



**Supplementary Figure S1. Gating Strategy for Systems Serology.** (A) Luminex-based gating strategy to determine antibody isotype and subclass binding to a target antigen. (B) Antibody-dependent neutrophil phagocytosis (ADNP) gating strategy to determine opsinophagocytic activity towards a target antigen by neutrophils. (C) Antibody-dependent cellular phagocytosis (ADCP) gating strategy to determine opsinophagocytic activity towards a target antigen by monocytes. (D) Antibody-dependent complement deposition (ADCD) gating strategy to determine the amount of complement deposited in response to a target antigen. (E) Natural killer cell activity gating strategy to determine the amount of degranulation as measured by surface CD107a expression or pro-inflammatory cytokine release as measured by interferon gamma (IFN- $\gamma$ ) and MIP-1b expression.

**Supplementary Table S2: Reagents and Resource<sup>1</sup>**

<b>REAGENT or RESOURCE</b>	<b>SOURCE</b>	<b>IDENTIFIER</b>
Anti-Human IgG1-PE	Southern Biotech	HP6001
Anti-human IgG2-PE	Southern Biotech	31-7-4
Anti-human IgG3-PE	Southern Biotech	HP6050
Anti-human IgG4-PE	Southern Biotech	HP6025
Anti-human IgM-PE	Southern Biotech	SA-DA4
Anti-human IgA1-PE	Southern Biotech	HP6025
Anti-CD66b Pac Blue	BioLegend	305112
Anti-CD107a	BD Biosciences	555802
Anti-CD3	BD Biosciences	558117
Anti-CD16	BD Biosciences	557758
Anti-CD56	BD Biosciences	557747
Anti-IFN $\gamma$	BD Biosciences	340449
Anti-CCL4	BD Biosciences	550078
Anti-C3b	MP Biomed	855385
PE-Streptavidin	Agilent Technologies	PB32-10
Guinea Pig Complement	Cedarlane	CL4051
Protein Transport Inhibitor	BD Biosciences	554724
Brefeldin-A	Sigma	B7651
NHS-Sulfo-LC-LC Kit	ThermoFisher	21435
Zebra-Spin Desalting and Chromatography Columns	ThermoFisher	89882
RosetteSep NK Enrichment Kit	Stem Cell Technologies	15065
Fix & Perm Cell Permeabilization Kit	ThermoFisher	GAS002S-100
R Studio V 1.4.1103	RStudio, PBC	Open Source
GraphPad Prism	GraphPad Software, LLC	Ragon Site License
FlowJo V. 10.8	FlowJo, LLC	<a href="http://www.flowjo.com/solutions/flowjo/downloads">www.flowjo.com/solutions/flowjo/downloads</a>
iQue Forecyt	Sartorius	60028
iQue Screener Plus	Intellicyt/Sartorius	11811
384-well HydroSpeed Plate Washer	Tecan	30190112
MagPlex Microspheres	Luminex MFG	MC12001-01
Y-2 HI COBRA sHA	Ted Ross Lab	(Cataloged by region)
Green, Fluorescent Neutravidin Microspheres	ThermoFisher	F8776
Red Fluorescent Neutravidin Microspheres	ThermoFisher	F8775

<sup>1</sup> All the reagents and resources needed for reproducing the experiments in this study, except for antigens.

**Supplementary Table S3: Antigen List for Systems Serology<sup>2</sup>**

<b>Antigens</b>	<b>SOURCE</b>	<b>IDENTIFIER</b>
A/California/07/2009 rHA wt H1N1	Ted Ross Lab	09242019CA2009H17871-P8
A/P-1 COBRA rHA-H1 P1-H1	Ted Ross Lab	P1-H1-7844-001
A/X-6 COBRA rHA H1 X6-H1	Ted Ross Lab	X6-H1-7918-001
A/Singapore/6/1986 H1N1 wt rHA	Ted Ross Lab	H3-7890-002
A/Brisbane/59/2007 (H1N1) wt rHA	Ted Ross Lab	H3-7919-005
A/Perth/16/2009 H3N2 wt rHA	Ted Ross Lab	H3-7975-002
A/Switzerland/9715293/2013 H3N2 wt rHA	Ted Ross Lab	H1-7921-001
A/Singapore/INFIMH-16-0019/2016 H3N2 wt rHA	Ted Ross Lab	06032019SING1986H17889-T
A/X-3 COBRA wt rHA	Ted Ross Lab	H1-7920-001
A/Brisbane/2/2018 wt rHA (H1N1)	Ted Ross Lab	H1-7817-001
A/TJ-5 COBRA wt rHA (H3)	Ted Ross Lab	H1-20018-001
A/J4 COBRA wt rHA (H3)	Ted Ross Lab	H3-7916-002
A/T10 COBRA wt rHA (H3)	Ted Ross Lab	05152019BRIS2007H37917-T
A/NG-2 COBRA wt rHA (H3)	Ted Ross Lab	07102019Perth2009H320191-T
A/Texas/50/2012 wt rHA (H3N2)	Ted Ross Lab	H3-20144-001
Y-2 H1 COBRA sHA	Ted Ross Lab	H1-7877-002
A/Japan/305/1957 wt rHA	Ted Ross Lab	H1-20235-001
Z-7 H2 COBRA sHA	Ted Ross Lab	TJ2-H3-7974-001
A/Panama/2007/1999 wt rHA	Ted Ross Lab	TJ5-H3-7976-001
A/South Australia/34/2019 wt rHA	Ted Ross Lab	H3-20230-001
J-2 H3 COBRA sHA	Ted Ross Lab	H3-20232-001
IAN-8 H5 COBRA sHA	Ted Ross Lab	H3-20165-001
B-COBRA-3 sHA	Ted Ross Lab	H3-20166-001
B/Brisbane/60/2008 wt rHA	Ted Ross Lab	H3-20227-001
NA-I (N1) COBRA tetNA	Ted Ross Lab	H3-20228-001
A/Brisbane/59/2007 tetNA	Ted Ross Lab	H3-20229-001
A/California/04/2009 tetNA	Ted Ross Lab	05152019TX2012H37872-T
A/Hong Kong/4801/2014 tetNA	Ted Ross Lab	H3-20153-001
B/Phuket3073/2013 wt rHA (Yamagata)	Ted Ross Lab	BY-7887-002
Human Cytomegalovirus (HCMV) Glycoprotein B (gB)	Sino Biological	10202-V08H1
Ebola Virus Glyoprotein	IBT Bioservices	0501-015

<sup>2</sup> All the antigens needed for reproducing the assays demonstrated in this study.