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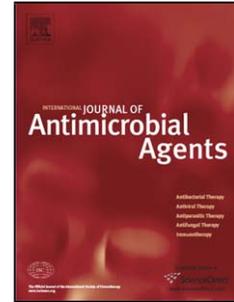
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## Treatment options for 2009 H1N1 influenza: evaluation of the published evidence

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## ABSTRACT

We evaluated the evidence regarding the effectiveness of various treatment strategies used for 2009 H1N1 influenza by reviewing available relevant studies. In total, 22 studies (15 cohort studies involving >10 patients, 5 cohort studies with ≤10 patients and 2 case reports) were included. A total of 3020 patients [1068 (35.4%) critically ill, 1722 (57.0%) hospitalised and 230 (7.6%) outpatients, including 909 (30.1%) children] were involved. Notably, 487 (16.1%) were obese [body mass index (BMI) >30], 362 (12.0%) had asthma or chronic obstructive pulmonary disease and 255 (8.4%) were pregnant. Antiviral treatment was administered to 1622 patients (53.7%), of whom 661 (40.8%) received oseltamivir monotherapy. Corticosteroids were administered in 323 (31.8%) of 1016 patients for whom relevant data were available. Similarly, 633 (85.0%) of 745 patients received antibiotics. Comparative data from the largest included study (involving 1088 patients) indicated that administration of antivirals within 2 days from symptom onset was significantly associated with reduced mortality ( $P < 0.001$ ). In summary, the scarcity of comparative available data hampered the establishment of any firm conclusions regarding the benefit that various treatment strategies may confer to patients with 2009 H1N1 influenza. Studies with a comparative design as well as randomised studies are needed to clarify further this issue of major importance.

## 1. Introduction

Influenza is an infection with significant morbidity and mortality that always attracts the interest of the health authorities, the media and the public [1,2]. During the previous century, humanity has engaged in encounters with three influenza pandemics that have been associated with considerable mortality. Notably, the Spanish pandemic of 1918 caused more deaths than the First World War. Consequently, national health authorities, as well as the World Health Organization (WHO), were always alert in order to identify a potential influenza pandemic early.

We are currently experiencing a new influenza pandemic, caused by the 2009 H1N1 influenza virus. From the beginning of the pandemic up to 1 November 2009, more than 199 countries had reported confirmed 2009 H1N1 cases, including over 6000 associated deaths [3]. Preliminary evidence from experience with this new pandemic has already appeared in the literature [4–7]. According to this evidence, 2009 H1N1 influenza appears to occur more frequently in young adults and children, whereas fatal cases refer mainly to older individuals [8]. Neuraminidase inhibitors (NAIs), in particular oseltamivir, have been used for the treatment of patients with 2009 H1N1 influenza. However, cases with oseltamivir-resistant pandemic strains have also been reported [9,10]. In addition, use of corticosteroids has been reported in some recent studies involving critically ill patients with 2009 H1N1 influenza.

Taking all the above factors into consideration, we sought to collect and evaluate the currently available published evidence in order to contribute to further understanding of treatment aspects of 2009 H1N1 influenza.

## **2. Data sources**

Studies to be included in this review were identified from searches performed in PubMed and Scopus databases, both last assessed in November 2009. The search term applied to both databases was '(swine flu OR H1N1 infection OR novel influenza) AND (treatment OR therapy)'. Bibliographies of relevant articles were also hand-searched.

## **3. Study selection criteria**

Two reviewers (EB and KP) independently performed the literature search, assessed the retrieved studies for eligibility for inclusion, and extracted the data. To be considered eligible for inclusion in the review, an article should have provided data regarding strategies used to treat patients of any age and from any clinical setting with 2009 H1N1 influenza infection worldwide. In addition, only articles for which a full-text version could be obtained were included in the review.

#### 4. Data extraction

Data extracted from each of the evaluated articles included: study design; characteristics of the evaluated patients; country to which each specific study referred; number of included patients with co-morbidity and/or any risk factors considered to be associated with severe complications from seasonal influenza; characteristics of the antiviral treatment administered (type, dosage, duration, time of initiation); other treatment administered (if any); and any complications from the 2009 H1N1 infection or any adverse event reported. In addition, information regarding the outcome of the 2009 H1N1 infection, in particular mortality, were also extracted. The abovementioned extracted data are presented in Table 1.

With regard to the patient populations enrolled, the studies included in this review were classified as follows: studies involving exclusively or a majority of patients with 2009 H1N1 influenza admitted to the Intensive Care Unit (ICU); studies involving exclusively or a majority of patients hospitalised due to 2009 H1N1 influenza; and studies involving exclusively or a majority of outpatients with 2009 H1N1 influenza. If a study involving mixed populations provided specific data for these subpopulations, the study was classified in more than one of the abovementioned categories.

## 5. Comparisons

In an attempt to evaluate the impact of antiviral treatment as well as the impact of early administration of antiviral treatment (within 2 days from symptom onset) on mortality, percentages of those who received antiviral treatment and who died versus those who did not receive antiviral treatment were compared for the subgroup of studies providing relevant data. All comparisons were performed using OpenEpi software [28].

