

1     **Antiviral treatment for outpatient use during an influenza pandemic: A decision tree**  
2                     **model of outcomes averted and cost-effectiveness**

3     **Sudhir Venkatesan**, Research Assistant and PhD student, Division of Epidemiology and  
4     Public Health, University of Nottingham, Nottingham, UK

5     **Cristina Carias**, Economist, Centers for Disease Control and Prevention, Atlanta, Georgia,  
6     USA

7     **Matthew Biggerstaff**, Epidemiologist, Centers for Disease Control and Prevention, Atlanta,  
8     Georgia, USA

9     **Angela P. Campbell**, Medical Officer, Centers for Disease Control and Prevention, Atlanta,  
10     Georgia, USA

11    **Jonathan S. Nguyen-Van-Tam**, Professor, Division of Epidemiology and Public Health,  
12    University of Nottingham, Nottingham, UK

13    **Emily Kahn**, Health Scientist, Centers for Disease Control and Prevention, Atlanta, Georgia,  
14    USA

15    **Puja R. Myles**, Associate Professor, Division of Epidemiology and Public Health, University  
16    of Nottingham, Nottingham, UK

17    **Martin I. Meltzer**, Senior Health Economist, Centers for Disease Control and Prevention,  
18    Atlanta, Georgia, USA

19    **Disclaimers:** The work and conclusions presented here are those of the authors and do not  
20    necessarily represent the official position of the U.S. Centers for Disease Control and  
21    Prevention (CDC) or the U.S. Department of Health and Human Services.

22 JSN-V-T is currently on secondment from the University of Nottingham to the Department of  
23 Health and Social Care (England). The work and conclusions presented here are those of the  
24 authors and do not necessarily represent the official position of the Department of Health and  
25 Social Care (England).

26 **Corresponding author:**

27 Sudhir Venkatesan

**Email:** [Sudhir.Venkatesan@nottingham.ac.uk](mailto:Sudhir.Venkatesan@nottingham.ac.uk)

28 **Address:** B104, Clinical Sciences Building, Nottingham City Hospital, Hucknall Road,  
29 Nottingham, NG5 1PB, UK

30 **Phone:** +44 0115 8231718

31 **Abstract word count:** 178 words

32 **Manuscript word count:** 3,000 words

33 **Abstract:**

34 **Background:** Many countries have acquired antiviral stockpiles for pandemic influenza  
35 mitigation and a significant part of the stockpile may be focussed towards community-based  
36 treatment.

37 **Methods:** We developed a spreadsheet-based, decision tree model to assess outcomes averted  
38 and cost-effectiveness of antiviral treatment for outpatient use from the perspective of the  
39 healthcare payer in the UK. We defined five pandemic scenarios– one based on the 2009  
40 A(H1N1) pandemic and four hypothetical scenarios varying in measures of transmissibility  
41 and severity.

42 **Results:** Community-based antiviral treatment was estimated to avert 14% to 23% of  
43 hospitalizations in an overall population of 62.28 million. Higher proportions of averted  
44 outcomes were seen in patients with high-risk conditions, when compared to non-high-risk  
45 patients. We found that antiviral treatment was cost-saving across pandemic scenarios for  
46 high-risk population groups, and cost-saving for the overall population in higher severity  
47 influenza pandemics. Antiviral effectiveness had the greatest influence on both the number of  
48 hospitalizations averted and on cost-effectiveness.

49 **Conclusions:** This analysis shows that across pandemic scenarios, antiviral treatment can be  
50 cost-saving for population groups at high risk of influenza-related complications.

## 51 **Introduction**

52 Influenza pandemics are rare, unpredictable events with potentially serious consequences.  
53 They are considered to be important public health emergencies by the World Health  
54 Organization, and a number of countries, with many having specific pandemic preparedness  
55 plans(1-3). Neuraminidase inhibitors (NAI) often feature prominently in pandemic influenza  
56 preparedness plans(2) and several high-income countries have acquired NAI stockpiles  
57 because pandemic specific vaccines may not be widely available for up to 6 months(4).  
58 Clinical trials show NAI effectiveness in modestly reducing duration of symptomatic illness  
59 in patients with uncomplicated seasonal influenza(5-14). However, these trials were under-  
60 powered to assess NAI impact on secondary outcomes such as hospitalizations(15-17). Two  
61 meta-analyses of the extant clinical trial data, examining outcomes based on the intention-to-  
62 treat-influenza infected (ITTI) approach, found that early NAI treatment ( $\leq 48$  hours of  
63 symptom onset) was associated with a risk reduction of 59%(18) and 63%(19) for hospital  
64 admission in otherwise healthy patients with influenza. Other meta-analyses of trial data that  
65 evaluated all outpatients with influenza-like-illness (ILI) using the intention-to-treat (ITT)  
66 approach did not find a reduction in hospitalizations in those treated with NAIs(20, 21).

67 If a future pandemic is severe, hospital capacity may be exhausted and therefore reserved for  
68 the severely ill who are most likely to benefit(22). Countries may decide to focus a significant  
69 part of their pandemic response plan towards community treatment aimed at averting  
70 hospitalizations. Policy makers considering NAI stockpiling for a future pandemic of  
71 unknown severity will have to consider both number of hospitalizations averted and the cost-  
72 effectiveness of such an intervention. NAI treatment for pandemic influenza has generally  
73 been estimated to be cost-effective for higher-income countries(23-25). However, a review  
74 identified that previous health economic evaluations often neglected pandemic uncertainty by  
75 only evaluating singular, fixed pandemic scenarios(26). Moreover, few models have

76 incorporated the increased risks of adverse pandemic influenza-related outcomes for patients  
77 with at-risk conditions. We present a spreadsheet-based decision tree model that evaluates the  
78 impact of community-based NAI treatment in terms of the averted influenza-related  
79 hospitalizations and associated cost-effectiveness in a range of pandemic scenarios.

