Supplemental Information— Data Supporting Antiviral and Vaccine Efficacy

Seasonal Influenza

Antiviral Treatment Efficacy

There are two categories of influenza antiviral drugs: neuraminidase inhibitors and adamantanes. Adamantanes are not recommended for treatment of seasonal influenza because currently circulating strains are resistant to adamantanes, therefore they are not considered in this analysis.[1]

There are three neuraminidase inhibitors used to treat seasonal influenza: oseltamivir, zanamivir, and peramivir. Antiviral treatment is most effective when administered within 48 hours of symptom onset.[2] Treatment efficacy was defined as the reduction in symptom duration of treated individuals infected with seasonal influenza in comparison to individuals receiving a placebo treatment. The weighted averages of the reduction in symptom duration for each antiviral are 39.6%, 18.2%, and 17.8% for oseltamivir, zanamivir, and peramivir, respectively.

Table S1. Reduction in Symptom Duration by Antiviral

Antiviral	Reduction in Symptom Duration	Reference
Oseltamivir	56%	3
	40%	4
	30%	5
	26%	6
Weighted average	**39.6%**	
Zanamivir	14.3%	7
	17%	8
	23%	9
	33%	10
Weighted average	**18.2%**	

[1] Centers for Disease Control and Prevention. Use of Antivirals: Background and Guidance on the Use of Influenza Antiviral Agents. http://www.cdc.gov/flu/professionals/antivirals/antiviral-use-influenza.htm. Last Update Feb 25, 2015. Accessed

[2] Ibid.

[3] Cheung DH *et al* (2015) Association of Oseltamivir Treatment With Virus Shedding, Illness, and Household Transmission of Influenza Viruses. *The Journal of infectious diseases* 212**:** 391-396

[4] Nicholson KG *et al* (2000) Efficacy and safety of oseltamivir in treatment of acute influenza: a randomised controlled trial. Neuraminidase Inhibitor Flu Treatment Investigator Group. *Lancet* 355**:** 1845-1850

[5] Treanor JJ *et al* (2000) Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza: a randomized controlled trial. US Oral Neuraminidase Study Group. *JAMA* 283**:** 1016-1024

[6] Whitley RJ *et al* (2001) Oral oseltamivir treatment of influenza in children. *The Pediatric infectious disease journal* 20**:** 127-133

[7] Monto AS *et al* (1999c) Efficacy and safety of the neuraminidase inhibitor zanamivirin the treatment of influenza A and B virus infections. *The Journal of infectious diseases* 180**:** 254-261

[8] Monto AS *et al* (1999a) Randomized, placebo-controlled studies of inhaled zanamivir in the treatment of influenza A and B: pooled efficacy analysis. *The Journal of antimicrobial chemotherapy* 44 Suppl B**:** 23-29

[9] Hedrick JA *et al* (2000) Zanamivir for treatment of symptomatic influenza A and B infection in children five to twelve years of age: a randomized controlled trial. *The Pediatric infectious disease journal* 19**:** 410-417

[10] Lalezari J *et al* (2001) Zanamivir for the treatment of influenza A and B infection in high-risk patients: a pooled analysis of randomized controlled trials. *Archives of internal medicine* 161**:** 212-217

Antiviral	Reduction in Symptom Duration	Reference
Peramivir	15.8%	11
	27.3%	12
	16.2%	13
	14.1%	14
Weighted average	**17.8%**	

Antiviral treatment is also associated with a reduced risk of mortality in influenza patients. Treatment of adult influenza patients with antivirals was associated with increased survival or reduced mortality (OR 0.22). The odds ratios below are reported as the ratio of treated to untreated risk of death. An OR of 0.22 indicates that treated influenza patients have about 5 times lower odds of dying than untreated influenza patients.

