Decision support systems for the treatment of community-acquired pneumonia

Dr. Scott R. Clark BSc. Hons. MBBS

The University of Adelaide

Faculty of Health Sciences

Department of Medicine

Health Informatics Unit

Submitted January 2009

Table of Contents

List of Tables

List of Figures

Abstract

Delay to antibiotic treatment of community-acquired pneumonia (CAP) greater than 4 hours following hospital admission is associated with a 15% increase in mortality. Paper-based guidelines have been widely introduced to improve CAP care, but these interventions have under-performed due to poor compliance in complex clinical workflows. Unlike passive paper-based guidelines, alerting systems based on computer-based decision support systems (CDSS) have the capacity to actively draw attention to delayed clinical processes. Formal consideration of local workflow is key to the design and successful implementation of CDSS.

I used workflow analysis techniques to develop an evidence-based alerting system designed to reduce the delay to treatment of CAP in the emergency department (ED) of an Australian tertiary hospital. A sample of 6 CAP patients were observed during October 2001 to derive a structural process flow model, which was refined via stakeholder interview. A deterministic process flow model was then developed using an existing retrospectively compiled CAP database, consisting of 246 patients admitted June-December 1998 and 146 patients admitted May-December 2000. A stratified control sample presenting with respiratory symptoms (n=74, January-December 2003) was collected for the assessment of diagnosis and chest x-ray (CXR) accuracy.

Treatment delay greater than 4 hours was associated with failure to diagnose CAP in the ED, the absence of CXR evidence, low triage score, delayed CXR, and failure to treat in the ED. ED physicians only identified 54-57% of those discharged with CAP. Radiologists only reported CAP features in 47% - 67% of initial CXRs for these patients.

I hypothesised that a CDSS-based alerting system, composed of a CAP early diagnosis model (EDM) and a simple risk model (CRB-65), would identify enough CAP patients to reduce the percentage treated after 4 hours. I constructed an evidence-based naïve Bayesian EDM (sensitivity = 36%, specificity = 93%). It was able to identify 24% of CAP patients that died in hospital, 38% of those with antibiotics delayed greater than 4 hours, and 26% of those with CXR delayed greater than 4 hours. CAP-specific risk models were equivalent to the Australasian Triage Score (ATS) in predicting mortality.

I simulated alerting policy by combining the CDSS with the deterministic process flow model. Alerting for treatment at triage or initial physician assessment, when the EDM was positive, approximately halved the median treatment time of 5.53 hours, and decreased the number treated after 4 hours (62%) by 1/3. Treating EDM-positive patients as ATS category 2 produced a similar effect.

Current triage practices, embodied mainly by the disease-independent, sign and symptom based ATS are too coarse to deal with conditions such as CAP, where there is high diagnostic uncertainty and delays in diagnosis and treatment are critical determinants of outcomes. Better outcomes may be achieved with quicker diagnostic and treatment workflows via: analysis of current diagnosis and treatment workflows, analysis and correlation of a comprehensive set of patient symptoms, signs and risk factors for the specific disease, and improving triaging and subsequent workflow through a disease-specific CDSS based on early diagnostic models derived from the previous analyses.

Acknowledgements

To my supervisors

Dr Malcolm Pradhan, MBBS, PhD Health Informatics; Director of Health Informatics, Faculty of Health Sciences, The University of Adelaide; VP Research & Development Alcidion Corporation, *and*

Associate Professor Robert Adams MBBS, MD, Grad Cert Health Econ, FRACP; Senior Lecturer, Discipline of Medicine, The University of Adelaide; Health Informatics, The University of Adelaide; Respiratory Physician, The Queen Elizabeth Hospital; Chair, Metro Clinical Sub-committee, South Australian Safety & Quality Council

thanks for your continued insight, patience and support.

Dr Jeff Faunt MBBS, FRACP; Senior Consultant, Royal Adelaide Hospital; Head of the Royal Adelaide Hospital Quality and Safety Unit, *and* the **Royal Adelaide Hospital Community Acquired Pneumonia Working Group**, *and* the **Royal Adelaide Hospital Quality and Safety Unit**

for access to clinical data and pneumonia working group meetings, as well as consultation over workflow models.

Dr Michael Davey MBBS, FACEM; Assistant Medical Director, Emergency Department, Royal Adelaide Hospital; Clinical Lecturer in Emergency Medicine, The University of Adelaide, *and*

Dr Marie Kuhn ABIM, ABEM, FACEM (deceased) former Director of the Royal Adelaide Hospital Emergency Department

for access to the Royal Adelaide Hospital Emergency Department for observational studies, access to the Emergency Department clinical data system, and for review and discussion of workflow modelling.

Royal Adelaide Hospital Information Technology Department

for access to clinical information system data.

Royal Adelaide Hospital Medical Records Unit
for access to patient case notes.

Professor Gary Wittert, MBBS, FRACP, Head of The University of Adelaide School of Medicine *and* **The University of Adelaide Department of Medicine**
for ongoing support and access to office space.

Brita Pekarsky, BA Health Economics, Hons
for continued support, friendship and draft review.

Dr Michael Edmonds, MBBS, Hons Medical Science
for continued support and friendship.

Dr Matthew Sinnott, BSc, PhD Experimental Physics
for continued support and friendship.

Dr Jayde Llewelyn, MBBS, FRACGP
for extreme patience and proof-reading.

This work was supported by an Australian **NH & MRC Dora Lush Biomedical Scholarship** (ID219405).

Parts of this work were submitted as peer reviewed conference papers and presented at the Australian Health Informatics Conferences in 2000, 2003, 2005, and at the 3rd Australasian Conference on Safety and Quality in Health Care in 2005.

Declaration

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

I give consent to this copy of my thesis, when deposited in the University Library, being made available for loan and photocopying, subject to the provisions of the Copyright Act 1968.

SIGNED: _____ DATE:_____

Dr. Scott R. Clark

1 Review of community-acquired pneumonia diagnosis and treatment in adults

Community-acquired pneumonia (CAP) is a common respiratory infection with high variability in presentation, severity and outcome. There is also a high degree of uncertainty in diagnosis, risk assessment and selection of treatment. Management occurs across all sites in the health care system from primary care to the intensive care unit (ICU). CAP has significant morbidity and mortality that is more prominent with increasing age. Given its breadth and complexity, CAP treatment encapsulates many of the problems of the current health care system. Despite the proliferation of evidence-based CAP guidelines, there is high variability in treatment, patient outcomes and health system cost (see section 1.2). This poor quality of care occurs in the context of complex workflows and complex multifactorial decision-making. Attempts to improve care have largely consisted of the construction and implementation of paper-based guidelines. These interventions have largely under-performed due to poor compliance. A significant proportion of this non-compliance is likely to be associated with the problems of high uncertainty in diagnosis and risk assessment, and implementation into poorly defined complex workflows (see chapter 2).

A particular problem in the hospital management of CAP is timely antibiotic treatment. There is a growing body of research suggesting increased mortality when antibiotics are delayed longer than 4 hours following hospital admission (see chapter 3). Treatment within this period has been targeted as a key performance indicator of CAP care in the US (see chapter 3), and is a goal in many paper-based guidelines (see chapter 2). The majority of published interventions designed to improve antibiotic delivery in hospitals have focused on improving the human/social aspects of policy or guideline implementation or the fine tuning of radiology and antibiotic delivery processes (see chapter 3). These interventions do not address the significant uncertainty that exists in diagnosis and risk assessment (see section 1.4 and chapter 3) and its impact on

complex workflow (see section 1.5). Workflow in the emergency department (ED) is particularly sensitive to the process of triage, whereby patients are rated on a scale that defines the urgency of their need for treatment. Physicians then assess patients in an order determined by triage score, the most urgent cases are seen first. Cases with less urgency for treatment based on the triage scale will have a longer delay to initial assessment and therefore treatment (see section 1.5). Current triage practices, embodied mainly by the disease-independent, sign and symptom based Australasian Triage Score (ATS) (see section 1.5) are too coarse to deal with individual, difficult to diagnose, conditions such as CAP, where diagnostic and treatment delays are critical determinants of outcomes. Better outcomes may be achieved with quicker diagnostic and treatment workflows via:

a Analysis of current diagnosis and treatment workflows.

b Analysis and correlation of a comprehensive set of patient symptoms, signs and risk factors for the specific condition.

c Improving triaging and subsequent workflow through a process alerting system driven by a disease-specific, computer-based decision support system (CDSS) based on early diagnostic models (EDMs) derived from a) and b).

The development of these techniques is the major contribution of this thesis. These techniques have wide ranging clinical applications. Similar problems with the complexity of decision and workflow uncertainty are likely to exist in the treatment of other life threatening diseases with time critical treatment processes (e.g. percutaneous intervention for myocardial infarction without ECG changes [1]).

Computer-based decision support systems (CDSS) designed for use in health care have 4 main components: [2, 2a, 2b]

1 A clinical terminology and set of heath care concepts and their relations (ontology) that sets the limits of the application of the CDSS

2 A maintainable knowledge representation or data structure, based on the health care ontology that can access clinical data in a coded form

3 Links into the hospital IT systems and other clinical data systems that trigger events within the CDSS; events can be based on data or user request

4 A decision support engine that applies decision support algorithms against the knowledge base to derive clinically meaningful output (e.g. recommendations and alerts)

They have several advantages over paper-based guidelines (see chapter 2). A paper-based guideline is a static representation of a simplified clinical protocol that relies completely on staff awareness of both an applicable diagnosis and of the existence of the actual guideline itself at a number of critical points during the treatment of any given patient. In contrast CDSS can be designed to dynamically integrate available clinical data to assist in evidence-based decision making, and actively alert staff to new information or recommendations.

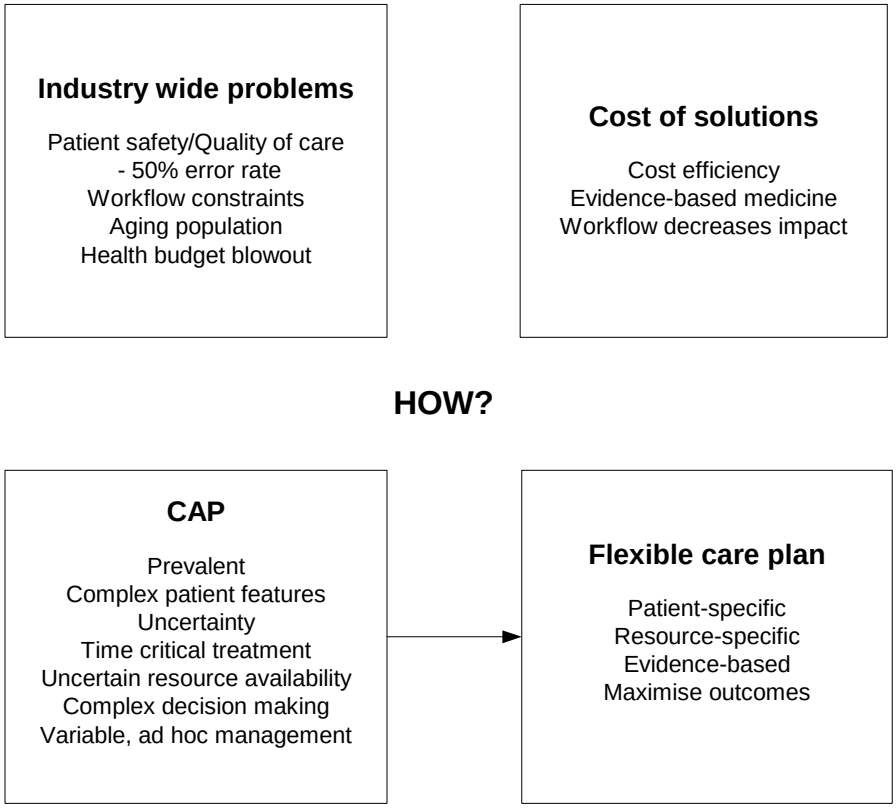

Figure 1.1: CAP management as a model for the role of a flexible care plan

One way to conceptualise the problem of delayed care is that there is loss in terms of time, resources and patient outcomes, due to a lack of a timely, specific and flexible care plan. Such plans should be sensitive to uncertainty and complexity in decision-making and process flow (see figure 1.1). Commonly, care plans are generated ad hoc, without formally addressing process and information flow or uncertainty in decision-making. Generic paper-based guidelines attempt to assist with uncertainty in decision-making, but lack sensitivity to local process flow and, due to the need for simplicity in presentation, are not highly patient-specific. This lack of flexibility adds to delays in time-critical processes. In diagnosis, for example, each investigation carries a cost or loss in terms of health dollars, delays to other time-critical processes, and a risk of adverse events. While monetary and health risk costs are commonly assessed in the development of guidelines, process delay in complex workflows is not. This process delay de-

creases the incremental value of obtaining each piece of additional information because of the losses that accrue with time. Where treatment delay from additional processes is significant, a lower pre-test probability may be considered adequate for treatment without further testing. I argue that CDSS can be designed to assist in the implementation of flexible care plans via the derivation of models and rules based on local workflow analysis and evidence-based diagnosis, risk assessment and treatment.

In this thesis I develop a method for describing overall workflow and building appropriate decision support interventions. To do so, I assessed the process flow and decision uncertainty components of workflow around the treatment of CAP patients. From this analysis I constructed a process flow model, a CAP early diagnostic model (EDM), and selected a CAP-specific risk model. The diagnostic and risk models were chosen to optimise the use of information from the clinical history and examination, the goal being the early identification of patients with high probability of CAP and high risk of mortality to promote early treatment. The incremental value of performing more investigations, thereby delaying treatment of these patients, is questionable. Finally, I combined these models in workflow simulation and determined the alerting policy best able to reduce time to antibiotic treatment.

In this chapter I introduce the nature and scope of problems in treating CAP, and review the uncertainty around decision-making and process flow. In Chapter 2 I discuss the relationship between health quality improvement, evidence-based medicine and decision support. I also examine the general factors contributing to non-compliance with both paper-based and computer-based decision support. I then summarise decision support interventions designed to improve CAP care. This includes large consensus statements produced by national clinical specialist bodies, paper-based guidelines derived for specific hospitals, and CAP specific CDSS. I then focus on the timing of initial antibiotic treatment in chapter 3. This includes a review of problems with recent antibiotic timing performance measures widely implemented in the US. I explore the relationship between antibiotic timing and negative outcomes in CAP and then review specific interventions designed to reduce the time to antibiotic treatment for CAP presenting to hospitals. In chapter 4 I review formal workflow and decision modelling and simulation methods. I also discuss important issues in CDSS implementation. Chapter 5 draws together these review chapters and discusses the rationale, study design and hypotheses for the thesis.

1.1 Community-acquired pneumonia (CAP): definition

Pneumonia may be defined as an acute infection of the pulmonary parenchyma accompanied by signs of lower respiratory tract infection such as fever or hypothermia, rigors, sweats, new productive or non-productive cough, chest pain, dyspnoea, fatigue and myalgia. Findings on physical examination include dullness to percussion over consolidation or effusion, as well as abnormal breath sounds such as crepitations and bronchial breathing above areas of consolidation. The disease is usually confirmed by the presence of acute infiltrate on chest x-ray (CXR) [3, 4]. CAP is differentiated from pneumonia acquired in hospitals (HAP), and that contracted by immunocompromised individuals, as these forms of pneumonia have distinct aetiological organisms, antibiotic sensitivity, severity and outcomes. HAP is defined as pneumonia with an onset of symptoms within 14 days of hospitalisation [3, 5]. In order to exclude patients with HAP from CAP studies, some authors only include subjects diagnosed with pneumonia within 48 hours of admission [6]. Immunocompromised patients include those with immune suppressing disease, such as HIV, and those with iatrogenic immune suppression, such as with treatment for malignancy, organ transplantation and autoimmune disease [7-9].

1.2 CAP incidence, treatment processes and outcomes

1.2.1 Incidence and hospital admission

CAP is a common cause of hospitalisation in adults, particularly in the elderly. The worldwide incidence of CAP ranges from 5-11/1000 adults per year. Rates increase from 6/1000 for those less than 60 years of age, to 20/1000 for those over 60, and 34/1000 for those over 75 [5]. In Australia, the incidence has been estimated at 2 /1000 adults per year [10]. The severity of CAP for many of these patients is low and many are treated safely at home. Hospital admission rates for patients diagnosed with CAP vary between 15-50% [5, 11]. In South Australia CAP accounts for 1.8% of all overnight hospital admissions [10].

1.2.2 Variability in outcomes

CAP treated in the community has a low risk of mortality at <1% - 5%, in comparison to 5-14% for those who are hospitalised [5, 11]. There is high variation between hospitals in the outcomes of CAP treatment, including mortality, length of stay in hospital (LOS), hospital costs, and readmission rates [12-28]. This variability has driven further investigation into risk factors for poor outcomes and poor quality care processes. Five to ten percent of hospitalised CAP patients are admitted to ICU where mortality rate ranges from 22-50% [5]. Minogue et. al. [29] found that mor-

tality in those readmitted following discharge from the emergency department was higher than those admitted to the ward (4.2% vs. 3%). Hospitalised CAP patients experience high rates of other significant complications such as pleural effusion (10.6%), respiratory failure (7.8%), empyema (5.2%), pulmonary cavitation (6.3%), pneumothorax (5.7%), nosocomial infection (5.5%), congestive heart failure (8.6%), shock (7.7%), and renal failure (10.4%) [18].

The effect of CAP on the community extends beyond time in hospital. Symptoms may persist up to 90 days beyond hospital stay resulting in personal and social costs of delayed return to normal activities [30, 31]. There are also significantly greater costs to large employers in terms of health plans, disability and absenteeism. For example, Birnbaum et. al. [32] found that health plan costs to major companies in the United States were increased 5 fold in comparison to other conditions.

1.2.3 Costs of CAP hospitalisation

No studies have directly assessed the costs of CAP treatment in Australian hospitals. In the United States the average cost of hospital treatment for CAP has been estimated at between $US 6000-7500, resulting in an overall annual inpatient cost of $US 7.4 billion [19, 33, 34] from around 1.1 million admissions. In comparison, the annual costs of CAP hospitalisation in the UK are approximately £384 million from an average 83153 cases, with an average cost of £4618. Given that treatment of CAP in the community costs only 2-5% of that in hospital [33, 35], there are considerable savings to be made in identifying low risk patients who have presented to the ED with CAP, that could be safely treated at home. Identifying these patients is a complex task, encompassing an assessment of the severity of CAP, the risk from other comorbidities, the patient's social situation and their functional status. It is not surprising that a significant proportion of those initially discharged from ED with a diagnosis of CAP return to hospital. Minogue et. al. [29] found that 7.5% were readmitted within 30 days and most (56%) of these readmissions were CAP-related. Patients who had failed treatment at home were older, had more comorbities and were more severe on initial assessment. Much effort has gone into developing models to identify CAP patients that may be safely discharged from the ED [36-39]. The most widely used model the Pneumonia Severity Index (PSI) has been implemented with varying success. Patients with low risk of CAP-related mortality are still commonly admitted for control of other comorbid illnesses or for social reasons. These factors are not encompassed by the PSI [36, 40-44].

Hospitalisation costs are directly related to the LOS. Most costs are incurred in the initial days of treatment, tapering off through the final few days of hospital stay. There are still significant savings to be made by safely reducing LOS by as little as 1 day (around $US 680 per patient) [34]. Earlier discharge also reduces the inherent risks associated with hospitalisation [45]. One of the key limiting factors in discharge is the requirement for intravenous (IV) antibiotics. Treatment is usually "switched" from IV to oral antibiotics as CAP resolves. Due to the practicalities and risks involved in establishing and maintaining IV access and dosing, this practice is generally carried out within the hospital. Consequently, two approaches have been developed to target safe early discharge: antibiotic switch and early discharge guidelines [46-50], and "Hospital in the Home" programs that promote IV antibiotic treatment outside of the hospital [51-53].

The method in which care is delivered has implications for treatment cost. For instance, antibiotic treatment for CAP varies widely between hospitals. Gilbert et. al. [14], in a large study of the treatment of CAP across a number of hospitals, found that median antibiotic costs ranged from $US 183.70 to $US 315.60 across sites with no significant variation in mortality (adjusted for demographic, comorbidity and severity variables). Hospital type (e.g. teaching versus non-teaching, urban versus rural) and the use of specialist services are associated with increased costs [28]. Processes of care also impact on LOS and health outcomes [54], and therefore on both costs and the overall quality of care.

1.2.4 Key processes in CAP care

Both processes and outcomes are used to measure quality in health care [55-57]. Key processes are a convenient surrogate measure of quality when outcomes are difficult to measure. These processes are identified via statistical association with treatment outcomes [58-60]. A recent multicentre survey of hospitals in the United States found that on average only 39% of all CAP patients receive high quality care as indicated by process measures [56].

Delay to the delivery of antibiotics (>4-8 hours from ED admission), the selection of antibiotic, and the performance of blood culture (>24 hours from ED admission), have all been related to increased 30 day mortality in CAP [22, 61, 62]. Meehan et. al. [22] found that those treated within 8 hours of presentation to the ED had an odds ratio of 0.85 for 30 day mortality. Houck et. al. [61] found a similar relationship for those treated within 4 hours, and calculated that treating within this time frame could save 1200 lives/year in the United States alone.

Inappropriate antibiotic selection, delay to antibiotic >4-8 hours, and failure to treat with antibiotics in the ED are associated with prolonged LOS [61, 63, 64]. Battleman et. al. [63] found that those with treatment delays beyond 8 hours had an odds ratio of 1.75 for long LOS (> 9 days).

These process indicators of quality of care in CAP have been adopted by major health insurance bodies in the United States, such as Medicare and Medicaid (CMS - Centres for Medicare and Medicaid Services), and the independent body for hospital accreditation, the Joint Commission on Accreditation of Health care Organizations (JCAHO). “Pay for performance” systems based on key indicators in CAP and other diseases are currently being implemented across the United States in both public and private health care. Under these systems hospitals are remunerated based on their ability to match standards of performance on key process indicators for the treatment of diseases such as CAP, congestive heart failure and myocardial infarction [65-68]. Table 1.1 shows the list of key CAP process indicators used by JCAHO and CMS to assess hospital performance.

Table 1.1: JCAHO/CMS key processes for quality of CAP care*

NOTE:
This table is included on page 26 of the print copy of the thesis held in the University of Adelaide Library.

* Reproduced from Landon et. al. [65]

Given the uncertainty in diagnosis, and the complexity of ED workflow, it is not surprising that there is high variability in the timing of antibiotic delivery. Within a single site one small study found a treatment range of 1.9 to 51 hours [69]. Two large studies looking at over 17000 patients combined found that significant numbers of patients may wait greater than 12 hours for antibiotics (the range spans 5.3-32.3% across sample sites) [22, 61]. Figure 1.2 shows that around 20% of over 4099 hospitals reviewed by JCAHO/CMS failed to treat greater than 30% of their CAP patients within 4 hours [70].

The goal of achieving antibiotic delivery to the majority of CAP patients within 4 hours of presentation to hospital has recently been acknowledged by JCAHO/CMS as being unrealistic.

These groups have relaxed the standard for quality antibiotic delivery to 6 hours and now exclude CAP patients whose diagnosis remains uncertain in the ED [66].

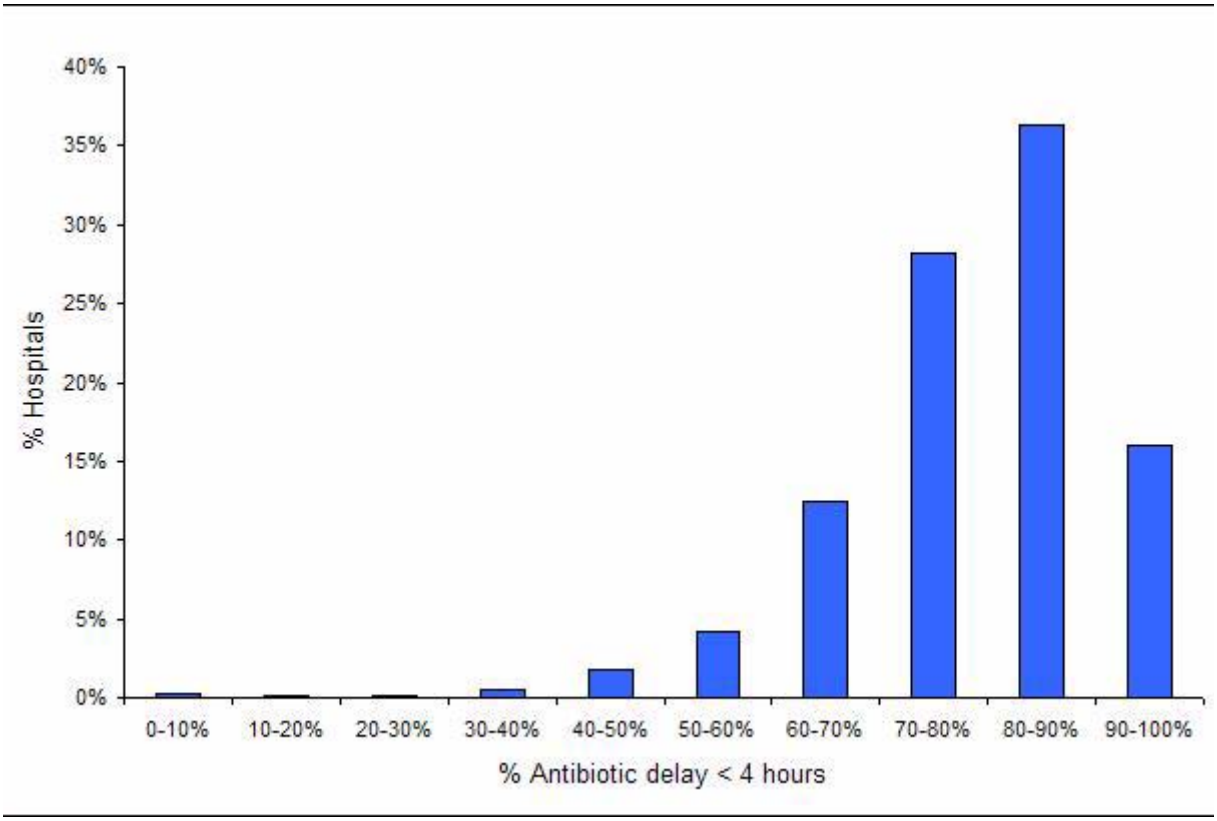

Figure 1.2: Percentage of US Hospitals assessed by JCAHO/CMS by percentage of CAP patients with antibiotic delay < 4 hours (July 2005- June 2006)*

* Calculated from the Hospital Compare Database available on the United States Department of Health and Human Services website [70]

The question of how to re-engineer hospital care to reduce delays to antibiotic treatment of CAP patients remains. Clinical practice is notoriously difficult to change, and efforts are costly both in terms of clinician time and in cost to the health system [71, 72]. One answer is simulation, a technique widely used in business and in the military to predict the feasibility and impact of changes to processes and policies prior to their implementation. The health care industry has been slow to adopt this technology, despite complex workflow and high risk of poor outcomes [73]. In this thesis I have combined decision theory and workflow assessment to generate practical solutions for the reduction of delay to CAP treatment. I plan to show via simulation that intelligent alerting systems are able to produce significant reductions in antibiotic delay by optimising the use of information available at key points in the diagnosis and risk assessment of CAP patients.

1.3 Understanding process performance: workflow

A broad definition of workflow subsumes both health care processes and all factors that impact on the performance of health care processes, including decision-making and information transfer [74]. This definition combines more traditional conceptions of workflow as simple flow from one process to the next with assessment of factors impacting on this flow, and the concept of decision uncertainty. Decision uncertainty refers to the probabilistic relationship between prior information, decisions and outcomes which can be represented using Bayesian mathematics [75].

A model that provides a convenient framework for understanding the factors that determine workflow has been developed by Pradhan et. al. (see figure 1.3) to describe the predictors of preventable harm in health care [74]. It combines a medical schema developed by Vincent et. al. with Reason's model of preventable error derived from studies of complex system failure [76, 77].

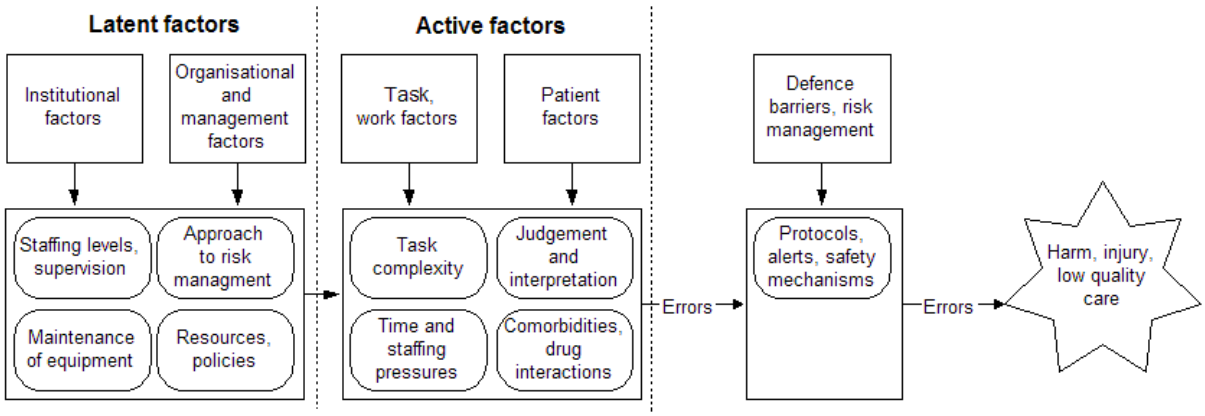

Figure 1.3: Causes of preventable harm/process performance*

* Modified from Pradhan et. al. [74]

I have simplified this model into basic elements impacting on process performance. Figure 1.4 shows this simple model which indicates that patient complexity, clinical policies, and resources at the point of care have an impact on process performance. This impact is mediated by local safety mechanisms, such as local guidelines, protocols and alerting or checking systems. Clinical policies will also indirectly affect process performance via determining the resources at the point of care. These categories provide a convenient classification for aspects of the clinical process re-engineering task. Patient complexity relates directly to the uncertainty of decision-making and can therefore be modelled using techniques from decision theory. Resource availability can be modelled using process flow techniques. Clinical policies may then be included

by the modelling of the impact of rules (e.g. the threshold probability to alert for CAP treatment).

In this thesis I will demonstrate how these models can be combined to create complex simulations of the impact of changes to health care processes or policy. For simplicity I will use the categories illustrated in figure 1.4 to organise information within the thesis document.

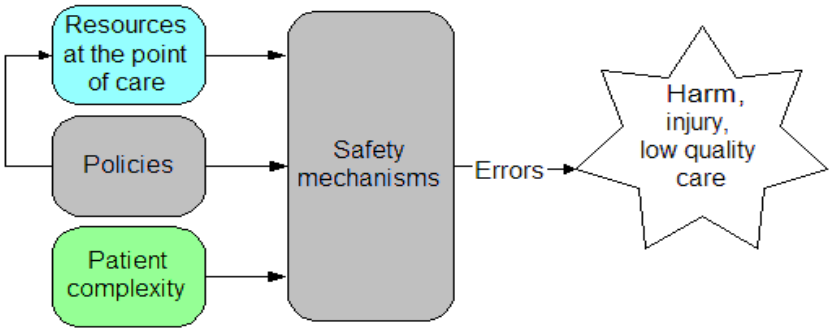

Figure 1.4: Simple model of predictors of process performance/error

The treatment of CAP is a complex series of decisions and processes that occur over a number of sites as shown in figure 1.5. The focus of this thesis is the initial delivery of antibiotics to CAP patients that present to hospital. The workflow that determines initial antibiotic delivery is most likely to occur in the ED and its interface to the wards or ICU. Assessment and simulation of the workflow around CAP patients at these sites will form the basis of my studies.

NOTE:
This figure is included on page 29 of the print copy of the thesis held in the University of Adelaide Library.

Figure 1.5: Overview of patient flow and decisions in CAP care by site*

* Modified from Nathwani et. al. [78]

1.4 Patient complexity

Decision-making for CAP patients is complex. CAP presentation is often non-specific, the severity and risk of CAP is highly variable, and the aetiology is often not identified. Figure 1.5 shows an overview of patient flow and decision-making in CAP treatment. The broad groups of major decisions involved in hospital care of CAP are:

1 Initial choice of history taking, examination and investigations in the ED/ward for diagnosis and risk assessment;
2 The need for supportive care (Oxygen, IV fluids, Mechanical Ventilation, Vasopressors);
3 Diagnosis;
4 Initial antibiotic selection;
5 Admission to ED/Ward/ICU based on severity and risk;
6 Further history, examination or investigation during the course of treatment;
7 Revision of antibiotic treatment (based on improvement, failure, or microbiological results).

Figure 1.6 shows the simple model of process performance, highlighting patient complexity. This section will deal with the uncertainty in the decisions of diagnosis, risk assessment and treatment selection for CAP patients.

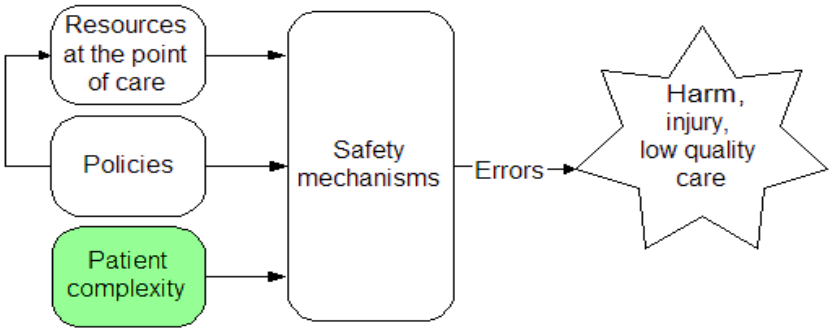

Figure 1.6: Simple model of predictors of process performance/error: patient complexity

1.4.1 The diagnostic problem

Diagnosis of CAP is difficult due to poor sensitivity, specificity, and inter-rater reliability of clinical signs and of the CXR. Once a diagnosis of CAP has been made, the poor sensitivity and delays to result return of microbial cultures and antibiotic sensitivity testing makes the selection of the correct treatment imprecise.

1.4.1.1 Presentation

The presentation of CAP is highly variable and there are no specific symptoms able to accurately predict the presence of pneumonia [4]. Findings on physical examination, such as altered breath sounds, crepitations and dullness to percussion over consolidation, have low sensitivity, specificity and inter-rater reliability [4, 79]. Symptoms may be modified by aetiology, comorbidity and age. Elderly patients are more likely to present with non-specific symptoms such as confusion, lethargy, falls, incontinence, and general deterioration, than with more specific symptoms such as fever, cough or pleuritic chest pain [5, 80, 81]. Other common forms of respiratory and cardiac disease, such as asthma, chronic obstructive airways disease (COAD) and left ventricular failure (LVF), also present with common CAP symptoms, such as shortness of breath, and altered breath sounds [5]. These conditions may be comorbid or be confused with a CAP diagnosis.

There is some evidence to suggest that differing aetiological agents produce different clinical presentations (see table 1.2), however, clinical signs are not reliable differentiators of aetiology [5]. Despite this lack of solid evidence, there is still a tendency to group CAP into atypical and typical presentations related to groups of infective organisms. Atypical pneumonias are attributed mainly to *Mycoplasma pneumoniae, Chlamydophila spp.* and *Legionella spp.* The atypical differentiation has some validity for treatment selection as these organisms are sensitive to macrolide, tetracycline and quinolone, but not to beta-lactam antibiotics [82]. Typical pneumonias consist of the remaining bacterial causes. Atypical pneumonias are generally perceived to present with milder symptoms, although they too may be fatal. There is commonly sore throat and a persistent dry cough without sputum production. The syndrome also includes an absence of leucoytosis and of consolidation on CXR. Blood and sputum cultures are usually negative. Extrapulmonary complications are more common including dermatitis, neurological complications, hepatitis, and renal disease [82].

