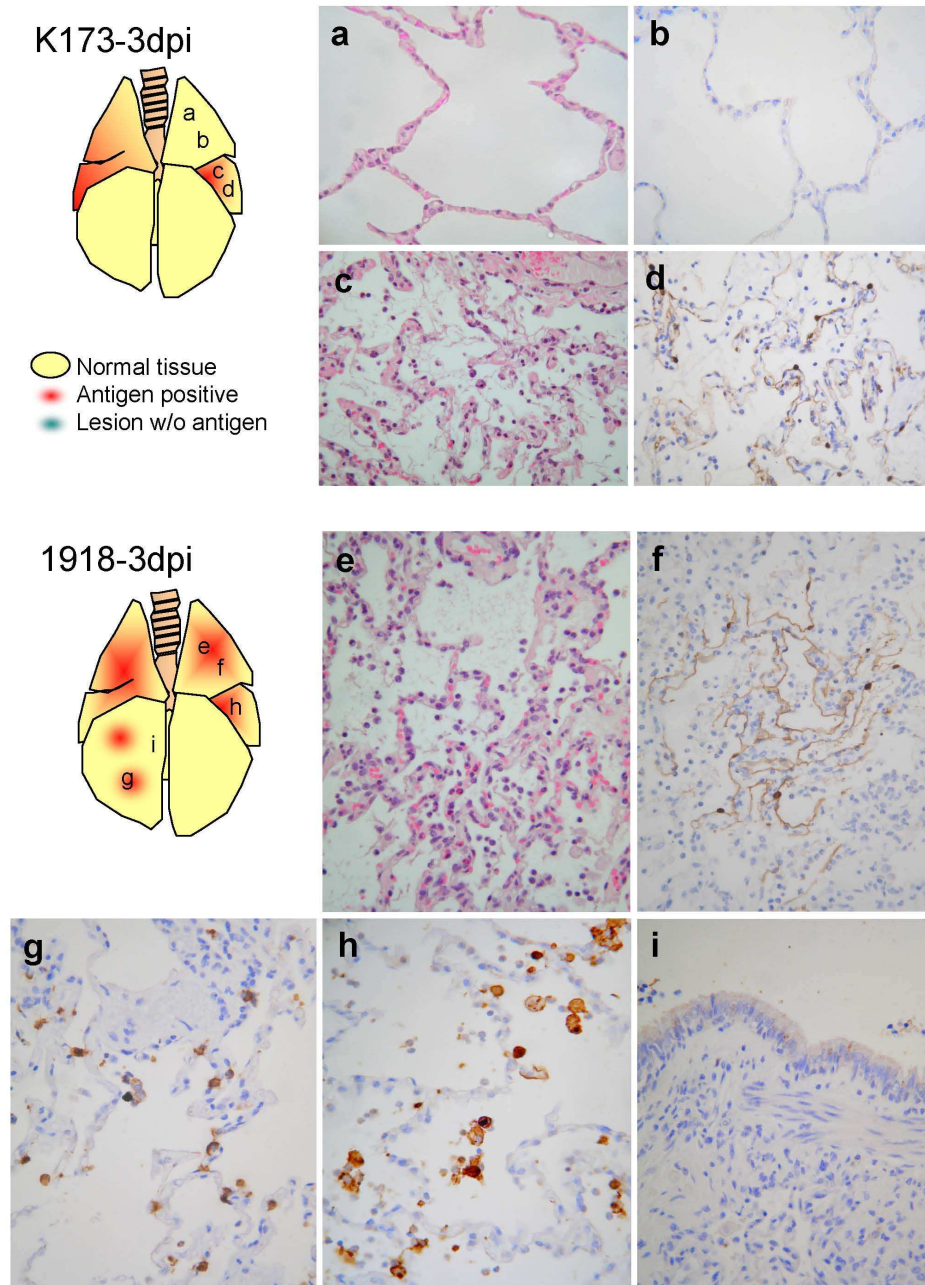
