**Predictors of adverse outcomes in uncomplicated lower respiratory tract infections**

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**Declarations**

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The manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Contributorship

SS developed the protocol; provided day to day overall management of the study; coordinated recruitment, follow-up, and data entry; and commented on drafts of the paper. MM developed the protocol for funding and contributed to the management of the study, developing the detailed plan for analysis, and led the drafting of the paper and is the guarantor for the paper, PL had the original idea for the protocol, led the funding application, supervised the running of the study, contributed to the analysis, contributed to the drafting of the paper. DM had the original idea for the study, led the original development of the protocol for the funding application, led the further protocol development and ethics submission, provided overall supervision of the study, and contributed to the analysis and the drafting of the paper. MJT, with SS and DM, led the development of the protocol for ethical approval, supervised the study, and contributed to the analysis and drafting of the paper. KK and ML helped develop the protocol and contributed to developing the detailed plan for analysis, the analysis, and the drafting of the paper. AvdB helped develop the protocol and contributed to developing the detailed plan for analysis and contributed to the drafting of the paper. BS developed the analysis protocol and led the quantitative analysis,with MM DM and PL, and contributed to drafting the paper.

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

The authors declare that they have no competing interests

Consent for publication- not relevant

**Abstract**

**Purpose** Presentation with acute lower respiratory tract infection (LRTI) in primary care is common. The aim of this study was to help clinicians target antibiotic prescribing for patients presenting with LRTI in primary care by identifying those at risk of serious adverse outcomes (death, admission, late onset pneumonia).

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**Methods** In a prospective cohort study patients presenting with LRTI symptoms patient characteristics and clinical findings were recorded and adverse events identified over subsequent 30 days by chart review. Multivariable logistic regression analyses identified predictors of adverse outcome.

**Results** Participants were recruited from 522 UK practices in 2009-13. The analysis was restricted to the 28846 adult patients not referred immediately to hospital.

Serious adverse outcomes occurred in (325/28846; 1·1%). Eight factors were independently predictive; these characterised symptom severity (absence of coryza, fever, chills, chest pain and clinician assessed severity), patient vulnerability (age 65 years+, comorbidity) and physiological impact (oxygen saturation <95%, low blood pressure). In aggregate, the 8 features had moderate predictive value (AUROC 0·71, 95%CI 0·68, 0·74); the 4% of patients with >=5 features had an approximately 1 in 17 (5·7%) risk of serious adverse outcome, the 35% with 3 or 4 features had an intermediate risk (1 in 50, 2·0%), whilst the 61% with <=2 features had a low (1 in 200, 0·5%) risk.

**Conclusions** In routine practice the vast majority of patients presenting with LRTI in primary care can be identified as at intermediate or low risk of serious outcome and can be managed without immediate antibiotics.

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**Introduction**

Acute uncomplicated respiratory tract infections are one of the commonest acute illnesses managed in primary care and the majority are treated with antibiotics.[1-3] The Cochrane review of antibiotics for bronchitis reported only small symptomatic benefit from antibiotics [4]findings confirmed in the largest clinical trial to date.[5] Despite the limited effect on symptoms, patients and clinicians are concerned about more severe or prolonged illness and complications.[6] To aid decision making in the consultation, it would help primary care clinicians if they understood who was at greatest risk of future serious adverse outcome. Such adverse outcomes are uncommon and require large numbers of subjects to produce robust risk estimates. We report the findings from a large prospective cohort of patients presenting with acute lower respiratory infection (LRTI) in UK primary care who were followed up for 30 days by clinical record review. We have already reported the clinical features which aid diagnosis of pneumonia at first consultation.[7] This manuscript reports the clinical features which predict future serious adverse outcomes - death, future hospitalisation, and late-onset pneumonia (diagnosed more than 7 days after presentation).

**Objective:** To help clinicians reduce inappropriate antibiotic prescribing for patients presenting with lower respiratory tract infection (LRTI) in primary care by identifying those at risk of serious adverse outcomes (death, admission, late-onset pneumonia).

**Method**

**Key design features**

This was a prospective cohort more fully reported elsewhere[8]. Clinical presenting features and management strategies were documented using a structured clinical proforma at an index consultation. Review of medical records was performed to ascertain x-ray findings, subsequent re-consultations with new or worsening illness, and hospitalisation or death during the next 30 days.