1.4.1.2 Chest x-ray (CXR)

The gold standard for diagnosis of pneumonia is the presence of an acute infiltrate on CXR [3, 5 11, 83, 84]. This form of imaging can provide information on specific aetiology (via the pattern of infiltrate), severity (such as bilateral or multilobar infiltrates), and on differential diagnoses (such as bronchogenic carcinoma) [84]. Surprisingly, there are few studies of the accuracy of CXR in CAP. Those available show that CXR has poor sensitivity and inter-rater reliability. These studies are difficult to directly compare as they use variable diagnostic gold standards.

In comparison to computer tomography (CT), the sensitivity of the initial CXR for infective infiltrates may be as low as 69% [85, 86]. The sensitivity of portable CXR is lower (41-52%) in comparison to CAP diagnosed via bronchoscopy and culture [87, 88].

The ability to identify infiltrates on CXR and therefore diagnose CAP varies between individuals and with experience. Studies comparing radiologist interpretation of infiltrates to other experts/expert panel show variation in radiologist sensitivity between 56 to 85.4% [84, 89-91]. One study directly comparing radiologists found agreement on the presence of infiltrate in 79.4% and on the absence of an infiltrate in 6.0% (kappa = 0.37) [92]. Residents and medical students are less likely to identify infiltrates on CXR than radiologists or respiratory physicians, who have similar sensitivity [89]. Given that radiologists are more accurate at identifying CAP, there is a higher risk of error when diagnosis is made without a radiology report. In the ED this occurs more frequently out of normal office hours, when radiology staff are reduced in numbers [93, 94]. There are high rates of false positive CAP diagnosis in the ED (i.e. primary diagnosis of CAP without CXR evidence as indicated by radiology report). The rate of false positives ranges from 20.4 to 47.7% across studies [94-97].

At least 1 study indicates that a significant proportion of patients with an International Classification of Disease (ICD) coded discharge of pneumonia (14.5%) had neither an ED diagnosis of pneumonia nor any CXR evidence of consolidation during their complete hospital stay [97]. These false positive diagnoses may arise either from diagnostic or discharge coding errors.

Timely antibiotic treatment is likely to be important regardless of CXR result. Basi et. al. [96] found that many patients CAP negative on initial CXR had severe lower respiratory infections with rates of bacteraemia (30-32%) and mortality (6-8%) similar to those positive for CAP on initial CXR. Only 7% of these patients went on to develop radiographic opacities across their hospital stay.

Together this evidence suggests that the CXR has a low sensitivity and poor reliability for the diagnosis of CAP. Clinical judgement plays a significant role in identifying those that require antibiotic treatment. Those with a negative initial CXR are at similar risk of mortality, even though few of them go on to develop consolidation.

1.4.1.3 Aetiology and microbiological investigations

Over 100 organisms have been associated with CAP [84]. Tables 1.2 and 1.3 show that incidence varies with geographic and care site. S. pneumoniae is the most common organism in hospitalised patients, ranging from 19-42% of all cases diagnosed. Some comorbidities, such as COAD and alcoholism, carry higher risk for infection with specific organisms (see table 1.2) [3, 5]. There are significant rates of infection with multiple organisms (4.7-19.6%) [98]. Seasonal variation in the distribution of infective agents has also been documented (see table 1.2) [5, 99]. Recent evidence suggests that variation in aetiology across time may be mirrored by changes in the effectiveness of antibiotic treatment [100]. The emergence of antibiotic-resistant strains of bacteria, most notably *S. pneumoniae,* has reduced the efficacy of commonly used antibiotic treatments such as penicillin [101-105].

Due to poor sensitivity, accurate identification of the infective organism is possible in around only 50% of CAP cases. Initial antibiotic selection is then usually empirical, based common local organisms [6]. Routine tests include sputum gram stain, and sputum and blood culture. The majority of patients are not able to produce adequate sputum samples. Invasive sampling procedures such as aspiration via thorocentesis and bronchoscopy carry significant risk and are reserved for those with severe CAP or for those with treatment failure [6]. Simple blood and sputum sampling is still widely recommended on the grounds that it may assist in the identification of organisms resistant to the chosen empiric antibiotic treatment, and that it enables specific targeting of the infective organism with a narrow spectrum antibiotic. The use of narrow spectrum antibiotics is associated with less cost and reduced development of resistance to broad spectrum antibiotics. The collection of data on local aetiology helps to fine tune empiric therapy [106, 107]. Despite these benefits identifying the microbial aetiology has been shown to have little impact on the use of antibiotics or on outcomes [108-111]. Antibiotics are more likely to be changed in those with severe CAP [112].

Poor return from microbiological testing has been associated with specific patient characteristics. Using multivariate analysis, Ewig et. al. [113] found that age > 70 years, renal and cardiac morbidity, and non-alveolar CXR infiltrates were all independently associated with failure to diagnose the infective organism. The authors postulate that age may predispose to aspiration and anaerobic infections or to viral infections. “Atypical” pathogens (e.g. *Mycoplasma pneumoniae, Chlamydophila spp.* and *Legionella spp.)* are likely to be more common in patients with

renal and cardiac comorbidity due to associated fluid overload. These organisms are difficult to identify using normal culture methods.

Table 1.2: Factors indicating specific aetiology of CAP*

Organism	Risk factors	High incidence areas	High incidence periods	Clinical findings
S. pneumoniae	CAP: increasing age, comorbidity CAP + bacteraemia: female, alcoholism, COAD		Winter, epidemics associated (overcrowding)	Acute onset, high fever, dry cough, chest pain, bacteraemia
H. influenzae	Elderly, COAD			
Legionella spp.	< 60 years, smoker, alcoholism, no comorbidity	Mediterranean	Autumn, epidemics (cooling towers)	High severity, diarrhoea, neurological symptoms, multisystem involvement (abnormal liver and renal function)
S. aureus			Winter, co-infection with Influenza	
M. catarrhalis	COAD			
Gram negative enteric bacilli	Male, nursing home, alcoholism, aspiration (*K. pneumoniae*)	Italy, South Africa (*K. pneumoniae*)		Low platelets, leukopaenia, bacteraemia, high mortality (*K. pneumoniae)*
M. pneumoniae	< 60 years, antibiotic prior to admission		Epidemics (4 yearly)	No multisystem involvement
C. pneumoniae	Alcoholism		Epidemics, co-infection with *S. pneumoniae*	Longer duration of symptoms before presentation, headache, mild illness if no co-infection
C. psittaci	Bird contact		Epidemics (poultry workers)	
C. burnetii	Male	Canada, Spain	Spring, sheep/animal contact	High fever, dry cough
M. tuberculosis		Developing countries		
Anaerobes	Nursing home, alcoholism, aspiration			
B. pseudomallei		Northern Australia, South East Asia		
Viruses				
Influenza A & B			Winter, epidemics	

* British Thoracic Society [5]

Table 1.3: Variation in CAP aetiology by country and care site

	UK (%)			Europe (%)			North America (%)		Australia/ New Zealand (%)	Adelaide, Australia (%)
Organism	**Community**[a]	**Hospital**[a]	**ICU**[a]	**Community**[a]	**Hospital**[a]	**ICU**[a]	**Community**[a]	**Hospital**[a]	**Hospital**[a]	**Hospital**[b]
S. pneumoniae	36	39	21.6	8.4	19.4	21.8		11.3	38.4	42
H. influenzae	10.2	5.2	3.8	1.1	3.9	5.3		6.3	9.5	9
Legionella spp.	0.4	3.6	17.8	2.8	5.1	5.5	0.7	4.8	7.5	3
S. aureus	0.8	1.9	8.7	0	1.2	7		1.2	3.1	3
M. catarrhalis		1.9		0	0.8	3.8		3.8	2.9	0
Gram negative enteric bacilli	1.3	1	1.6	0.2	3.3	8.6		5.3	4.6	8
M. pneumoniae	1.3	10.8	2.7	13.3	6	2	26.2	4.1	14.6	8
C. pneumoniae		13.1		8.7	6.3	6.6	14.8	5.9	3.1	0
C. psittaci		2.6	2.2	2	1.4	0.9	14.8	0.1	1.4	5
C. burnetii	0	1.2	0	0.8	0.9	0.7	2.7	2.3	0	0
Respiratory viruses	13.1	12.8	9.7	12.4	9.5	4	8.1	8.9	10.6	18
Influenza A&B	8.1	10.7	5.4	6.3	5.3	2.3	6	5.9	6.4	7.5
Mixed	11	14.2	6	4.7	6.3	5	4.7	8.5	19.6	18
Other	1.7	2	4.9	2	2	8.4	0	8	4	3 (*M. tuberculosis*)
No organism found	45.3	30.8	32.4	53.7	50.7	43.3	50.3	40.7	31.6	23

a: British Thoracic Society [5], b: Lim et. al. [106]

More severe CAP is also associated with higher yield from sputum gram stain, sputum and blood culture [6, 107]. Thaeerthakarai et. al. [114] found that a sample of CAP patients with a low pneumonia severity index (PSI) score produced a positive sputum culture in only 5% of cases, whilst sputum gram stain and blood cultures were all negative. Signs of severe or high risk CAP were also predictors of positive blood cultures in a large study by Metersky et. al. [115]. This group found that cultures were more likely to be positive in CAP patients with no antibiotic treatment prior to sample, liver disease, systolic blood pressure < 90, temperature <35 or >40 degrees Celsius, heart rate > 125, blood urea nitrogen >11 mmol/l, serum sodium< 130 mmol/l, white blood cell count < 5000/mm^3 or > 20000/mm^3. A multivariate model based on these factors was able to predict 90% of bacteraemias. Given the limitations of standard microbiological investigations, a more targeted approach focusing on those patients with risk factors for bacteraemia and poor outcome is likely to be more cost effective [6, 107, 110, 111, 114, 116-121].

Other tests available to identify CAP aetiology include bacterial and viral serology, specific bacterial antigen assays, and identification of bacterial DNA via polymerase chain reaction (PCR). Serological testing is widely available for *Legionella, M pneumoniae, C. Pneumoniae*, and viruses, however the lag time for results is too large for these tests to be useful in acute treatment. Rapid antigen tests applicable for use on serum, sputum and urine are available for *S. pneumoniae*, *L. pnuemophila* and some viruses [6]. There are several techniques which vary in sensitivity from 50-90% [122]. Results for some tests are available within 15 minutes to 2-3 hours, allowing the early selection of the appropriate antibiotic [123]. The addition of these tests to standard microbiology improved the sensitivity of aetiological diagnosis from 36.4 to 54.2% in one recent study [123]. Targeted antibiotic selection based on the urinary antigen test for *S. pneumoniae* had a 90% success rate in one small study. Interestingly, coinfection with atypical organisms occurred in 23% of antigen positive patients, and this subgroup's efficacy was only 83% [124]. This supports a role for simultaneous multi-organism testing.

PCR tests are available for a wide range of bacterial and viral causes of lower respiratory tract infection. Results from "real-time" PCR testing are available in around 2-6 hours at some sites [125, 126]. These tests have superior sensitivity and specificity to standard techniques and have shown yields of up to 76% [125, 127]. One study has shown, however, that their impact on management is limited, with only 6% of antibiotic regimens altered and outcomes not different to control in a PCR test group. Given a cost per patient in excess of 300 Euro for a multiplex test battery, these tests are not yet cost effective [127].

In summary, CAP results from infection with a number of different organisms which require different antibiotic treatment. Standard microbiological assessment is hampered by poor sensitivity, long delay to results and marginal impact on treatment. A more cost effective approach may be to target high risk individuals. Emerging technologies such as antigen detection and PCR offer more rapid diagnosis and higher yield. At this stage their cost effectiveness and clinical impact remain uncertain.

1.4.2 The risk assessment and treatment problems

Severity of disease and risk of mortality generally determine the nature and site of CAP treatment. Due to the wide range of CAP severity, treatment occurs across the full range of care sites (see figure 1.5). Those with mild forms are able to be safely managed at home, whilst severe cases may require ICU admission, cardiac ionotropes, and mechanical ventilation [3, 5, 83, 84]. Accurate assessment of risk is important to match the requirements of the patient to the care provided. The prediction of CAP mortality is complex. One widely used formal risk assessment model, the Pneumonia Severity Index (PSI) developed by Fine et. al. [128], contains 20 predictor variables, encompassing patient demographics, comorbidities, physical examination findings, and laboratory and CXR results. The integration of such large numbers of variables makes choice of care site difficult. Studies of the use of this model as decision support for the admission decision have shown that it is able to safely reduce the numbers of patients admitted to hospital, but a significant proportion of those at low risk of mortality from CAP are admitted due to social factors and comorbidity [42, 44, 129-131]. The CURB-65, a simpler model with only 5 variables (**C**onfusion, raised **U**rea, raised **R**espiratory rate, low **B**lood pressure and age **65** years and over), has been shown to have equivalent accuracy to the PSI and has been recommended for use in both the Swedish and British national CAP guidelines [121, 132]. The recent update and merger of the Infectious Diseases Society of America and the American Thoracic Society guidelines supports the use of either in combination with physician judgement [120].

ICU admission is required for patients with severe sepsis requiring ionotropic support or respiratory failure requiring mechanical ventilation. Prediction of which patients will develop these complications is again difficult. The British and American Thoracic Societies (BTS and AmTS) have developed models for prediction of the need for ICU, and high scores on the PSI and CURB-65 have been used as predictors [5, 11, 128, 133-135]. One recent prospective study indicates that, while the AmTS rule has the best accuracy as indicated by an area under the receiver op-

erating curve of 0.82, it has a poor sensitivity of 58.2%. The BTS model had the highest sensitivity at 98.2% but poor specificity at 51.9% [136].

Overall, the decision of site of care is complex, as reflected in the proliferation of decision support tools for both hospital and ICU admission. These models have been designed to carefully balance risk of mortality with the high system cost of general ward or ICU admission.

A wide range of antibiotics are useful for bacterial CAP treatment. Each of these drugs is effective against a different spectrum of organisms. Many drugs are available in both oral and intravenous (IV) forms. IV antibiotics are more effective in severe cases of CAP, where oral absorption may be poor, or there is bacteraemia present. Surprisingly, the strongest evidence of relative efficacy of these drugs, comes from in-vitro and observational cohort studies. Clinical trials of antibiotics in CAP have generally been designed to prove equivalence between drugs, and are therefore not useful for choosing between alternatives [137, 138]. Many guidelines, including the current Australian Therapeutic Guidelines, recommend coverage for atypical organisms by including a macrolide or fluroquinolone antibiotic [120, 121, 139]. The available evidence is conflicting. Meta-analyses of clinical trial data have found no overall benefit of including these treatments over beta-lactam antibiotics [140-142]. In contrast, there is support for improved outcomes with the use of macrolides in combination with beta-lactams or fluoroquinolones in large observational studies [62, 100, 143, 144]. Dual therapy appears to be more important for those with more severe pneumococcal disease with bacteraemia [145]. Increasing antibiotic resistance is yet to make a significant clinical impact on CAP outcomes [102, 145].

During hospital stay antibiotic regimens are modified with clinical improvement, clinical deterioration/treatment failure, or as a result of microbiological identification of the infective organism. Despite the theoretical reasons for narrowing the spectrum of antibiotic coverage to match microbiological results, as discussed previously, this is not often carried out in practice. A recent trial of directed versus empiric therapy according to the 1993 American Thoracic Society guidelines, showed no benefit in terms of mortality, treatment failure, LOS or symptom resolution, however patients were much more likely to suffer an adverse event if they remained on empirical therapy (60% vs. 17%) [146]. Table 1.4 shows that there were higher rates of gastrointestinal disturbance, phlebitis, reversible deafness and hair loss in the empirical treatment group.

Table 1.4: Adverse events in empirical versus directed CAP treatment*

Adverse event	Empirical treatment	Pathogen-directed treatment
Gastrointestinal disturbances	32.8%	6.7%
Phlebitis	29.7%	6%
Reversible deafness	10.9%	3.7%
Reversible hair loss	8.1%	3.7%
Urticaria	1.6%	1.5%

* van der Eerden et. al. [146]

With clinical improvement patients are “switched” from intravenous to oral forms of equivalent antibiotics. Physicians make the decision to switch to oral antibiotics based on the stabilisation of vital signs, mental status, and maintenance of oral intake, but there is significant inter-individual variation between doctors [46]. In a meta-analysis of trials of early switch criteria, Rhew et. al. [47] found that IV antibiotic time and LOS can be safely reduced. Studies carried out since this analysis have confirmed these findings [48, 147, 148], and have supported early antibiotic switch in patients with severe CAP who have stabilised [49].

Treatment failure (defined variably as inadequate clinical response after 7 days of therapy, persistent fever, clinical instability after 72 hours, or clinical deterioration after 24 hours of therapy), occurs in 10-25% of patients across studies. Reasons for treatment failure can be categorised into host-related, infection-related, incorrect diagnosis and incorrect treatment groups. Host-related factors include the severity of CAP/degree of clinical instability, the presence of undetected infection sites (e.g. empyema), comorbidities, smoking, recent infection and age related decline in immunity. Infection-related factors include antibiotic resistance, coinfection, secondary hospital acquired infection, or infection with an unusual organism. Incorrect diagnoses include non-infectious causes of pneumonia and heart failure. These are often mistaken for infectious pneumonia [105, 149-153].

The decision to discharge from hospital relies on multiple factors including the assessment of the resolution of symptoms, the available home support and functional status, the transfer to oral antibiotics, the stability of comorbid disease, and the need for further diagnostic work up [47, 154]. Those with signs of clinical instability at discharge are at increased risk of delayed return to normal activities, readmission, and death [155]. The authors of one large retrospective study recently

concluded that there is no benefit from hospital stay for observation following switch to oral antibiotics which normally occurs around day 3-4 of CAP admission [50]. This corresponds to estimates of the median time to clinical stability which occurs at around day 3 (day 7 for conservative models) [156]. At some sites where "Hospital in the Home" programs provide intensive home services, selected patients may be discharged whilst still on IV antibiotics [51-53].

In summary, risk assessment occurs at a number of points throughout the course of CAP hospital treatment. Key decision points include the initial site of care, selection of initial antibiotic, alteration of antibiotic treatment based on microbiological aetiology or treatment failure, and fitness for discharge. Assessment of risk at each of these points is difficult and formal risk algorithms have been derived to assist clinician judgement. Due to the poor sensitivity of aetiological diagnosis and delay to the return of results, the initial selection of antibiotic is empirical. The majority of patients receive purely empirical antibiotic therapy. Patients that remain on broad spectrum therapy risk increased rates of adverse drug reactions. Failure to switch to narrow spectrum drugs has been theoretically associated with an increased risk of the development of antibiotic resistance, however, changes in resistance patterns are yet to have a clinically significant impact. Clinical improvement is generally associated with a switch from intravenous to oral antibiotics. Once stable enough for this switch patients are likely to be well enough to be discharged. All of these decisions carry a high degree of uncertainty that is reflected in variability of key processes of care.

1.5 Resources at the point of care

Figure 1.7 shows the simple model of process performance, highlighting the resources available at the point of care. This section will deal with the characteristics of ED workflow that make it difficult to organise timely care.

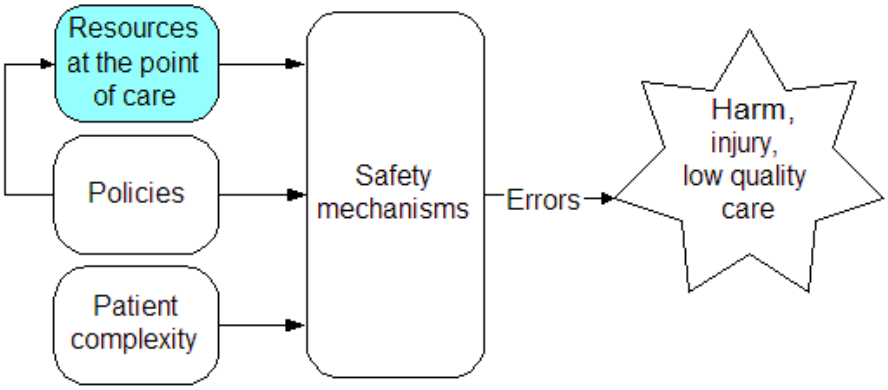

Figure 1.7: Simple model of predictors of process performance/error: resources

1.5.1 The Emergency Department (ED) workflow problem

A broad definition of workflow subsumes both health care processes, and all factors that impact on the performance of health care processes, including the decision-making and information transfer [74]. For the majority of CAP patients, hospital workflow begins at the triage desk of the ED. The ED has arguably the most complex workflow of all sites in the hospital. In general, patients arrive with undifferentiated, heterogeneous disease. There is high uncertainty around diagnosis, prognosis, and urgency of care on admission. This results in a high demand for investigations and specialist opinion. Many of these processes require transfer of the patient, patient samples or information to sites other than the ED, or of personnel into the ED. Commonly, there are significant delays to performance of investigation or assessment, and to the return of results. A single doctor is usually responsible for requesting and acting on information from other sources, including nursing staff, radiology, laboratory, and specialist consultations [74]. Doctors are not able to accurately predict when any of these services will be provided. They are responsible for multiple patients who may deteriorate at any given time and are often interrupted and diverted to more urgent tasks [157-159]. Consequently, a single task may take a number of attempts to complete. There is demarcation of responsibilities amongst staff, such that doctors are responsible for decision-making tasks, whilst nurses and other allied health staff perform most of the manual tasks. This means that there is often a delay between decision and action (e.g. the administration of antibiotics) and accurate communication is required for actions to be carried out. This communication consists of both verbal requests and written orders. Written orders without verbal requests may increase the delay to action as they are not always noticed immediately. Despite the complexity of this environment, workflow is generally poorly supported. There is usually only a single channel for communication of investigation results (i.e. computer-based laboratory result systems) and there are no guarantees that high risk results will be treated any more urgently than low risk [74]. Consequently, there is an increased probability of delayed assessment of new information and therefore of delayed treatment. Kilpatrick et. al. [160], in a study of urgent requests for test results from the ED of a large hospital, found that 45% were never accessed and 30% were accessed more than 1 hour after their initial availability. Three percent of the results not accessed would have led to immediate changes in management, as indicated by abnormal levels of serum potassium or amylase, alone. Other studies have shown that patients deemed to be at low risk or of low treatment urgency, are more likely to experience delays in care [161-163].

Upon presentation to the ED initial formal risk assessment is carried out by a trained triage nurse. Triage is a process developed to allocate scarce medical resources in emergency situations by assessing the urgency of patient treatment. In Australia this is carried out using the ATS (see appendix figure 9.1). Patients are rated from 1 (severely ill and in need of immediate clinical assessment) to 5 (non-severe illness, maximum waiting time to clinical assessment of 2 hours), based on the patient's presenting signs, symptoms and history. Achievement of the time to assessment targets for each category is one of the major indicators for the emergency department performance [164].

There is variable evidence concerning the accuracy and reliability of triage scoring. Inter-rater reliability between nurses, and between doctors and nurses, ranges widely across sites. This reinforces that triage is a difficult exercise which is dependent on local training and expertise [165-180]. One Australian study indicated that although more common in high urgency patients, few patients receive objective measures of clinical stability at triage [181]. There is some evidence that triage nurses rely more on visual cues than physical observations [170], but when presented, vital signs do have an impact on nurse triage scoring. Cooper et. al. [169], in a large prospective study, found that patient observations resulted in a change of triage destination in 8% of cases. Seventy percent of these were to a higher urgency care site. Given that there is evidence of variability in the quality of triage and that triage impacts significantly on assessment timing, inaccurate triage to lower urgency categories places patients at risk of delayed treatment and poor outcomes. Lower urgency triage categories are known to contain the majority of patient mortality, despite having lower rates of in-category mortality in comparison to high urgency categories [182]. It is possible some of this mortality is secondary to delayed assessment and treatment.

In summary, the ED is a highly complex environment with unpredictable loads on limited resources and variable workflows. The triage process attempts to manage these resources but shows high variability at some sites, is not always based on objective physiological measures and may be responsible for some delay to treatment for patients which are triaged at a lower urgency. These factors are likely to impact significantly on the ability of staff in the ED to diagnose and treat CAP patients within 4 hours of presentation.

1.6 Summary

CAP is a common respiratory infection that is responsible for significant morbidity, mortality and cost to health systems world-wide. Patient complexity, in terms of difficult diagnosis, risk

assessment and antibiotic selection, results in highly variable treatment practices that have proved difficult to standardise despite widespread policy interventions. The initial site of hospital care is the ED which has highly complex process flow that is poorly supported. These factors combined make the treatment of CAP a prime target for the development of flexible care plans driven by CDSS. Currently the dominant paradigm for intervention is the paper-based guideline. In Chapter 2 I discuss the relationship between health quality improvement, evidence-based medicine and decision support. I also examine the general factors contributing to non-compliance with both paper-based and computer-based decision support. I then summarise interventions designed to improve CAP care. This includes large consensus statements produced by national clinical specialist bodies, paper-based guidelines derived for specific hospitals, and CAP-specific CDSS.

2 Review of community-acquired pneumonia quality interventions

2.1 Quality interventions in health care

The Institute of Medicine in its recent vision for the future of health care in the United States, "Crossing the Quality Chasm: A New Health System for the 21st Century", supports that quality health care should be safe, effective, patient-centred, timely, efficient, and equitable [183]. The under use, over use and misuse of care processes is common and has significant impact on costs to individual health and to the health system [184]. Quality interventions take numerous forms. Grol and Grimshaw [71] recently reviewed the performance of interventions to change clinical practice. In data from over 230 trials derived from 54 systematic reviews they identified 16 types of intervention. These included: educational materials, conferences and courses, interactive small group meetings, educational outreach visits, use of opinion leaders, education strategies, feedback on performance, reminders, computerised decision support, introduction of computers in practice, substitution of tasks (e.g. academic detailing by pharmacists), multiprofessional collaboration, mass media campaigns, total quality management/continuous quality improvement, financial interventions, and patient-mediated interventions. Although the findings are mixed, all of these approaches have been shown to improve practice in some circumstances, but none by more than 10-15%. Multiple methods are usually superior to singular methods. In most cases (73% of all studies) implementations are multi-faceted [71]. The author's suggest that the key ingredients for success are the selection of a feasible and economic set of evidence-based strategies based on an assessment of the specific problem at hand, with regular review of progress, using well-defined performance indicators. The selection of "attractive" targets, where there is likely to be little resistance to change and the involvement of interested staff and local clinical opinion leaders, are also important. Each of these approaches addresses a subset of barriers to behaviour change.

Even with current quality improvement techniques, it now takes an average of 17 years for new knowledge generated by randomised controlled trials to be incorporated into practice, and even then application is highly uneven [183]. Current approaches to improving the quality of CAP treatment are similar to most other medical conditions and focus mainly on improving the decision-making processes of clinical workers, ignoring the important systemic deficiencies that have been identified throughout health care [74, 183]. This chapter will discuss decision-making in medicine and the role of decision support. I will also review the content and performance of implementations of CAP treatment decision support.

Figure 2.1 shows the simple model of process performance, highlighting policies and safety mechanisms and patient complexity. The majority of policies and safety mechanisms for the improvement of CAP care are paper-based guidelines designed to assist with the handling of patient complexity. Current approaches generally fail to address workflow in its entirety by considering factors affecting resources at the point of care. In this way they do not provide a care plan which is flexible to local process limitations.

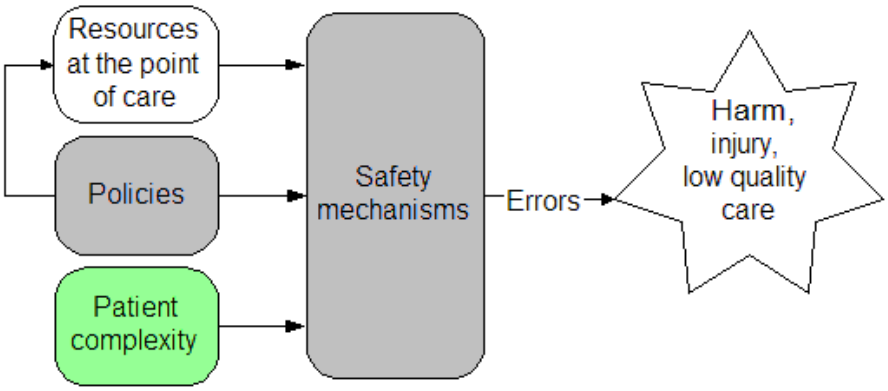

Figure 2.1: Simple model of predictors of process performance/error: patient complexity, policies and safety mechanisms

2.2 Clinical decisions, evidence-based medicine (EBM) and decision support

2.2.1 Clinical decisions and EBM

Clemens [75] identifies 4 sources of difficulty in decision-making: uncertainty, multiple perspectives, multiple objectives and complexity. A single disease may present in many different ways, between individuals and within individuals across time. For example, fever is a common sign of pneumonia in adults, however in older patients with CAP, body temperature may be normal or low [81]. Just as no presentation is certain, the efficacy of no single treatment is certain. Human reasoning in these uncertain circumstances relies on a number of heuristics that do not conform

to the laws of probability. Decision-making thus contains errors or biases that result in poor decisions. Due to the probabilistic nature of outcomes in health, poor decisions may still lead to acceptable outcomes, but are more likely to result in poor outcomes [185].

Physicians make errors due to cognitive biases in both diagnosis and treatment decisions [186]. Diagnostic biases include: selectively gathering evidence to support a diagnosis (confirmation); ignoring base rates of a disease, ignoring regression to the mean, gamblers fallacy - predicting the pattern of events in a small sample will mirror that in the population (biases due to a representativeness heuristic); over-estimating diagnoses that are more salient or familiar (bias due to an availability heuristic); over-estimating the probability of a diagnosis after it is known (hindsight bias); and over-estimating the probability of a diagnosis with poor outcome (regret bias). Treatment biases include: more strongly associating positive outcomes with active treatment (regret bias); more often choosing treatments with high risk profiles if outcomes are described as losses in comparison to gains (framing bias); and finally, it has been illustrated that increasing the number of new alternative treatments decreases the likelihood of changing inadequate treatment. The basis of the EBM movement is that these biases can be avoided via the formal application of evidence to clinical decisions.

EBM is “the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients [187]. EBM involves 4 steps: the formulation of a clinical question, a search for evidence, formal appraisal of the evidence (a systematic review or meta-analysis) and application to the patient [188]. It is widely acknowledged the practice of EBM by individual clinicians is not practical. It has been estimated that to keep up with the literature in the field of general medicine alone, a physician would have to read 19 articles per day, when the time available for reading is less than 1 hour per week [187]. A simple PubMed [189] search indicates that in the year 2004 alone 181 papers concerning adult community-acquired pneumonia were published (search terms: “community acquired pneumonia”, search limits: publication date 1-1-2004 to 31-12-2004, adult 19 years +). The role of decision support in this environment is then to assist clinicians to practice EBM without the need to carry out the complete process.

2.2.2 Decision support

Decision support can be defined as any technology that assists in decision-making. Formats range from simple reminders to paper-based guidelines and complex computer-based systems able to synthesise large amounts of information. They have been constructed and implemented

to assist with diagnosis, test selection, test interpretation, risk assessment, and treatment decisions [190-192]. Clinical decision support systems may be categorised by their level of sophistication, their use characteristics, and their methods of implementation. A decision support system's level of sophistication is indicated by its use of data. Presentation systems, such as paper-based or computer-based guidelines, simply present specific information required to assist decision-making. Triggered response systems present information tailored to a specific clinical situation. An example is a clinical rule-based alerting system for laboratory results. Inferential systems calculate new data based on patient parameters, for example a Bayesian decision model that predicts risk of mortality from pneumonia. The term “use characteristics” refers to the level of automaticity of the system. Passive systems require information to be requested or sought out; computer and paper-based guidelines are examples. Active systems collect data and present relevant information automatically; an example is an alerting system for laboratory results. Autonomous systems are of the closed loop variety; they automatically collect and act on clinical information. Autonomous systems are rare in medicine, but one example is that some respirators are able to adjust their parameters automatically to optimise ventilation of critically ill patients. The third level of categorisation concerns the “method of implementation” of the decision support system. This encompasses the method chosen to manipulate data to derive the decision recommendation. Examples include simple clinical formulae, database tables, clinical rules, decision models and neural networks. Table 2.1 uses the above categorisation to describe the types of decision support developed for the diagnosis and treatment of CAP.

Table 2.1: Categorisation of decision support

System	Example	Level of sophistication	Use characteristics	Implementation
Paper-based	Simple guideline recommendations	Presentation	Passive	Antibiotic delivery within 2 hours of presentation to ED [5]
	Score-based guideline recommendations	Presentation	Passive	Pneumonia Severity Index (PSI) risk score for the decision to admit to hospital [120]
Computer-based	Simple guideline recommendations	Presentation	Passive	Empirical antibiotic treatment recommendations [193]
	Score-based guideline recommendations	Presentation	Passive	PSI risk score for the decision to admit to hospital [42]
	Rule-based alerting	Triggered response	Active	Alert for antibiotic delivery prior to ED discharge [194]
	Model-based alerting	Inferential	Active	Bayesian diagnostic model for CAP triggers PSI CAP risk model for admission decision and an empiric antibiotic guideline [195]
	Closed loop controllers	Triggered response	Autonomous	Automatic control of mechanical ventilation [196]

2.2.3 Paper-based guidelines

Guidelines are systematically developed statements designed to assist clinicians in making treatment decisions under specific circumstances [78]. These documents have proliferated throughout clinical medicine, reflecting the growing focus on evidence-based medicine (EBM), managed care, and concern over medico-legal issues [197]. Estimates of the number of guidelines used in the US alone range from 1600 to in excess of 26000 [198]. The paper-based guideline is the most common form of decision support implemented to improve CAP treatment. More than 30 different paper-based CAP guidelines have been published during the past decade [199]. A study of hospitals in the United Kingdom indicated 83% had a local CAP guideline [200]. CAP guidelines have been specifically designed to suit both primary care and hospital settings. Hospital guidelines include those covering outpatients, wards and ICU. This form of decision support is passive in nature and has a low level of operational sophistication (see table2.1). These characteristics along with problems in construction, maintenance, alternative staff opinion, patient preference and systemic factors contribute to poor compliance which can be as low as 20% [40].

Paper-based guidelines are labour intensive and costly to construct and implement. Due to the difficulty of interpreting clinical evidence and variable skills in EBM across the work force, guidelines suffer from bias in construction. Guidelines generally lack the flexibility to deal with uncertain values in medicine. Taking a traditional statistical approach they divide patients into discrete categories, which may not truly represent the likelihood of certain outcomes. They contain hidden utility judgements of the value of medical outcomes. Once fixed in a guideline these judgements do not allow for situational variables such as patient preference [201]. Guidelines require constant maintenance to keep pace with clinical science, drug development and demographic variation of illness [202]. In the year 2000 alone 234 new CAP papers were published [203]. The cost in lag time and dollars of assembling review committees and dispersing updates for paper-based guidelines is large [72, 78, 204].

Large complex guidelines are more difficult to adhere to [205, 206]. Complexity arises with the embedding of procedures within procedures, and when there are complicated temporal or causal relationships among steps in a procedure [207]. Consequently, paper-based guidelines tend to be simple. Simplicity may be associated with inadequate classification of patients into a small number of groups with high variance, and with a sub-optimal range of treatments. Thus, guidelines may succeed in reducing overall process variation at the expense of suboptimal outcomes

for any given patient in the group. Non-compliance with such systems may be explained by the numbers of patients that actually fall between treatment categories. This occurs when catergorisation is ambiguous, and when there are logical gaps and contradictions in recommendations [207]. Patients with higher severity and comorbidities are more complex and are less likely to be treated according to guidelines as they are hard to classify into simple categories [40].