## 80 **Methods**

81 We built a decision tree model (Figure 1) to calculate the impact of community-based NAI  
82 treatment for five pandemic scenarios. The first scenario is based on the United Kingdom's  
83 (UK) A(H1N1)pdm09 experience, with a clinical attack rate (CAR) of 7% and a case  
84 hospitalization risk (CHR) of 0.3% and 1.5% among non-high-risk and high-risk patients,  
85 respectively (Table 1). The other four scenarios were based on hypothetical pandemics that  
86 varied the CAR (20% and 30%) and the CHR (1.05% to 4.0% for non-high-risk patients; 5%  
87 to 20% for high-risk patients) (Table 1). The hypothetical scenarios are based on a risk  
88 assessment framework developed by the CDC(27, 28). A standardized risk space was defined  
89 based on previous influenza pandemics, and hypothetical pandemic scenarios were identified  
90 from this risk space to allow easy comparisons to future economic evaluations. The CHRs for  
91 the high-risk groups in these four hypothetical pandemics were assumed to be five times the  
92 CHR for the non-high-risk group of patients based on estimates from the 2009 A(H1N1)  
93 pandemic(29). We also assumed that the percentage of patients seeking  
94 outpatient/ambulatory care would increase with the CHR of the pandemic, ranging from 40%  
95 among non-high-risk patients in a 2009-type pandemic to approximately 81% among high-  
96 risk patients when the CHR is 20% (Table 1). We estimated the number of deaths averted  
97 through averting hospitalizations by multiplying the number of hospitalizations averted with  
98 an in-hospital mortality risk that was constant across the scenarios.

99 We did not differentiate between oseltamivir and zanamivir in the definition of NAIs in our  
100 model; however, we based our cost and treatment effectiveness estimates on data specific for  
101 oseltamivir. We focus on community-based treatment and do not consider NAI prophylaxis.  
102 We used NAI effectiveness estimates from an individual participant data (IPD) meta-analysis  
103 of clinical trials data on otherwise healthy patients with seasonal influenza(19) based on ITTI  
104 analysis (relative risk: 0.37, 95% confidence interval: 0.17 to 0.81) since NAIs are not active  
105 against non-influenza respiratory infections(30). To account for NAI prescriptions to patients  
106 with non-influenza ILI, we assumed a ‘wastage factor’ of 40%, i.e. patients with non-  
107 influenza ILI would be prescribed 40% of the number of regimens that are prescribed to  
108 patients with influenza(31). We assumed that all patients would start NAI treatment  $\leq 48$   
109 hours of symptom onset in our main model and then performed a sensitivity analysis varying  
110 the promptness of care-seeking within 48 hours of symptom onset from 25% to 75%  
111 (percentage of all care-seeking patients who do so  $\leq 48$  hours of symptom onset). Based on  
112 estimates from 2009, we also assumed that 64% of patients would be compliant with the  
113 prescribed regimen(32).

114 Unit cost data for our model were obtained from secondary sources including the British  
115 National Formulary and UK-based reports on the cost of health and social care (Table 1).  
116 Briefly, we used a weighted average cost of physician-based consultation of £24.20. This cost  
117 was calculated as a weighted average cost of either a conventional primary care consultation  
118 or a phone-based consultation with the 2009 National Pandemic Flu Service (NPFs)(33). The  
119 weighting of the costs was done using the proportion of assessments routed through each  
120 consultation service in 2009. We used a cost of £16 for an NAI prescription, which included  
121 the cost of delivery. Costs of hospitalizations ranged from £436 for non-high-risk patients to  
122 £1,727 for high-risk patients (Table 1). All costs were inflated to the 2017 British Pound  
123 Sterling (£) using the hospital & community health services (HCHS) index(34).

124 The overall population of 62.28 million was based on the 2009 UK population(35). We  
125 performed the analyses from the perspective of the healthcare payer, the UK National Health  
126 Service (NHS). Given that we did not undertake a full cost-utility analysis, we chose to  
127 measure our outcomes in natural units (deaths and hospitalizations) rather than in  
128 standardized units (QALYs)(36). We considered a time horizon of less than one year (one  
129 pandemic event), therefore a discounting rate would not apply.

130 In each pandemic scenario, we compared the number of outcomes averted (hospitalizations  
131 and deaths) and total costs associated with NAI treatment compared to no NAI treatment. We  
132 assessed cost-effectiveness of community-based NAI treatment by estimating the cost per  
133 averted hospitalization. Our primary analysis was performed using the middle values of our  
134 input parameters using formulas provided in Appendix 1. To account for uncertainty in  
135 parameter estimates, we performed sensitivity analyses by probabilistically varying input  
136 parameters along pre-defined probability distributions (Table 1) and using Monte Carlo  
137 simulations (5,000 iterations using Latin hypercube sampling) to calculate mean output  
138 values and 95% confidence intervals for different combinations of input parameters. The  
139 sensitivity analyses were performed using the software @Risk version 7.3 (Palisade  
140 Corporation). Further, we also performed two-way sensitivity analysis to assess the impact of  
141 varying NAI effectiveness and patient compliance on the outcome (hospitalizations averted).