**Participants**

A cohort of 28883 adult patients with acute cough attributed to LRTI was recruited from 522 practices in 2009-13; 28846 patients not immediately referred to hospital were eligible for this analysis.

*Inclusion criteria*: Patients had to be aged 16 or over and presenting with a new illness. We used a pragmatic definition of LRTI consistent with the Cochrane review of antibiotics for ‘bronchitis’[4]: acute cough (new or worsening cough for three weeks or less) presenting as the main symptom, and judged to be infective in origin by the physician.

*Exlusion criteria:* other cause of acute cough (e.g. heart failure, acid reflux, fibrosing alveolitis etc); participants unable to fill out the diary (e.g. severe mental illness, dementia or mental impairment); immune compromised; previously presented with the same episode of illness. These criteria are comparable to those applied in several previous LRTI trials and cohort studies. [5, 9-11]

**Patient involvement**

Working general practitioners were involved in the design of the clinical record form and in interpreting findings. Patients were involved in the programme grant application; advising about the patient information leaflets, consent forms, clinical record form, and outcomes; and participating regularly in study management meetings.

**Data collection**

*Clinical Record Form (CRF):* A clinical data collection form was completed at the point of recruitment by the physician - collecting data on age, smoking history, prior duration of symptoms, nature and severity of symptoms (dry cough, productive cough, shortness of breath, coryza, fever, chills/shivering, chest pain, headache, muscles aches, sleep disturbance, confusion, diarrhoea, sputum colour) examination (respiratory rate, pulse, blood pressure, oxygen saturation, temperature, presence of wheeze, crepitations or bronchial breathing), a rating of the overall severity of the illness (Visual Analogue Score (VAS) ranging from ‘well’ to ‘ very unwell’), and if antibiotics were prescribed. No training was provided to calibrate the severity scale which reflected the GPs overall assessment of the patient or ‘gut feeling’.

*Notes Review:* Data on x-ray findings were collected at notes review. All reports were considered by the authors and rated as definite pneumonia, probable pneumonia, possible pneumonia, unlikely pneumonia and not pneumonia based on the text in the report. Other diagnoses (i.e. TB and cancer) were also noted and differences were resolved by discussion to achieve consensus. Outcome data were abstracted by practice staff overseen either by local research network staff or research staff from the Oxford centre. Where a clinical diagnosis of pneumonia was recorded in the record without x-ray confirmation this was accepted as accurate and included in the outcome measure. No further corroboration was possible. The national deprivation index of the patient’s place of residence was derived from their postcode. Data submitted by practices on paper forms were double entered by the data management team in Oxford who also followed up data inconsistencies or missing data with individual practices. We have previously shown that clinical records can be assessed reliably using a very similar structured proforma.[12] Admissions unrelated to the index consultation (e.g. elective admissions) were recorded but excluded from the analysis

**Other data**. Cardio- or cerebro-vascular morbidities and lung co-morbidities noted in the medical records were also documented. Lung co-morbidity included acute and chronic obstructive airways disease (i.e. asthma, COPD) or history of other significant lung disease requiring hospital investigation, and the use of steroids or bronchodilators. Vaccination status (pneumovax) was also recorded.

**Sample size**

The overall recruitment target of 28000 patients was originally designed to achieve 80% power to identify predictive variables of adverse outcome following LRTI with an odds ratio of 3 (alpha =0·01) on the assumption of an antibiotic prescribing rate of 50% and an event rate of 0·005.

**Primary Outcome**

Participants were included as cases if there was evidence from the record of death or hospital admission/clinical diagnosis of pneumonia after day 1 (ie arising 2-30 days from presentation). Patients admitted on the day of the consultation were excluded from the analysis as we were interested in predicting subsequent admission or death. On the same basis, we excluded pneumonia diagnosed on the basis of a x-ray report (but without additional consultation) within the first seven days (assuming this diagnosis was based on x-ray investigations requested at the time of the index consultation). Diagnosis of pneumonia was based on a clinical record entry and/or an x-ray report.