Table S2. Antiviral Treatment Associated with Reduced Mortality in Influenza Patients

Number of Patients	Odds Ratio	Reference
449	0.13	15
327	0.21	16
539	0.27*	17
356	0.26	18
Weighted average	**0.22**	

**Hazard ratio*

Seasonal influenza patients treated with antivirals have been shown to have lower virus titers and shed the virus for a shorter duration. Patients treated with oseltamivir experience, on average, a 34.5% reduction in viral titer compared to untreated patients, while patients treated with zanamivir experience an 18.3% reduction in viral titer. Based on one study, oseltamivir-treated patients saw a reduction of 46.7%,[19] while the viral shedding in zanamivir patients was reduced by 26%. Peramivir treatment can reduce up to 73.2% of the virus titer, and 68.8% of the time of virus shedding.[20]

Table S3. Reduction in Viral Titer

Treatment	Treated Virus Titer	Untreated Virus Titer	Percent Reduction	Reference
Oseltamivir	243 $\log_{10}$ $TCID_{50}$ x h/ml	303 $\log_{10}$ $TCID_{50}$ x h/ml	19.8%	21
	1.3 $\log_{10}$ $TCID_{50}$/ml	2.3 $\log_{10}$ $TCID_{50}$/ml	43.5%	22

[11] Whitley R *et al* (2014) Single dose peramivir for the treatment of acute seasonal influenza: integrated analysis of efficacy and safety from two placebo-controlled trials. *Antiviral therapy*

[12] Kohno S *et al* (2010) Efficacy and safety of intravenous peramivir for treatment of seasonal influenza virus infection. *Antimicrob Agents Chemother* 54**:** 4568-4574

[13] ClinicalTrials.gov. Evaluation of the Efficacy and Safety of Peramivir in Subjects With Uncomplicated Acute Influenza. https://clinicaltrials.gov/ct2/show/results/NCT00419263. Last Update Jan 28, 2015. Accessed Aug 24, 2015.

[14] Hata A *et al* (2014) Safety and efficacy of peramivir for influenza treatment. *Drug design, development and therapy* 8**:** 2017-2038

[15] Hanshaoworakul W *et al* (2009) Severe human influenza infections in Thailand: oseltamivir treatment and risk factors for fatal outcome. *PLoS One* 4**:** e6051

[16] McGeer A *et al* (2007) Antiviral therapy and outcomes of influenza requiring hospitalization in Ontario, Canada. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 45**:** 1568-1575

[17] Lee N *et al* (2010) Outcomes of adults hospitalised with severe influenza. *Thorax* 65**:** 510-515

[18] Lee N *et al* (2008) Antiviral treatment for patients hospitalized with severe influenza infection may affect clinical outcomes. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 46**:** 1323-1324

[19] Hayden FG *et al* (1999) Use of the selective oral neuraminidase inhibitor oseltamivir to prevent influenza. *The New England journal of medicine* 341**:** 1336-1343

[20] Barroso L *et al* (2005) Efficacy and tolerability of the oral neuraminidase inhibitor peramivir in experimental human influenza: randomized, controlled trials for prophylaxis and treatment. *Antiviral therapy* 10**:** 901-910

[21] Whitley RJ *et al* (2001) Oral oseltamivir treatment of influenza in children. *The Pediatric infectious disease journal* 20**:** 127-133

[22] Treanor JJ *et al* (2000) Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza: a randomized controlled trial. US Oral Neuraminidase Study Group. *JAMA* 283**:** 1016-1024

Treatment	Treated Virus Titer	Untreated Virus Titer	Percent Reduction	Reference
	78.2 log_{10} $TCID_{50}$ x h/ml	130.8 log_{10} $TCID_{50}$ x h/ml	40.2%	23
Average			**34.5%**	
Zanamivir	199.08 log_{10} $TCID_{50}$ x day/ml	219.82 log_{10} $TCID_{50}$ x day/ml	9.4%	24
	2.7 vRNA log_{10} copies/ml	3.71 vRNA log_{10} copies/ml	27.2%	25
Average			**18.3%**	
Peramivir	2.2 log_{10} $TCID_{50}$ x day/ml	8.2 log_{10} $TCID_{50}$ x day/ml	73.2%	26

