The University Of Sheffield.

PRIEST

The PRIEST study: Pandemic Respiratory Infection Emergency System Triage

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The PRIEST study: Pandemic Respiratory Infection Emergency System Triage
Planned investigation:

Research objectives
We aim to optimise the triage of people using the emergency care system (111 and 999 calls, ambulance conveyance, or hospital emergency department) with suspected respiratory infections during a pandemic and identify the most accurate triage method for predicting severe illness among patients attending the emergency department with suspected respiratory infection.

Our specific objectives during the pandemic are:

1. To undertake continuous monitoring of the performance of the emergency care triage method (or methods) used for suspected respiratory infections during a pandemic
2. To identify clinical characteristics and routine tests associated with under-triage (false negative assessment) or over-triage (false positive assessment) during a pandemic
3. To determine the discriminant value of alternative triage methods for predicting severe illness in patients presenting with suspected respiratory infection during a pandemic
4. To inform policy makers and practitioners during a pandemic of the study's emerging findings.

Our specific objectives after the pandemic are:

1. To determine the discriminant value of emergency department triage methods for predicting severe illness in patients presenting with suspected pandemic respiratory infection
2. To determine the discriminant value of presenting clinical characteristics and routine tests for identifying severe illness
3. To determine the independent predictive value of presenting clinical characteristics and routine tests for severe illness
4. To develop new triage methods based upon presenting clinical characteristics alone or presenting clinical characteristics, electrocardiogram (ECG), chest X-ray and routine blood test results, depending upon the data available and the predictive value of variables evaluated in objective 3

Existing research
Prior to the 2009 H1N1 pandemic, the United Kingdom (UK) influenza pandemic contingency plan predicted around 750,000 excess emergency department attendances and 82,500 excess hospitalisations during a pandemic [1]. A 2011 consultation document suggested that a pandemic could result in 50% of population having some symptoms, of whom 30% would seek primary care and 1-4% would need hospital admission [2]. The Pandemic Influenza Advisory Committee Subgroup on Modelling have estimated a likely clinical attack rate of 3-35% (worst case scenario 50%), with 10-25% of these to have complications and a peak demand in the worst case scenario of 13% of the population being ill [3].

Pandemic planning needs to encompass a wide range of potential scenarios, but even projections at the less severe end of the spectrum could cause substantial problems of overcrowding at emergency departments that are already often working close to capacity. Methods of triage for patients presenting to the emergency department with suspected pandemic influenza and other respiratory infections are therefore required and need to be fair, robust and reproducible [4].

The term triage is often used to describe a brief initial assessment in the emergency department to determine patient order of priority in the queue to be seen. In this proposal we use the term triage more broadly to include the full process of emergency department assessment, potentially including investigations such as blood tests and X-rays, and apply it to decision-making regarding whether the patient should be admitted and whether they should be referred for high dependency or intensive care.

Emergency department triage methods need to accurately predict the individual patient's risk of death or severe illness. The predicted risk can then guide decision-making. Patients with a low risk may be discharged home, those with a high risk admitted to hospital, and those with a very high risk referred for high dependency or intensive care. Risk predictors need to recognise that thresholds for decision making may differ as a pandemic progresses and resource availability differs.

Health Protection Agency (HPA) guidance prior to the 2009 pandemic, supported by the British Thoracic Society and British Infection Society, recommended the use of the CURB-65 pneumonia score [5] for patients with suspected influenza-related pneumonia. This score uses five variables (confusion, urea level, respiratory rate, blood pressure and age) to generate a score between zero and five. Subsequent Department of Health guidelines on surge capacity in a pandemic also considered use of a physiological-social score (Pandemic Modified Early Warning Score (PMEWS)) [6]. This score uses physiological variables, age, social factors, chronic disease and performance status to generate a score between zero and seven. National guidance specific to the 2009 H1N1 pandemic included a swine flu hospital pathway for emergency department management with seven criteria, any one of which predicts increased risk and the need for hospital assessment [7].

We used the autumn/winter phase of the 2009 H1N1 pandemic in Sheffield and Manchester to evaluate the discriminant value of three potential systems for triage of pandemic respiratory infection patients in the emergency department: CURB-65, PMEWS and the swine flu hospital pathway [8,9]. However, the pandemic in these areas was less severe than predicted and only five patients of the cohort of 481 met our predefined criteria for critical illness. Within this cohort the discriminant value (c-statistic) of the three systems for predicting critical illness was moderate (CURB-65 0.78 (95% confidence interval (CI) 0.58 to 0.99), PMEWS 0.77 (0.55 to 0.99) and the swine flu hospital pathway 0.70 (0.45 to 0.96)). Their performance in predicting hospital admission was worse: CURB-65 0.65 (95% CI, 0.54 to 0.76), PMEWS 0.76 (0.66 to 0.86) and the swine flu hospital pathway 0.62 (0.51 to 0.72). These findings suggested that clinicians were not using the recommended triage methods when deciding whether to admit or discharge patients, and raised concerns about the accuracy of these methods for predicting adverse outcome.

Other research during the pandemic cast doubt on the utility of existing triage systems. The SwiFT study of patients admitted to critical care with H1N1 found 68% scored 0 or 1 using CURB-65 (i.e. recommended for hospital discharge)[10]. This is supported in evidence from a Canadian seasonal flu cohort, where no triage system performed well in predicting intensive care admission (c-statistics PMEWS 0.63 (0.57-0.69), CURB-65 0.58 (0.52-0.64)[11]. The best discriminator in this cohort was SMART-COP, a system specifically developed to predict intensive care admission in community-acquired pneumonia [12] which achieved a c-statistic of 0.73 (0.67-0.79) but has not to our knowledge been examined in a pandemic cohort. The SwiFT study [10] also developed a new score based on systolic blood pressure, temperature, heart rate, respiratory rate, neurological status and inspired oxygen concentration to predict adverse outcome. The SMART-COP and SwiFT scores therefore offer alternative triage methods that require validation in a pandemic. We are not aware of any other new scores to emerge since the 2009 pandemic.

In addition to our study and SwiFT, a number of cohort studies were undertaken during the 2009 H1N1 pandemic to identify risk factors for poor outcome in various groups (see appendix). The predominant predictors of adverse outcome were chronic co-morbidities and obesity [13-18] with conflicting evidence regarding the risk of pregnancy [10,15]. Acute physiological disturbances, particularly hypoxia, were also found to have prognostic value [10,14, 19-25]. Further studies [26-61] have confirmed these findings and identified a number of other predictors of adverse outcome, but no well validated and widely accepted prediction rules have been developed.

The existing research therefore suggests that, although there are a number of patient characteristics and clinical measures that can predict adverse outcome, the available data do not support the use of any specific triage methods in suspected pandemic respiratory infection.

We developed the PAINTED study (PAndemic INfluenza Triage in the Emergency Department) to evaluate emergency department triage methods during a pandemic, based on pre-pandemic pilot work and a protocol that would be placed in “hibernation” until a pandemic occurred. Pilot work showed that a standardised data collection form that doubled as a clinical record was acceptable to clinicians and could be used to collect research data in an influenza pandemic, but analysis may be limited by missing data [62].

There have been a number of developments since the PAINTED protocol was written that have created a need to update the protocol:

1. Awareness of the threat from other respiratory infections, such as COVID-19, has resulted in a need for the NIHR portfolio of pandemic influenza studies to be applicable to other respiratory infections.
2. Ambulance services are increasingly training and supporting paramedics to manage patients without transport to hospital and NHS111 has pathways that advise alternatives to emergency ambulance dispatch. This has created a need for triage methods to be applicable to prehospital use.
3. Electronic patient report forms, triage records and hospital records are increasingly used as alternatives to paper records.