## 6. Study characteristics

A total of 22 individual articles (15 cohort studies involving >10 patients [4–8,11–20], 5 cohort studies involving up to 10 patients [21–25] and 2 case reports [26,27]) were regarded as eligible for inclusion in the review. Nine of these studies referred to the USA [5,8,13,16,17,20,21,23,24], two to Mexico [7,12], two to Canada [11,26], three to European countries (UK [6], Spain [14] and Cyprus [19]), two to China [25,27] and the remaining to Argentina [15], Australia and New Zealand [4], Japan [18] and Singapore [22]. In addition, 7 of the 20 included cohort studies and case series were prospective [4,11,15,16,18,22,25], whereas the remaining 13 were retrospective [5–8,12–14,17,19–21,23,24]. Regarding the 15 cohort studies involving >10 patients, 5 involved mainly ICU patients [4,11–14], 6 involved mainly hospitalised patients [5–8,16,17] and 3 involved mainly outpatients [18–20]. The remaining 1 of these 15 cohort studies involved a mixed population of ICU and hospitalised patients

[15]. Specific data were provided for these two subpopulations, thus this study was classified into two categories (data are presented in Table 1).

## **7. Patient characteristics**

A total of 3020 patients with confirmed or probable 2009 H1N1 influenza infection were evaluated, including 909 (30.1%) children aged <18 years. From the total of 3020 reported patients, 1068 (35.4%) were ICU patients, 1722 (57.0%) were hospitalised patients in general wards and 230 (7.6%) were outpatients. In addition, 255 (8.4%) of the 3020 patients were pregnant, 487 (16.1%) were obese [body mass index (BMI) >30] and 136 (4.5%) were morbidly obese (BMI > 40). Furthermore, 362 (12.0%) of the 3020 patients had asthma or chronic obstructive pulmonary disease (COPD). Detailed data regarding the proportion of included patients with specific co-morbidities are presented in Table 1.

## **8. Antiviral treatment characteristics**

A total of 1622 (53.7%) of the 3020 reported patients received antiviral treatment. Specifically, 661 (40.8%) of these 1622 patients received only oseltamivir, 95 (5.9%) received only zanamivir (including 2 patients who switched to oseltamivir), 8 (0.5%) received only amantadine and 1 (0.06%) received only rimantadine. In addition, 25 (1.5%) of the 1622 patients received a combination of oseltamivir and amantadine, 18 (1.1%) received a combination

of oseltamivir and rimantadine and 1 (0.06%) received a combination of oseltamivir and zanamivir.

Data regarding the administered dosages of antiviral treatment were scarcely reported. Specifically, a dosage of 150 mg oseltamivir twice daily was administered in the ICU patients included in two studies [14,21], whereas in another study regular oseltamivir doses were administered in the included paediatric ICU patients [15]. An oseltamivir dosage of 75 mg twice daily was administered in the hospitalised patients involved in two studies [7,15] as well as in outpatients involved in another study [25]. Data regarding the duration of antiviral treatment were also scarcely reported. Specifically, oseltamivir dosage schedules beyond the standard 5-day course were administered in ICU patients reported from two studies [14,21], whereas a 5-day oseltamivir course was administered in paediatric outpatients according to another study [19].

Regarding the time of initiation of antiviral treatment, oseltamivir was administered within 2 days from symptom onset in 529 (35.3%) of 1498 patients for whom relevant data were available. Detailed data regarding the duration as well as the time of initiation of antiviral treatment are presented in Table 1.

## **9. Other treatment characteristics**

Corticosteroids were administered in 323 (31.8%) [232 (71.8%) were ICU patients and 91 (28.2%) were hospitalised patients] of the 1016 patients for whom relevant data were available. Of the 745 patients with available relevant data, 633 (85.0%) received antibiotics. Among 548 patients with available

relevant data, 205 (37.4%) received vasopressor drugs. Recombinant activated protein C was administered in two ICU patients. Specific data regarding the type of treatment other than antivirals administered to patients included in the evaluated studies appear in Table 1.

## 10. Complications

Viral pneumonia or acute respiratory distress syndrome (ARDS) occurred in 1055 (55.9%) of a total of 1886 patients for whom relevant data were available. In particular, the majority of these 1886 patients were included in three studies [4,8,16]. Percentages of patients with viral pneumonia or ARDS ranged between 34.6% and 65.6% among the three studies. In another study providing relevant data for 32 ICU patients, the reported percentage of patients with viral pneumonitis was 90.6% [14]. Bacterial pneumonia complicated H1N1 infection in 290 (12.8%) of 2263 evaluated patients. Detailed data regarding the complications observed in the evaluated patients are presented in Table 1.

## 11. Mortality

Of the 3020 reported patients, 386 (12.8%) died. Specifically, 216 deaths (20.2%) occurred in a total of 1068 ICU patients, 156 deaths (9.1%) occurred in a total of 1722 hospitalised patients and 14 deaths (6.1%) occurred in a total of 230 outpatients. In addition, 60 children (6.7%) died from a total of 901 with available mortality data. Specifically, in the largest of the included studies, 110 (14.8%) of the 744 included adults died, whereas 8 (2.3%) of the 344 included

children died [8]. The scarcity of data regarding the proportions of patients with co-morbidities among those who died precluded any further evaluations.