Passive decision support such as the paper-based guideline requires the user to actively seek out recommendations. One systematic review of the barriers to guideline compliance (see table 2.2) indicates that a lack of knowledge about a specific guideline is the major barrier to use [208]. Swizter et. al. [209], in a study of 352 physicians across 7 hospitals, found that 41% were not aware of a local CAP guideline's existence. At one hospital 14% indicated a local guideline existed when there was none implemented. Predictors of accurate knowledge of a local guideline included: practising at a non-teaching hospital, spending more hours in direct patient care, having seen a higher number of CAP patients per year, more positive attitudes toward guidelines, and a risk adverse disposition. Only 30% of physicians aware of their local hospital guideline used it more than 50% of the time. These physicians were more likely to be generalists and to have more positive attitudes towards guidelines. Lack of agreement with a guideline, reluctance to change past practice, and difficulty with guideline use, are also present in a high proportion of cases of non-compliance. Patient preference accounts for over 10% of non-compliance [208].

Systemic factors, such as insufficient staff, increased costs, and lack of time, individually account for greater than 10% of guideline non-compliance on average across studies. The implementation of CAP guidelines is difficult because treatment spans many departments of care and responsibility changes as the patient moves from the ED to the ward [69].

Table 2.2: Barriers to compliance with guidelines

* Cabana et. al. [208]

In conclusion, paper-based guidelines are difficult to construct in terms of bias in construction and adequate representation of information. They are difficult to disseminate, are often not available at the point of care, and are generally not designed to fit in with local workflow. These factors, along with resistance to practice change and patient preferences, account for high rates of non-compliance.

2.2.4 Computer-based decision support (CDSS)

Computer-based decision support systems (CDSS), when integrated with a clinical information system (CIS) that gathers patient data into an electronic health record (EHR), offer greater flexibility in presentation and added active functions in comparison to paper-based guidelines [191]. An EHR is a data structure containing the essential clinical and demographic information for each individual patient. Any clinical information technology (IT) system may form part of a CIS. Much hospital data currently exists in isolated legacy databases and systems, such as lab-

oratory results, patient management indexes and specific local systems such as those in the ED and in surgical perioperative systems. In order to maximise the utility of this information these sources should be drawn together to form an individual EHR for each patient [74]. Key systems include laboratory results, pharmacy systems, radiology systems, and administrative databases. Linkage between these systems alone can provide improved patient safety and health care performance [210]. Data from the clinical consultation, including history, symptoms, signs, as well as treatment plans currently remains in paper-based records at most sites.

In comparison to paper-based guidelines, CDSS allow more complexity in guideline display. To improve understanding and compliance the evidence base behind recommendations can also be made available [191]. CDSS can be updated and distributed electronically; this is likely to assist in the reduction of the significant costs associated with the implementation and revision current of paper-based systems [202].

Active CDSS functions include alerting, order entry, data linkage and tracking of processes. Data from other local legacy systems can be used to automatically calculate clinical algorithms and individualise guideline recommendations for specific patients. Alerting systems are then able to direct the attention of busy clinical staff to the appropriateness of a guideline, errors in treatment, the presence of new information such as test results, or the need for treatment action [191, 211]. Order entry systems have been implemented to assist with dose, contraindications and drug interactions at the point of prescribing [210, 212-215]. New technologies such as bar coding or radio frequency identification of patients, staff and medication packaging offer the chance of greatly improved safety through realtime monitoring of treatment processes [216]. Automatic summary functions combining these systems may be implemented to audit health care processes at the individual, unit or hospital level to provide feedback on performance without the need to trawl through case notes [191].

In summary CDSS offer many advantages over current paper-based systems. These include greater richness in presentation, the integration and abstraction of available data, and active functions designed to intervene to improve decision-making and workflow. The ability to modify and distribute these systems electronically is likely to saved on dissemination costs.

2.3 Performance of CDSS

Three systematic reviews of CDSS implementations have supported their efficacy in improving both clinical practice (64-68%) and patient outcomes (13-43%). Hunt et. al. [190] performed a systematic review of studies of CDSS implementation and found that out of 68 controlled trials, 66% had a significant impact on physician performance. Forty three percent of studies had a significant effect on patient outcome (where measured). The majority of studies with no effect on outcome were under powered (5/8 studies). Reminder, disease management recommendations, and drug dosing systems all produced improvements in > 50% of the studies performed. Systems designed to change test ordering behaviour and to improve functional assessment were shown to improve physician performance in a limited number of studies. Prescribing and diagnostic systems were not as often successful as other types of CDSS, with improvements in around 25% of studies. Diagnostic decision support has been more successful when implemented in small, domain-specific applications such as the interpretation of ECG waveforms [217].

Kawamoto et. al. [218] found that 68% of 70 trials produced significant improvement in clinical practice. Multiple logistic regression analysis identified that automatic provision of decision support as part of clinician workflow, provision of recommendations rather than just assessments, and provision of decision support at the time and location of decision-making were all independent predictors of success. Ninety four percent of systems with all of these features produced clinical process improvement.

Garg et. al. [2] reviewed 100 trials and found that CDSS improved practitioner performance in 64% (40% with diagnostic systems, 76% with reminder systems, 62% with disease management systems, and 66% with prescribing systems). Thirteen percent of trials measuring patient outcomes reported improvements. They identified prompting (73% success) and local development (74% success) as key factors associated with improvement in care.

The performance of decision support thus depends both on characteristics of the tool itself and those of its implementation environment. Successful implementation of decision support is associated with the degree of matching between characteristics of the tool, stakeholder requirements and the interaction of these with systemic factors that are represented by workflow. Aspects of the decision support tool that effect its performance include the type of tool, the ev-

idence used to construct the tool, the scope of the tool, and the format of presentation. Bates et. al. [219] have proposed 10 rules for designing successful CDSS.

1 "Speed is everything" - user satisfaction declines significantly if the system is slow to operate.
2 "Anticipate needs and deliver in real time" - the system must anticipate the information needs of clinicians and provide integrated, relevant data.
3 "Fit into the users' workflow"- information needs to be actively presented at the point and time of decision-making.
4 "Little things can make a big difference" - small changes in screen design and flow can make a large difference in usability.
5 "Recognize that physicians will strongly resist stopping" - doctors are adept at devising ways around recommendations.
6 "Changing direction is easier than stopping" - offering an alternative action is often more successful than attempting to stop a behaviour.
7 "Simple interventions work best"- minimising the number of screens and the complexity of information presented increases uptake.
8 "Ask for additional information only when you really need it"- an increased number of manually entered data items decreases CDSS uptake.
9 "Monitor impact, get feedback, and respond".
10 "Manage and maintain your knowledge-based systems" - systems must be regularly monitored and updated in terms of the medical evidence base and in local practice and workflow.

From these points workflow emerges as a key aspect of design and implementation of CDSS. Items 1-4 and 7-8 all relate to the ability of a CDSS to integrate easily with the workflow of clinical staff. Workflow analysis is important in designing simple systems that are available and attractive to use at the point of care. Assessing all processes to be supported, the decisions involved and the information required should help to better identify key factors for process improvement, such as the best target sites for the implementation of simple models, the availability of existing data in clinical information systems (CIS) for integration, and physical sites for CDSS access.

2.4 CAP quality interventions

2.4.1 CAP national consensus statements

National consensus statements for the treatment of CAP have been produced for the United States, Canada, Europe, Britain, France, Spain, Germany, Switzerland, South Africa, Japan and Australia [220]. In the last 10 years there have been major revisions of consensus statements by the Infectious Disease Society of America (IDSA) [83], the Canadian Infectious Disease Society (CIDS) [84], the American Thoracic Society (AmTS) [11], and the British Thoracic society (BTS) [5]. The BTS updated their guideline in 2004 [121] and the AmTS and IDSA have recently merged their guidelines into a single document [120]. The majority of these statements attempt to address all of the issues and decisions in the treatment of CAP, making them large and impractical for general use. They identify standards for diagnosis and investigation of microbiological aetiology. They cover new developments in diagnosis and severity assessment techniques and the emergence of antibiotic resistance [221]. The IDSA document released in 2000 also includes a discussion of bioterrorism-related CAP, using organisms such as *Bacillus anthracis* (anthrax), *Yersinis pestis* (plague) and *Francisco tularensis* (Tuleraemia) [83]. The 2003 update of these guidelines also includes recommendations for the diagnosis and treatment of severe acute respiratory syndrome (SARS) [222]. National CAP guidelines generally identify preferred antibiotics based on their spectrum of action against locally prevalent microbes, modified by patient risk factors, the severity of disease, antibiotic allergies and the site of care [220]. Some of these documents have a reduced scope, focusing only on antibiotic selection (e.g. The Australian Medicines Handbook [223]).

For logistic and cost reasons, most large consensus statements are revised only periodically and consequently tend to become outdated. For example, there was an 8 year lag during the 1990s between the AmTS statements and a 6 year lag to the latest combined statement with the IDSA [11, 120, 133]. The IDSA stated that they intended to update their document at 6-12 month intervals [83], however the group only managed updates at 2, 3 and 4 years in recent times [3, 83, 120]. Recently published documents reflect the movement towards evidence-based practice by using formal methods of evaluation of evidence for each of their recommendations. Despite a large body of research on the aetiology, diagnosis, risk assessment, treatment efficacy, and the relationship between processes of care and outcomes, much of the evidence available is not of the highest quality (see table 2.3). Consensus then plays a large part in determining the recommendations in these documents. Differing interpretations of the evidence by the constructors of na-

tional consensus statements have resulted in differences in recommendations. They also reflect the development of new diagnostic and severity assessment techniques and the emergence of antibiotic resistance [221].

.

Table 2.3: Quality of evidence in CAP national consensus statements*

NOTE:
This table is included on page 55 of the print copy of the thesis held in the University of Adelaide Library.

* Woodhead et. al. [221]

2.4.1.1 Recommended diagnostic investigations

CXR is considered the gold standard for CAP diagnosis. It is recommended by all groups that a CXR be performed before antibiotic treatment in all patients presenting to hospital with probable CAP [5, 11, 83, 84, 120, 121, 139]. All of the current British and North American consensus statements acknowledge that in some cases the aetiology of CAP is predictable from history, examination, or radiological findings, however, all also conclude that these findings are not reliable enough to use in the selection of antibiotic treatment.

The role of microbiological testing to determine aetiology is controversial with several differences between statements (see table 2.4). Standard investigations include sputum gram stain and culture, and blood culture. There is a recent trend toward the reservation of microbiological testing for severe or high risk CAP due to the low yield of tests. Particular attention is paid to sampling and processing techniques in an attempt to maximise the accuracy of these tests [120] [121]. The AmTS/IDSA [120] now only recommend blood and sputum culture in cases where the result is likely to change antibiotic management or the test is likely to have the highest yield. They list intensive care unit admission (ICU), failure of outpatient antibiotic therapy, cavitating infiltrates, leukopaenia, active alcohol abuse, chronic severe liver disease, severe obstructive/ structural lung disease, asplenia (anatomic or functional), recent travel (within past 2 weeks), positive *L. pneumoniae* urinary antigen result, positive Pneumococcal urinary antigen result, and pleural effusion, as indicators for blood and sputum culture and for further intensive inves-

tigations. The BTS indicate that in non-severe CAP the extent of microbiological investigations should be guided by clinical factors (i.e. age, co-morbid illness, severity indicators), epidemiological factors, and prior antibiotic therapy. This group still support sputum cultures in non-severe patients able to produce sputum [121]. Interestingly, the Australian Therapeutic Guidelines (ATG) use the pneumonia severity index (PSI) to identify those at higher risk and restrict microbiological testing to risk groups II-V. Given the majority of patients in group I are likely to be discharged, this effectively means that all hospitalised patients are likely to be tested under this recommendation [139].

Serology is generally only recommended for severe CAP or for those with high risk of specific aetiologies. Antibodies are rarely positive at presentation and need to be compared to samples taken 7-10 days later presentation to confirm the diagnosis [5]. The AmTS [11] and CTS/CIDS [84] do not recommend serology for common CAP aetiologies. Both the individual AmTS [11] and IDSA [83] statements indicate HIV serology should be performed in those at risk. The BTS support the use of serology where CAP is severe, unresponsive to beta-lactam antibiotics, when there are epidemiological risk factors, or when the diagnosis is important for public health reasons [5]. The IDSA [83] indicate that serum should be frozen on presentation and saved in case it is later needed for serological assessment.

In contrast, the results for some antigen tests are available within 15-30 minutes of sampling (e.g. Pneumococcal, Legionella) [120]. The use of *L. pneumophila* serogroup 1 urinary antigen in cases of severe CAP is supported by all groups. The BTS suggests the use of Pneumococcal urinary antigen and Chlamydial antigen tests in severe CAP [5]. The combined AmTS/IDSA statement also supports the use of Pneumococcal urinary antigen in severe CAP presentations as does the ATG [120, 139].

Invasive sampling techniques such as bronchoscopy or thorocentesis are reserved for those with severe or non-resolving CAP as these procedures carry iatrogenic risks and require highly trained staff. The BTS also recommend invasive tests for those with risk factors for poor outcome or specific organisms, and for cases where neoplasm or foreign body is expected [5]. Thorocentesis and laboratory testing of pleural fluid is recommended in pleural effusion; the AmTS and CTS/CIDS recommend this be done in any effusion over 10mm thick [11, 84].

Table 2.4: Recommended microbiological investigations for those presenting to hospital

	IDSA 2000 [83]	CIDS/CTS 2000 [84]	AmTS 2001 [11]	BTS 2001 [5]	IDSA 2003 [222]	BTS 2004 [121]	ATG 2006 [139]	AmTS/IDSA 2007 [120]
Gram stain	For all patients	Ward admission - if prior to antibiotics and good sample ICU admission - all patients	For cases expected drug resistant or not covered by usual empiric therapy	For all patients	For all patients	For those with severe CAP or CAP with complications	For those PSI group > I	When clinically indicated, if good quality specimen and processing
Sputum culture	For all patients	Ward admission - if prior to antibiotics and good sample ICU admission - all patients	For cases expected drug resistant or not covered by usual empiric therapy	For all patients For those with severe CAP, epidemiological indicators - specific culture for Legionella	For all patients	For those with severe CAP For others if adequate sample and no prior antibiotic	For those PSI group > I	When clinically indicated, if good quality specimen and processing
Blood culture	For all patients	For all patients	For all patients	For all patients	For all patients	For those with severe CAP For others if adequate sample and no prior antibiotic	For those PSI group > I	For severe or high risk CAP (see text)
Serology	Not recommended for initial evaluation Serum saved and frozen for analysis if needed (viral and atypical pathogens)	Not recommended for initial evaluation	Not recommended for initial evaluation	For those with severe CAP or unresponsive to beta-lactam antibiotics, epidemiological risk factors, diagnosis for public health measures - viral and atypical bacterial serology	Not recommended for initial evaluation	No change to previous recommendations mentioned	For those at risk - Mycoplasma, Chlamydia, Legionella	Not recommended for initial evaluation
Antigen (Ag) testing	For those at risk of *L. pneumophila* - Legionella urinary Ag	For those with severe CAP or ICU admission - Legionella urinary Ag	For those with severe CAP - Legionella urinary Ag	For those with severe CAP - **Sputum:** viral and atypical bacterial Ags **Urine:** Pneumococcal and Legionella Ag **Blood:** Pneumococcal Ag	For those at risk of Influenza, *S. Pneumoniae* or Legionella - specific Ag tests	No change to previous recommendations mentioned	For those PSI group > I - Pneumocccal, Legionella urinary Ag	For severe or high risk CAP - Pneumococcal and Legionella urinary Ag
Invasive sample	**Bronchoscopy:** immunosuppressed, chronic CAP, suspected *M. tuberculosis* or *P. carinii*, neoplasm, foreign body **Transtracheal aspiration:** enigmatic CAP **Induced sputum:** suspected *M. tuberculosis* or *P. carinii* **Thorocentesis:** effusions	**Thorocentesis:** pleural effusion >10mm thick **Other:** fulminant CAP, unresponsive to standard therapy	**Bronchoscopy:** severe CAP **Thorocentesis:** pleural effusion >10mm thick	For severe CAP	For “selected” patients, performed by physicians with appropriate expertise - testing as listed in previous document	No change to previous recommendations mentioned	No recommendations	**Bronchoscopy:** severe CAP **Thorocentesis:** pleural effusion

In summary CAP national guidelines all support CXR as the gold standard for diagnosis. Recent updates to national consensus statements have seen a shift away from intensive microbiological testing for all patients to only those with high risk, severe CAP, or in those with treatment failure. This shift reflects the low yield and poor cost effectiveness of current tests. Antigen testing of body fluids is considered appropriate in those with severe CAP or in those with risk factors for organisms for which tests are available (i.e. pneumoccal and *Legionella* species).

2.4.1.2 Recommendations for risk assessment and site of care

Judgement of the optimal site of care, be it home, ward or ICU, requires an assessment of the severity of CAP and the risk of poor outcomes. Risk assessment of CAP patients is difficult as there are no accurate individual predictor variables on admission [86]. Physicians tend to overestimate the risk of mortality from CAP and therefore are likely to admit patients that could be safely treated at home, thus incurring significant cost to the health system and in some cases failing to acknowledge patient preference to be treated at home [38].

At least 13 CAP-specific risk models have been developed to predict either mortality or admission to ICU using a wide array of variables. The majority have been derived via multivariate statistical analysis. For a more extensive review see Auble et. al. [38] and the Medical Algorithms Project website [224]. Generally, those with more severe examination and investigation findings, and those with other comorbidities, are at a greater risk of mortality. Age, male gender and nursing home residency are also significant positive risk factors [86].

All consensus statements reviewed here acknowledge the utility of standardised risk or severity assessment scores. Consensus groups qualify their support with a number of reasons why these algorithms should not be relied on in isolation. Highlighted are important considerations for home treatment including the ability to maintain oral intake and reliably take oral antibiotics, the availability of suitable outpatient support resources, the stability of comorbidities, social factors, and patient preferences. Some consensus groups have also expressed reservations concerning the oversimplification of continuous variables by thresholding and the heavy weighting of age in current risk algorithms. An example is the thresholding of blood pressure. Most algorithms group all patients with a blood pressure of 90 mmHg systolic or less into a single category, however, there is significant difference in risk between 90 and much lower values. Heavy weighting on age means that younger patients must be significantly sicker to be classified in higher risk categories [11, 120, 139].

The risk models discussed in these consensus statements have been derived for different reasons and emanate from three sources. Both the AmTS and BTS have proposed criteria for the identification of severe CAP that requires ICU admission. The initial BTS model was derived from a prospective study of 25 British hospitals. Patients with two or more abnormal findings (from respiratory rate 30/minute or greater, diastolic BP 60 mmHg or less, and urea greater than 7 mmol/L) were found to have 21 times the risk of mortality [225]. The 1993 BTS CAP guidelines recommended the use of this rule to identify patients needing ICU admission [134]. Neill et. al. [226] in a single site study found that the addition of the presence of confusion to this rule identified those with a 36-fold increased risk of death and produced a rule with a sensitivity of 95% and a specificity 0.71% (the modified BTS or mBTS or CURB rule).

In order to identify both low risk patients (safe for discharge) and high risk patients requiring ICU, Lim et. al. [135] derived the CURB-65 rule using similar variables from the BTS rules previously discussed. CURB-65 is an acronym for severity factors included in the model (**C**onfusion - new onset with abbreviated mental state score less than 8; **U**rea greater than 7 mmol/l; **R**espiratory rate 30/minute or greater, low **B**lood pressure - systolic less than 90 mmHg and/or diastolic blood pressure less than 60 mmHg, age greater than **65** years). The sum of these factors was found to correspond to a specific risk of mortality (0 - 0.7%, 1 - 3.2%, 2 - 3%, 3 - 17%, 4 - 41.5%, and 5 - 57%). Those at low risk of mortality (score < 2, mortality 1.5%) were deemed as safe for discharge to home. Those with intermediate risk of mortality (score = 2, mortality 9.2%), were thought to be unstable enough to require hospitalisation on a general ward, and those with a high risk of mortality (score > 2, mortality 22%), were considered suitable for ICU admission. This model has been validated in a number of prospective studies (See Table 2.8). A second rule, lacking the measurement of urea, was also derived for use in the primary care setting where blood testing is not so readily available (the CRB-65 rule). A score of 0 (mortality 1.2%) on this rule was deemed to be safe for home care. Those with a score of 1 to 2 (mortality 8.15%) were believed to need hospital admission, and those with a score > 2 (mortality 31%) were assumed to need urgent hospital admission.

The pneumonia severity index (PSI) was derived from a large multisite population (n=14199) to identify CAP patients at low risk of mortality, that could be safely discharged for outpatient follow up [128]. The prediction rule includes two stages and 20 factors. The initial stage assesses risk based on age, signs and symptoms. Patients who are negative for selected risk factors and severity signs (age greater than 50 years, neoplastic disease, congestive heart failure, cerebrov-

ascular disease, renal disease, liver disease, altered mental status, heart rate 125 beats per minute or greater, respiratory 30 per minute or greater, systolic blood pressure less than 90 mm-Hg, temperature less than 35^{o}C or 40^{o}C or greater) are deemed class I, with low risk of mortality and may be treated a home. In stage 2, a weighted score is calculated for patients who are positive for any of the previous factors. This score includes the stage 1 variables, plus a second set of factors associated with CAP mortality (pH greater than 7.35, blood urea nitrogen greater than 10.7mmol/L, Serum sodium greater than 130 mEq/L, glucose greater than 13.9 mmol/L, haematocrit less than 30%, pO2 less than 60mmHg, and pleural effusion on CXR). The overall risk is equal to the sum of the weighted risk factor scores. This score corresponds to a mortality risk group (II 70 or less, III 71-90, IV 91-130, V > 130) [128]. Patients in groups I to III are at low risk of mortality (between 0.1 and 2.8%) and may be discharged. Those in groups IV and V have a mortality risk of 8.5% and 31.1% respectively, and therefore require hospitalisation [128].

The PSI is the only rule shown to safely increase the numbers of patients treated as outpatients in randomised clinical trials (see table 2.5). Low risk patients are often admitted to hospital for reasons outside the scope of the PSI. Psychosocial and frailty factors important in the admission decision include patient preference [40, 41], inadequate home support [40, 41], inability to maintain oral intake [36], homelessness [41] and substance abuse [41]. Marras et. al. [41] found that close to 25% of low risk CAP patients (PSI groups I-III) were admitted for these reasons.

.

Table 2.5: Implementation studies of the PSI

Study	Design	Outcomes
Renaud et. al. [227]	Multi-site, prospective, observational, controlled cohort study in EDs (n= 925)	PSI-user EDs - 42.8% of low risk patients treated as outpatients vs. 23.9% in PSI-nonuser EDs (adjusted odds ratio, 7.0 vs. 4.6 respectively); lower mortality in PSI-user EDs
Atlas et. al. [228]	Prospective intervention cohort (n = 146) vs. retrospective control group (n=147)	Increased outpatient treatment from 42 to 57% with no deaths in 4 week follow up
Yealy et. al. [229]	Cluster-randomized, controlled trial of differing intensity of guideline implementation including PSI (n = 3219)	More low-risk patients treated as outpatients in the moderate-intensity and high-intensity groups than in the low-intensity group (high-intensity group, 61.9%; moderate-intensity group, 61.0%; low-intensity group, 37.5%)
Marrie et. al. [230]	Cluster randomised controlled trial of guideline using the PSI (n= 1743)	Reduced admission of low risk patients (31% vs. 49%)

The AmTS defined 7 criteria for severe CAP warranting ICU admission in their 1993 guidelines, the presence of any of which indicate the need for ICU admission [133]. These included respiratory rate > 30 breaths per minute, respiratory failure (pO2/FIO2 < 250), requirement for mechanical ventilation, multilobar infection or increase in CXR opacity by 50% within 48 hours of admission, shock (blood pressure: systolic < 90mmHg or diastolic < 60mmHg), requirement for vasopressors > 4 hours, and urine output < 20mL/hour or requirement for dialysis. Ewig et. al. [231] prospectively assessed these criteria and found that they were highly sensitive for mortality (98%) but had low specificity (32%). They proposed a modified rule that separated these parameters into major and minor criteria. Major factors warranting admission alone include septic shock requiring vasopressors and acute respiratory failure with intubation and mechanical ventilation. ICU or a high level monitoring unit is also recommended for patients with 3 or more minor risk criteria. These include: respiratory rate > 30 breaths/min, PaO2/FiO2 ratio < 250, multilobar infiltrates on CXR, and acute renal failure (creatinine >2mg/dl or increase of 2mg/dl or dialysis). The modified AmTS rule showed a sensitivity of 75% and a specificity of 95%. The AmTS then adopted this modified rule in its 2001 consensus statement [11].

The new joint AmTS/IDSA statement has extended the minor criteria to include confusion, leukopaenia (WBC count < 4000 cells/mm^3), thrombocytopenia (platelet count < 100000 cells/mm^3), hypothermia (core temperature < 36^oC), or hypotension requiring aggressive fluid resuscitation [120]. The performance of this rule is yet to be tested.

Table 2.6 shows a comparison of the recommended risk assessment algorithms for the decision to admit to the ward and to ICU. The ATG point out that those with PSI risk classes IV and V are most likely to need ICU admission, but no model is formally recommended for this decision [223].

.

Table 2.6: Recommended risk assessment for admission decisions

Guideline	Ward	ICU
IDSA 2000, 2003 [83, 222]	PSI	-
CIDS/CTS 2000 [84]	Discuss PSI but no direct recommendation	Discuss modified AmTS criteria but give no direct recommendation
AmTS 2001 [11]	Discuss PSI and BTS rules as adjuncts to decision-making but no recommendation	Modified AmTS criteria
BTS 2001 [5]	Modified BTS (CURB score > 0)	Modified BTS (CURB score > 1)
BTS 2004 [121]	CURB-65 (score > 1)	CURB-65 (score > 2)
ATG 2006 [139]	PSI	PSI classes IV and V may require ICU admission
AmTS/IDSA 2007 [120]	PSI or CURB-65	Extended modified AmTS criteria

Table 2.7 contrasts the variables used in the risk models approved by national CAP consensus groups. The PSI is the only model to include comorbidities in its assessment of the risk of mortality. The PSI, CRB-65 and CURB-65 include age as a predictor. Measures of respiratory rate, blood pressure and renal function are common to all rules. CXR findings are included in only the PSI and the AmTS rules. The PSI exclusively includes a number of blood parameters (sodium, pH, glucose and haematocrit) and body temperature. The AmTS model includes a number of variables that may not be assessable in the ED (requirement for vasopressors > 4hours and increase in infiltrates over 48 hours), and is therefore designed to be utilised after the initial site of care decision has been made.

Table 2.7: Variables used in CAP prognosis algorithms cited in national guidelines

	PSI [128]	BTS [134]	BTSm [226]	CURB-65 [135]	AmTS/AmTSm [133, 231]
Age	> 50			> 65	
Sex	●				
Nursing home	●				
Congestive cardiac failure	●				
Chronic liver disease	●				
Chronic renal failure	●				
Neoplasm	●				
Cerebrovascular disease	●				
Temperature (^{0}C)	< 35, >40				
Respiratory rate (breaths/minute)	> 30	> 30	> 30	> 30	> 30
Heart rate (beats/minute)	> 125				
Blood pressure: systolic (mmHg)	< 90			< 90	< 90
Blood pressure: diastolic (mmHg)		< 60	< 60	< 60	< 60
CXR: multilobar/bilateral infiltrate					●
CXR: increase in infiltrate by > 50%					●
CXR: Effusion	●				
Altered mental Status	●		●	●	
Arterial pO2	< 60mmHg				pO2/FiO2 < 250
Arterial pH	< 7.35				
Haematocrit	< 30%				
Serum sodium	< 130mmol/L				
Serum glucose	> 14mmol/L				
Acute Renal Failure	BUN > 11mmol/L	Urea > 7mmol/L	Urea > 7mmol/L	Urea > 7mmol/L	Urine output < 20mL/hour
Use of vasopressors					Use for > 4 hours
Need for mechanical ventilation					●

Despite their differences, table 2.8 shows that the CURB-65, CRB-65 and the PSI have equivalent overall performance in predicting mortality as indicated by the area under the receiver operating characteristic (ROC) curve. The PSI contains 20 predictor variables in comparison to 6 for the CURB-65 and is more labour intensive to calculate, making it more difficult to use. Both the CURB-65 and the PSI require the return of investigation results which would produce delay in severity assessment in comparison to the CRB-65 which is based on parameters readily available on examination and history taking. The CRB-65 is therefore a more practical tool for rapid assessment of mortality risk in CAP patients.

Table 2.8: Validation studies of CURB and PSI rules: performance on mortality prediction

Study	n	Rule	Area under ROC curve
Aujesky et. al. [232]	3181	CURB-65	0.76
Spindler et. al. [233]*	114	CURB-65	0.84
Capelastegui et. al. [234]	1776	CURB-65	0.87
Barlow et. al. [235]	419	CURB-65	0.78
Capelastegui et. al. [234]	1776	CRB-65	0.86
Bauer et. al. [236]	1343	CRB-65	0.79
Barlow et. al. [235]	419	CRB-65	0.73
Aujesky et. al. [232]	3181	PSI	0.81
Capelastegui et. al. [234]	1776	PSI	0.89

* Pneumococcal pneumonia only

In summary, clinical prediction rules have been shown to have reasonable accuracy in identifying CAP patients at risk of mortality. They have been supported by national bodies in the UK, North America and Australia to assist the decision to admit to a general hospital ward or ICU. Current rules do not account for social and comorbid factors that are associated with the admission of low risk patients, and therefore it is recommended that they are only an adjunct to physician judgement for admission decisions.

2.4.1.3 Recommendations for empirical antibiotic treatment

All consensus statements reviewed define empirical antibiotics for CAP treatment. All groups agree that patients hospitalised with severe CAP should receive antibiotics via the intravenous (IV) route. Most of these documents acknowledge that long delay to initial antibiotic treatment is associated with poor outcomes. The BTS recommend treatment within 2 hours of admission [3]. IDSA guidelines acknowledge studies that indicate greater than 4-8 hour delays increase mortality [3, 83, 222]. The 2001 AmTS statement refers to this information in the context of balancing the need for rapid treatment against the search for an aetiology [11]. The combined AmTS/IDSA document supports that treatment should occur while the patient is in the ED rather than setting a threshold time [120]. These observations are consistent with current evidence that there is a 15% increase in mortality if antibiotics are delayed more than 4-8 hours [22, 61, 62].

Each of these consensus groups use different methods to stratify patients into treatment groups (see tables 2.9 and 2.10). Overall there are 4 characteristics used to divide up treatment groups based on risk: severity, site of care (outpatient, ward, ICU), risk of mortality (age, comorbidities, nursing home residency, aspiration), and risk of specific organism (nursing home residency, prior antibiotic treatment, aspiration, Pseudomonal infection, tropical aetiology). Site of care can be seen as a marker of severity - severe cases are most likely to be treated in ICU and mild cases are most likely to be treated as outpatients. Age and comorbidity are likely to influence both the severity of disease and the aetiology. In tables 2.9 and 2.10 I have separated treatment regimens into those with and without risk modifying factors.

North American guidelines (IDSA, AmTS and CTS/CIDS) favour an approach based on site of care, comorbidity assessment and Pseudomonas risk assessment, with comorbidity assessment more prominent in the outpatient group. The BTS do not acknowledge a robust association between comorbidity and aetiology, only with severity of CAP, and therefore do not use comorbidity to partition treatment [5]. This group favours formal severity assessment using the simple CURB-65 model [121, 135]. Severity and site of care are then used to determine empirical antibiotics. Both Australian guidelines divide up treatment based on mortality risk assessment and risk of tropical aetiology [139, 223]. The ATG use the PSI [139], while the Australian Medicines Handbook (AMH) suggest a non-formal risk assessment [223]. It should be noted that there is no current evidence on the efficacy of the PSI or the CURB-65 for determining antibiotic treatment. These algorithms were devised to determine site of care not treatment selection [237].

Recommended treatment for uncomplicated CAP treated on an outpatient basis consists of various combinations of beta-lactam (e.g. penicillins, amoxicillin, cephalosporins, carbepenems), macrolide (e.g. azithromycin, clarithromycin, erythromycin, roxithromycin), tetracycline (e.g. doxycyline), respiratory fluoroquinolone (e.g. ciprofloxacin, levofloxacin and moxifloxacin), and aminoglycoside (e.g. gentamicin) antibiotics.

For patients with no modifying factors, who are stable enough for outpatient treatment (see table 2.10), monotherapy is preferred by all groups. North American guidelines favour macrolides as first line treatment, followed by doxycycline. In contrast, British and Australian guidelines regard amoxicillin as first line and a macrolide or doxycycline as alternatives. The underlying assumption being that most undocumented infections are *S. pneumoniae.* This approach avoids promoting resistance to macrolides and fluoroquinolones which is already becoming a problem in some parts of the world [220]. For outpatients with modifying factors, North American statements promote the use of fluoroquinolones and various combinations of beta-lactam, macrolide, tetracycline and fluoroquinolone antibiotics.

For those admitted to hospital (see table 2.9) on a general ward without modifying factors, North American and British statements generally support either monotherapy with a fluoroquinolone or combination therapy with a beta-lactam and a macrolide. Australian guidelines suggest monotherapy with a beta-lactam, a macrolide, or doxycycline. The AMH also offers a combination of clarithromycin and doxycycline if atypical organisms are suspected. For those with modifying comorbidities the AmTS 2001 statement suggests combination therapy with a beta-lactam and either a macrolide or doxycycline, or monotherapy with a fluoroquinolone.

The majority of North American regimens for patients admitted to ICU consist of combination therapy of beta-lactam plus a macrolide or a fluoroquinolone. The CTS/CIDS in their 2000 statement support monotherapy with a fluoroquinolone or combination therapy with a beta-lactam and a macrolide. For the treatment of severe CAP the BTS guidelines support the use of a beta-lactam in combination with a macrolide, with the addition of rifampicin and a fluoroquinolone if required. For those with risk factors for pseudomonal infection North American guidelines propose variable combinations of anti pseudomonal beta-lactams, fluoroquinolones, aminoglycosides and macrolides.

The Australian guidelines propose similar treatments based on mortality risk groups. For moderate risk both guidelines recommend combination therapy with a beta-lactam plus doxycycline or a macrolide with the option of adding gentamicin. For moderate risk with a probable tropical infection (*B. pseudomallei, A. baumannii*) both guidelines recommend combination therapy with the beta-lactam ceftriaxone and a macrolide. The AMH also suggests adding gentamicin. For high risk patients both groups propose a beta-lactam plus a macrolide or gentamicin. If tropical infection is expected in high risk patients the use of a carbepenem plus a macrolide is supported by both groups.

2.4.1.4 Other recommendations

With the exception of the Australian guidelines which focus on antibiotic selection, all consensus statements include recommendations for ongoing assessment, supportive care, investigation and management of antibiotic treatment failure, IV to oral antibiotic switch, criteria for discharge, follow-up and prevention. Given that this thesis concerns only the initial management these areas will not be discussed in detail.