The development of electronic records means that the original intention of the pandemic portfolio studies, to produce findings that would influence practice during the pandemic, is now more achievable. However, a detailed analysis using a locked data set to compare alternative triage methods and develop new methods would not be completed until it was too late to influence practice during a pandemic. Furthermore, although there are limited data to support current triage methods, emergency departments and ambulance services need to use a triage method to manage demand as soon as a pandemic develops. The objectives and analysis of the study therefore need to focus on using descriptive interim analysis to improve the triage method in use.

Research methods

We plan to undertake an observational cohort study using routine electronic data capture from people using the emergency care system (via 111 and 999 calls, ambulance conveyance, or hospital emergency department) with suspected respiratory infections during a pandemic.

Predictor variable data collection

Participating emergency departments will be provided with electronic and/or paper forms that can be integrated into the patient record and used to collect standardised triage assessment data. The form can be used at triage or at full patient assessment, and will form part of the clinical record. It can also be used by the emergency department to guide triage assessment. For example, the data recorded can be used to recommend diversion away from the hospital if criteria are not met or admission to hospital if criteria are met. The form will include key variables used in recommended triage methods, such as PMEWS and the swine flu hospital pathway, and other variables considered to be potentially useful predictors of adverse outcome. We will allow participating sites to adapt the form to their local circumstances, for example omitting variables that are already routinely collected.

The electronic and/or paper forms can also be used by paramedics in participating ambulance services. The electronic form will be used to collect data as part on the electronic case report form (eCRF) and can be used to support decisions, such as a decision not to transport the patient to hospital if triage criteria are not met. Alternatively, for 111 and 999 triage calls Ambulance services could provide the University of Sheffield with the routinely collected triage question of patients with suspected respiratory infection pandemic. Though this routine data would not match data collected from participating hospitals it would a) closer reflect the data ambulances are collecting with patients and b) lesson the work load placed on front line staff. We will work with participating Ambulance trusts to choose a data collection approach that best fits their capacity.

Participating emergency departments and ambulances could also provide regular data set of the study's predictor variables to the University of Sheffield. Sites business intelligence units or equivalent would be handle file transfers through a secure file transfer system, such as a FTP server.

Planned Interventions

The study will be observational and will not change patient care, other than introducing standardised data recording. Participating hospitals and ambulance trusts will use whatever triage method is determined to be most appropriate on the basis of national and local guidance. Decisions to transport the patient to hospital or admit the patient to hospital will be made on the basis of clinician discretion, drawing upon whatever guidance and triage methods are in place. We anticipate that a clinical pathway similar to the swine flu clinical pathway or PMEWS is likely to be in operation and guiding triage decisions at most hospitals and ambulance services. The participating sites will be free to adapt the standardised form to local needs, so that it is used for routine clinical care.

We will evaluate triage methods used to determine whether a patient suspected to be infected with pandemic respiratory infection should be admitted to hospital or not, and whether they should be admitted to intensive or high dependency care. These may include the CURB-65 score, PMEWS, the swine flu hospital pathway, SMART-COP, the SwiFT score and any new methods developed before the next pandemic. We will also develop two new triage methods based upon (a) presenting clinical characteristics alone and (b) presenting clinical characteristics, electrocardiogram (ECG), chest X-ray and routine blood test results.

The first score will only use variables available at initial patient assessment, i.e. history and examination, including simple technologies such as automated blood pressure measurement and pulse oximetry. This triage method can be used to assess patients for the need for hospital investigation and identify patients that can be discharged without further assessment. It could potentially be used, with appropriate validation, to assess patients in the community.

The second triage method will be based upon all available emergency department data, including routine blood tests, ECG and chest X-ray findings. This triage method can be used for two potential purposes: (1) Identification of patients with a low risk of adverse outcome who can be discharged home after emergency department assessment; and (2) Identification of high-risk patients who are likely to need high dependency or intensive care.

We will evaluate the ability of each method to predict whether patients die or require respiratory, cardiac or renal support. We will not evaluate the impact of triage methods upon patient care. Intervention in the study will therefore only consist of data collection and follow-up. Patient management will continue according to whatever Department of Health and Social Care guidance is in place at the time of the pandemic.

We will initially aim to develop triage methods that can be applied to the whole population of patients presenting to the emergency department. Age dependent variables will be assessed and included in the triage method in relation to age specific normal ranges. We will then explore whether different triage methods may be appropriate for different patients, particularly whether a different triage method may be appropriate for children.

Planned inclusion/exclusion criteria

We will include all adults and children with suspected respiratory infection during a pandemic who present at the emergency department of a participating hospital, call 111 or 999 services or are attended by a 999 ambulance from a participating ambulance trust.

Patients will be eligible for inclusion if they meet the current clinical diagnostic criteria of (1) fever (pyrexia ≥38°C) or a history of fever and (2) influenza-like illness (two or more of cough, sore throat, rhinorrhoea, limb or joint pain, headache, vomiting or diarrhoea) or severe and/or life-threatening illness suggestive of an infectious process; or if they meet any future clinical diagnostic criteria recommended by the Department of Health and Social Care. Inclusion will be determined on the basis of the assessing clinician recording on the patient record that the patient has suspected pandemic infection, which will result in standardised data being collected.

Proposed outcome measures

Patients who die or require respiratory, cardiovascular or renal support they will be defined as having an adverse outcome. If patients survive to 30 days without requiring respiratory, cardiovascular or renal support they will be defined as having no adverse outcome. If a severe pandemic leads to hospital resources being overwhelmed we will categorise patients as having an adverse outcome if they were deemed to have needed respiratory, cardiovascular or renal support but were denied this due to lack of resources.

Respiratory support is defined as any intervention to protect the patient's airway or assist their ventilation, including non-invasive ventilation or acute administration of continuous positive airway pressure. It does not include supplemental oxygen alone or nebulised bronchodilators. Cardiovascular support is defined as any intervention to maintain organ perfusion, such as inotropic drugs, or invasively monitor cardiovascular status, such as central venous pressure or pulmonary artery pressure monitoring, or arterial blood pressure monitoring. It does not include peripheral intravenous canulation and/or fluid administration. Renal support is defined as any intervention to assist renal function, such as haemoperfusion, haemodialysis or peritoneal dialysis. It does not include intravenous fluid administration.

We have selected an outcome measure that has a relatively clear definition and unequivocally indicates a case in which hospital admission and high dependency care would be desirable. The disadvantage of this definition is that it excludes patients who might benefit from other aspects of hospitalisation, such as nursing care, oxygen supplementation or intravenous fluids. However, oxygen and intravenous fluids are often administered to patients with little clinical need for these treatments, administration is often poorly recorded and administration may be based on the clinical variables being tested in this project rather than objective clinical need. Including these treatments in our definitions of respiratory or cardiovascular support would thus carry a substantial risk of over-estimating the prevalence of serious outcome and of over-estimating the association between predictor variables and outcome.

We will also not attempt to determine whether deaths were likely to be amenable to treatment and will thus not explore the issue of whether treatment would be futile. It is possible that a severe pandemic could result in a need to identify cases where treatment would be futile, but this is beyond the scope, and possibly incompatible with the aims, of this proposal`.