## **12. Antiviral treatment and mortality**

Three studies provided specific data in order to be included in the analysis regarding the impact of antiviral treatment on the outcome of 2009 H1N1 infection (death versus survival) [8,15,16]. One of these three studies was the largest study included in the review, involving a total of 1088 patients [8]. The differences observed for these three studies were non-significant, with the exception of the comparison regarding the subgroup of patients older than 18 years who were included in the study of Louie et al. [8]. Detailed data are presented in Table 2. In addition, another study, which did not provide adequate data in order to be included in the above comparisons, reported that survivors were most likely to have received treatment with NAIs compared with those who died (odds ratio = 7.4, 95% confidence interval 1.8–31.0;  $P = 0.006$ ) (Table 1) [12].

## **13. Early administration of antiviral treatment and mortality**

Adequate data for the comparison regarding the impact of early administration of antiviral treatment (within 2 days of symptom onset) were provided from one study [8]. Statistically significant differences were observed in the comparisons regarding the subgroup of patients who were older than 18 years as well as in patients of all ages combined. Specific data are presented in Table 2. In

addition, in the multivariate analysis of another study [16] the administration of antiviral treatment within 2 days of symptom onset was significantly associated with a favourable outcome of the infection.

## 14. Discussion

According to the findings of this review, approximately one-half of patients with 2009 H1N1 influenza infection included in the reviewed studies received antiviral treatment (mainly oseltamivir). Notably, the majority of these patients were hospitalised and ICU patients. However, the scarcity of comparative data provided from the studies included in the review as well as the lack of available relevant studies with a randomised design precluded us from assessing the effectiveness of the various treatment regimens, as well as their combinations, in reducing morbidity and mortality from 2009 H1N1 influenza. However, the impact of early administration of antiviral treatment (within 2 days of the onset of influenza symptom) in reducing mortality from 2009 H1N1 infection appears to be much more clear according to the findings of this review.

Novel H1N1 influenza began in Mexico in April 2009 and quickly spread worldwide, confirming its pandemic nature. Up to 8 November 2009, more than 206 countries and overseas territories or communities have reported laboratory-confirmed cases of 2009 H1N1 influenza, whereas the reported deaths associated with this infection, up to this writing, have risen up to 6250 [29]. On the other hand, since testing and reporting of 2009 H1N1 influenza cases is not obligatory, these data may be underestimations of the real respective numbers.

Various probabilistic models may account for a one hundred-fold higher incidence of the disease for every laboratory-confirmed case [30]. Preliminary data also suggest that this new infection occurs more frequently in children and young adults [31]. In this review, children younger than 18 years represented a considerable percentage (30%) of the included patients.

NAIs, especially oseltamivir that has the advantage of being available in an oral formulation, have been used for the treatment of seasonal influenza. NAIs have been proven effective in reducing seasonal influenza symptoms, yet their effectiveness in reducing influenza complications and mortality still remains unclear [32,33]. Based on this experience from seasonal influenza, NAIs have been used to treat patients with 2009 H1N1 influenza. Specifically, in this review more than one-half of the evaluated patients (53.7%) received antiviral treatment. Notably, the majority of these patients received oseltamivir monotherapy, whereas lower percentages received monotherapy with other antivirals or combinations of antivirals.

The dosage schedules of oseltamivir treatment varied considerably among the included studies. Specifically, maximum dosages of 150 mg twice daily and for a duration longer than the conventional 5-day regimen were administered to a considerable number of ICU patients involved in the evaluated studies.

Corticosteroids were also administered in a considerable proportion (31.8%) of the evaluated patients for whom relevant data were available. Most of these patients were ICU patients with co-morbidity. Owing to the lack of comparative

data provided from the non-randomised studies included in this review, evaluation of the potential benefit that corticosteroids might confer on the outcome of the infection was hampered. Of note, a large number of evaluated patients for whom relevant data were available received antibiotics. On the other hand, bacterial pneumonia complicated 2009 H1N1 influenza infection in 12.8% of the 2263 evaluated patients. This leads to the explanation that a significant number of patients received antibiotics on an empirical basis before a definitive diagnosis of 2009 H1N1 influenza was established. In contrast, high percentages (up to 90.6%) of patients were reported to have viral pneumonitis caused from the 2009 H1N1 influenza virus or ARDS in the studies evaluated in this review.

According to our findings, the mortality rate of 2009 H1N1 influenza is 12.8%. Most of the patients who died were ICU and hospitalised patients. Official data from the WHO suggest that as of 8 November 2009 at least 6260 deaths (1.2%) have occurred in a total of over 503 536 confirmed influenza cases [29]. An explanation for the discrepancy between the mortality rate of 2009 H1N1 infection observed in this review and the one reported from the WHO is the fact that a considerable proportion of the 2009 H1N1 influenza cases presented in the studies included in this review had co-morbidity. Specifically, 16.1% of the evaluated patients were obese and 12.0% had asthma or COPD. Moreover, 8.4% of the evaluated patients were pregnant. Pregnancy has already been associated with higher morbidity from seasonal influenza [34]. Current reports also suggest that pregnant women have an increased risk for complications

from 2009 H1N1 influenza [17]. In addition, selection bias may be a reason for the relatively high mortality and morbidity observed in this review, since 92% of the reported patients were hospitalised and ICU patients. However, if hospitalisation is warranted for 2009 H1N1 influenza, physicians have to be alert to treat the disease and its complications. In view of this finding despite the lack of definitive data for 2009 H1N1 influenza, treatment with antivirals for those hospitalised is probably warranted. To await the results of randomised controlled trials (RCTs) as the pandemic goes on may not be practical. Even ethical issues may arise, i.e. who should get the medication. Publication bias may also have led to a relatively high reported mortality in this review.

