

EFFECTIVENESS OF NEURAMINIDASE INHIBITORS IN REDUCING MORTALITY IN HOSPITALISED INFLUENZA A(H1N1)pdm09 PATIENTS: AN INDIVIDUAL PATIENT DATA META-ANALYSIS

Supplementary information

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† Baseline characteristics of each constituent dataset are presented in Supplementary Appendix 7.

‡ Centres not included in the current analysis as they include only outpatient data.

Supplementary Appendix 2: Minimum dataset requirement

Data variables	Description/definition
About the data	
1. Source of data	E.g. hospital or emergency department, community/ GP sentinel data, national surveillance data etc.
2. Patient identifier	A unique identifier for each patient e.g. a specific number that corresponds to each patient
Patient characteristics	
1. Age	Date of birth/ age at hospital admission
2. Sex	Male/ female
3. Any other risk factors	Such as obesity/ BMI, smoking status etc.
4. Seasonal influenza vaccination status	Yes/no
Clinical characteristics	
1. Underlying Co-morbidities a) Asthma b) COPD c) Pneumonia d) Other pulmonary diseases e) Other chronic conditions	List of underlying medical conditions for each individual patient
2. Pregnancy	Pregnancy/ fetal wellbeing assessments e.g. weeks of gestation including pregnancy outcome
3. Clinical examinations a) Influenza presenting symptoms on hospital admission b) Admission laboratory examinations performed c) Chest x-ray examination	<ul style="list-style-type: none"> - Date of symptoms onset - List of symptoms presenting at hospital admission - E.g. technique used for laboratory confirmation of influenza AH1N1 e.g. RT-PCR, viral culture, etc. - Date chest x-ray taken - Findings upon x-ray examination
Treatment characteristics	
1. In-hospital antiviral treatment (oseltamivir, zanamivir etc.)	- Date of prescription/ treatment including name of antiviral agent (i.e. oseltamivir/ zanamivir), route of administration(e.g. inhaled, oral , IV), dosage and dose frequency, treatment duration
2. In-hospital antibiotics treatment	- List of names of administered antibiotics including route(e.g. inhaled, oral , IV), dose and dose frequency, duration and dates prescribed
3. Other in-hospital additional treatment therapies e.g. corticosteroids, antipyretics etc.	- List of names of other administered treatments including route(e.g. inhaled, oral , IV), dose and dose frequency, duration and dates prescribed
Outcome (please provide data on at least one of the outcome measures)	
1. Hospitalisation	<ul style="list-style-type: none"> - Dates of admission and discharge - Primary admitting diagnosis for cases

Data variables	Description/definition
	admitted to hospital - Secondary diagnoses
2. Pneumonia	- Yes/ no, Unilateral or bilateral etc.
3. Admission to critical care facilities i.e. ICU and/ or HDU	- Specific dates of transfer and discharge to/ from the HDU or ICU - Primary cause of transfer to HDU/ ICU - Need for invasive mechanical ventilation (MV) including non-invasive mechanical ventilation(NIV) and ECMO - Other severity scores e.g. duration MV, NIV, ECMO
4. Mortality in hospital	- Date of death - Primary cause of death

Supplementary Appendix 3: Standardised dataset - data dictionary

Variable name in Stata	Description	Coding
About the data		
study_group_id	Study group identifier (lookup codes in MS Excel metadata file)	Auto-numbering (_n); string
Patid	Study specific patient ID as provided by study groups; this will only be retained in the individual datasets but dropped from the pooled dataset	string
auto_patid	Auto-numbered patient ID generated for each study group dataset; this will only be retained in the individual datasets but dropped from the pooled dataset	Auto-numbering (_n)
pride_patid	Unique patient identifier created by concatenation of study_group_id and auto-numbered patient id (auto_patid)	String
data_source	Whether hospital, community or ICU	1=hospital 2= ICU 3= community
Country	Country identifier	String
Patient characteristics		
age_years	Age (at admission) in years; continuous variable	Place all under 1s in one category (replace <1s as '0')
sex	gender	1=male 0=female
obese	Either clinically recorded obesity or derived from BMI (BMI>30)	1= yes 0= no
smoking	Current smoking status (ex and non-smokers will be considered one category)	1= yes 0= no
pregnant	Pregnancy (for sub-group analyses including pregnant women, only women of child-bearing age (13-54 years) will be considered)	1= yes 0= no (no separate code for 'not applicable'; men and women not of child-bearing age will be dropped from any analyses including pregnant women)
comorbidity	Whether any co-existing comorbidity was present (either as recorded or derived on the basis of a record of one of the	1= any comorbidity 0= no recorded comorbidity

Variable name in Stata	Description	Coding
	following comorbidities: asthma, COPD, other chronic lung disease, heart disease, cerebrovascular disease (not including uncomplicated hypertension), chronic liver disease, chronic renal disease, diabetes, neurological disease (including neurodevelopmental disorders), lymphoma, leukaemia, other malignancy, immunosuppression) Note: pregnancy will not be considered a 'comorbidity' and nor will obesity	
asthma	Asthma as recorded	1= yes 0= no
copd	COPD as recorded	1= yes 0= no
other_lung_ds	Chronic pulmonary diseases (other than asthma or COPD)	1= yes 0= no
heart_ds	Chronic heart disease as recorded (includes congenital heart disease, hypertension with cardiac complications, chronic heart failure, individuals requiring regular medication and/or follow-up for ischaemic heart disease)	1= yes 0= no
renal_ds	Chronic kidney disease (CKD) as recorded including CKD at stage 3, 4 or 5, chronic kidney failure, nephrotic syndrome, kidney transplantation.	1= yes 0= no
liver_ds	Chronic liver disease as recorded (including cirrhosis, biliary atresia, chronic hepatitis)	1= yes 0= no
cerebrovascular_ds	Cerebrovascular disease as recorded (including stroke, transient ischaemic attack but not including uncomplicated hypertension)	1= yes 0= no
neurological_ds	Neurological disease as recorded (including	1= yes 0= no

Variable name in Stata	Description	Coding
	neurodevelopmental disorders)	
diabetes	Diabetes as recorded (including Type 1 diabetes, type 2 diabetes requiring insulin or oral hypoglycaemic drugs, diet controlled diabetes.)	1= yes 0= no
immunosuppression	Immunosuppression due to disease or treatment. Includes patients undergoing chemotherapy leading to immunosuppression; asplenia or splenic dysfunction and HIV infection at all stages.	1=yes 0= no
swine_flu_vac	Swine H1N1 vaccination	1= yes 0= no
clinical characteristics		
onset_date	Date of onset of influenza like illness (ILI)	Recorded as date dd/mm/yy
admission_date	Date of first admission to hospital (whether to a general ward, HDU or ICU)	Recorded as date dd/mm/yy
time_to_admission	Time (in days) from onset of symptoms to hospital admission	Recorded as number of days
symptom_score	Severity of illness on presentation to hospital; non-weighted score derived by assigning a score of 1 for each of the following symptoms and then adding these together (myalgia; malaise; headache; sore throat; cough; nasal symptoms including runny nose, stuffy nose, sneezing; diarrhoea/vomiting) Note: fever and shortness of breath will be considered as separate variables to emphasise greater weighting of these symptoms	Recorded as score (maximum score of 7 possible)
fever	Fever on presentation (as recorded)	1= yes 0= no
shortness_of_breath	Shortness of breath at presentation (as recorded)	1= yes 0= no
severe_respiratory_distress	Severe respiratory distress at admission	1= yes 0= no
flu_diag	Method of diagnosis of swine flu whether clinical or laboratory diagnosis (this	1= clinical 2= laboratory diagnosis (not otherwise specified) or

