Supplementary Figure Legends

Supplementary Fig. 1. Representative gate strategy used for neutrophils analysis.

A classic forward-scatter (FSC) vs side-scatter (SSC) characteristic dot plot was used to select neutrophils population (A) from peripheral blood collected from healthy donors and patients. Autofluorescent (B) and doublets (C-D) were excluded and live cells were selected (E). CD66b+ positive cells (F) were gated and the MFI of surface markers, such as CD62L (G) were assessed. Around 96% of CD66b+ cells are mature neutrophils (CD66b-high/CD16-high) and 4% of CD66b+ cells are CD66b-high/CD16-low, which is suggestive of immature neutrophils or eosinophils (H). Approximately 100,000 gated
events were collected in each analysis. The analysis was performed in a FACSVerse using FACSuite software (BD Biosciences) and FlowJo software (FlowJo LLC).
Supplementary Fig. 2. LPS reduces surface α2-3 sialic acids from human neutrophils. Whole blood containing $1 \times 10^6$ leukocytes from healthy donors were stimulated with 1 µg/mL LPS for 90 min and α2-3 sialic acid contents were assessed by staining cells with biotinylated *Maackia Amurensis* Lectin II (MAL-II) (A) followed by streptavidin-phycoerythrin (PE) incubation. Siglec-9 ligands (B) were labeled by incubation of chimeric protein containing Siglec-9 sialic acid-Ig binding domain fused to a human IgG-Fc portion (Siglec-9-Fc). Siglec-Fc-9 were incubated with α-IgG1-Alexa Fluor 488 before adding the probe to cells. The MFI was analyzed on CD66b$^+$ cells using the gate strategies shown in Supplementary Fig. 1. *$P < 0.05$. Symbols represent
individual donors and data are shown as mean ± SEM from pooled data of two to three independent experiments (n=6-9). Unt = untreated cells; LPS = lipopolysaccharide; dotted line = unstained cells.
Supplementary Fig. 3. Phagocytosis of *E. coli* pHrodo bioparticles at 4 °C and 37 °C. Total leukocytes (1 x10^6) were incubated with *E. coli* pHrodo bioparticles (100 µg/mL) for 60 min at 4°C or 37 °C and the phagocytosis in viable CD66b+ cells was assessed. Symbols represent individual donors and data are shown as mean ± SEM from pooled data of three to four independent experiments (n = 9-12). *P < 0.001.*
Supplementary Fig. 4. CpNeu-induced human neutrophil activation. Total leukocytes (1 x 10⁶) were incubated or not with CpNEU (10 mU, 60 min, 37 °C, 5%
CO₂) CpNEU plus Oseltamivir (100 µM), CpNEU plus Zanamivir (30 µM) or CpNEU plus MAL-II (1 µg/mL). Leukocytes were stained with MAL-II to detect α2-3 sialic acids (A-C) or with cell activation markers CD62L (D-F) and CD66b (G-I). The MFI was analyzed on CD66b⁺ cells. Symbols represent individual donors and data are shown as mean ± SEM from pooled data of two to three independent experiments (n = 5-9) except for F that was made once with n=3. *P < 0.05; **P < 0.01; ***P < 0.001. MAL-II = *Maackia amurensis* lectin II; CpNEU = neuraminidase *Clostridium perfringens*. 
Supplementary Fig. 5. ROS production in neutrophils stimulated with LPS, CpNEU, or PMA. Whole blood from healthy donors containing 1 x 10^6 leukocytes were exposed or not to LPS (1 µg/mL, 90 min) (B and D). Total leukocytes (1 x 10^6) were incubated or not with CpNEU (10 mU, 60 min) (C-D), CpNEU plus Oseltamivir (100 µM) or CpNEU plus Zanamivir (30 µM) (E-G). Leukocytes were incubated with 5 µM CM-H2DCFDA fluorescent probe for 15 min and PMA (10 µM) was used to stimulate ROS production for 10 min (A and E-G). The MFI was analyzed on CD66b^+ cells. Symbols represent individual donors and data are shown as mean ± SEM from pooled data of two independent experiments (n = 2-6). *P < 0.05; **P < 0.01; ***P < 0.001. C = control; CM-H2DCFDA = 5-(and-6)-chloromethyl-2',7'-dichlorodihydrofluorescein diacetate.
acetyl ester; LPS = lipopolysaccharide; CpNEU = neuraminidase *Clostridium perfringens*; PMA = phorbol 12-myristate 13-acetate.
Supplementary Fig. 6. Oseltamivir improved the outcome of *E. coli*-induced sepsis. Sepsis was induced by intraperitoneal (IP) administration of $1 \times 10^7$ CFU/mice *E. coli* (ATCC 25922). Mice were randomly pretreated *per oral* (PO) via (2 hr before infection) and posttreated (6 hr after infection, 12/12 hr, PO, for 4 days) with Oseltamivir
phosphate (Osel, 10 mg/Kg) or saline and their survival rates were monitored over 168 hr (A, n=16). In another set of experiments (n=3-5) mice were randomly pretreated (2 hr before infection) with Oseltamivir phosphate (10 mg/Kg, PO) and the number of neutrophils in bronchoalveolar lavage (BAL, B) and in lung tissue (C) was counted. In peritoneal lavage (PL) infiltrating neutrophils counts (D), TNF (G), IL-17 (H) and the number of colony-forming units (CFU) in PL (E) or blood (F) were determined 4 or 6 hr after infection. Plasma levels of TNF (I), IL-17 (J), AST (K), ALT (L), ALP (M) and total bilirubin (N) were evaluated. The amount of surface α2-3 sialic acids were also assessed in PL SSC\textsuperscript{high}/Gr-1\textsuperscript{high} cells as shown by the representative histograms (O) or MFI (P); dotted line = unstained cells. Mice were also randomly posttreated (starting 6 hr after infection, 12/12 hr, PO, for 4 days) with saline or Oseltamivir phosphate (10 mg/Kg) and their survival rates were monitored over 168 hr (Q). The results are expressed as percent of survival (n=16), mean or median (only for FACS data) ± SEM. *P < 0.05; **P < 0.01; ***P < 0.001. These experiments were repeated 3 times for survival analysis and twice for other parameters. Osel = Oseltamivir; AST = alanine aminotransferase; ALT = aspartate aminotransferase; ALP = alkaline phosphatase; MAL-II = *Maackia amurensis* lectin II.
Supplementary Fig. 7. Oseltamivir enhanced host survival in CLP-induced sepsis.