Table 2.9: Inpatient antibiotics recommended by consensus statements

	CIDS/CTS 2000 [84]	AmTS 2001 [11]	IDSA 2003 [222]	BTS 2001, 2004 [5 121]	ATG 2006 [139]	AmTS/IDSA 2007 [120]	AMH 2007 [223]
No modifying factors	Respiratory fluoroquinolone or 2nd/3rd/4th generation cephalosporin + macrolide	Azithromycin or antipneumococcal fluoroquinolone	Respiratory fluoroqunolone or macrolide + beta-lactam	LOW SEVERITY: amoxicillin + either erythromycin or clarithromycin or anti-pneumococcal fluoroquinolone (alone) or either IV ampicillin or benzylpenicillin + erythromycin or clarithromycin or levofloxacin	PSI I&II: amoxycillin or if atypical organism suspected - clatrithromycin or roxithromycin or doxycycline	Fluoroquinolone or a beta-lactam plus a macrolide	LOW RISK: oral amoxycillin or azithromycin or clarithromycin + doxycycline if atypical infection suspected.
Modifying factors	ICU: IV Respiratory fluoroquinolone or macrolide + cefotaxime or ceftriaxone or beta-lactam-B-lactamase inhibitor. ICU + PSEUDOMONAS RISK: Antipseudomonal fluoroquinolone (ciprofloxacin) + antipseudomonal beta-lactam (or aminoglycoside) or Antipseudomonal beta-lactam + aminoglycoside + macrolide	AGE, COMORBIDITY, NURSING HOME, RECENT ANTIBIOTICS: IV beta-lactam (cefotaxime, cetriaxone, ampicillin-sulbactam, high dose ampicillin) + macrolide or doxycycline or antipneumococcal fluroquinolone (alone). ICU: IV beta-lactam (cefotaxime, ceftriaxone) + IV azithromycin or IV fluoroquinolone. ICU + PSEUDOMONAS RISK: IV anti-pseudomonal beta-lactam (cefepime, imipenem, meropenem, piperacillin/tazobactam) + IV quinolone (ciprofloxacin) or IV anti-pseudomonal beta-lactam + IV aminoglycoside + either IV azithromycin or IV non-pseudomonal fluoroquinolone.	ICU: beta-lactam + macrolide or respiratory fluoroquinolone. ICU + PSEUDOMONAS RISK: Antipseudomonal beta-lactam + ciprofloxacin or aminoglycoside and respiratory fluoroquinolone or a macrolide.	HIGH SEVERITY: co-amoxiclav or cefuroxamine or ceftriaxone or cefotaxime + erythromycin or clarithromycin +/- rifampicin or antipneumococcal fluoroquinolone + benzylpenicillin	PSI III:& IV NON TROPICAL: IV benzylpenicillin or amoxycilllin or ampicillin or cephalosporin + doxycycline or clarithromycin or roxithromycin +/- gentamicin. PSI III:& IV TROPICAL: IV ceftriaxone + gentamicin. PSI V NON TROPICAL: IV azithromycin or erythromycin + ceftriaxone or cefotaxime or benzylpenicillin + gentamicin. PSI V TROPICAL: meropenem or imipenem + azithromycin or erythomycin	ICU: beta-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) **+** either azithromycin **or** fluoroquinolone. ICU + PSEUDOMONAS RISK: Anti-pseudomonal beta-lactam + ciprofloxacin or levofloxacin or aminoglycoside and azithromycin or aminoglycoside and fluoroquinolone	MODERATE RISK NON TROPICAL: IV benzylpenicillin or amoxycillin or cephazoline or ceftriaxone + doxycycline or azithromycin or clarithromycin. If G-ve suspected add gentamicin. MODERATE RISK TROPICAL: IV gentamicin + ceftriaxone + erythromycin or azithromycin. HIGH RISK NON TROPICAL: IV azithromycin or erythromycin + cefotaxime or ceftriaxone or benzylpenicillin + gentamicin. HIGH RISK TROPICAL: IV meropenem or imipenem + erythromycin + azithromycin

Table 2.10: Outpatient antibiotics recommended by consensus statements

	CIDS/CTS 2000 [84]	AmTS 2001 [11]	IDSA 2003 [222]	BTS 2001, 2004 [5] [121]	ATG 2006 [139]	AmTS/IDSA 2007 [120]	AMH 2007 [223]
No modifying factors	Macrolide (erythromycin, clarithromycin or azithromycin) or doxycycline	Macrolide (Clarithromycin) or doxycycline	Macrolide or doxycycline	Amoxicillin, macrolide (erythromycin, clarithromycin)	PSI I&II: amoxycillin or doxycycline or macrolide (clarithromycin or roxithromycin)	Macrolide or doxycycline	LOW RISK: Amoxycillin or azithromycin or clarithromycin
Modifying factors	COAD, NO RECENT ANTIBIOTIC OR STEROID USE: Macrolide (Clarithromycin), Doxycycline COAD, RECENT ANTIBIOTIC OR STEROID USE: amoxicillin-clavulanate or 2nd generation cephalosporin plus a macrolide, fluoroquinolone (levofloxacin, moxifloxacin or gatifloxacin) ASPIRATION: amoxicillin-clavulanate + macrolide Respiratory fluoroquinolones + clindamycin or metronidazole NURSING HOME: Respiratory fluoroquinolone (alone) or amoxicillin-clavulanate + macrolide or 2nd generation cephalosporin + macrolide	AGE, COMORBIDITY, NURSING HOME, RECENT ANTIBIOTICS: Oral cefodoxime, cefuroxamine, high dose amoxicillin plus doxycycline or clarithromycin, amoxicillin-clavulanate or IV ceftriaxone followed by oral cefpodoxime plus doxycycline or clarithromycin, fluoroquinolone (levofloxacin, moxifloxacin or gatifloxacin)	RECENT ANTIBIOTICS: Respiratory fluoroquinolone or macrolide + amoxycillin or amoxycillin-clavulanate. COMORBIDITIES: Macrolide or respiratory fluoroquninolone. COMORBIDITIES + RECENT ANTIBIOTIC: Respiratory fluoroquinolone or macrolide + beta-lactam SUSPECTED ASPIRATION: Amoxycillin-clavulanate or clindamycin INFLUENZA + BACTERIAL: beta-lactam or respiratory fluoroquinolone. NURSING HOME: respiratory fluoroquinolone or amoxicillin-clavulanate + macrolide			COMORBIDITY, RECENT ANTIBIOTIC: Flouroquinolone or a beta-lactam plus a macrolide	

2.4.1.5 Implementation of CAP consensus statements

The North American and British national consensus statements are large documents covering most aspects of care across the complete spectrum of care facilities. They are therefore more reference documents rather than practical guidelines for implementation. The true impact of these documents on individual patient care is near impossible to assess. A number of observational studies have measured compliance and outcomes with antibiotic recommendations of national consensus guidelines (see table 2.11). These show a relatively high level of compliance (around 80%) with antibiotic guidelines, with a variable impact on outcomes. It is interesting to note that physicians are not always clear about their knowledge of national guidelines. Marras et. al. [238] found that 22% of those that believed they were complying were actually deviating, 46% of those that thought they were deviating were actually complying, and 64% that were uncertain were complying. Switzer et. al. [209] assessed the knowledge and use of national CAP guidelines in over 300 US hospital physicians. They found that 29% had not heard of the national AmTS guidelines, 30% had seen the guidelines, 20% had read them, and 20% had used them. Those using the guideline were more likely to be pulmonary or infectious disease specialists, spend fewer hours per week in direct patient care, read journals more frequently, rated higher on “intellect” personality trait, and had more positive attitudes to guidelines. These figures suggest that the dissemination of recommendations is mainly via methods other than the documents themselves, which are reviewed mainly by specialists and academics.

Table 2.11: Compliance with national consensus statements

Authors	Consensus statements	Effect on processes	Effect on outcomes
Marras et. al. [238]	AmTS, CIDS, CTS	80% compliance with antibiotic recommendations, 54% of non-compliance occurs where aspiration is likely	Non-compliance had no significant effect on length of stay (median = 6 days) or mortality (12 vs. 14% with compliance)
Gleason et. al. [15]	AmTS		Outpatients <60 years with no comorbidity had 3-fold lower antimicrobial costs ($US 5.43 vs. $US 18.51; P<.001) and outpatients > 60 years or with comorbidity had 10-fold higher antimicrobial costs ($US 73.50 vs. $US 7.50; P<.001), with no significant differences in outcomes.
Menendez et. al. [239]	AmTS, SEPAR (Spanish)	Compliance with antibiotic recommendations 88% for AmTS and 66% for SEPAR guidelines	Mortality in severe CAP (PSI class V) was significantly higher in patients with nonadherent treatments (SEPAR relative risk = 2.6; AmTS relative risk = 2.5).
Dudas et. al. [143]	AmTS	Compliance 81%	
Menendez et. al. [240]	SEPAR		Decreased costs (€1,665.5 vs. €1,710.5) for adherent treatment; mortality and readmission were 10% and 2.1% for adherent treatment vs. 13.6% and 6.2% for nonadherent treatment

Given the uncertainty in CAP diagnosis and risk assessment and the complexity and scope of CAP treatment it is not surprising that national consensus documents are so large and unwieldy. The challenge is then to organise this information into a format that can practically change local care processes to improve the overall quality of CAP treatment. The need for locally derived guidelines and other health quality activities such as education and quality audit to promote national practice recommendations is acknowledged by the BTS [5], AmTS, and IDSA [120].

2.4.2 Local CAP guidelines

Broad consensus documents are adapted and simplified by local institutions to suit their needs. A survey of local CAP guidelines in the United Kingdom indicated 83% of hospitals had a local CAP guideline which broadly followed the BTS national consensus statement of the time [200]. Local guidelines reflect the concerns of stakeholders involved in their construction, the generalisability of national recommendations, and the local resources available. An Australian example is the local CAP guideline at the Royal Adelaide Hospital (see appendix figure 9.1) [241, 242]. This one page document was developed from the Intermountain Health CAP guideline, which in turn is derived from the AmTS 1993 consensus statement [243].

Much of the compliance with national consensus statements is likely to be due to the implementation of local guidelines. Hagaman et. al. [147] found that a local guideline increased physician awareness of American Thoracic Society recommendations (5% to 40%) and use of switch therapy (60% to 86%). This was associated with a decreased length of stay from 3.6 to 2.4 days.

2.4.2.1 Efficacy of local guidelines

Despite low rates of compliance [40] the implementation of local CAP guidelines has resulted in variable improvements in the quality of care, outcomes, and reduction of treatment costs for CAP patients. Table 2.12 summarises studies of local guidelines. Only two studies have shown a reduction in mortality with guideline introduction [244, 245]. Other studies have indicated reduced hospitalisation rates for low-risk patients [230, 244], earlier switch from IV to oral antibiotics and earlier discharge for low risk patients [230 246], decreased delay to initial antibiotic [247, 248], decreased length of stay [230, 243, 247, 248], less medical complications [148], and reduced costs [245]. These studies are highly heterogeneous, both in guideline content and in study design. Implementation factors (e.g. dedicated study nurses, and improved home care on discharge) are likely to confound improved outcomes as they increase the level of care and follow up offered, independent of the guidelines themselves.

Table 2.12: Recent studies of the effectiveness of CAP guidelines

Author	Design	Subjects	Guideline scope	Implementation factors	Outcomes
Wiengarten et. al. [246]	Alternate month time series	Control n = 78 Intervention n = 68	Oral to IV antibiotic guideline	Case note alerts and direct treating doctor contact when low risk criteria met	No significant increase in percentage treated according to the guideline (Intervention 76% vs. 64%)
Rhew et. al. [249]	Prospective, randomised, multisite trial	Low risk patients n = 242	Discharge guideline		No significant change in guideline compliance, length of stay, patient outcomes, care following hospital discharge, or patient satisfaction scores
Benenson et. al. [247]	Retrospective: 3 months prior to intervention, 10-12 months after, 34-36 months after	Pre-intervention n = 64 Post-intervention 1 n = 96 Post-intervention 2 n = 122	Guidelines for antibiotic selection, antibiotic switch based on culture, timing of antibiotic delivery in ED	Pneumonia pathway nurse, social services, standard antibiotic order sheet	Mean time to antibiotic decreased from 5.25 to 2.85 hours at 3 years; antibiotic delivery in ED increased from 58% to 97%; LOS decreased from 9.7 to 6.4 days; non-significant decrease in hospital mortality from 9.6 to 5%
Estrada et. al. [245]	Retrospective consecutive series	Intervention n = 97 Control n = 275	Guidelines for antibiotic selection, tests, ancillary care (procedures, O2, bronchodilators, nutrition evaluation, early mobilisation, patient assessment and education)	Study nurse, home care available	Total costs significantly lower (by $US 2456 unadjusted, by $US1807 adjusted); significantly reduced mortality (0 vs. 5%) in unadjusted analysis; no significant difference in mortality in adjusted analyses.
Dean et. al. [244]	Prospective study after implementation vs. retrospective control	Pre-intervention n = 199 Post-intervention n = 264	Guidelines for risk assessment, admission to ward or ICU, and antibiotics	Guideline plus data proforma	Guideline proforma use in 90%; reduced percentage of CAP patients admitted in 30 days of presentation (13.6 vs. 6.4%); no change in mortality
Marrie et. al. [230]	Cluster randomised trial	n = 1743	Guidelines including the PSI for the admission decision, antibiotics, IV to oral antibiotic switch, and discharge criteria	Daily assessment by study nurse, case note alert for reaching criteria for IV to oral antibiotic switch and for discharge	Significantly shorter time on IV antibiotics (4.5 vs. 6.3 days) and length of stay; lower admission of low risk patients (18% less); no difference in patient outcome measures.
Meehan et. al. [248]	Retrospective before/after comparison	Pre-intervention n = 1242 Post-intervention n = 1146	Generic pathway modified by local committees focusing on rapid antibiotic administration, blood culture collection, and oxygenation assessment	Peculiar to local site	Increased antibiotics within 8 hours (83.4 vs. 88.8%).; increase in oxygenation assessment within 24 hours of admission (93.6 vs. 95.4%); decreased length of stay (7 vs. 5 days); no difference in percentage blood cultures taken, mortality or readmission.
Dean et. al. [243]	Multisite, retrospective before/after study	n = 28661, 7719 admitted to hospital	Guidelines for risk assessment, admission to ward or ICU, and antibiotics	Guideline plus data proforma	3.2% reduction in mortality; significant 0.6 day reduction in length of stay; increase in recommended antibiotics from 28.1% to 56.3%
Fine et. al. [148]	Cluster randomised trial: practice guideline alone vs. multifaceted strategy	Control n = 325 Intervention n = 283	Guidelines for conversion from IV to oral antibiotics and discharge based on clinical stability criteria.	Daily assessment by study nurse, alert of attainment of criteria in case notes, follow up recommendation to treating doctor, offer to arrange home nursing care	Significantly less medical complications in the intervention group (55% vs. 63%); no significant difference in time of antibiotic switch from IV to oral

2.4.3 CAP CDSS

There are few studies of CDSS implemented specifically to treat CAP. Implementations have addressed the issues of diagnosis, admission, and antibiotic selection. The majority include a computer-based version of the PSI [42, 194, 195]. Both Leber et. al. [42] and Wright et. al. [194] have trialled a computer-based version of the PSI coupled to antibiotic prescribing guidelines. Leber et. al. [42] implemented a computer-based version of the PSI in an emergency department setting and found high rates of disagreement with recommendations. Seventy two percent of low risk patients were admitted when the PSI indicated they were fit for discharge (PSI groups I and II), and in 78% of low risk cases there was disagreement in recommended antibiotic treatment. Where disagreement occurred, doctors most often believed that patients were sicker than the PSI indicated (85%), or admitted them due to comorbidities. The greatest disagreement with the admission recommendations occurred when psychosocial factors were involved. For high risk patients (PSI group III or above) there was 100% agreement. The initial diagnosis of CAP was erroneous in 40% of cases.

Wright et. al. [194] implemented a computer-based version of the PSI in an Australian ED. The PSI software was coupled to an alerting system for recommended antibiotics and a clinical pathway for IV to oral antibiotic switch following normalisation of fever. An audit and physician-initiated feedback capability was also included in this system. The introduction of this intervention was associated with a 51% reduction in the mean time to antibiotic (from 6 to 3 hours), an improvement from 29 to 100% of treatment matching initial antibiotic selection recommendations and improvement from 60% to 100% of IV to oral switch within 24 hours of defeverescence.

Stevenson et. al. [193] implemented an internet-based guideline for CAP antibiotic selection across 5 North American rural hospitals. In a pre-test / post-test study they found that agreement with recommendations significantly improved, but compliance was highly variable (0-71%). Many physicians refused to use the system due to the time taken for data entry (at least 5 minutes). There was also poor communication between allied health staff using the system and treating doctors.

The medical informatics group at the University of Utah have designed and piloted an alerting system at Latter Day Saints Hospital (Salt Lake City) that combines a Bayesian pneumonia diagnosis model, a natural language processing system to identify CAP-positive CXR reports, au-

tomatic calculation of the PSI, and a treatment guideline [195]. The system combines data collected by ED nurses (demographic, examination, and history), with CXR report and laboratory findings, to calculate the likelihood of pneumonia and the risk of mortality. The decision to admit is based on the PSI, which then triggers an online protocol for patient treatment including antibiotic selection. The Bayesian diagnosis model combines CAP risk factors, symptoms, and severity signs, with CXR data and has a sensitivity of 95% and a specificity of 96.5% in retrospective testing [250]. This model was developed using a large and rich local data set, enabling the authors to derive correlations between variables and include dependencies in model structure. The culture of clinical data entry at this site is unusual in comparison to the vast majority of clinical environments, but this system provides a good example of the benefits of linking of investigation, history and physical examination data. Prospective evaluation of this system is yet to be performed.

In summary, CDSS for CAP diagnosis and treatment have been implemented at few sites. The most promising results come from the Wright et. al. [194] study which shows that CDSS are able to significantly reduce the delay to initial antibiotic, improve the selection of antibiotics and reduce the delay to safe IV to oral antibiotic switch. It is interesting to note that this study combines some of the factors identified in systematic reviews as important in CDSS success (local involvement in development and feedback) [2, 218]. No published study has examined the impact of CAP CDSS on patient outcomes.

2.5 CAP diagnosis models

It is surprising, given the high uncertainty associated with CAP diagnosis and the support for risk algorithms, that diagnostic decision support is not recommended in CAP national consensus statements. A number of authors have derived algorithms to assist in CAP diagnosis. Table 2.13 summarises the characteristics and performance of simple CAP diagnosis models. Predictor variables differ considerably between the models (See Table 2.14). Only body temperature is included in more than half of the models reviewed (5/8). Cough and heart rate appear in half of the group. Some models focus exclusively on objective signs of infection (e.g. fever, tachycardia and increased respiratory rate) [251], while others focus more on patient reported symptoms [252].

Only Singal et. al. [253] include a formal assessment of physician estimate of CAP prior probability in their diagnosis model. The majority of models were derived from samples of patients

with expected respiratory disease. It is likely that some estimate of CAP probability, based on an overall impression of the patient, is included in the derivation of these models.

.

Table 2.13: Studies of simple CAP diagnostic models

Author	Subjects	Model	Performance
Diehr et. al. [252]	Adults with low severity illness presenting ED with a cough of < 1 month duration (n = 1819)	In those presenting with cough - discriminant analysis identified a rule that allocates point scores for rhinorrhoea (-2), sore throat (-1), night sweats (1), myalgias (1), sputum all day (1), respiratory rate > 25 (2), and temperature > 37.3 (2)	A summed score of 0 gave a sensitivity of 74% and specificity of 70%.; a score of -1 had a sensitivity of 91% and specificity of 40%; at this threshold performance was superior to clinician judgement as indicated by antibiotic treatment ordered
Heckerling et. al. [254]	Adults presenting to ED with a respiratory complaint or fever who had a CXR (n = 464)	Any abnormal auscultatory finding	Positive predictive value 55.5%, negative predictive value 93.2%; operationalisation of this rule would have halved the number of CXRs taken with a 7% false negative rate.
Singal et. al. [253]	Adults presenting to ED with a respiratory complaint who had a CXR (n = 225)	Logistic regression: pCAP = $1/(1 + e^{-y})$; y = -3.095 + 1.214 (cough present) + 1.007 (fever present) + 0.823 (crackles present)	There was no significant difference between physician accuracy and model accuracy (Area under receiver operating curve = 0.75 vs. 0.729 respectively).
Gennis et. al. [255]	Adults patients presenting to ED with a respiratory illness (n = 308)	1 of temperature > 37.8 ^{o}C, heart rate > 100/minute, respiratory rate > 20/minute, any abnormal auscultatory finding	1 abnormal vital sign was 97% sensitive and 18% specific or 1 abnormal auscultatory finding was 80% sensitive and 38% specific for CAP.
Heckerling et. al. [256]	Adults presenting to ED with a respiratory complaint or fever who had a CXR (derivation n = 1134; 2 validation cohorts n = 150 and n = 152)	Stepwise logistic regression: temperature > 37.8 ^{o}C, heart rate > 100/minute, rales, decreased breath sounds, absence of asthma; nomogram based calculation of pneumonia probability based on population prevalence and the number of findings present; increased prevalence and number of findings equates to increased probability	Area under the ROC curve = 0.76 to 0.82, sensitivity = 90-93%, specificity = 35-43%.
Okimoto et. al. [257]	Outpatients with one of fever, cough, sputum or coarse crackles, who had a CXR (n = 79)	Presence of all of fever, cough, sputum, and coarse crackles	Sensitivity = 91.7%, specificity = 92.7%
Kyriacou et. al. [258]	Adults presenting to ED with CXR confirmed CAP (n = 100), matched with influenza-like illness controls (n = 100)	Presence of temperature > 100.4 ^{0}F, heart rate > 110 bpm, and SaO^2 < 96%	Sensitivity = 70.8%, specificity = 71.9%
Khalil et. al. [251]	Adults presenting to ED (n = 8811)	Presence of one respiratory symptom (cough, chest pain or shortness of breath) and any abnormality of the vital signs (temperature > 38 °C, heart rate >100 beats/minute, respiration rate 20 breaths/minute or pulse oximetry < 95%)	Sensitivity = 90%, specificity = 76%

Table 2.14: Symptoms used in CAP diagnostic algorithms

	Diehr et. al. [252]	**Heckerling et. al.** [254]	**Singal et. al.** [253]	**Gennis et. al.** [255]	**Heckerling et. al.** [256]	**Okimoto et. al.** [257]	**Kyriacou et. al.** [258]	**Khalil et. al.** [251]
CAP population prevalence					●			
Physician pre-test probability			●					
Age					●			
Asthma					●			
Cough			●	●		●	●	
Dyspnoea							●	
Chest Pain							●	
Fever			●			●		
Rhinorrhoea	●							
Sore Throat	●							
Night Sweats	●							
Myalgias	●							
Sputum	●					●		
Temperature	●			●	●		●	●
Respiratory rate	●			●			●	
Heart rate				●	●		●	●
Rales/crackles			●		●	●		
Decreased breath sounds					●			
Any abnormal auscultatory finding		●						
SaO^2							●	●

Performance of these models is reasonable with sensitivity ranging from 74-97% and specificity from 38 to 92.7%. Emerman et. al. [259] prospectively compared the accuracy of 4 of these models and found that sensitivity ranged from 62 to 76% and specificity from 55 to 76%. Physician judgement was assessed based on the treating physician's intention to order a CXR to investigate possible CAP. The sensitivity of physician judgment was 86% and specificity was 58% indicating a relatively conservative decision process. None of the models were more sensitive than physician assessment, however, 3 were more specific for CAP (Gennis et. al. [255] 76%, Heckerling et. al. [256] 67%, and Diehr et. al. [252] 67%). The overall accuracy (accuracy = true positives + true negatives / total patients) of 2 models (Gennis et. al. [255] 76%, Heckerling et. al.

[256] 68%) was superior to that of physician judgement (60%). There were no common predictor variables associated with this superior performance.

Okimoto et. al. [257] derived a diagnosis model with a sensitivity and specificity in the 90% range, from an outpatient sample. The model has a mix of both symptoms, signs and includes pulse oximetry. The study population consisted of outpatients rather than those presenting to ED. This model's accuracy may be confounded by the likelihood that outpatient samples contain reduced proportions of elderly patients with comorbidity, that are harder to diagnose with CAP due to atypical presentation. This aside, the model's performance supports the use of pulse oximetry as an early diagnostic tool in CAP.

Overall there is no clear set of strong predictor variables across these studies. Further studies are required to assess an optimal subset. There are 3 major problems for validity and generalisability of CAP diagnostic rules. Firstly, there is a lack of an accurate and reliable gold standard - both CXR and microbiological testing have poor sensitivity and specificity [86]. Secondly, there is poor inter-rater reliability of the clinical signs of CAP [4, 79, 86]. Finally, the presentation of CAP varies with age - older patients who are more likely to have CAP, are less likely to report common CAP symptoms [81]. Studies of predictor variables and outcomes using chest CT as the gold standard may provide superior prediction, however both the increased risk from radiation dose and cost of testing are prohibitive. In such studies, age-based sub-group analysis of predictor variables may help to design age-specific models for diagnosis. Local training and consensus may be the only way to improve inter-rater reliability of CAP signs. Given the geographic variation in CAP aetiology, and in diagnostic inter-rater reliability, models may best be derived locally with regular revision.

More complex mathematical models using large numbers of variables have shown superior performance to simple models. Aronsky and Haug [250] developed a Bayesian network model using 24 variables including blood test and CXR results. This model, with sensitivity fixed at 95%, returned specificities ranging from 95.6-97.3% and an area under the ROC curve of 0.977 to 0.991 across 3 samples. In a prospective analysis at a fixed sensitivity of 95%, the model was 68.5% specific with an area under the ROC curve of 0.93 [260].

Heckerling et. al. [261-263] have achieved improved accuracy (area under the ROC curve of up to 0.954) using artificial neural networks optimised by genetic algorithms based on larger numbers

of variables (35). One direct comparison has shown that artificial neural networks have slightly superior accuracy to Bayesian networks for diagnosing CAP, significant in a large sample (area under the ROC curve 0.99 vs. 0.98, p = 0.0044). The clinical significance of this difference is negligible [264].

These models require investigation result return, are not practical for early implementation, and are therefore less likely to have an impact on CAP treatment processes in the ED. Given the amount of data entry required for the high number of variables used, there is less likelihood of compliance at most sites where clinical data entry is not routine.

2.6 Conclusions on CAP decision support

The predominant model for decision support in CAP care is the paper-based guideline. These documents are largely concerned with handling patient complexity in terms of diagnosis, risk assessment and treatment selection. They do not address issues with process flow and resources at the point of care. National medical specialist bodies have developed large statements that attempt to assess all of the current evidence and recommend processes at each stage of care. Much of the evidence behind these documents is low grade and the final form is dictated by consensus and opinion. Consequently, they show considerable variation in recommendations. These statements are too complex to be anything but reference documents and are read mainly by specialists and academics who are not usually involved in initial treatment decisions. Surprisingly, some studies of national recommendations have shown that there is reasonable compliance with antibiotic selection, however much of this may be due to local guidelines. Overall the compliance with local guidelines is highly variable. While there has been some success in improving processes, few have shown improvement in patient outcomes.

Modelling for risk of CAP-related mortality has become widely accepted as useful within the limitations of current models. The most widely recommended models such as the PSI and CURB-65 do not account for social factors and patient preferences which limit their applicability to “real life” admission decisions. In contrast, the authors of national consensus on CAP care have largely dismissed multivariate models of diagnosis. CXR remains the gold standard despite its poor sensitivity and specificity (as discussed in chapter 1). Currently available diagnostic models based on simple symptoms and signs have achieved sensitivity of around 70-90% and specificity of between 35-90%. Such models may help identify more patients early in their admission, thereby reducing delays to treatment. There is a current consensus that timely anti-

biotic treatment is important to reduce the risk of mortality. Given that CAP is difficult to diagnose and that the requirement for CXR produces significant delays, targets of 2-8 hours are likely to be difficult to achieve.

CDSS are superior to paper-based systems in terms of ease of revision, dissemination, presentation, sophistication and active use characteristics. There is a growing body of evidence supporting their positive impact on health care performance. Few systems have been implemented to specifically improve CAP care, but one small Australian study by Wright et. al. [194] has shown that CDSS are effective in the enhancement of antibiotic treatment time, selection and oral switch. CDSS based around linkage of available patient data offer the opportunity to improve the quality of care and patient safety. Entry of some data from the clinical history and examination adds to the predictive strength of these models, but in general the current hospital working environment is not geared to collection of this data. Reliability in data entry is likely to be achieved by minimising the items required, optimising the user interface and designing the system to fit in with existing workflow.

Having introduced the problems of CAP treatment in chapter 1, and in this chapter reviewed efforts to address these problems via decision support, I will move on to focus on a key aspect of CAP care likely to be amenable to improvement via CDSS - antibiotic timing. In chapter 3 I discuss the relationship between antibiotic timing and outcomes, and the use of antibiotic timing as a quality indicator of CAP care. I then review current efforts to improve antibiotic timing for CAP patients. Finally, I analyse studies of the predictors of delayed antibiotic treatment for CAP.

3 Review of interventions to improve antibiotic timing in community-acquired pneumonia

3.1 Timing of initial antibiotic as a quality indicator of CAP treatment

High intra and inter-hospital variation in the timing of initial antibiotic treatment to patients diagnosed with CAP is well documented [69, 70, 265]. Antibiotic delay greater than 4 to 8 hours has been associated with increased mortality and length of stay (LOS) in hospital (See table 3.1). Based on this evidence, major health assessment and funding bodies in the United States, such as Medicare and Medicaid (CMS - Centres for Medicare and Medicaid services), and the independent body for hospital accreditation the Joint Commission on Accreditation of Health Care Organizations (JCAHO), identified the timely delivery of antibiotics within 4 hours as one of 6 key performance indicators for CAP treatment. These groups have also targeted process indicators for quality care of myocardial infarction, heart failure, post-surgical infections, and pregnancy related conditions. In 2003 CMS was funded with $US 400-450 million in incentive payments for collection of hospital data on the performance of these quality indicators, under Section 501(b) of the Medicare Modernization Prescription Drug, Improvement and Modernization Act. This data has been publicly reported for comparison of hospital performance. A proportion of CMS funding was also used to set up a pilot of a "pay for performance system" (i.e. the Premier group program - "Hospital Quality Incentive Demonstration Project", including 268 hospitals) based around these indicators [65, 266, 267]. Under such systems the hospital reimbursement for patients is based on achievement of targets for indicators associated with their diagnosed condition [67]. At some sites staff bonus schemes have been introduced based on achievement of these targets [97].

Despite this industry-wide drive to improve the timeliness of antibiotic delivery to patients with CAP there has only been a small improvement in performance and outcomes. The mean rate of

antibiotics within 4 hours at CMS hospitals across the US improved by 7.2% between 2002 and 2004, however on average only 69% of patients were treated in this time frame [268]. Recently published data indicate that the system thus far has failed to significantly improve CAP in-hospital mortality, but has reduced geometric mean length of stay from 4.1 to 3.7 days [269].

The criteria for this benchmark (known as "PN-5b") are controversial for a number of reasons. Some authors argue that the 4 hour goal is not possible given diagnostic uncertainty, that it promotes inappropriate antibiotic use prior to diagnosis and may limit return from subsequent microbiological testing. Inappropriate antibiotic use may increase antibiotic resistance and increase adverse drug reactions. It has also been argued that the target encourages the inappropriate selection or deselection of CAP patients, that it promotes disadvantage to those in urban areas due to greater risk of overcrowding and increased antibiotic delay, it promotes a "shot gun" approach to diagnosis in terms of ordering unwarranted tests, it directs resources away from other conditions (CAP accounts for as low as 1% of total workload at some sites [270]), and that the criteria have not had adequate testing in pilot studies [267, 270-274]. For these reasons Pines et. al. [271] argue the timing criteria fail to meet some of the guidelines set by the American Medical Association for pay for performance systems [275].

The identification of all CAP patients in the ED is unlikely due to both the inaccuracy of CXR and its poor inter-rater reliability (see chapter 1). Given these problems, significant changes have been made to the CMS/JCAHO criteria for case inclusion in PN-5b reporting. Initially selection was based on patients with an International Classification of Disease (ICD) discharge diagnosis of CAP and a working or even a differential diagnosis of CAP made by physicians in the ED which could be listed prior to investigation return [68]. Subsequently, these criteria were altered to a final ED diagnosis of CAP plus CXR or CT evidence of CAP in the 24 hours prior to, or at any time during admission [97, 276]. Concerns were then expressed regarding the feasibility of treating within 4 hours if based on a positive CT scan. Pines et. al. [94] state that the ordering, performance and reporting of CT scans uniformly exceeds 4 hours. Maroun et. al. [277] found that CAP patients with delay longer than 4 hours to initial antibiotic treatment, were significantly more likely to have a negative CXR followed by a positive CT scan (17.7% vs. 1.3%, 95% CI 7%-26%, P = 0.02). One third of these CT scans were abdominal indicating that the primary presenting complaint was abdominal pain.

More recently, the criteria have been further refined to extend the goal antibiotic time to 6 hours and address the difficulty in diagnosis by not including cases where diagnosis is documented as "uncertain" [66]. The current combined American Thoracic Society (AmTS) and Infectious Disease Society of America (IDSA) guidelines promote a further relaxation of the timing goal to "treatment prior to transfer from the ED" [120]. Reporting of hospital performance in bands rather than actual percentages may allow for diagnostic uncertainty and reduce unwarranted pressure on unrealistic goals [267].

There are also inconsistencies between the literature and the current CMS/JCAHO PN-5b inclusion and exclusion criteria. Currently all adult patients meeting diagnostic criteria are included. Some authors indicate that the reporting population should be limited to those over 65, to match the patient population in the original studies that identified the relationship between antibiotic timing and mortality [22, 61, 267, 272, 273]. These studies also exclude those with HIV and those who are immunocompromised (due to leukaemia, lymphoma, corticosteroid treatment, chemotherapy, or secondary to treatment following organ transplantation) [22, 61]. In contrast, the PN-5b criteria exclude only those with cystic fibrosis and those with a "not for resuscitation" or "comfort care only" order (i.e. those close to death for reasons other than CAP).

There is some evidence that the implementation of the reporting of CAP performance has promoted system gaming to achieve required goals. This includes the diagnosis of CAP with incomplete evidence resulting in inappropriate use of antibiotics. Pines et. al. [278] recently surveyed a sample of US ED training medical directors and chairpersons and found that 37% reported local policies of administering antibiotics before obtaining CXR results in those suspected to have CAP. In support Pines et. al. [94] found that at one institution patients given their first antibiotic within 4 hours were significantly more likely to have been treated prior to CXR (31 vs. 10%, odds ratio = 0.3, $p < 0.0001$).

Kanwar et. al. [273] found the implementation of reporting at one site saw an improvement in the percentage of patients treated within 4 hours (53.8% to 65.8%; $p = 0.007$) at the same time as a significant increase of patients with CAP diagnoses without CXR evidence (20.6 to 28.5%, $p=0.04$), and an increase in the diagnosis of CAP in the ED (approximately 60%) with a < 25% increase in CAP discharge diagnosis (a decrease from 75.9 to 58.9% of all CAP diagnosed in the ED was discharged as CAP). There was a larger improvement in reaching the 4 hour goal for those without a discharge diagnosis of CAP (18.5 vs. 9.8%). For those positive for CAP in

the ED, but discharged without a diagnosis of CAP, the most common discharge diagnoses were non-infectious cardiac and pulmonary diseases (only 9% were infectious in nature). There was also a reduction in physical examination findings supporting CAP diagnosis with the implementation of performance reporting. The percentage of those with a diagnosis of CAP in the ED, positive CXR evidence, and one or more clinical findings, that were treated in 4 hours, dropped from 44.7 to 36%. Only 27 to 32.7% had a positive CXR and 2 or more clinical findings. Together this information indicates the pressure to deliver antibiotics within 4 hours is associated with an increase in both the number CAP patients treated without objective evidence and the number inappropriately treated.

