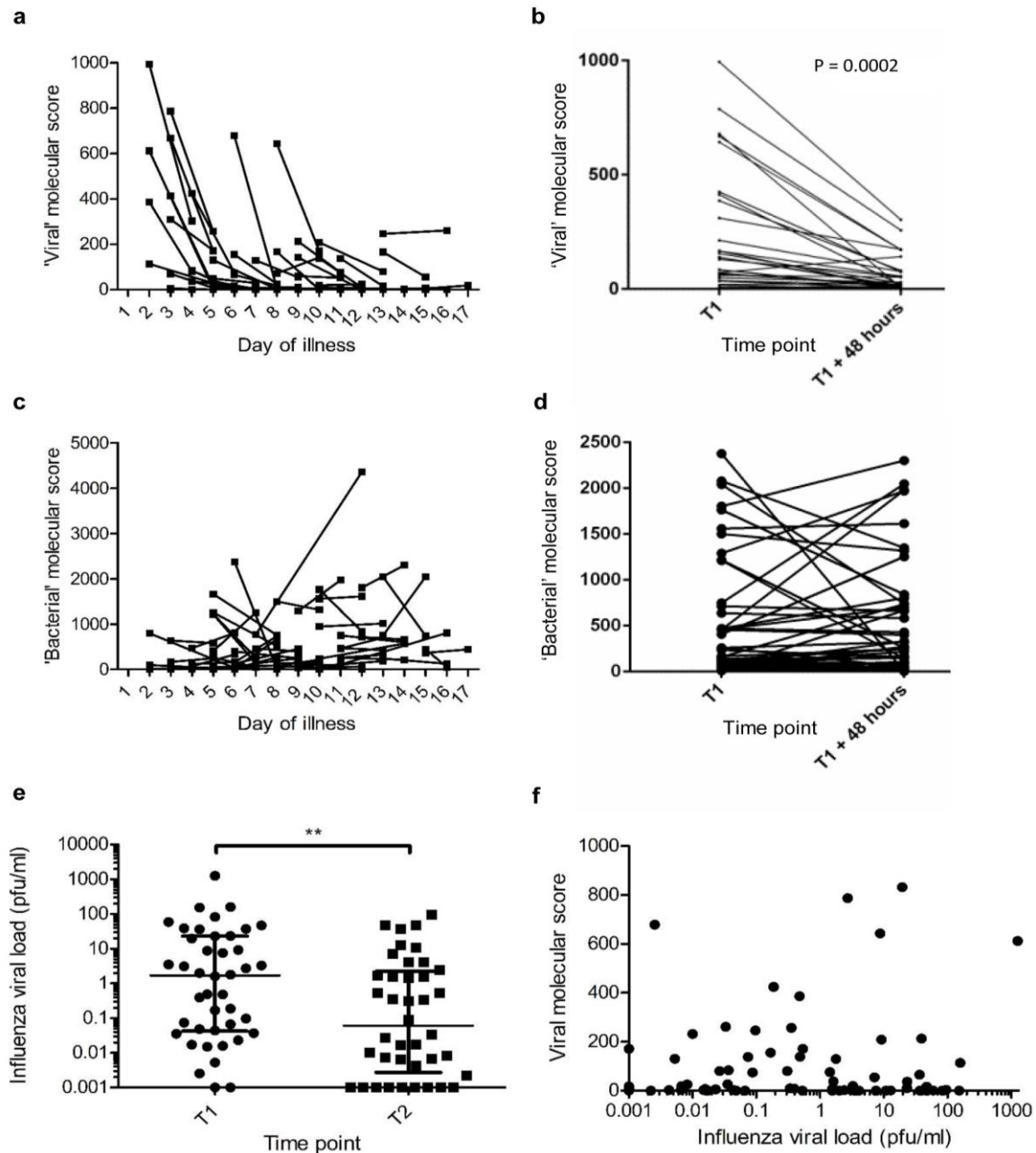
IPA canonical pathway for interferon signaling, identified as one of the top five canonical pathways for upregulated transcripts shown in Figure 1d (2010/11 cohort). Red shading represents up-regulated genes, blue represents down-regulated genes.



