Influenza-associated mortality in hospital care: a retrospective cohort study of risk factors and impact of oseltamivir in an English teaching hospital, 2016 to 2017

Mark Reacher1,2, Ben Warne3, Lucy Reeve1, Neville Q. Verlander1, Nicholas K. Jones3, Kyriaki Ranellou3,5, Silvana Christou3, Callum Wright7, Saher Choudhry7, Maria Zambon6, Clare Sander3, Hongyi Zhang2, Hamid Jalal2

1. Public Health England Field Service, Cambridge Institute of Public Health, Cambridge, United Kingdom
2. Public Health England and Cambridge Universities Hospitals NHS Foundation Trust Cambridge, Cambridge, United Kingdom
3. Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom
4. Statistics Unit, Statistics, Modelling and Economics Department, National Infection Service – Data and Analytical Sciences, Public Health England, London, United Kingdom
5. Division of Virology, Department of Pathology, University of Cambridge, Cambridge, United Kingdom
6. National Infection Service, Public Health England, London, United Kingdom

Correspondence: Mark Reacher (Mark.Reacher@phe.gov.uk)

Background: Evidence of an oseltamivir treatment effect on influenza A(H3N2) virus infections in hospitalised patients is incomplete. Aims: This cohort study aimed to evaluate risk factors for death among PCR-confirmed hospitalised cases of seasonal influenza A(H3N2) of all ages and the impact of oseltamivir. Methods: Participants included all 332 PCR-confirmed influenza A(H3N2) cases diagnosed between 30 August 2016 and 17 March 2017 in an English university teaching Hospital. Oseltamivir treatment effect on odds of inpatient death was assessed by backward stepwise multivariable logistic regression analysis. Results: The odds of death were reduced by two thirds (odds ratio (OR): 0.32; 95% confidence interval (CI): 0.11–0.93), in inpatients treated with a standard course of oseltamivir 75 mg two times daily for 5 days – compared with those untreated with oseltamivir, after adjustment for age, sex, current excess alcohol intake, receipt of 2016/17 seasonal influenza vaccine, serum haemoglobin and hospital vs community attribution of acquisition of influenza. Conclusions: Oseltamivir treatment given according to National Institutes of Clinical Excellence (NICE); United States Centres for Disease Control and Prevention (CDC); Infectious Diseases Society of America (IDSA) and World Health Organization (WHO) guidelines was shown to be effective in reducing the odds of mortality in inpatients with PCR-confirmed seasonal influenza A(H3N2) after adjustment in a busy routine English hospital setting. Our results highlight the importance of hospitals complying with relevant guidelines for prompt seasonal influenza PCR testing and ensuring standard oseltamivir treatment to all PCR-confirmed cases of seasonal influenza.

Introduction

Seasonal influenza, which recurs annually in winter, remains a leading cause of morbidity and mortality worldwide and a major challenge to hospitals, which face severe pressures during this period of the year [1,2]. Hospitalisation and mortality from influenza disproportionately affect the elderly [3-5], with the risk of mortality increasing with age over 65 years [6,7]. Other factors associated with mortality include underlying comorbidities [5,8], delay in presentation to medical care [8] and viral subtype, with infection with influenza A(H3N2) virus strains being of highest risk [3,5,7].

Circulating influenza virus strains and vaccine effectiveness vary from season to season [9-11]. Understanding risk factors for poor outcome in seasonal influenza is therefore important in optimising the prevention and management of high-risk patients presenting to primary and secondary care and requires appropriately designed observational studies [9,12].

In common with many hospitals in the northern hemisphere winter of 2016/17, Cambridge University Hospitals (CUH) National Health Service (NHS) Foundation Trust was severely challenged by large numbers of patients admitted with influenza virus infection [13].
During this season, influenza A(H3N2) virus strain predominated and seasonal influenza vaccine was estimated to have moderate effectiveness of between 30% and 40% with lower levels of effectiveness in older patients [14-17].

Although recommended by several national and international agencies for the treatment of seasonal influenza in patients requiring hospitalisation, including the National Institute for Health and Care Excellence (NICE) [18,19], the United States (US) Centers for Disease Control and Prevention (CDC) [20,21], the Infectious Disease Society of America (IDSA) [22] and the World Health Organization (WHO) [16], the evidence of an effect of oseltamivir on influenza-associated mortality in hospitalised patients is limited [10]. Randomised controlled trials (RCTs) have predominantly been undertaken in outpatients and have indicated that oseltamivir reduced symptom duration and lower respiratory tract complications in otherwise healthy adults [23,24].

A retrospective cohort study was undertaken in our hospital of the clinical management of inpatients diagnosed by PCR with influenza A(H3N2) virus strain infection during the 2016/17 season to better understand risk factors for inpatient death and whether any effect of a standard course of oseltamivir 75 mg twice daily for 5 days was observed.

Methods

Institutional setting and approval
The CUH NHS Foundation Trust is a 1,100-bed university teaching hospital providing district general hospital services for Cambridgeshire and surrounding counties and specialised tertiary-level services across the East of England with a population of approximately six million.

Ethical statement
The study was registered with the Safety and Quality Support department of CUH NHS Foundation Trust under a Service Evaluation/Outbreak Investigation remit (Project Registration Number PRN 7053; 15 January 2018).

Legal basis for processing personal identifying information
Processing and analysis of individual patient level data was undertaken in compliance with the General Data Protection Regulations [25,26].

Virological and bacteriological methods
A nose and a throat swab placed in a single tube of viral transport medium were collected from each patient. Detection of respiratory viruses was done by using a multiplex real-time PCR assay as described previously [27,28]. Bacteriology specimens were processed using standard Public Health England (PHE) methods.

Individuals considered in the study
Individuals in this study were patients of any age admitted to our hospital with a laboratory-confirmed diagnosis of influenza A(H3N2) virus strain infection, between 20 August 2016 and 17 March 2017. They were identified through our hospital laboratory information system (LIMS) and linked to electronic hospital medical record and general practitioner (GP) information systems. Death or discharge alive was recorded for the admission episode during which the virological swab testing positive for the influenza A(H3N2) virus strain was obtained.

Clinical data collection
Demographic and clinical details of the admission episode, date and time of admission, discharge, transfer and death, full blood count, blood chemistry, C-reactive protein, virology and bacteriology test results, oseltamivir prescriptions and receipt of seasonal influenza vaccination were extracted from the electronic hospital medical record and GP information systems described earlier to a structured epidemiological proforma.