There is much to learn from the difficulties experienced with the introduction of antibiotic timing goals for the treatment of CAP. These issues could have been highlighted prior to implementation via a thorough examination of the decision-making and overall workflow issues associated with the diagnosis and treatment of CAP. Such studies still promise to provide better solutions to this problem.

This remainder of this chapter examines the evidence for the link between antibiotic timing and outcomes in CAP, the interventions designed to reduce the delay to antibiotic treatment, and the impact of these interventions. Attempts to improve antibiotic timing have tended to focus on the improvement of the resources available at the point of care, and policy implementation via education and simple safety mechanisms such as paper-based guideline statements that indicate CAP patients should be treated within a specified time (See figure 3.1). Patient complexity in terms of diagnosis and risk assessment has been largely ignored, and the current CMS/JCAHO criteria for reporting on antibiotic timing now avoids the issue by placing difficult diagnostic cases outside of its net.

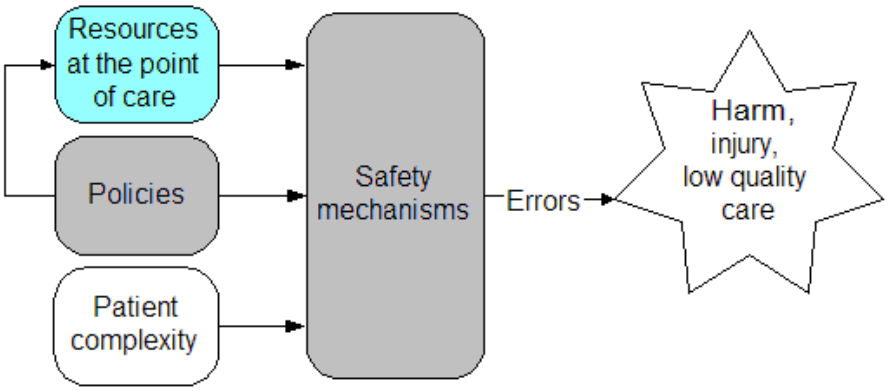

Figure 3.1: Simple model of predictors of process performance/error: resources, policies and safety mechanisms

3.2 Evidence for the relationship between antibiotic timing and outcomes

Table 3.1 summarises studies of the association between the timing of initial antibiotic treatment and outcomes for patients with CAP. The major evidence cited by CMS/JCAHO for the basis of minimising the delay to antibiotic treatment consists of 3 large retrospective studies [264]. The first of these was published in 1990 by Kahn et. al. [279]. This study assessed the process indicators of adequate oxygenation, intubation, and antibiotic timing. The patients receiving the top 25% of care rated on these indicators had significantly less mortality than those in the bottom 25%. The second of these studies was undertaken by Meehan et. al. [22]. In a retrospective review of 14069 patients aged 65 and greater, these authors found that delay to antibiotic treatment longer than 8 hours was associated with an independent 15% increase in mortality at 30 days post admission (adjusted for demographics, comorbidities, examination findings, investigation findings and other processes of care). Finally, Houck et. al. [61], in a study of 18209 CAP patients aged over 65 years, found that treatment delayed longer than 4 hours was also associated with a 15% increase in 30 day mortality (adjusted for PSI score, ICU admission in the first 24 hours, region of hospitalisation, other processes of care, choice of initial antibiotic, previous antibiotic treatment and ethnicity).

A further study by Werner et. al. [280] across in excess of 3500 hospitals, found a small but significant absolute relative risk reduction (ARRR) for mortality at 30 days (ARRR = 0.005, P =.001) between hospitals in the 25th verses the 75th percentiles of antibiotic timing adjusted for hospital characteristics.

The evidence for an association between in-hospital mortality and delay to antibiotic treatment is mixed. The previously mentioned Houck et. al. study [61] found a significantly increased risk of in-hospital mortality associated with antibiotic delay greater than 4 hours (odds ratio (OR) = 0.85). Dedier et. al. [281] found no significant relationship between antibiotic timing and in-hospital mortality, as did Marrie et. al. [282] in a study excluding patients admitted to ICU. Wilson et. al. [283], in the only published Australian study of antibiotic timing, found a significant association between in-hospital mortality and initial delay to antibiotic greater than 4 hours (OR = 3.45) in ICU patients.

A number of studies have failed to report whether their mortality outcome was measured in-hospital or at 30 days. Waterer et. al. [287] found an increased OR of mortality with delay to antibiotics greater than 4 hours (OR = 2.82). Ziss et. al. [285], Low et. al. [288] and Irvin et. al. [286] found no relationship between mortality and antibiotic timing. Since these studies appear to be based on hospital records alone then it is likely they refer to in-hospital mortality.

Three studies have investigated the relationship between length of stay (LOS) and antibiotic timing. Houck et. al. [61] found that antibiotic administration within 4 hours was associated with a 10% decreased risk of LOS greater that the median value of 5 days. Battleman et. al. [63] found that the risk of LOS greater than the 75th percentile increased significantly with additional 8 hour delays to first antibiotic treatment (OR = 1.75). In contrast the Dedier et. al. study [281] found no significant relationship between antibiotic timing and LOS.

One study has assessed the relationship between time to clinical stability and timing of initial antibiotic, but no significant relationship was found in moderate to severe cases of CAP [284].

Some authors have cited the variability of associations between antibiotic timing and all outcomes as evidence against a significant relationship [287, 289]. One explanation is that the relationship is confounded by the manner in which patients present - those without the typical clinical features of CAP are less likely to be diagnosed and treated early, and also have a higher risk of mortality [287, 289]. Waterer et. al. [287] found that statistical adjustment for altered mental status, and absence of fever negated a positive relationship between delay to antibiotics and mortality. Pines et. al. [94] found that both in-hospital mortality and delay to antibiotic treatment were significantly associated with presentation without typical pneumonia symptoms (ORs of 4.4 and 2.2, respectively). Houck [267] rationalises that studies with negative findings, such as

Table 3.1: Studies of the relationship between antibiotic timing and outcomes

Study	Design	n	Outcome
Kahn et. al. [279]	Multicentre retrospective cohort study	14012 (includes other disease)	Appropriate oxygen therapy, intubation and antibiotics within 2-4 hours, mortality significantly increased for poor levels of care (20.2 vs. 14.8%, $p < 0.01$, relative risk (RR) of mortality = 1.36)
Meehan et. al. [22]	Multicentre retrospective cohort, aged > 65, OR calculated via multiple regression adjusted for demographics, comorbidities, examination findings, investigation findings and other processes of care	14069	Lower 30 day mortality with antibiotic administration within 8 hours of hospital arrival (OR = 0.85), 75.5% received antibiotics within this time (range by state 49-89.7%)
Dedier et. al. [281]	Multicentre retrospective cohort, adult sample, OR calculated via multiple regression adjusted for other processes of care and PSI score	1062	Antibiotic administration within 8 hours of hospital arrival was not significantly associated with in-hospital mortality (OR = 1.69), or LOS greater then median (odds ratio = 0.89), 76.2% received antibiotics within this time (range 53-100%)
Battleman et. al. [63]	Multicentre retrospective cohort, random sample of 100 adult patients selected from 700 cases, OR calculated via multiple regression adjusted for clinical and demographic variables	100	Patients treated in the ED had a significantly risk of LOS greater than the 5th percentile (OR = 0.31), time to first antibiotic significantly related to prolonged LOS (OR = 1.75 per 8 hours delay)
Silber et. al. [284]	Prospective single site cohort study of adult patients with moderate to severe CAP (PSI class III to V)	410	No difference in time to clinical stability based on physical signs and SaO2 (mean approximately 3 days) when patients received initial antibiotic within 4 hours, 54% of patients received antibiotics in this time
Ziss et. al. [285]	Retrospective single site cohort study (includes 54 patients under 18 years)	154	Significant increase in LOS for those with antibiotic delay longer than 4 hours (3 vs. 4 days, $p < 0.01$), no significant difference in mortality between those treated before and after 4 and 8 hours, 81% received first antibiotic in 8 hours
Houck et. al. [61]	Multicentre retrospective cohort, aged > 65 years. ORs calculated via multiple regression adjusted for PSI score, ICU admission in the first 24 hours, region of hospitalisation, processes of care, choice of initial antibiotic, and ethnicity	18209	Antibiotic administration within 4 hours of hospital arrival associated with reduced in-hospital mortality (OR = 0.85), reduced 30 day mortality (OR = 0.85) and reduced LOS exceeding the median value of 5 days (OR = 0.9), 60.9% received antibiotics within this time
Irvin et. al. [286]	Retrospective single site cohort study of adult patients	609	No significant difference in unadjusted LOS, mortality or intubations for those treated within 4 hours
Marrie et. al. [282]	Prospective multisite cohort study of adult patients not admitted to ICU	3043	Mean time to antibiotic of 8.5 hours across sites. No significant association of in-hospital mortality (early or late) with time to antibiotic
Wilson et. al. [283]	Retrospective dual site cohort study of adult patients, admitted to 2 Australian ICUs	96	Longer mean time to antibiotic in those that died (2.7 vs. 4.4 hours, $p = 0.02$), in-hospital mortality higher in those with antibiotic treatment delayed longer than 4 hours (25 vs. 59%, $p = 0.02$; OR = 3.45, $p = 0.035$), no significant difference in mortality with antibiotic choice, PSI was significantly higher in those that received early treatment but still died (135 vs. 111, $p = 0.018$)
Waterer [287]	Prospective single site study of adult patients	451	Increased mortality with antibiotic delay greater than 4 hours (OR = 2.82, p=0.017), no relationship when adjusted for altered mental status, absence of fever, absence of hypoxia, and increased age
Werner et.al. [280]	Multicentre retrospective cohort, comparison of performance between the 75th and the 25th centiles of antibiotic timing in adult patients, Bayesian adjustment for hospital characteristics	3657 hospitals	Reduced absolute relative risk reduction (ARRR) of 30 day and 1 year mortality between hospitals in the 75th and 25th percentiles of performance (ARRR = 0.005, P =.001; ARR = 0.010, $p = 0.001$)
Low et. al. [288]	Multicentre (3 hospitals) retrospective cohort of adult patients	15335	No relationship between time to antibiotic and mortality, mortality associated with signs of sepsis (12.4% vs. 4.9%)

that of Waterer et. al. [287], are under-powered, and have different selection criteria in comparison to the original positive studies (include patients younger than 65 years and exclude nursing home patients). He also argues that there was no significant association between mental status and mortality in the supportive Houck et. al. study [267].

In both the Houck et. al. [267] and Meehan et. al. [22] studies patients treated rapidly, within 1-2 hours, actually had increased rates of mortality (non-significant). The reason for this anomaly is yet to be defined. A likely scenario is that those that present as more unwell get treated more quickly but receive less benefit due to severity. There are likely to be shorter delays to treatment for those that present as more unwell based on the ED triage system alone. There is evidence to suggest that triage is based as much on visual cues as objective physical examination, so that patients that look more unwell are likely to be treated quicker regardless of their physiological instability [170, 181]. Waterer et. al. [287] found that severity indicators such as shock (OR = 3.63), fever > 101.0°F (OR = 2.20), and hypoxia (OR = 1.69) were significantly associated with treatment within 2 hours. Wilson et. al. [283] found that CAP patients admitted to ICU who die despite treatment within 4 hours, have higher PSI scores than those who live. This relationship was not apparent for those treated after 4 hours. This evidence is contrary to opinion that only the sickest patients benefit from early antibiotics [274]. Interestingly, historical data comparing the pre and early post-antibiotic eras shows little difference in CAP mortality rates up to day 5 of hospitalisation [102].

Some authors have suggested that aspects of the treating hospital such as ED crowding and general nursing care may confound both antibiotic timing and mortality. Hospitals with crowded EDs and low levels of nurse staffing are likely to have longer delays to treatment, reduced quality of treatment and higher mortality, regardless of the type of CAP presentation [97, 289].

Taken together these results suggest that there is a significant increase in 30 day mortality for those aged 65 and over with delay to initial antibiotic treatment in excess of 4 to 8 hours. There is variable evidence for an association between delayed antibiotics and in-hospital mortality or LOS. The only study that has looked at antibiotic timing and time to resolution of CAP symptoms found no relationship. Overall it is clear that the question of the relationship of antibiotic timing and mortality in CAP needs further investigation. Prospective studies are needed that take into account the uncertainty of diagnosis, prior treatment with antibiotics, the severity and

risk of the patient at presentation, the relationship between the presenting signs of the patient and outcomes, hospital characteristics, and other processes of care.

It may also be useful to delineate the time delay from the onset of symptoms to presentation to define whether late presenters are at higher risk due to further disease progression (a study more likely to be retrospective in nature). The way CAP patients die may also reveal how delays in antibiotic treatment affect outcomes. Mortensen et. al. [290] were able to divide the cause of death into CAP-related and unrelated groups. CAP-unrelated mortality increased as a proportion of total mortality with time up to 90 days after presentation. My review above indicates that initial antibiotic timing is more closely related to 30 day mortality than to in-hospital mortality. Older patients (i.e. those aged over 65 years) are more at risk of common causes of mortality not related to CAP (e.g. malignancy and cardiac disease). The protective effect of early antibiotics may be for those with other comorbidities that predispose them to organ failure and death later in the course of the disease.

Antibiotic timing regardless of its relationship to mortality remains a valuable indicator of diagnostic and treatment performance as it is a surrogate for the accuracy of CXR interpretation and the organisation of treatment once a diagnosis of CAP is made [287]. Most authors agree that early antibiotic treatment for CAP is not an unworthy goal. The current argument is more focused on getting the criteria right in terms of population selection, and timing thresholds for quality management. In the current age of conflicting interest in research it should be noted that developers of the CMS/JCAHO indicators are also authors of both of the major papers supporting the association between antibiotic timing and mortality [291].

3.3 Predictors of antibiotic delay

There are currently no published studies of overall workflow in the treatment of CAP, however there are an increasing number of papers that assess uni and multivariate predictors of key process performance [63, 292-297]. Figure 3.2 shows the simple model of process performance. This section reviews specific studies of predictors of antibiotic timing from all groups of the model.

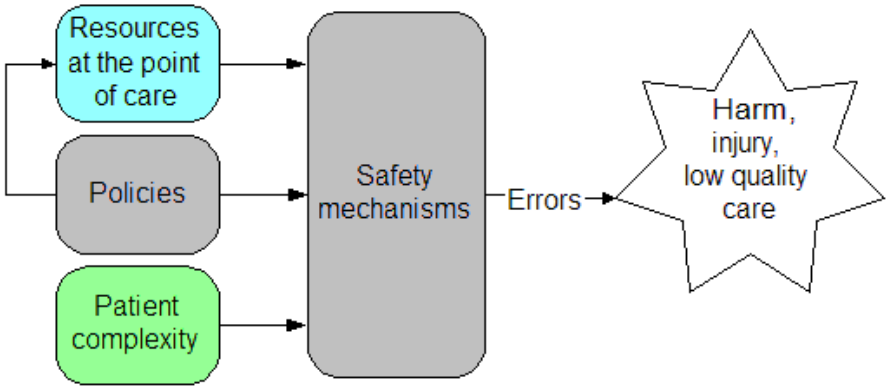

Figure 3.2: Simple model of predictors of process performance/error

3.3.1 Patient complexity

CAP is a difficult disease to diagnose within the ED. At one site Fee et. al. [97] found 58.5% of patients with antibiotics delayed greater than 4 hours did not have a final ED diagnosis of community-acquired pneumonia, this represented 20.4% of all patients with a hospital discharge diagnosis of CAP. Many CAP patients without an ED diagnosis have a normal initial CXR [94, 97]. Delay to antibiotic treatment in CAP has also been associated with an absence of typical clinical findings. Metersky et. al. [272] identified 22% of cases were associated with some diagnostic uncertainty. This interpretation was significantly associated with the absence of rales, a normal SaO2 and an absence of CXR infiltrates. Pines et. al. [94] found that those without dyspnoea, cough or upper respiratory tract symptoms were more likely to both receive delayed antibiotics and to die. Other studies have shown treatment delay to be associated with absence of fever, tachycardia, tachypnoea, hypoxia, raised white cell count, the presence of altered mental status and with increasing age [63, 265, 287, 292-294]. These findings are important in both the diagnosis and risk assessment of CAP. The impact of diagnostic uncertainty may also be measured by the delay caused by the use of investigations for alternative or comorbid diagnoses. Examples of such investigations that are associated with delays in CAP treatment include lumbar puncture [293] and diagnosis on CT scan [94, 277].

Timely antibiotic delivery has been associated with low haematocrit, low oxygen saturation and low blood oxygen concentration [86, 128, 292]. While there is evidence that signs of severe CAP are associated with more timely treatment, the association between CAP-specific multivariate risk scores and workflow is unclear. To date mixed results have been obtained for their association with time to antibiotic [78, 94, 292, 294]. This relationship may be confounded by the possi-

bility that those with more comorbidity and therefore greater risk of mortality are also those more likely to present in an atypical fashion [287, 289].

Comorbidities linked to delay to antibiotic include chronic renal disease, cerebrovascular disease and chronic obstructive airways disease (COAD). These comorbidities are significant risk factors for CAP mortality [265, 292, 294]. Patients with confounding comorbidities, such as asthma, also experience delay to treatment [287, 293].

The prescription of antibiotics within 48 hours prior to admission has been linked with reduced antibiotic delay [294], possibly due to diagnosis prior to admission. Delay to antibiotics has also been related to minority racial group [292, 294, 296] and female gender [292].

In summary, patients with atypical presentation, absence of CXR evidence, those with less severe CAP and those with confounding comorbidities are more likely to have significant delays to antibiotic treatment. Early diagnostic and risk assessment decision support may help to reduce the delay to antibiotic treatment for these groups.

3.3.2 Resources at the point of care and local policies

Delays to treatment that are likely to be associated with resources at the point of care can be divided into those that occur within the ED and those that occur once the patient has been transferred to a ward. Pines et. al. [94] found substantial delays across all processes of CAP treatment in the EDs of 24 US hospitals. The median time between CXR order and CXR performance was 38 minutes (Interquartile range (IQR) = 16-89 minutes). The median delay between CXR performance and CXR assessment was 61 minutes (IQR=34-150 minutes). That between CXR assessment and antibiotic order was 40 minutes (IQR=16-105 minutes), and between antibiotic order and administration was 69 minutes (IQR=39-108 minutes). In a separate study Pines et. al. [1] found that delay to the return of CXR results was negatively correlated with the number of CAP patients treated in 4 hours ($r = 0.83$, $p = 0.001$). Fee et. al. [97] indicated that for those with a CAP diagnosis in the ED, delayed treatment was associated with delay in obtaining a bed in ED, delay in the performance of CXR and accessing CXR results, delay in obtaining IV access and blood cultures, and delay in antibiotic ordering and delivery. Problems with the availability of antibiotics in the ED, and the misdirection of antibiotics to the ward due to incorrect data entry or pharmacy error were also identified as significant predictors of delay in antibiotic treatment by McGarvey et. al. [297].

Increased workload in the ED is likely to exacerbate these delays by reducing available resources. Fee et. al. [298] illustrated that increased patient load in the ED, as well as more patients requiring ward admission, impacted negatively on percentage of CAP patients receiving antibiotics within 4 hours. Pines et. al. [1] found that an increase in overall ED LOS and LOS in patients waiting admission to a ward (access block) were negatively correlated with the number of patients treated with antibiotics in 4 hours ($r = -0.44$, $p = 0.04$; $r = -0.37$, $p = 0.08$, respectively). In a separate study, Pines et. al. [299] found that increased ED crowding as indicated by boarding burden, volume, total care hours, waiting room numbers, and LOS in ED for those admitted, was associated with antibiotic delay. Access block is likely to be a significant predictor of delayed treatment of CAP in Australian EDs. One study at an Australian hospital showed that 6% of patients with respiratory diagnoses in the ED experienced access block [300].

Interestingly, one study comparing the timing of treatment processes for CAP and percutaneous intervention for myocardial infarction (MI) found that MI processes were not sensitive to ED workload measures [1]. The authors argue that there are more processes and more uncertainty in the diagnosis of CAP in comparison to MI, which only requires ST segment elevation on ECG or cardiac enzyme elevation. It is also likely that MI is treated with more urgency on the whole, given there is significant variation in the severity of CAP at presentation [1].

There are mixed results concerning the association between time of work shift and time to antibiotic. Fine et. al. [294] found that those treated on the 3pm to 11pm shift were more likely to receive antibiotics in a timely fashion. In contrast, Nathwani et. al. [295] found no relation between work shift and antibiotic timing.

When treatment of CAP does not occur until after ward admission, there are significantly longer delays to the delivery of antibiotics. One study found that approximately 80% CAP patients were admitted through the ED, however, around a quarter of these did not receive antibiotics until ward admission [301]. Schouten et. al. [265] found that the main positive predictor of timely administration of antibiotics was treatment in the ED (OR = 3.9). Battleman et. al. [63] found that those treated after arriving on a ward experienced average treatment delay in excess of 9 hours. The policy of direct ward admission for CAP treatment without the initiation of investigations in the ED has also been associated with delayed antibiotic treatment [297]. Patients that arrive on the ward without a diagnosis of CAP may face a long delay to ward physician assessment, particularly those admitted overnight, when medical staff are reduced in numbers. Treatment delay

could also be associated with the timing of medication rounds in relation to ward admission or ward CAP diagnosis.

Some specific hospital characteristics have been associated with delay to treatment, including teaching hospitals, larger hospitals and specific geographic locations [292, 294]. High workload has been associated with increased treatment delay in terms of lower nurse to bed ratios, and higher bed occupancy rates [292, 294].

The regularity with which CAP is treated by a given physician or at a particular site does not appear to be associated with the ability to treat in a timely fashion when comparing those in the 1st and 4th quartiles of performance. Hospitals that treat CAP more often are actually less likely to treat within 4 hours [302].

Qualitative stakeholder assessment of the reasons for antibiotic delay agree with the quantitative findings and identify other limiting sub-processes of care. Schouten et. al. [303] found delay to antibiotics was related to conflicting guidelines (i.e. obtaining sputum and blood cultures before treatment), delayed laboratory results, local antibiotic availability, lack of time to administer antibiotics, delays in IV access and commencement of IV therapy, belief that prompt antibiotics are only necessary for severe CAP, prioritisation of non-medical issues such as diet and social problems, delaying prescribed medication until regular medication rounds, a tendency for inexperienced doctors to wait for all the results before they can establish the diagnosis of CAP and the perceived need to consult with a supervisor before starting therapy, poor clarity of local guideline recommendation, less experience of ward nurses with acute illness, and poor clarity of treatment orders and drug charts.

In summary, due to the finite resources available at the point of care there are delays in each of the individual processes of diagnosis (particularly CXR) and treatment of CAP. These resources and, therefore CAP process delays, are sensitive to increased workload in the ED. Those not treated until after ward admission face a much longer wait for antibiotic treatment. CAP is a difficult disease to diagnose and, as previously discussed, those that present atypically are more likely to be missed in ED and are exposed to longer waiting times for treatment.

A more thorough understanding of the way processes interact to produce local workflow should help to design targeted interventions for the improvement of CAP processes at a given treatment

site. The correct mix of solutions is likely to vary given the local mix of resources and the complexity of presenting patients. The challenge is not only to identify the uncertain decisions and the decision sites that are key to improving workflow and process performance, but to assess if decisions are amenable to change through practical decision support implementation that fits in with local workflow. Alerting for key processes may improve individual process performance, thereby shortening the delay to antibiotic.

3.3.3 Attempts to improve initial antibiotic timing for CAP

Table 3.2 summarises recent studies of attempts to reduce delay to antibiotic delivery for patients with CAP. The majority of these interventions (88%) produced some reduction in the delay to antibiotic treatment when assessed in retrospective pre-post studies. The exact magnitude of effect is difficult to assess across all studies as implementations are multifaceted and there is high variation in manner in which antibiotic timing is reported (e.g. mean time vs. median time vs. % treated in 4 hours vs. % treated in 8 hours vs. % treated in ED). Four studies report associated small reductions in LOS ranging from 1 to 3.3 days [247, 248, 304, 305]. In two studies, interventions were associated with reductions in unadjusted mortality [305, 306].

Figure 3.3 shows the simple model of process performance, highlighting policies and safety mechanisms and resources at the point of care. Interventions in these studies have focused on variable combinations of improvement of the resources available at the point of care and the promotion of timing policy or simple safety mechanisms such as guideline statements indicating CAP patients should be treated within a certain time.

.

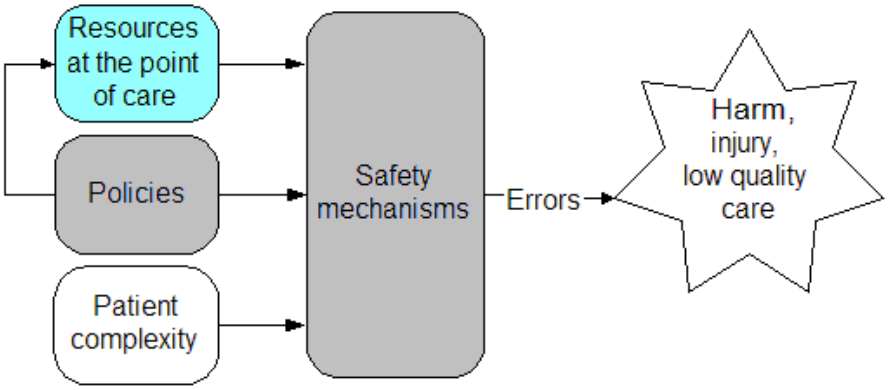

Figure 3.3: Simple model of predictors of process performance/error: resources, policies and safety mechanisms

Guideline and policy interventions commonly used multidisiplinary teams, and education and feedback in the design and implementation process [248, 297, 305-311]. Local opinion leaders were formally utilised in three studies [248, 308, 310]. Academic detailing was incorporated in one intervention [304]. Simple reminders in the form of laminated cards or posters were used in a subset of studies [304, 305, 307, 308], while others used computer-based versions of guidelines [248, 305]. Only one study reported a formal stakeholder review of barriers to implementation prior to the development of strategies to reduce delays [305].

Studies that targeted resource availability attempted to reduce the delay to performance and review of CXR and other investigations. The methods used include decision support for investigation ordering at triage [312], standing orders for investigations [308], workflow modifications to radiology processes [309], and alerting systems for positive CXR results [308]. Both standing antibiotic orders [247, 248, 306-308] and improving the availability of guideline-compliant antibiotics in the ED imprest [308, 311, 313] have been used to expedite antibiotic delivery following diagnosis. Other approaches that focus on resource availability include the allocation of a specific CAP bed in the ED [313], and the use of a CAP-specific triage protocol to fast track physician assessment [314].

Table 3.2: Studies of attempts to reduce delay to initial antibiotic for CAP patients

Author	Design	Subjects	Intervention	Outcomes
McGarvey et. al. [297]	Retrospective multisite pre-post cohort study	Baseline n = 353 Post-intervention n = 517	Feedback from external quality assessor, local education and multidisiplinary team for implementation of guideline including sputum cultures, blood cultures, antibiotics in 4 hours, antibiotic coverage for atypical organisms and specialist consultation in 48 hours	Increased antibiotics within 4 hours from 42% to 87% of CAP patients
Benenson et. al. [247]	Retrospective single site time series: 3 months prior to intervention, 10-12 months after, 34-36 months after	Baseline n = 64 Post-intervention 1 n = 96 Post-intervention 2 n = 122	Paper-based CAP guideline developed by multidisciplinary team, detailing steps and decisions in treatment from ED presentation to hospital discharge, standing antibiotic orders, CAP pathway nurse, social services, standard antibiotic order sheet	Mean time to antibiotic decreased from 5.25 to 2.85 hours at 3 years, antibiotic delivery in ED increased from 58% to 97%, LOS decreased from 9.7 to 6.4 days, non-significant decrease in in-hospital mortality from 9.6 to 5%
Metersky et. al. [310]	Retrospective multisite pre-post cohort study	5 hospitals 713 elderly patients	Feedback from an external quality assessor, locally derived quality interventions that varied from site to site (paper-based guideline, local opinion leader, staff education, local multidisciplinary team)	Mean time to antibiotic decreased form 5.5 to 4.7 hours ($p<0.0001$), percentage of patients who received antibiotics within 4 hours increased from 41.5 to 61.8% ($p <0.0001$)
Meehan et. al. [248]	Retrospective multisite pre-post cohort study	31 hospitals Baseline n = 1242 Post-intervention n = 1146	Paper-based CAP guideline modified by interhospital consensus and by local users using a decision support tool, implementation factors peculiar to each site (small group multidisciplinary team discussion, simple documentation forms, standing orders, education, opinion leaders, audit, feedback)	Increased percentage treated within 8 hours (83.4 vs. 88.8%), decreased LOS (7 vs. 5 days). No effect on mortality or readmission
Lawrence et. al. [311]	Prospective single site pre-post study	Baseline n = 52 Post-intervention n = 67	Multidisciplinary team based education sessions, stocking the ED imprest with the correct antibiotics	Significantly reduced mean time to initial antibiotic (6.88 vs. 4.85 hours, $p < 0.01$), increased the percentage treated within 8 hours (82.1 vs. 65.4%, $p = 0.04$) and 4 hours (59.7 Vs 34.6%, $p < 0.01$) hours, increased the percentage treated in the ED (68.7 vs. 46.2%, $p = 0.01$), no significant improvement in timing for those treated in ED, significant OR adjusted for immune status and PSI were achieved for antibiotics within 4 hours (OR = 2.6) and first antibiotic in ED (OR = 2.3), there was no significant effect on LOS or mortality
Cregin et. al. [304]	Retrospective multisite pre-post cohort study	8 hospitals Baseline n = 83 Post-intervention n = 93	Local multdisciplinary team, local antibiotic guideline based on AmTS/ISDA recommendations and modified by local antibiotic resistance data, guideline distributed via laminated card with memo, academic detailing by pharmacists	Significant increase in percentage treated in the ED (66 vs. 94%, $p < 0.01$), reduction in LOS of 1 day for those with antibiotics initiated in the ED, this was calculated to equate to a cost saving of $105000 per year across 8 hospitals

Table 3.2: Studies of attempts to reduce delay to initial antibiotic for CAP patients

Author	Design	Subjects	Intervention	Outcomes
Chu et. al. [306]	Retrospective multisite cohort control cross over study in small hospitals (<200 beds)	Intervention: 20 hospitals, baseline n =757, intervention n = 369 Control and crossover: 16 hospitals, baseline n = 108, baseline 2 n = 440, intervention n = 413	Feedback from external quality organisation (direct meeting with medical staff, written feedback package individualised to each hospital's performance), variable local factors included in the implementation of a paper-based guideline or standing orders	Increased percentage treated in ED and within 4 hours of admission in both groups post intervention (intervention - 5.9 vs. 16.8%, 57.2 vs. 69.1% respectively, $p < 0.001$; crossover intervention - 4.1 vs. 13.8%, 51.4 vs. 66.3% respectively, $p < 0.001$), no significant change in the control group, significant decrease in unadjusted mortality in the crossover intervention (9.8 vs. 5.6%, $p = 0.04$)
Capelastegui et. al. [315]	Retrospective multisite controlled pre-post cohort study	5 hospitals Baseline n = 377 Post-intervention n = 417 Baseline control n = 467 Post-intervention control n = 654	Paper-based guideline including admission based on PSI, prompt administration of antibiotic based on Spanish SEPAR guidelines, an IV to oral antibiotic switch policy, and discharge criteria	No significant changes in control groups pre to post-intervention. No change in percentage treated within 8 hours
Halm et. al. [307]	Retrospective multisite pre-post cohort study	4 hospitals Baseline n = 1013 Intervention n = 1081	Paper-based guideline, multidisciplinary team, opinion leaders, educational sessions with physicians, pocket reminder cards, standardized orders, bilingual patient education	No improvement in time to initial antibiotic treatment, no change in mortality or LOS or readmission rates
Stone et. al. [316]	Cluster randomized controlled clinical trial	25 hospitals Intervention n = 240 Control n = 209 Excludes severe CAP	Paper-based guideline including recommended antibiotic therapy, discharge criteria, regular twice daily assessment for discharge	Median time to antibiotic shorter in intervention group (3.8 vs. 4.3 hours, $p < 0.04$)
Capelastegui et. al. [317]	Prospective single site time series cohort study across 4 years	n = 1206	Paper-based guideline including admission based on PSI, prompt administration of antibiotic based on Spanish SEPAR guidelines, an IV to oral antibiotic switch policy, and discharge criteria	Improvement in the percentage of antibiotics within 8 hours over a 4 year period from 60.6 to 87.3% ($p < 0.001$)
Van Hoy et. al. [308]	Retrospective single site pre-post cohort study	Post-intervention n =117	Multidisciplinary team including clinical and quality staff, triage protocol (diagnostic model for CAP, pre-printed order set for radiology and laboratory testing, antibiotic guideline, direct notification of ED physician by triage nurse, x-rays indicative of CAP placed in blue folders by radiology staff, ED physician paged and informed of result), laminated posters, educational meetings, use of medication dispenser for more rapid access to correct antibiotics	Percentage treated within 4 hours increased from 60-83%

Table 3.2: Studies of attempts to reduce delay to initial antibiotic for CAP patients

Author	Design	Subjects	Intervention	Outcomes
Barlow et. al. [305]	Retrospective single site pre-post cohort control study	Baseline n = 181 Intervention n = 209 Baseline control n = 60 Intervention control n = 53	Structured survey of junior doctors to identify barriers, paper-based guideline, multidisciplinary team, information packs for staff, interactive group educational sessions, reminders (laminated colour posters and electronic versions on ward computers), audit and feedback of antibiotic timing data compared with baseline data	Results adjusted for age, gender and CURB-65 score, 15% increase in antibiotics in the ED within 4 hours (p = 0.028), increase in the number receiving guideline recommended antibiotics within 4 hours 17% (p = 0.035), median time to antibiotic reduced from 4 hours to 2.3 hours, no difference percentage treated within 8 hours, decrease in LOS by 1 day and mortality by 9% (significant only in unadjusted analyses), cost of reducing time to antibiotic for an individual patient was £452, cost per life saved was calculated at £16632 including a limited post intervention assessment
Covington et. al. [313]	Retrospective single site pre-post cohort study	Baseline n= 40 Post-intervention (4 months) n = 23 Post-intervention (5 months) n = 38	Nursing committee, nurse education, ED physician goal to interpret CXR within 15 minutes of patient return from radiology, pharmacy goal to maintain correct antibiotics in ED imprest, specific “pneumonia bed” in the ED	Baseline - 42.5% antibiotics in 4 hours - the most common reason for failure was delay to ED bed, at 4 months post implementation 65.2% were treated in 4 hours, at 5 months 74% were treated in 4 hours (74.1% total improvement), over 57% of nurses rated pre-shift meetings as the best way to deliver information
Cooper et. al. [312]	Retrospective single site pre-post cohort study	Baseline n = 4709 Post-intervention n = 4742	CXR automatically ordered at triage for patients with a presenting complaint of chest pain, shortness of breath, upper respiratory infection, hemoptysis, cough, or fever; if age > 50 with a temperature >100.4F or <96.8F, respiratory rate >20, or heart rate >100, or age < 50 with any of the following: immunocompromise, cancer, diabetes, transplant, or chronic alcoholism	16% of CXRs ordered automatically, mean time to antibiotic was significantly lower for those with a CXR ordered at triage (3.4 hours VS. 4.2 hours, p=0.01), significant improvement in the percentage treated within 4 hours from 51 to 68% (p = 0.05)
Katz et. al. [309]	Retrospective single site time series study	Total n = 197	Multdisciplinary team, agreement between providers for selection and timing of antibiotics, continuous monitoring of performance, CXR workflow improvements, personnel empowerment	Gradual quarterly improvement in median delay to antibiotic treatment (312, 209, 269, 216, 192, and 190 minutes), significant improvement from beginning to end of the study (p=0.028)
Stemper-Bartkus et. al. [314]	Retrospective single site pre-post cohort study	Baseline n = 123 Post-intervention n = 129	Triage rule: if pulse oxygen < 91% and the triage nurse suspected CAP, patients were triaged at level 2 if 2 or more criteria were present (abnormal breath sounds, respiratory rate >29 breaths/min, systolic blood pressure <90 mmHg, or temperature >38.3ºC)	Significant improvement in the mean time to antibiotic administration (177 vs. 144 minutes, p < 0.001) and in the percentage of patients who received antibiotics within 4 hours (77.4% vs. 98.4%, p < 0.001)

Only 3 of the interventions reviewed address the uncertainty in CAP diagnosis and risk assessment. Van Hoy et. al. [308] were able to increase the percentage of patients treated within 4 hours from 63 to 80% via a multifaceted intervention that included diagnostic criteria for investigation ordering at triage (two or more of the following: fever (>100.48^{0}F), cough, dyspnoea, pleuritic chest pain, hypoxia (SaO^2 94% in room air), altered breath sounds, tachycardia (heart rate > 90 beats/minute), or increased white blood cell count (> 12,000/uL)). There is no report of model accuracy for this study, so it is not possible to assess the impact of errors on patient outcomes or the costs of care.