Our attempt to evaluate the effectiveness of antiviral treatment in reducing mortality from 2009 H1N1 influenza was hampered by the lack of studies with a randomised design as well as by the scarcity of comparative data. Of note, no RCT focusing on the treatment of patients with 2009 pandemic influenza was available up to this writing. On the other hand, despite the fact that randomisation procedures could eventually manage to eliminate any known or unknown confounding factors regarding the effectiveness of different treatment strategies used for 2009 pandemic influenza, one should bear in mind that during the critical times of a pandemic such as the influenza pandemic that we are currently witnessing, there might be insufficient time to conduct RCTs. Moreover, ethical issues might also be raised in regard to the conduction of such trials. In this regard, collection and evaluation of relevant observational data from different clinical settings may aid considerably in the understanding

and clarification of the field of 2009 pandemic influenza treatment. However, the favourable impact that early administration of antiviral treatment (within 2 days of symptom onset) has on mortality became more obvious from the comparisons performed in this review. The need for early administration of antiviral treatment was also borne out by individual studies included in the review [14].

This review has specific limitations that should be taken into consideration in the interpretation of its findings. First, considerable heterogeneity was observed among the patient populations presented in the included studies. Specifically, patients with differences in the severity of the 2009 H1N1 influenza infection, such as ICU patients, hospitalised patients and outpatients, were evaluated. Moreover, mixed populations, including otherwise healthy patients and patients with co-morbidity or risk factors considered to predispose to serious influenza infection such as pregnancy or obesity, were involved in the included studies. In this regard, the generalisability of the findings to influenza treatment in general practice may be limited. In addition, all of the studies included in this review were observational studies describing the strategies used to treat 2009 H1N1 infection of involved patients, whereas no relevant RCTs were identified through the literature searches. In this regard, many factors could have possibly confounded the findings of the individual studies included. Moreover, a considerable number of studies included in the review were retrospective studies. Consequently, the bias of retrospective data collection should also be considered in the interpretation of the findings of this review. The

abovementioned factors precluded the establishment of firm conclusions regarding the effectiveness of various treatment strategies used against 2009 H1N1 influenza.

In conclusion, our findings suggest that treatment with NAIs, and specifically administration of NAIs within 2 days of symptom onset, may be associated with a favourable outcome of 2009 H1N1 influenza infection. However, no firm conclusions could be established based only on observational studies. In this regard, comparative studies or randomised studies are needed to clarify further the benefit that various treatment strategies might confer to patients with 2009 H1N1 infection and particularly to specific subpopulations such as critically ill patients as well as patients with risk factors predisposing for influenza complications such as pregnancy. Nevertheless, the severity of the disease in patients in need of hospitalisation probably mandates the use of available specific antivirals.

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**Competing interests**

None declared.

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**Table 1**

Main characteristics of the studies included in the review

Reference	Study design	Characteristics of patients evaluated	Country	Patients with co-morbidity/risk factors	Antiviral treatment: Type Dosage Duration	Time of initiation of antiviral treatment	Other treatment	Complications	Outcomes other than mortality	Mortality
Cohort studies involving >10 patients										
Studies involving (mainly) ICU patients										
[4]	Prospective	722 patients with confirmed infection (median age 40 years)	Australia and New Zealand	Pregnant, 66/722 (9.1%); obese adults (BMI > 35), 172/601 (28.6%); diabetes, 112/700 (16.0%); asthma/COPD, 231/707 (32.7%); chronic heart failure, 74/703 (10.5%); co-existing conditions, 192/687 (27.9%)	NR	NR	Steroids, 91/494 (18.4%); renal replacement, 27/506 (5.3%); vasopressor drugs, 176/498 (35.3%)	Viral pneumonitis/ARDS, 336/689 (48.8%); secondary bacterial pneumonia, 140/689 (20.3%); exacerbation of airflow limitation, 95/689 (13.8%); mechanical ventilation, 456/706 (64.6%)	Discharged, 505/722 (69.9%)	In-hospital mortality, 103/722 (14.3%) <sup>a</sup>