## 142 **Results**

143 In a 2009-like pandemic scenario, we estimated that in our base-case model (no NAI  
144 treatment) there would be 28,773 hospitalizations in the overall population. We estimated that  
145 1.9 million regimens of NAIs would be dispensed for outpatient treatment. NAI treatment  
146 would have averted 4,034 (14%) hospitalizations in a population of 62.28 million (65  
147 hospitalizations averted/million population) at a cost of £7,110 per hospitalization averted

148 (Table 2). The cost to avert one hospitalization was £2,238 in high-risk populations and  
149 £20,473 in the non-high-risk population (Table 2).

150 In the 20% CAR-Severity 1 scenario (CHR: non-high-risk=1.05%; high-risk=5.25%), we  
151 estimated that 287,734 hospitalizations would occur. 8.07 million regimens of NAIs would be  
152 dispensed, averting 57,281 (19.9%) hospitalizations at a cost per averted hospitalization of  
153 £1,008 in the overall population and £5,497 in the non-high-risk population. NAI treatment  
154 was seen to be cost-saving in the high-risk population.

155 In the 20% CAR- Severity 2 scenario (CHR: non-high-risk=4%; high-risk=20%), we  
156 estimated that over 1.09 million hospitalizations would occur. 9.34 million NAI regimens  
157 would be dispensed, averting 250,478 (22.9%) hospitalizations in the total population at a  
158 cost per averted hospitalization of £1,079 in the non-high-risk population. NAI treatment was  
159 seen to be cost-saving in the overall population and in the high-risk population.

160 In the 30% CAR- Severity 1 scenario, (CHR: non-high-risk=1.05%; high-risk=5.25%), we  
161 estimated that over 430,000 hospitalizations would occur. 12.1 million NAI regimens would  
162 be dispensed, averting 85,922 (19.9%) hospitalizations at a cost per averted hospitalization of  
163 £1,008 in the overall population and £5,497 in the non-high-risk population. NAI treatment  
164 was seen to be cost-saving in the high-risk population.

165 In the fourth pandemic scenario, (CHR: non-high-risk=4%; high-risk=20%), we estimated  
166 that over 1.6 million hospitalizations would occur. 14.01 million NAI regimens would be  
167 dispensed, averting 375,717 (22.9%) hospitalizations in the overall population at a cost per  
168 averted hospitalization of £1,079 in the non-high-risk population. NAI treatment was seen to  
169 be cost-saving in the overall population and in the high-risk population.

170 We found that varying the proportion of care-seeking patients who do so within 48 hours of  
171 symptom onset, while keeping all other variables constant, lowered the percentage of averted



172 hospitalizations in the overall population from 14.0% (assuming 100%) to 3.5% (assuming  
173 25%) in the 2009-like pandemic scenario (Table 2, Supplemental Table 1).

174 Our sensitivity analyses revealed that using just the middle values of input parameters in a  
175 simple multiplicative model without probability distributions was likely to overestimate the  
176 number of hospitalizations averted and underestimate the cost per averted hospitalization. For  
177 the 2009-like pandemic scenario, multiplying the middle values of input parameters (Table 2)  
178 overestimated the overall number of averted hospitalizations by 28% and underestimated the  
179 overall cost per-averted hospitalization by 34% when compared to the mean estimated from  
180 the Monte Carlo simulation (Supplemental Table 2). Similar differences in estimates were  
181 observed in the other scenarios as well.

182 The sensitivity analyses, based on a 2009-like pandemic scenario, indicated that NAI  
183 effectiveness had the greatest impact on both the total number of hospitalizations averted, as  
184 well as on the cost per hospitalization averted (see Figure 2 for 2009 scenario). When the  
185 NAI effectiveness was varied from 19% to 83%, the resulting overall proportion of averted  
186 hospitalizations ranged between 6% and 15%, at a cost per averted hospitalization of £6,936  
187 to £19,338. The percentage of care-seeking patients who were prescribed NAI, the proportion  
188 of NAI prescriptions to non-influenza patients, and NAI treatment compliance were in the top  
189 three influential parameters for one or both outcomes (Figure 2). In our two-way sensitivity  
190 analysis we varied the treatment compliance level along with NAI effectiveness beyond the  
191 95% confidence intervals of our input parameter (from 90% effectiveness to 10%  
192 effectiveness). Increased compliance levels were consistently associated with an increased  
193 number of averted hospitalizations across NAI effectiveness estimates (Figure 3). The impact  
194 of prescribing NAIs to non-influenza ILI patients had a considerable effect on the cost per  
195 averted hospitalization. For the 2009-like pandemic scenario, this ranged from £7,983 per

196 averted hospitalization (wastage factor=30%) to £11,032 per averted hospitalization (wastage  
197 factor=70%).

## 198 **Discussion**

### 199 **Main finding of this study**

200 We found that community-based NAI treatment would avert a significant proportion of  
201 hospitalizations and deaths, particularly in high-risk patients, across the pandemic scenarios  
202 we explored in this analysis. However, a substantial number of hospitalizations and deaths  
203 would continue to occur even with community-based NAI treatment. The proportion of  
204 hospitalizations averted by NAIs could be an important consideration while planning for  
205 conditions when hospital capacity could be exceeded. Community-based NAI treatment was  
206 seen to be cost-saving for the overall population in a pandemic with a high CAR and high  
207 severity, and cost-saving for patients at high risk of complications from influenza across all  
208 the pandemic influenza scenarios tested. The value of NAI treatment for population groups  
209 not at high risk and for milder pandemic scenarios will have to be determined by careful  
210 review under country-specific willingness-to-pay thresholds and the desire to reduce the  
211 number of hospitalizations and potential hospital capacity issues.

