

1 **Neuraminidase inhibitors and hospital length of stay: an**
2 **individual participant data (IPD) meta-analysis of treatment**
3 **effectiveness in patients hospitalised with non-fatal**
4 **A(H1N1)pdm09 virus infection**

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23 **Running title:** NAI treatment & hospital length of stay

24 **Abstract word count:** 199 words

25 **Manuscript word count:** 3,255 words

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33 *Abstract*

34 **Background:** The effect of neuraminidase inhibitors (NAI) treatment on
35 length of stay (LoS) in patients hospitalised with influenza is unclear.

36 **Methods:** We conducted a one-stage individual participant data (IPD)
37 meta-analysis exploring the association between NAI treatment and LoS in
38 patients hospitalised with influenza A(H1N1)pdm09. Using mixed-effects
39 negative binomial regression, adjusting for propensity to receive NAIs,
40 antibiotic and corticosteroid treatment, incidence rate ratios (IRRs) and
41 95% confidence Intervals (95% CI) were calculated. Patients with LoS <1
42 day, and in-hospital deaths were excluded.

43 **Results:** We analysed data on 18,309 patients from 70 clinical centres.
44 After adjustment, NAI treatment initiated at hospitalisation, compared to
45 later or no NAI treatment, was associated with a 19% reduction in LoS in
46 patients with clinically suspected or laboratory-confirmed influenza
47 A(H1N1)pdm09 virus infection (IRR: 0.81; 95% CI: 0.78-0.85). Similar
48 statistically significant associations were seen in all clinical sub-groups.
49 NAI treatment (any time) compared to no NAI treatment, and NAI
50 treatment initiated <2 days of onset compared to later/no NAI treatment
51 showed mixed patterns of association with LoS.

52 **Conclusions:** When patients hospitalised with influenza are treated with
53 NAIs, treatment initiated on admission regardless of time since illness
54 onset, is associated with reduced LoS compared with later or non-
55 treatment.

56 **Key words:** Neuraminidase inhibitors, pandemic influenza, IPD meta-
57 analysis, length of stay, antivirals

58

59 **Introduction:**

60 Seasonal influenza epidemics and pandemics increase pressure on hospital bed
61 capacity. Early initiation of monotherapy with neuraminidase inhibitors (NAIs)
62 reduces illness duration in patients with uncomplicated influenza;¹⁻³ associated
63 reductions in complications, hospitalisation and mortality are supported by
64 systematic reviews of observational data.⁴⁻⁸ The evidence is less clear that NAI
65 treatment reduces length of stay (LoS) in hospitalised influenza patients,
66 compared with supportive care without antiviral treatment.⁹⁻¹⁵ Minimising LoS is
67 important in managing hospital surge and limiting healthcare costs due to
68 seasonal influenza epidemics and pandemics. We undertook a one-stage
69 individual participant data (IPD)¹⁶ meta-analysis to explore the association
70 between NAI treatment of patients hospitalised with influenza A(H1N1)pdm09
71 and length of inpatient stay during the 2009-10 influenza pandemic.

72 **Methods:**

73 Details regarding identification of study centres and inclusion of patients have
74 been published previously.⁶ Briefly, we requested data on patients admitted to
75 hospital with laboratory-confirmed or clinically diagnosed influenza
76 A(H1N1)pdm09 virus infection for whom a minimum dataset was available, from
77 multiple clinical centres worldwide. Of the individual participant data that we
78 received, we excluded patients who had a laboratory-confirmed absence of
79 A(H1N1)pdm09 virus infection, retaining only those patients who had laboratory-
80 confirmed A(H1N1)pdm09 virus infection and patients with clinically diagnosed
81 pandemic influenza (i.e. the clinical suspicion and working diagnosis was one of
82 pandemic influenza, but laboratory confirmation was not performed).⁶ The PRIDE
83 study protocol was registered with the PROSPERO register of systematic reviews
84 (CRD42011001273) prior to data collection.¹⁷ This states that the study will

85 investigate NAI impact on multiple outcomes of public health interest in
86 A(H1N1)pdm09-infected patients using mixed-effects models. After collection
87 and standardisation of the data, sufficient data existed to assess two indicators
88 of “severe hospital outcomes” – requirement for ventilatory support (ICU
89 admission) and hospital LoS. In this manuscript, we present the findings relating
90 to hospital LoS.

91 **Data Standardisation, Exposure and Outcome**

92 We standardised data from individual datasets prior to pooling (Supplementary
93 Table 1). Primary outcome was length of hospital stay (in whole days). We
94 excluded patients with known pre-admission NAI treatment to ensure uniform
95 potential for treatment to influence LoS. We excluded patients with continuing
96 post-discharge NAI treatment; patients with length of hospital stay <1 day on the
97 grounds that they would have received a maximum two doses of NAI inpatient
98 treatment and their admission may have been precautionary; and also patients
99 with nosocomial influenza (symptom onset after hospital admission date, see
100 Figure 1). Finally, since rapid deterioration and early death in hospital would be
101 an adverse outcome associated with paradoxically short LoS, those who died in
102 hospital were excluded from analysis.