Table S4. Reduction in Duration of Virus Shedding

Treatment	Shedding Duration (treated) (days)	Shedding Duration (untreated) (days)	Percent Reduction	Reference
Oseltamivir	2.4	4.5	**46.7%**	27
Zanamivir	3.25	4	18.8%	28
	4	6	33.3%	29
Average			**26.0%**	
Peramivir	1	3.2	68.8%	30

Antiviral Prophylaxis

The effectiveness of antiviral prophylaxis in preventing seasonal influenza infection was defined as the percent of individuals that were protected from fever or infection. The weighted averages of protective efficacy from prophylaxis were 79.7%, 82.9%, and 81.8% for oseltamivir, zanamivir, and peramivir, respectively. Only one study on peramivir prophylaxis in humans was identified, but other studies have indicated that peramivir is as effective as oseltamivir in treating seasonal influenza, which indicates that any neuraminidase inhibitor may be effective in prevent infections of neuraminidase inhibitor-sensitive influenza viruses.[31]

Table S5. Effectiveness of Antiviral Prophylaxis

Antiviral	Protective Efficacy	Reference
Oseltamivir	89%	32
	74%	33

[23] Nicholson KG *et al* (2000) Efficacy and safety of oseltamivir in treatment of acute influenza: a randomised controlled trial. Neuraminidase Inhibitor Flu Treatment Investigator Group. *Lancet* 355**:** 1845-1850

[24] Boivin G *et al* (2000) Rapid antiviral effect of inhaled zanamivir in the treatment of naturally occurring influenza in otherwise healthy adults. *The Journal of infectious diseases* 181**:** 1471-1474

[25] Puhakka T *et al* (2003) Zanamivir: a significant reduction in viral load during treatment in military conscripts with influenza. *Scandinavian journal of infectious diseases* 35**:** 52-58

[26] Barroso L *et al* (2005) Efficacy and tolerability of the oral neuraminidase inhibitor peramivir in experimental human influenza: randomized, controlled trials for prophylaxis and treatment. *Antiviral therapy* 10**:** 901-910

[27] Hayden FG *et al* (1999) Use of the selective oral neuraminidase inhibitor oseltamivir to prevent influenza. *The New England journal of medicine* 341**:** 1336-1343

[28] Boivin G *et al* (2000) Rapid antiviral effect of inhaled zanamivir in the treatment of naturally occurring influenza in otherwise healthy adults. *The Journal of infectious diseases* 181**:** 1471-1474

[29] Hayden FG *et al* (1997) Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenzavirus infections. GG167 Influenza Study Group. *The New England journal of medicine* 337**:** 874-880

[30] Barroso L *et al* (2005) Efficacy and tolerability of the oral neuraminidase inhibitor peramivir in experimental human influenza: randomized, controlled trials for prophylaxis and treatment. *Antiviral therapy* 10**:** 901-910

[31] Yoo JW *et al* (2015) Peramivir is as effective as oral oseltamivir in the treatment of severe seasonal influenza. *Journal of medical virology* 87**:** 1649-1655

[32] Welliver R *et al* (2001) Effectiveness of oseltamivir in preventing influenza in household contacts: a randomized controlled trial. *JAMA* 285**:** 748-754

[33] Hayden FG *et al* (1999) Use of the selective oral neuraminidase inhibitor oseltamivir to prevent influenza. *The New England journal of medicine* 341**:** 1336-1343

Antiviral	Protective Efficacy	Reference
Weighted average	**79.7%**	
Zanamivir	84%	34
	84%	35
	82%	36
Weighted average	**82.9%**	
Peramivir	**81.8%**	37

Vaccine Effectiveness

Based on the CDC's reported adjusted overall vaccine effectiveness (the reduction in risk of needing a doctor's visit) for influenza seasons from 2005-2015 (excluding the 2008-2009 influenza season), the weighted average of vaccine effectiveness for seasonal influenza is 44.2%.[38]