### 212 **What is already known on this topic**

213 NAI treatment for pandemic influenza has generally been shown to be cost-effective, when  
214 compared to no NAI treatment(23-25, 37). Previous studies have found that NAI  
215 effectiveness is, by far, the most influential factor affecting the numbers of outcomes averted  
216 and the associated cost-effectiveness(23, 31). Results from our sensitivity analysis support  
217 this finding. A study based in the United States that used a similar model(31) showed slightly  
218 lower proportions of hospitalizations averted due to NAI treatment when compared to ours,  
219 but the difference could be because of the lower level of treatment effectiveness assumed in

220 the U.S. study. The U.S. study further found that while NAI treatment averted many  
221 hospitalizations, large numbers of hospitalizations would remain(31), which is similar to  
222 what we have found.

### 223 **What this study adds**

224 We found that variations in NAI prescription rate, treatment compliance and healthcare-  
225 seeking behaviour (to include the choice to seek care and the promptness in care-seeking)  
226 impacted considerably on the outcomes, suggesting that even with a drug of fixed  
227 effectiveness, factors relating to healthcare-seeking and healthcare delivery could  
228 significantly influence the total number of hospitalizations and deaths averted. These data  
229 indicate that a successful pandemic stockpiling strategy must be linked to operational  
230 procedures which optimise timely access to antivirals, widespread treatment implementation,  
231 and high levels of compliance in targeted groups.

232 One recognised limitation of some previous economic analyses of NAI treatment has been  
233 that entire populations have been modelled homogenously without accounting for the  
234 increase in the likelihood of influenza-related care-seeking and complications in patients with  
235 underlying at-risk conditions(23, 24). In our model, we vary the propensity to seek care and  
236 CHR by patients' at-risk status. The significance of this is that countries with limited  
237 resources could consider obtaining smaller antiviral stockpiles to target at-risk population  
238 groups and avert a higher number of hospitalizations and deaths for each antiviral course  
239 dispensed than if they adopted a treat-all approach.

240 The CAR was an important factor in determining the number of NAI regimens that would be  
241 needed for community-based treatment. Our model showed that a highly transmissible, but  
242 low severity pandemic would require a larger NAI stockpile than a pandemic with lower  
243 transmissibility and higher severity. However, across all pandemic scenarios, the number of

244 NAI regimens dispensed for outpatient treatment was well below the UK's published national  
245 NAI stockpile size of almost 40 million courses of the drug(38).

246 We have adopted a simple and transparent approach to model building in which we account  
247 for important epidemiological factors, population healthcare-seeking behaviour and service  
248 utilization rates in a range of pandemic scenarios. Our analyses are UK-focussed, but the  
249 spreadsheet tool is easily adaptable to represent other healthcare systems. While the  
250 epidemiological parameters are unlikely to change drastically by country, input parameters  
251 relating to healthcare utilization and costs will need to be replaced with country-specific ones.  
252 We provide the simple version of the spreadsheet tool (without the sensitivity analysis) in  
253 Appendix 2. We used updated NAI effectiveness estimates from seasonal influenza data,  
254 although observational data from the 2009 A(H1N1) pandemic in a high-severity (high risk  
255 of hospitalization) population suggest similar estimates of NAI effectiveness ( $\leq 48$  hours from  
256 symptom onset)(39). We assumed NAI effectiveness is the same in patients with and without  
257 at-risk conditions. While there is some evidence to suggest that the level of effectiveness  
258 against hospitalization is similar for both groups (39), there is also evidence that suggests a  
259 reduction in NAI effectiveness in patients with at-risk conditions(40).

## 260 **Limitations of this study**

261 This study is subject to limitations. We used a decision tree model (not a transmission  
262 dynamic model) and assumed no effect of NAI treatment on transmission. There is evidence  
263 to suggest that NAI treatment, at a population level, is likely to have minimal impact on  
264 influenza transmission(41). However, decision tree models are known to be limited,  
265 especially in their ability to describe the change in influenza attack rates in different risk  
266 groups over the course of a pandemic(37). A comparison of static and dynamic models of  
267 NAI treatment for pandemic influenza concluded NAI treatment was seen to be cost-effective

268 with both modelling paradigms; although the associated cost-effectiveness ratios were seen to  
269 differ(37). Due to a lack of evidence specific to hospitalization, we did not consider benefits  
270 of NAI treatment >48 hours of symptom onset. NAI treatment has, however, been shown be  
271 beneficial even when started beyond 48 hours from symptom onset(12). The use of NAIs  
272 may be associated with additional costs to the healthcare system due to possible adverse  
273 effects of NAIs(21) but we have not considered these costs in our model since most side  
274 effects are known to be minor(19). Finally, we have assumed that the multiplier for high-risk  
275 patients remains constant between severity scenarios resulting in a CHR as high as 20%.  
276 CHRs of 20%, even for high-risk patients, may be unlikely.