Follow up and data management

Follow up data can be captured either by local research staff conducting a search of patient records and inputting patient outcomes onto the study database or by sending data sets from sites' Business Intelligence Unit (or equivalent) directly to the University of Sheffield.

If local research staff are identifying patient outcomes, research nurses employed by each hospital (and funded by the Clinical Research Network, where possible) will identify patients with suspected respiratory infection for whom standardised data were collected. The research nurse will check the hospital computer system for deaths or hospital admissions. If death or hospital admission has occurred the research nurse will retrieve hospital notes to record details of any adverse events. Once complete the research nurse will enter anonymised data into a secure online database provided by the Sheffield Clinical Trials Research Unit (CTRU). The only patient identifiable information recorded onto the database and viewable by the research team will be NHS numbers and date of death, if applicable.

If data sets are to be sent to the University of Sheffield, site Business Intelligence Unit (or equivalent) at each participating hospital or ambulance service will undertake regular searches of electronic records during the pandemic to identify cases of suspected pandemic infection. Data from these cases will be sent to research nurses and paramedics at each trust, along with the University of Sheffield. The hospital Business Intelligence Unit will also keep a record of these attendances and undertake regular checks to identify any patients admitted to hospital up to 30 days after the initial attendance. They will send details of any admissions (date, length of stay, use of critical care, death) to the research nurse.

Personal identifiers from the patient cohort will be sent at regular intervals to NHS Digital, where record linkage will be used to (1) identify and exclude patients who do not wish their data to be used for research, (2) link ambulance and hospital attendances where both the hospital and ambulance service are participating in the study, (3) determine whether ambulance transport resulted in hospital admission, and (4) identify subsequent admissions to hospital up to 30 days after initial hospital or ambulance attendance. Details of hospital admissions (date, length of stay, use of critical care, death) will be sent to the relevant research nurse or paramedic.

Research nurses will review the hospital records of all admitted patients who has suspected pandemic respiratory infection (initial or subsequent attendance up to 30 days) to determine whether the criteria for adverse outcome are met. If the criteria are not met or if there is no record of hospital admission, then it will be assumed that there was no adverse outcome. The research nurse will also collect more detailed data from two specific patient groups:

1. The records of patients who were not admitted to hospital at initial attendance but had an adverse outcome (false negative triage decision) will be reviewed in detail to identify any potential predictors of adverse outcome that could have improved triage
2. The records of patients who were admitted to hospital at initial attendance but did not have an adverse outcome (false positive triage decision) will be reviewed to determine the reason for admission, and specifically which positive triage criteria could have prompted admission.

For all patients with an adverse outcome (admitted on initial attendance, or false negatives), site research staff at hospitals will retrospectively collect any missing data from the standardised assessment and additional non identifiable patient data that could have helped to predict adverse outcome, e.g. long-term conditions, ethnicity, lifestyle (smoking, alcohol, drug use), recent travel history, patient history, and medications. This additional information will allow for a greater understanding of which patients may require prioritisation during a pandemic. For false positives we will also collect the reason for patient admission. Additional data on false positives and all patents with an adverse outcomes will be recorded on the existing study database.

Once complete the research nurse will securely transfer data to the Sheffield Clinical Trials Research Unit (CTRU). Patient NHS number is being collected and sent to the University of Sheffield for linkage purposes with outcome data and to allow additional data enquiries at sites. The use of NHS number has been approved with section 251 approval.

In the case of Scottish sites involved in the study, their equivalent of the NHS number – the Community Health Index (CHI) number – will not be available to the research team. However, at the discretion of the sites involved, the local principal investigator may hold the link between the CHI and study number to enable such a cross-check.

Proposed sample size

The sample size will ultimately depend upon the size and severity of the pandemic. Our pragmatic data collection methods will ensure that we maximise any opportunity to evaluate emergency department triage methods in a pandemic.

Our experience in the 2009 pandemic has shown us that pre-pandemic estimates of case hospitalisation and case fatality rates can be very misleading and that sample size estimates must take into account considerable uncertainty in these estimates. Nevertheless, we have also shown that informative findings can be generated even in a pandemic with a very low rate of adverse outcome.

Given that most cases of suspected pandemic respiratory infection (even in a severe pandemic) do not result in an adverse outcome, the key variable in determining study power is the number of cases with an adverse outcome. A single cohort including at least 150 cases with adverse outcome would allow us to estimate the c-statistic of a triage method, clinical variable or test with a standard error of 0.03 (assuming the true c-statistic was 0.8). The table below shows the standard error resulting from samples with smaller numbers of adverse outcomes.

N with adverse outcome	Standard error (assuming c-statistic was 0.8)
150	0.033
125	0.036
100	0.040
75	0.046
50	0.056

A sample with N=150 adverse outcome would estimate the sensitivity of a dichotomised rule, variable or test with a standard error as outlined in the table below, depending on the sensitivity at the threshold used. Estimates of specificity would obviously be very precise given the anticipated low prevalence of adverse outcome.

Sensitivity	Lower limit of 95% CI
1.00	0.98
0.95	0.90
0.90	0.84
0.85	0.78
0.80	0.73

The same cohort could be used to identify independent predictors of outcome and develop new triage methods (objectives 3 and 4). The number of variables that could be tested as independent predictors of outcome in a multivariable model and for inclusion in a triage method would depend upon the sample size. Based on the rule of thumb of needing at least 10 events for each independent regression variable in a logistic regression, a cohort with 150 cases with adverse outcome would allow us to test up to 15 parameters [26].

These estimates assume that each triage method and predictor variable will be used and tested on the whole cohort. However, we plan to explore whether different patients require different triage methods, particularly whether a different triage method is required for children and adults. Data from the 2009 H1N1 pandemic suggest that around a quarter to a third of adverse outcomes may occur in children [14,33]. To increase the probability that we will have at least 50 cases with adverse outcome among children we will aim to recruit a total of 200 cases with adverse outcome rather than 150.

If we assume that the prevalence of adverse outcome is the same as our 2009 cohort (1%) then we would need to collect data from 20,000 cases to identify 200 with an adverse outcome. We have therefore used this estimate in planning, although it is likely to be a overestimate of the total numbers required given the mild nature of the 2009 pandemic. A more severe pandemic would allow more precise estimates to be made with no additional costs or would allow us to reduce the total number of cases required to identify 200 with an adverse outcome.

If we are able to develop a new triage method that appears to have superior discriminant value to existing methods then we would want to validate this method in a new cohort. A sample including 421 cases with adverse outcome would provide 80% power to compare an area under the ROC curve of 0.85 versus 0.90 at 5% significance, assuming a correlation of 0.6 between scores. We have not included validation of a new triage method in our objectives because this would require (a) successful development of a new method and (b) a much larger sample size, with associated costs and assumptions about pandemic severity. However, if the pandemic is severe (i.e. the prevalence of adverse outcome exceeds 3%, so the number with adverse outcome exceeds 450) we will split the cohort into two equal cohorts to allow testing of existing rules and derivation of new rules on one half and validation of new rules, with comparison to existing rules, on the other.

We plan to collect data across 40 hospitals and have based our sample size calculation on the assumption of receiving 500 completed forms, including an average of 5 adverse outcomes, per hospital over the course of the pandemic.