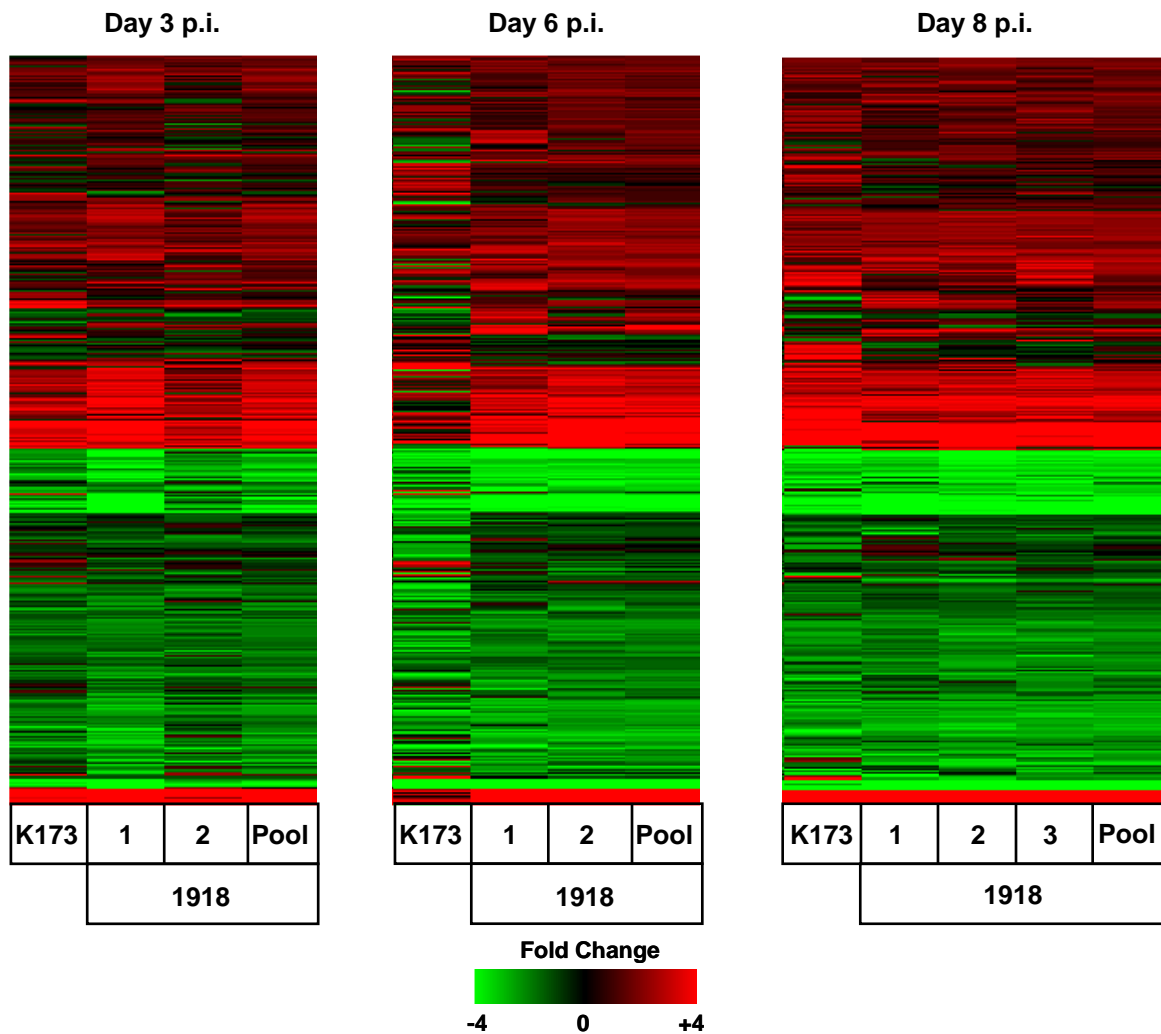