103 The primary exposure variable was in-hospital NAI treatment received on the day
104 of hospital admission, compared to later NAI treatment or no NAI treatment.
105 Additionally, where data were available, we defined three further exposure
106 variables: NAI treatment (at any time) versus no NAI treatment; early NAI
107 treatment (initiated within ≤ 2 days after symptom onset) versus no NAI
108 treatment; and early NAI treatment versus later treatment (initiated > 2 days
109 after symptom onset).

110 **Propensity scores**

111 We derived propensity scores via multivariable logistic regression for each
112 exposure variable, as described by Hirano and Imbens,¹⁸ separately for individual
113 study centres, based on patient characteristics recorded on admission.
114 Propensity score derivation models included, *a priori*: age, sex, comorbidity (yes/
115 no) and an indicator of disease severity, plus additional covariates that remained
116 statistically significant in a regression model, from: obesity, smoking, pregnancy,
117 asthma, chronic obstructive pulmonary disease, lung disease, heart disease,
118 immunosuppression, neurological disease, renal disease, and diabetes. Variables
119 with >25% missing data were excluded from propensity score derivation.

120 **Statistical analysis**

121 To investigate the impact of NAI treatment on length of hospital stay, we
122 performed a one-stage IPD meta-analysis using a mixed effects negative
123 binomial regression model, including study centre as a random intercept, to
124 account for clustering. A negative binomial model was chosen to account for
125 overdispersion in the LoS data (as represented in Supplementary figure 1). We
126 tested a zero-inflated negative binomial regression model on a sub-group of the
127 data and found that the model fit was inferior to that of a negative binomial
128 regression model.

129 In our primary analysis, we aimed to quantify the potential benefits of a
130 pragmatic 'treat-on-admission' policy (irrespective of the time elapsed since
131 symptom onset), compared to patients who received no NAI treatment and those
132 whose treatment was delayed until after the day of admission. By way of
133 sensitivity analysis, we restricted the comparator group to patients who did not
134 receive NAI treatment at any point. For both analyses, we adjusted for propensity
135 score quintile, in-hospital antibiotic treatment and in-hospital corticosteroid
136 treatment, and the time delay between symptom onset and hospital admission.

137 In addition, we performed secondary analyses for the following exposures: NAI
138 treatment (at any time) versus no NAI treatment, early NAI treatment (≤ 48 h
139 from symptom onset) versus later NAI treatment (> 48 h from symptom onset),
140 and early NAI treatment versus no NAI treatment, adjusting for propensity score,
141 in-hospital antibiotic and corticosteroid treatment.

142 We performed, *a priori* specified, analyses for the following sub-groups: patients
143 with laboratory-confirmed A(H1N1)pdm09, children (< 16 years), elderly patients
144 (≥ 65 years), patients with chest radiograph-confirmed influenza-related
145 pneumonia (IRP), and patients with a confirmed absence of IRP. We looked at
146 pregnant women and patients with obesity as *post hoc* sub-groups. Furthermore,
147 we investigated, by stratification, the impact of NAI treatment on total hospital
148 LoS in patients admitted to critical care (ICU) facilities at any point, and patients
149 managed exclusively using standard ward-based care.

150 Both unadjusted and adjusted models were run, and results are presented as
151 unadjusted or adjusted incidence rate ratios (IRR/aIRR) with 95% confidence
152 intervals (95% CI). Missing data in the covariates were included in the analysis as
153 dummy variable categories. Using aIRR point estimates, we calculated the
154 difference in LoS (in days) between a treated and untreated patient with similar
155 characteristics by scaling the model prediction for LoS without treatment by
156 (aIRR-1). Repeating this for all patients in our dataset gave us a distribution of
157 expected changes in LoS due to treatment (with timing as defined for each
158 regression analysis). This does not account for error in the estimates of model
159 covariates, which would require a Bayesian approach; however it offers a
160 clinically relevant interpretation of aIRRs. The statistical analyses were
161 performed using Stata (version 14.2; StataCorp LP, College Station, TX, USA).

162 **Results:**

163 We identified 29,234 patients admitted to hospital between 2nd January 2009 and
164 14th March 2011 with laboratory-confirmed or clinically diagnosed
165 A(H1N1)pdm09.⁴ The analysis population included 18,309 (62.6%) patients
166 (Figure 1).