Seasonal influenza vaccination is also effective in preventing severe influenza. Severe influenza was defined as an influenza case that resulted in hospitalization. Each year, on average, vaccination produces, a 15% reduction in hospitalizations due to influenza illness.[39,40,41]

Table S6. Reduction in Hospitalizations Due to Influenza by Age Group

Age Group	Reduction in Hospitalization
0-4	19.4%
5-19	10.5%
20-64	11.5%
≥65	18.7%
Unweighted average	**15.0%**

One study suggests that a previous year's influenza vaccine may confer protection against current circulating viruses. During the 2012-2013 season, the vaccine effectiveness against influenza A(H3N2) among people who received the 2012-2013 vaccination was similar to those who received only the 2011-2012 vaccination (Table S7).[42]

[34] Calfee DP *et al* (1999) Safety and efficacy of intravenous zanamivir in preventing experimental human influenza A virus infection. *Antimicrob Agents Chemother* 43**:** 1616-1620

[35] Monto AS *et al* (1999b) Zanamivir in the prevention of influenza among healthy adults: a randomized controlled trial. *JAMA* 282**:** 31-35

[36] Monto AS *et al* (2002) Zanamivir prophylaxis: an effective strategy for the prevention of influenza types A and B within households. *The Journal of infectious diseases* 186**:** 1582-1588

[37] Barroso L *et al* (2005) Efficacy and tolerability of the oral neuraminidase inhibitor peramivir in experimental human influenza: randomized, controlled trials for prophylaxis and treatment. *Antiviral therapy* 10**:** 901-910

[38] Centers for Disease Control and Prevention. Seasonal Influenza Vaccine Effectiveness, 2005-2015. http://www.cdc.gov/flu/professionals/vaccination/effectiveness-studies.htm. Last Update June 24, 2015. Accessed Aug 11, 2015.

[39] Kostova D *et al* (2013) Influenza Illness and Hospitalizations Averted by Influenza Vaccination in the United States, 2005-2011. *PLoS One* 8**:** e66312

[40] Centers for Disease C, Prevention (2013) Estimated influenza illnesses and hospitalizations averted by influenza vaccination - United States, 2012-13 influenza season. *MMWR Morbidity and mortality weekly report* 62**:** 997-1000

[41] Reed C *et al* (2014) Estimated influenza illnesses and hospitalizations averted by vaccination--United States, 2013-14 influenza season. Ibid. 63**:** 1151-1154

[42] McLean HQ *et al* (2015) Influenza vaccine effectiveness in the United States during 2012-2013: variable protection by age and virus type. *The Journal of infectious diseases* 211**:** 1529-1540

Table S7. Adjusted Vaccine Effectiveness Against Influenza A(H3N2) by Age	
Vaccination Group	**Adjusted Vaccine Effectiveness (95% CI)**
Overall	
Vaccination in current and prior season	35% (21%-47%)
Vaccination in current season only	37% (19%-51%)
Vaccination in prior season only	33% (12%-49%)
Relative effectiveness of prior vaccine*	**89.2%**
Age 9-17 years old	
Vaccination in current and prior season	9%
Vaccination in current season only	72%
Vaccination in prior season only	51%
Relative effectiveness of prior vaccine*	**70.8%**
Age 18-49 years old	
Vaccination in current and prior season	33%
Vaccination in current season only	32%
Vaccination in prior season only	40%
Relative effectiveness of prior vaccine*	**125%**
Age 50-64 years old	
Vaccination in current and prior season	55%
Vaccination in current season only	38%
Vaccination in prior season only	12%
Relative effectiveness of prior vaccine*	**31.6%**
Age ≥65 years old	
Vaccination in current and prior season	16%
Vaccination in current season only	11%
Vaccination in prior season only	10%
Relative effectiveness of prior vaccine*	**90.9%**
**Prior season vaccination compared to current season vaccination only*	