Statistical analysis

Analysis will be undertaken in two ways:

1. Weekly analysis of the emerging data, while data collection is ongoing
2. Full analysis at the end of the first wave of the pandemic (and after any subsequent wave, if appropriate), after data collection is complete or at another point as determined by the specific pandemic characteristics

Weekly analysis of the emerging data will involve descriptive presentation of:

1. The number and geographical distribution of new cases
2. The proportion with an adverse outcome and details of adverse outcomes
3. Potential predictor variables identified in patients who were not admitted at initial presentation but had an adverse outcome
4. Triage criteria identified in patients who were admitted to hospital and had no adverse outcome

These findings will be reviewed weekly by an expert group who will summarise emerging findings to, when appropriate, inform policy makers and practitioners during a pandemic/epidemic.

In all analyses only age will be treated as a continuous variable (with possible reparameterisation). All other continuous variables will be categorised on the basis of their use in existing risk scores or previous studies. This is because most continuous variables used in risk prediction have a non-linear association with adverse outcome, with increased risk at high and low values.

It is likely that a proportion of data for most predictor variables (especially blood results) will be missing. The most likely reason is that a measurement would not be made or test performed if it was expected to be normal. Missing data will therefore be handled in constructing scores and in multivariable analysis by assuming that all missing values are normal (i.e. score zero in the relevant risk score). A sensitivity analysis will be performed by imputing missing values and comparing results between the three scenarios of excluding cases with missing values, treating missing values as normal and using imputed values for missing values.

Existing triage methods will be assessed by calculating the area under the ROC curve (c-statistic) for discriminating between cases with and without an adverse outcome (defined as death or need for support of respiratory, cardiovascular or renal function) and sensitivity and specificity at key decision-making thresholds.

The discriminant value of each clinical variable or test for adverse outcome will be assessed by calculating the c-statistic and, for dichotomous variables, the sensitivity and specificity.

Independent predictors of outcome will be identified by entering all clinical variables with an association with outcome ($p<0.2$) into a multivariate logistic regression model.

New triage methods will be developed by combining the independent predictors of outcome into two new triage scores: one based on clinical variables measured at initial assessment only and the other based on all clinical variables (including blood tests and x-rays) measured in the emergency department. Integer weights will be assigned to each category of predictor variable according to the coefficient derived from a multivariate model using categorised independent predictors. This will generate a composite clinical score in which risk of positive outcome increases with the total score.

To determine whether different clinical scores are required for adults and children we will derive separate scores for adults (age >=16) and children. If any variables are included in one and not in the other we will compare c-statistics separately in each age group for models with and without the relevant variable. We will also test whether the weights attached to each variable differ sufficiently to affect prediction. The outcome may be that models with different predictors and/or different weights are required for adults and children.

If the pandemic is severe enough to allow the cohort to be split into derivation and validation cohorts with sufficient numbers of adverse outcome we will compare new triage methods developed during the project to existing triage methods by calculating c-statistics and sensitivity/specificity at key decision-making thresholds in the second cohort.

Activation of the full study

The project will be activated if and when a respiratory infection pandemic is declared by the UK's Department of Health and Social Care. We will update our literature review (as outlined above) and monitor reports from areas where the pandemic develops to identify any potentially new predictors of adverse outcome that may be unique to the emerging pandemic. If any potentially new predictors are identified we will cascade information to clinical staff and amend the paper and electronic forms to ensure that they are systematically recorded. We will undertake preparatory activities during the initial phase of a pandemic but will not promote the use of the standardised form until the infection has spread and large numbers of suspected cases are presenting to emergency care. The standardised form is designed to be used when large numbers of cases require rapid assessment, rather than in the early phase, when a relatively small number of cases may require detailed assessment.

Ethical arrangements

We have sought Research Ethics Committee (REC) approval prior to piloting and in advance of any pandemic. We have sought approval to activate the project in the event of a pandemic without a further REC review. Our previous similar project in the 2009 H1N1 pandemic was approved by the REC. The planned processes for informing patients of the project and managing data are very similar to those approved in our 2009 project. During the previous 2009 project patient identifiable information was taken to allow monitoring, data validation and GP contact. The National Information Governance Board (NIGB) gave section 251 approval to this use of identifiable patient data without consent. However the

NIGB was unable to give approval to the use of patient identifiable information in the pilot phase of this project. Since 2013, section 251 applications are reviewed by the Confidentiality Advisory Group (CAG) of the Health Research Authority.

Following revision of the protocol, we will submit a revised application to the CAG requesting section 251 approval for the following activities:

1. Staff employed by hospital and ambulances trusts who are not members of the direct care team to undertake processing of personal data, specifically pseudo-anonymisation before sending data to Sheffield CTRU. This is because it would not be possible during a pandemic for hospital and ambulance trusts to limit this activity to member of the direct care team.
2. Sharing of pseudo-anonymised data with the Sheffield CTRU (personal details removed but with a unique study identifier linking the CTRU record to the hospital or ambulance service record), on the basis that record linkage is essential to allow data queries between the CTRU and participating trusts.
3. Sharing of personal data between the participating trusts and NHS Digital, to allow identification of adverse outcomes and removal of records from patients who have requested exemption of their data for research purposes. Identifying adverse events is an essential outcome and due to the need to respect patient wishes regarding use of their data for research.

Risks and anticipated benefits for trial participants and society

The study will not alter patient management and will simply collect routinely available data at presentation and follow-up. No additional diagnostic tests will be performed. The risks to patients involved in the study are therefore very low and principally relate to data protection and confidentiality.

The standardised form is designed to support routine clinical care and will not increase the burden on health care professionals. Electronic data collection and management will be promoted to ensure that the study can be delivered even when the health services is under extreme pressure. We will seek approval from CAG to allow record linkage by NHS Digital using personal data and the use of a unique study identifier to allow data queries between the CTRU and participating trusts. Record linkage through NHS Digital will allow us to exclude people who do not want their routine data used for research.

Patients involved in the study will potentially benefit from the use of the standardised form. This will ensure that important variables are recorded and communicated between staff providing care. The standardised form can also be used to remind staff of current guidance for management.

Future patients with suspected pandemic respiratory infections and society in general will benefit from evaluation and development of accurate triage methods that have the potential to improve clinical decision-making and ensure that patients receive the right care and health service resources are optimally used.

Informing potential trial participants of possible benefits and known risks

Posters in all participating departments will be prominently displayed advising patients of the project and providing contact details for further information. Information leaflets will be provided for staff to hand to patients with suspected pandemic respiratory infection that briefly describe the nature and purpose of the study and provides contact details for further information.

Obtaining informed consent from participants

We will not seek patient consent to participate on the basis that the study is limited to collection of routinely available data and any delays in patient assessment would risk compromising patient care. The information leaflet outlined above will provide a tear-off slip with contact details that patients can use to inform the hospital or research team if they wish to withdraw from the study. Patients who wish to withdraw from the study will have their study records deleted. Their decision to withdraw will not be communicated to clinical staff providing further care and will not influence their subsequent management.

Proposed time period for retention of relevant study documentation

The original data collection form will constitute the clinical notes and be kept in each hospital according to normal practice. The anonymised database will be maintained by the Clinical Trials Unit until ten years after the end of the project.

Proposed action to comply with 'The Medicines for Human Use (Clinical Trials) Regulations 2004'.

Not applicable – this is not a clinical trial or a medicinal product of device.