[11]	Prospective	168 patients (162 confirmed, 6 probable) [children, 50/168 (30%)]	Canada	Any co-morbidity, 165/168 (98%); major co-morbidity, 51/168 (30.4%); chronic lung disease, 69/168 (41.1%); obesity, 56/168 (33.3%); morbid obesity (BMI > 40), 28/168 (16.7%); hypertension, 41/168 (24.4%); pregnant, 13/168 (7.7%)	NAIs, 152/168 (90.5%) NR Median 5 days	Nearly all patients received early treatment with NAIs	Antibiotics, 166/168 (99%); corticosteroids: 85/168 (50.6%)	Secondary bacterial pneumonia, 41/168 (24.4%)	NA	Overall, 29/168 (17.3%); 14-day, 18/168 (10.7%); 28-day, 24/168 (14.3%); children, 4/50 (8.0%). APACHE II and Day 1 SOFA scores were associated with overall mortality ( $P < 0.001$ and $P = 0.002$ , respectively)
[12]	Retrospective	58 patients (median age 44 years, including 2 children) [confirmed, 29 (50%); probable, 14 (24%); suspected, 15 (26%)]	Mexico	Any co-morbidity, 49/58 (84.5%); obesity, 21/58 (36.2%); morbid obesity (BMI > 40), 8/58 (13.8%); ever-smoked, 20/58 (34.5%); hypertension, 15/58 (25.9%)	NAIs, 45/58 (78%) [oseltamivir, 44/58 (76%); zanamivir, 6/58 (10%); amantadine, 8/58 (14%); rimantadine, 1/58 (2%)] NR NR	NR	Antibiotics, 52/55 (95%); corticosteroids, 40/55 (72.7%); recombinant activated protein C, 2/55 (3.6%)	Secondary bacterial pneumonia, 4/58 (6.9%)	Mechanical ventilation, 54/58 (93.1%)	24/58 (41.4%). Survivors were more likely to have received treatment with NAIs (OR = 7.4, 95% CI 1.8–31.0; $P = 0.006$ ) <sup>b</sup>

[13]	Retrospective	36 children <18 years [<5 years, 7/36 (19%)] who died from 2009 H1N1 influenza; outpatients, 7/36 (19%); unknown, 3/36 (8%)	USA	High-risk medical conditions, 24/36 (67%); neurodevelopmental conditions, 22/24 (92%)	Oseltamivir, 16/36 (44%); oseltamivir + amantadine, 1/36 (3%); oseltamivir + rimantadine, 1/36 (3%); none, 12/36 (33%); NR, 5/36 (13.9%); unknown antiviral, 1/36 (3%) NR NR	≤2 days from symptom onset, 4/19 (21%); >2 days after symptom onset, 12/19 (63%); unknown, 3/19 (16%)	NR	Documented bacterial co-infections, 10/23 (43%) <sup>c</sup>	NA	36/36 (100%)
[14]	Prospective	32 patients (median age 36 years)	Tarragona, Spain	Pre-existing medical complications, 16/32 (50%); obese, 10/32 (31%); pregnant, 2/32 (6.3%); asthma, 5/32 (16%); exacerbated COPD, 4/32 (12.5%)	Oseltamivir, 32/32 (100%) Higher dose (up to 150 mg orally twice daily), 10/32 (31.3%) 8.0 ± 3.3 days (IQR 5–10 days)	Median 4 days after symptom onset; 21/32 (65.6%) received empirical antiviral treatment	Initial empirical antibiotic therapy, 32/32 (100%) <sup>d</sup> ; i.v. steroids at ICU admission, 11/32 (34.4%); mechanical ventilation, 24/32 (75%); vasopressor drugs, 20/32 (62.5%)	Viral pneumonitis, 29/32 (91%); bacterial pneumonia, 1/32 (3%); COPD exacerbation, 2/32 (6%)	Cure, 24/32 (75%); multiorgan dysfunction, 24/32 (75%); invasive candidiasis, 1/32 (3%); secondary superinfection with <i>Pseudomonas aeruginosa</i> , 3/32 (9%); renal replacement, 7/32 (22%)	8/32 (25%)

[15]	Prospective	Adult ICU, 14 patients	Buenos Aires, Argentina	NR	Oseltamivir, 14/14 (100%) NR-adjusted in case of renal insufficiency NR	At admission	NR	Severe pneumonia, 14/14 (100%)	Favourable outcome, 7/14 (50%)	7/14 (50%)
		Paediatric ICU, 27 patients (mean age 47.5 months)		Prematurity, 5/27 (18.5%); congenital cardiopathy, 4/27 (15%); asthma, 3/27 (11%); genetic syndromes, 3/27 (11%); neurological diseases, 2/27 (7.4%); immunosuppression, 2/27 (7.4%); other, 2/27 (7.4%)	Oseltamivir, 23/27 (85%) Regular doses NR			RSV co-infection, 7/27 (26%); <i>Mycoplasma</i> co-infection, 4/27 (15%); pneumonia from <i>Staphylococcus aureus</i> , 1/27 (4%)	Favourable outcome, 21/27 (78%)	6/27 (22%) (including 2 children who did not receive oseltamivir)
Studies involving (mainly) hospitalised patients										
[8]	Retrospective	1088 patients hospitalised or who died (median age 27 years) [children <18 years, 344/1088 (32%)] <sup>e</sup>	California, USA	Underlying conditions previously associated with severe influenza: total, 741/1088 (68%); adults, 536/744 (72%); children, 206/344 (60%) Obese (BMI ≥ 30): adults, 156/268 (58%); morbidly obese (BMI ≥ 40), 67/156 (43%); obese adults with underlying conditions, 103/156 (66%) Pregnant: 115/1088 (11%)	Antivirals, 701/884 (79%) [496/701 (71%) with risk factors]	≤2 days of symptom onset, 357/700 (51%)	NR	Infiltrates on chest radiograph, 547/833 (66%); secondary bacterial pneumonia, 46/1088 (4%)	ICU admission, 340/1088 (31%); mechanical ventilation, 227/915 (25%)	Overall, 118/1088 (11%); children, 8/344 (2.3%)