Active medical conditions were recorded and the non-age adjusted Charlson comorbidity index score calculated [29]. Risk factors and conditions not included in the Charlson index were also recorded, comprising radiological evidence of pneumonia, current smoker, excessive alcohol use, admission with trauma, admission for surgery, pregnancy, hypertension, body mass index (BMI) ≥ 40 kg/m² and receipt of respiratory support. Respiratory support was categorised as oxygen therapy, continuous positive airways pressure (CPAP), non-invasive ventilation (NIV) and invasive ventilation. Immune suppression was categorised as absent or present and, if present, categorised as: high dose steroids ≥ 40 mg of prednisolone daily or equivalent; receiving or within 6 months of receiving chemotherapy or generalised radiotherapy, organ transplant or bone marrow transplant.

The clinical data abstraction proforma for oseltamivir exposure posed the question ‘was this patient prescribed oseltamivir, yes or no? If yes, did this patient receive standard oseltamivir treatment 75 mg twice daily for 5 days, yes or no? If no, describe why not.’

The British National Formulary (BNF) standard course of oseltamivir for treatment of seasonal influenza is 75 mg twice daily for 5 days. For children modified doses are given according to body weight. Patients whose treatment was completed according to this standard were categorised as standard course.

In renal failure the standard 5-day dose is reduced in adults to 30 mg twice daily if estimated glomerular filtration rate (eGFR) is 30-60 mL/minute/1.73 m² or to 30 mg once daily if eGFR is 10-30 mL/minute/1.73 m². In children this is 40% of normal dose for weight twice daily if eGFR is 30-60 mL/minute/1.73 m² or 40% of
### Table 1a
Analysis of single variables potentially associated with influenza A(H3N2) virus strain infection related deaths, Cambridge, England, 2016/17 (n = 332)

| Variable                                      | Category or measure | Expired | Not expired | OR (95% CI) | p value |
|-----------------------------------------------|---------------------|---------|-------------|-------------|---------|
| **Age at positive specimen (years)**          | Minimum             | 34      | 0           |             |         |
|                                               | 25th centile        | 71      | 53          |             |         |
|                                               | Median              | 84      | 74          | 1.04 (1.01–1.06) per year | < 0.001 |
|                                               | 75th centile        | 88      | 85          |             |         |
|                                               | Maximum             | 102     | 101         |             |         |
| **Sex**                                       | Female              | 13      | 162         | Reference   | 0.15    |
|                                               | Male                | 19      | 138         | 1.72 (0.82–3.60) |       |
| **Body mass index (BMI) ≥ 40 Kg/m²**          | Yes                 | 1       | 3           | 0.00 (not estimable) |       |
|                                               | No                  | 31      | 295         | 1.90 (0.22–16.8) |       |
| **Pregnancy**                                 | Pregnant            | 0       | 3           | Reference   | 0.3     |
|                                               | Not pregnant        | 13      | 159         |             |         |
|                                               | Male                | 19      | 138         | 1.68 (0.80–3.54) |       |
| **Oseltamivir course completed**              | 1. Not given        | 7       | 66          | Reference   | 0.7     |
|                                               | 2. Non-standard course | 3   | 18          | 1.57 (0.37–6.70) |       |
|                                               | 3. Appropriately modified | 6 | 40          | 1.41 (0.44–4.51) |       |
|                                               | 4. Standard course  | 16      | 176         | 0.86 (0.34–2.18) |       |
| **Days between onset of influenza illness and first dose of oseltamivir** | Minimum             | 0       | 0           |             |         |
|                                               | 25th centile        | 2       | 2           |             |         |
|                                               | Median              | 3       | 3           | 0.89 (0.74–1.06) per day delay | 0.4     |
|                                               | 75th centile        | 5       | 5           |             |         |
|                                               | Maximum             | 11      | 18          |             |         |
| **Current smoker**                            | Yes                 | 2       | 29          | 0.60 (0.13–2.68) | 0.5     |
|                                               | No                  | 23      | 200         | Reference   |         |
| **Long-term oxygen therapy**                  | Yes                 | 1       | 2           | 4.69 (0.41–53.6) | 0.3     |
|                                               | No                  | 24      | 225         | Reference   |         |
| **Hypertension**                              | Yes                 | 14      | 111         | 1.32 (0.63–2.77) | 0.5     |
|                                               | No                  | 18      | 189         | Reference   |         |
| **Trauma**                                    | Yes                 | 1       | 4           | 2.39 (0.26–22.0) | 0.5     |
|                                               | No                  | 31      | 296         | Reference   |         |
| **Excessive alcohol use**                     | Yes                 | 3       | 5           | 6.10 (1.39–29.8) | 0.03    |
|                                               | No                  | 29      | 295         | Reference   |         |
| **Surgery**                                   | Yes                 | 3       | 13          | 2.28 (0.61–8.48) | 0.25    |
|                                               | No                  | 29      | 287         | Reference   |         |
| **Immune suppressed**                         | Yes                 | 3       | 61          | 0.40 (0.12–1.37) | 0.11    |
|                                               | No                  | 29      | 238         | Reference   |         |
| **Receipt of 2016/17 influenza vaccine**       | Yes                 | 11      | 110         | 0.90 (0.42–1.95) | 0.8     |
|                                               | No                  | 21      | 190         | Reference   |         |
| **Steroids**                                  | Yes                 | 0       | 2           | 0.00 (not estimable) | 0.5     |
|                                               | No                  | 32      | 298         | Reference   |         |
| **Chemotherapy**                              | Yes                 | 0       | 21          | 0.00 (not estimable) | 0.04    |
|                                               | No                  | 32      | 279         | Reference   |         |
| **Radiotherapy**                              | Yes                 | 1       | 1           | 9.65 (0.59–15.8) | 0.14    |
|                                               | No                  | 31      | 299         | Reference   |         |
| **Organ transplant**                          | Yes                 | 0       | 12          | 0.00 (not estimable) | 0.12    |
|                                               | No                  | 32      | 288         | Reference   |         |
| **Bone marrow transplant**                    | Yes                 | 0       | 4           | 0.00 (not estimable) | 0.4     |
|                                               | No                  | 32      | 296         | Reference   |         |
| **Immune deficiency syndrome**                | Yes                 | 0       | 0           | Not estimable | NA      |
|                                               | No                  | 32      | 300         | Reference   |         |
| **Other category of immune suppression**       | Yes                 | 2       | 21          | 0.89 (0.20–3.96) | 0.9     |
|                                               | No                  | 30      | 279         | Reference   |         |