167 The included patients came from 70 clinical centres in 36 countries across all six
168 World Health Organization regions. The Americas contributed most data (46.2%),
169 followed by Europe (33.3%). The country that contributed the most to the pooled
170 dataset was Mexico (28.8%), followed by Spain (8.6%), USA (7.6%) and the UK
171 (7.5%). The majority of the patients in the final study population were adults
172 (67.4%), with laboratory-confirmed influenza A(H1N1)pdm09 virus infection
173 (81.1%); general characteristics of the included population are further described
174 in Table 1.

175 Among the 8,621 patients (47.1%) for whom data on timing of NAI treatment
176 were available, 3,678 (42.7%) received early NAI treatment and 4816 (55.9%)
177 had treatment started on the day of admission. The median delay from illness
178 onset to hospital admission was 2 days (interquartile range (IQR): 1-5) and,
179 where data on timing of treatment were available, 42.7% presented ≤ 48 h after
180 symptom onset; median LoS was 5 days (IQR: 3-9) (Supplementary Figure 1). In
181 patients whose NAI treatment was initiated on the day of hospital admission, the
182 median interval between symptom onset and admission was 2 days (IQR: 1-4).

183 **Impact of NAI treatment on length of stay**

184 In our primary analysis, we observed that NAI treatment started on the day of
185 admission, compared with no treatment or later initiation of NAI treatment, was
186 associated with an overall 19% reduction in LoS [aIRR:0.81 (0.78-0.85)], median
187 decrease 1.19 days (IQR: 0.85-1.55). This association was of similar magnitude
188 and remained significant in all subgroups (Table 2 and Supplementary Table 3).

189 In the sensitivity analysis, we observed that NAI treatment on the day of hospital
190 admission was associated with an 8% reduction in LoS compared to no NAI
191 treatment, in non-ICU cases [aIRR: 0.92 (0.85-0.98) median decrease: 0.50 days
192 (IQR: 0.43-0.57)], a 19% reduction in patients with a confirmed absence of IRP
193 [aIRR: 0.81 (0.73-0.90) median decrease: 1.24 days (0.93-1.38)], but a 28%
194 increase in LoS in patients with confirmed presence of IRP [aIRR: 1.28 (1.11-1.48)
195 median increase: 1.73 days (1.29-2.07)].

196 **Secondary analyses**

197 After adjustment, NAI treatment at any time was associated with an overall 11%
198 increase in LoS [aIRR: 1.11, (1.07-1.16), median increase: 0.74 days (0.60-1.05)],
199 when compared to no NAI treatment. By exploring subgroups we identified
200 corresponding statistically significant findings in laboratory-confirmed cases,
201 children, ICU patients and in patients with confirmed IRP, but not in the elderly,
202 patients requiring non-ICU care, or in patients with a confirmed absence of IRP
203 (Table 2). We did not find any evidence for effect-modification by pandemic
204 influenza vaccination (p-value: 0.68) or by in-hospital antibiotic treatment (p-
205 value: 0.20); however, a borderline significant effect-modification was observed
206 for in-hospital corticosteroid treatment (p-value: 0.05), with NAI treatment plus
207 corticosteroids being associated with marginally increased LoS [aIRR: 1.17 days
208 (1.00-1.36)].

209 In contrast, early NAI treatment compared to no NAI treatment was associated
210 with a 7% overall reduction in LoS [aIRR: 0.93 (0.87-0.99), median decrease:
211 0.40 days (0.36-0.45)]. Similar or larger reductions were observed in most sub-
212 groups; however, this association was not statistically significant in children, ICU
213 patients, and in patients with confirmed IRP (Table 2). Early NAI treatment
214 compared to later NAI treatment was associated with an overall 23% reduction in

215 LoS [aIRR: 0.77 (0.74-0.80), median decrease: 1.78 days (1.34-2.49)], which
216 varied across all *a priori* specified sub-groups but remained statistically
217 significant (Table 2).

218 In pregnant women and obesity subgroups, early NAI treatment compared to
219 later NAI treatment was associated with statistically significant reductions in LoS
220 by 39% [aIRR: 0.61 (0.52-0.70), median decrease: 3.10 days (2.34-4.56)] and
221 27% [aIRR: 0.73 (0.65-0.83), median decrease: 2.11 days (1.62-3.10)]
222 respectively. NAI treatment at any time and early NAI treatment, when compared
223 to no NAI treatment, were not statistically significantly associated with LoS
224 (Supplementary table 3).

225 **Discussion**

226 Our study extends the existing literature by offering data on the association
227 between NAI treatment and LoS in over 18,000 adult and paediatric patients, of
228 whom >80% had a laboratory confirmed diagnosis of A(H1N1)pdm09 virus
229 infection. We found a mixed pattern of association between NAI treatment and
230 LoS depending on the delay to initiation of treatment, age, and case severity.