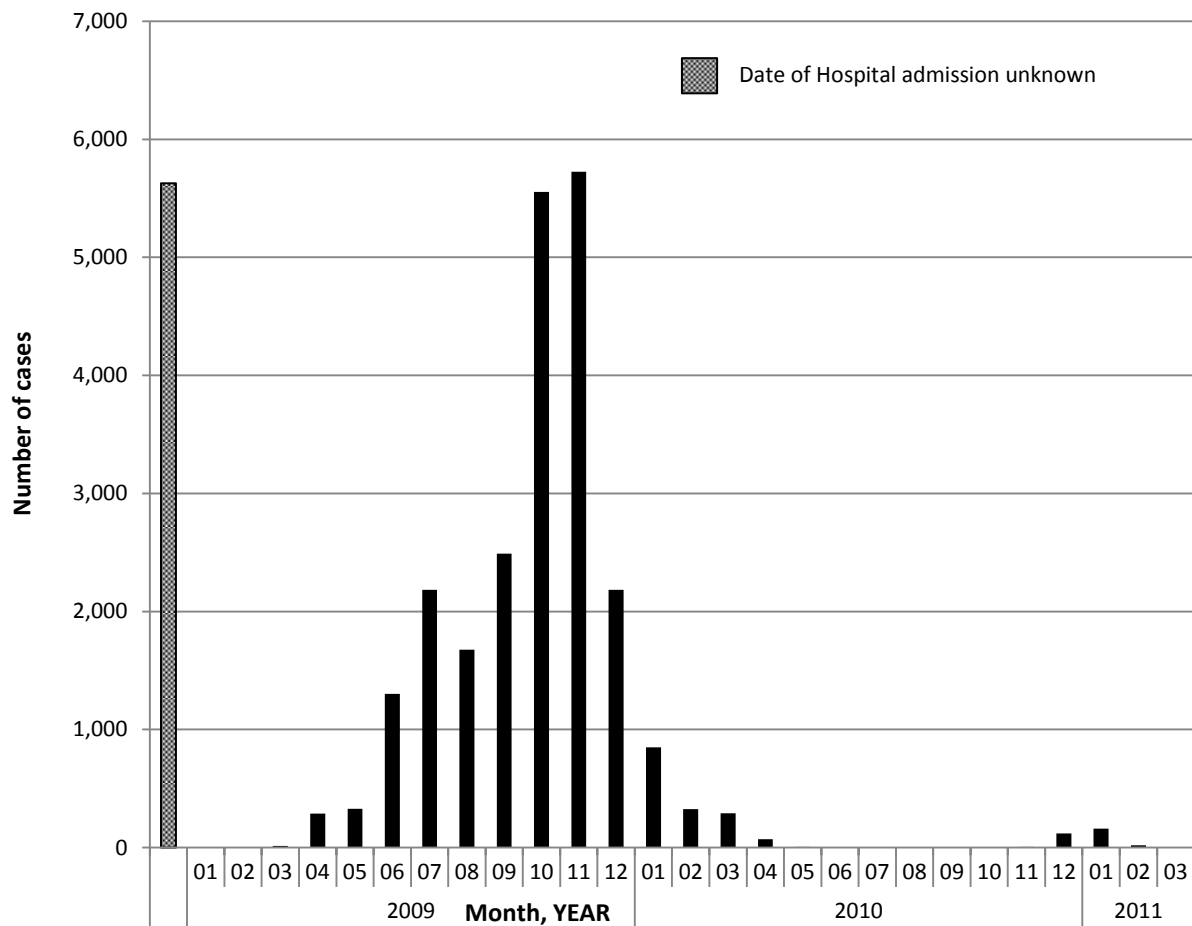
Variable name in Stata	Description	Coding
	includes RT-PCR, Direct Fluorescent Antibody test (DFA), Viral Culture, Rapid Antigen test)	confirmed using various laboratory tests
severe_disease	Severity was defined using standard severity measures such as AVPU, GCS, SOFA or CURB-65 scores where available. Alternatively, the following proxy indicators were used in order of preference: i) severe respiratory distress (tachypnoea, dyspnoea, evidence of alveolar flooding on radiograph, arterial blood gas analysis, cyanosis, excessive respiratory effort) ii) shortness of breath, iii) Symptom score (as defined earlier).	As provided
Treatment		
antiviral_start_date	Date of start of antiviral treatment	Recorded as dd/mm/yy
preadmit_antiviral	Preadmission antiviral (either oseltamivir, zanamivir or peramivir)	1= yes 0= no
oseltamivir_start_date	Date of start of oseltamivir treatment	Recorded as dd/mm/yy
preadmit_oseltamivir	Preadmission oseltamivir	1= yes 0= no
zanamivir_start_date	Date of start of zanamivir treatment	Recorded as dd/mm/yy
preadmit_zanamivir	Preadmission zanamivir	1= yes 0= no
antibiotic_start_date	Date of start of antibiotic treatment	Recorded as dd/mm/yy
hospital_oseltamivir	Oseltamivir given in hospital	1= yes 0= no
hospital_zanamivir	Zanamivir given in hospital	1= yes 0= no
hospital_peramivir	Peramivir given in hospital	1=yes 0=no
hospital_antibiotic	Antibiotics given in hospital	1= yes 0= no
antiviral_anytime	Antiviral administered at any time (whether in the community or in hospital)	1= yes 0= no
early_antiviral1	Antiviral administered ≤ 2 days of symptom onset (whether in	1= early antiviral 0= no antiviral

Variable name in Stata	Description	Coding
	the community or in hospital) versus no antiviral treatment	
early_antiviral2	Antiviral administered ≤ 2 days of symptom onset (whether in the community or in hospital) versus late antiviral treatment	1= early antiviral 0= late antiviral
lt_2days	Antiviral administered > 2 days of symptom onset (whether in the community or in hospital) versus no antiviral treatment	1= late antiviral (> 2 days) 0= no treatment
lt_5days	Antiviral administered ≥ 5 days of symptom onset (whether in the community or in hospital) versus no antiviral treatment	1= late antiviral (> 5 days) 0= no treatment
oseltamivir_anytime	Oseltamivir administered at any time (whether in the community or in hospital)	1= yes 0= no
early_oseltamivir1	Oseltamivir administered ≤ 2 days of symptom onset (whether in the community or in hospital) versus no antiviral treatment	1= early oseltamivir 0= no antiviral treatment
early_oseltamivir2	Oseltamivir administered ≤ 2 days of symptom onset (whether in the community or in hospital) versus late oseltamivir (administered > 2 days after symptom onset)	1= early oseltamivir 0= late oseltamivir
zanamivir_anytime	Zanamivir administered at any time (whether in the community or in hospital)	1= yes 0= no
early_zanamivir1	Zanamivir administered ≤ 2 days of symptom onset (whether in the community or in hospital) versus no antiviral treatment	1= early zanamivir 0= no antiviral treatment
early_zanamivir2	Zanamivir administered ≤ 2 days of symptom onset (whether in the community or in hospital) versus late zanamivir (administered > 2 days after symptom onset)	1= early zanamivir 0= late zanamivir
peramivir_anytime	Peramivir administered at any time (whether in the community or in hospital); note: peramivir was authorised for emergency use in patients with swine flu during the pandemic in some	1= yes 0= no