OR: odds ratio; CI: confidence interval; QF: quadratic function; NA: not applicable.
| Variable                      | Category or measure | Expired | Not expired | OR (95% CI)          | p value |
|-------------------------------|---------------------|---------|-------------|----------------------|---------|
| Haemoglobin concentration g/L| Minimum             | 68      | 45          | 0.98 (0.96–0.99) per g/L | 0.01    |
|                               | 25th centile        | 98.5    | 108         |                      |         |
|                               | Median              | 112     | 123         |                      |         |
|                               | 75th centile        | 124     | 135         |                      |         |
|                               | Maximum             | 153     | 175         |                      |         |
| Total white cell count × 10^9/L | Minimum             | 2.1     | 0           |                      |         |
|                               | 25th centile        | 7.7     | 5.3         |                      |         |
|                               | Median              | 10.1    | 7.3         |                      |         |
|                               | 75th centile        | 14.3    | 9.6         |                      |         |
|                               | Maximum             | 48.5    | 53.6        |                      |         |
| Lymphocyte count × 10^9/L     | Minimum             | 0.2     | 0           |                      |         |
|                               | 25th centile        | 0.5     | 0.5         |                      |         |
|                               | Median              | 0.8     | 0.8         |                      |         |
|                               | 75th centile        | 1.2     | 1.2         |                      |         |
|                               | Maximum             | 2.3     | 46.7        |                      |         |
| C-reactive protein mg/L       | Minimum             | 48      | 8           |                      |         |
|                               | 25th centile        | 69      | 64          |                      |         |
|                               | Median              | 99      | 84          |                      |         |
|                               | 75th centile        | 114     | 111         |                      |         |
|                               | Maximum             | 187     | 742         |                      |         |
| Creatinine mmol/L             | Minimum             | 4.5     | 1.6         |                      |         |
|                               | 25th centile        | 7.2     | 4.6         |                      |         |
|                               | Median              | 9.2     | 6.2         |                      |         |
|                               | 75th centile        | 11      | 8.6         |                      |         |
|                               | Maximum             | 18.6    | 39.2        |                      |         |
| Urea mmol/L                   | Minimum             | 4.5     | 1.6         |                      |         |
|                               | 25th centile        | 7.2     | 4.6         |                      |         |
|                               | Median              | 9.2     | 6.2         |                      |         |
|                               | 75th centile        | 11      | 8.6         |                      |         |
|                               | Maximum             | 18.6    | 39.2        |                      |         |
| Glucose mmol/L                | Minimum             | 5.1     | 3.4         | 1.04 (0.95–1.13) per mmol/L | 0.4    |
|                               | 25th centile        | 6.7     | 6           |                      |         |
|                               | Median              | 7.8     | 6.9         |                      |         |
|                               | 75th centile        | 8.9     | 8.7         |                      |         |
|                               | Maximum             | 24      | 36.2        |                      |         |
| Required oxygen               | Yes                 | 8       | 32          | 2.79 (1.16–6.73)     | 0.03    |
|                               | No                  | 24      | 268         | Reference            |         |
| Continuous positive airways pressure | Yes             | 1       | 3           | 3.20 (0.32–31.6)   | 0.4     |
|                               | No                  | 31      | 297         | Reference            |         |
| Non-invasive ventilation      | Yes                 | 3       | 3           | 10.2 (1.98–53.1)    | 0.01    |
|                               | No                  | 29      | 297         | Reference            |         |
| Invasive ventilation          | Yes                 | 5       | 22          | 2.34 (0.82–6.68)    | 0.14    |
|                               | No                  | 27      | 278         | Reference            |         |
| Charlson comorbidity index    | Minimum             | 0       | 0           | 1.21 (1.03–1.43)    | 0.03    |
|                               | 25th centile        | 2       | 1           |                      |         |
|                               | Median              | 2       | 2           |                      |         |
|                               | 75th centile        | 4       | 3           |                      |         |
|                               | Maximum             | 8       | 10          |                      |         |

OR: odds ratio; CI: confidence interval; QF: quadratic function; NA: not applicable.
1 QF: linear part OR: 1.28 (95% CI: 1.11–1.47); quadratic part OR: 1.00 (95% CI: 0.99–1.00).
2 QF: linear part OR: 1.05 (95% CI: 1.01–1.09); quadratic part OR: 1.00 (95% CI: 1.00–1.00).
3 QF: linear part OR: 2.45 (95% CI: 1.48–4.06); quadratic part OR: 0.97 (95% CI: 0.94–0.99).

| Variable                              | Category or measure | Expired | Not expired | OR (95%CI)               | p value |
|---------------------------------------|---------------------|---------|-------------|--------------------------|---------|
| Cycle threshold (CT) value            | Minimum             | 19      | 16          | 0.96 (0.88–1.04)         | 0.3     |
|                                       | 25th centile        | 23      | 27          |                          |         |
|                                       | Median              | 27      | 30          |                          |         |
|                                       | 75th centile        | 32      | 32          |                          |         |
|                                       | Maximum             | 38      | 41          |                          |         |
| Place of acquisition of infection     | Community           | 15      | 219         | Reference                | 0.003   |
|                                       | Hospital            | 17      | 81          | 3.06 (1.46–6.42)         |         |
| Admitted from                         | Own home            | 25      | 251         | Reference                | 0.5     |
|                                       | Residential care     | 4       | 28          | 1.43 (0.47–4.42)         |         |
|                                       | Another hospital     | 3       | 13          | 2.32 (0.62–8.68)         |         |
|                                       | Other               | 0       | 4           | 0.00 (not estimable)     |         |
| Oselamivir prescribed for post-exposure prophylaxis | Yes                 | 2       | 8           | 2.43 (0.49–12.0)         | 0.3     |
|                                       | No                  | 30      | 292         | Reference                |         |
| Pneumonia                             | No imaging          | 2       | 34          | Reference                |         |
|                                       | No pneumonia on image | 16     | 214         | 1.27 (0.28–5.78)         | 0.005   |
|                                       | Pneumonia on image  | 14      | 52          | 4.58 (0.98–21.4)         |         |
| Myocardial infarction                 | Yes                 | 6       | 32          | 1.93 (0.74–5.05)         | 0.2     |
|                                       | No                  | 26      | 268         | Reference                |         |
| Congestive heart failure              | Yes                 | 5       | 33          | 1.50 (0.54–4.16)         | 0.5     |
|                                       | No                  | 27      | 267         | Reference                |         |
| Peripheral vascular disease           | Yes                 | 3       | 8           | 3.78 (0.95–15.0)         | 0.09    |
|                                       | No                  | 29      | 292         | Reference                |         |
| Cerebro vascular disease              | Yes                 | 8       | 47          | 1.79 (0.76–4.23)         | 0.2     |
|                                       | No                  | 24      | 253         | Reference                |         |
| Dementia                              | Yes                 | 8       | 38          | 2.30 (0.96–5.48)         | 0.08    |
|                                       | No                  | 24      | 262         | Reference                |         |
| Chronic lung disease                  | Yes                 | 16      | 88          | 2.41 (1.15–5.03)         | 0.02    |
|                                       | No                  | 16      | 212         | Reference                |         |
| Connective tissue disease             | Yes                 | 2       | 21          | 0.89 (0.20–3.96)         | 0.9     |
|                                       | No                  | 30      | 279         | Reference                |         |
| Peptic ulcer                          | Yes                 | 3       | 6           | 5.07 (1.20–21.3)         | 0.047   |
|                                       | No                  | 29      | 294         | Reference                |         |
| Mild liver disease                    | Yes                 | 1       | 2           | 4.81 (0.42–54.5)         | 0.3     |
|                                       | No                  | 31      | 298         | Reference                |         |
| Moderate or severe liver disease      | Yes                 | 5       | 49          | 0.95 (0.35–2.58)         | 0.9     |
|                                       | No                  | 27      | 251         | Reference                |         |
| Diabetes without end organ damage     | Yes                 | 5       | 46          | 1.02 (0.37–2.79)         | 0.97    |
|                                       | No                  | 27      | 254         | Reference                |         |
| Diabetes with end organ damage        | Yes                 | 2       | 15          | 1.27 (0.28–5.81)         | 0.8     |
|                                       | No                  | 30      | 285         | Reference                |         |
| Hemiplegia                            | Yes                 | 1       | 13          | 0.71 (0.09–5.63)         | 0.7     |
|                                       | No                  | 31      | 287         | Reference                |         |
| Moderate or severe kidney disease     | Yes                 | 5       | 46          | 1.02 (0.37–2.79)         | 0.97    |
|                                       | No                  | 27      | 254         | Reference                |         |
| Tumour without metastasis             | Yes                 | 3       | 22          | 1.31 (0.37–4.63)         | 0.7     |
|                                       | No                  | 29      | 278         | Reference                |         |
| Tumour with metastasis                | Yes                 | 1       | 6           | 1.58 (0.18–13.6)         | 0.7     |
|                                       | No                  | 31      | 294         | Reference                |         |
| Leukaemia                             | Yes                 | 0       | 11          | 0.00 (not estimable)     | 0.13    |
|                                       | No                  | 32      | 289         | Reference                |         |
| Lymphoma                              | Yes                 | 0       | 16          | 0.00 (not estimable)     | 0.07    |
|                                       | No                  | 32      | 284         | Reference                |         |