## 277 **Conclusions**

278 Our analyses shows that NAI treatment in outpatients can be cost-saving, particularly for  
279 population groups at high risk of influenza-related complications. Model-based estimates like  
280 these of the potential hospitalizations, deaths and costs associated with different pandemic  
281 scenarios can help countries consider different treatment options and inform stockpiling  
282 decisions while developing pandemic preparedness plans. NAI stockpiling decisions are also  
283 influenced by other costs to the healthcare system related to storage and maintenance of the  
284 NAI stockpile. Currently, the shelf-life for the 75 mg hard capsules of oseltamivir phosphate  
285 that comprise most of the NAI stockpile is estimated to be 10 years if stored as per  
286 instructions(42). However, influenza pandemics cannot be predicted, and NAI stockpiles  
287 could remain unused at the end of their shelf-life, or they may be rendered ineffective or less  
288 relevant by the development of antiviral drug resistance or newer, more effective influenza  
289 antiviral therapies. Additionally, evidence suggests that in-hospital NAI treatment may also  
290 be associated with protective effects(43, 44) and NAI treatment has been shown to be cost-  
291 effective if the benefits of NAI usage are confined only to those treated in hospital(45). If a  
292 pandemic treatment policy was pursued which combined community use of NAIs to prevent

293 hospital admission and NAI treatment of hospitalised patients to reduce mortality, then cost-  
294 effectiveness and stockpile strategies across both scenarios would need to be considered.  
295 Future research in optimizing NAI distribution to risk groups during a pandemic will further  
296 inform the cost-effectiveness of stockpiling.

297

298 **Acknowledgements:** We would like to thank Anita Patel from CDC, Atlanta, for reviewing  
299 this manuscript and offering helpful comments.

300 SV, JSN-V-T and PRM are currently working on outputs from the PRIDE study which is  
301 supported by an unrestricted educational grant from F. Hoffman La Roche. JSN-V-T reports  
302 grants from F. Hoffmann-La Roche, personal fees from Shionogi Ltd. (in 2016), outside the  
303 submitted work and is currently on secondment from the University of Nottingham to the  
304 Department of Health and Social Care (England). The work and conclusions presented here  
305 are those of the authors and do not necessarily represent the official position of the  
306 Department of Health and Social Care (England). All other authors report no conflicts of  
307 interest.

308

309 **References**

310 1. DH Pandemic Influenza Preparedness Team. UK influenza pandemic preparedness strategy  
311 2011. 2012.

312 2. Programme WHOI. Pandemic influenza preparedness and response: a WHO guidance  
313 document: World Health Organization; 2009.

314 3. U.S. Department of Health and Human Services. Pandemic Influenza Plan: 2017 update.  
315 2017.

316 4. Centers for Disease Control and Prevention. Selecting Viruses for the Seasonal Influenza  
317 Vaccine. 2016 [cited; Available from: <https://www.cdc.gov/flu/about/season/vaccine-selection.htm>

318 5. Monto AS, Fleming D, Henry D, De Groot R, Makela M, Klein T, et al. Efficacy and safety of  
319 the neuraminidase inhibitor zanamivir in the treatment of influenza A and B virus infections. *The*  
320 *Journal of infectious diseases*. 1999;180(2):254-61.

321 6. Monto AS, Webster A, Keene O. Randomized, placebo-controlled studies of inhaled  
322 zanamivir in the treatment of influenza A and B: pooled efficacy analysis. *Journal of Antimicrobial*  
323 *Chemotherapy*. 1999;44(suppl\_2):23-9.

324 7. Nicholson K, Aoki F, Osterhaus A, Trottier S, Carewicz O, Mercier C, et al. Efficacy and safety  
325 of oseltamivir in treatment of acute influenza: a randomised controlled trial. *The Lancet*.  
326 2000;355(9218):1845-50.

327 8. Treanor JJ, Hayden FG, Vrooman PS, Barbarash R, Bettis R, Riff D, et al. Efficacy and safety of  
328 the oral neuraminidase inhibitor oseltamivir in treating acute influenza: a randomized controlled  
329 trial. *Jama*. 2000;283(8):1016-24.

330 9. Hedrick JA, Barzilai A, Behre U, Henderson FW, Hammond J, Reilly L, et al. Zanamivir for  
331 treatment of symptomatic influenza A and B infection in children five to twelve years of age: a  
332 randomized controlled trial. *The Pediatric infectious disease journal*. 2000;19(5):410-7.

333 10. Whitley RJ, Hayden FG, Reisinger KS, Young N, Dutkowski R, Ipe D, et al. Oral oseltamivir  
334 treatment of influenza in children. *The Pediatric infectious disease journal*. 2001;20(2):127-33.

335 11. Heinonen S, Silvennoinen H, Lehtinen P, Vainionpää R, Vahlberg T, Ziegler T, et al. Early  
336 oseltamivir treatment of influenza in children 1–3 years of age: a randomized controlled trial. *Clinical*  
337 *Infectious Diseases*. 2010;51(8):887-94.

338 12. Fry AM, Goswami D, Nahar K, Sharmin AT, Rahman M, Gubareva L, et al. Efficacy of  
339 oseltamivir treatment started within 5 days of symptom onset to reduce influenza illness duration  
340 and virus shedding in an urban setting in Bangladesh: a randomised placebo-controlled trial. *The*  
341 *Lancet infectious diseases*. 2014;14(2):109-18.

342 13. Kohno S, Kida H, Mizuguchi M, Hirotsu N, Ishida T, Kadota J, et al. Intravenous peramivir for  
343 treatment of influenza A and B virus infection in high-risk patients. *Antimicrobial agents and*  
344 *chemotherapy*. 2011;55(6):2803-12.

345 14. Whitley R, Laughlin A, Carson S, Mitha E, Tellier G, Stich M, et al. Single dose peramivir for  
346 the treatment of acute seasonal influenza: integrated analysis of efficacy and safety from two  
347 placebo-controlled trials. *Antivir Ther*. 2014.

348 15. Kelly H, Cowling B. Evidence and policy for influenza control. *Euro Surveill*. 2014;19(27):2-4.