Research Governance

Sheffield Teaching Hospitals NHS Foundation Trust will be the study sponsor and the project will be managed by the School of Health and Related Research (ScHARR) in the University of Sheffield. The Hospital Trust and University share a joint research office in Sheffield to facilitate management of collaborative projects such as this. The Project Management Group (PMG), consisting of the co-applicants and any appointed research staff, will manage the study. The PMG will meet prior, during and after the pilot phase. After that meetings will be held annually until a pandemic emerges and the project is activated. During the pandemic the PMG will meet at least monthly, either in person or by teleconference. The Sheffield CTRU will manage data entry, data management and provide data ready for analysis by the study statistician.

A Steering Committee has been formed to oversee study progress. This consists of an independent Chair (Professor Tim Coats) and at least three independent members (including a relevant clinician, statistician and public/patient representative), the Chief Investigator and the Project Manager.

Project timetable and milestones:

T0: Project activated
T0 to T0+3 months: Data collection from 20,000 cases, including 200 with an adverse outcome, across 40 hospitals (see sample size section for details)
T0+3 to T0+6 months: Analysis and reporting

Expertise:
The research team combines experts on emergency management of suspected pandemic influenza (KC, DW and AB) with expertise in paediatric emergency medicine (IM, CF), critical care (AB) and public health (AL), and the statistical expertise and research infrastructure of the Sheffield Clinical Trials Unit (SG, EL, KB).

The Team collaborated on a similar previous project during the 2009 H1N1 pandemic (HTA09/84/66). This project was completed and reported despite difficulties caused by research governance procedures and the unexpectedly mild course of the pandemic.

Steve Goodacre was Chief Investigator for HTA09/84/66 and is lead applicant for this proposal. He has undertaken many major national evaluations in emergency care, including development of clinical prediction methods. His current projects provide the necessary infrastructure to rapidly undertake the proposed research. Andrew Lee is a Senior Clinical University Teacher in Public Health who has a research interest in emergency planning and collaborated with SG, KC and DW on an NIHR Service Delivery and Organisation project involving scoping the emergency planning literature.

Kirsty Challen and Darren Walter are emergency physicians with research interests in pandemic influenza and emergency planning, and Andrew Bentley is an accredited critical care and respiratory physician. They have previously evaluated triage methods for pandemic influenza and are leading experts in this field. Ian Maconochie is a paediatric emergency physician who has evaluated paediatric early warning scores, the predictive value of clinical features in sick children and the management of febrile children.

Service Users:
Enid Hirst has agreed to be the patient/public representative for the project and has reviewed the proposal. She acted as patient and public representative for our project in the 2009 pandemic and was an independent member of the study Steering Committee.

Enid is a founder member of the Sheffield Emergency Care Forum. This is a patient and public representative group with a specific interest in emergency care research. The Forum has reviewed this proposal and provided feedback. Enid will continue to provide a link between the project and the Forum.

Enid previously spent eight years with Sheffield Community Health Council, was a lay member of the Steering Committee for NHS Direct Yorkshire and Humber, was a member of Unscheduled Care Network Board in Sheffield, spent three years with Sheffield Children's Hospital Patient Forum, and has attended Trust Board meetings at Sheffield Children's Hospital for many years as an observer for the Community Health Council and then the Patient Forum. She is now a member of Sheffield LINks (Local Involvement Network), a lay member of the Out of Hours Accreditation Group, is on the Dental Services Joint Planning Group for Sheffield, is a patient representative for the Group looking into Dentally Anxious Patients, and is a patient representative on the new Critical Care/Emergency Medicine Priority Group.

Her role will include the following:

1. Reviewing the protocol and specifically advising on ethical issues and arrangements for data protection and confidentiality
2. Reviewing the poster and information leaflet
3. Patient/public representation on the Steering Committee
4. Lay input into reporting and dissemination of findings
5. Liaison between the project and the Sheffield Emergency Care Forum

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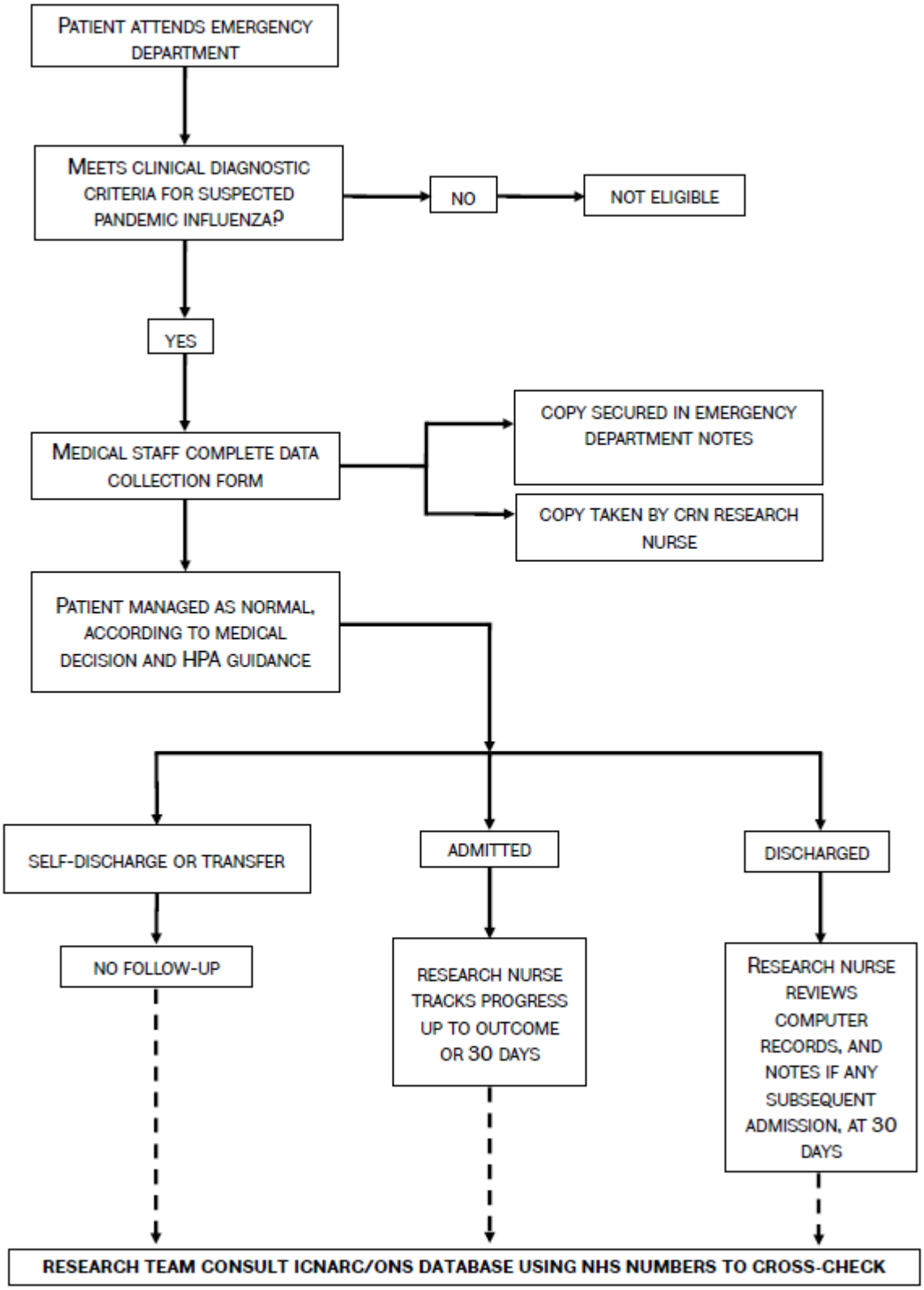
Flow diagram