231 The most pragmatic and important question is whether NAI treatment, started on
232 admission, irrespective of delay since symptom onset, reduces LoS in
233 hospitalised influenza patients. Clinically, this is important as there can be
234 significant uncertainty in ascertaining symptom onset even by the attending
235 physician. The uncertainty in ascertaining symptom onset could mean
236 prescribing NAI treatment outside the recommended (licensed) window of 48
237 hours from symptom onset. However, there is evidence pointing to NAI
238 effectiveness, albeit reduced, even when given >48 hours from symptom onset.⁶
239 Statistically, by defining our exposure variable based on treatment decisions
240 made on admission, we avoid introducing correlations between exposure and

241 LoS which can lead to survivorship bias in linear regression models of time-to-
242 event data.^{19,20} Additionally this approach ensures that the propensity scores,
243 modelled on symptom severity at admission, should appropriately correct for
244 treatment bias.²¹ However, this choice of exposure variable also reflects the
245 clinical reality, that patients present to hospital with varying delays since
246 symptom onset (in our study, ranging from 0-20 days); and that clinicians and
247 policy makers want to know if a 'treat at the door' policy, applied to patients
248 admitted to hospital with clinically recognised influenza will be beneficial
249 compared with no NAI treatment or a 'watch and see' approach. This was
250 addressed by our primary analysis which revealed NAI treatment started on the
251 day of admission, compared to later or no treatment, was associated with an
252 19% reduction in LoS (median 1.19 days), with similar statistically significant
253 findings across all patient subgroups including children, pregnant women and
254 obese patients. These findings emphasise the importance of presumptive NAI
255 treatment in patients admitted to hospital with suspected influenza, coupled with
256 early diagnosis using standard laboratory or rapid diagnostic tests.

257 In our sensitivity analysis we found a significant reduction in LoS of 19% (median
258 1.24 days) in patients with a confirmed absence of IRP and reduction in LoS of
259 8% (median 0.5 days) in patients who required supportive ward-based care. In
260 contrast, NAI treatment (compared with none) was associated with an increase in
261 LoS by 28% (median 1.73 days) in patients with IRP. These data suggest that
262 NAIs may be more effective in reducing LOS when patients do not have IRP and
263 is consistent with the fact that NAIs have no known antibacterial properties.

264 In secondary analyses, we observed an 11% increase in LoS associated with NAI
265 treatment, equivalent to about 0.74 days, irrespective of the time between
266 symptom onset and initiation of therapy in the overall study population. NAI
267 treatment initiated within 48h of symptom onset, compared with no treatment,

268 was associated with an overall 7% reduction in LoS, equivalent to a median
269 reduction by 0.40 days; this effect was not observed in children and patients
270 requiring ICU care. This finding is clinically important because it suggests that
271 rapid access to antiviral treatment after symptom onset may influence LoS in
272 adults and the elderly; nevertheless, we did not observe the same in patients
273 requiring ICU. Our results in children may be influenced by higher influenza
274 A(H1N1)pdm09 viral load in children²² than adults leading to prolonged hospital
275 stay, suboptimal dosing in very young children,²³ increased likelihood of antiviral
276 resistance emergence in children,²⁴ secondary bacterial infections, and
277 confounding by indication related to baseline illness severity,²⁵ or a combination
278 of these factors. Although we attempted to adjust for severity using propensity
279 scores, we found ICU care to be very strongly associated with prolonged LoS
280 (IRR=2.96; 95% CI: 2.84-3.09), and NAI treatment to be associated with a higher
281 likelihood of requiring ICU care (aOR: 3.11; 95% CI: 2.42-3.98). Furthermore, we
282 found that patients who presented to hospital >2 days from symptom onset were
283 73% more likely to eventually require ICU care than patients who presented
284 earlier (OR: 1.73; 95% CI: 1.53-1.95). In addition, patients requiring ICU care
285 have frequently developed extra-pulmonary manifestations of influenza, and
286 multi-organ decompensation, therefore inhibition of virus replication may not
287 correspond with rapid clinical recovery.

288 We noted no association between NAI treatment and LoS in hospitalised children
289 with influenza when considering early treatment versus no treatment. The study
290 may have been underpowered in children, but other factors might have
291 contributed to our findings. LoS is typically shorter in children than in adults,
292 mortality and serious outcomes are less common in hospitalised children with
293 influenza compared with adults; different discharge policies and thresholds for
294 children could also influence the findings. In addition, vomiting is a recognised

295 side-effect of oseltamivir in children,³ and this may have prevented discharge in
296 some cases.