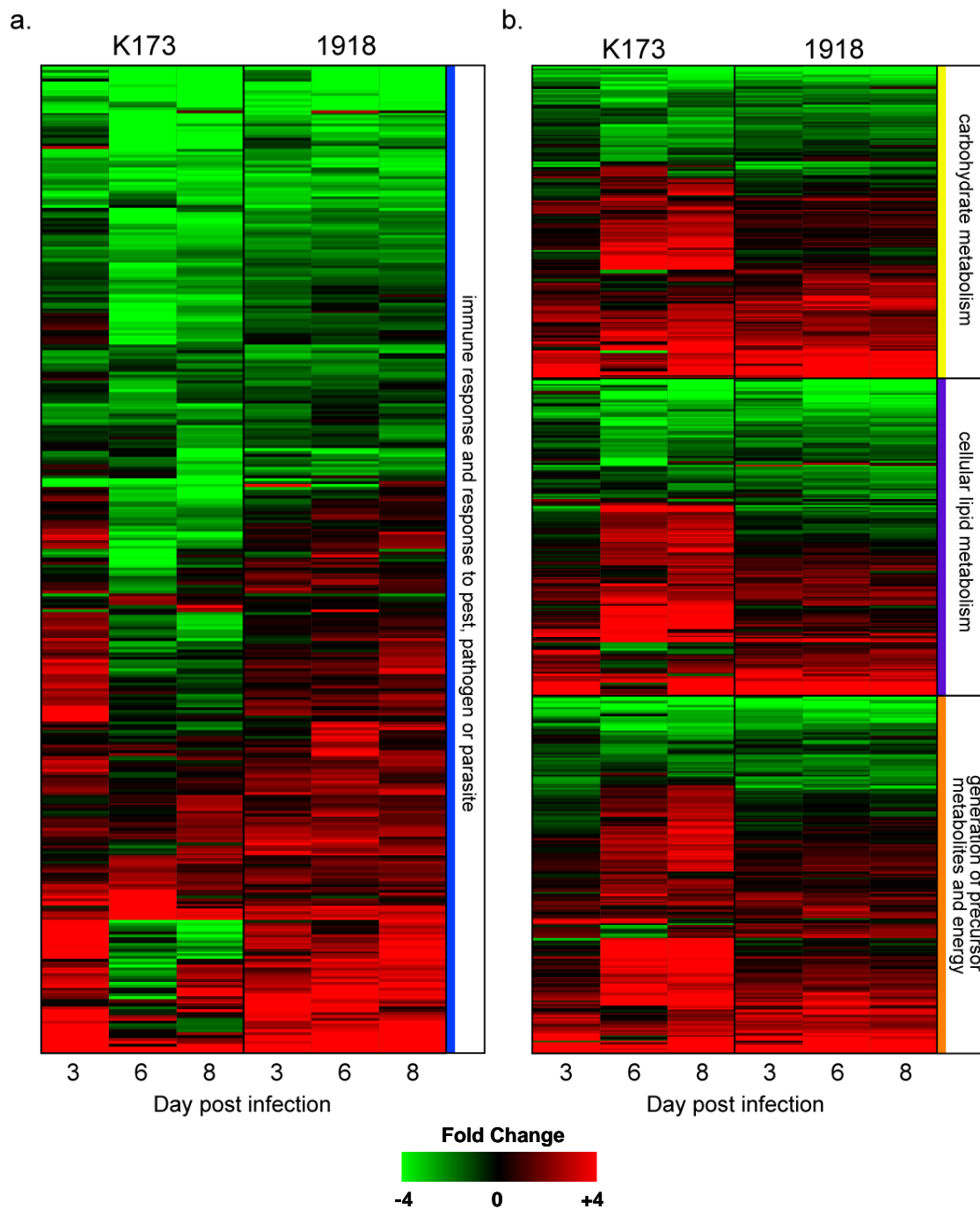
Supplementary Figure 1 Gross pathology of lungs on day 8 postinfection. **a**, Extensive lesions and haemorrhage are visible in the lungs of 1918 virus-infected animals, consistent with the severe clinical signs and reduced lung function in all of these animals by day 8 p.i. **b**, By contrast, lungs of the K173-infected animal were not visibly affected by infection.