349 16. Nguyen-Van-Tam JS, Openshaw PJM, Nicholson KG. Antivirals for influenza: where now for  
350 clinical practice and pandemic preparedness? *The Lancet*.384(9941):386-7.

351 17. Jefferson T, Jones MA, Doshi P, Del Mar CB, Heneghan CJ, Hama R, et al. Neuraminidase  
352 inhibitors for preventing and treating influenza in healthy adults and children. *Cochrane Database*  
353 *Syst Rev*. 2012;1(1).

354 18. Kaiser L, Wat C, Mills T, Mahoney P, Ward P, Hayden F. Impact of oseltamivir treatment on  
355 influenza-related lower respiratory tract complications and hospitalizations. *Archives of Internal*  
356 *Medicine*. 2003;163(14):1667-72.

357 19. Dobson J, Whitley RJ, Pocock S, Monto AS. Oseltamivir treatment for influenza in adults: a  
358 meta-analysis of randomised controlled trials. *The Lancet*. 2015 2015/05/02/;385(9979):1729-37.

- 359 20. Ebell MH, Call M, Shinholser J. Effectiveness of oseltamivir in adults: a meta-analysis of  
360 published and unpublished clinical trials. *Family practice*. 2012;30(2):125-33.
- 361 21. Jefferson T, Jones M, Doshi P, Spencer EA, Onakpoya I, Heneghan CJ. Oseltamivir for  
362 influenza in adults and children: systematic review of clinical study reports and summary of  
363 regulatory comments. *BMJ : British Medical Journal*. 2014;348.
- 364 22. Department of Health. Pandemic influenza: Guidance for primary care trusts and primary  
365 care professionals on the provision of healthcare in a community setting in England. 2007.
- 366 23. Siddiqui MR, Edmunds WJ. Cost-effectiveness of Antiviral Stockpiling and Near-Patient  
367 Testing for Potential Influenza Pandemic. *Emerging Infectious Diseases*. 2008;14(2):267-74.
- 368 24. Carrasco LR, Lee VJ, Chen MI, Matchar DB, Thompson JP, Cook AR. Strategies for antiviral  
369 stockpiling for future influenza pandemics: a global epidemic-economic perspective. *Journal of the*  
370 *Royal Society Interface*. 2011;8(62):1307-13.
- 371 25. Balicer RD, Huerta M, Davidovitch N, Grotto I. Cost-Benefit of Stockpiling Drugs for Influenza  
372 Pandemic. *Emerging Infectious Diseases*. 2005;11(8):1280-2.
- 373 26. Drake TL, Chalabi Z, Coker R. Cost-effectiveness analysis of pandemic influenza  
374 preparedness: what's missing? *Bulletin of the World Health Organization*. 2012;90:940-1.
- 375 27. Reed C, Biggerstaff M, Finelli L, Koonin LM, Beauvais D, Uzicanin A, et al. Novel Framework  
376 for Assessing Epidemiologic Effects of Influenza Epidemics and Pandemics. *Emerging Infectious*  
377 *Diseases*. 2013;19(1):85-91.
- 378 28. Meltzer MI, Gambhir M, Atkins CY, Swerdlow DL. Standardizing Scenarios to Assess the Need  
379 to Respond to an Influenza Pandemic. *Clinical Infectious Diseases*. 2015;60(suppl\_1):S1-S8.
- 380 29. Health Protection Agency. Pandemic (H1N1) 2009 in England; an overview of initial  
381 epidemiological findings and implications for the second wave. HPA London; 2009.
- 382 30. Academy of Medical Sciences, Wellcome Trust. Use of neuraminidase inhibitors in influenza  
383 2015 [cited; Available from: <http://www.acmedsci.ac.uk/policy/policy-projects/treating-influenza/>
- 384 31. O'Hagan JJ, Wong KK, Campbell AP, Patel A, Swerdlow DL, Fry AM, et al. Estimating the  
385 United States demand for influenza antivirals and the effect on severe influenza disease during a  
386 potential pandemic. *Clinical Infectious Diseases*. 2015;60(suppl\_1):S30-S41.
- 387 32. Rutter P, Mytton O, Ellis B, Donaldson L. Access to the NHS by telephone and Internet during  
388 an influenza pandemic: an observational study. *BMJ open*. 2014;4(2):e004174.
- 389 33. Department of Health. The National Pandemic Flu Service: An Evaluation. 2011.
- 390 34. Curtis LA. Unit costs of health and social care 2017. 2017.
- 391 35. World Bank. UK Population total. 2017 [cited 12/05/2017]; Available from:  
392 <https://data.worldbank.org/indicator/SP.POP.TOTL?locations=GB>
- 393 36. Whitehead SJ, Ali S. Health outcomes in economic evaluation: the QALY and utilities. *British*  
394 *Medical Bulletin*. 2010;96(1):5-21.
- 395 37. K. LA, D. MS, Jacco W. Dynamic versus static models in cost-effectiveness analyses of anti-  
396 viral drug therapy to mitigate an influenza pandemic. *Health Economics*. 2010;19(5):518-31.
- 397 38. Public Accounts Committee. 2 Stockpiling Tamiflu and the management of the stockpile In:  
398 Parliament U, editor.; 2013.
- 399 39. Venkatesan S, Myles PR, Leonardi-Bee J, Muthuri SG, Al Masri M, Andrews N, et al. Impact of  
400 Outpatient Neuraminidase Inhibitor Treatment in Patients Infected With Influenza A(H1N1)pdm09 at  
401 High Risk of Hospitalization: An Individual Participant Data Metaanalysis. *Clinical Infectious Diseases*.  
402 2017;64(10):1328-34.
- 403 40. Marra F, Chong M, Henry B, Patrick DM, Kendall P. Effectiveness of neuraminidase inhibitors  
404 in preventing hospitalization during the H1N1 influenza pandemic in British Columbia, Canada.  
405 *Journal of Antimicrobial Chemotherapy*. 2013;69(5):1397-406.
- 406 41. Ghani A, Baguelin M, Griffin J, Flasche S, van Hoek AJ, Cauchemez S, et al. The Early  
407 Transmission Dynamics of H1N1pdm Influenza in the United Kingdom. *PLoS Currents*. 2010 06/13  
408 10/26/created



409 11/20/accepted;1:RRN1130.