297 Previous studies examining whether use of NAIs in patients hospitalised with
298 influenza affects LoS have generally been of smaller size (n<1300) in comparison
299 to our own, and reached variable conclusions. Of note, eight studies^{11-15,26-28} (of
300 which one was a randomised trial)¹² assessed NAI treatment of hospitalised
301 children, but only two (observational) concluded that total hospital days in the
302 NAI treated hospital cohort were reduced (by 18% and 8.3 days respectively),^{11,28}
303 the other six reporting no differences.^{12-15,26,27} Only four studies have addressed
304 the same question in adults. In Hong Kong, a study of 356 adult patients
305 hospitalised with laboratory confirmed seasonal influenza showed that early
306 oseltamivir treatment, compared with none or later treatment, was associated
307 with reduced LoS in both unadjusted and multivariable analyses,⁹ median LoS
308 was reduced from six to four days and accords with our primary analysis. A
309 Canadian study of adult patients with seasonal influenza found oseltamivir
310 treatment was not associated with LoS in surviving patients.²⁹ A further study in
311 13 Spanish hospitals, in 538 patients with laboratory confirmed A(H1N1)pdm09,
312 noted LoS increased by 7% (OR =1.07) after adjustment for confounders, if NAI
313 treatment was instigated <48h after symptom onset; however this was of
314 borderline statistical significance.¹⁰ A recent American study analysed data on
315 201 adult patients with laboratory-confirmed seasonal influenza reporting that
316 NAI treatment was not associated with LoS overall, but was associated with a
317 reduced LoS in vaccinated individuals [hazard ratio of discharge: 1.6 (1.0-2.4), p-
318 value:0.04].³⁰ Finally, two studies included patients of all age groups. One of
319 them, performed in 813 hospitalised patients with A(H1N1)pdm09 virus infection
320 in Spain, found that early NAI treatment reduced LoS by 1.9 days (p-value:
321 <0.001).³¹ The other, an American study using insurance claims data from

322 seasonal influenza patients reported that patients treated with NAI spent fewer
323 days in hospital (p-value: <0.0001).³²

324 This study has a number of strengths and weaknesses. We combined data from
325 geographically diverse centres, offering broad generalisability of our findings. We
326 used propensity scores to adjust for major confounders. By excluding patients
327 who died (10%), we removed the paradoxical possibility that short LoS (a
328 positive outcome in our analyses) was associated with an extremely
329 unfavourable clinical outcome. However, a limitation of this approach is that it
330 does not explain NAI impact on the relationship between LoS and in-hospital
331 mortality. In our primary analysis, we adjusted for delay from illness onset to
332 admission to address length bias²⁰ and have chosen our exposure variable to
333 avoid time-dependent/survivorship bias.^{19,21} However, our secondary analyses,
334 which use time since onset to define the exposure variable, are subject to time-
335 dependent biases and must therefore be interpreted with caution. Indeed, the
336 benefit of early vs late treatment (Table 2) will be partially driven by this bias.¹⁹
337 All of our analyses may be subject to residual competing risk bias which has not
338 been removed through adjustment; for example, we found a significant
339 difference between propensity scores to receive NAIs in hospital for surviving
340 and non-surviving patients in the data set (Kruskall-Wallis: p<0.05), signalling
341 that our removal of non-surviving patients alters the aggregate presenting
342 patient characteristics for which our results hold.

343 Our data, generated during the 2009-10 pandemic, contained relatively few
344 elderly patients and children, consistent with patterns of A(H1N1)pdm09 virus
345 infection,³³ and differs in profile from seasonal influenza (A(H3N2)) where
346 patients admitted to hospital tend to be much older, and median LoS higher than
347 the five days we observed.^{34,35} In addition, the prevalence of clinically recorded
348 obesity (12%) and pregnancy (23%) were both comparatively high.

349 Optimally, clinicians wish to treat influenza patients within 48h of symptom
350 onset, yet in many cases influenza patients do not seek medical care during this
351 therapeutic window. Our data show that 57.3% of included patients were
352 hospitalised >48h after symptom onset. What then matters is whether initiation
353 of treatment upon hospitalisation (on the day of admission) irrespective of the
354 time elapsed since symptom onset is effective, and whether this is preferable to
355 non-treatment or further delays in treatment. We reveal a 19% reduction in LoS
356 (median 1.19 days) in patients treated with an NAI upon admission, rather than
357 remaining untreated or being treated later on; the trend is observed across all
358 subgroups including children. This treatment approach would avoid the
359 uncertainties associated with ascertaining the symptom onset date.

360 Our data support current recommendations to treat adults hospitalised with
361 clinically suspected influenza with NAIs as soon as possible upon admission;
362 furthermore, this approach appears superior to no-treatment or delayed
363 treatment in terms of reduced LoS. If applied consistently, this strategy would
364 contribute to the management of surge pressures and healthcare costs during
365 seasonal influenza epidemics and pandemics.