**Statistical analysis**

***Prediction of imparted risk of adverse outcome***

The explanatory variables assessed were patient characteristics (age, gender, social deprivation and medical history), presenting symptoms, and clinical signs elicited by examination at the index consultation. Symptoms were included if reported as present, irrespective of their severity. Adjustment of crude relative risks for the effect of other variables was done using a generalised linear model for the binomial family with robust clustered variance estimators to allow for clustering of patients by doctor. Participants were included regardless of whether or not they were prescribed antibiotics and antibiotic prescription was included in the multivariate model.

**Statistical modelling of prognostic values**

The value of combining statistically predictive variables was assessed by including them in a statistical model, starting with the most predictive and then sequentially adding in the variables that most increased the area under the receiver-operator curve (AUC), with 1000 bootstrapped samples to avoid overfitting. Goodness of fit was assessed by the Hosmer-Lemeshow test. Oxygen saturation is regarded as normal within the range of 95-99% and so values were dichotomised at <95%. Temperature was dichotomised at > 37·8°C and tachycardia at >100bpm to be consistent with previous diagnostic models [13]. Age and blood pressure cut-offs were chosen to align with the CRB 65 score. [14]

**Sensitivity analyses**

Sensitivity analyses were carried out to assess the effect of varying four analytic parameters: 1) Definition of pneumonia (by excluding “possible” pneumonia; 2) By excluding cases of pneumonia recorded only in the GP clinical record and without x-ray confirmation 3) Severity of symptoms (by including symptoms only if reported as severe); 4) Imputation of missing values for O2 saturation (by assuming the extreme positions that all missing values were <95% or all were >95%). We did not impute missing data for every variable as levels of missing-ness were mostly low. [7]

**Results.**

**Frequency of serious adverse outcomes**

Of the cohort of 28,883 participants, 1782 had a chest x-ray within 30 days, 1062 between 8-30 days. Those referred for chest x-ray were older, more likely to be a smoker, more severe by global assessment and more likely to have positive physical signs than the whole cohort. The baseline characteristics of the cohort have been reported elsewhere and the baseline table is reproduced in Web Table 1.[7] Table 1 shows the x-ray results: 120 cases of pneumonia were included in the primary analysis on this basis (i.e. only cases assessed as ‘unlikely’ or ‘not’ pneumonia were excluded; pneumonia secondary to cancer or TB were included). An additional 34 non x-ray confirmed late-onset ‘pneumonia’ cases were also included in the analysis based on a clinical diagnoses recorded in the medical record, of these 12 were also confirmed by subsequent x-ray or admission.

**Table 1 here**

Thirty-seven of the 28,883 participants were hospitalized on the day of consultation. In the remaining 28,846, there were 221 hospitalisations and 30 deaths (some deaths occurring following admission). Twenty-five of the hospital admissions and 1 death were unrelated to the index consultation. Respiratory infections accounted for the greatest number of hospitalisations and deaths (respectively 132 and 7); there were 20 hospitalisations and 8 deaths from cardiovascular and cerebrovascular events, 20 hospitalisations and 4 deaths from other circulatory issues (dehydration, renal failure, ‘collapse’), 12 hospitalisations and 9 deaths from cancer, and 12 hospitalisations and 1 death from other infections. Late onset pneumonia was present in 34 with subsequent x-ray confirmation/admission in 12.

In summary, the frequency of one or more serious adverse events potentially related to the initial consultation for LRTI (and therefore included in the predictive analysis) was 1.1% (325/28846), with 29 deaths (0.1%), 120 cases of late onset pneumonia (including cancer/TB) (0.4%), and 196 hospital admissions occurring after the date of the index consultation (0.7%) (Table 2).

Table 2 here

**Predictors of severe adverse outcome**

Table 3 shows the prognostic value for severe adverse outcome, expressed as adjusted risk ratios, of the patient characteristics, presenting symptoms and clinical examination findings at the initial consultation for LRTI. There was evidence of clustering of the outcome at the GP level, with an ICC of 0.06 (95% confidence interval 0.03, 0.13) and therefore the adjusted model uses robust clustered variance estimates.

**Table 3 here**

**Developing a clinical prediction score**

Taking forward those variables that are statistically significant within each group and entering them into a multivariable regression model, starting with the most predictive, reveals 8 independent predictors of serious adverse outcome (at the 1% probability level). These independent predictors are: oxygen saturation <95%, age 65+, low blood pressure, fever, comorbidity, no coryza, severity score>5/10, and chest pain.