Pandemic H1N1 Influenza

Antiviral Treatment Efficacy

During the outbreak of pandemic H1N1 influenza, most patients were treated with oseltamivir, based on the CDC's recommendation. A meta-analysis of H1N1 cases noted that of 18,803 patients receiving antiviral therapy, only 2% received zanamivir, and <1% received peramivir.[43] Of 3,362 2009 pandemic influenza A (H1N1) virus isolates collected, only three did not show resistance to adamantanes.[44] Patients that received oseltamivir treatment had a survival rate of 90.3%, and antiviral treatment was associated with a reduced mortality risk when compared to no treatment (odds ratio 0.81).[45] In addition, patients

[43] Muthuri SG *et al* (2014) Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. *The Lancet Respiratory medicine* 2**:** 395-404

[44] Gubareva LV *et al* (2010) Comprehensive assessment of 2009 pandemic influenza A (H1N1) virus drug susceptibility in vitro. *Antiviral therapy* 15**:** 1151-1159

[45] Muthuri SG *et al* (2014) Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. *The Lancet Respiratory medicine* 2**:** 395-404

receiving early oseltamivir treatment had shorter fever durations than patients who did not receive antiviral treatment.[46,47]

Table S8. Likeliness of Oseltamivir Treatment Outcome		
Oseltamivir Treatment Outcome	**Parameter**	**Reference**
Reduction in fever duration	50%	48
Reduction in mortality risk	OR: 0.81	49
Reduction in mortality risk	83%	50

Antiviral treatment is also effective in reducing viral titer and duration of viral shedding in pH1N1 patients. According to one study, antiviral treatment reduced the mean viral load of patients by 14.3%.[51] On average, antiviral treatment reduced the duration of viral shedding in patients by 34% when compared to untreated patients, or patients who received antiviral treatment after 48 hours, which has been shown to be less effective.[52]

Table S9. Reduction in Duration of Virus Shedding			
Treated Shedding Duration (days)	**Untreated Shedding Duration (days)**	**Percent Reduction**	**Reference**
5	8.5*	41.2%	53
7.2	7.7	6.5%	54
4	6.5	38.5%	55
2	4**	50%	56
Average		**34.0%**	
***** *Baseline group was patients that received antiviral treatment 5 days after symptom onset* ****** *Baseline group was patients that received antiviral treatment more than 48 hours after symptom onset*			

Antiviral Prophylaxis

A study in ferrets reported that prophylaxis with oseltamivir did not protect ferrets from H1N1 infection.[57] However, a household contact study showed that contacts under 20 years old who received antiviral

[46] Yu H *et al* (2010) Effectiveness of oseltamivir on disease progression and viral RNA shedding in patients with mild pandemic 2009 influenza A H1N1: opportunistic retrospective study of medical charts in China. *BMJ* 341**:** c4779

[47] Li IW *et al* (2010) The natural viral load profile of patients with pandemic 2009 influenza A(H1N1) and the effect of oseltamivir treatment. *Chest* 137**:** 759-768

[48] Ibid.

[49] Muthuri SG *et al* (2014) Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. *The Lancet Respiratory medicine* 2**:** 395-404

[50] Yang SG *et al* (2012) Antiviral therapy and outcomes of patients with pneumonia caused by influenza A pandemic (H1N1) virus. *PLoS One* 7**:** e29652

[51] Meschi S *et al* (2011) Duration of viral shedding in hospitalized patients infected with pandemic H1N1. *BMC infectious diseases* 11**:** 140

[52] Nicholson KG *et al* (2000) Efficacy and safety of oseltamivir in treatment of acute influenza: a randomised controlled trial. Neuraminidase Inhibitor Flu Treatment Investigator Group. *Lancet* 355**:** 1845-1850

[53] Ling LM *et al* (2010) Effects of early oseltamivir therapy on viral shedding in 2009 pandemic influenza A (H1N1) virus infection. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 50**:** 963-969

[54] Meschi S *et al* (2011) Duration of viral shedding in hospitalized patients infected with pandemic H1N1. *BMC infectious diseases* 11**:** 140

[55] Fielding JE *et al* (2014) Systematic review of influenza A(H1N1)pdm09 virus shedding: duration is affected by severity, but not age. *Influenza and other respiratory viruses* 8**:** 142-150