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383 **Author contributions:** JSN-V-T, PRM, SV, and SGM conceived and designed the
384 study. All authors, apart from SV, KJB, and SGM, contributed to the acquisition
385 and local preparation of constituent datasets. SV, PRM, KJB and SGM contributed
386 to data set amalgamation and standardisation, design of statistical analyses, and
387 data analysis. JSN-V-T, PRM, KJB, and SV interpreted the data and wrote the
388 manuscript. All authors contributed to critical examination of the paper for
389 important intellectual content and approval of the final report. Each author acted
390 as the guarantor of data from their individual study centre. SV had full access to
391 the pooled dataset in the study and takes responsibility for the accuracy of the
392 data analysis. JSN-V-T acts as overall guarantor of the manuscript.

393 **Funding:** The PRIDE study is funded via an unrestricted educational grant from
394 F. Hoffmann-La Roche, Switzerland (the manufacturers of Oseltamivir
395 (Tamiflu®)). The Funder has had no role in protocol design, no opportunity to
396 comment on it, and no opportunity to see it other than via the PROSPERO
397 website; no access to any data (and no rights to future access); no role in
398 analysis or interpretation; no opportunity to preview results/findings before entry
399 into the public domain; no opportunity to contribute to, preview or comment on
400 manuscripts and presentations arising from this work. The research contract
401 between the University of Nottingham and the Funder is freely available for

402 inspection (commercial details redacted) at:

403 [http://www.nottingham.ac.uk/research/groups/healthprotection/projects/
404 pride.aspx](http://www.nottingham.ac.uk/research/groups/healthprotection/projects/pride.aspx)

405 No data were provided or funded for collection by pharmaceutical companies.

406 **Acknowledgements:** We would like to thank Dr. Jerome Tokars and Dr. Alicia
407 Fry from CDC Atlanta, USA, for their comments on the manuscript.

408 **Declaration of interests:** GM reports grants and other funding from Pfizer,
409 MSD and Gilead outside the submitted work; KGIM reports personal fees from
410 Sanofi-Aventis Norway AS outside the submitted work; DT reports grants from
411 Canadian Institutes of Health Research/SickKids Foundation New Investigator
412 Grant XG08-049R, grants from Canadian Institutes of Health Research Catalyst
413 Grant CAT86860, grants from University of Toronto Dean's Fund Pilot Study
414 Grant, during the conduct of the study. WV reports grants from Canadian
415 Pediatric Society during the conduct of the study. KJB reports funding from a
416 University of Nottingham Anne McLaren Fellowship. JSN-V-T reports grants from
417 F. Hoffmann-La Roche for the conduct of this study, and personal fees from
418 Shionogi Ltd. (in 2016) outside the submitted work. He is currently on
419 secondment to the Department of Health and Social Care, England. The findings
420 and conclusions in this report are those of the authors and do not necessarily
421 represent the official position of the UK Government or the United States Centers
422 for Disease Control and Prevention. All other authors report no conflicts of
423 interests.

424 Preliminary results from this paper were presented at the Sixth ESWI Influenza
425 Conference, Riga, Latvia, held between 10th and 13th of September 2017.

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550 **Figure 1.** Identification of the study population

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77 **Table 1.** General Characteristics of study population (n= 18,309)

Characteristic (denominator)*	Total study population n (%)	No NAI treatment n (%)	In-hospital NAI treatment n(%)
Number of patients	18,309 (100)	6,075 (33.2)	12,234 (66.8)
Number of male cases (n=18,306)	9,114 (49.8)	2,852 (47)	6,262 (51.2)
Age: median (IQR) in years (n=18,238)	26 (10-44)	24 (6-41)	27 (12-46)
Adults (≥16 years)	12,331 (67.4)	3,686 (60.8)	8,645 (70.7)
Children (<16 years)	5,907 (32.3)	2,344 (38.6)	3,563 (29.1)
Elderly (≥65 years)	1,035 (5.7)	304 (5)	731 (6)
Patients with obesity (n=13,695)	1,677 (12.3)	475 (8.9)	1,202 (14.4)
Smoking (n=12,851)	1,728 (13.5)	429 (8.2)	1,299 (17.1)
Pregnant women‡ (n=5,318)	1,197 (22.5)	380 (21.1)	817 (23.2)
WHO Regions (n=18,309)			
African Region	23 (0.1)	0 (0)	23 (0.19)
Region of the Americas	8466 (46.2)	4,606 (75.8)	3,860 (31.6)
Eastern Mediterranean Region	1649 (9)	41 (0.7)	1,608 (13.1)
European Region	6090 (33.3)	918 (15.1)	5,172 (42.3)