**Table 4 here**

A simple score based on the presence or absence of each of these 8 items where each is assigned a value of 1, based on 1000 bootstrapped samples, has an AUROC of 0·71 (0·68, 0·74). Table 5 shows how such a score is likely to be distributed in the population (percentages are based on the participants in the cohort with complete data on these 8 items). Using continuous variables for oxygen saturation, age, blood pressure, temperature and severity score the AUROC is 0·74 (95% CI 0·71, 0·77). Although using continuous variables would improve predictive values the confidence interval overlaps with the score using binary presence/absence variables which is easier to translate into clinical practice.

**Table 5 here**

**Sensitivity analyses**

Clinicians traditionally give more weight to lateralising (asymmetric) symptoms. Treating wheeze, crackles and bronchial breathing as categorical (none/unilateral/bilateral) does not add precision; although significant in the univariate analysis, they are not significant in the multivariate analysis and are not included in the final model. Excluding the “possible pneumonia” from the model reduced the number of pneumonia cases to 106 but did not change the predictive variables selected in the final model. Similarly, excluding all but severe symptoms from the analysis had little impact: chest pain was excluded from the final model but severe shortness of breath and severe chills were included. The AUROC for this model was also similar – 0·70 (95% CI 0·67, 0·73). Excluding cases of late onset pneumonia only recorded in the clinical record and without subsequent admission or x-ray did not change the variables selected for the model AUROC 0.71 (0.68, 0.74)

Imputing missing values for oxygen saturation had little impact on the assessed relative risk nor on the statistical model. Imputing these values using the extremes gives the same model regardless of the assumption. However, this does not improve the model’s discrimination. Assuming all missing oxygen saturation values were <95% gave an AUC of 0·69 (0·66, 0·72) and assuming all the missing values are >95% gave an AUC of 0·68 (0·66, 0·71). The Hosmer-Lemeshow test indicated that calibration is poor (p<0.001).

**Diagnostic performance of an 8-item score in clinical practice**

Table 6 shows the probable prognostic performance of the predictive variables in clinical practice. Using the score would enable the clinician to identify high, intermediate and low risk groups. Using a cut point of 5 or more would identify 4% of the population at 1 in 17 (5·7%) risk of serious adverse outcome; 35% would have a score of 3 or 4 with an intermediate risk of 1 in 50 (2.0%); 61% would have a score <2 with a low 1 in 200 (0·5%) risk.

**Table 6 here**

**Discussion**

**Principal findings**

Serious adverse outcomes (late onset pneumonia, admission, death) are uncommon following presentation with uncomplicated LRTI (1·1%, 325/28846) and in almost half the cases of hospital admission and death (44·4% of all cases, 76% of deaths) respiratory infection was not stated as the primary cause on the discharge summary and/or the death certificate. The likelihood of a serious adverse outcome depends on three factors: symptom severity (absence of coryza, fever, chills, chest pain and clinician assessed severity), patient vulnerability (age 65 years+, comorbidity), and physiological impact (oxygen saturation <95%, low blood pressure). These eight individual features can be used to predict adverse outcome by conversion to an 8-point score.

Although antibiotic prescribing was not identified as an independent risk factor and prospective cohorts do not clearly show that the prescribing of antibiotics reduces the risk of death or admission[8], observational data is potentially limited by uncontrolled confounding and it difficult to definitively say that antibiotics have no impact on risk of adverse outcome, particularly as there is a small benefit in preventing late onset pneumonia suggested from analysis of routine data sets.[15] The fact that the GRACE trial showed a halving of symptom duration in patients with LRTI who did not have frank pneumonia at presentation but had X ray evidence of consolidation also suggests that antibiotics can slow progression of respiratory infection, and potentially therefore onset of late-stage pneumonia.[16]

However, the reported causes of hospitalisation and death in this study highlight that disease progression to a serious outcome is not simply a case of worsening respiratory infection; cardiovascular morbidity is common and antibiotics may well not be the most important treatment to prevent progression. Moreover, antibiotic induced vomiting/diarrhoea may precipitate dehydration, another potential contributor to the non-respiratory admissions. It is unlikely that clinicians would want to withhold antibiotics for the 4% at higher risk (those with >5% risk of major adverse outcome). However, they are more likely to be willing to withhold antibiotics for the 60% at low risk (those with a 0.5% risk of major adverse outcome), whilst those with intermediate risk could potentially be offered a delayed antibiotic.[10]

The analysis does not take into account the risk of pneumonia diagnosed by x-ray without an additional consultation in the first 7 days- as these were assumed related to requests made at the index consultation – it predicts the risk of serious adverse outcome, including late-onset pneumonia, in patients who have a LRTI who were not admitted at the first presentation.