OR: odds ratio; CI: confidence interval; QF: quadratic function; NA: not applicable.
normal dose by weight once daily if eGFR is 10–30 mL/minute/1.73 m². In patients with immune suppression the standard course is extended from 5 to 10 days. Patients whose treatment was modified for renal failure or immune suppression in accordance with the BNF were categorised as having received an appropriately modified standard course.

Cases whose oseltamivir treatment was neither standard, 75 mg twice daily for 5 days, nor appropriately modified, were categorised as having received a non-standard course of oseltamivir.

Oseltamivir exposure was categorised from these responses as not received (category 1); received a non-standard course (category 2); received an appropriately modified course (category 3); or received a standard course of oseltamivir.

Oesophageal ulcers were defined as ulcers that were deep and widespread and whose length exceeded 3 cm.

Statistical analysis
Statistical analysis was undertaken in STATA15.1. using single variable and multivariable regression methods [31]. Single variable analysis associations between inpatient death and individual risk factors, including the individual components of the Charlson comorbidity index and the non-age adjusted Charlson comorbidity index, were examined by logistic regression using likelihood ratio tests (LRT) and p values and odds ratios (OR) and 95% confidence intervals (CI) determined. Variables with \( p < 0.2 \) by LRT in the single variable analysis and sex were considered in the stepwise multivariable logistic regression analysis. Appropriate functional forms for continuous variables were determined by successively fitting cubic, quadratic and linear functions and selecting the simplest for which no improvement in fit was observed by LRT in both single and multivariable analyses.

The initial model consisted of sex and variables with \( p \leq 0.01 \) by LRT from the single variable analysis. A backwards stepwise procedure was undertaken dropping non-confounding variables with the largest LRT \( p \leq 0.1 \) one at a time. A variable was judged to be confounding if its omission resulted in a change of more than 20% in the OR in one or more of the parameters still in the model. The process continued until no further variables could be removed.

Variables with \( p \leq 0.1 \) in the single variable analysis were then added in a forward procedure and the above procedure repeated, at the end of which the remaining variables with \( p > 0.1 \) were added and the backwards stepwise procedure implemented.

The variables for the category of oseltamivir treatment completed and receipt of 2016/17 seasonal influenza vaccine were then added to the model. Following this, variables which had been dropped from the model were again added singly and then removed before adding another to check that they should still be omitted. Variables found to be substantial confounders were then added to the model. The appropriate functions of the continuous variables still in the model were then again determined to give the final multivariable model of risk factors independently associated with inpatient death, adjusting for the category of oseltamivir treatment received and receipt of an NHS approved 2016/17 seasonal influenza vaccine.

A second multivariable model was fitted replacing the variable for the category of oseltamivir treatment with the variable for the delay between the date of onset of influenza illness and the date of commencing oseltamivir treatment.

Interactions
Interaction terms were tested between the categories of oseltamivir treatment received, delay in receipt of oseltamivir, receipt of approved 2016/17 seasonal influenza vaccine and if immune suppressed. The variable of the delay was considered in two two-way interactions, one being with the receipt of seasonal vaccine and the other immune suppressed. The two-way interaction between immune suppression and seasonal vaccine receipt and the three-way interaction between delay, seasonal vaccine receipt and immune suppression were tested. These interactions were considered in both the single and multivariable analysis.

Results
Single variable analysis
The cohort comprised 332 patients with a mean age of 68.6 years (range: 0–102) of whom 175 (52.7%) were female. A total of 32 (9.6%) of these patients died during admission (Table 1). The time from admission...
to death, discharge or transfer to other hospitals was median 7 days (interquartile range: 3–23). Eight (2.4%) patients were aged under 18 years: one under 1 year; three aged 2 years; one aged 5 years; one aged 8 years; and two aged 17 years, none of whom expired during admission. Twenty-six (8.1%) of the patients were admitted to an intensive care unit (ICU).

Oseltamivir was not prescribed for 73 of the 332 (22%) of patients. Among these patients, the reasons for not having been prescribed oseltamivir were because more than 48 hours had elapsed since onset of symptoms (n = 10; 13.7%), discharged before the positive PCR test result for influenza A(H3N2) virus strain was available (n = 18; 24.7%), clinically improved (n = 8; 11%), died before the test result was received (n = 2; 2.7%), drugs stopped for palliative care (n = 1; 1.4%), and no reason given (n = 34; 46.6%). No patients were detected as having received oseltamivir before admission.