South-East Asia Region	180 (1)	107 (1.8)	73 (0.6)
Western Pacific Region	1901 (10.3)	403 (6.6)	1,498 (12.2)
A(H1N1)pdm09 diagnosis (n=18,309)			
Laboratory confirmed	14,844 (81.1)	3,588 (59.1)	11,256 (92)
Clinically diagnosed	3,465 (18.9)	2,487 (40.9)	978 (8)
Comorbidities			
Any comorbidity (n=18,282)	7,017 (38.4)	1,749 (28.8)	5,268 (43.2)
Asthma (n=16,625)	2,461 (14.8)	607 (10.2)	1,854 (17.4)
COPD (n=13,812)	792 (5.7)	187 (3.6)	605 (7.1)
Other chronic lung disease (n=9,800)	1,393 (14.2)	190 (12.9)	1,203 (14.5)
Heart disease (n=12,146)	1,030 (8.5)	140 (8.2)	890 (8.5)
Renal disease (n=11,373)	401 (3.5)	44 (3.1)	357 (3.6)
Liver disease (n=9,564)	187 (2)	24 (1.7)	163 (2)
Cerebrovascular disease (n=7,751)	239 (3.1)	32 (3.2)	207 (3.1)
Neurological disease (n=8,929)	743 (8.3)	105 (7)	638 (8.6)
Diabetes (n=17,377)	1,375 (7.9)	418 (7.3)	957 (8.2)
Immunosuppression (n=17,180)	1,051 (6.1)	245 (4.3)	806 (7)
Chest radiograph-confirmation of influenza-related pneumonia (n=7,611)			

Confirmed presence of influenza-related pneumonia	4,591 (60.3)	426 (46.1)	4,165 (62.3)
Confirmed absence of influenza-related pneumonia	3,020 (39.7)	498 (53.9)	2,522 (37.7)
Pandemic H1N1 vaccination (n=5,371)	292 (5.4)	33 (4.7)	259 (5.5)
Time from symptom onset to hospital admission (days), median (IQR) (n=16,736)	2 (1-5)	2 (1-5)	2 (1-5)
Antiviral agents used			
No NAI treatment	6,075 (33.2)	6075 (100)	-
Any NAI	12,234 (66.8)	-	12,234 (100)
Treated with oral oseltamivir (n=12,234)	11,082 (90.6)	-	11,082 (98.8)
Treated with intravenous/inhaled zanamivir (n=12,234)	295 (2.4)	-	295 (4.3)
Treated with intravenous peramivir (n=12,234)	13 (0.1)	-	13 (0.2)
Early NAI (≤ 2 days of symptom onset) (n=8,621)	3,678 (42.7)	-	3,678 (42.7)
Later NAI (> 2 days after symptom onset) (n=8,621)	4,943 (57.3)	-	4,943 (57.3)
Time from symptom onset to antiviral treatment, days, median (IQR) (n=7,433)	3 (2-5)	-	3 (2-5)
Treated with any NAI on the day of hospital admission (n=12,234)	4,816 (39.4)	-	4,816 (39.4)
Antibiotics (n=14,599)	9,153 (62.7)	2,981 (52.2)	6,172 (69.5)
Corticosteroids (n= 8,075)	2,024 (25.1)	165 (15.3)	1,859 (26.6)
Hospital LoS, days†, median (IQR) (n=18,309)	5 (3-9)	4 (2-6)	6 (3-10)

Admission to critical care (n=17,348)	4,243 (24.5)	411 (6.9)	3,832 (33.7)
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78 *IQR: Interquartile range; *Percentages have been calculated using the individual denominators (brackets) for each table row.*

79 *‡Proportions were calculated as a percentage of pregnant patients among female patients of reproductive age (13-54 years); the broader age range was*

80 *selected in preference to the WHO definition (15-44 years) after consultation with data contributors to reflect the actual fertility experience of the sample;*

81 *this also includes data from a hospital obstetrics unit (n=72)*

82 *†LoS in the NAI treated group is the overall LoS in this group; precise NAI administration dates were not uniformly available to work out LoS after NAI*