[56] Leung YH *et al* (2012) Delayed oseltamivir treatment is associated with longer viral shedding of pandemic (H1N1) 2009 virus. *Epidemiology and infection* 140**:** 814-817

[57] Oh DY *et al* (2014) Evaluation of oseltamivir prophylaxis regimens for reducing influenza virus infection, transmission and disease severity in a ferret model of household contact. *The Journal of antimicrobial chemotherapy* 69**:** 2458-2469

prophylaxis with oseltamivir or zanamivir were less likely to be infected with pandemic H1N1 influenza than those who did not receive antiviral prophylaxis (odds ratio 0.15).[58] Additionally, other observational studies indicate that prophylaxis may be effective in preventing H1N1 infection.[59,60]

Table S10. Prophylaxis Outcome in H1N1 Prevention

Prophylaxis Outcome	Odds Ratio	Reference
Infection risk reduction	0.15	61

Vaccine Effectiveness

Monovalent pH1N1 influenza vaccine demonstrated an average effectiveness of 66% (range 60-93%).[62,63]

Avian Influenza

Antiviral Treatment Efficacy

H5N1 Avian Influenza

Approximately 62.2% of human H5N1 viruses contain markers for adamantane resistance;[64] while adamantanes may be effective in treating infections of susceptible H5N1 viruses, the WHO does not recommend treating H5N1 infections with adamantanes unless it is known that the virus is susceptible to these drugs or if neuraminidase inhibitors are unavailable.[65] No information on the efficacy of adamantanes against adamantane-susceptible H5N1 infections could be identified in the literature.

Treatment efficacy for H5N1 infections was reported as the percent of patients who receive antiviral treatment and survive. On average, 53.5% of H5N1 infected patients receiving oseltamivir treatment survived. Infected individuals who did not receive treatment had a survival rate of 18% (Table S11).[66] These studies indicate the death rate of treated patients drops by 56% (46.5%/82%).

[58] Odaira F *et al* (2009) Assessment of secondary attack rate and effectiveness of antiviral prophylaxis among household contacts in an influenza A(H1N1)v outbreak in Kobe, Japan, May-June 2009. *Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin* 14

[59] Asiedu-Bekoe F *et al* (2012) Mass oseltamivir prophylaxis halts pandemic influenza A H1N1 2009 outbreak in a secondary school in Ashanti Region, Ghana. *Ghana medical journal* 46**:** 219-224

[60] Leung YH *et al* (2011) A school outbreak of pandemic (H1N1) 2009 infection: assessment of secondary household transmission and the protective role of oseltamivir. *Epidemiology and infection* 139**:** 41-44

[61] Odaira F *et al* (2009) Assessment of secondary attack rate and effectiveness of antiviral prophylaxis among household contacts in an influenza A(H1N1)v outbreak in Kobe, Japan, May-June 2009. *Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin* 14

[62] Griffin MR *et al* (2011) Effectiveness of non-adjuvanted pandemic influenza A vaccines for preventing pandemic influenza acute respiratory illness visits in 4 U.S. communities. *PLoS One* 6**:** e23085

[63] Osterholm MT *et al* (2012) Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. *The Lancet Infectious diseases* 12**:** 36-44

[64] Govorkova EA *et al* (2013) Antiviral resistance among highly pathogenic influenza A (H5N1) viruses isolated worldwide in 2002-2012 shows need for continued monitoring. *Antiviral Res* 98**:** 297-304

[65] Schunemann HJ *et al* (2007) WHO Rapid Advice Guidelines for pharmacological management of sporadic human infection with avian influenza A (H5N1) virus. *The Lancet Infectious diseases* 7**:** 21-31

[66] Adisasmito W *et al* (2010) Effectiveness of antiviral treatment in human influenza A(H5N1) infections: analysis of a Global Patient Registry. *The Journal of infectious diseases* 202**:** 1154-1160