Cooper et. al. [312] found that the median delay to antibiotic and the percentage treated within 4 hours were significantly reduced by automatically ordering a CXR at triage for those with CAP-related symptoms, signs and historical risk factors. Again, these authors did not report any measure of model accuracy.

Stemper-Bartkus et. al. [314] used a set of symptoms and signs, combined with nurse judgement at triage, to increase triage urgency for patients with a high likelihood of CAP to at least triage category 2. This resulted in reduced mean antibiotic delay and an increased percentage of patients treated within 4 hours. Given that triage systems determine the order in which patients are assessed by physicians based on urgency of care [164], increasing triage urgency is likely to result in reduced time to assessment with flow on effects to investigation ordering, CAP diagnosis, and treatment. Again these authors did not report the accuracy of their criteria, preventing an assessment of the impact of errors on outcomes. A high rate of false positives triaged at category 2 may divert limited ED resources away from patients in need of urgent assessment.

Pines et. al. [278] recently surveyed a sample of 90 US ED medical directors and chairpersons and found that the most common methods of improving antibiotic timing for CAP patients were education (70%), automating CXR ordering at triage for those with suspected CAP (51%), prioritising patients with suspected CAP (41%), administering antibiotics before obtaining CXR results in those suspected of CAP (37%), improving turnaround time for CXR results (37%), prioritising CXRs over other x-rays (14%), and improving inpatient bed availability (13%). Representatives from all hospitals reported using at least 3 of these methods (median methods = 5). This study shows that a large number of sites in the US are using formal or informal systems to fast-track CAP investigations and treatment. Given the low rate of formal assessment

of these models in the published literature it is likely that the impact of these systems beyond the target measures such as antibiotic timing has not been assessed.

3.4 Summary

The relationship between antibiotic timing and mortality is complex and requires further investigation, however it remains a valuable indicator of diagnostic and treatment performance.

Antibiotic treatment is likely to be delayed for patients that present in an atypical fashion (few signs and symptoms, normal CXR, normal blood investigations), or for those that are not treated until they reach the hospital ward. These groups commonly overlap due to the poor accuracy of the gold standard CXR. There are significant delays in all processes of CAP care, secondary to available resources, that are sensitive to workload in the ED.

Interventions to improve antibiotic timing are highly heterogeneous. The majority of published studies have focused on improving the human/social aspects of policy or guideline implementation or the fine tuning of radiology and antibiotic delivery processes. None of the few interventions that address patient complexity in terms of criteria for early diagnosis and risk assessment report the local accuracy of these models. Many sites in the US report the use of fast-tracking of investigation ordering and antibiotic treatment, but again the impact of these systems has not been assessed beyond their target quality indicators (e.g. delay to antibiotic). There is some evidence that the implementation of such systems has increased the rate of timely antibiotic treatment at the expense of an increased false positive diagnoses. There are concerns that increasing the rate of false positives will result in the unnecessary use of antibiotics. In turn, this may increase the risk of drug related adverse events and the development of antibiotic resistance, whilst decreasing the accuracy of later infection diagnosis, and diverting scare resources away from other serious conditions.

None of the interventions published have formally assessed both patient complexity and process flow issues in their design. I argue that better quality improvement interventions can be developed by formally modelling the interaction of new policy with both patient complexity (i.e. uncertainty in diagnosis and risk assessment), and resources at the point of care (via process flow models), in an overall workflow model. This process should allow policy and decision support systems to be better optimised prior to implementation, thereby increasing compliance, and avoiding unintended effects such as increased false positive diagnosis.

In the next chapter I discuss formal techniques for assessing and modelling both clinical decisions, and process flow. I then introduce the concept of workflow simulation for the investigation of the impact of decision support implementation. I plan to use this process to design an alerting system to reduce the delay to antibiotic treatment of CAP patients.

4 Review of workflow modelling and simulation

The diagnosis and treatment of community-acquired pneumonia (CAP) in a hospital setting is a highly complex undertaking given the inherent uncertainty in decision-making and in process flow. Current attempts to improve care have consisted mainly of paper-based guidelines, which have made improvements at some sites, but on the whole compliance is poor (see chapter 2).

Studies of the predictors of CAP care processes, such as timing of initial antibiotic delivery, have shown that patient complexity, uncertain resources at the point of care and current policies all impact on performance (see chapter 3). To date, no studies have considered compliance with CAP care processes, in the context of all of these factors (i.e. in the context of workflow). A broad definition of workflow subsumes both health care processes and all factors that impact on the performance of health care processes, including decision-making and information transfer [74]. The growing number of references in current literature supports an increasing awareness of workflow as an issue in the delivery of care. A simple search of PubMed [318] using the search string "health* AND workflow" retrieved 342 abstracts that refer to workflow. The first of these papers was published in 1988 and 89% have been published from 1999 onwards (see figure 4.1). Despite the increasing awareness of the impact of workflow on process performance, the majority of interventions designed to improve health care quality do not formally consider workflow in its entirety [74] (see chapters 2 and 3).

This chapter will review both process flow and clinical decision assessment, modelling and simulation techniques. I will argue that by combining these approaches, decision support that is sensitive to both local process flow and decision uncertainty may be developed. This form of decision support is more likely to produce a "flexible care plan" that will better promote high quality performance of care processes in the context of local workflow.

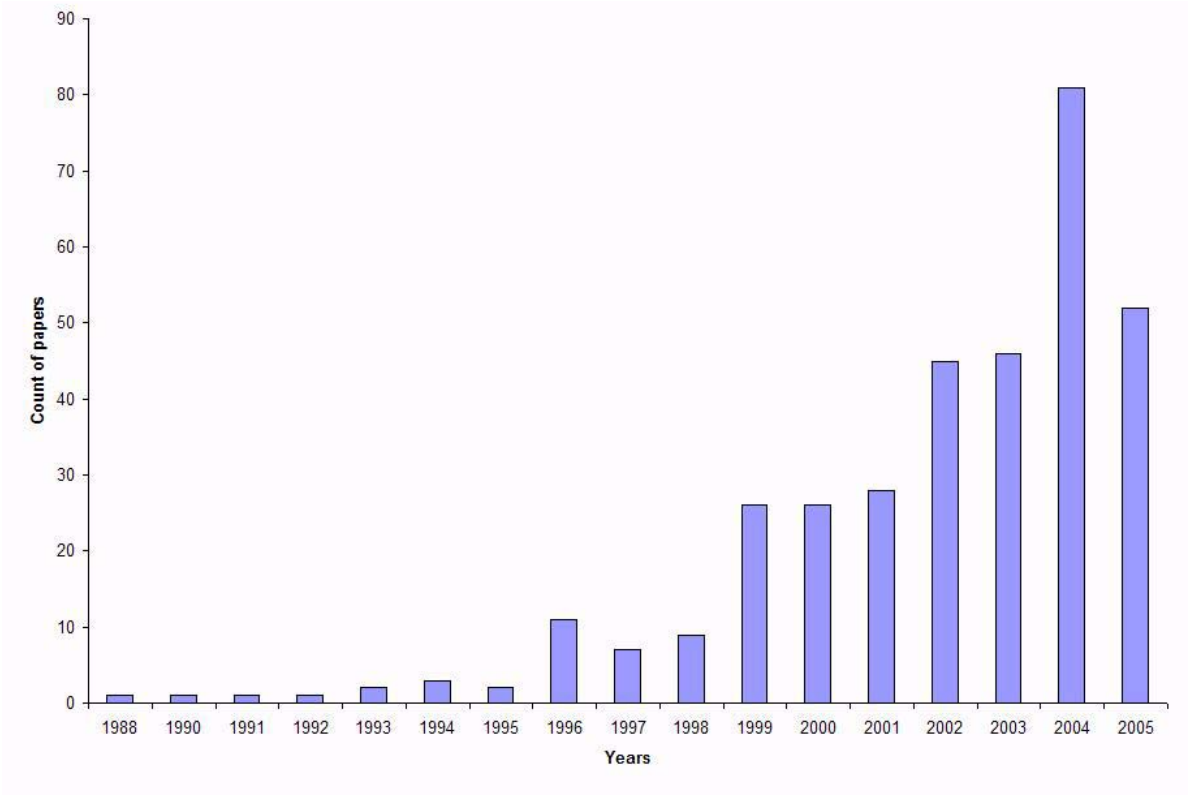

Figure 4.1: PubMed abstracts referring to workflow published prior to December 2005

4.1 Process and workflow assessment and modelling

Business process and workflow modelling are a collection of techniques for the mapping, simulation, and analysis of complex systems at the process level. They have been used successfully to re-engineer business, manufacturing, and health care workflows [74, 319-324]. A business process may be defined as a set of partially ordered and coordinated activities by which an organisation creates and delivers products and services to its customers [321, 325, 326]. A business process model is then an abstract description of the activities important to the successful completion of a process. This includes a description of the activities in a process and their interactions, the actors involved in the process, the organisational structure, the timing of all activities, and the transfer of information [321, 322, 326]. Business process re-engineering (BPR) involves the assessment, analysis, modelling, definition and implementation of business processes [327]. One of the major goals of BPR is to provide models of workflow that can be automated using information technology in the form of workflow management systems [321, 322, 326]. This approach has proved successful in optimising complex business workflows composed of simple repetitive actions, as in financial transactions, employee collaboration and communication, and automation of documents and forms via approval processes [74, 321, 322, 326, 328]. The modelling of health domains

has so far been restricted to areas with well defined processes and boundaries, such as the radiology department, pathology laboratories, pharmacy, and billing procedures [74]. This is paralleled by the success of BPR in optimising and automating complex business workflows composed of simple repetitive actions. In contrast, the modelling of the overall delivery of patient care is difficult, given the uncertain nature of decisions and the complexity, and variability of treatment processes [319-322]. Such complexity is difficult to describe without multi-level and multi-perspective systems analyses [74, 320].

4.1.1 Issues for the design of health care computer-based workflow management systems

Salient current areas of research include: user specifications (case individualisation and parallel pathways), monitoring clinical environments and engaging staff to attend to events (task monitoring and escalation), the representation of process timing and triggers for action within the information system (temporal constraints and triggers), the implementation of clinical knowledge and guideline rules (event-condition-action rules), and the integration between existing clinical information systems and of systems into current workflow (web services and data flow support).

4.1.1.1 Case individualisation and parallel tasks

Specifications for health information systems are difficult to define as there are multiple users (doctors, nurses, administration, patients), processes, and computing systems that interact in complex ways. Graphical modelling is one way to formally assess and represent these interactions. Unified Modelling Language (UML) is a graphical language used to qualitatively map complex information and process flow across organisations, developed for software engineering, UML “use case” diagrams are graphical models of how a system should operate for specific instances of use by a particular stakeholder group [329, 330]. In this way a computing system can be individualised for the major groups of users.

It is important that CDSS are designed considering parallel tasks that occur in complex clinical workflows. Diagnosis, risk assessment and treatment are parallel tasks in that they all overlap and evolve as more clinical information is acquired and as the patient's state changes (e.g. if a CAP patient has low blood oxygenation at admission and is dehydrated then they are treated with oxygen and IV fluids before a diagnosis is determined). Treatment processes use information from diagnosis and risk assessment processes. For instance, empirical antibiotic treatment in CAP is usually based on patient risk and likely aetiology (see chapters 1 and 2). A core set

of clinical information can then be used to monitor all of these interacting procedures and thus optimally select the next recommended process. Formal workflow modelling is required to identify these parallel pathways.

In the case of CDSS an important aspect of case individualisation is in the clinical process recommendations that the system outputs. Due to the complexity of presentation, risk and efficacy of treatment, the best evidence-based process to perform will vary between individuals and across time. This is reflected in current CAP guidelines (see chapter 2). CDSS may be designed to produce individualised evidence-based recommendations based on a given patient's clinical parameters at a given time [190-192].

4.1.1.2 Task monitoring and escalation

Risk management of processes is extremely important in complex environments with clinically unstable patients such as the ED. If critical processes such as antibiotic delivery are delayed then a patient may deteriorate (see chapter 3). To prevent this occurring a clinical system needs 4 main components:

1. patient risk monitoring
2. clinical processes monitoring
3. a set of rules to determine response to modify workflow based on patient risk, including a clinical hierarchy for response escalation (e.g. event-condition-action-rules
4. a communication/alerting system

Risk states can be monitored via integration of legacy IT systems [210] and local data entry. Much clinical data remains in case notes. Specific improvements are needed in the entry of clinical observations and the recording of treatment processes. Order entry systems [210, 212-215]and novel technologies such as radio frequency identification tagging may provide better process tracking [331]. Diagnostic and risk decision support can be used to identify patients that need more urgent treatment and alert staff to this. If responsible staff have not addressed these issues within a critical time then staff both across and up a clinical hierarchy can be alerted, thus escalating the urgency of treatment. This requires a knowledge of the local clinical hierarchy and a set of rules encompassing responsibility across time. One example of such a system was able to significantly reduce the delay to the assessment of laboratory results in a large ED [211].

4.1.1.3 Temporal constraints and triggers

Due to the uncertainty of diagnosis, risk, and process flow in the treatment of conditions such as CAP, the operationalisation and storage of time data for decision support is complex (For a detailed review see Augusto [332]). Temporal constraints are time values used to represent:

1. the pattern of temporal relationships between clinical findings in specific disease states that can be used in diagnosis and risk assessment
2. the logical ordering of clinical processes (i.e. mutually exclusive processes such as CXR and transfer to a ward cannot occur together; processes should progress in a logical sequence - e.g. a physical exam will occur before other investigations are instigated).

Temporal constraints are influenced by:

1. the nature of the clinical presentation
   a. patients at high risk of immediate or emergent poor outcomes require more urgent treatment
   b. increased uncertainty around diagnosis generally translates to uncertain constraints around the timing of investigation and treatment
2. variable diagnostic, risk assessment and treatment process workflow
   a. the delay to the commencement of a process
   b. the duration of the process
   c. the possibility of parallel processes
3. treatment efficacy
   a. generally reduces with delay to initiation if there is a trend toward clinical deterioration
   b. may be influenced by point 1
   c. intra-individual and inter-individual staff competency in treatment processes

Triggers are patient or process states that are used to initiate new process recommendations. They must operate within temporal constraints. Recent developments in this field include sensing more complex events such as identification of complex disease patterns and trends over time. Workflow management systems are able to generate logical and feasible process plans by the combining triggers, and event-condition-action-rules in the context of temporal constraints [332].

4.1.1.4 Event condition action rules

Event-condition-action (ECA) rules are a method of encoding processes from clinical guidelines in computer executable form [333]. A clinical event is registered by the system (e.g. a new serum potassium level is returned from the laboratory). The event is then compared to a critical value or condition (e.g. serum potassium value should be between 3.5 and 5 mmol/L). Based on the outcome of this comparison actions are performed. Such actions may include alerting clinical staff, the collection and assessment of further data, or the modification of treatment parameters (i.e. closed loop systems used in mechanical ventilators [194]). In the case of assessing serum potassium level, actions may include an alert to clinical staff that the potassium is abnormal, a suggestion to repeat the test for values outside of but close to this range, performing an ECG to check for arrythmia if the value was significantly outside to this range, checking for drug interactions that may raise potassium and alerting for a medication review. A number of computer languages have been developed to implement these rules but significant problems remain in managing the clinical knowledge base, and in interoperability (managing variable medical terminology, integrating data from multiple sources and formats, and transfer of interventions across sites) [334, 335].

4.1.1.5 Web services and data flow support

There are 2 main aspects to consider when supporting data flow in health-based decision support systems: improving the interoperability of existing clinical information systems, and improved integration of systems into local clinical workflow. More recently the approach to improve health CDSS interoperability has been to separate the clinical information system responsible for collecting data from the decision support component by inserting a middle layer of software that translates between systems, using web services over the internet [336, 337]. Web services can combine internet communication protocols with messaging technology (e.g. extensible mark-up language XML) in a service oriented architecture (SOA) approach that allows decision support to operate on computer servers remote from the site of data gathering, and interact with multiple formats of local systems. In this paradigm the remote decision support software provides a decision support “service” that monitors clinical data from heterogeneous sources (e.g. legacy systems such as patient management indexes, laboratory and radiology result systems, stand alone devices such as clinical monitors, and user interface systems for clinical data entry). This data is transformed into standardised messages (e.g. XML documents based on HL-7 standards). ECA rules are then applied by a “guideline engine” to the standardised input producing standardised output which may be re-translated to drive heterogeneous

clinical systems (e.g. alerting systems, and user interfaces). The use of XML protocols allows for the collection of meta-data about the operation of the system, thus enabling higher level abstraction about the management and use of the knowledge-base (rules) and performance of the system.

Designing a clinical system to fit in with local workflow improves data flow and is key to its performance (see section chapter 2). Key aspects of CDSS design include:

a a minimal set of key clinical data entered as required at the point of care

b point of care delivery of recommendations from decision support

c alerting and escalation (as described above in 4.1.1.2)

d integration of digitalised information from exisiting clinical devices (e.g. basic clinical monitors)

e introduction novel devices for patient (e.g. new point of care tests) or process monitoring (e.g. order entry, radio frequency tagging or bar coding of drug delivery devices).

4.1.2 A risk management based workflow framework

Pradhan et. al. [74] have proposed a model of workflow for the understanding of preventable harm in health care that combines a medical framework developed by Vincent [76] with Reason's model of preventable error derived from studies of complex system failure [77] (see figure 4.2).

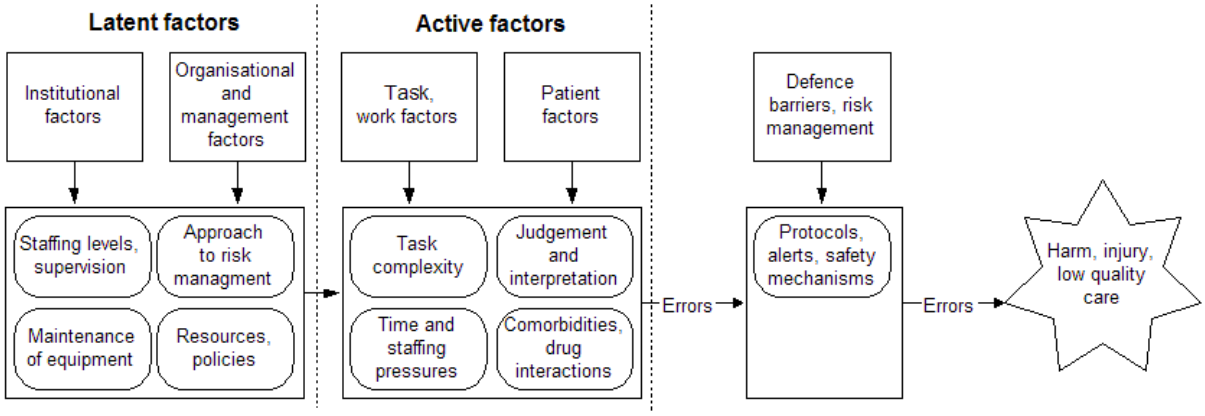

Figure 4.2: Causes of preventable harm/process performance*

* Modified from Pradhan et. al. [74]

This model provides a convenient framework for the understanding of the factors that determine clinical process performance, including uncertainty around decision-making and process flow. The factors contained in this model are similar to those found to predict clinical guideline compliance (see table 4.1) [40, 207, 208].

Table 4.1: Factors associated with guideline compliance and preventable harm

General groups	Guideline compliance factors [40, 207, 208]	Preventable harm factors [74, 76]
Patient factors	Comorbidity and sociodemographic variables	Complexity (comorbidity, drug interactions)
	Patient severity	Severity
	Patient preferences	
System factors (institutional, organisational and management factors, work environment factors, and team factors)	Insufficient staff or consultant support	Staffing levels/supervision
	Lack of time, time of day	Time and staffing pressures
	Lack of resources	Resources
	Conflicting guidelines	Policies
		Approach to risk management
		Maintenance of equipment
Task factors	Belief of task difficulty	Task complexity
Decision support factors	Guideline characteristics, lack of a reminder system	Protocols, alerts, safety mechanisms
Health care worker factors	Perceived patient severity	Judgement and interpretation
	Knowledge, belief of task difficulty	Knowledge and skills
	Attitudes	

I have simplified the Pradhan et. al. [74] model into a representation that includes the basic elements impacting on process performance. Figure 4.3 shows that patient complexity, clinical policies, and resources at the point of care have an impact on process performance which is mediated by local safety mechanisms, such as local guidelines, protocols and alerting or checking systems. Clinical policies will also indirectly affect process performance via determining the resources at the point of care. These categories provide a convenient classification for aspects of the clinical process re-engineering task. Patient complexity relates directly to the uncertainty of decision-making and can therefore be modelled using techniques from decision theory such as probabilistic Bayesian models [75, 338]. Resource availability at the point of care can be modelled using workflow techniques, which will be discussed subsequently. Clinical policies may then be included by the modelling of the impact of rules concerning the use of diagnostic and treatment processes. I have used this model to organise information within this thesis.

Pradhan et. al. [74] have also proposed a method of workflow modelling that uses workflow observation and stakeholder review to generate sequence diagrams of clinical workflow (see figure 4.4).

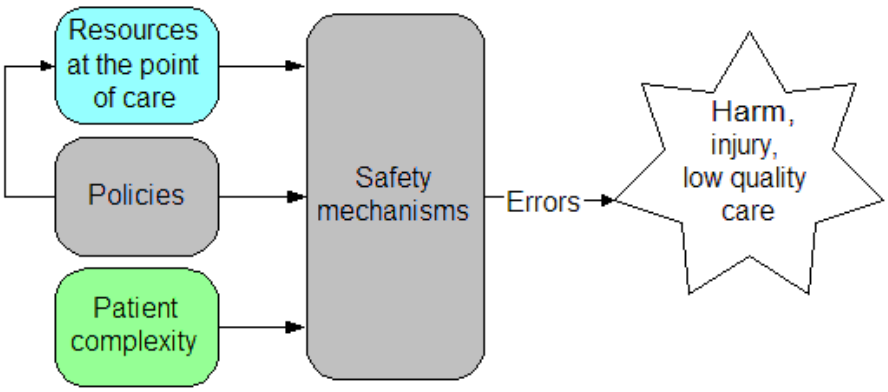

Figure 4.3: Simple model of predictors of process performance/error

This approach was derived from Unified Modelling Language (UML) used for software engineering. UML is a graphical language used to qualitatively map complex information and process flow across organisations to assist in software and information system design [329, 330].

Stakeholder analysis is a set of tools designed to assess the behaviour, intentions, inter-relations and interests of individuals, and organisations. This information can be used to assess past and future policy development, facilitate project implementation, and manage important stakeholders. The use of stakeholder analysis to structure health policy has increased over the last 20 years [339, 340].

In the Pradhan et. al. [74] approach, sequence diagrams are used to map the complex interaction between actors, information, processes, and decision-making. Stakeholder review also assists in the identification of local policies and opinions that are not apparent from simple observation, but have effects on workflow. The development of sequence diagrams is an iterative process, involving stakeholder feedback to fine-tune model structure. Figure 4.4 shows a sequence diagram of a simple clinical episode. Each vertical column represents the time that an actor is involved in patient care. Actors may be individual staff, abstracted information or service sources (e.g. laboratory), and information systems or hard copy medical records. Red broken arrows indicate information requests. Blue solid arrows indicate information or service provision. Red dots indicate decision points. This simple example consists of a doctor taking a history and examination from a patient (A), followed by the doctor making a treatment decision and requesting a blood test from the laboratory (B), then recording its details in the clinical record (C). Later a nurse consults the record (D) and carries out a treatment task that is then recorded in the notes (E). The doctor returns at a later time to request results from the laboratory (H) and then assesses

the patient (I). Further test results and treatment decisions are then recorded in the notes (J). The technique displays the progress of workflow over time and therefore is useful for identifying rate limiting care processes, risk of delays in the transfer of the information required for decision-making, and high-risk processes (i.e. processes that are likely to be delayed or to fail). For example, where there are long vertical gaps between information request and delivery, indicated by long vertical columns in the sequence diagram, there is increased risk for information to be overlooked. In this example there is a delay between request for a laboratory test and the return of a result. There is also high risk if the entity receiving the information is different to the one requesting it, if the request is outside unit boundaries, or if there are multiple transfers of information [74]. Such situations arise during working shift changes or transfer of patients across care units.

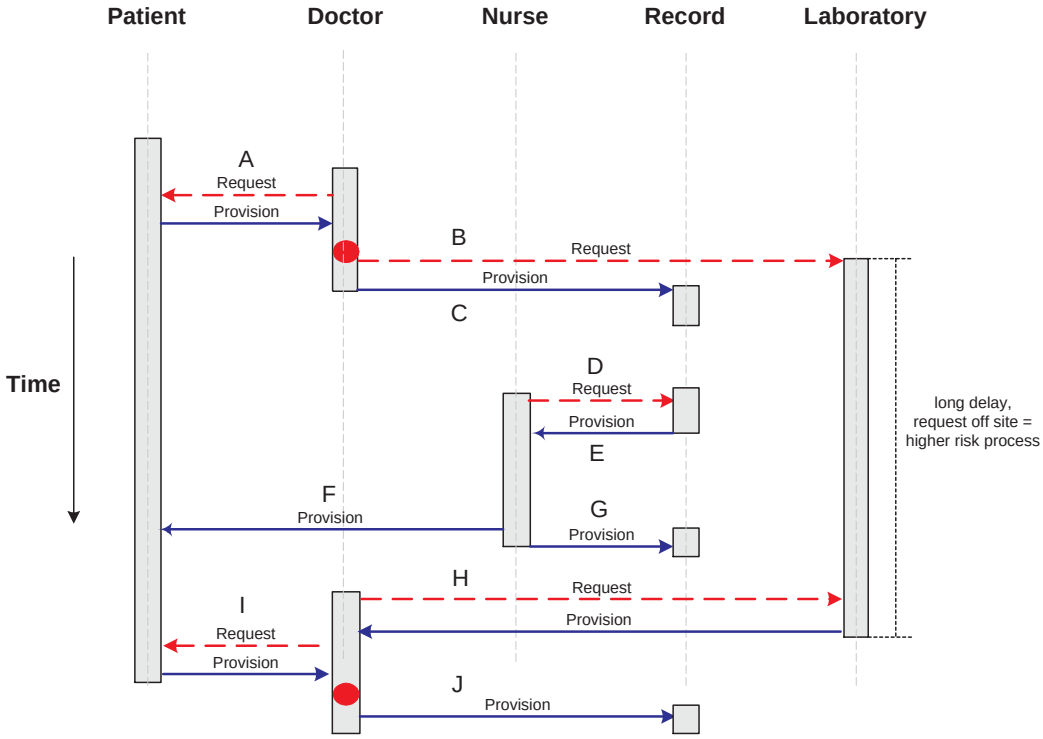

Figure 4.4: Simple workflow sequence diagram

Once the structure of workflow has been defined, sequence diagrams can be used to interpret process performance, and patient characteristic data from existing clinical information systems (CIS), and paper-based case notes. CIS generally contain data on processes, process timings, test results, and patient demographics. There is generally only limited historical and examination finding data. Table 4.2 shows a mapping of likely data sources to the Pradhan et. al. [74] workflow factors. High risk processes can then be assessed and re-designed with the factors contained in the Pradhan et.al. [74] preventable harm model in mind (figure 4.2).

Table 4.2: Data types from different methods of workflow analysis

Factors from Pradhan et. al. [72]	Literature review	Workflow observation	Stakeholder analysis	Clinical information system data	Medical records
Staffing levels, supervision		Staff/patient ratio	Rosters, governance, management structure, roles	Staff/patient ratio	
Maintenance of equipment			Schedules		
Information processing/ documentation		Use of forms and computers	IT systems, networking, performance, quality of data	Systems, quality of data, use of systems	Forms, quality of data, duplication of data
Approach to risk management		Assessment procedures	Policies, protocols, performance	Online policies and protocols, performance	Performance
Resources, policies		Resources used, consultation of protocols	Resource limitations, local formal and informal policies	Online policies and protocols	Protocol forms
Communication		Channels used, timing, quality, participants	Channels used, timing, quality, participants	Timing, quality, participants, order entry, result access	Timing, quality, participants, orders
Task complexity	Quality of clinical evidence for diagnosis and treatment, published guidelines, consensus statements and clinical prediction rules	Multi-tasking, interruptions, amount of data, use of references, procedure complexity	Perceived difficulty, match between training and job requirements	Amount of data, type of data	Amount of data, type of data
Time and staffing pressures		Staff/patient ratio	Perceived workload	Staff/patient ratio	
Judgement and interpretation	Cognitive biases	Presentation and availability of information, decisions, decision-making processes	Individual heuristics and local policies for risk assessment	Coded diagnoses and outcomes for assessment of accuracy, online policies	Assessment and planning notes for assessment of accuracy
Comorbidities, drug interactions (patient complexity)	Studies of patient risk factors and drug interactions	Risk assessment processes	Individual heuristics and local policies for risk assessment	Coded history and outcomes	History, outcomes, medication charts
Protocols, alerts, safety mechanisms	Published protocols, quality and safety studies	Use of protocols, availability of protocols, alerting systems, checking procedures	Protocols, checking procedures, alerting systems	Online protocols and alerting systems	Protocol forms, checking systems (e.g. sticky labels)
Process measures	Published studies of performance, links to outcome, predictors of process performance	Description, Actors, organisation, timing, relationship between processes	Description, actors, organisation, timing, relationship between processes	Processes performed, timing	Processes performed, timing
Outcome measures	Published studies of outcome and clinical prediction rules		Perception of predictors of outcome	Coded outcomes (clinical and financial)	Outcomes

4.2 Decision modelling

Key decisions occur at particular points in workflow and in turn influence further workflow. Figure 4.4 above illustrates 2 such decision points: the decision to perform a laboratory test based on a hypothesis formed from information taken during history and examination, and the decision to perform a treatment based on a likely diagnosis formed with the addition of information from a test result. Each new item of information either increases or decreases the probability of a given differential diagnosis. Bayes' Theorem (see figure 4.6) approximates this serial use of information in clinical decision-making and uses probability to quantify uncertainty. This formal assessment of the uncertainty around decisions allows for the construction of decision models that can be used to predict individual risk of disease or outcome, and thereby simplify the practice of evidence-based medicine (EBM) [338]. These models can be used to quantify patient complexity as a predictor of process performance (see figure 4.5).

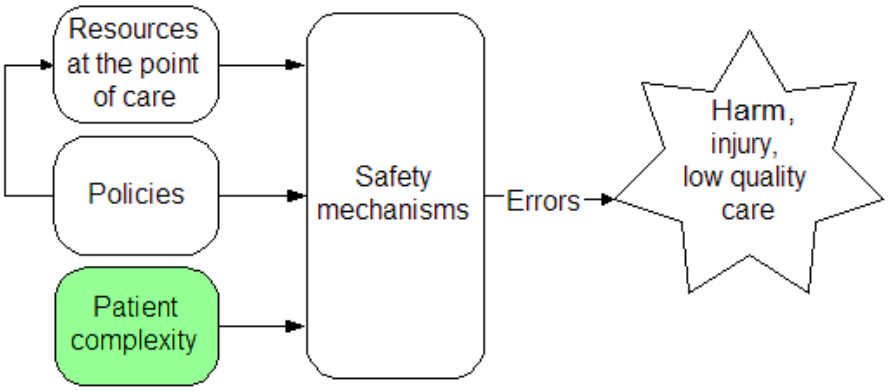

Figure 4.5: Simple model of predictors of process performance/error: patient complexity

4.2.1 Bayesian modelling

The Bayesian approach assesses the probability of a hypothesis in light of the data available. The use of Bayes' Theorem (see figure 4.6) allows the calculation of the posterior probability of an event (i.e. the probability of an event given the information available), by combining the prior probability of the event in a particular population (i.e. the overall probability of an event in a given population), and the conditional probability of that event given new information.

For example, in the diagnosis of CAP the prior probability of CAP in any patient presenting to a given ED is equal to the local incidence of CAP. Consider a patient presenting to an ED with a cough. Cough is a common presenting symptom of CAP, but not all CAP patients present with a cough. The probability of CAP in a patient that presents with a cough is the conditional prob-

ability of CAP in patients with a cough (i.e. the probability of CAP conditional on cough or p(CAP|cough)). Serial estimations of posterior probability can be made when new information becomes available, by using the current posterior probability as the prior probability for the next calculation. For example, the patient presenting to ED with a cough may be found to have dullness to percussion on chest examination, indicating lung consolidation. Bayes theorem can then be used to combine the posterior probability of CAP in those with a cough, with the conditional probability of CAP in those with dullness to percussion (p(CAP|dullness to percussion)). This increases the posterior probability of CAP, given that CAP is associated with dullness to percussion. If dullness to percussion was absent in this patient, the posterior probability of CAP would be reduced. If a CXR indicative of heart failure was then obtained, the reduced conditional probability of this evidence would result in a reduced posterior probability of CAP. This process mirrors the clinical decision-making, where accumulated evidence increases or decreases the probability of a given differential diagnosis [75, 338].

$$P\langle B|A\rangle = \frac{P\langle A|B\rangle \times P\langle B\rangle}{P\langle A|B\rangle \times P\langle B\rangle + P\langle A|\bar{B}\rangle \times P(\bar{B})}$$

$P\langle B\rangle$ = Probability of event B
$P(\bar{B})$ = Probability of event B not occuring
$P\langle B|A\rangle$ = Probability of event B given condition A
$P\langle A|B\rangle$ = Probability of condition A given event B
$P\langle A|\bar{B}\rangle$ = Probability of condition A given event B has not occured

Figure 4.6: Bayes' Theorem

Where a large evidence base exists, the prior probability distribution can be established through data summary techniques such as meta-analysis and systematic review [341]. Where there is a lack of research evidence, the distribution can be determined by analysis of expert opinion. In some cases local data is more relevant than data derived via summary techniques. For example, the types of disease that present to EDs varies geographically and across time (e.g. increased CAP in winter, different common infective organisms between countries, local disease incidence when calculating disease probability) [75, 338]. These characteristics make Bayesian modelling particularly suitable for clinical applications where the quality of evidence is variable, as is the case in the diagnosis and treatment of CAP (see chapter 2).