Variable name in Stata	Description	Coding
	countries	
early_peramivir1	Peramivir administered ≤ 2 days of symptom onset (whether in the community or in hospital) versus no antiviral treatment	1= early peramivir 0= no antiviral treatment
early_peramivir2	Peramivir administered ≤ 2 days of symptom onset (whether in the community or in hospital) versus late peramivir (administered > 2 days after symptom onset)	1= early peramivir 0= late peramivir
non_nai_anytime	Treatment with non-NAI antiviral drugs at any time (amantadine, rimantadine, ribavirin)	1= yes 0= no
hosp_non_nai	In-hospital treatment with non-NAI antiviral drugs (amantadine, rimantadine, ribavirin)	1= yes 0= no
hosp_steroid	New steroids administered in hospital (dexamethasone, hydrocortisone, prednisolone)	1= yes 0= no
Outcomes		
discharge_date	Date of discharge from hospital	Recorded as date dd/mm/yy
length_of_stay	Length of stay in hospital (whether general ward or ICU) in days	Number of days
critical_care	Admission to critical care facilities (ICU)	1= yes 0= no
icu_admit_date	Date of admission to ICU	Recorded as dd/mm/yy
icu_discharge_date	Date of ICU discharge	Recorded as dd/mm/yy
icu_lengthstay	Length of ICU stay	Recorded as a continuous variables (no. of days)
Pneumonia	Pneumonia as recorded (whether clinically diagnosed or radiologically diagnosed or discerned from free text chest x-ray report findings)	1= yes 0= no
pneum_diag	Method of diagnosis of pneumonia (clinical or radiological)	1= radiological diagnosis 0= clinical diagnosis
death	Death (as recorded)	1= yes 0= no
dod	Date of death	Recorded as dd/mm/yy
death_cause	Primary cause of death	Free text
death_cause_code	Cause of death categories	1= unrelated to flu 2= influenza related

Variable name in Stata	Description	Coding
		3= sepsis 4= ARDS/ respiratory failure 5= pneumonia 6= multiorgan failure 7= brain death (unspecified) 8= renal failure 9= liver failure 10= shock 11= CVS
P	Propensity scores for treatment-yes vs. no	Recorded as a continuous variable between 0 and 1
ps_quintile	Propensity scores categorised into quintiles for each individual study for NAI treatment- yes vs. no	Categorical variable with values from 1 to 5 (1=lowest quintile and 5=highest quintile)
p_1	Propensity scores for treatment- Early treatment (≤ 2 days) vs. no NAI treatment	Recorded as a continuous variable between 0 and 1
ps1_quintile	Propensity scores categorised into quintiles for each individual study for early treatment (≤ 2 days) vs. no treatment	Categorical variable with values from 1 to 5 (1=lowest quintile and 5=highest quintile)
p_2	Propensity scores for treatment- Early treatment (≤ 2 days) vs. Later treatment (> 2 days)	Recorded as a continuous variable between 0 and 1
ps2_quintile	Propensity scores categorised into quintiles for each individual study for early treatment (≤ 2 days) vs. later treatment (> 2 days)	Categorical variable with values from 1 to 5 (1=lowest quintile and 5=highest quintile)
p_lt2	Propensity scores for treatment- Later treatment (> 2 days) vs. no NAI treatment	Recorded as a continuous variable between 0 and 1
pslt2_quintile	Propensity scores categorised into quintiles for each individual study for late treatment (> 2 days) vs. no NAI treatment	Categorical variable with values from 1 to 5 (1=lowest quintile and 5=highest quintile)

Supplementary Appendix 4: Date of admission of 29,234 patients hospitalized with A(H1N1)pdm09 infection (by month)



** Due to scale, small numbers of hospitalisations are not visible; there were no hospitalisations in June 2010. Some patients were hospitalised due to other conditions but contracted nosocomial influenza (interval between hospital admission and symptom onset ≥ 3 days) (n=226; 1.03%).

Supplementary Appendix 5: Absolute risks of mortality for various exposure categories and subgroups

Population Subgroups	Number of deaths, n/N (%)		
	No NAI antiviral	NAI Antiviral at any time	Early Antiviral (initiated ≤ 2 days of symptom onset)
Lab and clinically confirmed (all ages)	959/10431 (9.2)	1825/18803 (9.7)	358/5995 (6.0)
Lab confirmed cases (all ages)	721/7319 (9.9)	1765 /17682 (10.0)	356/5882 (6.1)
Adults (16 years and above)	830/6813 (12.2)	1620/13,003 (12.5)	307/3796 (8.1)
Children (below 16 years)	122/3540 (3.5)	203/5678 (3.6)	50/2155 (2.3)
Pregnant women	45/845 (5.3)	132/1321 (10.0)	21/458 (4.6)
ICU patients (all ages)	387/881 (43.9)	1570/5967 (26.3)	318/1310 (24.3)
Adults (≥ 16 years)	326/610 (53.4)	1393/4493 (31.0)	276/1000 (27.6)
Children (<16 years)	58/267 (21.7)	176/1458 (12.1)	42/305 (13.8)

Supplementary Appendix 6: Characteristics of individual studies contributing to the pooled analysis and publications arising from them