Appendix: Studies evaluating clinical predictors of adverse outcome in pandemic influenza

Author	Site	Subjects	N	Outcome	Variable	Results
Rowan (ICNARC) [10]	UK	ICU suspected H1N1 (nb only 562 confirmed)	1725	Death	Current/recent pregnancy Severe chronic organ dysfunction Immunocompromise SOFA score (per point)	HR 0.13 (0.19-0.98) p=0.048 HR 1.53 (1.16-2.02) p=0.008 HR 1.65 (1.16-2.33) p=0.005 HR 1.05 (1.02-1.08) p=0.001
Miller [13]	Utah	ICU adm age>15 PCR confirmation H1N1	47	ICU admission	Hispanic Pacific/Hawaiian BMI 30-39 BMI >39	23% v 13% popn p=0.01 26% v 1% popn p<0.001 38% v 19% popn p<0.001 36% v 3% popn p<0.001
Nguyen-van-Tam (fluCIN) [14]	UK	Hospitalised confirmed H1N1	631	Death/ICU/ HDU	Chronic lung dis (not asthma/COPD)* Obesity* Altered consciousness CXR pneumonia* CRP >100* Sa02<94% on air	OR 3.41 (1.33-8.71) p=0.010 OR 6.96 (1.46-27.28) p=0.008 OR 1.11 (1.04-1.17) p=0.001 OR 5.28 (2.95-9.47) p=0.001 OR 4.41 (2.14-9.1) p=0.001 OR 3.6 (2.17-6.27) p=0.001
ANZIC [15]	Australia/ NZ	ICU confirmed H1N1	722	ICU admission	Pregnancy BMI >35 Chronic pulm disease Maori/Pacific islander	9.1% v 1% popn 28.6% v 5.3% popn 32.7% v 13% popn 25% v 13.6% popn
Harris [16]	Australia	H1N1 confirmed	181	Hosp admission	Aboriginal/Torres Strait Pregnant Diabetes Renal disease Cardiac disease Obese	37.7% v 60.3% p=0.004 29% v 8.1% p=0.013 24.6% v 4.2% p<0.001 18% v 3.3% p=0.001 26.2% v 8.3% p=0.001 28.3% v 10% p=0.002
Santaolalla [17]	Spain	Inpatients H1N1	3025	ICU/death	Asthma COPD BMI >40 Diabetes Other metabolic disease Cardiovascular disease Chronic hepatic disease Seizures Chronic renal insufficiency	14.5% v 22.7% p<0.001 11.5% v 16.9% p<0.001 19.3% v 11.1% p<0.001 13.8% v 9.4% p<0.001 11.5% v 8.8% p=0.001 16.1% v 9.6% p<0.001 9% v 6.1% p=0.025 6.5% v 3.4% p=0.001 7.3% v 4.1% p=0.003
Cui [18]	China	Inpatient H1N1	68	Death	BMI >27	8/10 death v 14/58 alive p=0.001
Zimmerman [19]	Tel Aviv	Adults, CDC definition, PCR confirmation	191	ICU admission	SaO2 Exam lung findings CRP	Median 92% v 97% p=0.006 71% v 31% p=0.002 Median 123 v 40 p<0.001
Martin-Loeches [20]	Spain	Adults, ICU admission for respiratory failure, no pre-existing CRF, microbiological confirmation	661	Acute kidney injury	Diabetes SOFA score MODS WCC CK CRP	16.2% v 9.2% p=0.04 Mean 8.7 v 4.8 p<0.001 92.4% v 54.7% p<0.001 8.3 v 6.8 p<0.001 290 v 170 p<0.001 28 v 20 p<0.001
Echevarria-Zuno [21]	Mexico	Confirmed H1N1	6945	Death	Chronic disease Tachypnoea Cyanosis Time onset-admission (days)	OR 6.1 (2.37-15.99) OR 4.26 (2.14-8.47) OR 3.46 (1.63-7.31) OR 1.19 (1.11-1.28)
Louie [22]	US	Age<18 hospitalised H1N1	345	Death/ICU	Hispanic (v white) Pulmonary disease Cardiac disease Neuro disease	OR 0.4 (0.2-0.8) OR 1.6 (1.0-2.6) OR 4.3 (1.9-9.5) OR 2.8 (1.6-5.0)

					GI disorder Acute altered mental status	OR 2.4 (1.3-4.5) 2% v 15% p<0.001
Stein [23]	Israel	Age<18 hospitalised H1N1	478	ICU admission	Neurologic disease Cardiovasc disease Metabolic disease Tachypnoea Hypoxia CXR effusion CXR diffuse infiltrate	19% v 7.6% p=0.02 14.3% v 5.7% p=0.03 9.5% v 1.6% p=0.01 61.9% v 34.9% p=0.001 57.1% v 21.8% p<0.001 9.5% v 2.1% p=0.005 33.3% v 8.1% p<0.001
Vasoo [24]	USA	ED presentations H1N1	83	Admission ICU	History of prematurity Haemoglobinopathy Chronic neurologic disease Malignancy Tachypnoea SaO2 <92 Acute renal failure CXR infiltrate Chronic pulmonary disease History of prematurity Chronic neurologic disease Tachypnoea SaO2 <92 Acute renal failure CXR infiltrate	18.8% v 0 p=0.002 12.5% v 0 p=0.02 OR 6.9 (1.3-35.5) 9.4% v 0 p=0.054 OR 4.7 (1.7-13) 31.3% v 0 p<0.0001 15.6% v 0 p=0.007 37.9% v 0 p=0.001 OR 4.5 (1.4-14.0) OR 30 (3.2-281.8) OR 4.1 (1-17.7) OR 5.4 (1.7-17.5) OR 84.9 (9.3-772) OR 22.0 (2.3-214.2) 68.9% v 37.9 (inpts) p<0.0001
Bagdure [25]	USA	Paediatric adm H1N1	307	PICU	Neurologic disorder Immunocompromise Seizures (acute) Mental status change Hypoxia Decreased breath sounds WCC <4 CRP >mg/dl pH<7.35	38% v 19% p=0.002 3% v 9% p=0.08 15% v 3% p<0.001 20% v 2% p<0.001 76% v 58% p=0.007 48% v 30% p=0.006 13% v 26% p=0.04 82% v 57% p=0.03 75% v 27% p=0.002
Fajardo-Dolci [27]	Mexico	First 100 H1N1 confirmed deaths	100	Death	Cardiovascular disease Metabolic syndrome Diabetes Respiratory disease Hypertension	20.9% v 4.1% popn 39.5% v 14.5% popn 19.8% v 7% popn 8.1% v 0.4% popn 19.8% v 15.4% popn
Lee [28]	Hong Kong	Adults seasonal flu A/B	754	Death	Oseltamivir Male Major co-morbidity	HR 0.27 (0.13-0.55) p<0.001 HR 3.92 (1.8-8.57) p=0.001 HR 2.27 (1.02-5.09) p=0.045
Libster [29]	Argentina	Age <18 confirmed H1N1 by PCR	251	ICU admission	Asthma	OR 4.92 (1.38-17.33) p=0.002
Chien [30]	Korea	H1N1 pneumonia	96	IPPV/NIV	Pregnancy Chronic renal insufficiency SOFA	2% v 9% p=0.05 14% v 1% p = 0.04 4 v 1 p=0.000
Jain [31]	US	Confirmed H1N1	272	ICU/death	Age Neurocognitive disease Neuromuscular disease CXR pneumonia Antivirals <48h	Median 19 v 29 5% v 13% 5% v 13% 28% v 73% 45% v 23%
Tuite [32]	Canada	Confirmed H1N1	3152	Death	Age >50	OR 28.6 (7.3-111.2)
Campbell [33]	Canada	Hospital admission H1N1	1479	Death/ICU	Heart disease Diabetes Immunosuppression	RR 2.1 (1.6-2.7) RR 2.2 (1.7-2.7) RR 1.5 (1.1-2.0)