Table S11. Survival Rate in H5N1 Infected Patients Receiving Oseltamivir Treatment				
Treatment	**Treated Survival Rate**	**Untreated Survival Rate**	**Drop in Mortality Rate**	**Reference**
Oseltamivir	60%	24%	52%	67
	47%	12%	60%	68
Unweighted average	**53.5%**	**18%**	**56%**	

While H5N1 influenza infections are generally treated with oseltamivir, 78% of H5N1 infected mice survived when treated with peramivir within 24 hours, indicating that other neuraminidase inhibitors could be effective in treating H5N1 infections.[69]

H7N9 Avian Influenza

The sequences of H7N9 viruses isolated from patients show that these viruses contain an M2 mutation known to confer amantadine resistance, therefore adamantanes are not included in this analysis.[70] No clinical studies could be found on H7N9 antiviral treatments. In a study of patients with severe H7N9 infections, patients receiving therapy had a survival rate of 63.7%, however patients who did not receive antiviral therapy had a survival rate of 61.5%. In a separate study of 27 H7N9 infected patients, two-thirds of patients receiving oseltamivir survived. These survival rates suggest that there is no benefit from oseltamivir treatment of H7N9 patients.

Table S12. Survival Rate in H7N9 Infected Patients Receiving Oseltamivir Treatment		
Treatment	**Survival Rate**	**Reference**
Oseltamivir	63.7%	71
	66.7%	72
Weighted average	**64.3%**	

Antiviral Prophylaxis

H5N1 Avian Influenza

No studies on antiviral prophylaxis to protect against H5N1 infections in humans could be identified. In ferrets, prophylaxis with oseltamivir did not prevent H5N1 infection, but receiving prophylactic treatment lowered viral titers in lung, brain, liver, spleen, and small intestine tissues.[73] Another study demonstrated that zanamivir prophylaxis reduced viral titers in ferrets, but did not prevent infection.[74] These studies indicate that antiviral prophylaxis may not be effective in preventing H5N1 infections in humans.

[67] Adisasmito W *et al* (2010) Effectiveness of antiviral treatment in human influenza A(H5N1) infections: analysis of a Global Patient Registry. *The Journal of infectious diseases* 202**:** 1154-1160

[68] Writing Committee of the Second World Health Organization Consultation on Clinical Aspects of Human Infection with Avian Influenza AV *et al* (2008) Update on avian influenza A (H5N1) virus infection in humans. *The New England journal of medicine* 358**:** 261-273

[69] Boltz DA *et al* (2008) Intramuscularly administered neuraminidase inhibitor peramivir is effective against lethal H5N1 influenza virus in mice. *Antiviral Res* 80**:** 150-157

[70] Gao R *et al* (2013) Human infection with a novel avian-origin influenza A (H7N9) virus. Ibid. 368**:** 1888-1897

[71] Xiao YY *et al* (2015) Prognosis and survival of 128 patients with severe avian influenza A(H7N9) infection in Zhejiang province, China. *Epidemiology and infection* 143**:** 1833-1838

[72] Ji H *et al* (2014) Epidemiological and clinical characteristics and risk factors for death of patients with avian influenza A H7N9 virus infection from Jiangsu Province, Eastern China. *PLoS One* 9**:** e89581

[73] Govorkova EA *et al* (2007) Efficacy of oseltamivir therapy in ferrets inoculated with different clades of H5N1 influenza virus. *Antimicrob Agents Chemother* 51**:** 1414-1424

[74] Stittelaar KJ *et al* (2008) Evaluation of intravenous zanamivir against experimental influenza A (H5N1) virus infection in cynomolgus macaques. *Antiviral Res* 80**:** 225-228

H7N9 Avian Influenza

Currently, the WHO does not recommend post-exposure antiviral prophylaxis for exposure to H7N9 influenza virus, unless the person experiences prolonged or unprotected exposure.[75] No studies could be identified detailing the effectiveness of antiviral prophylaxis in humans or mammals.