Significantly raised odds (p < 0.05) for inpatient death were observed for age (OR: 1.04; 95% CI: 1.01–1.06) per year, Charlson comorbidity index (OR: 1.57; 95% CI: 0.37–6.70) or appropriate modified course consistent with the BNF (OR: 0.34; 95% CI: 0.09–1.28). No significant association was seen for delay starting oseltamivir (OR: 0.89; 95% CI: 0.74–1.06), with having received the 2016/17 seasonal influenza vaccine (OR: 0.90; 95% CI: 0.42–1.95) or with being immune suppressed (OR: 0.40; 95% CI: 0.12–1.37).

Six patients, all of whom survived, were confirmed to have bacterial infection synergistic with influenza A(H3N2) virus strain infection by positive cultures for *Streptococcus pneumoniae* or *Haemophilus influenzae* in blood or sputum. None of the patients who expired had evidence of synergistic bacterial infection with influenza A(H3N2) virus strain infection.

### Multivariable analysis

The variables age, sex, place of acquisition, serum haemoglobin concentration, excessive alcohol use, category of oseltamivir course completed and receipt of 2016/17 seasonal influenza vaccine met the criteria for inclusion in the final multivariable model (Table 2).

Cases who received a BNF standard course of oseltamivir of 75 mg two times daily for 5 days were significantly

---

**Table 2**

Final multivariable analysis of variables independently associated with inpatient death, Cambridge, England, 2016/17 (n = 329)

| Variable | Category | OR (95% CI) | p value |
|----------|----------|-------------|---------|
| Age | NA | 1.06 per year (1.03–1.10) | <0.001 |
| Sex | Female | Reference | |
| | Male | 1.73 (0.76–1.94) | 0.19 |
| Place of acquisition | Community | Reference | |
| | Hospital | 1.82 (0.79–4.23) | 0.16 |
| Haemoglobin concentration g/L | NA | 0.97 (0.95–1.00) per g/L | 0.02 |
| Excessive alcohol use | Yes | 13.2 (9.39–90.5) | 0.01 |
| | No | Reference | 0.23 |
| Oseltamivir course completed | Not given | Reference | |
| | 2. Non-standard course | 0.3 (0.06–1.54) | |
| | 3. Appropriately modified course | 0.34 (0.09–1.28) | |
| | 4. Standard course | 0.32 (0.11–0.93) | |
| Receipt of 2016/17 seasonal influenza vaccine | Yes | 0.63 (0.26–1.49) | 0.3 |
| | No | Reference | |

CI: confidence interval; NA: not applicable; OR: odds ratio.

*Of 332 patients, 329 had serum haemoglobin concentration results.*
protected against death compared with those not given oseltamivir (OR: 0.32; 95% CI: 0.11–0.93) A protective though non-significant association was also observed for receipt of a non-standard course of oseltamivir (OR: 0.3; 95% CI: 0.06–1.54) and a BNF appropriately modified course of oseltamivir (OR: 0.34; 95% CI: 0.09–1.28). Receipt of the 2016/17 seasonal influenza vaccine was not significantly protective (OR: 0.63; 95% CI: 0.29–1.49).

History of excessive alcohol use was associated with a 13-fold (OR: 13.2; 95% CI: 1.93–90.5) higher odds of death. Higher serum haemoglobin was significantly protective (OR: 0.97; 95% CI: 0.95–1.00) per gram per litre. Males and those whose acquisition of infection was in hospital had non-significantly raised odds (OR: 1.73; 95% CI: 0.76–1.94 and OR: 1.82; 95% CI: 0.79–4.23 respectively).

In a second multivariable model, the category of oseltamivir course received was replaced by the delay in days between onset date and starting date of oseltamivir treatment (Table 3). This delay was not significantly associated with inpatient death (OR: 0.92; 95% CI: 0.77–1.09). The remaining variables had similar odds as in the first multivariable model Tables 2 and 3.

None of the following interactions tested in the model shown in Table 3 reached statistical significance: delay in starting oseltamivir and receipt of 2016/17 seasonal influenza vaccine p = 0.6, delay and immune suppressed p = 0.6, immune suppressed and receipt of 2016/17 seasonal influenza vaccine p = 0.3, and delay and immune suppressed and receipt of 2016/17 seasonal influenza vaccine p>0.999.

Variables significantly associated with raised odds in single variable analysis p < 0.05 (Table 1) but excluded in our multivariable model building (Tables 2 and 3) were chemotherapy, total white cell count, serum C-reactive protein, serum creatinine, serum urea, supplementary oxygen therapy, non-invasive ventilation, Charlson comorbidity index, radiological evidence of pneumonia, chronic lung disease, and peptic ulcer.

### Discussion

This study of a large cohort of laboratory-confirmed seasonal influenza A (H3N2) cases admitted to a United Kingdom (UK) NHS hospital measured the odds of all-cause inpatient mortality. Our study has chronicled the effectiveness of oseltamivir in reducing inpatient mortality in a hospital typical of the UK NHS in winter season 2016/17 for the influenza A(H3N2) virus strain and that a proportion of patients had not received oseltamivir treatment at standard BNF dose according to NICE and WHO guidelines for several operational reasons, some of which were amenable to improvement.

While RCTs of oseltamivir treatment of influenza virus infection have been conducted in outpatients, there are currently no completed placebo-controlled RCTs of oseltamivir for treatment of influenza in hospitalised patients, thus the need for observational studies [10].

The need for observational studies to supplement RCTs is recognised [9] and can provide up to date measures of effectiveness of interventions and treatments in routine clinical settings with external validity. This is important in seasonal influenza where the effectiveness of vaccines and the virulence of circulating influenza virus strains vary over time [10,11].

We identified clinical parameters in single variable analysis recognised as risk factors for poor outcome including elevated total white cell count and C-reactive protein, pneumonia, and the need for supplementary oxygen and ventilation [32], but these did not meet our inclusion criteria for our final multivariable models.

### Table 3

| Variable                        | Category          | OR (95% CI)     | p value |
|---------------------------------|-------------------|-----------------|---------|
| Age                             | NA                | 1.06 per year (1.03–1.10) | <0.001  |
| Sex                             | Female Reference  | 1.74 (0.75–4.01) | 0.19    |
|                                 | Male Reference    | 1.43 (0.57–3.58) | 0.4     |
| Place of acquisition            | Community Reference | 0.97 (0.95–0.99) | 0.01    |
|                                 | Hospital Reference | 0.62 (0.25–1.40) | 0.22    |
| Excessive alcohol use           | Yes               | 16.7 (1.77–156)  | 0.02    |
|                                 | No Reference      | 0.92 per day (0.77–1.09) | 0.1    |
| Receipt of 2016/17 seasonal influenza vaccine | Yes | 0.59 (0.25–1.40) | 0.22    |
|                                 | No Reference      | 0.92 per day (0.77–1.09) | 0.1    |

CI: confidence interval; NA: not applicable; OR: odds ratio.