Study No.	Country	Patients source	Total No. of cases supplied	No. of cases used†	Median age, years at hospital admission (Range)	Male (%)	No. of cases with any comorbidity § (%)	Time to hospital admission, days, median (IQR)	No. treated with NAI (%)	Time to NAI after symptoms, days, median (IQR)	Length of hospital stay, days, median (IQR)	No. of cases admitted to ICU (%)	No. of deceased patients (%)	Publications arising from dataset‡
1	Singapore	ED; Single Center	110	110	24 (10-56)	62 (56)	7 (6)	2 (1 - 3)	110 (100)	-	4 (3 - 5)	0(0)	0 (0)	1
2	Bangladesh	Hospital; Surveillance	147	141	23 (<1 -72)	85 (60)	43 (31)	3 (2 - 5)	26 (18)	4 (2 - 6)	5 (3 - 6)	-	5 (4)	2
3	Iran	Hospital; Single Center	46	46	32 (15 - 66)	26 (57)	19 (41)	5 (3 - 7)	46 (100)	5 (3 - 7)	-	20 (43)	7 (46)	3
4	Spain	ICU; Multi-center	1091	1078	47 (1 - 86)	663 (62)	571 (54)	4 (2 - 6)	1063 (99)	5 (3 - 7)	15 (9 - 28)	1078 (100)	265 (25)	4, 5
5	Mexico	Outpatients, Hospitalised; Multi-center	446	266	39 (<1 - 85)	161 (61)	63 (24)	0 (0 - 0)	266 (100)	5 (0 - 8)	15 (11 - 22)	76 (29)	28 (11)	6
6	UK	ICU; Single Center	8	6	5 (<1 - 8)	3 (75)	5 (83)	-	6 (100)	-	-	6 (100)	0(0)	7
7	Netherlands	ICU; Multi-center	14	14	13 (<1 - 16)	9 (64)	8 (57)	-	14 (100)	3 (2 - 11)	-	14 (100)	0(0)	8
8	Hong Kong, China	ICU; Single Center	17	17	54 (19 - 65)	11 (65)	6 (35)	4 (3 - 7)	16 (94)	*	41 (24 - 60)	17 (100)	1 (6)	-
9	Lithuania	Hospital; Multi-center	121	121	31 (18 - 83)	52 (43)	42 (35)	2 (1 - 3)	70 (58)	3 (2 - 6)	6 (4 - 8)	9 (8)	6 (5)	9
10	Switzerland	Outpatients, Hospitalised; Single Center	15	14	43 (30 - 82)	10 (71)	9 (64)	5 (2 - 6)	14 (100)	7 (3 - 9)	9 (8 - 13)	6 (43)	0(0)	10
11	Germany	Hospital; Single Center	315	154	1 (<1 - 18)	85 (55)	98 (64)	2 (1 - 4)	42 (27)	-	3 (1 - 5)	11 (7)	1 (1)	-
12	China	Outpatients, Hospitalised; Single Center	65	50	43 (14 - 75)	31 (62)	32 (64)	5 (4 - 7)	50 (100)	5 (4 - 7)	7 (5 - 11)	34 (68)	9 (18)	-
13	China	Hospital; Multi-center	155	155	39 (15 - 93)	90 (58)	62 (40)	5 (3 - 7)	132 (85)	*	10 (4 - 17)	74 (48)	27 (17)	11
14	Turkey	ICU; Single Center	20	20	36 (15 - 72)	10 (50)	10 (50)	5 (3 - 6)	20 (100)	5 (4 - 6)	5 (4 - 8)	20 (100)	9 (45)	12
15	Argentina	Outpatients, Hospitalised; Single Center	36	23	38 (16 - 82)	14 (61)	9 (39)	3 (2 - 4)	23 (100)	3 (2 - 4)	8 (4 - 19)	7 (30)	5 (22)	13
16	Spain	Outpatients, Hospitalised; Multi-center	57	48	46 (18 - 84)	28 (58)	26 (54)	5 (3 - 7)	48 (100)	6 (3 - 7)	5 (3 - 9)	11 (23)	2 (4)	14

Study No.	Country	Patients source	Total No. of cases supplied	No. of cases used†	Median age, years at hospital admission (Range)	Male (%)	No. of cases with any comorbidity § (%)	Time to hospital admission, days, median (IQR)	No. treated with NAI (%)	Time to NAI after symptoms, days, median (IQR)	Length of hospital stay, days, median days (IQR)	No. of cases admitted to ICU (%)	No. of deceased patients (%)	Publications arising from dataset‡
17	Iran	Outpatients, Hospitalised; Single Center	434	143	34 (14 - 86)	66 (46)	66 (48)	4 (2 - 6)	143 (100)	4 (2 - 6)	3 (2 - 5)	52 (36)	17 (12)	15
18	Canada	Outpatients, Hospitalised; Single Center	148	32	5 (<1 - 18)	20 (63)	20 (63)	3 (1 - 5)	27 (84)	-	4 (2 - 9)	7 (22)	0(0)	16
19	South Africa	Hospital; Single Center	46	41	27 (<1 - 70)	4 (10)	26 (63)	1 (0 - 4)	41 (100)	2 (0 - 4)	15 (7 - 26)	26 (62)	14 (34)	17
20	Argentina	Hospital; Multi-center	112	112	27 (<1 - 79)	32 (29)	39 (35)	2 (1 - 4)	109 (97)	3 (1 - 5)	5 (3 - 11)	43 (38)	23 (21)	-
21	Poland	Hospital; Single Center	24	24	7 (<1 - 17)	8 (33)	8 (33)	-	24 (100)	2 (1 - 4)	4 (3 - 5)	1 (4)	0(0)	18
22	Jordan	Hospital; Single Center	81	45	7 (1 - 19)	27 (60)	42 (100)	-	45 (100)	1 (1 - 1)	4 (3 - 6)	6 (14)	0(0)	19
23	Israel	Outpatients, Hospitalised; Single Center	73	37	6 (1 - 17)	19 (51)	23 (62)	-	25 (68)	-	3 (2 - 6)	2 (5)	0(0)	20
24	Australia	Hospital; Single Center	106	95	28 (<1 - 76)	35 (37)	62 (65)	-	84 (88)	-	2 (1 - 4)	13 (14)	2 (2)	21
25	Turkey	Hospital; Single Center	204	204	31 (16 - 86)	98 (48)	98 (48)	3 (2 - 4)	196 (96)	-	3 (2 - 5)	19 (9)	4 (2)	22
26	Morocco	Outpatients, Hospitalised; Single Center	640	16	29 (1 - 42)	6 (38)	12 (75)	-	16 (100)	-	4 (3 - 4)	2 (13)	0(0)	23
27	France	Hospital; Single Center	1770	1220	38 (<1 - 104)	638 (52)	616 (50)	2 (1 - 4)	1101 (90)	2 (1 - 5)	6 (3 - 14)	881 (72)	175 (14)	24, 25
28	Spain	Hospital; Multi-center	698	697	41 (16 - 97)	366 (53)	345 (50)	3 (2 - 5)	665 (94)	3 (2 - 6)	6 (3 - 9)	118 (17)	37 (5)	26, 27
29	Singapore	Outpatients, Hospitalised; Single Center	584	339	19 (<1 - 93)	175 (52)	161 (47)	2 (1 - 3)	284 (84)	3 (2 - 5)	2 (1 - 4)	22 (6)	3 (1)	28
30	Canada	Hospital; Multi-center	300	299	6 (<1 - 19)	176 (59)	196 (66)	2 (1 - 5)	270 (90)	3 (1 - 5)	5 (3 - 11)	131 (44)	7 (2)	29, 30
31	Australia	Hospital; Single Center	105	105	42 (15 - 79)	49 (47)	71 (68)	3 (2 - 5)	89 (85)	3 (2 - 5)	5 (3 - 8)	27 (26)	3 (3)	31
32	Hong Kong	Hospital; Single Center	69	61	45 (18 - 95)	24 (39)	43 (70)	2 (1 - 3)	55 (90)	3 (2 - 5)	4 (2 - 6)	3 (5)	1 (2)	32
33	Argentina	Hospital; Single Center	197	196	36 (<1 - 89)	94 (48)	116 (59)	3 (1 - 7)	196 (100)	5 (2 - 7)	6 (3 - 12)	73 (38)	49 (25)	-