[16]	Prospective	272 (median age 21 years) [children <18 years, 122/272 (45%), ≥65 years, 14/272 (5.1%)]	USA	Pregnant, 18/272 (7%); ≥1 underlying medical condition, 198/272 (73%); obese, 47/161 (29%) <sup>†</sup> ; morbidly obese, 26/100 (26%) <sup>‡</sup>	200/268 (75%) [oseltamivir, 188/200 (94%); zanamivir, 19/200 (10%); oseltamivir + amantadine, 13/200 (7%); oseltamivir + rimantadine, 14/200 (7%)] NR NR	Median time from symptom onset, 3 days (range 0–29 days); ≤2 day from symptom onset, 75/195 (38%)	Antibiotics, 206/260 (79%) <sup>§</sup> ; steroids, 86/239 (36%); invasive mechanical ventilation, 42/260 (16%)	Pneumonia, 100/249 (40%); ARDS, 25/245 (10%)	ICU, 67/272 (25%); discharged, 253/272 (93%)	Overall, 19/272 (7%); adults, 14/150 (9%); children, 5/122 (4%). Multivariate analysis: antivirals ≤2 days from symptom onset significantly associated with positive outcome
[6]	Retrospective	78 children (median age 5.7 years)	Birmingham, UK	31/77 (40%) <sup>h</sup>	Oseltamivir, 26/65 (40%) NR NR	NR	Antibiotics, 22/61 (36%)	Bacterial infections (possible or probable), 10/63 (16%)	Intensive care, 6/78 (7.7%)	0/78 (0%)
[5]	Retrospective	22 patients [<5 years, 4/22 (18%)]	USA	Chronic medical conditions, 9/22 (41%); pregnant, 1/22 (5%)	Oseltamivir, 14/19 (74%) NR NR	After admission to hospital, 14/19 (74%)	NR	Pneumonia, 11/22 (50%); ICU admission, 8/22 (36%); mechanical ventilation, 4/22 (18%)	Cure, 18/22 (82%); remained in critical condition, 2/22 (9%)	Overall, 2/22 (9.1%); children, 1/4 (25%)
[15]	Prospective	Adult general wards, 110 patients (mean age 45 years); 21/110 (19%) confirmed	Buenos Aires, Argentina	Asthma, 18/110 (16%); COPD, 10/110 (9%); obesity, 8/110 (7%); pregnant, 6/110 (5.5%); HIV, 5/110 (4.5%); diabetes, 5/110 (4.5%); cardiopathy, 5/110 (4.5%)	Oseltamivir, 110/110 (100%) 75 mg twice daily NR	At admission	Clarithromycin, 110/110 (100%) Ampicillin/sulbactam, 110/110 (100%)	Severe hypoxaemia, 43.5%	NR	Total, 6.8%; confirmed, 9.1%

		Paediatric general wards, 49 confirmed (median age 10 months)		High-risk, 34/49 (69%) [previous respiratory diseases, 16/49 (32.7%); prematurity, 8/49 (16.3%); haematological malignancies, 3/49 (6.1%); Down's syndrome, 2/49 (4.1%); congenital cardiopathy, 2/49 (4.1%); neurological diseases, 2/49 (4.1%); obesity, 1/49 (2.0%)]	Oseltamivir, NR 2 mg/kg NR		NR	Bacterial co- infections, 0/49 (0%)	ICU, 6/49 (12%)	The 6 children admitted to the ICU died
[17]	Retrospective	34 pregnant women	USA	Asthma, 7/34 (21%); insulin-treated diabetes in pregnancy, 1/34 (3%); hypertension + hyperthyroidism, 1/34 (2.9%)	Oseltamivir, 17/34 (50%); oseltamivir + amantadine, 1/34 (2.9%); oseltamivir + zanamivir, 1/34 (2.9%)	≤2 days from symptom onset, 8/17 (47%)	Acetaminophen, 16/34 (47%)	Pneumonia, 6/34 (17.6%); dehydration, 2/34 (5.9%)	ICU, 3/34 (9%); emergency Caesarean delivery, 2/34 (6%); live births during hospitalisation, 2/34 (6%); 9- week spontaneous abortion, 1/34 (2.9%)	1/34 (2.9%)

[7]	Retrospective	18 patients (median age 38 years) with pneumonia and ILI	Mexico	Pre-existing medical conditions, 8/18 (44%)	Oseltamivir, 14/18 (78%) 75 mg twice daily Minimum 5 days	At admission (mean 8 days after symptom onset), 11/18 (61%); between 2 days and 10 days after admission, 3/18 (17%)	Corticosteroids, 5/18 (28%), ceftriaxone, 17/18 (94%); clarithromycin, 10/18 (56%) <sup>†</sup> ; epinephrine, 9/18 (50%)	Pneumonia (infiltrates), 18/18 (100%); respiratory distress requiring intubation, 10/18 (55.6%); MSF, 7/18 (39%); VAP, 4/18 (22%); renal failure, 6/18 (33%); myocardial ischaemia, 1/18 (5.6%)	Cure, 11/18 (61%)	7/18 (39%)
		22 healthcare workers caring for patients [3/22 (14%) laboratory- confirmed]		NR	22/22 (100%) NR 5 days	NR	NR	NR	Cure, 22/22 (100%)	0/22 (0%)
Studies involving (mainly) outpatients										
[18]	Prospective	171 patients [children, 148/171 (86.5%)]	Osaka, Japan	Asthma, 2/171 (1%)	Oseltamivir, 95/171 (56%); zanamivir, 68/171 (40%); zanamivir switched to oseltamivir, 2/171 (1%) NR NR	At onset, 39/171 (23%); 1 day from onset, 39/171 (23%); 2–6 days from onset, 12/171 (7%)	NR	None	Cure, 171/171 (100%); hospitalised, 18/171 (11%)	0/171 (0%)