**Supplementary Figure 2**

### Validation of transcriptional signatures in an independent cohort

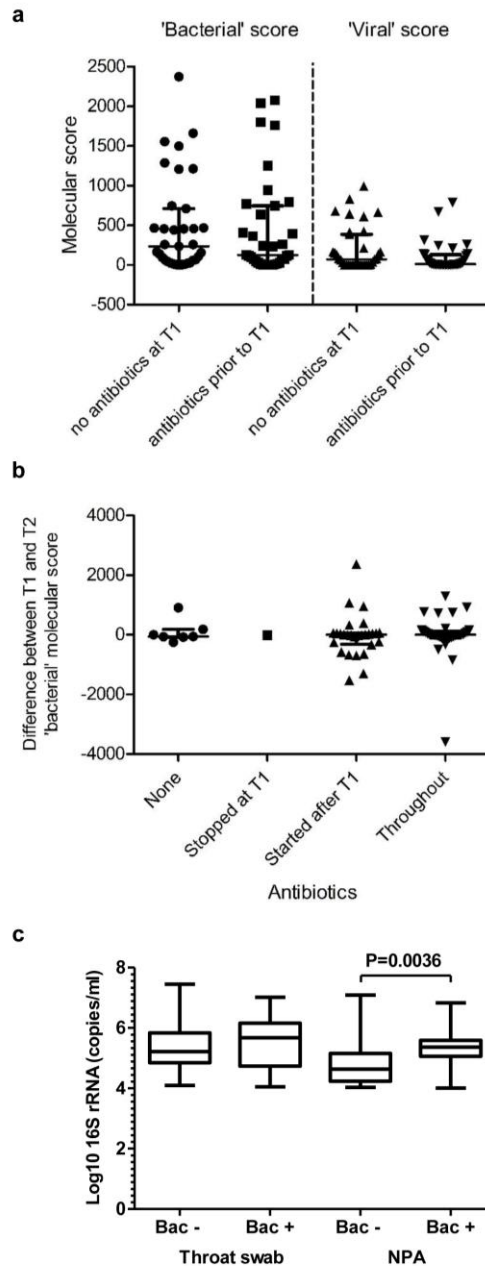
a) 2009/2010 cohort clustered on individuals and transcripts (Pearson's uncentered with averaged linkage) using 1255 transcript list (from Figure 1). (b) 2009/2010 cohort clustered on individuals and transcripts (Pearson's uncentered with averaged linkage) using 25 transcript list (from Figure 1). (c) 2009/2010 cohort clustered on individuals and transcripts (Pearson's uncentered with averaged linkage) using 231 transcript list of severity (from Figure 2, transcripts retained if >2FC between severity 3 and severity 1&2). GO Terms analysis of 3 major branches of the transcripts dendrogram was undertaken and listed next to the heat-map. (d) Using 51 and 112 transcripts lists (from Figure 3) 'viral response' and 'bacterial response' molecular scores were calculated and plotted for each influenza patient (relative to healthy controls). Cases were coded according to severity of illness, indicated by the colour of the respective dots (severity 1, black; severity 2, blue; severity 3, red).



**Supplementary Figure 3**

### Change of 'viral' and 'bacterial' molecular scores over time and association with influenza viral load

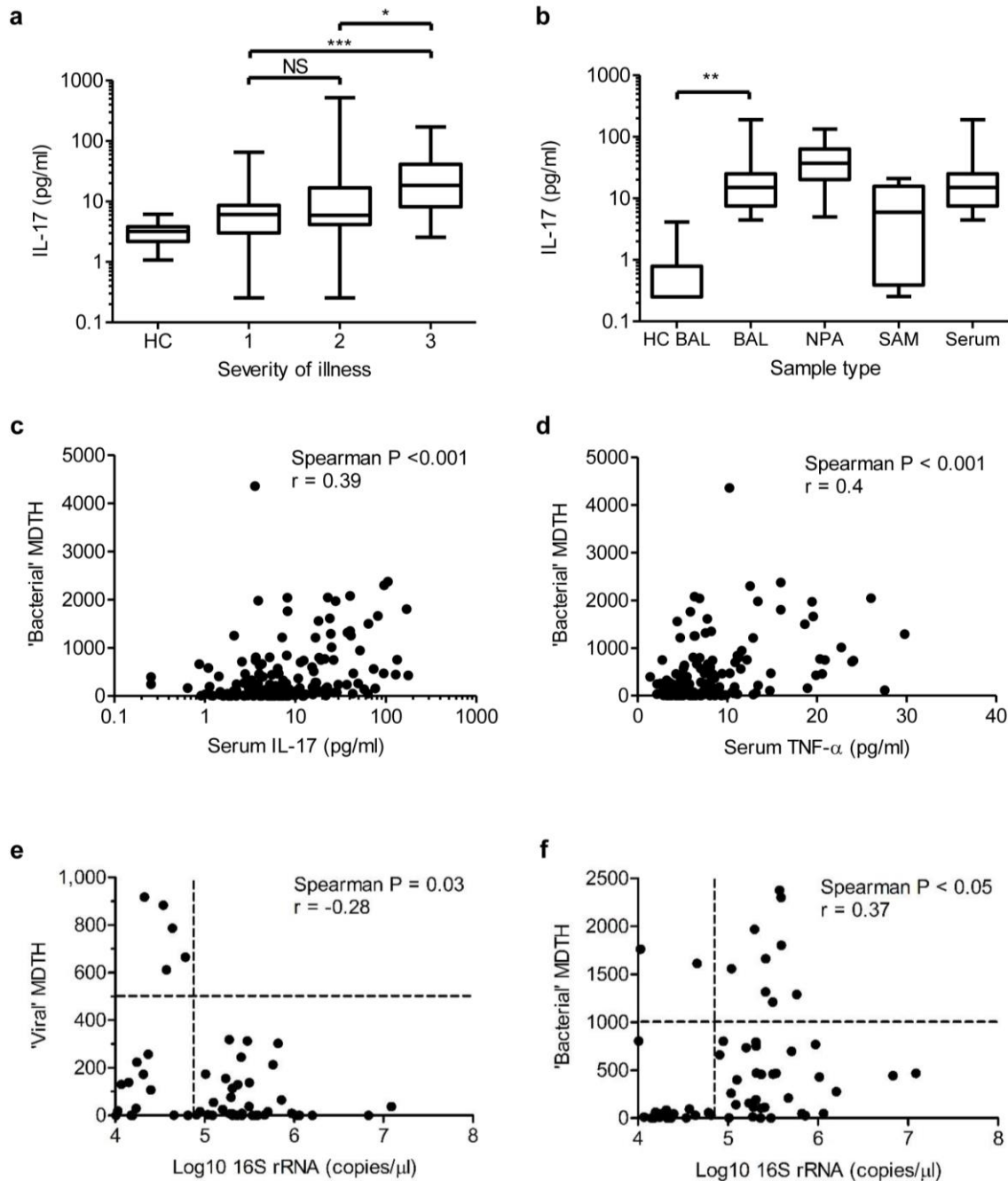
**(a)** 'Viral' molecular scores plotted for 59 influenza patients (2010/11 cohort) who provided T1 and T2 samples, plotted against respective day of illness at time of sampling. **(b)** Change in 'viral' molecular score between first (T1) and precise second time point (48 hours after T1) in 41 patients with appropriate samples available ( $P = 0.0002$ , Mann-Whitney test, two-tailed). **(c)** 'Bacterial' molecular score plotted for 59 influenza patients who had both a T1 and a T2 sample, shown plotted against respective day of illness. **(d)** Change in 'bacterial' molecular score between T1 and precise T2 (48h post T1), in 41 patients with appropriate samples available (NS, Mann-Whitney test, two-tailed). **(e)** Influenza viral load estimation (pfu/ml) in nasopharyngeal samples obtained at T1 ( $n=42$ ) and T2 ( $n=40$ ). Bars show the median and interquartile range. Zero values were reassigned a value of 0.001 for display purposes. Mann-Whitney test (two-tailed); \*\*  $P=0.0094$ . **(f)** Relationship between influenza viral load (pfu/ml) at T1 or T2 and the simultaneous 'viral' molecular score on whole blood ( $n=82$ ).