Study No.	Country	Patients source	Total No. of cases supplied	No. of cases used†	Median age, years at hospital admission (Range)	Male (%)	No. of cases with any comorbidity § (%)	Time to hospital admission, days, median (IQR)	No. treated with NAI (%)	Time to NAI after symptoms, days, median (IQR)	Length of hospital stay, days, median (IQR)	No. of cases admitted to ICU (%)	No. of deceased patients (%)	Publications arising from dataset‡
34	Argentina	ICU, Hospitalised, Outpatients; Single Center	354	194	33 (<1 - 84)	97 (51)	36 (19)	4 (2 - 6)	116 (60)	-	5 (2 - 8)	29 (15)	27 (14)	-
35	Spain	Hospital; Single Center	91	91	42 (13-79)	37 (41)	63 (69)	2 (0 - 3)	83 (91)	2 (0 - 4)	7 (4 - 23)	30 (33)	7 (8)	33
36	Argentina	Outpatients, Hospitalised; Single Center	513	68	34 (<1 - 80)	36 (53)	16 (24)	-	49 (72)	-	-	16 (24)	5 (7)	34
37	UK	Hospital; Surveillance	272	222	27 (16 - 48)	0 (0)	70 (32)	2 (0 - 4)	186 (84)	2 (1 - 5)	3 (2 - 6)	44 (20)	2 (1)	35, 36
38	Italy	Hospital; Single Center	81	81	32 (1 - 81)	45 (56)	43 (53)	-	69 (85)	2 (1 - 3)	5 (3 - 7)	9 (11)	2 (2)	37
39	Turkey	Hospital; Single Center	15	15	2 (<1 - 8)	7 (47)	1 (7)	0 (0 - 1)	15 (100)	0 (0 - 1)	1 (1 - 3)	4 (27)	1 (7)	38
40	Israel	Hospital; Multi-center	506	504	43 (16 - 93)	240 (48)	305 (61)	3 (1 - 4)	450 (89)	3 (2 - 5)	6 (5 - 10)	34 (7)	18 (4)	39
41	Brazil	Hospital; Single Center	21	21	23 (15 - 32)	0 (0)	1 (5)	1 (0 - 2)	21 (100)	1 (0 - 2)	6 (3 -12)	6 (30)	0 (0)	40
42	France	Outpatients, Hospitalised; Single Center	549	84	24 (14 - 42)	0 (0)	26 (33)	2 (1 - 2)	73 (87)	2 (1 - 2)	4 (3 - 4)	1 (1)	0 (0)	41
43	Greece	Hospital; Single Center	34	34	34 (14 - 65)	23 (68)	25 (74)	-	34 (100)	*	6 (5 - 6)	0 (0)	0 (0)	42
44	Brazil	ICU; Multi-center	37	37	33 (18 - 80)	17 (46)	13 (35)	6 (4 - 10)	33 (89)	-	9 (6 - 23)	37 (100)	21 (57)	43
45	Brazil	Hospital; Multi-center	164	163	32 (<1 - 73)	81 (50)	-	5 (3 - 7)	93 (57)	5 (3 - 7)	6 (3 - 11)	92 (56)	49 (30)	44
46	Finland	ICU; Multi-center	132	132	49 (<1 - 88)	85 (64)	96 (73)	3 (1 - 6)	126 (95)	4 (2 - 6)	14 (7 - 26)	132 (100)	10 (8)	45
47	Egypt	Hospital; Surveillance	1943	1941	21 (<1 - 88)	1067 (55)	360 (19)	2 (1 - 3)	1941 (100)	2 (1 - 3)	5 (4 - 7)	375 (83)	457 (24)	-
48	USA	Hospital; Single Center	307	304	6 (<1 - 22)	185 (61)	216 (71)	3 (1 - 5)	268 (88)	3 (1 - 5)	3 (2 - 6)	79 (26)	8 (3)	46
49	Turkey	Hospital; Surveillance	114	114	6 (<1 - 16)	68 (60)	67 (59)	2 (2 - 4)	114 (100)	2 (2 - 4)	6 (5 - 10)	12 (11)	0 (0)	47
50	Canada	Hospital; Single Center	81	80	1 (<1 - 16)	42 (53)	38 (48)	4 (2 - 7)	53 (66)	5 (4 - 7)	4 (2 - 9)	12 (15)	1 (1)	48
51	Denmark	ICU; Surveillance	53	51	47 (3 - 80)	30 (59)	37 (73)	3 (1 - 6)	47 (92)	5 (2 - 8)	15 (3 - 26)	51 (100)	18 (35)	49

Study No.	Country	Patients source	Total No. of cases supplied	No. of cases used†	Median age, years at hospital admission (Range)	Male (%)	No. of cases with any comorbidity § (%)	Time to hospital admission, days, median (IQR)	No. treated with NAI (%)	Time to NAI after symptoms, days, median (IQR)	Length of hospital stay, days, median (IQR)	No. of cases admitted to ICU (%)	No. of deceased patients (%)	Publications arising from dataset‡
52	Saudi Arabia	Hospital; Single Center	127	127	27 (11 - 79)	100 (79)	67 (53)	3 (1 - 4)	127 (100)	3 (1 - 4)	6 (5 - 9)	15 (12)	4 (3)	50
53	Brazil	Outpatients, Hospitalised; Surveillance	16383	3139	26 (<1 - 94)	1283 (41)	1334 (48)	-	555 (18)	-	-	-	171 (5)	-
54	Slovenia	Outpatients, Hospitalised; Single Center	78	50	30 (<1 - 87)	36 (72)	20 (40)	2 (1 - 5)	33 (66)	4 (2 - 6)	4 (2 - 6)	4 (8)	3 (6)	-
55	Japan	Hospital; Single Center	104	103	7 (<1 - 72)	53(51)	27 (26)	2 (1 - 3)	103 (100)	2 (1 - 3)	7 (5 - 9)	5 (5)	1 (1)	51
56	India	Hospital; Single Center	61	61	22 (<1 - 60)	35 (57)	16 (26)	5 (3 - 7)	61 (100)	5 (3 - 7)	7 (6 - 11)	3 (5)	9 (15)	-
57	Mexico	Outpatients, Hospitalised; Surveillance	127289	6520	29 (<1 - 99)	2940 (45)	1581 (24)	2 (1 - 5)	1167 (18)	-	4 (2 - 7)	563 (9)	795 (12)	52
58	China	Hospital; Single Center	72	72	41 (18 - 66)	54 (75)	23 (32)	8 (6 - 10)	72 (100)	7 (4 - 9)	10 (6 - 19)	35 (49)	10 (14)	53
59	Croatia	Hospital; Single Center	169	169	29 (<1 - 83)	95 (56)	71 (42)	2 (1 - 4)	139 (82)	2 (1 - 5)	6 (4 - 10)	34 (20)	4 (2)	54
60	UK	Hospital; Multi-center	1520	1520	26 (<1 - 95)	720 (47)	745 (49)	2 (1 - 4)	1124 (74)	3 (1 - 5)	3 (2 - 7)	250 (16)	81 (5)	55
61	Poland	Hospital; Single Center	13	13	27 (6 - 75)	4 (31)	5 (38)	2 (0 - 2)	10 (77)	5 (2 - 9)	11 (7 - 16)	4 (31)	3 (23)	-
62	Slovenia	Hospital; Single Center	66	64	39 (16 - 87)	31 (48)	37 (58)	4 (2 - 6)	62 (97)	4 (2 - 6)	4 (3 - 6)	9 (14)	2 (3)	56
63	Serbia	Hospital; Single Center	98	98	27 (14 - 88)	68 (69)	18 (18)	3 (1 - 5)	69 (70)	3 (1 - 5)	7 (6 - 9)	6 (6)	2 (2)	57
64	UK	ICU; Single Center	24	24	48 (22 - 80)	13 (54)	20 (83)	5 (3 - 8)	24 (100)	5 (3 - 9)	22 (8 - 43)	24 (100)	7 (29)	58
65	Argentina	Hospital; Multi-center	251	250	0.8 (<1 - 19)	130 (52)	81 (34)	4 (2 - 7)	208 (83)	7 (4 - 10)	8 (5 - 13)	46 (18)	13 (5)	59
66	China	Hospital; Multi-center	367	367	21 (<1 - 84)	214 (58)	52 (14)	2 (1 - 4)	362 (99)	3 (1 - 5)	7 (5 - 10)	57 (16)	20 (5)	-
67	Austria	Outpatients, Hospitalised; Multi-center	540	341	21 (<1 - 91)	241 (71)	122 (36)	-	241 (71)	-	7 (5 - 9)	47 (14)	14 (4)	60
68	Iran	Hospital; Multi-center	484	484	31 (1 - 84)	201 (42)	45 (9)	3 (2 - 6)	464 (96)	3 (2 - 7)	2 (2 - 4)	44 (9)	6 (1)	61
69	Mongolia	Hospital; Surveillance	204	202	21 (1 - 76)	105 (52)	80 (40)	3 (1 - 5)	107 (53)	-	5 (4 - 7)	6 (3)	0 (0)	-