410 42. Electronic Medicines Compendium (eMC). Tamiflu 30 mg, 45 mg and 75 mg Hard Capsules.  
411 2017 [cited; Available from: <http://www.medicines.org.uk/emc/medicine/20294>

412 43. Muthuri SG, Venkatesan S, Myles PR, Leonardi-Bee J, Al Khuwaitir TSA, Al Mamun A, et al.  
413 Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with  
414 influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. *The Lancet*  
415 *Respiratory Medicine*. 2014 5//;2(5):395-404.

416 44. Muthuri SG, Venkatesan S, Myles PR, Leonardi-Bee J, Lim WS, Al Mamun A, et al. Impact of  
417 neuraminidase inhibitors on influenza A(H1N1)pdm09-related pneumonia: an individual participant  
418 data meta-analysis. *Influenza and Other Respiratory Viruses*. 2016;10(3):192-204.

419 45. Watson S, Chen Y, Nguyen-Van-Tam J, Myles P, Venkatesan S, Zambon M, et al. Evidence  
420 synthesis and decision modelling to support complex decisions: stockpiling neuraminidase inhibitors  
421 for pandemic influenza usage [version 2; referees: 2 approved]; 2017.

422 46. Department of Health. Scientific Summary of Pandemic Influenza & its Mitigation: Scientific  
423 Evidence Base Review. 2011.

424 47. Brooks-Pollock E, Tilston N, Edmunds WJ, Eames KT. Using an online survey of healthcare-  
425 seeking behaviour to estimate the magnitude and severity of the 2009 H1N1v influenza epidemic in  
426 England. *BMC infectious diseases*. 2011;11(1):68.

427 48. Biggerstaff M, Jhung MA, Reed C, Fry AM, Balluz L, Finelli L. Influenza-like illness, the time to  
428 seek healthcare, and influenza antiviral receipt during the 2010–2011 influenza season—United  
429 States. *The Journal of infectious diseases*. 2014;210(4):535-44.

430 49. Public Health England. Seasonal influenza vaccine uptake amongst GP patient groups in  
431 England: Provisional monthly data for 1 September 2016 to 30 November 2016. In: Department of  
432 Health, editor.; 2017.

433 50. Hine D. The 2009 Influenza Pandemic: An independent review of the UK response to  
434 the2009 influenza pandemic. 2010.

435 51. Myles PR, Semple MG, Lim WS, Openshaw PJM, Gadd EM, Read RC, et al. Predictors of  
436 clinical outcome in a national hospitalised cohort across both waves of the influenza A/H1N1  
437 pandemic 2009–2010 in the UK. *Thorax*. 2012;67(8):709.

438 52. Curtis L. Unit Costs of Health and Social Care 2008. Kent: Personal Social Services Research  
439 Unit, University of Kent at Canterbury. 2009.

440 53. British Medical Association and the Royal Pharmaceutical Society of Great Britain. British  
441 national formulary 58, September 2009 edition. 2009.

442 54. Department of Health. NHS reference costs 2008. 2008.

443 55. Baguelin M, Van Hoek AJ, Jit M, Flasche S, White PJ, Edmunds WJ. Vaccination against  
444 pandemic influenza A/H1N1v in England: a real-time economic evaluation. *Vaccine*.  
445 2010;28(12):2370-84.

446

447  
448

**Table 1: Input parameters used to estimate the number of outcomes averted by neuraminidase inhibitors (NAI) treatment and the cost per averted hospitalization**

Parameter	Value	Range (probability distribution)	Source
<b>Total population</b>	62280000	Fixed	(35)
<b>Clinical attack rate (CAR)</b>			
2009 pandemic	7%	Fixed	Box A1, page 31 of (46)
Transmissibility scenario 1	20%	Fixed	(28)
Transmissibility scenario 2	30%	Fixed	(28)
<b>% Seeking outpatient care (non-high-risk)*</b>			
2009 pandemic	40%	32% to 43% (Uniform)	(47)
Severity 1	60%	Fixed	(28)
Severity 2	70%	Fixed	(28)
<b>% Seeking outpatient care (high-risk)</b>			
2009 pandemic	51.2%	43.2 to 54.2 (Uniform)	Assumed from (48)
Severity 1	71.2%	Fixed	Assumed in line with: (48) and (28)
Severity 2	81.2%	Fixed	Assumed in line with: (48) and (28)
<b>% of high-risk individuals</b>	30%	27% to 33% (Uniform)	(49)
<b>Case hospitalization risk (non-high-risk)</b>			
2009 pandemic	0.30%	0.27% to 0.33% (Uniform)	From Annex G, page 171 of (50)
Severity 1	1.05%	Fixed	(28)
Severity 2	4.00%	Fixed	(28)
<b>Case hospitalization risk (high-risk)</b>			
2009 pandemic	1.50%	1.35% to 1.65% (Uniform)	Assumed from page 10 of (29) that at-risk groups would have an increased risk of hospital admission by five times
Severity 1	5.25%	Fixed	Assumed in line with: (28) and (29)
Severity 2	20.00%	Fixed	Assumed in line with: (28) and (29)
<b>% of care-seeking patients prescribed NAI</b>	73%	60% to 85% (Triangular)	(32)
<b>Prescription of NAIs for non-influenza ILI as a % of those receiving NAIs for influenza</b>	40%	30% to 50% (Uniform)	Assumed from (31)

