**Supplementary Figure 1 A(H3N2)vpM virus-induces significantly higher levels of pro-inflammatory cytokines.** Similar cytokine production profile as shown in Figure 1 was observed in PBMCs from four additional donors**.** The production of IL-1β, IL-6 and IFN-α in the culture supernatants of PBMC from four additional donors was examined by Bio-Plex assay as detailed in Materials and Methods section.

**Supplementary Figure 2 UV-inactivation diminished the virus-induced antiviral cytokine production.** IN/11, WS/09 and MN/10 viruses were placed on ice and irradiated using a 254-nm UV stratalinker (Stratagene) for 30 min. No viral growth of UV inactivated samples was observed in a plaque assay. Isolated monocytes were mock infected or infected with either untreated or UV-inactivated viruses and the production of IFN-α and IFN-β in culture supernatants were assayed by ELISA.

**Supplementary Figure 3 RIG-1 and IRF3/7 activation in virus-induced dendritic cells upon H3N2v virus infection.** (A) To detect RIG-I expression, isolated monocytes from PBMCs were infected with IN/11, WS/09 and MN/10 viruses at an MOI of I for 6 h and cells were harvested to assay for RIG-I expression by immunoblotting as described in materials and methods. (B) To examine for IRF7 and 3 translocation, purified monocytes from PBMCs were first infected with IN/11, WS/09 and MN/10 viruses at an MOI of 1 for 6h. Cells were then harvested and cytosolic and nuclear fractions of infected cells were separated using Qproteome Cell Compartment Kit from Qiagen. Proteins specific to each fraction were detected using β-actin for cytosolic fraction and Fibrillarin for nuclear fraction. The expression of IRF3 and7 in both subcellular fractionations was detected by immunoblotting.

**Supplementary Figure 4 Antiviral treatment decreases the production of interferon by dendritic cells.** (A) Monocytes were treated with anti-viral drug Oseltamivir (200µM, Neuraminidase inhibitors) 1 h before or 1 h after IN/11 virus infection (MOI=1, IN/11+Oseltamivir -1h and IN/11+Oseltamivir +1h). 16 h later, supernatants were collected to measure virus titer by plaque assay to confirm the effect of antiviral drug treatment. (B) Isolated monocytes were infected with IN/11 (MOI=1) for 16 h with or without Oseltamivir treatment as described in A. The production of IL-1β, IL-6 and IFN-α in the culture supernatants was assayed by ELISA.

**Supplementary Figure 5 HA and NA from H3N2 virus together with pdmM2 are needed for inflammasome activation.** Two reverse genetics-derived viruses A/swine/Texas/1998 (H3N2) (sw/Tx/98) virus containing either A/California/04/2009(H1N1) (Cal/09) HA and NA (sw/TX/98:Cal/09 HANA) or Cal/09 HA, NA and M (sw/TX/98:Cal/09 HANAM) were provided by Dr. Adolfo García-Sastre (Mount Sinai School of Medicine). Isolated monocytes from PBMC were infected with wild type sw/TX/98 virus or sw/TX/98:Cal/09 HANA or sw/TX/98:Cal/09 HANAM (all infected at an MOI 1) for 6h, 12h, 24h or48h and culture supernatants were collected for assessing IL-1β (A) and IL-6 (B) production. As controls, isolated monocytes were also infected with IN/11, WS/09 and MN/10 viruses with an MOI of 1 for 24h to assay for cytokine production.