Study No.	Country	Patients source	Total No. of cases supplied	No. of cases used†	Median age, years at hospital admission (Range)	Male (%)	No. of cases with any comorbidity § (%)	Time to hospital admission, days, median (IQR)	No. treated with NAI (%)	Time to NAI after symptoms, days, median (IQR)	Length of hospital stay, days, median (IQR)	No. of cases admitted to ICU (%)	No. of deceased patients (%)	Publications arising from dataset‡
70	Germany	Hospital; Single Center	92	92	4 (<1 - 18)	47 (51)	13 (14)	2 (1 - 4)	28 (30)	2 (1 - 5)	3 (2 - 5)	6 (7)	0 (0)	62
71	Australia	Hospital; Multi-centre	601	458	4 (<1 - 15)	266 (58)	208 (45)	2 (1 - 4)	245 (53)	2 (1 - 6)	2 (1 - 5)	54 (12)	3 (1)	63
72	Saudi Arabia	Outpatients, Hospitalised; Surveillance	3228	2362	17 (<1 - 90)	1187 (50)	533 (23)	2 (1 - 3)	2296 (97)	2 (1 - 4)	-	209 (9)	25 (1)	-
73	Bangladesh	Hospital; Single Center	28	8	23 (3 - 50)	2 (25)	1 (13)	1 (0 - 4)	8 (100)	1 (0 - 4)	6 (4 - 6)	-	0 (0)	64
74	USA	ICU; Multi-center	630	630	47 (13 - 92)	285 (45)	367 (58)	4 (2 - 7)	586 (93)	3 (2 - 6)	11 (5 - 21)	630 (100)	146 (23)	65
75	USA	ICU; Multi-center	838	838	6 (<1 - 20)	485 (58)	558 (67)	2 (1 - 5)	758 (90)	1 (0 - 3)	7 (4 - 15)	838 (100)	74 (8)	66
76	UK	Hospital; Single Center	41	34	4 (<1 - 15)	17 (50)	16 (53)	3 (1 - 5)	27 (79)	4 (1 - 6)	6 (3 - 15)	14 (41)	9 (26)	67
77	Canada	Hospital; Single Center	1014	1014	29 (<1 - 92)	523 (52)	541 (53)	3 (1 - 5)	746 (73)	*	3 (2 - 7)	167 (16)	55 (5)	-
78	Norway	Hospital; Single Center	129	129	47 (15 - 93)	59 (46)	60 (47)	3 (1 - 7)	94 (73)	3 (1 - 6)	3 (1 - 6)	7 (5)	1 (1)	68
SUMMARY OF AVAILABLE DATA														
Studies with information on Early (≤2 days) versus Late (>2 days) NAI treatment														
TOTAL (63 studies)				13,254	27 (<1 - 97)	6918 (52)	5408 (41)	2 (1 - 5)	13254 (100)	3 (1 - 5)	6 (3 - 11)	4079 (34)	1300 (10)	
Studies with information on timing of NAI administration (as continuous variable)														
TOTAL (59 studies)				12,284	27 (<1 - 97)	6404 (52)	4896(40)	2 (1 - 5)	12284 (100)	3 (1 - 5)	6 (3 - 11)	3838 (35)	1224 (10)	
ALL STUDIES														
TOTAL (78 studies)				29,234	26 (<1 - 104)	14431(49)	11011 (38)	2 (1 - 5)	18803 (64)	3 (1 - 5)	5 (2 - 9)	6848 (28)	2784 (10)	

ED, Emergency department; IQR, interquartile range (25th and 95th percentile)

†Include hospitalised patients with complete information on NAI treatment and survival status; §comorbidity as a defined in supplementary appendix 3; ‡ publications emerging from these datasets whether referring specifically to mortality or not; * data supplied as binary variable (Early (≤2 days) versus Later (>2 days) NAI treatment)

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Supplementary Appendix 7: Comparison of hospitalised patients included in analysis compared with excluded patients

Variable	All hospitalised patients included in analysis (NAI treatment known) n/N (%)	All hospitalised patients excluded from analysis (NAI status unknown) n/N (%)	P value
Number of patients, n=32,818	29,234 (89.1)	3,584 (10.9)	
Number of male cases, n=32,808	14,431 (49.4)	1,704 (47.6)	0.082
Age: median (IQR) in years, n=32, 586 Mean (SD)	26 (11 - 44) 28.6 (20.7)	30 (10 – 50) 32.0 (23.9)	<0.001
Population groups (no. of persons)			
Adults (≥16 years)	19,816 (67.8)	2461 (68.7)	0.170
Children (<16 years)	9,218 (31.5)	1091 (30.4)	
Obese* n=25,992	2,607 (9)	154 (4)	<0.001
Smoking, n=21,991	2,406 (8.2)	67 (1.9)	<0.001
Pregnant women **, n=8,041	2,166 (22.8)	84 (7.8)	<0.001
WHO Regions, n=32,818			<0.001
African region	41(0.1)	1 (0.03)	
Region of the Americas	14,186 (48.5)	2,894 (80.8)	
Eastern Mediterranean Region	5,262 (18.0)	20 (0.6)	
European Region	7,272 (24.9)	583 (16.3)	
South-East Asia Region	210 (0.7)	6 (0.2)	
Western Pacific Region	2,263 (7.7)	80 (2.2)	
A(H1N1)pdm09 diagnosis, n=32,818			
Laboratory confirmed	25,001 (85.5)	1758 (49.1)	<0.001
Clinically diagnosed	4,233 (14.5)	1,826 (50.9)	
Comorbidities			
Any comorbidity, n=32,243	11,011(37.7)	952 (26.6)	<0.001
Asthma, n=23,965	2,820 (9.7)	135 (3.8)	
COPD, n=19,907	1,012 (3.5)	57 (1.6)	
Other chronic lung disease, n=18,544	2,479 (8.5)	177 (4.9)	
Heart disease, n=19, 087	1,624 (5.6)	30 (0.8)	
Renal disease, n=20,514	710 (2.4)	19 (0.5)	
Liver disease, n=12,346	295 (1.0)	0	
Cerebrovascular disease, n=10,327	304 (1.0)	6 (0.2)	
Neurological disease, n=13,718	1,013 (3.5)	5 (0.1)	
Diabetes , n=28,217	2,087 (7.1)	149 (4.2)	
Immunosuppression, n=28,775	1,803 (6.2)	116 (3.2)	
Pandemic H1N1 vaccination, n=4,443	347 (7.9)	3 (0.1)	<0.001
Time from symptom onset to hospital admission, days, n=27,060			
Median (IQR),	2 (1 - 5)	2 (1-5)	
Mean (SD)	3.25 (5.15)	3.61 (6.02)	0.0002