**Strengths and limitations**

The main strengths of the study are: 1) the power of the study due to the substantial size of the cohort of more than 28000 participants; 2) the completeness of follow-up using notes review was very high; 3) the study included patients from routine consultations and was designed for very easy recruitment - to create little or no selection bias and a large generalisable cohort; 4) those recruiting for the study represented a wide range of practices and doctors; 5) the diagnosis of chest infections used criteria similar to those used in the Cochrane review[4] and in other studies in primary care[5, 9-11]; 6) the clinical characteristics of included participants were similar to prior observational cohorts and trials in primary care[5, 9-11, 17].

An important limitation was the absence of prior training or standardisation of recorded history or clinical features (although again this adds to the generalisablility of our findings). There may be incomplete recording of consultation details in routine records although this is unlikely to pertain to details included in the primary outcomes of interest. Patients were also recruited at the busiest times of year and, as with other studies of acute infection,[18, 19] documentation of the details of those not approached was poor due to time pressures. The inclusion in the model of x-ray diagnosis of pneumonia only after seven days relates to the potential delayed reporting of routine x-rays in UK practice and may not apply in other settings. We have reported the clinical signs/symptoms associated with early diagnosis of pneumonia elsewhere[7], the focus of this model is on late complications/diagnosis/admission.

While including only symptoms rated as severe did result in a small change in the final model, it did not add precision and the added complexity of assessing severity rather than the presence or absence of symptoms would reduce clinical utility. Although approximately 20% of individuals had missing data for oxygen saturation the sensitivity analyses which imputed missing values for the model did not alter the inferences. A clinical diagnosis of pneumonia recorded in the record was accepted as accurate, there is evidence to support GP diagnosis of pneumonia being specific but lacking sensitivity[20]. A sensitivity analysis excluding those with a clinical diagnosis of pneumonia but without x-ray confirmation or admission did not alter the model items or performance. In the GRACE cohort (a cohort with comparable entry criteria but where x-rays were available in the majority) the finding of infiltrates on the CXR was present in 5%. It is likely that in this population where a small proportion received x-rays that there was under ascertainment of pneumonic infiltrates. We are restricted in this analysis to those with more severe outcomes (admission/death/ x-ray pneumonia/clinical pneumonia) which came to the attention of the attending physician.

**Comparison with the literature**

We are not aware of any comparable cohort studies powered to determine the frequency and predictors of longer-term adverse outcomes and even the largest randomised trials are underpowered in this respect. For instance in the largest randomised trial in LRTI to date there were only three admissions in the month following randomisation in the 2061 participants.[5] The most widely accepted decision rule for the diagnosis of pneumonia in those presenting with LRTI is that derived from the GRACE study[21, 22] which includes absence of runny nose and presence of breathlessness, crackles and diminished breath sounds on auscultation, tachycardia (>100·min–1) and fever (temperature ≥37.8°C); the decision rule for pneumonia derived from this cohort included Oxygen saturation, tachycardia, crackles and fever[7]. That the predictors of pneumonia differ somewhat from the predictors of longer term adverse is not surprising. Fever and absence of coryza are the shared items and point to a more severe index illness whilst some of the model factors for longer-term adverse outcome probably reflect to a greater extent the individual susceptibility to complications (age co-morbidity).

**Clinical implications**

This is the first study to provide robust estimates of the likely frequency and predictors of longer-term adverse outcomes following presentation with LRTI in primary care. As a minimum, our data show that the vast proportion of patients presenting with symptoms of lower respiratory infection in primary care are not going to suffer a serious adverse outcome.  And as serious adverse outcomes clearly depend not only on current symptoms but on patient vulnerability factors and physiological impact, which may well change over time, it is not surprising that it is impossible at initial presentation to predict outcome at 30 days with great accuracy.