Supplementary Figure 2 Pathologic examination of lungs infected with the 1918 or K173 virus on day 3 p.i. **a**, In a K173-infected animal most of the lung, including the cranial and caudal lobes, were normal in appearance and **b**, no viral antigen was detected. **c**, Focal mild alveolitis with intra-alveolar exudation of neutrophils, lymphocytes, and macrophages was detected in the middle lobes of both lungs. **d**, Many of the nuclei and the flattened linear cytoplasm in the regions with mild alveolitis were positive for viral antigen (brown). However, there were no antigen-positive cells in the alveolar space. **e**, Histology revealed scattered mild to moderate alveolitis. **f**, Viral antigen was sporadically detected as linear staining (brown) along the alveolar wall, similar to lungs of the K173 virus-infected animal. **g**, However, most viral antigen was observed in cells with plump cytoplasm lining the alveolar wall. **h**, In contrast to the K173-infected animal, many desquamated antigen-positive cells were detected in parts of the alveolar space. **i**, Viral antigen was not frequently detected in the bronchioles.



Supplementary Figure 3 Overall gene expression profiles in individual and pooled infections. Hierarchical clustering diagram showing the expression profiles of individual animals (n=4 arrays per animal) and Resolver analysis software error-weighted *in silico* pooling of replicate animals (n=8 arrays for 1918 days 3 and 6 p.i., and n=12 arrays for 1918 day 8 p.i.). Individual animals are denoted as numbers 1 to 3 and the *in silico* pooled samples are denoted as Pool. Genes displayed were changed >2-fold (P<0.01) in at least 1 of the experiments compared to uninfected controls.



Supplementary Figure 4 Selected gene ontology (GO) analysis of differentially regulated genes in K173 and 1918 virus infected bronchus. Hierarchical clustering diagram showing the expression profiles of individual K173 animals ($n=4$ arrays per animal) and in silico pooled 1918 replicate animals ($n=8$ arrays for 1918 days 3 and 5 p.i., and $n=12$ arrays for 1918 day 8 p.i.). GO analysis was performed using the FatiGO analysis suite (<http://fatigo.bioinfo.cipf.es/>).

Supplementary Table 1 Virus isolation from swabs ^a											
Swab	Day p.i.	1918 animals							K173 animals		
		1	2	3	4	5	6	7	1	2	3
Nasal	3	+	+	-	+	-	+	+	-	-	-
	6	+	+	+	NA ^b	+	+	NA ^b	+	NA ^b	-
	8	-	+	NA ^c	-	-	NA ^c	-	NA ^c	-	-
Throat	3	+	+	-	+	-	-	+	-	-	-
	6	+	+	+	NA ^b	-	-	NA ^b	+	NA ^b	+
	8	-	+	NA ^c	-	-	NA ^c	-	NA ^c	-	-

^avirus isolated (+), virus not isolated (-) in MDCK cells.

^bNot available, euthanized on day 3 p.i.

^cNot available, euthanized on day 6 p.i.

Supplementary Table 2 Description of genes listed in Fig.4

Fig. 4B Gene List

Primary Sequence Name	Sequence Description	Accession #
IFNA17	Interferon, alpha 17	NM_021268
IFNA21	Interferon, alpha 21	NM_002175
IFNA6	Interferon, alpha 6	NM_021002
IFNA16	Interferon, alpha 16	NM_002173
IFNA1	Interferon, alpha 1	NM_024013
IL17B	Interleukin 17B	NM_014443
CCL27	Chemokine (C-C motif) ligand 27	NM_006664
CXCL6	Chemokine (C-X-C motif) ligand 6	NM_002993
CXCL1	Chemokine (C-X-C motif) ligand 1	NM_001511
CXCL13	Chemokine (C-X-C motif) ligand 13	NM_006419
CCL11	Chemokine (C-C motif) ligand 11	NM_002986
IL8	Interleukin 8	NM_000584
CXCL11	Chemokine (C-X-C motif) ligand 11	NM_005409
CXCL10	Chemokine (C-X-C motif) ligand 10	NM_001565
CXCL2	Chemokine (C-X-C motif) ligand 2	NM_002089
IL6	Interleukin 6 (interferon, beta 2)	NM_000600