* Of 332 patients, 299 had information on time delay and haemoglobin concentration.
The variables meeting our selection criteria for our final multivariable model (Table 2) were age, sex, place of acquisition, serum haemoglobin concentration, excessive alcohol use, category of oseltamivir treatment and receipt of 2016/17 seasonal influenza vaccine.

The significant independent protective association against inpatient death of higher serum haemoglobin concentration is consistent with this being a marker of good general nutrition and better health [33]. Excessive alcohol use emerged as a major confounder and may be explained at least in part, by its association with severe liver disease, which is a well-recognised risk factor for severe influenza virus infection. We combined moderate and severe liver disease as a single variable as required for the Charlson comorbidity index but this was not associated with raised odds of inpatient death in our single variable analysis (Table 1).

Recorded receipt of 2016/17 seasonal influenza vaccine neither protected our cases from infection with influenza (A(H3N2) virus strain nor modified the protective effect of oseltamivir on inpatient death as shown by the non-significance of its interaction terms. These results are in keeping with the observed poor effectiveness of the vaccine against influenza A(H3N2) particularly in the elderly [14,15,17].

The effectiveness of oseltamivir in the prevention and treatment of seasonal and pandemic influenza remains a subject of debate [34-36].

Acceptance of the protective effect of oseltamivir against inpatient mortality in seasonal influenza A(H3N2) virus strain infection shown in our study, may be perceived to be at variance with meta-analyses of RCTs, which have concluded that the benefits of oseltamivir treatment are confined to shortening of symptom onset to cessation of viral replication [46,47]. However, these trials have been done in outpatients and almost exclusively in younger adults with no comorbidities and are probably not generalisable to the largely elderly hospitalised population in this study [9,39] for whom oseltamivir treatment is recommended by NICE, IDSA, CDC and WHO [16,18,19,22,40]. Our findings concur with meta-analyses of observational studies concluding a protective effect of oseltamivir on mortality in patients hospitalised with Influenza [41,42]. However, Jones and Wolkewitz have raised concerns about the meta-analysis by Muthuri et al. on handling of time-dependent treatment and the absence of follow up beyond hospital discharge [43,44].

In keeping with previous observational studies [42,45], we found no evidence to support the notion that the protective benefit of oseltamivir was limited in this high-risk population to within 48 hours after the onset of symptoms. The additional benefit found in our cohort may reflect the higher proportions of elderly and immunocompromised patients who have longer times from symptom onset to cessation of viral replication [46,47].

The failure to give oseltamivir treatment to cases of influenza A (H3N2) virus strain admitted to hospital may expose cases to an avoidable threefold higher odds of inpatient mortality than would have been the case had they been treated and as recommended by national and international guidance. Infection ascribed to being acquired in hospital as compared to being acquired in the community met our selection criteria for inclusion in our final multivariable models and weak but non-significant association with raised odds of inpatient mortality was seen. This may be explained by greater comorbidity in the former group of patients.

We measured the odds of inpatient mortality as our outcome using logistic regression and showed a protective effect of oseltamivir treatment in hospitalised patients. Our conclusion of a protective effect of oseltamivir against inpatient mortality in hospitalised patients is congruent with the conclusion of a recent systematic review of systematic reviews [36].

Our conclusions contrast with studies measuring duration of admission as well as inpatient mortality using survival analysis. A case for modelling discharge from the population at risk as a competing hazard for death during admission has been made [44,48]. Multistate models were used comprising hospital admission, oseltamivir treatment, discharge, and death timed from onset of influenza symptoms using 1,391 case records of confirmed pandemic influenza A(H1N1) virus strain infection collected during 2009 and 2010 in the UK by the UK Flu collaboration [48,49]. A corrected hazard ratio (HR) of death in hospital associated with oseltamivir treatment was found to be non-significant (HR: 1.03; 95% CI: 0.64–1.66) but significant for discharge (HR: 1.89; 95% CI: 1.65–2.16). Lytras et al. modelled discharge from ICUs alive as a competing hazard for death within the ICUs, for oseltamivir exposure dichotomised to early (<48 hours after onset) vs later (≥48 hours) for influenza A(H3N2) virus strain infection in a cohort of 1,330 patients admitted to ICUs in Greece over eight influenza seasons between 2010 and 2018 [50]. Although early treatment with oseltamivir was associated with significantly lower mortality (relative risk (RR): 0.69; 95% CI: 0.49–0.94), the authors ascribed this effect purely to increased cause-specific hazard for discharge.

The absence of demonstrable protective effect of oseltamivir on inpatient mortality in these studies contrast to our results. This could be explained by the differences in the influenza A virus strains being studied; treating discharge from the population at risk as a competing hazard with patient death rather than considering death alone as the outcome; and differences in adjustment for confounding. For example, no adjustment was made for excessive alcohol use in these studies, while we observed excessive alcohol use to be a significant confounder of the relationship between seasonal influenza A(H3N2) virus strain infection and inpatient death.
**Limitations**

Our study was limited by being for a single season from a single hospital and for cases only infected by influenza A(H3N2) virus strain. We enrolled all influenza A(H3N2) virus strain positive patients to our study cohort, but it is possible that some cases may still have been missed from viral swabbing. The small proportion of children we recruited may reflect this. Because we had few children aged under 18 years, we were unable to draw specific conclusions on this age group. It is possible that we may not have recorded fully oseltamivir given before admission to hospital, but we think this is unlikely because data abstractors were clinicians reviewing the entire clinical record including drugs given before admission and primary care physician referral letters and with a study remit to search for reasons why a completed standard course of oseltamivir had not been given. No case of oseltamivir having been given before admission was reported.

It is possible that a further proportion of our patients had received seasonal influenza vaccine than we recorded, because influenza vaccination is offered in pharmacies and supermarkets from which vaccination records may not have been completely transferred to the primary care records which we used. We do not think this would have led to a major impact on our conclusions because we did not detect a protective effect for seasonal influenza vaccination alone or as an interaction term with oseltamivir, and because the 2016/17 influenza vaccine was of low effectiveness particularly in the elderly [14]. Corroboration of our results in future seasons in other centres and for other virus strains of seasonal influenza is desirable.

**Conclusions**

Standard oseltamivir treatment of 75 mg twice daily for 5 days was shown to be effective in reducing the odds of inpatient mortality by two thirds (OR:0.32; 95% CI: 0.11–0.93) in patients hospitalised with PCR-confirmed seasonal influenza A(H3N2) virus strain infection in a routine NHS setting.

Rapid treatment with oseltamivir requires rapid diagnosis of seasonal influenza virus infections and this means hospitals must ensure routine use of influenza molecular assays with high sensitivity and specificity as recommended by NICE, CDC and IDSA.