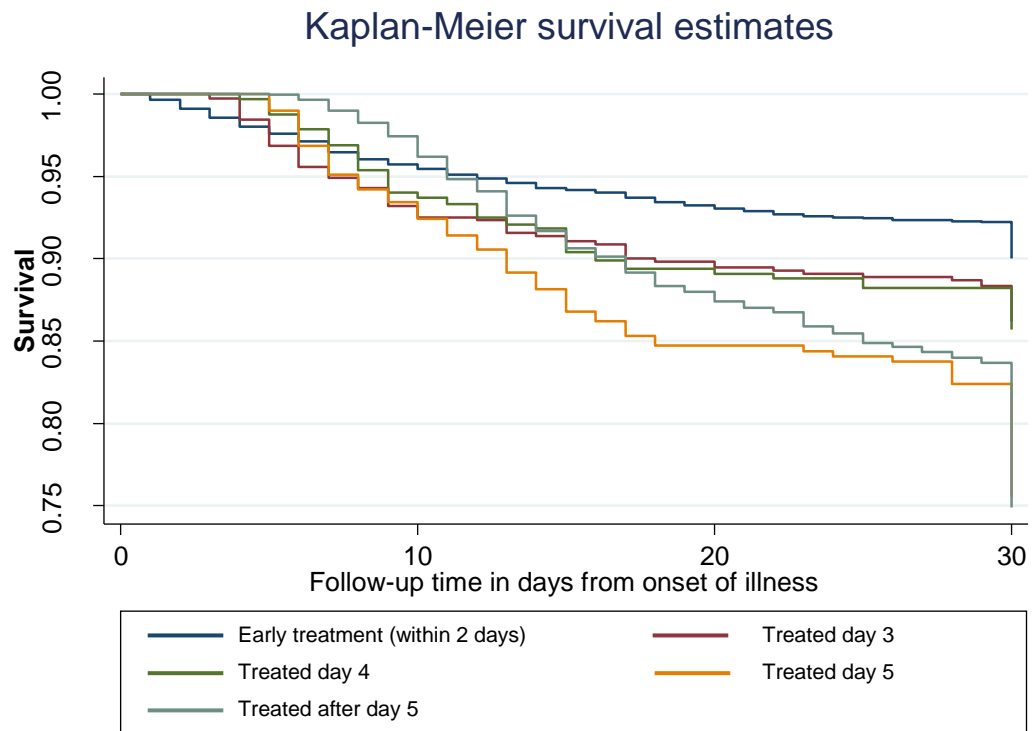
Variable	All hospitalised patients included in analysis (NAI treatment known) n/N (%)	All hospitalised patients excluded from analysis (NAI status unknown) n/N (%)	P value
Other in-hospital treatment			
Antibiotics, n=20,613	13,230 (45.3)	228 (6.4)	<0.001
Corticosteroids, n=10,006	2,745 (9.4)	6 (0.2)	<0.001
Hospital length of stay, days, median (IQR), n=24,468	5 (2 - 9)	3 (1-8)	<0.001
Outcomes			
Influenza-related pneumonia, n=17,190	7,225 (24.7)	75 (2.1)	<0.001
Admission to critical care, n=27,966	6,848 (23.4)	652 (18.2)	<0.001
Mortality, n=32,818	2,784 (9.5)	235 (6.6)	<0.001

Supplementary Appendix 8: Table summarising the laboratory confirmed or clinically diagnosed results for children <1 and <5 (all exposures)

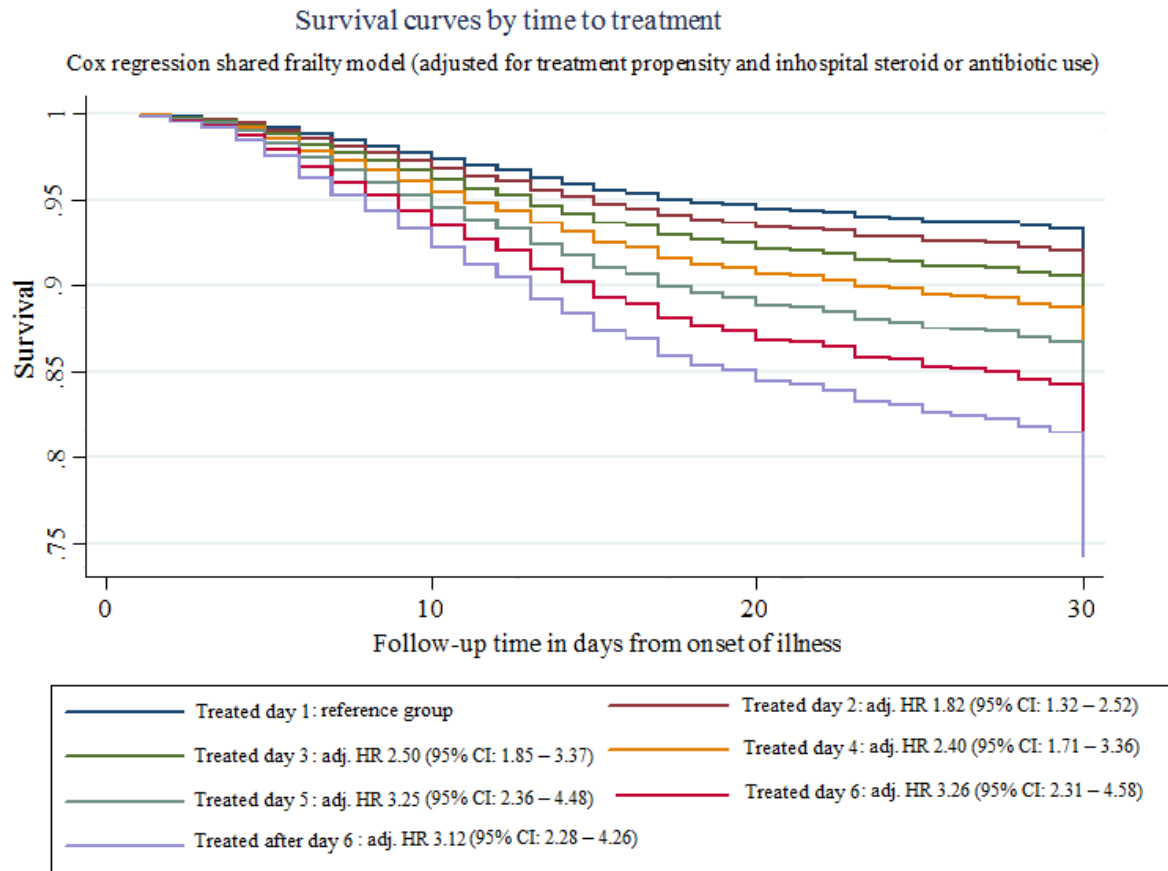
Treatment Exposure	Children <=1 year old		children <=5 years	
	Adjusted† OR (95% CI)	P value	Adjusted † OR (95% CI)	P value
NAI treatment vs. No NAI treatment	1.03 (0.56 to 1.89)	0.932	1.05 (0.66 to 1.68)	0.832
ET (≤ 2 days) vs. LT (> 2 days)	0.77 (0.28 to 2.11)	0.613	1.01 (0.54 to 1.90)	0.969
ET (≤ 2 days) vs. No NAI treatment	1.12 (0.35 to 3.55)	0.849	1.20 (0.58 to 2.49)	0.623
LT (> 2 days) vs. No NAI treatment	1.73 (0.78 to 3.83)	0.179	1.38 (0.62 to 3.11)	0.432