4.2.2 Odds Ratio (OR) form of Bayes' Theorem

Most published data from CAP process, outcome and diagnosis studies is reported in the format p(finding|CAP) - i.e. the probability of a finding given that the patient is known to have CAP. This data is not useful for deriving models to predict CAP from findings [241]. Some diagnostic studies have used likelihood ratios (LR) to describe CAP predictor variables [4, 86]. The LR of a disease is an estimate of how much new information will change the odds of the disease. LRs are appropriate for use in the OR form of Bayes' theorem. In this simple formula the post-test odds of a disease are equal to the product of the pre-test odds and the LR for the disease given new information (e.g. cough in the diagnosis of CAP) (see figure 4.7) [338]. The posterior probability is then calculated from the post-test odds. The initial pre-test odds can be established from the population incidence of the disease. Serial calculations of posterior probability can be made by multiplying the new post-test odds by the LR of the disease given further new information, similar to Bayes' Theorem (e.g. cough, then dullness to percussion in the diagnosis of CAP) [338].

$$p\langle CAP|Findings\rangle = \text{Post-test Odds} / (1 + \text{Post-test Odds})$$
$$\text{Posttest Odds} = \text{Pre-test Odds} \times \text{Likelihood Ratio}$$

$$\text{Negative Likelihood Ratio} = \text{Sensitivity} / (1 - \text{Specificity})$$
$$\text{Positive Likelihood Ratio} = (1 - \text{Sensitivity}) / \text{Specificity}$$

$$\text{Sensitivity} = \text{True Positives} / (\text{True Positives} + \text{False Negatives})$$
$$\text{Specificity} = \text{True Negatives} / (\text{False Positives} + \text{True Negatives})$$

True Positive = Disease positive and finding positive
False Positive = Disease negative and finding positive
True Negative = Disease negative and finding negative
False Negative = Disease positive and finding negative

$$\text{Initial Pre-test Odds} = \text{Population Incidence} / (1 + \text{Population Incidence})$$

Figure 4.7: OR form of Bayes' theorem*

*Sox et. al. [338]

A positive LR is the ratio of the probability of a specific disease in patients when a clinical finding is present, to the probability of the same finding in those without the disease. A negative LR is the ratio of the probability of the absence of a specific disease in patients when a clinical find-

ing is present, to the probability of the same finding in those with the disease. A positive LR greater than 1 indicates a finding is associated with the presence of the disease in question. An negative LR greater than 1 indicates a finding is associated with the absence of the disease in question. The stronger the relationship, the greater the LR will vary from 1 [338].

4.2.3 Dependence amongst variables

Bayesian models have an advantage over statistical models in that they allow the representation of dependency between variables via model structure [342]. Dependency refers to the tendency of the predictor variables to change together due to a confounding mechanism (i.e. they are correlated). Naive Bayesian methods assume there is independence in the relationship between predictor and outcome variables and adds their full individual effects. The inclusion of correlated predictor variables in the same model, results in overconfidence (i.e. the model predicts an outcome is more likely than it actually is). In reality, because of their correlation, there is some joint effect of these variables on the probability of the outcome in question, which is less than their individual effects combined. For example, in the diagnosis of CAP, patients often have both cough and dullness to percussion. Figure 4.8 shows an influence diagram of the relationship between these variables and CAP. Influence diagrams are used in decision theory to represent probabilistic relationships between events or states [338]. Both cough and dullness to percussion can co-occur, due to the mucus production that is associated with bacterial infection. Therefore, they are dependent upon each other, and the probability of CAP is unlikely to increase by the full amount associated with each individual condition if they are both present. This dependency can be calculated by assessing the correlations between variables, and represented by a latent variable in the Bayesian model (e.g. mucus in figure 4.8) [342].

Aronsky and Haug [250] have used bayesian networks to model the dependencies between CAP diagnostic variables. Monti and Cooper [342] found that modelling dependencies between the predictors of poor outcomes for CAP patients, improves the calibration (i.e. the match between the predicted probability of an outcome and the proportion of cases with that outcome), but not the classification accuracy of Bayesian models. Naive Bayes models that do not consider dependencies amongst variables, still exhibit a high level of accuracy and are simpler to construct [342].

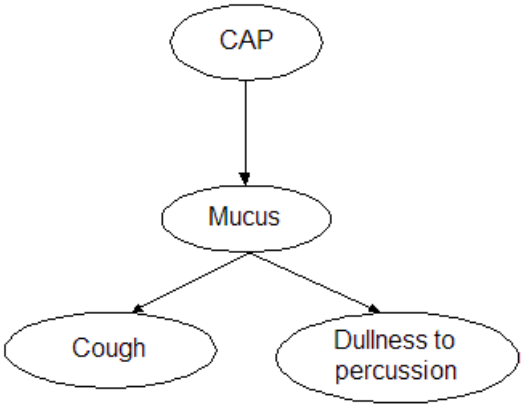

Figure 4.8: Simple pathophysiological model of the dependence between cough and dullness to percussion

4.3 Workflow simulation

Simulation is the process of using a model to predict how a given system will act under specific circumstances [343]. Computer-based simulation of workflow, one of the key tools of BPR, enables the testing of hypotheses and interventions in complex systems, prior to their introduction. The practicality of an intervention can then be assessed prior to the costly exercise of implementation. The systematic modification of model parameters then allows the optimisation of model output, thus deriving the best solution given model constraints [343]. CAP-related decision support has so far under-performed, showing variable rates of compliance, and producing unintended negative effects on care (see chapters 2 and 3). Given the high cost of developing clinical interventions, simulation of their impact prior to implementation makes good managerial and economic sense.

Simulation is largely under-utilised in health care. Baldwin et. al. [73] identify evolving use in areas such as epidemiology, health care systems design and operations (e.g. patient flow and resource allocation), and medical decision-making. One method commonly used to model patient and process flow is discrete event simulation [344, 345]. This technique simulates the transition of patients or processes between different states across time, based on events. The construction of a discrete event model requires the derivation of statistical distributions of the timing of clinical events. This process is both data and labour intensive [346, 347].

An alternative approach, that considers both patient complexity and process flow, emanates from the Virtual Design Team (VDT) research group at Stanford University. These researchers have produced a complex tool, CAVHAT (Context Aware Virtual Health Administration

Team), that simulates the interaction of health workers, organisational structure, information, and decision-making [324]. This approach is comprehensive, but it may be argued that the level of detail included adds unmanageable complexity to the simulation process, requiring all significant interactions of actors to be modelled.

A complete workflow representation is not required to derive the benefits of workflow simulation. Simple deterministic spreadsheet models are often used to model health care process flow [348, 349]. A simple process model consists of a group of mean or median process times for sequential or parallel processes. Figure 4.9 shows a hypothetical set of distributions for the timing of 3 processes (A-C) that generally occur consecutively in normal workflow (e.g. triage assessment, physician assessment and CXR in CAP treatment). The dotted lines represent median values for the time of process performance.

The inter-relationship between processes can be derived as a part of qualitative workflow analysis. Descriptive statistics can then be obtained via quantitative analysis of local process timing [350]. The impact of changes in timing of one process may be simulated by adjusting other process times in the sequence, accordingly. For example, if the median timing of a specific process was improved by 30 minutes, then the median timing of subsequent dependent processes could be improved by the same amount (e.g. if CAP patients were seen an average 30 minutes earlier by an ED physician, then they may receive a CXR on average 30 minutes earlier, and therefore be treated earlier on average 30 minutes earlier). This approach ignores the random process variability that occurs in any system, but provides a simple representation of local process flow. If there are concerns over the ability of local resources to deal with simulated changes, then expert opinion can be used to determine whether changes in process flow are practical. Alternatively, more detailed process modelling can be carried out prior to implementation. Such a simple process flow model, should be easier to combine with decision models for representation of patient complexity, and existing local policies in the form of rules. These 3 components cover all predictors from my simple model of process performance (see figure 4.10). I will discuss the incorporation of these components into an overall model of workflow in chapter 5.

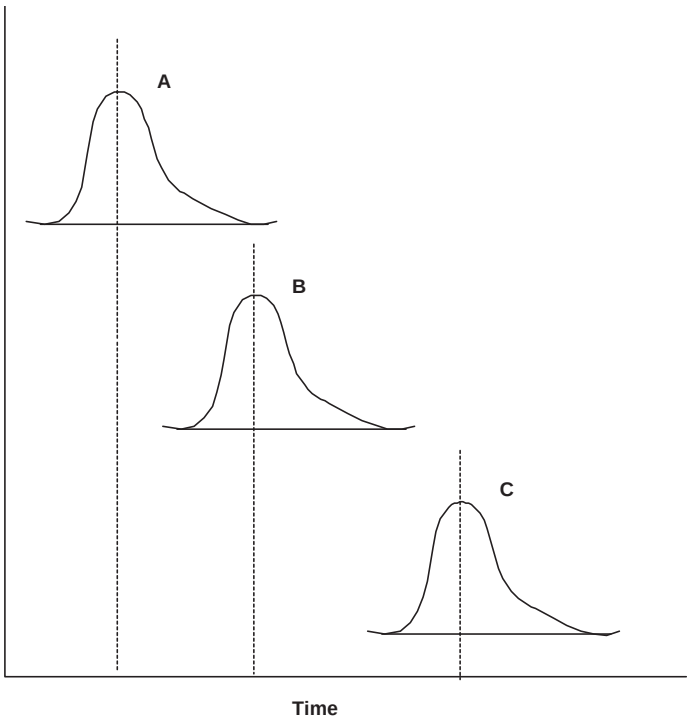

Figure 4.9: Simple model of process flow

4.4 Conclusions

There is an emerging body of literature on the key role of workflow in determining clinical process performance, however, workflow assessment, modelling, and simulation are under-utilised. Clinical workflow is far more complex than simple flow from one process to the next. At an abstracted level, patient complexity, local policy and resources available at the point of care all contribute to overall workflow and process performance (see figure 4.10).

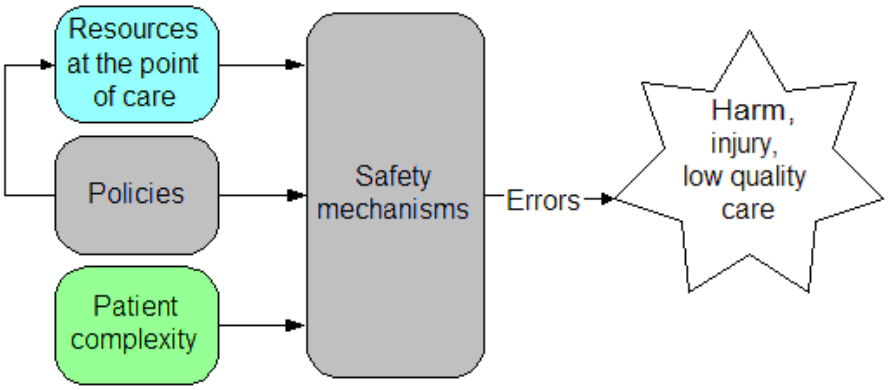

Figure 4.10: Simple model of predictors of process performance/error

Given the complex nature of process and information flows, graphical techniques such as sequence diagrams are useful to qualitatively map workflow and to identify high risk processes.

Simulation techniques offer an opportunity to assess the local feasibility of clinical practice change prior to implementation. The techniques currently in use, such as discrete event simulation, are data and time intensive, and do not cover all of the determinants of workflow. The combination of a simple deterministic process flow model, simple decision models, and abstractions of local policies, may provide a more cost effective method of representing the major aspects of clinical workflow. Using these techniques, I plan to design an alerting system for the early investigation and treatment of CAP. In Chapter 5 I will further explore the rationale for using this approach, and introduce the methodology, and hypotheses for the resulting studies.

5 Rationale, study design and hypotheses

5.1 Rationale

Chapters 1, 2, and 3 summarise the presentation, diagnosis, and treatment of community-acquired pneumonia (CAP), as well as decision support designed to improve CAP care. Figure 5.1 shows a simple model that identifies groups of factors associated with health care process performance: patient complexity, resources at the point of care, and local policies and safety mechanisms. The problems highlighted by my literature review support that each of these factors needs to be formally considered in the design of interventions to improve CAP care.

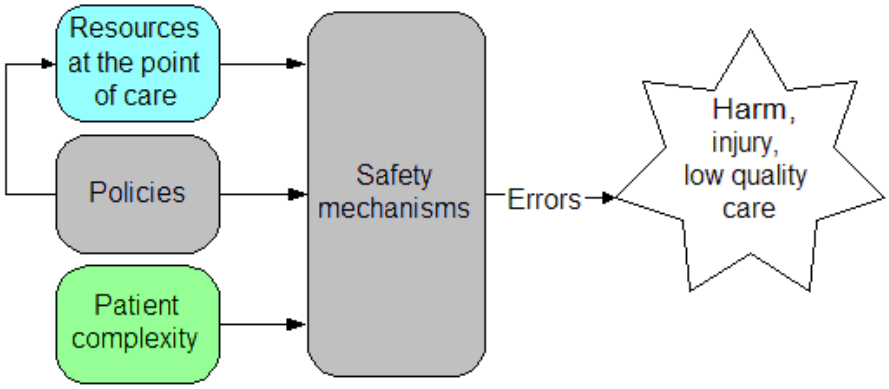

Figure 5.1: Simple model of predictors of process performance/error

There was evidence of uncertainty or patient complexity in diagnosis and risk assessment, leading to delays in diagnosis and antibiotic treatment (see chapters 1 and 3). Delays in antibiotic treatment greater than 4 hours are associated with a 15% increase in morality (see chapter 3). Delays due to reduced resources at the point of care occur across all processes and are influenced by increased ED and hospital workload. Significant delay to treatment is incurred if treatment does not take place in the ED, due to a lack of resources on the ward.

Current policies and safety mechanisms rely on decision support in the form of paper-based guidelines and feedback of performance on key clinical process indicators. The improvements in CAP care brought about by these methods have largely fallen short of expectations, secondary to poor compliance (see chapters 2 and 3). Triage policy is likely to exacerbate process delays for CAP with low urgency scores (see chapter 1).

Many patients are not treated in the emergency department (ED) leading to long delays to treatment upon ward transfer (see chapter 3). At the site of my analysis, a large Australian tertiary hospital, a paper-based CAP guideline failed to reduce delay to antibiotics below a 4 hour goal. Prior to implementation the mean time to antibiotic was 9 hours. In the 6 months following implementation, a subsample of patients aged > 65 years still had a mean delay to antibiotic treatment of 8.5 hours (unpublished audit results).

In this thesis I argue that a care plan able to optimise processes, given both patient complexity and local workflow conditions (a “flexible care plan”), is more likely to be used by clinical staff. I will further argue that such a flexible care plan can be operationalised through computer-based decision support systems (CDSS) that formally model patient complexity, and are designed to fit into local workflow. In comparison, paper-based guidelines generally divide patients into rigid categories that inadequately represent patient complexity. They also contain process recommendations that are inflexible to the variations in the local workflow that determine resources at the point of care (see chapter 2). Automatic functions of CDSS, such as alerting systems, offer the promise of improved compliance with key process targets and guideline recommendations (see chapter 2). Alerting systems have been shown to be successful in improving guideline use, reducing errors in treatment, and improving the awareness of new information such as test results [191, 211].

One of the keys to designing functional decision support is optimising its implementation into local workflow (see chapter 2). The interaction of workflow and decision support can be assessed prior to the expensive and disruptive process of implementation by workflow simulation (see chapter 4). This is a 3 step process which involves workflow assessment, modelling, and finally, simulation. I plan to use these techniques to design a CDSS based alerting system to reduce antibiotic delay for CAP patients, that present to the ED of a large Australian teaching hospital.

Current guidelines recommend chest x-ray (CXR) and blood test investigations as a part of the diagnostic work up (see chapter 2), however, waiting for the return of these test results produces significant delays (see chapter 3). Despite being the gold standard, CXR has questionable sensitivity, specificity and inter-rater reliability. In cases that present with high probability of CAP, based on history and physical examination, it may be of benefit to treat prior to CXR (see chapter 1). If the delay to treatment associated with waiting for a CXR extends beyond the 4 hour mark, then there is an increase in the risk of mortality, or a loss in the manageability of CAP (see the following section for a further discussion). Under new managed care policies implemented in the US, many sites are already informally treating prior to CXR in order to reach treatment targets. This is occurring without formal modelling of the diagnostic criteria, thus increasing the risk of an early false positive diagnosis and inappropriate antibiotic treatment (see chapter 3).

Significant reductions in delay to CAP treatment can be made by ordering tests at triage or treating prior to the return of investigations. There are a small number of studies that have found simple CAP-specific diagnosis and risk models, implemented at triage, are effective in reducing the delay to antibiotic treatment (see chapter 3). Early diagnostic models (EDMs) and early risk models, validated at their site of implementation, may then be used to promote the timely investigation and treatment of CAP in an evidence-based fashion. Monitoring of diagnostic and risk criteria may also help to control inappropriate test ordering and treatment.

5.1.1 Treatment loss model

The treatment of CAP is a time dependent process - there is a loss in the manageability of CAP with the passage of time. A decrease in antibiotic efficacy is coupled to an increase in the complexity of information required to manage CAP as the patient becomes more unstable (i.e. more assessment and integration is required, there is greater uncertainty/increased risk of poor outcomes, more knowledge is required to treat the condition). Consequently, for patients with high probability of a disease, the marginal incremental benefit of delaying treatment for further investigation (e.g. a CXR, or for a complex risk score) is cancelled out by the loss incurred. Figure 5.2 illustrates this graphically. In this case waiting for more diagnostic certainty by treating after CXR, or for more certainty of the risk of mortality by waiting for return of results for pneumonia severity index risk calculation (PSI), reduces the efficacy of antibiotic treatment. In mapping this workflow space a number of definitions are useful. Minimal acceptable management is the highest loss tolerable or the lowest standard of care acceptable. Current best management is the

best level of care measured. Best management practical refers to the best level of care obtainable with workflow optimised, considering diagnostic and risk uncertainty. My workflow modelling approach is designed to calculate this value. Manageability is the area between the minimal acceptable management and the best management practical. The establishment of these parameters using simulation should promote the development of achievable interventions with realistic goals that are more likely to be successful.

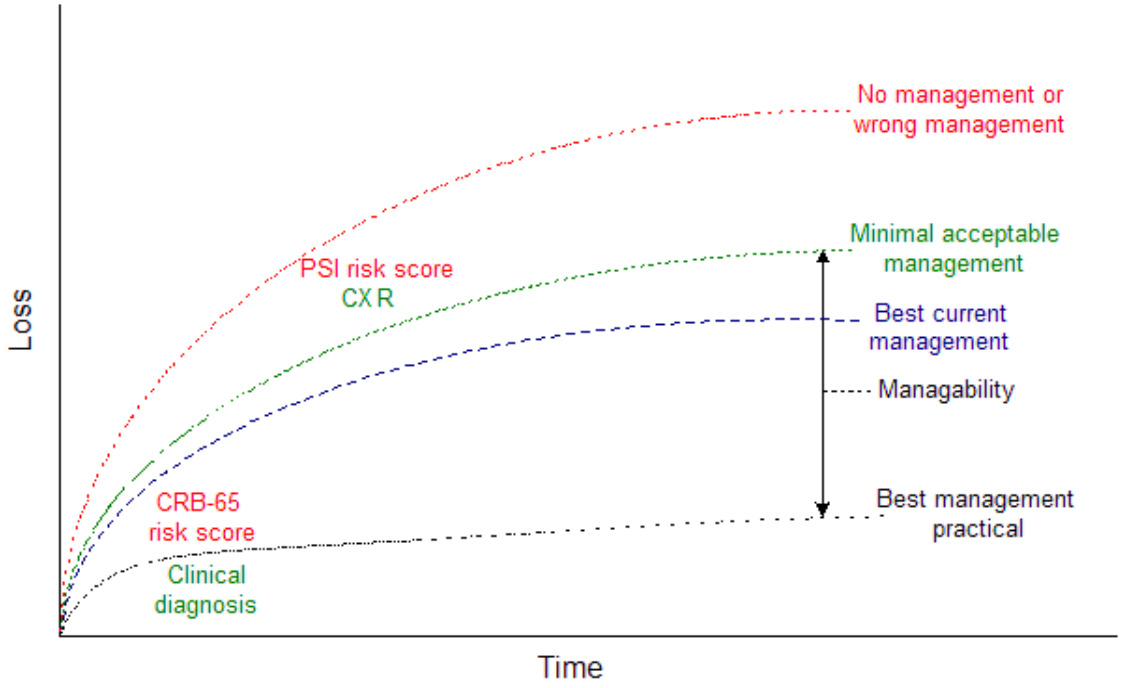

Figure 5.2: Loss function over time for testing in antibiotic treatment of CAP

Figure 5.3 shows the hypothesised impact of the introduction of an alerting system based on a early diagnostic and risk model. It displays a reduction in loss (increase in treatment efficacy) for a subset of patients identified by an alerting system and treated promptly prior to the return of CXR or blood results at either triage or initial physician review. This change in the distribution of treatment timing is likely to increase the percentage of CAP patients treated within 4 hours, thus improving mean and median treatment times overall. Given the difficulty of CAP diagnosis it is likely that a percentage of patients will still have delayed treatment.

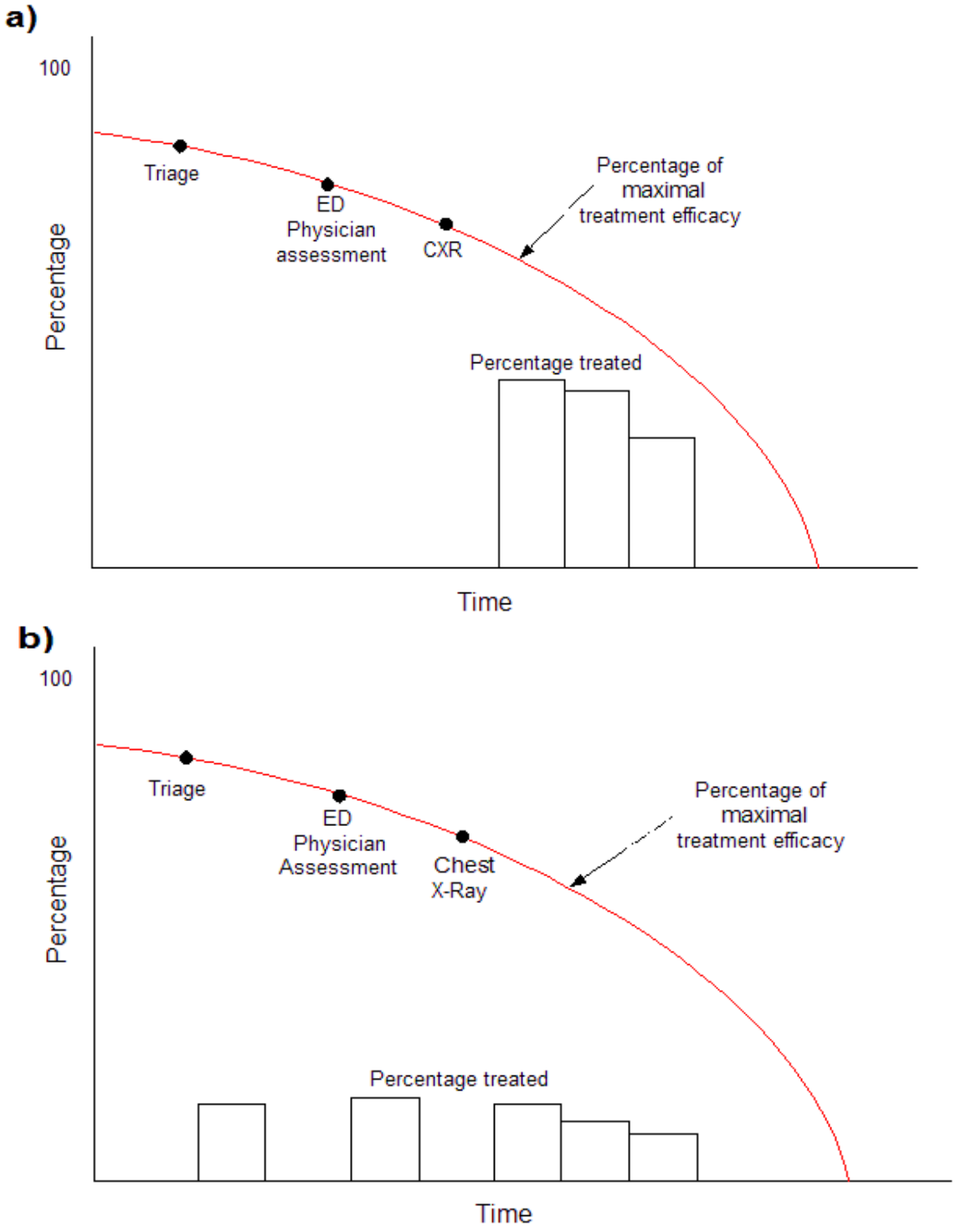

Figure 5.3: Hypothesised improvement in antibiotic delivery timing and treatment efficacy with the implementation of an alerting system based on an early diagnostic model and an early risk model: a) pre-intervention, b) post-intervention

5.2 Study design

5.2.1 Overview

This work will comprise of 3 major groups of studies of CAP patients and CAP treatment processes at a large Australian metropolitan teaching hospital. The first stage of studies is an assessment of the workflow around CAP patients in the ED. This will involve observation, stakeholder interview, and will utilise an existing CAP patient database compiled to assess the impact of a local paper-based guideline (see appendix figure 9.1). The goal of this section of the study is to describe the local workflow both structurally and statistically. This process should identify key points in the workflow for decision support implementation and provide the data for decision model assessment and workflow simulation. The second stage is the selection or construction and validation of diagnosis and risk models. The goal of this section is to assess whether simple models calculable at initial assessment are comparable to more complex models requiring the return of test results. The final stage is to simulate the introduction of an alerting system based on CAP diagnosis and risk models, using the retrospective patient and workflow data obtained in the previous steps.

5.2.2 Workflow assessment and modelling

Figure 5.4 shows a flow diagram of the steps involved in the workflow assessment and modelling. The structure of workflow pathways will be visualised via the construction of sequence diagrams (see chapter 3) based on prospective observation of workflow around CAP patients, modified by stakeholder review. These models will then be quantified by retrospective data from the CAP database. I will assess which processes are associated with delay to antibiotic delivery, the accuracy of key diagnostic and risk assessment processes, and the accuracy of the ED primary diagnosis. In order to determine the accuracy of initial CXR, I will parse CXR reports for CAP-related findings, comparing a CAP-positive group from the database with a CAP-negative control sample. I will then compare ED diagnosis and CXR evidence to assess if inaccuracy in diagnosis is associated with interpretation of CXR evidence. I will review the relationship between triage score and process timing to assess its impact on process timing. I will assess the validity of ATS scoring in CAP by comparing the rate of complications and percentage of total complications in each triage group.

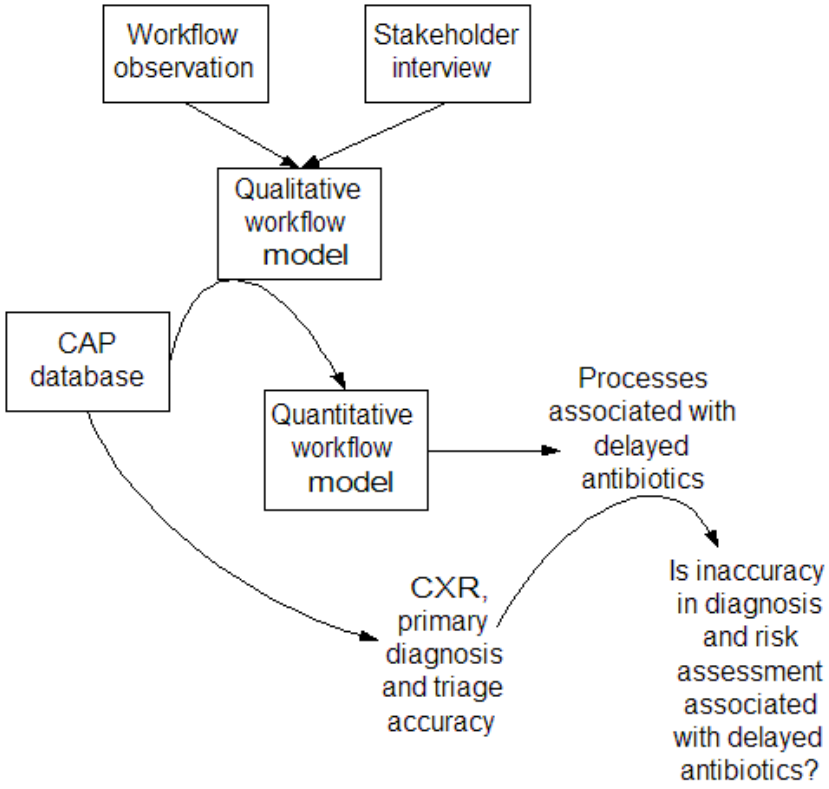

Figure 5.4: Workflow assessment and modelling of CAP antibiotic treatment

5.2.3 Diagnosis and risk model selection, construction and validation

I propose to construct or identify existing evidence-based predictive models of CAP diagnosis and risk assessment, in order to develop a computer-based alerting system. Figure 5.5 shows a flow diagram of the planned steps involved in model construction/selection. The goal of such a system is to maximise the number of CAP patients treated within 4 hours of presentation. The CDSS will be composed of a diagnostic model and a risk model. I plan to select models that do not require the return of investigation results. There are no widely implemented CAP diagnosis models in current practice (see chapter 2). A recent systematic review summarised CAP predictor variables from the clinical history and exam in terms of likelihood ratios (LRs) [4, 86]. I will use these variables to construct an early diagnostic model (EDM) for CAP, based on the odds ratio (OR) form of Bayes' theorem (see chapter 4). In setting a diagnostic threshold for the EDM I will focus on maximising specificity in order to limit false negative alerts and inappropriate resource usage. I will validate this model by comparing its accuracy to a similar model constructed from LRs calculated from local data. I will also assess the influence of dependence amongst predictor variables (see chapter 4) by comparing the EDM's accuracy to that of an alternative model with calculated joint LRs for commonly co-occurring findings. I will also com-

pare the accuracy of the model to that of CXR and ED primary diagnosis to assess if the model is superior to current diagnostic systems.

To identify the optimal early risk model for CAP treatment I intend to compare the ATS and a locally-derived risk model with published CAP-specific algorithms. Only the PSI and the CURB-65 models are currently supported by national consensus groups (see chapter 2). The CRB-65 rule, a subset of the CURB-65 rule, has similar accuracy and does not require the return of test results, making it a good candidate for an early risk model. This model lacks a measure of renal function. To assess whether history of renal impairment at presentation can replace the measurement of urea in the CURB-65, I will construct an alternative model, the "CRB-65RF" including this variable.

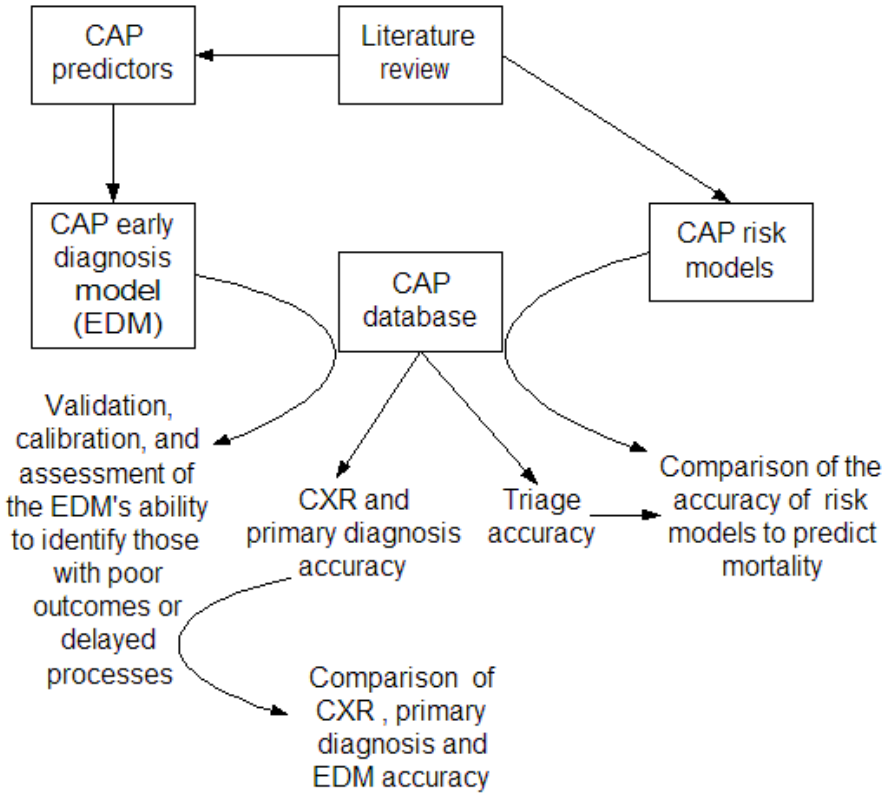

Figure 5.5: Construction and selection of diagnosis and risk models

5.2.4 Alerting simulation

Critical to the success of a CDSS is integration into local workflow (see chapter 2). In order to optimise alerting rules I will simulate the introduction of the alerting system into local workflow using a simple deterministic process flow model which subsumes the complex factors that contribute to resources available at the point of care including existing local policies (see chapter

4). Figure 5.6 illustrates the CAP ED alerting system simulation model. This model will combine the Bayesian EDM (A), 1 of 5 CAP-specific risk models (B), and the deterministic model of local process flow (C) with practice changes (D). Theoretically this approach could be used to simulate the treatment of any disease in any health care environment. The model covers the 3 key determinants I have previously outlined: patient uncertainty around diagnosis and risk, resources available at the point of care, and local policies (see figure 5.1). These parameters should cover most of the perceivable changes to a health care system. For instance, new diagnostic technology, new studies of existing techniques, changes in practice due to cost or local preference, can be incorporated into the diagnostic model (A). Similarly, improvements in risk assessment may be used to change the risk model (B). Any impact these modifications have on process flow could then be incorporated into the process flow model (C). Changes in practice that are related to purely organisational issues that impact directly on resources at the point of care, such as cost, staffing, system workload, improved communication and organisation, and physical changes to the health care environment, can be simulated by modifying the process flow model (C).