[19]	Retrospective	45 children aged <16 years	Nicosia, Cyprus	Asthma, 3/45 (7%)	Oseltamivir, 19/45 (42%) NR 5 days, 15/17 (88%)	>5 days after symptom onset, 4/19 (21%)	NR	Mild complicating pneumonia, 1/45 (2%)	Cure, 40/45 (89%); hospitalised, 5/45 (11%)	0/45 (0%)
[20]	Retrospective	22 cases (median age 30 years) (including 8 hospitalised patients)	USA	Obese, 7/22 (32%); hypertension, 4/22 (18%); asthma, 3/22 (14%); diabetes, 2/22 (9%); HIV, drug use, COPD, hypothyroidism, stroke, previous splenectomy, thyroid adenoma, hepatitis B, cardiovascular disease, smoking, 1/22 (4.5%) each	Antivirals, 9/22 (41%); none, 7/22 (32%); NR, 6/22 (27%) NR NR	NR	Antibiotics, 10/22 (45.5%)	Bacterial pneumonia, 22/22 (100%)	NA	22/22 (100%)
Cohort studies involving ≤10 patients										
[21]	Retrospective	10 patients (median age 46 years)	USA	Obese (BMI > 30), 9/10 (90%); morbidly obese (BMI > 40), 7/9 (78%)	Oseltamivir, 10/10 (100%); amantadine, 10/10 (100%) Oseltamivir 150 mg twice daily Both beyond the standard 5-day course	Median time after symptom onset, 8 days (range 5–12 days)	Antibiotics, 10/10 (100%); i.v. steroids, 5/10 (50%); steroids before transfer to the SICU, 4/10 (40%)	Severe pneumonia or ARDS, 10/10 (100%); pulmonary embolism, 5/10 (50%)	SICU, 2/10 (20%); stable condition, 5/10 (50%); renal replacement, 6/10 (60%)	3/10 (30%)

[22]	Prospective	10 patients treated in Tan Tock Seng Hospital (median age 27.6 years)	Singapore	Lymphoma in remission, 1/10 (10%)	Oseltamivir, 10/10 (100%) NR NR	1 day from onset, 3/10 (30%); 2 days from onset, 2/10 (20%); 3 days from onset, 3/10 (30%); 4 days from onset, 1/10 (10%); 7 days from onset, 1/10 (10%)	NR	None	Discharged, 8/10 (80%); hospitalised recovering, 2/10 (20%)	0/10 (0%)
[23]	Retrospective	4 hospitalised children with nH1N1 infection	Dallas, USA	Asthma, 1/4 (25%)	Patient A, oseltamivir; Patients B,C and D, oseltamivir + rimantadine NR Patients A, B and D, oseltamivir 5 days; Patient C, rimantadine, 5 days	Patients A and D, 2 days from symptom onset; Patient B, 8 days from symptom onset; Patient C, 3 days from symptom onset	Ceftriaxone, 2/4 (50%) [cefotaxime, lorazepam, fosphenytoin, acyclovir, vancomycin, levetiracetam, amoxicillin, clindamycin, each 1/4 (25%)]	Mental status changes, 4/4 (100%); seizures, 2/4 (50%); encephalopathy, 2/4 (50%); pneumonia, 1/4 (25%)	Cure with no neurological sequelae, 4/4 (100%); intensive care, 1/4 (25%)	0/4 (0%)

[24]	Retrospective	3 hospitalised pregnant women among 13 with available data (median age 26 years)	USA	Asthma, 2/3 (67%)	Oseltamivir, 2/3 (66.7%) NR NR	Patient who died, 10 days from onset; patient who survived, 1 day from onset	Antibiotics, 2/3 (66.7%); non-steroidal anti-inflammatory medication, 1/3 (33.3%); acetaminophen, 1/3 (33.3%); anti-nausea drugs, 1/3 (33.3%)	ARDS, 1/3 (33.3%)	Cure, 2/3 (66.7%)—pregnancy proceeding normally; mechanical ventilation, 1/3 (33.3%)	1/3 (33.3%)
[25]	Prospective	3 patients with confirmed infection	China	None	Oseltamivir, 3/3 (100%) 75 mg twice daily 5-day course	NR	NR	None	Cure, 3/3 (100%)	0/3 (0%)
Case reports										
[26]	NA	32-year-old man presented in end-stage renal disease with fluid overload	Manitoba, Canada	Renal disease	Oseltamivir 75 mg daily 5 days	NR	Antibiotics	Haemodialysis, ICU, mechanical ventilation, nosocomial pneumonia ( <i>Escherichia coli</i> )	Survived	NA
[27]	NA	42-year-old man previously healthy co-infected with nH1N1 and CAP MRSA	Hong Kong, China	None	None	NA	Mechanical ventilation, haemodialysis, vancomycin, clindamycin, piperacillin/tazobactam, clarithromycin	Mixed bacterial and viral pneumonia; respiratory, circulatory and acute renal failure	NA	Death