83 *administration in the NAI-treated group*

	Unadjusted	Adjusted^a
	IRR (95%CI)	IRR (95%CI)
Primary analysis: NAI treatment on the day of hospital admission vs Later/No NAI treatment^b		
Overall	0.83 (0.79- 0.87)	0.81 (0.78- 0.85)
Laboratory-confirmed A(H1N1)pdm09	0.83 (0.79- 0.86)	0.81 (0.77- 0.85)
Children (age <16 years)	0.90 (0.83- 0.97)	0.85 (0.78- 0.92)
Elderly (age ≥65 years)	0.78 (0.67- 0.91)	0.78 (0.67- 0.91)
Patients requiring standard ward-based care only	0.81 (0.77- 0.85)	0.81 (0.78- 0.86)
ICU patients only ^c	0.80 (0.73- 0.88)	0.79 (0.72- 0.87)
Confirmed absence of Influenza-related pneumonia	0.71 (0.66- 0.77)	0.73 (0.68- 0.79)
Confirmed presence of Influenza-related pneumonia	0.91 (0.84- 0.98)	0.85 (0.79- 0.93)
Sensitivity analysis: NAI treatment on the day of hospital admission vs No NAI treatment^b		
Overall	1.14 (1.07- 1.22)	1.06 (0.99- 1.13)
Laboratory-confirmed A(H1N1)pdm09	1.15 (1.07- 1.22)	1.04 (0.97- 1.12)
Children (age <16 years)	1.09 (0.98-	0.98 (0.88-

	1.20)	1.09)
Elderly (age ≥65 years)	0.84 (0.67- 1.06)	0.83 (0.65- 1.07)
Patients requiring standard ward-based care only	0.93 (0.87- 0.99)	0.92 (0.85- 0.98)
ICU patients only ^c	1.14 (0.96- 1.36)	1.08 (0.90- 1.31)
Confirmed absence of Influenza-related pneumonia	0.83 (0.75- 0.92)	0.81 (0.73- 0.90)
Confirmed presence of Influenza-related pneumonia	1.28 (1.12- 1.47)	1.28 (1.11- 1.48)
Secondary Analyses		
NAI anytime vs No NAI treatment		
Overall	1.21 (1.17- 1.26)	1.11 (1.07- 1.16)
Laboratory-confirmed A(H1N1)pdm09	1.31 (1.25- 1.37)	1.17 (1.12- 1.23)
Children (age <16 years)	1.18 (1.11- 1.25)	1.11 (1.04- 1.18)
Elderly (age ≥65 years)	1.00 (0.86- 1.17)	0.98 (0.83- 1.14)
Patients requiring standard ward-based care only	1.06 (1.02- 1.10)	1.02 (0.98- 1.05)
ICU patients only ^c	1.33 (1.19- 1.49)	1.26 (1.13- 1.41)
Confirmed absence of Influenza-related pneumonia	0.98 (0.90- 1.07)	0.97 (0.89- 1.06)
Confirmed presence of Influenza-related pneumonia	1.36 (1.24- 1.49)	1.28 (1.16- 1.40)

Early NAI treatment vs Later NAI treatment		
Overall	0.70 (0.68-0.73)	0.77 (0.74-0.80)
Laboratory-confirmed A(H1N1)pdm09	0.70 (0.68-0.73)	0.77 (0.74-0.80)
Children (age <16 years)	0.80 (0.74-0.86)	0.87 (0.81-0.93)
Elderly (age ≥65 years)	0.71 (0.62-0.81)	0.71 (0.62-0.82)
Patients requiring standard ward-based care only	0.78 (0.75-0.81)	0.83 (0.79-0.86)
ICU patients only ^c	0.69 (0.64-0.74)	0.74 (0.69-0.80)
Confirmed absence of Influenza-related pneumonia	0.80 (0.75-0.86)	0.84 (0.78-0.90)
Confirmed presence of Influenza-related pneumonia	0.84 (0.78-0.90)	0.82 (0.77-0.88)
Early NAI treatment vs No NAI treatment		
Overall	1.04 (0.98-1.11)	0.93 (0.87-0.99)
Laboratory-confirmed A(H1N1)pdm09	1.05 (0.98-1.11)	0.93 (0.87-0.99)
Children (age <16 years)	1.00 (0.91-1.10)	0.92 (0.83-1.01)
Elderly (age ≥65 years)	0.82 (0.67-1.01)	0.79 (0.63-0.997)
Patients requiring standard ward-based care only	0.93 (0.87-0.99)	0.88 (0.82-0.94)
ICU patients only ^c	1.01 (0.86-	0.93 (0.79-

	1.20)	1.10)
Confirmed absence of Influenza-related pneumonia	0.79 (0.71-0.89)	0.76 (0.68-0.85)
Confirmed presence of Influenza-related pneumonia	1.09 (0.95-1.24)	1.01 (0.88-1.16)

585 IRR: Incidence Rate Ratio; 95%CI: 95% Confidence Interval (bold font indicates statistical
586 significance at the 5% level ($p < 0.05$); a) IRR adjusted for propensity scores (quintiles) for receiving
587 treatment, antibiotic treatment received in hospital, steroid treatment received in hospital; b) IRR
588 further adjusted for time from onset to admission; c) patients admitted to ICU at any point - IRR
589 calculated for total length of hospital stay, not time on ICU.
590 Our sensitivity analyses and secondary analyses must be interpreted with caution as they may be
591 affected by various time-dependent biases