<b>NAI (any time) compliance (as a %)</b>	64%	55% to 70% (Uniform)	(32)
<b>Effectiveness of NAI treatment (&lt;48 hours from symptom onset) on hospitalization (risk reduction)</b> (Intention-to-treat-infected)	63%	83% to 19% (Triangular)	Assumed for pandemic influenza from (19)
<b>Mortality risk (in-hospital)</b>			
2009 Pandemic	5.3%	Fixed	(51)
Severity 1	5.3%	Fixed	Assumed to be fixed between scenarios
Severity 2	5.3%	Fixed	Assumed to be fixed between scenarios
<b>Costs</b>			
Before being input into the model, all costs listed below were inflated to the 2017 UK Pound Sterling (£) (The hospital & community health services (HCHS) index)			
Cost of GP consultation	£ 37		(52) and (55)
Cost of telephone consultation	£ 22		(52) and (55)
Average (weighted) outpatient consultation cost	£24.2	£22 to £37 (Truncated log normal)	
Cost of NAI (+delivery)	£ 16	Fixed	(53)
High-risk patients: Cost of Hospitalization due to influenza (per patient)	£1,727	£1,263 to £2,075 (Truncated log normal)	(54) and (55)
Low-risk patients: Cost of Hospitalization due to influenza (per patient)	£436	£307 to £504 (Truncated log normal)	(54) and (55)

\*This includes consultations made through the National Pandemic Flu Service (NPFS) telephone line

Table 2: Outpatient NAI treatment for averting outcomes and the cost per averted hospitalization

	NAI regimens dispensed to pandemic influenza patients	NAI regimens dispensed to non-influenza ILI patients	Total NAI regimens dispensed	Total Hospitalizations	NAI costs (£)	Total costs (£)	Hospitalizations averted (%)	Incremental cost per averted hospitalization (£)	Deaths averted, No.
<b>2009 A(H1N1) pandemic</b>									
<i>High-risk patients</i>									
No NAI treatment	NA	NA	NA	19,618	NA	56,713,354	NA	NA	NA
NAI treatment	488,833	195,533	684,367	16,662	12,397,546	63,330,048	2,956 (15.1)	2,238	157
<i>Non-high-risk patients</i>									
No NAI treatment	NA	NA	NA	9,155	NA	37,976,039	NA	NA	NA
NAI treatment	891,102	356,441	1,247,543	8,077	22,599,693	60,043,645	1,078 (11.8)	20,473	57
<i>Total population</i>									
No NAI treatment	NA	NA	NA	28,773	NA	94,689,393	NA	NA	NA
NAI treatment	1,379,935	551,974	1,931,910	24,739	34,997,239	123,373,693	4,034 (14.0)	7,110	214
<b>20% CAR- Severity 1</b>									
<i>High-risk patients</i>									
No NAI treatment	NA	NA	NA	196,182	NA	456,499,003	NA	NA	NA
NAI treatment	1,942,239	776,896	2,719,135	155,069	49,258,106	425,367,141	41,113 (21.0)	CS	2,179
<i>Non-high-risk patients</i>									
No NAI treatment	NA	NA	NA	91,552	NA	188,534,796	NA	NA	NA
NAI treatment	3,819,010	1,527,604	5,346,613	75,383	96,855,827	277,409,315	16,168 (17.7)	5,497	857



No NAI treatment	NA	NA	NA	1,121,040	NA	2,316,706,026	NA	NA	NA
NAI treatment	3,322,538	1,329,015	4,651,554	853,111	84,264,570	1,877,080,913	267,929 (23.9)	CS	14,200
<i>Non-high-risk patients</i>									
No NAI treatment	NA	NA	NA	523,152	NA	509,097,257	NA	NA	NA
NAI treatment	6,683,267	2,673,307	9,356,574	415,364	169,497,697	625,386,237	107,788 (20.6)	1,079	5,713
<i>Total population</i>									
No NAI treatment	NA	NA	NA	1,644,192	NA	2,825,803,283	NA	NA	NA
NAI treatment	10,005,805	4,002,322	14,008,127	1,268,475	253,762,267	2,502,467,151	375,717 (22.9)	CS	19,913

CAR: Clinical Attack Rate; CS: Cost Saving; NA: Not Applicable

**Fig. 1: Decision analytical model tree comparing outcomes in 'NAI treatment' and 'no NAI treatment' groups for patients with symptomatic pandemic influenza**

**Fig. 2: Probabilistic sensitivity analysis. (A) shows the impact of various parameters on total hospitalizations averted, and (B) shows the impact of various parameters on cost-effectiveness (2009-like pandemic scenario).** The width of the bars indicate the change in the output from several replications when each parameter is varied over its range. NAI: Neuraminidase inhibitors; ILI: Influenza-like illness

**Fig. 3: Impact of varying treatment compliance on hospitalizations averted at different NAI effectiveness estimates.**

This plot is based on a 2009-like influenza pandemic where the number of hospitalizations in the base-case scenario was estimated to be 24,739;

NAI: Neuraminidase inhibitor