ICU, Intensive Care Unit; BMI, body mass index; COPD, chronic obstructive pulmonary disease; NR, not reported; ARDS, acute respiratory distress syndrome; OR, odds ratio; CI, confidence interval; NAI, neuraminidase inhibitor; NA, not applicable; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment Score; IQR, interquartile range; i.v., intravenous; RSV, respiratory syncytial virus; HIV, human immunodeficiency virus; ILI, influenza-like illness; MSF, multiorgan system failure; VAP, ventilator-associated pneumonia; SICU, Surgical Intensive Care Unit; CAP MRSA, community-acquired pneumonia due to meticillin-resistant *Staphylococcus aureus*.

- <sup>a</sup> Factors independently associated with in-hospital mortality (OR, 95% CI; *P*-value): (a) requirement for invasive ventilation at ICU admission (5.51, 3.05–9.94; *P* < 0.001); (b) older age (OR/year of age: 1.02, 1.01–1.04; *P* = 0.002); and (c) any co-existing condition (2.56, 1.52–4.30; *P* < 0.001).
- <sup>b</sup> This observation occurred after excluding patients dying early (within 72 h of illness onset), who may have had less opportunity to be exposed to NAIs.
- <sup>c</sup> Invasive bacterial co-infection was defined as laboratory detection of a bacterial pathogen in a specimen from a normally sterile site or a post-mortem lung biopsy.
- <sup>d</sup>  $\beta$ -Lactam + fluoroquinolones (*n* = 20; 62.5%),  $\beta$ -lactam + macrolides (*n* = 6; 18.8%) and  $\beta$ -lactam + linezolid (*n* = 5; 15.6%); 1 patient (3.1%) received levofloxacin as monotherapy.
- <sup>e</sup> Overall hospitalisation rate and/or fatality/100 000 for all age groups: 2.8, ranging from 11.9 in infants <1 year to 1.5 in those  $\geq$ 70 years. In infants <1 year, the highest hospitalisation rates/100 000 were in infants 1 month old (35.8) and 2 months old (21.1); between 3 months and 12 months the hospitalisation rates ranged from 4.2 to 12.6/100 000.
- <sup>f</sup> Obesity, BMI 30–39.9 in adults  $\geq$ 18 years or BMI percentile 95–100 in children 2–18 years old; and morbid obesity, BMI  $\geq$  40 in adults only; the BMI was not calculated in pregnant women.
- <sup>g</sup> Commonly used antibiotics were ceftriaxone (94 patients), azithromycin (84 patients), vancomycin (56 patients) and levofloxacin (47 patients).
- <sup>h</sup> Including asthma, chronic lung disease, developmental delay, neuromuscular disease, immunodeficiency, prematurity, recurrent chest infections, and metabolic and endocrine disease.
- <sup>i</sup> Arterial hypertension (3 patients), non-type 1 diabetes mellitus (3 patients, 1 of whom also had hypertension), asthma (2 patients) and obstructive sleep apnoea (1 patient).

<sup>j</sup> Additional antibiotics were prescribed in several patients on the basis of their clinical course: levofloxacin, 3/18 (17%); vancomycin, 7/18 (39%); cefepime, 5/18 (28%); imipenem, 5/18 (28%); and dicloxacillin, 2/18 (11%).

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**Table 2**

Comparisons regarding the impact of antiviral treatment and early initiation of antiviral treatment on the outcome of 2009 H1N1 infection

Reference	Death [n/N (%)]	Survival [n/N (%)]	P-value
<b>Patients who received antiviral treatment</b>			
Louie et al. [8]			
Age group 1–17 years	5/8 (62.5)	205/267 (76.8)	$\chi^2$ : uncorrected, N/S; Yates' correction, N/S
Age group $\geq 18$ years	65/89 (73.0)	426/520 (81.9)	$\chi^2$ : uncorrected, $P = 0.04$ ; Yates' correction, N/S
All ages	70/97 (72.2)	631/787 (80.2)	$\chi^2$ : uncorrected, $P = 0.06$ ; Yates' correction, N/S
Jain et al. [16]			
All patients	17/19 (89.5)	183/253 (72.3)	$\chi^2$ : Fisher exact, N/S
Raffo et al. [15]			
Paediatric ICU patients	4/6 (66.7)	19/21 (90.4)	$\chi^2$ : Fisher exact, N/S
<b>Patients who received antiviral treatment within 2 days of symptom onset</b>			
Louie et al. [8]			
Age group 1–17 years	1/5 (20)	117/205 (57)	$\chi^2$ : uncorrected, N/S; Yates' correction, N/S
Age group $\geq 18$ years	17/65 (26)	222/427 (52)	$\chi^2$ : uncorrected, $P < 0.001$ ; Yates' correction, $P < 0.001$
All ages	18/70 (26)	339/632 (54)	$\chi^2$ : uncorrected, $P < 0.001$ ; Yates' correction, $P < 0.001$

N/S, not significant, ICU, Intensive Care Unit.