Fig. 4C Gene List

Primary Sequence Name	Sequence Description	Accession #
HLA-DRB3	Major histocompatibility complex, class II, DR beta 3	NM_022555
HLA-DRB5	Major histocompatibility complex, class II, DR beta 3	AF490771
HLA-DRB1	Major histocompatibility complex, class II, DR beta 4	NM_002124
IFITM2	Interferon induced transmembrane protein 2 (1-8D)	NM_006435
IFITM3	Interferon induced transmembrane protein 3 (1-8U)	NM_021034
IFIT5	Interferon-induced protein with tetratricopeptide repeats 5	NM_012420
IFIH1	(MDA5) Interferon induced with helicase C domain 1	NM_022168
IFI35	Interferon-induced protein 35	NM_005533
IRF1	Interferon regulatory factor 1	NM_002198
RTP4	28kD interferon responsive protein	NM_022147
IFI16	Interferon, gamma-inducible protein 16	NM_005531
EIF2AK2	Eukaryotic translation initiation factor 2-alpha kinase 2	NM_002759
HLA-B	Major histocompatibility complex, class I, B	NM_005514
MR1	Major histocompatibility complex, class I-related	NM_001531
SP110	SP110 nuclear body protein	NM_004510
ADAR	Adenosine deaminase, RNA-specific	NM_001111
HLA-A	Major histocompatibility complex, class I, A	NM_002116
HLA-C	Major histocompatibility complex, class I, C	NM_002117
IFITM1	Interferon induced transmembrane protein 1 (9-27)	NM_003641
G1P3	Interferon, alpha-inducible protein (clone IFI-6-16)	NM_002038
DDX58	(RIG-I) DEAD (Asp-Glu-Ala-Asp) box polypeptide 58	NM_014314
IRF2BP2	Interferon regulatory factor 2 binding protein 2	BC020516
SOC56	Suppressor of cytokine signaling 6	NM_004232
IFIT2	Interferon-induced protein with tetratricopeptide repeats 2	NM_001547
IFIT3	Interferon-induced protein with tetratricopeptide repeats 3	NM_001549
IFIT1	Interferon-induced protein with tetratricopeptide repeats 1	NM_001001887
MX2	Myxovirus (influenza virus) resistance 2 (mouse)	NM_002463
IRF7	Interferon regulatory factor 7	NM_001572
G1P2	Interferon, alpha-inducible protein (clone IFI-15K)	NM_005101
OAS3	2'-5'-oligoadenylate synthetase 3, 100kDa	NM_006187
OAS2	2'-5'-oligoadenylate synthetase 2, 69/71kDa	NM_016817
OAS1	2'-5'-oligoadenylate synthetase 1, 40/46kDa	NM_016816
HLA-E	Major histocompatibility complex, class I, E	NM_005516
HLA-F	Hypothetical protein FLJ35429	NM_018950
IFI44	Interferon-induced protein 44	NM_006417
STAT1	Signal transducer and activator of transcription 1, 91kDa	NM_139266
MX1	Myxovirus (influenza virus) resistance 1, interferon-inducible protein p78	NM_002462
ISG20	Interferon stimulated exonuclease gene 20kDa	NM_002201
GBP1	Guanylate binding protein 1, interferon-inducible, 67kDa	NM_002053
OASL	2'-5'-oligoadenylate synthetase-like	NM_003733