Aviram [34]	Israel	ED H1N1 CXR in 24h	97	ICU/death	Bilateral opacities Multizonal opacities	60% v 15% p=0.049 60% v 6% p=0.01
Bassetti [35]	Italy	Inpatients confirmed H1N1	81	ICU/death	Neurocognitive disease COPD/asthma Pneumonia on admission	33.3% v 7% p=0.02 19.7% v 50% p=0.03 100% v 44% p=0.0008
Xi [36]	China	Adult inpatients H1N1	155	Inpatient death	Hypertension Dyspnoea at presentation	37% v 19.5% p=0.048 77.8% v 47.7% p=0.004
Pebody [37]	UK	UK national statistics (estimated case fatality rate)	440 deaths	Death	Chronic renal disease Heart disease Respiratory disease Liver disease Diabetes Immunosuppression Stroke/TIA Chronic neurological disease	RR 36.3 (20.9-63.2) RR 15.2 (9.6-24.1) RR 11.3 (7.9-16.1) RR 63.3 (38.6-103.7) RR 9.2 (5.6-14.9) RR 52.8 (36.3-76.6) RR 7.5 (2.3-23.7) RR 115.3 (84.3-157.6)
Wilking [38]	Germany	National statistics	226075	Death	Age 15-34 (ref 35-60) Age >60	OR 0.18 (0.13-0.26) OR 5.4 (3.86-7.56)
Martin-Loeches [39]	Spain	ICU adm, PCR confirmed H1N1 (also assessed 2010-11 post-pandemic)	648	Death	SOFA APACHE Age Comorbidity Heart failure Chronic renal disease Autoimmune disease Haematologic disease Respiratory coinfection	Mean 4.9 vs 8.4 p<0.001 Mean 12.53 vs 19.69 p<0.001 Mean 43.7 vs 48.4 p<0.001 69.6% vs 79.4% p=0.02 6% vs 11% p=0.03 4% vs 10% p=0.003 2.6% vs 5.7% p=0.06 3.7% vs 14.9% p<0.001 14.6% vs 23.4% p=0.01
Pereira [40]	Multiple (ESICM)	ICU adm	265	Death	SAPS III APACHE II	Mean 51 vs 60 p<0.001 Mean 25 vs 20 p<0.001
Delgado-Rodriguez [41]	Spain	Hospitalised	813	Death/ICU	Age 46-65 (ref <19) Age >65 (ref <19) Ex-smoker (note current smoker not sig) COPD DM Corticosteroids H2 blockers 2-3 comorbidities (ref 0) >3 comorbidities (ref 0)	OR 2.21 (1.09-4.71) OR 2.44 (1.03-5.83) OR 1.97 (1.07-3.52) OR 2.02 (1-3.87) OR 2.25 (1.21-4.02) OR 3.05 (1.14-7.35) OR 2.08 (1.05-6.66) OR 2.21 (1.09-4.6) OR 2.98 (1.47-6.24)
Bramley [42]	US	ICU adm	108 (plus 46 childr en)	Death	Illness to adm <2 days Asthma CXR pneumonia Treatment <2 days Sepsis syndrome	10/37 deaths vs 51/115 p =0.06 4/11 death vs 33/117 p=0.05 32/35 death vs 69/107 p<0.001 2/28 death vs 34/97 p<0.01 21/30 death vs 15/100 p<0.01
Chen [43]	Taiwan	Paediatric adm	61	Death/ICU	BMI >25 SOB CRP >3 2ary bacterial infection Infiltration on CXR Pleural effusion on CXR	3/11 w outcome vs 0/37 p=0.008 8/14 w outcome vs 8/47 p=0.008 6/12 w outcome vs 5/46 p=0.008 4/14 w outcome vs 2/47 p=0.03 6/14 w outcome vs 33/42 p=0.03 3/14 w outcome vs 0/42 p=0.02
Chen [44]	Taiwan	ED presentations (note 2007-9 all flu)	146	Hospital adm	Underlying illness SOB Headache General ache CXR positive finding WCC	89% adm vs 69% 13% adm vs 6% 0 adm vs 5% 2% adm vs 8% 29% adm vs 15%

					Neutrophil Hb	High 9% adm vs 6%, low 25 vs 19 High 25% adm vs 12%, low 11 v 9 Low 29% adm vs 20%
Kok [45]	Australia	ICU adm	173	Death (hospital)	Obesity	6% in obese vs 20% nonobese Note: nonsignificant when corrected for severity of illness
Estella [46]	Spain	Hosp adm with viral pneumonia	24	ICU adm	SaO2	96.6+/-2 ward vs 87.7 +/-5 ICU
Garnacho-Montero [47]	Spain	ICU adm H1N1	1120	Death	Age>65	32% mortality vs 22%
	Spain	ICU adm H1N1 age>65 (subgroup of above)	129	Death	Haematologic disease Immunosuppression >48h before oseltamivir	OR 5.1 (1.7-14.7) OR 3.7 (1.5-8.7) OR 2.7 (0.9-7.6)
Esterman [48]	Australia	Adm <6 months	28	Admission	Smoker in household NICU/SCBU Preterm birth Median household size	36% vs 20% population 25% vs 14.4% population 14% vs 8.2% population 5 vs 2.5 population
Dalziel [49]	Internatio nal (PERN)	Children adm	265 + 265 age-match ed	Severe outcome	Asthma Chronic lung disease Heart disease Renal disease Cerebral palsy Preterm birth Dyspnoea Increase/purulent sputum Seizures (acute) Irritable/drowsy Wheeze (complaint) Resp rate Heart rate SaO2 <93/supplemental O2 Chest retraction Accessory muscle use Creps Wheeze o/e Prolonged CRT Altered mental status Signs of dehydration Abnormal CXR	All OR: 2.7 (1.7-4.2) 9.8 (4.2-22.8) 6.0 (2.3-15.5) 8.0 (1.0-64.0) 34.5 (8.5-141) 4.1 (2.0-8.5) 9.9 (5.7-17.1) 11.0 (3.4-35.9) 5.6 (2.2-14.5) 2.9 (1.7-5.1) 7.0 (3.5-14.10) 0.15 (0.046-0.26) -0.19 (-0.3—0.086) 39.7 (12.6-125) 18.5 (9-38) 25.2 (10.7-59.7) 7.8 (4.1-14.8) 8.1 (4.6-14.4) 16.7 (5.2-53.4) 76.3 (10.3-564) 12.3 (4.5-33.6) 6.2 (3.1-12.5)
Capelastegui [50]	Spain	Hospitalised >18y	618	Severe complicatio n (death, IPPV, septic shock, ARDS, “resuscitati on maneuvers”	Age Male Smoker Number comorbidities Multilobar/bilateral Pneumonia Confusion Fever Dyspnoea Score: 1 pt for age>45, male, >2 comorbidities, pneumonia; 2 pt for confusion, dyspnoea	OR 2.6 (1.4-5) 46-65y, 2.8 (1.3-6) >65y OR 2.2 (1.3-3.8) 2.1 (1.1-3.9) yes, 2.2 (1.1-4.4) ex 2.9 (1.4-5.8) >2 (ref 0) 2.5 (1-5.9) 1.8 (1-3) 3.9 (1.8-8.5) 0.4 (0.2-0.8) 4.7 (2-11) AUROC 0.74 (0.68-0.8)
Lopez-Delgado [51]	Spain	ICU with respiratory failure from H1N1	60	Hospital mortality	BMI >30 Dyslipidaemia Creatinine	37% survivors vs p 0.021 18% survivor vs 8% p 0.049 108.4+/-74 survivor vs 186.4+/220 p 0.043