Consideration should be given to revising current NICE and PHE guidelines for hospitalised patients diagnosed with seasonal influenza virus infection that oseltamivir should be started within 48 hours of onset of influenza symptoms, to align them with CDC and IDSA guidelines, which recommend that oseltamivir treatment for confirmed and suspected hospitalised influenza cases should be started on oseltamivir treatment 75 mg twice daily for 5 days regardless of the duration of influenza illness before hospitalisation.

As new antivirals for influenza viruses are developed, further studies will be required to determine their effectiveness in high-risk patients and inpatient settings.

**Conflict of interest**

None declared.

**Authors’ contributions**

Mark Reacher was responsible for the design of the study, coordinated and oversaw the conduct and statistical analysis of the study and wrote the paper.

Ben Warne contributed to the design of the study, data collection and contributed to the writing of the paper.

Lucy Reeve oversaw data collection, designed the study data base, oversaw data entry, data quality and data cleaning and contributed to the writing of the paper.

Neville Q. Verlander undertook the statistical analysis and reviewed the paper.

Nicholas Jones, Kyriaki Ranellou, Silvana Chirstou, Callum Wright and Saher Choudhry undertook the review of medical records and data abstraction and reviewed the paper.

Clare Sander supervised the review of medical records and data abstraction and reviewed the paper.

**References**

1. Iuliano AD, Roguski KM, Chang HH, Muscatello DJ, Palekar R, Tempia S, et al. Global Seasonal Influenza-associated Mortality Collaborator Network. Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. Lancet. 2018;391(10127):1285-1300. https://doi.org/10.1016/S0140-6736(17)33293-2 PMID: 29248255

2. Lee VJ, Ho ZJM, Goh EH, Campbell H, Cohen C, Cozza V, et al. WHO Working Group on Influenza Burden of Disease. Advances in measuring influenza burden of disease. Influenza Other Respir Viruses. 2018;12(2):3-9. https://doi.org/10.1111/irv.12533 PMID: 29460425

3. Thompson WW, Shay DK, Weintraub E, Brummer LR, Bridges CB, Cox NJ, et al. Influenza-associated hospitalizations in the United States. JAMA. 2004;292(11):1333-40. https://doi.org/10.1001/jama.292.11.1333 PMID: 15367555

4. Thompson WW, Shay DK, Weintraub E, Brummer LR, Cox N, Anderson LJ, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA. 2003;289(2):179-86. https://doi.org/10.1001/jama.289.2.179 PMID: 12517228

5. Chaves SS, Aragon D, Bennett N, Cooper T, D’Mello T, Farley M, et al. Patients hospitalized with laboratory-confirmed influenza during the 2010-2011 influenza season: exploring disease severity by virus type and subtype. J Infect Dis. 2013;208(8):1305-14. https://doi.org/10.1093/infdis/jit136 PMID: 23863950

6. van Asten L, van den Wijngaard C, van Pelt W, van de Kassteele J, Meijer A, van der Hoek W, et al. Mortality attributable to 9 common infections: significant effect of influenza A, respiratory syncytial virus, influenza B, norovirus, and parainfluenza in elderly persons. J Infect Dis. 2012;206(5):828-39. https://doi.org/10.1093/infdis/jis415 PMID: 22723641

7. Wu P, Goldstein E, Ho LM, Yang L, Nishiura H, Wu J, et al. Excess mortality associated with influenza A and B virus in Hong Kong, 1998-2009. J Infect Dis. 2012;206(12):1862-71. https://doi.org/10.1093/infdis/jis566 PMID: 23045625

8. McGeer A, Green KA, Plevenesi A, Shigayeva A, Siddiqui N, Raboud J, et al. Toronto Invasive Bacterial Diseases Network. Antiviral therapy and outcomes of influenza requiring hospitalization in Ontario, Canada. Clin Infect Dis. 2007;45(12):1568-75. https://doi.org/10.1086/523584 PMID: 18190317

9. Frieden TR. Evidence for Health Decision Making - Beyond Randomized, Controlled Trials. N Engl J Med.
20. Center for Disease Control and Prevention (CDC). Influenza Vaccine Effectiveness, 2004-2018. Atlanta: CDC, 2018. Available from: https://www.cdc.gov/flu/professionals/vaccination/effectiveness-studies.htm.

21. Hernán MA, Lipsitch M. Oseltamivir and risk of lower respiratory tract complications in primary care and hospital levels in Europe. Euro Surveill. 2017;22(7):30464, https://doi.org/10.2807/1560-7917.ES.2017.22.7.30464, PMID: 28230524.

22. World Health Organisation (WHO). WHO Guidelines for Pharmacological Management of Pandemic Influenza A(H1N1) 2009 and other Influenza Viruses Revised February 2010. Geneva: WHO; 2009.

23. Centers for Disease Control and Prevention (CDC). Seasonal Influenza Vaccine Effectiveness, 2004-2018. Atlanta: CDC. 2018. Available from: https://www.cdc.gov/flu/professionals/vaccination/effectiveness-studies.htm.

24. Dobson J, Whitley RJ, Pocock S, Monto AS. Oseltamivir and risk of lower respiratory tract complications in primary care and hospital levels in Europe. Euro Surveill. 2017;22(7):30464, https://doi.org/10.2807/1560-7917.ES.2017.22.7.30464, PMID: 28230524.

25. Kissling E, Rondy MI-MOVE/-i-MOVE+ study team. Early 2016/17 vaccine effectiveness estimates against influenza A(H3N2): -i-MOVE multicentre case-control studies at primary care and hospital levels in Europe. Euro Surveill. 2017;22(7):30464, https://doi.org/10.2807/1560-7917.ES.2017.22.7.30464, PMID: 28230524.

26. UK Government. The Data protection Act 2018.

27. Clark TW, Medina MJ, Batham S, Curran MD, Parmar S, Nicholson KG. C-reactive protein level and microbial aetiology in patients hospitalised with acute exacerbation of COPD. Eur Respir J. 2015;45(7):76-86, https://doi.org/10.1183/09031936.00022114, PMID: 25186260.

28. Charlsön ME, Pompei P, Ales KL, Mackenzie CR. A new method of classifying pharmacological comorbidities: a meta-analysis of longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83, https://doi.org/10.1016/0021-9681(87)90171-8, PMID: 3558716.

29. British National Formulary (BNF). Free online access to the UK BNF (British National Formulary) can be published by NICE. Oseltamivir Directions for Administration. [Accessed 29 Oct 2019]. Available from: https://bnf.nice.org.uk/drug/oseltamivir.html#DirectionsForAdministration.

30. Rothman KJ, Greenland S. Modern Epidemiology. 2nd. ed. Philadelphia: Lippincott, Williams and Wilkins; 1998. Chapter 4, Measures of effect and association 47-66; Chapter 5 Types of epidemiological study 67-78; Chapter 20 Introduction to Regression Models 359-358; Chapter 21 Introduction to Regression Modeling. p 401-343.