Nevertheless, our findings are likely to be useful to clinicians and help them potentially target antibiotic use in patients with symptoms of LRTI but not pneumonia on examination. Individuals scoring <=2 using the 8 point score are at low risk (1 in 200) of adverse outcome. Whilst a score >=5) defines a group above about a 5% risk of serious adverse outcome.

Understanding the factors predicting a higher risk of adverse outcome could also potentially prompt clinicians to follow-up more closely individuals thus identified– not simply to identify development of late-onset pneumonia but to recognise and treat appropriately the other causes of admission/death that we have documented, and which may have been triggered by an initial respiratory illness.[23, 24] Whether such approaches will modify adverse outcomes is currently unknown.

**Conclusions**

Serious adverse outcomes (late onset pneumonia, admission, death) occur in only 1.1% of individuals following presentation with LRTI but may be predicted with moderate accuracy by assessment of symptom severity, patient vulnerability and physiological impact. Eight individual features can be used clinically by conversion to an 8-point score. It is already clear that patients derive little if any symptomatic benefit from antibiotics, the use of the score may give clinicians more confidence to target prescribing on the basis of predicted risk whilst highlighting a much smaller higher risk group who may benefit from closer monitoring.

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**Table 1 Attribution of diagnosis reported on x-rays for all reports and those 8-30 days.**

|  |  |  |
| --- | --- | --- |
|  | All X-rays | X-rays 8-30 days |
|  |  |  |
| Not pneumonia | 1539 (86.4%) | 938 (88.3%) |
| Unlikely pneumonia | 8 (0.5%) | 4 (0.4%) |
| Definitely pneumonia | 184 (10.3%) | 95 (9.0%) |
| Probable pneumonia | 28 (1.6%) | 12 (1.1%) |
| Possible pneumonia | 18 (1.0%) | 9 (0.9%) |
| Cancer | 4 (0.2%) | 3 (0.3%) |
| TB | 1 (0.1%) | 1 (0.1%) |

Table 2 Contribution of categories to total adverse event tally

|  |  |  |  |
| --- | --- | --- | --- |
|  | Total | Also contributed to this category | Total excluding duplicates.(Hierarchy death admission pneumonia) |
|  |  | x ray pneumonia>1w | Clinical (notes review) pneumonia | Admission after day 1 | Death |  |
| X ray pneumonia>1w | 120 | N/A | 5 | 22 | 0 | 93 |
| Clinical (notes review) pneumonia | 34 | 5 | N/A | 6 | 1 | 22 |
| Admission after day 1 | 196 | 22 | 6 | N/A | 14 | 182 |
| Death | 29 | 0 | 1 | 14 | N/A | 29 |
|  |  |  |  |  | Total  | 325 |

**Table 3. Risk factors at first consultation for severe adverse outcome (death or hospitalization from LRTI complications within 30 days or late-onset or pneumonia confirmed by x-ray or re-consultation 8-30 days after first consultation) (n=325)**