					Hb Platelets* pH pCO2 (mmHg) Bacterial coinfection	13+/-2 survivor vs 11.4+/-3.2 p 0.033 214 +/-101 survivor vs 113+/-82 p 0.002* 7.4+/-0.7 survivor vs 7.28+/-0.15 p<0.001 41+/-21 survivor vs 58+/-24 p0.04 10.4% survivor vs 41.6% p 0.022 *Retained in multivariate
Greenbaum [52]	US	Hospitalised 18-65y with lab-confirmed flu (not all pandemic)	9092	Mortality or ICU admission	Heavy alcohol use Chronic lung disease Asthma Cardiovasc disease Chronic metabolic disease	RR 1.34 (1.04-1.74) RR 1.35 (1.23-1.48) RR 0.85 (0.77-0.93) RR 1.12 (1.02-1.24) RR 1.29 (1.19-1.4)
		Hospitalised >65y with lab-confirmed flu (not all pandemic)	6584		Heavy alcohol use Chronic lung disease Cardiovasc disease	RR 2.47 (1.69-3.6) RR 1.51 (1.36-1.68) RR 1.41 (1.26-1.57)
Delgado-Rodriguez [53]	Spain	Hospitalised with lab-confirmed flu	1520	Mortality or ICU admission	Respiratory failure Cardiovasc disease* Cancer* Systemic steroids pre-adm* Pneumonia at adm Number organ malfunction at adm (continuous)* Alcohol >80g/day	OR 2.14 (1.12-4.08) OR 3.10 (1.89-5.09)* OR 2.61 (1.61-4.24)* OR 4.69 (2.46-8.95)* OR 1.98 (1.332-9.5) OR 3.31 (2.62-4.2)* OR 1.99 (1.09-3.64) *Retained in multivariate
Borse [54]	India	Adult ICU adm with lab-confirmed H1N1	100	Hospital mortality	No significant clinical or radiological predictors	
Mortensen [55]	California	Hospitalised/died with influenza A & asthma	170	ICU adm/death	Renal disease Infiltrates on CXR	OR 3.87 (1.08-13.87) OR 9.71 (3.93-23.99)
Semple [56]	UK	Hospitalised (FLU-CIN) >16y	1040	HDU/ICU/death	Severe resp distress Increased resp rate SaO2 <93% Resp exhaustion Severe dehydration/shock Altered consciousness Other clinical concern	OR 2.27 (1.63-3.16) OR 2.37 (1.69-3.31) OR 6.42 (4.49-9.18) OR 6.13 (2.64-14.2) OR 2.89 (2.01-4.16) OR 4.99 (2.82-8.81) OR 2.19 (1.39-4.36)
		Hospitalised (FLU-CIN) <16y	480		Severe resp distress SaO2 <93% Severe dehydration/shock Altered consciousness Other clinical concern	OR 3.16 (1.91-5.22) OR 4.95 (2.97-8.25) OR 11 (1.98-61.1) OR 6.44 (3.49-11.9) OR 2.38 (1.16-4.9)
Kusznierz [57]	Argentina	Hospitalised, lab-confirmed H1N1	242	Death	Obesity Diabetes Heart disease Hypertension Renal disease CXR consolidation Secondary bacterial inf ARDS Sepsis/shock Tamiflu <48h	4% survivors vs 40% p<0.001 6% survivors vs 19% p 0.002 6% survivors vs 19% p 0.02 16% survivors vs 38% p 0.03 4% survivors vs 11% p 0.04 75% survivors vs 38% p<0.001 0.6% survivors vs 7% p0.002 19% survivors vs 72% p <0.001 6% survivors vs 54% p<0.001 27% survivors vs 13% p0.012

Mertz [58]	Multiple	Meta-analysis (seasonal flu)	75871	Death	Obesity Cardiovascular disease Immunocompromise Endocrine disease	OR 30.10 (1.17-773.12) OR 1.97 (1.06-3.9) OR 3.81 (1.28-11.35) OR 13.92 (3.71-52.13)
				ICU admission	Chronic lung disease	OR 4.46 (1.34-14.79)
		Meta-analysis (pandemic flu)	534911	Death	<4/52 postpartum Obesity Chronic lung disease Cardiovasc disease Immunocompromise Malignancy Neuromusc disease Anaemia/haemoglobinopathy Diabetes Liver disease Metabolic disease Renal disease	OR 4.43 (1.24-15.81) OR 2.74 (1.56-4.8) OR 1.71 (1.17-2.51) OR 2.92 (1.76-4.82) OR 3.67 (1.78-7.58) OR 3.1 (2.35-4.1) OR 2.68 (1.91-3.75) OR 2.28 (1.35-3.84) OR 2.21 (1.37-3.57) OR 2 (1.32-3.04) OR 1.83 (1.19-2.79) OR 3.11 (1.54-6.28)
				ICU admission	Obesity Chronic lung disease Cardiovasc disease Neuromusc disease Diabetes Liver disease	OR 1.81 (1.48-2.22) OR 1.48 (1.19-1.83) OR 1.7 (1.39-2.08) OR 2.63 (1.83-3.79) OR 1.6 (1.32-1.94) OR 2.65 (1.44-4.88)
Morton [59]	UK	Adults admitted to hospital with PCR-confirmed H1N1 2010-11	101	Critical care admission	Simple Triage score PaO2/FiO2 ratio	AUROC 0.816 (0.72-0.9) AUROC 0.885 (0.81-0.96)
				Mechanical Ventilation	Simple Triage score PaO2/FiO2 ratio	AUROC 0.798 (0.7-0.89) AUROC 0.885 (0.82-0.95)
Garcia [60]	US	Children (<18) presenting to hospital with laboratory-confirmed H1N1 2009-10	695	Non-hospitalised vs hospitalised vs ICU	Dysnpoea Fatigue Fever Headache Myalgia Tachycardia Haematological disease Lung disease Prematurity Seizure disorder	7% vs 24% vs 55% p=0.006 8% vs 10% vs 16% p=0.004 96% vs 94% vs 84% p=0.001 26% vs 10% vs 9% p=0.003 22% vs 8% vs 5% p=0.001 5% vs 5% vs 13% p=0.006 4% vs 10% vs 8% p=0.009 2% vs 9% vs 15% p=0.001 3% vs 6% vs 16% p=0.001 1% vs 4% vs 12% p<0.001
Khandaker [61]	Australia	Children <15 admitted to hospital with laboratory-confirmed influenza	601 (506 with H1N1)	PICU admission	Neurologic disease Lung disease Bacterial coinfection	OR 2.3 (1.14-2.61) OR 3.58 (1.41-9.07) OR 6.89 (3.15-15.06)
				Mechanical ventilation	Lung disease Bacterial coinfection	OR 5.18 (1.8-14.86) OR 5.61 (2.2-14.28)