**Supplementary Figure 4**

#### Administration of antibiotics does not affect 'bacterial' or 'viral' molecular scores

**(a)** Influenza patients (2010/11 cohort) presenting within the first 14 days of illness grouped by administration of any antibiotic (n=35) or no administration of antibiotics (n=35) in the 24 hours prior to T1 sampling. There was no difference (NS, Mann-Whitney test, two tailed) in either bacterial or viral molecular scores between the two groups. Bars show the median and interquartile range. **(b)** Prescription of antibiotics after T1 did not significantly influence 'bacterial' molecular score ( $P=0.9616$ , Kruskal Wallis test). Fifty-nine influenza patients who had both T1 and T2 samples were grouped by those who did not receive antibiotics (n=7), those whose antibiotics were stopped at T1 (n=1), those who had antibiotics prescribed after T1 but before T2 (n=24), and those who were receiving antibiotics at both T1 and T2 (N=27). Bars show median with interquartile range. **(c)** Total 16S rRNA copies at T1 in throat swabs and NP aspirate in patients adjudicated to be with or without bacterial co-infection. Those with confirmed bacterial infections (Bac +) had greater levels of total 16S rRNA copies in NP aspirate than those deemed to be without co-infection (Bac -) (Mann-Whitney test,  $P = 0.036$ ). Throat swab Bac -, n=44; throat swab bac +, n=53; NP aspirate Bac -, n=17; NP aspirate Bac +, n=41.



**Supplementary Figure 5**

**Correlation of serum cytokines and bacterial load in nasopharynx with 'viral' and 'bacterial' molecular distance to health**

**(a)** Levels of IL-17 in the serum of healthy controls (HC,  $n=36$ ) and influenza infected patients (severity 1-3;  $n=59$ ,  $n=43$ , and  $n=31$ , respectively). **(b)** Concentration of IL-17 in bronchoalveolar lavage (BAL) of HC ( $n=11$ ) and from influenza patients' BAL ( $n=8$ ), NPA ( $n=8$ ), nasadoptin fluid (SAM;  $n=8$ ) and serum ( $n=8$ ). **(c)** Correlation of levels of IL-17 in serum ( $n=165$ ) with the bacterial MDTH (Spearman  $R = 0.39$ ,  $P < 0.001$ ). **(d)** Correlation of levels of TNF- $\alpha$  in serum ( $n=165$ ) with bacterial MDTH (Spearman  $R = 0.4$ ,  $P < 0.01$ ). **(e)** Total 16S rRNA gene copies in NP aspirate samples ( $n=58$ ) are inversely correlated with the viral MDTH (Spearman  $R = -0.28$ ,  $P$  value  $< 0.05$ ). **(f)** Total 16S rRNA gene copies in NP aspirate samples ( $n=58$ ) are positively correlated with the bacterial MDTH (Spearman  $R = 0.37$ ,  $P$  value  $< 0.05$ ).