Vaccine Effectiveness

H5N1 Avian Influenza

There are two influenza A (H5N1) vaccines approved by the FDA to prevent H5N1 influenza infections in humans. Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted was shown to induce protective immune responses in 91% of adults (18-64 years old) and 74% of elderly (65 years and older).[76] The H5N1 influenza vaccine was tested only in adults and induced an antibody response expected to reduce H5N1 influenza infections by 45%.[77] Both vaccines are inactivated influenza virus vaccines, but the Monvalent Vaccine, Adjuvanted contains an adjuvant to enhance the immune response and requires two doses for full effectiveness.

Table S13. Vaccine Efficacy Rate by Age Group

Vaccine Type	Age Group	Effectiveness
H5N1 Virus Monovalent Vaccine, Adjuvanted	18-64	91%
	≥65	74%
H5N1 influenza vaccine	18-64	45%

H7N9 Avian Influenza

Influenza A (H7N9) vaccines are under development, but there are currently no vaccines providing protection against H7N9 influenza infections in humans.[78]

SARS

Antiviral Treatment Efficacy

There are no specific antiviral treatments for SARS infections. During the SARS outbreak, the most common treatment was with ribavirin, but the results of studies investigating the effectiveness of ribavirin

[75] World Health Organization (2014) Avian influenza A(H7N9) virus: Post-exposure antiviral chemoprophylaxis of close contacts of a patient with confirmed H7N9 virus infection and/or high risk poultry/environmental exposures.

[76] Food and Drug Administration. Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted, manufactured by ID Biomedical Corporation - Questions and Answers. http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/VaccineSafety/ucm376465.htm. Last Update Mar 18, 2015. Accessed Aug 23, 2015.

[77] Food and Drug Administration. H5N1 Influenza Virus Vaccine, manufactured by Sanofi Pasteur, Inc. Questions and Answers. http://www.fda.gov/BiologicsBloodVaccines/Vaccines/QuestionsaboutVaccines/ucm080753.htm. Last Update Aug 5, 2015. Accessed Aug 23, 2015.

[78] Centers for Disease Control and Prevention. H7N9: Frequently Asked Questions. http://www.cdc.gov/flu/avianflu/h7n9-faq.htm. Last Update Sep 9, 2014. Accessed Aug 23, 2015.

are generally inconsistent or inconclusive.[79] Therefore, it is assumed that there is no reliable antiviral treatment for SARS.

Vaccine Effectiveness

There is currently no vaccine to prevent SARS infections in humans.

MERS

Antiviral Treatment Efficacy

Currently, there is no specific antiviral treatment to treat MERS infections.[80] Ribavirin and interferon treatment has been shown to be effective in treating rhesus macaques, but has not been shown to be consistently effective in human cases.[81] A cohort study showed that at 28 days post-infection, there was no significant difference in survival between patients treated with ribavirin and untreated patients.[82]

Vaccine Effectiveness

There is currently no vaccine to prevent MERS infections in humans.[83]

[79] Momattin H *et al* (2013) Therapeutic options for Middle East respiratory syndrome coronavirus (MERS-CoV)--possible lessons from a systematic review of SARS-CoV therapy. *International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases* 17**:** e792-798

[80] Centers for Disease Control and Prevention. Middle East Respiratory Syndrom (MERS) Prevention & Treatment. http://www.cdc.gov/coronavirus/mers/about/prevention.html. Last Update Jun 2, 2015. Accessed Jul 20, 2015.

[81] Falzarano D *et al* (2013) Treatment with interferon-alpha2b and ribavirin improves outcome in MERS-CoV-infected rhesus macaques. *Nat Med* 19**:** 1313-1317

[82] Omrani AS *et al* (2014) Ribavirin and interferon alfa-2a for severe Middle East respiratory syndrome coronavirus infection: a retrospective cohort study. *The Lancet Infectious diseases* 14**:** 1090-1095

[83] Centers for Disease Control and Prevention. Middle East Respiratory Syndrom (MERS) Prevention & Treatment. http://www.cdc.gov/coronavirus/mers/about/prevention.html. Last Update Jun 2, 2015. Accessed Jul 20, 2015.