|  |  |
| --- | --- |
|  |  |
|  | **Proportion of patients suffering adverse outcome** | **Risk ratio** | **Adjusted risk ratio1** |
| *Characteristic +* | *Characteristic -* | *Ratio (95%CI)* | *p* | *Ratio (95%CI)* | *P* |
| *Patient characteristics* |
| **Age 65+ years** | 163/7921 (2·1%) | 162/20925 (0·8%) |  2·66 (2·14, 3·30)  | <0·001 | 2·15 (1·72, 2·67)  | <0·001 |
| **Male** | 157/11743 (1·3%) | 16/17098 (1·0%) | 1·36 (1·10, 1·70) | 0·005 | 1·20 (0·96, 1·50)  | 0·112 |
| **Influenza vaccine** | 152/9,842 (1.5%) | 173/19,004 (0.9%) | 170 (1.37, 2.11)  | <0.001 | 0.80 (0.61, 1.05)  | 0.110 |
| **Pneumovax <10y** | 95/5294 (1·8%) | 230/23552 (1·0%) | 1·84 (1·45, 2·33) | <0·001 | 1·01 (0;·79, 1·29)  | 0·939 |
| **Ever smoked** | 1997/15165 (1·3%) | 120/13212 (0·9%) | 1·43 (1·14, 1·79) | 0·002 | 1·25 (0·99, 1·57)  | 0·060 |
| **Any co-morbidity** | 210/13100 (1·6%) | 115/15746 (0·7%) | 2·19 (1·75, 2·75) | <0·001 | 1·57 (1·24, 1·99)  | <0·001 |
| **Lung co-morbidity** | 112/7461 (1·5%) | 213/21385 (1·0%) | 1·51 (1·20, 1·89) | <0·001 | 1·00 (0·75, 1·32)  | 0·976 |
| **Steroids/bronchodilators** | 93/6537 (1·4%) | 218/20997 (1·0%) | 1·37 (1·08, 1·75) | 0·010 | 0·87 (0·67, 1·12)  | 0·278 |
| **Living in deprived area4**  | 69/5750 (1·2%) | 256/23096 (1·1%) | 1·08 (0·83, 1·41) | 0·556 | 1·10 (0·81, 1·50)  | 0·530 |
| *Presenting symptoms* |
| **Shortness of breath** | 246/18498 (1·3%) | 77/10229 (0·8%) | 1·77 (1·37, 2·28) | <0·001 | 1·55 (1·18, 2·04)  | 0·002 |
| **Fever** | 126/10978 (1·2%) | 198/17800 (1·1%) | 1·03 (0·83, 1·29) | 0·782 | 1·01 (0·80, 1·29)  | 0·919 |
| **Chills** | 128/9146 (1·4%) | 195/19621 (1·0%) | 1·41 (1·13, 1·76) | 0·002 | 1·41 (1·11, 1·79)  | 0·005 |
| **Chest pain** | 146/10644 (1·4%) | 178/18130 (1·0%) | 1·40 (1·12, 1·74) | 0·003 | 1·31 (1·03, 1·67)  | 0·028 |
| **Confusion** | 25/1860 (1·3%) | 300/26968 (1·1%) | 1·21 (0·81, 1·81) | 0·360 | 1·11 (0·75, 1·65)  | 0·605 |
| **No coryza** | 184/13029 (1·4%) | 139/15718 (0·9%) | 1·60 (1·28, 1·99) | <0·001 | 1·60 (1·27, 2·02)  | <0·001 |
| **Headache** | 131/13254 (1·0%) | 193/15507 (1·2%) | 0·79 (0·64, 0·99) | 0·041 | 0·73 (0·57, 0·94)  | 0·014 |
| **Muscle aches** | 112/10497 (1·1%) | 211/18267(1·2%) | 0·92 (0·74, 1·16) | 0·495 | 0·82 (0·63, 1·07)  | 0·140 |
| **Diarrhoea** | 27/2508 (1·1%) | 298/26312 (1·1%) | 0·95 (0·64, 1·41) | 0·800 | 0·89 (0·60, 1·31)  | 0·557 |
| **Sputum: purulent** | 186/18221 (1·0%) | 139/10621 (1·3%) | 0·78 (0·63, 0·97) | 0·026 | 0·70 (0·57, 0·87)  | 0·001 |
| **Sputum bloody/rusty** | 16/1023(1·6%) | 309/27819 (1·1%) | 1·19 (0·92, 1·52) | 0·179 | 0·99 (0·76, 1·27)  | 0·917 |
| *Clinical examination findings* |
| **Severity assessment > 5/10** | 198/11893 (1·7%) | 126/16943 (0·7%) | 2·24 (1·79, 2·80) | <0·001 | 1·48 (1·13, 1·93)  | 0·004 |
| **Resp rate > 24/min** | 61/2885 (2·1%) | 263/25844 (1·0%) | 2·08 (1·58, 2·74) | <0·001 | 1·42 (1·07, 1·88)  | 0·016 |
| **Temp > 37·8°C** | 40/1,656 (2·4%) | 28/ 27,169 (1·1%) | 2·31 (1·67, 3·21)  | <0·001 | 1·82 (1·28, 2·58)  | 0·001 |
| **Pulse > 100/min** | 45/2801 (1·6%) | 280/26033 (1·1%) | 1·49 (1·09, 2·04) | 0·012 | 1·03 (0·75, 1·40)  | 0·858 |
| **O2sat < 95%** | 60/1698 (3·5%) | 205/22047 (0·9%) | 3·80 (2·86, 5·05) | <0·001 | 2·76 (2·08, 3·65)  | <0·001 |
| **SBP< 90 or DBP < 60 mmHg** | 39/2193 (1·8%) | 286/26653 (1·1%) | 1·66 (1·19, 2·31) | 0·003 | 1·72 (1·20, 2·46)  | 0·003 |
| **Crackles** | 1922/12256 (1·6%) | 133/16582 (0·8%) | 1·95 (1·57, 2·43) | <0·001 | 1·39 (1·01, 1·90)  | 0·044 |
| **Bronchial breathing** | 37/2166 (1·7%) | 288/26667 (1·1%) | 1·58 (1·13, 2·22) | 0·008 | 1·07 (0·71, 1·60)  | 0·758 |
| **Wheeze** | 107/7071 (1·5%) | 218/21765 (1·0%) | 1·51 (1·20, 1·90) | <0·001 | 0·89 (0·67, 1·18)  | 0·412 |