31. Kmietowicz Z. Critics attack chief medical officer’s advice to use antivirals for flu. BMJ. 2014;348(feb12 4):g1496. https://doi.org/10.1136/bmj.g1496, PMID: 24646608.

32. Myles PR, Semple MG, Lim WS, Openshaw PJ, Gadd EM, Read RC, et al. Influenza Clinical Information Network (FLU-CIN). Predictors of clinical outcome in a national hospitalised cohort across both waves of the influenza A/H1N1 pandemic 2009-2010 in the UK. Thorax. 2012;67(8):709-17, https://doi.org/10.1136/thoraxjnl-2011-200266, PMID: 22426790.

33. Zhang Z, Pereira SL, Luo M, Mathers CD. Evaluation of Blood Bacteria Associated with Risk of Malnutrition in Older Adults: A Systematic Review and Meta-Analysis. Nutrients. 2017;9(8):E829. https://doi.org/10.3390/nu9080829, PMID: 28771192.

34. Heneghan CJ, Onakpoya I, Jones MA, Doshi P, Del Mar CB, Hama R, et al. Neuraminidase inhibitors for influenza: a systematic review and meta-analysis of regulatory and mortality data. Health Technol Assess. 2016;20(2):1-242, https://doi.org/10.3310/hta20420, PMID: 27246259.

35. Heneghan CJ, Onakpoya I, Jones MA, Doshi P, Del Mar CB, Hama R, et al. Neuraminidase inhibitors for influenza: a systematic review and meta-analysis of regulatory and mortality data. Health Technol Assess. 2016;20(2):1-242, https://doi.org/10.3310/hta20420, PMID: 27246259.

36. Fiore AE, Fry A, Shay D, Gubareva L, Breese JS, Uyeki TM. Centers for Disease Control and Prevention (CDC). Antiviral medications: summary for clinicians: Treatment of influenza#content=view-index.

37. Heneghan CJ, Onakpoya I, Jones MA, Doshi P, Del Mar CB, Hama R, et al. Neuraminidase inhibitors for influenza: a systematic review and meta-analysis of regulatory and mortality data. Health Technol Assess. 2016;20(2):1-242, https://doi.org/10.3310/hta20420, PMID: 27246259.

38. Jefferson T, Jones M, Doshi P, Spencer EA, Onakpoya I, Heneghan CJ. Oseltamivir for influenza in adults and children: a systematic review of clinical study reports and summary of regulatory comments. BMJ. 2014;348(feb12 4):g1496. https://doi.org/10.1136/bmj.g1496, PMID: 24526786.

39. Prevention CDCa. “Have You Heard?” CDC recommendations for influenza antiviral medications remain unchanged. [Accessed 30 Jul 2019]. Available from: https://www.cdc.gov/media/haveyouheard/stories/Influenza_antiviral2.html.

40. Bhandari KL, Greenlaw SM. Modern Epidemiology. 2nd. ed. Philadelphia: Lippincott; 1998. Chapter 4, Measures of effect and association 47-66; Chapter 5 Types of epidemiological study 67-78; Chapter 20 Introduction to Regression Models 359-358; Chapter 21 Introduction to Regression Modeling. p 401-343.

41. J Antimicrob Chemother. 2017;72(1):2990-3007. https://doi.org/10.1093/jac/dkw321, PMID: 28961794.

42. Heneghan CJ, Onakpoya I, Jones MA, Doshi P, Del Mar CB, Hama R, et al. Neuraminidase inhibitors for influenza: a systematic review and meta-analysis of regulatory and mortality data. Health Technol Assess. 2016;20(2):1-242, https://doi.org/10.3310/hta20420, PMID: 27246259.

43. Heneghan CJ, Onakpoya I, Jones MA, Doshi P, Del Mar CB, Hama R, et al. Neuraminidase inhibitors for influenza: a systematic review and meta-analysis of regulatory and mortality data. Health Technol Assess. 2016;20(2):1-242, https://doi.org/10.3310/hta20420, PMID: 27246259.

44. BMJ. 2014;348(feb12 4):g2228. https://doi.org/10.1136/bmj.g2228, PMID: 24646608.

45. Heneghan CJ. Critics attack chief medical officer’s advice to use antivirals for flu. BMJ. 2014;348(feb12 4):g1496. https://doi.org/10.1136/bmj.g1496, PMID: 24526786.

46. Wolkekewitz M, Schumacher M. Statistical and methodological concerns about the beneficial effect of neuraminidase inhibitors on mortality. Lancet Respir Med. 2014;2(7):e8-9. https://doi.org/10.1016/j.jinf.2014.07.023, PMID: 25108123.
45. Hsu J, Santesso N, Mustafa R, Brozek J, Chen YL, Hopkins JP, et al. Antivirals for treatment of influenza: a systematic review and meta-analysis of observational studies. Ann Intern Med. 2012;156(7):512-24. https://doi.org/10.7326/0003-4819-156-7-201204300-00411 PMID: 22371849

46. Lee N, Chan PK, Hui DS, Rainer TH, Wong E, Choi KW, et al. Viral loads and duration of viral shedding in adult patients hospitalized with influenza. J Infect Dis. 2009;200(4):492-500. https://doi.org/10.1086/600383 PMID: 19591575

47. Leekha S, Zitterkopf NL, Espy MJ, Smith TF, Thompson RL, Sampathkumar P. Duration of influenza A virus shedding in hospitalized patients and implications for infection control. Infect Control Hosp Epidemiol. 2007;28(9):1071-6. https://doi.org/10.1086/520101 PMID: 17932829

48. Wolkewitz M, Schumacher M. Neuraminidase Inhibitors and Hospital Mortality in British Patients with H1N1 Influenza A: A Re-Analysis of Observational Data. PLoS One. 2016;11(9):e0160430. https://doi.org/10.1371/journal.pone.0160430 PMID: 27583403

49. Wolkewitz M, Schumacher M. Survival biases lead to flawed conclusions in observational treatment studies of influenza patients. J Clin Epidemiol. 2017;84:121-9. https://doi.org/10.1016/j.jclinepi.2017.01.008 PMID: 28188897

50. Lytras T, Mouratidou E, Andreopoulou A, Bonovas S, Tsiodras S. Effect of early oseltamivir treatment on mortality in critically ill patients with different types of influenza: a multi-season cohort study. Clin Infect Dis. 2019. https://doi.org/10.1093/cid/ciz101 PMID: 30753349

License, supplementary material and copyright

This is an open-access article distributed under the terms of the Creative Commons Attribution (CC BY 4.0) Licence. You may share and adapt the material, but must give appropriate credit to the source, provide a link to the licence and indicate if changes were made.

Any supplementary material referenced in the article can be found in the online version.

This article is copyright of the authors or their affiliated institutions, 2019.