Severe sepsis was induced by the cecal ligation and puncture (CLP) model. Mice were randomly treated (starting 6 hr after infection, 12/12 h, PO, for 36 hr, n=16) with saline or Oseltamivir phosphate (10 mg/kg) and their survival rates were monitored over 48 hr (A). In another set of experiments, CLP mice were randomly IP treated (started 6 hr after infection, 12/12 hr) during 4 days with 100 µL metronidazole (15 mg/kg)/ceftriaxone (40 mg/kg) (ABX) plus saline or Oseltamivir phosphate (10 mg/kg) by PO and their survival rates (n=12) were monitored over 168 hr (B). Also, mice were subjected to CLP and treated with ABX + saline or ABX + Olsetamivir as described in B.
and euthanized 48 hr after surgery to evaluate the number of neutrophils in BAL (C), lung tissue (D), and peritoneal lavage (PL) (E); TNF (H), IL-17 (I), and CFU (F) were also determined in PL. Blood CFU (G) and plasmatic levels of TNF (J), IL-17 (K), AST (L), ALT (M), ALP (N) and total bilirubin (O) were also evaluated 48 hr after surgery. The amount of surface α2-3 sialic acids were assessed by MAL-II staining in SSC\textsuperscript{high}/Gr-1\textsuperscript{high} cells in PL and analyzed by FACS, as shown by the representative histograms (P) and MFI (Q); dotted line = unstained cells. The results are expressed as percent of survival (n=16), mean or median (only for FACS data) ± SEM. *P < 0.05; ***P < 0.001. These experiments were repeated 3 times for survival analysis and twice for other parameters (n=3-7). ABX = antibiotics (metronidazole/ceftriaxone); Sham = sham-operated. Osel = Oseltamivir; AST = alanine aminotransferase; ALT = aspartate aminotransferase; ALP = alkaline phosphatase; CFU = colony-forming units.
Supplementary Fig. 8. Expression of NEU1 in cell types from COVID-19 critical patients. (A) Gene expression of NEU1, NEU3 and NEU4 across cell types in two critical COVID-19 patients (BIH-CoV-01 and BIH-CoV-04). Size of the circle is proportional to the percentage of cells expressing the reported genes at a normalized expression level higher than one. (B) UMAP analysis colored-coded by cell types in NS, BL, and PSB samples from two critical COVID-19 patients. (C) Normalized expression of NEU1 overlaid on the UMAP space.
Supplementary Fig. 9. NEU activity is increased in plasma from severe COVID-19 patients. NEU activity was evaluated in fresh plasma from severe COVID-19 patients in the presence or absence of Oseltamivir (100 µM) or Zanamivir (30 µM) (A) and in heat-inactivated plasma from COVID-19 patients (B). Neuraminidase isolated from *Clostridium perfringens* (CpNEU) was used to validate the NEU activity assay. MAL-II = *Maackia amurensis* lectin II; CpNEU = neuraminidase *Clostridium perfringens*. 
Supplementary Fig. 10. Working model. PAMPs and DAMPs in severe diseases such as sepsis and COVID-19 lead to neuraminidase activation with shedding of surface sialic acid and neutrophil overactivation, resulting in tissue damage and high mortality rates. On the other hand, neuraminidase inhibitors (e.g., Oseltamivir, Zanamivir) prevent
the sialic acid release to regulate neutrophil response, resulting in infection control and high survival rates.