***Notes****: 1) adjusted by multivariate analysis for antibiotic prescribing, clustering, and other co-variates in same category (i.e. patient characteristics, presenting symptoms, or examinations findings respectively); 2) living in area of England with deprivation index in top 10%.*

**Table 4: Independent predictors of adverse outcome (p<0·01)**

|  |  |  |
| --- | --- | --- |
|  | Risk Ratio (95% CI) | p-value |
| O2sat < 95% | 2·30 (1·74, 3·04) | <0·001 |
| Age 65+ years | 2·13 (1·65, 2·75)  | <0·001 |
| SBP< 90 or DBP < 60 mmHg | 1·59 (1·13, 2·25) | 0·008 |
| Temp > 37·8°C | 1·81 (1·32, 2·47)  | <0·001 |
| Any co-morbidity\* | 1·55 (1·17, 2·05) | 0·002 |
| No coryza | 1·50 (1·17, 1·92)  | 0·001 |
| Severity assessment > 5/10 | 1·45 (1·11, 1·90)  | 0·007 |
| Chest pain | 1·43 (1·11, 1·86)  | 0·006 |

\*Any co-morbidity as defined in the notes review

**Table5 Distribution of the score in the presenting population**

|  |  |
| --- | --- |
| Score | N (%) of total cohort with each score |
| None | 1982 (8·4%) |
| 1 | 5529 (23·4%) |
| 2  |  6946 (29·4%) |
| 3  |  5482 (23·2%) |
| 4  | 2672 (11·3%) |
| 5  | 783 (3·3%) |
| 6 |  201 (0·9%) |
| 7 | 18 (0·1%) |
| 8 | 3 (0·01%) |

**Table 6 Sensitivity, specificity and predictive values for each score and for suggested cut points**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Cut off score to use | N (%) of total cohort | Sensitivity | Specificity | NPV | PPV | LR+ | LR- |
| 1 or more | 21634 (91·6%)  | 99·2% | 8·5% | 99·9% | 1·2% | 1·08 | 0·09 |
| 2 or more | 16105 (68·2%) | 91·6% | 32·1% | 99·7% | 1·5% | 1·35 | 0·26 |
| 3 or more | 9159 (38·8%)  | 69·8% | 61·6% | 99·5% | 2·0% | 1·82 | 0·49 |
| 4 or more | 3677(15·6%) | 39·3% | 84·7% | 99·2% | 2·8% | 2·57 | 0·72 |
| 5 or more | 1005 (4·3%) | 21·8% | 95·9% | 99·1% | 5·7% | 5·36 | 0·82 |
| 6 or more | 222 (0·9%)  | 8·4% | 99·1% | 99·0% | 9·9% | 9·81 | 0·92 |
| 7 or more | 21 (0·1%) | 1·9% | 99·9% | 98·9% | 23·8% | 27·86 | 0·98 |
| 8 or more | 3 (0·01%) | 0·8% | 100·0%  | 98·9% | 66·7% | 178·27 | 0·99 |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 2 or less | 14,457 (61·2%) | 30·2% | 38·4% | 98·0% | 0·5% | 0·49 | 1·82 |
| 3-4 | 8,154 (34·5%) | 69·8% | 61·6% | 99·5% | 2·0% | 1·82 | 0·49 |
| 5 or more | 1005 (4·3%) | 21·8% | 95·9% | 99·1% | 5·7% | 5·36 | 0·82 |