†adjusted for treatment propensity (by quintile), corticosteroid use and antibiotic use

Supplementary Appendix 9: Unadjusted Kaplan-Meier survival curves by time to treatment initiation (up to 5 days and after)



Supplementary Appendix 10: Adjusted survival curves by time to treatment initiation (up to 6 days and after)



Supplementary Appendix 11: Total population at risk, number of deaths and patients lost to follow-up over the study period for the survival analysis

Time Interval (days)	Total population at risk	Events (deaths)	Losses (loss to follow-up)
0-7	25421	545	6809
7-14	18067	697	5641
14-21	11729	345	1609
21-28	9775	144	609
28-30	9022	35	95
30	8892	428	8464

Supplementary Appendix 12: Characteristics of pooled dataset of 9,218 paediatric patients (<16 years) hospitalised with A(H1N1)pdm09 virus infection included in mortality analysis

Characteristic (denominator)	All hospitalised patients n (%)	Deceased n (%)	Survived n (%)
Number of patients ^a	9,218 (100.0)	325 (3.5)	8,893 (96.5)
Number of male cases (n=9,215) ^b	5,199 (56.4)	147 (45.2)	5,052 (56.8)
Age: median (IQR) in years (n=9,218) ^b	5 (1 - 10)	5 (1 - 10)	5 (1 - 10)
Pregnant ‡ (n=307) ^b	33 (5.7)	1 (3.6)	32 (5.8)
WHO Regions (n=9,218) ^b			
African region	9 (0.1)	0 (0)	9 (0.1)
Region of the Americas	4,940 (53.6)	225 (69.2)	4,715 (53.0)
Eastern Mediterranean Region	1,885 (20.5)	48 (14.8)	1,837 (20.7)
European Region	1,426 (15.5)	44 (13.5)	1,382 (15.5)
South-East Asia Region	46 (0.5)	1 (0.3)	45 (0.5)
Western Pacific Region	912 (9.9)	7 (2.2)	905 (10.2)
A(H1N1)pdm09 diagnosis (n=9,218) ^b			
Laboratory confirmed	7,946 (86.2)	298 (91.7)	7,648 (86.0)
Clinically diagnosed	1,272 (13.8)	27 (8.3)	1,245 (14.0)
Comorbidities§ ^b			
Any comorbidity (n=9,066)	2,946 (32.0)	165 (50.2)	2,781 (31.3)
Asthma (n=6,304)	988 (10.7)	27 (8.3)	961 (10.8)
Other chronic lung disease (n=6,268)	786 (8.5)	47 (14.5)	739 (8.3)
Heart disease (n= 5,676)	267 (2.9)	24(7.4)	243 (2.7)
Renal disease (n= 6,349)	112 (1.2)	11 (3.4)	101(1.1)
Liver disease (n= 4,025)	40 (0.4)	3 (0.9)	37 (0.4)
Cerebrovascular disease (n= 3,151)	21 (0.2)	2 (0.6)	19 (0.2)
Neurological disease (n= 4,855)	571 (6.2)	61 (18.2)	510 (5.7)
Diabetes (n= 7,468)	84 (0.9)	8 (2.5)	76 (0.9)
Immunosuppression (n= 8,256)	430 (4.7)	30 (9.2)	400 (4.5)
Pandemic H1N1 vaccination (n= 1,538) ^{b¶}	157 (3.5)	7 (4.1)	150 (3.1)
Time from symptom onset to hospital admission, days, median (IQR) (n= 7570) ^b	2 (1 - 4)	3 (1 - 5)	2 (1 - 4)
Antiviral agents used			
No NAI treatment	3,540 (38.4)	122 (37.54)	3,418 (38.4)
Treated with any NAI	5,678 (61.6)	203 (62.5)	5,475 (61.6)
Treated with oral oseltamivir (n=5,678) ^{bc}	5,316 (93.6)	188 (92.6)	5,128 (93.7)
Treated with intravenous/inhaled zanamivir (n=5,678) ^{bc}	78 (2)	2 (1.0)	76 (1.4)
Treated with intravenous peramivir (n=5,678) ^{bc}	22 (0.4)	11 (5.4)	11 (0.2)
Treated with NAI (regimen unknown) (n= 5,678) ^{bc}	309 (5.4)	13 (6.4)	296 (5.4)
Treated with both NAI and Non-NAI (n=1,312) ^{bc}	31 (2.4)	2 (2.9)	29 (2.3)
Treated with NAI combination therapy (n= 5,678) ^{bc}	47 (0.8)	11 (5.4)	36 (0.7)
Early NAI (≤2 days of symptom onset) (n= 3,899) ^{bc}	2,155 (23.4)	50 (15.4)	2,105 (23.7)
Later NAI (>2 days after symptom onset) (n= 3,899) ^{bc}	1,744 (18.9)	67 (20.6)	1,677 (18.9)
Time from symptom onset to antiviral treatment, days, median (IQR) (n= 3,629) ^b	2 (1 - 4)	3 (1 - 6)	2 (1 - 4)
Other in-hospital treatment^b			
Antibiotics (n=6,381)	4,165 (45.2)	119 (36.6)	4,046 (45.5)
Corticosteroids (n= 3,052)	825 (9.0)	69 (21.2)	756 (8.5)
Hospital length of stay, days, median (IQR) (n=6,753) ^b	4 (2 - 7)	7 (2 - 14)	4 (2 - 7)
Other patient outcomes^b			
Influenza-related pneumonia¥ (n=5,532)	1,851 (20.1)	108 (33.2)	1,743 (19.6)
Admission to critical care (n=7,632)	1,725 (18.7)	234 (72.0)	1,491 (16.8)

Table legend:

^a All percentages have been calculated using these denominators unless otherwise specified

^b Missing data present; 'n' indicates number of cases with data

^c Percentages calculated as a proportion of the sample receiving NAI therapy

[†] Reported as clinically obese or using WHO definition for obesity (BMI ≥ 30 in adults aged ≥ 20 years)

‡ Proportions were calculated as a percentage of pregnant patients among female patients of reproductive age (13 to 54), n=580; the broader age range was selected in preference to the WHO definition (15-44 years) after consultation with data contributors to reflect the actual fertility experience of the sample.

§ For definition of comorbidity, see Supplementary appendix 3

¶ Denominators for pandemic vaccine based on patients admitted after October 1st 2009 (when vaccine potentially available): total: 4,989; deceased: 170; survived: 4,819

‡ Clinically or radiologically diagnosed pneumonia