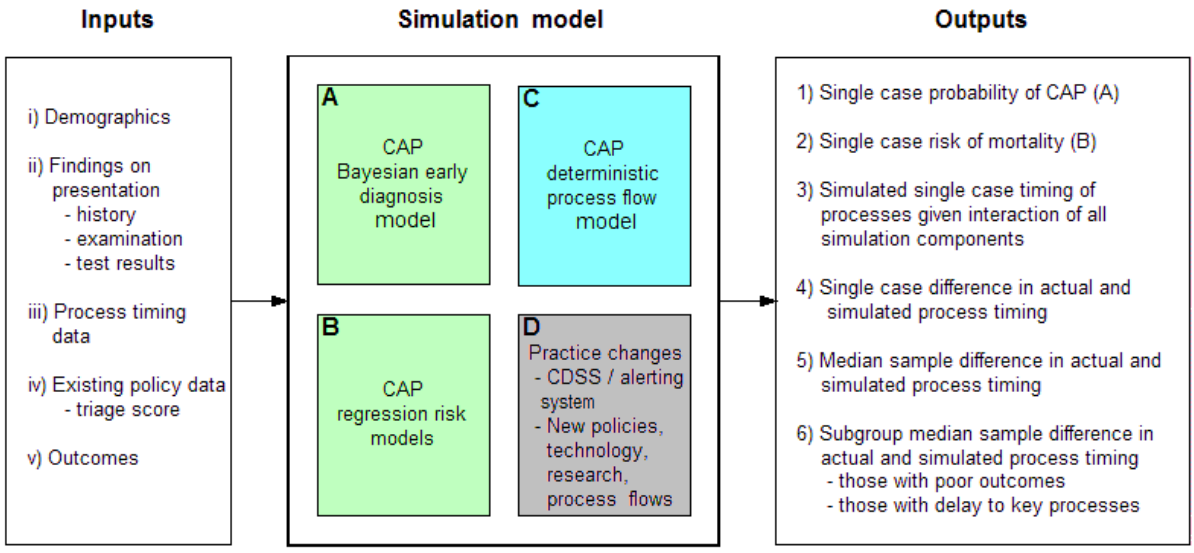

Figure 5.6: CAP alerting system simulation model

Using this method I will investigate the simulated impact of different antibiotic treatment alerting systems based on various combinations of the EDM, the most accurate simple risk model, ED physician diagnosis, and CXR report, using retrospective data from the CAP database. The impact of these models will be assessed by calculating the hypothesised treating time across all subjects in a retrospective database. A given subject's simulated treating time will be reduced if the EDM is positive given their presenting symptoms. Treatment will be assumed to take

place within 30 minutes of an alert at triage, physician assessment, or by ED discharge, depending on the implementation of the model. Antibiotic timing will only be adjusted for patients who were actually treated after the calculated alerting time.

5.3 Hypotheses

5.3.1 Major hypothesis

An alerting system, triggered by a CAP-specific Bayesian EDM, will reduce the simulated percentage of CAP patients with a treatment delay of greater than 4 hours.

5.3.2 Minor hypotheses

5.3.2.1 Alerting simulation studies

1 Increasing the urgency of triage score for CAP patients identified by a Bayesian EDM can significantly reduce the simulated percentage of patients with delay to antibiotic greater than 4 hours.
2 A hybrid alerting system combining a Bayesian EDM, ED primary diagnosis and CXR report, will provide a larger simulated decrease in the percentage of patients with delay to antibiotic greater than 4 hours, than any of these triggers alone.

5.3.2.2 Process flow assessment

1 Failure to diagnose CAP in the ED will be associated with a significantly increased percentage of patients with delay to antibiotic greater than 4 hours.
2 Failure to treat CAP in the ED will be associated with a significantly increased percentage of patients with delay to antibiotic greater than 4 hours.
3 Low urgency triage score will be associated with a significantly increased percentage of patients with delay to antibiotic greater than 4 hours.

5.3.2.3 Diagnostic decision studies

1 The absence of evidence of CAP on initial CXR will be significantly associated with a non-CAP primary diagnosis.
2 The absence of evidence of CAP on initial CXR will be significantly associated with antibiotic treatment delay greater than 4 hours.

5.3.2.4 Construction and validation of the EDM

1 A Bayesian EDM for CAP populated with LRs from literature review will have an equivalent accuracy to one using locally derived LRs, as indicated by area under the ROC curve.
2 Due to dependence amongst commonly co-occurring variables, post-test probability calculated using joint LRs for CAP will be significantly less than that for combined LRs.
3 A Bayesian early diagnostic model will have an equivalent or higher sensitivity for CAP than CXR.

5.3.2.5 Risk decision studies

1 CAP-specific risk models will display higher accuracy for the prediction of CAP mortality in comparison to the Australasian Triage Score as indicated by a larger area under the ROC curve.
2 Adding a historical measure of renal impairment to the CRB-65 will improve its performance closer to that of the CURB-65 model as indicated by area under the ROC curve.

6 Methods

6.1 Subjects

6.1.1 Qualitative workflow assessment

To construct an accurate sequence diagram of workflow around community-acquired pneumonia (CAP) patients presenting to the emergency department (ED) I observed a sample of patients and discussed my observations with stakeholders involved in their treatment.

6.1.1.1 Workflow Observation

I observed the workflow around a convenience sample of 6 patients with probable CAP, presenting to the ED of a large Australian metropolitan teaching hospital during October 2001. These patients were identified by triage staff who were asked to contact our department if any patient with pneumonia-like symptoms presented to the ED. I was able to observe these patients from within 30 minutes of presentation until ward admission. Four patients were discharged from ED, 3 with diagnosis of pneumonia and 1 with bronchitis. One patient died in the ED. One patient was admitted to the ward but died soon after of multiple system failure. Australasian Triage Score (ATS) ranged from 2 to 4 for this group.

6.1.1.2 Stakeholder assessment

The stakeholders interviewed included the clinical director of the ED, 3 consultant emergency physicians, the doctors and nurses directly involved in the care of the observed patients, the laboratory manager and ED information technology (IT) staff. Feedback was also gained from presentations at meetings of a local committee involved in the construction, implementation, and assessment of a CAP treatment guideline. This group consisted of consultant physicians from the departments of Medicine, Pharmacology, Microbiology, Thoracic Medicine, Radiolo-

gy, and the ED, as well as representatives from the pharmacy department, and the hospital's Quality and Safety Unit.

6.1.2 Quantitative workflow analysis

I utilised a database compiled by the Quality and Safety Unit at the study site to assess the implementation of a paper-based guideline. Table 6.1 describes the data sources and types of data compiled in this database. The linkage of clinical findings, process timing, coded diagnoses, and outcomes provided a powerful resource for decision and workflow analysis.

Table 6.1: CAP database description

Source	Data
Hospital administration system	ICD-9 diagnosis and procedure codes, costs, length of stay, ward admission times, demographics
ED clinical information system	Primary diagnosis codes, triage score, ED admission, discharge, and physician review times, site of discharge
Laboratory reporting system	Blood test request timing and results
Radiology reporting system	CXR timing and radiology reports
Paper-based case notes	Presenting history, and examination findings, antibiotic selection and delivery timing

Table 6.2 describes the 3 patient samples used in quantitative analysis of decisions and workflow. Two of these samples were CAP-positive patients from the original database. I collected a third sample of CAP-negative patients to calculate the accuracy of my CAP early diagnostic model (EDM) and compare it to the accuracy of chest x-ray (CXR) and physician diagnosis.

Baseline data for the CAP guideline implementation study was collected from June to December 1998 by the hospital's Quality and Safety Unit. Two hundred and sixty eight CAP admissions were identified by ICD-9 principle discharge diagnosis codes. The infective organism was only identified in 14.7% of cases (see appendix table 9.2). Cases with missing ED admission times were excluded from the study (n=22). These subjects may have been directly admitted to the ward. Eight patients were admitted more than once and 1 patient was admitted 3 times for CAP during the study period. Each admission was included as a separate episode. The sample was predominantly elderly (mean age = 68 years) and male (60.5%). The majority of patients were assessed at triage score 3 (56.8%). This data set was used to assess the relationship between CAP treatment processes, including the association between CXR order time, ED diag-

nosis, site of antibiotic delivery, Australasian Triage Score (ATS), and time of initial antibiotic dose. I also used this sample to investigate the accuracy and validity of the ATS, by comparing the rate of complications and percentage of total complications in each triage group.

Following the implementation of the CAP guideline, the Quality and Safety Unit collected data from a sample of patients aged greater than 65 years, that presented between May to December 2000. One hundred and forty six cases were identified. The infective organism was only identified in 2.7% of cases (see appendix table 9.2). The sample had a mean age 81.2 years (range 66-99) and 54.1% were male. Two patients had 2 admissions for pneumonia that were treated as individual cases. This data was used to assess the relationship between ED diagnosis, site of antibiotic delivery, CXR result, and time of initial antibiotic dose. I also calculated the sensitivity and specificity of initial CXR. CXR reports were available for 132 of these patients. Cases were excluded if directly admitted to the ward (n=9). This data was also used to validate the early diagnosis model (EDM), compare the accuracy of CAP-specific risk models in comparison to the ATS, and for workflow simulation studies.

The vast majority of CAP-positive patients were coded as non-specific, lobar, or bronchopneumonia at discharge (84.3 and 97.3% for the 1998 and 2000 samples, respectively; see appendix table 9.2). Final discharge diagnosis often varied from the diagnosis in ED (see appendix table 9.3). For both CAP-positive groups the most common non-CAP primary diagnosis was respiratory tract infection. Diagnoses of COAD and cardiac failure were also frequent in both groups. Chest pain and angina were common in the 1998 sample, whilst arrythmia and PE occurred more often in the 2000 sample.

To calculate the accuracy of CXR and validate the EDM, I collected data from a sample of CAP-negative patients over the age of 65 years that presented to the ED with respiratory symptoms in January-December 2003. Data sources used were similar to those captured in the existing CAP-positive database (see table 6.1). Subjects were identified via a free text search of the presenting complaint field of the local ED database. This field was coded by triage staff upon presentation to ED. The search used the terms “shortness of breath”, “cough”, “chest pain”, “bronchitis”, “chest infection”, and “respiratory failure”. This approach identified an initial sample of 6030 presentations of possible respiratory disease. Patients with a primary diagnosis of pneumonia (n=387) were excluded. Cases were randomly selected from each non-CAP primary diagnosis group in order to stratify the sample (see appendix table 9.2). ED diagnoses

were then compared to the discharge diagnosis recorded in the medical record to exclude any CAP cases not diagnosed in the ED. The final non-CAP sample consisted of 74 patients. Mean age was 76.9 years (range 66-95). There was an equal number of male and female subjects. The majority of these patients were admitted (66.2%). CXR reports were available for 71 of these patients. The most frequently recorded presenting complaints were chest pain and dyspnoea (see appendix table 9.4). Arrythmia was the most common primary diagnosis, followed by COAD and asthma, respiratory tract infection, cardiac failure, pulmonary embolism, respiratory failure and viral infection. The ICD-9 discharge diagnoses for CAP-negative cases were relatively well spread across common non-pneumonic diseases that present with respiratory symptoms. The most common was COAD, followed by respiratory tract infection, atrial fibrillation, asthma, heart failure and pulmonary embolism.

All 3 samples were approximately equivalent in terms of gender and severity at presentation as indicated by triage score. The 1998 sample had a lower mean age and larger range in comparison to the 2 samples that were selected over the age of 65 (see table 6.2).

Table 6.2: Subjects for quantitative workflow analysis

	Data Set	CAP +ve 1998	CAP +ve 2000	CAP -ve 2003
Subjects	**Total admissions**	268	146	74
	Exclusions	22	9	3
	Admissions included	246	137	71
	Patients with multiple admissions (%)	8 (3.3)	2 (1.4)	0
	Patients included	238	144	74
Demographics	**Mean age in years (range)**	68 (18-104)	81.2 (66-99)	76.9 (66-95)
	Male n (%)	144 (60.5)	79 (54.1)	37 (50)
Number of patients in each ATS category (% of all patients)	**1**	8 (3.3)	5 (3.6)	3 (4.1)
	2	69 (28)	29 (21.2)	25 (33.8)
	3	139 (56.5)	84 (61.3)	44 (59.5)
	4	30 (12.3)	19 (13.9)	2 (2.7)
	5	0	0	0

6.2 Workflow assessment

6.2.1 Structural modelling: sequence diagrams

I developed a sequence diagram of the workflow around CAP patients with an ATS greater than 1. Those with an ATS of 1 were generally examined, investigated and treated in a much more timely fashion than those with higher scores. The sequence diagram was constructed and modified through an iterative process of observation, model building and stakeholder interview [74]. Diagrams were developed using the business modelling software package Visio 2000 (Microsoft Corporation). Initial diagrams were used as tools for discussion of decision points, processes, the role of actors and policies, and sources of available data for the quantification of workflow and process timings. These diagrams were modified based on discussions and integrated into the final model.

6.2.2 Quantification of workflow

To quantify this model I used the CAP database compiled by the hospital's Quality and Safety Unit. I reviewed data from local clinical information systems and medical records to complete the dataset where there were missing values.

6.2.2.1 Analysis of process timings

All statistical procedures were carried out using the S-PLUS statistical package (Versions 6-6.2, Insightful Corporation, Seattle). I calculated the time to key processes from ED admission by subtracting admission time from the process time. I also calculated the time between individual processes by subtracting the time of processes more proximal to admission from those more distal. I then calculated descriptive statistics for time to physician assessment, time to CXR, time to antibiotic, time to ED discharge, and the time between these processes. My initial assessment indicated that the distributions of all timings were positively skewed, therefore median values were reported. Correlations were carried out between process timings to assess the interrelationship between the completion of processes.

I recoded the continuous time to antibiotic treatment variable to binary variables with cut off points at 4 and 8 hours. I determined the site of antibiotic administration by identifying whether the first dose occurred after ED discharge time (recoded as ED or ward). I used ED primary diagnosis codes to identify whether a patient had been diagnosed with CAP in the ED (recoded as CAP-positive or CAP-negative). I also calculated descriptive statistics for CXR and antibi-

otic timing by site of antibiotic dose, ED primary diagnosis, triage score, and by triage score and site of antibiotic dose combined.

6.2.2.2 Inferential statistics

I used the chi-square procedure to test the significance of the association between individual categorical variables (ED diagnosis, site of antibiotic delivery and triage score) and between binary antibiotic timing variables (greater than 4 hours and greater than 8 hours) and categorical variables.

6.2.3 Analysis of outcomes

6.2.3.1 Descriptive statistics

Mortality was determined using the codes for discharge site (“died - autopsy”, “died - no autopsy”) derived from the local administrative database. Rates of other complications (use of vasopressors, mechanical ventilation, atrial fibrillation, sepsis, hypotension, renal failure, pleural effusion, empyema, lung collapse, heart failure, respiratory failure) were identified in ICD-9 discharge codes and via casenote review.

6.2.3.2 Inferential statistics

I used the chi-square procedure to test for significance of the association between mortality and between the two binary antibiotic timing variables and other categorical variables such as CXR result and ED diagnosis. I also assessed the significance of the relationship between triage and mortality.

6.3 Analysis of the use of CXR

In order to assess the accuracy of initial CXR results for the diagnosis of pneumonia, I compared the CXR reports of CAP-positive patients aged over 65 years from the year 2000 sample, to those of CAP-negative patients aged over 65 from the year 2003 sample.

6.3.1 CXR report analysis

I reviewed a sample of CXR reports and identified common terms associated with pneumonia and other common chest diagnoses. I then parsed the CXR reports of the CAP-positive and CAP-negative samples, and recorded the presence of these terms for each patient. I derived two criteria for a CAP-positive CXR. A broad model that included the terms "pneumonia", "consolidation", "opacity", "infection", and "shadowing", and a conservative model including "pneu-

monia" and "consolidation". I considered a CXR report to be positive under a specific model if it contained evidence of the presence of any of the model's criteria.

6.3.2 Assessment of sensitivity and specificity for ED and discharge diagnosis

In order to determine the accuracy of the initial CXR, I calculated the sensitivity and specificity for both the broad and conservative models, in comparison to both ED diagnosis and discharge diagnosis.

6.3.3 Interaction of CXR with workflow

6.3.3.1 Descriptive statistics

I also calculated descriptive statistics for both conservative and broad models, by the binary antibiotic timing groups, and site of antibiotic delivery.

6.3.3.2 Inferential statistics

I used the chi-square procedure to test for significance of the association between CXR report result (both broad and conservative models) and categorical antibiotic timing, site of antibiotic delivery, and ED and discharge diagnoses.

6.4 Diagnosis model

6.4.1 Qualitative model

I performed a literature review and identified relevant history, examination, and investigation variables significantly related to CAP. The majority of these variables came from two recent systematic reviews [4, 86]. The data in these reviews was expressed in the form of likelihood ratios (LRs). A further search of the PubMed database and of the internet using the Google search engine, found no other significant references. These variables were used to construct an influence diagram of the relationship of findings to CAP (see figure 6.1). I generated a spreadsheet (Excel, Microsoft 2000) model using the odds ratio (OR) form of Bayes' theorem to calculate CAP probability (p[CAP]) given a set of clinical and test findings (post-test odds = pre-test odds x LR; p[CAP] = post-test odds / (1+ post-test odds)) [338].

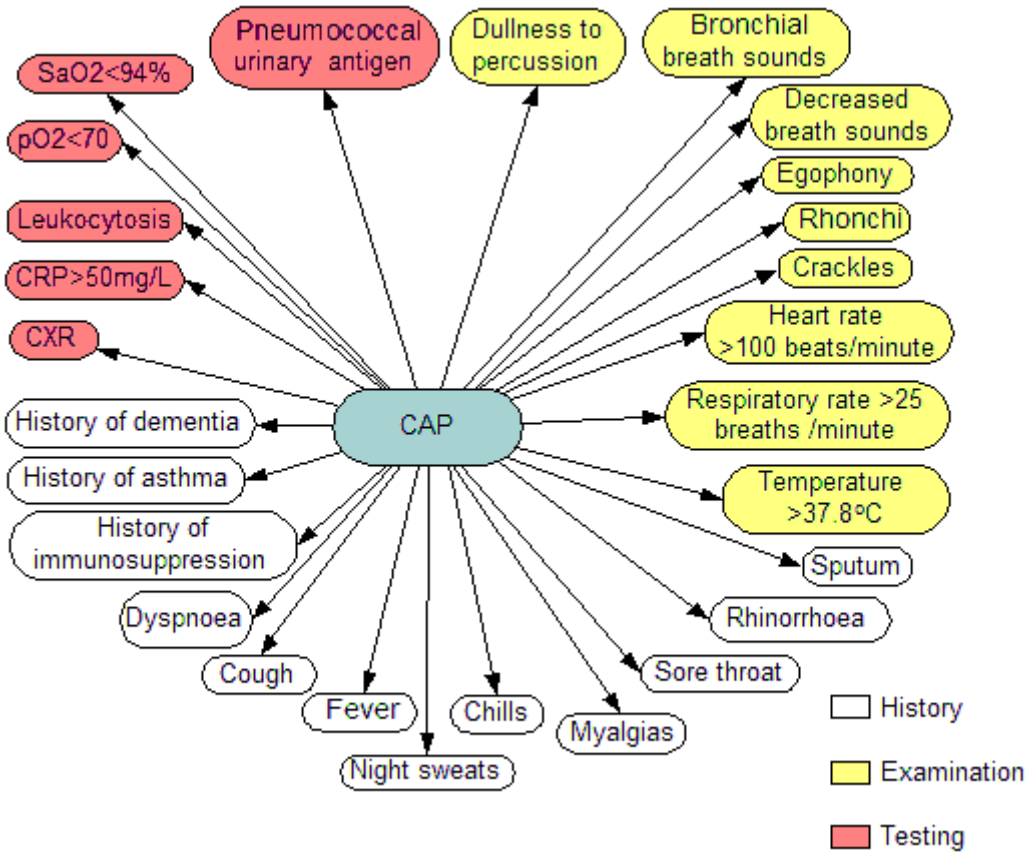

Figure 6.1: Influence diagram of CAP diagnosis model

SaO2 = oxygen saturation of blood (%)
pO2 = partial pressure of oxygen in arterial blood (mmHg)
CRP = C-reactive protein

6.4.2 Quantitative Model

Pre-test odds of CAP (p=0.014) on presentation were derived from local ED CAP incidence, calculated from ED primary diagnosis codes. Positive and negative LRs for CAP given specific clinical findings were obtained from literature review, or were calculated given the sensitivity and specificity of test values form literature (see table 6.3). Where there was variability in the LR for a finding across studies, an average of these values was calculated. Findings included: cough, dyspnoea, sputum, fever, chills, sore throat, rhinorrhoea, history of dementia, history of asthma, immunosuppression, myalgias, night sweats, increased respiratory rate, tachycardia, fever, dullness to percussion, decreased breath sounds, crackles, bronchial breath sounds, rhonchi [4, 86, 252, 254-256], leukocytosis, elevated C-reactive protein [86], low blood oxygen as indicated by pulse oximetry [351] and chest x-ray opacity. Despite being the gold standard for pneumonia diagnosis there is little evidence concerning the accuracy of CXR in current literature [86]. I therefore calculated LRs from local data.

.

Table 6.3: Likelihood ratios used in the CAP diagnosis model

Variable	(+)LR	(-)LR	References/Calculations
Cough	1.8	0.31	Singal et. al. [253]
Dyspnoea	1.4	0.67	Gennis et. al. [255]
Sputum	1.3	0.55	Diehr et. al. [252]
Fever	1.9	0.65	Mean of Diehr et. al. [252] and Heckerling et. al. [256]
Chills	1.53	0.76	Mean of Diehr et. al. [252], Gennis et. al. [255] and Heckerling et. al. [256]
Night sweats	1.7	0.83	Diehr et. al. [252]
Myalgias	1.3	0.58	Diehr et. al. [252]
Sore throat	0.78	1.6	Diehr et. al. [252]
Rhinorrhoea	0.78	2.4	Diehr et. al. [252]
History of asthma	0.1	3.8	Heckerling et. al. [256]
History of immunosuppression	2.2	0.85	Heckerling et. al. [256]
History of dementia	3.4	0.94	Heckerling et. al. [256]
Respiratory rate >25	2.45	0.8	Metlay and Fine [86]
Heart rate >100	1.95	0.61	Metlay [4]
Temperature >37.8^{o}C	2.65	0.67	Metlay [4]
Dullness to percussion	3.25	0.95	Metlay [4]
Decreased breath sounds	2.4	0.71	Metlay [4]
Crackles	2.15	0.78	Metlay [4]
Bronchial breath sounds	3.5	0.9	Metlay [4]
Ronchi	1.45	0.81	Metlay [4]
Vocal fremitis (egophony)	5.3	0.89	Metlay [4]
Leukocytosis	2.8	0.45	Metlay and Fine [86]
CRP>50mg/L	5	0.6	Metlay and Fine [86]
CXR positive for CAP	3.33	0.61	Calculated from local data
pO2<70	1.63	0.51	Heckerling et. al. [254]
pO2<80	1.47	0.28	Heckerling et. al. [254]
SaO2<94	8.89	0.22	Kaye et. al. [351]

6.4.3 Early diagnostic model (EDM)

I identified history and examination CAP predictor variables that would be available at initial assessment and were recorded in the local CAP database [4, 86]. I then modified the existing influence diagram (see figure 6.2) and spreadsheet (Excel, Microsoft 2000) model to include only these variables. I refer to this model as an early diagnosis model or EDM.

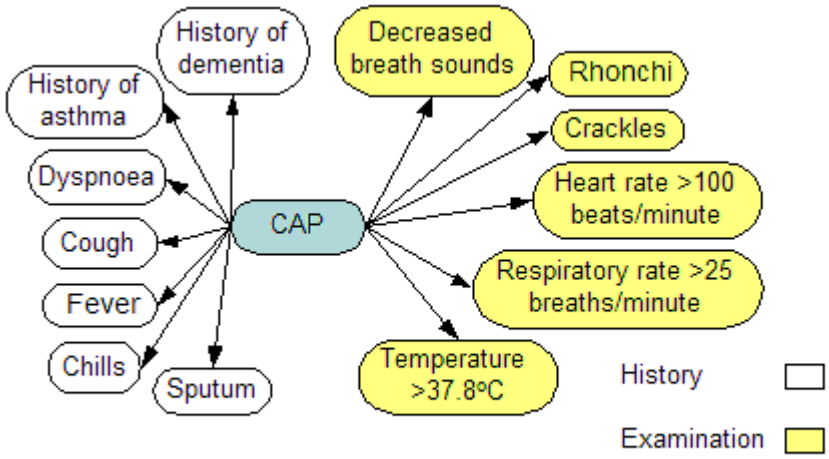

Figure 6.2: Influence diagram of the EDM

6.5 EDM validation, calibration and assessment of dependence amongst predictor variables

To validate the literature-based EDM, I compared its output to an identical EDM populated with LRs calculated from local data (positive LR = true positive rate/false positive rate; negative LR = false negative rate/true negative rate). Pre-test odds of CAP (p=0.014) on presentation were derived from local ED CAP discharge incidence, calculated from ED primary diagnosis codes. Both literature-based and local data-based EDMs were used to calculate the post-test probability for each patient in the sample given their set of findings. The sensitivity, specificity and receiver operating characteristic curves (ROC curves) and calibration curves were then calculated for both models to compare their accuracy [342]. ROC curves were calculated and compared using the Analyse-it add-on (version 2.11, Analyse-it Software, Ltd. http://www.analyse-it.com/, 2008; DeLong, Delong, Clarke-Pearson ROC curve comparison method) software package for Microsoft Excel (Microsoft, 2000).

I attempted to further calibrate the diagnostic model by assessing the effect of dependence amongst variables. I identified commonly co-occurring diagnostic findings in the local data set,

selected on the basis of possible underlying pathophysiology. To assess for an effect of dependence amongst these variables on model accuracy I calculated the joint LRs for commonly co-occurring pairs. Joint LRs were calculated from a series of dummy variables that were positive if patients presented with both findings. Posterior odds for the joint LRs were calculated by multiplying the prior probability of CAP by the joint LR. Posterior odds for the combined individual LRs were obtained by calculating the posterior odds of CAP given finding 1 (prior probability of CAP in the ED multiplied by the LR of finding 1) and multiplying it by the LR of finding 2. Post-test odds were then converted to post-test probabilities for comparison (p[CAP] = post-test odds / (1+ post-test odds).

I calculated the percentage of patients identified by the literature EDM that experienced significant delays to CXR or antibiotic, or died in hospital. This quantifies the influence of the model over patients with poor processes and outcome.

6.6 CAP risk modelling

6.6.1 Validity and accuracy of the Australasian Triage Score (ATS) for CAP

To assess the validity of the triage process for CAP patients I calculated the percentage of significant complications per triage group in the 1998 sample and calculated chi-square statistics to assess if there was a significant difference in the presence of complications between groups. To assess the accuracy of ATS mortality prediction in CAP, I calculated an ROC curve for mortality prediction, using the Analyse-it add-on (version 2.11, Analyse-it Software, Ltd. http://www.analyse-it.com/; 2008) software package for Microsoft Excel (Microsoft, 2000).

6.6.2 Accuracy of CAP-specific risk models

I calculated mortality risk for each case in the year 2000 CAP-positive dataset using Excel (Microsoft, 2000) spreadsheet models of the PSI [128], CURB-65 [135], CRB-65 [135], and a local guideline risk model (see appendix figure 9.1) [242]. Retrospective analysis has been shown to provide similar results to prospective data in the assessment of CAP-specific risk models [352]. To assess whether a history of renal failure could replace blood urea level in the CURB-65 model, I generated a further spreadsheet risk model using confusion, respiratory rate > 30/minute, low systolic(<90 mmHg) or diastolic (<60 mmHg) blood pressure, age greater than or equal to 65 years, and history of renal impairment. I compared ROC curves for each model and for the ATS across the 2000 sample. ROC curves were calculated and compared using the Analyse-it add-on (ver-

sion 2.11, Analyse-it Software, Ltd. http://www.analyse-it.com/, 2008; DeLong, Delong, Clarke-Pearson ROC curve comparison method) for Microsoft Excel (Microsoft, 2000).

Table 6.4 lists the variables omitted from the PSI and the local CAP risk model (see appendix figure 9.1), due to missing data. A number of other variables with moderate levels of missing data were retained under the assumption that missing values were normal. All other missing values were assumed normal as is common practice in similar studies [232].

Table 6.4: Missing data

Risk Model	Variable	Omit/ Include	Comment
Local guideline	Nursing Home resident	Omit	Data unavailable
	Mechanical ventilation required	Omit	Data unavailable
	Blood gas values - pO2, pCO2 and pH	Include	Not routinely performed unless poor oxygen saturation - if missing assume normal
	Abnormal liver function tests	Include	Not routinely performed unless poor liver function expected - if missing assume normal
PSI	Nursing home resident	Omit	Data unavailable
	Haematocrit	Omit	Haematocrit not a locally used parameter
	Blood gas values - pO2, pCO2 and pH	Include	Not routinely performed unless poor oxygen saturation - if missing assume normal

pO2 = partial pressure of oxygen in arterial blood (mmHg)
pCO2 = partial pressure of carbon dioxide in arterial blood (mmHg)

6.7 Combining diagnosis, risk and workflow modelling for alerting simulation

I used a simple deterministic approach to simulate the introduction of a number of different antibiotic treatment alerting systems based on various combinations of the EDM, the CRB-65 risk model, ATS, ED physician diagnosis, and CXR report. The impact of these models was assessed by calculating the hypothesised treating time given an alert for each patient in the retrospective CAP database. A given subject's simulated treating time was reduced if the EDM was positive given their presenting symptoms. Treatment was assumed to take place within 30 minutes of an alert at triage, physician assessment, or by ED discharge depending, on the implementation of the model. Antibiotic timing was only adjusted for patients who were treated after the calculated alerting time.

All models were combined in a multi-sheet Excel (Microsoft, 2000) file. An interface sheet was constructed linking calculation sheets allowing the manipulation of CAP incidence, presence of CAP findings, process timings (onset and length), and triage scoring. It also displayed graphs of pCAP by process time, calculated CAP risk score (CURB-65), and calculated triage score (based on ATS rules, see appendix figure 9.1). The interface allowed manual entry of clinical findings, enabling the simulation of hypothetical individual cases of CAP. A single case from the retrospective data set could be viewed. EDM simulations were performed using the data table function to run each case through the calculation sheets. This format, coupled with the simple naive Bayesian model, produced an easily modifiable tool with which the value of additional clinical findings in terms of diagnosis probability (e.g. pulse oximetry or urinary antigen testing) can be easily calculated.

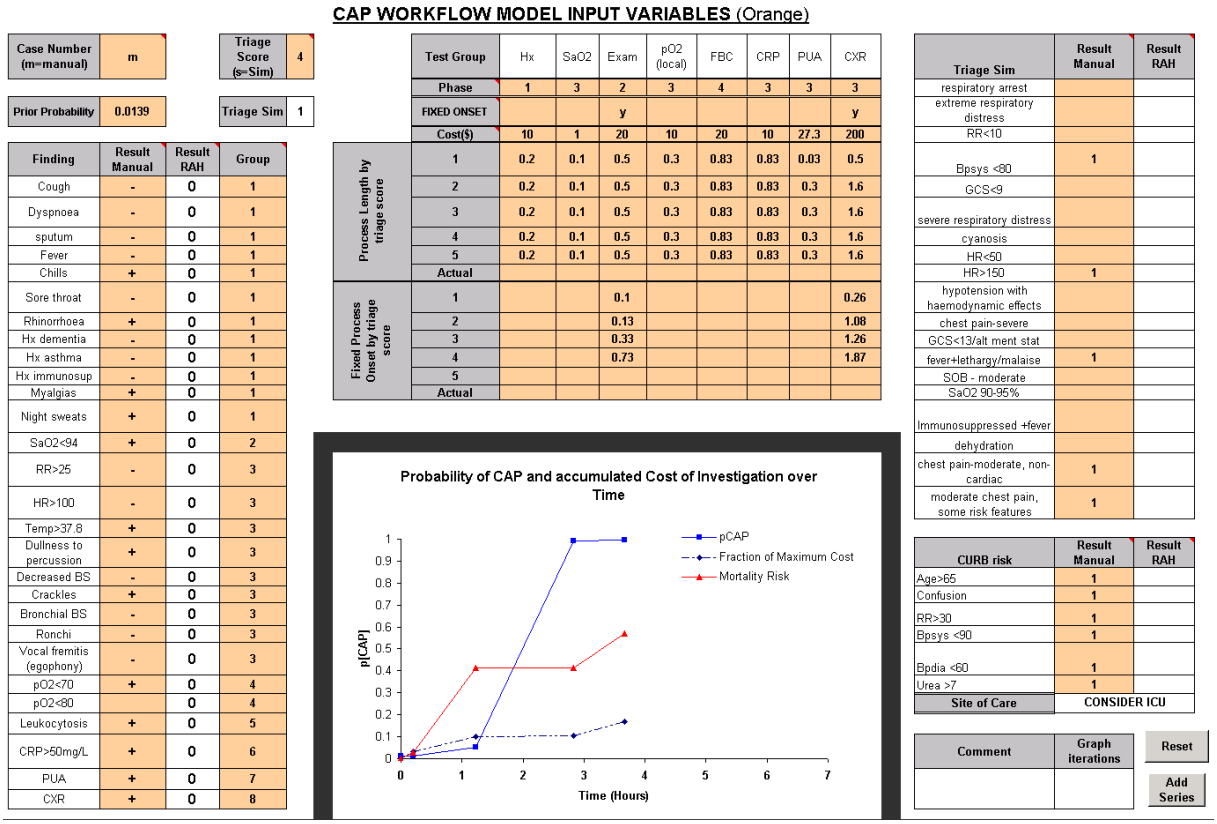

Figure 6.3: Simulation interface

To enable rule-based alerting simulation the output of the spreadsheet diagnosis and risk models were combined with timing data in an Access database (Microsoft, 2000). Rules were implemented using nested IF statements written in SQL (Structured Query Language). Table 6.5 describes the rules used to implement simulated alerting interventions based on the EDM, ATS, the CRB-65 score, ED primary diagnosis codes, and CXR reports. Note that the table commences at simulation label 2 as label 1 was used for the actual study data, in graphs of the simulations. I calculated the simulated effect of rule implementation on median time to antibiotic and the percentage of patients treated within 4 and 8 hours.

Table 6.6 shows a mapping of CRB-65 score to ATS score used in simulation 2 (EDM-positive, triage with CRB-65 risk model). CRB-65 scores were calculated for each EDM-positive patient in the simulation sample. CRB-65 scores were then equated to an ATS based on this table. The treatment time for these patients was then changed to the median calculated for the ATS category allotted.

Table 6.5: Simulation Rules

Simulation label	SQL database queries	Description of rules
2) EDM-positive, triage with CRB-65 risk model	If(EDM Probability>0.3,If(CRB-65 Triage AB Time<Actual AB Time,CRB-65 Triage AB Time,Actual AB Time),Actual AB Time)	If the EDM is positive, use the CRB-65 model to assign a triage group; the antibiotic treatment time becomes equal to the median of the triage group that the case is assigned to
3) EDM-positive, treat by ED discharge	If((Actual AB Time>ED Discharge Time),If(EDM Probability>0.3,ED Discharge Time, Actual AB Time),Actual AB Time)	If the EDM is positive and the patient was treated after transfer to a ward, change the treatment time to equal the time of ED discharge
4) ED primary diagnosis positive, treat by ED discharge	If((Actual AB Time>ED Discharge Time),If(ED Dx CAP,ED Discharge Time, Actual AB Time),Actual AB Time)	If ED primary diagnosis is positive and the patient was treated after transfer to a ward, change the treatment time to that of ED discharge
5) CXR report positive, treat by ED discharge	If((Actual AB time>ED Discharge Time), If(CXR positive,ED discharge time, ED discharge Time),Actual AB Time)	If CXR is positive and the patient was treated after transfer to a ward, change the treatment time to that of ED discharge
6) EDM-positive, investigations ordered at triage, treat by ED discharge	If(EDM Probability>0.3,If(ED Discharge Time - Physician Assess Time<Actual AB Time,ED Discharge Time - Physician Assess Time,Actual AB Time),Actual AB Time)	If EDM is positive, change the treatment time to that of ED discharge; subtract the time to physician assessment from the ED discharge time for these patients, to simulate the ordering of investigations at triage
7) EDM-positive or ED diagnosis positive, treat by ED discharge	If((Actual AB Time>ED Discharge Time),If(ED Dx CAP,ED Discharge Time,If(EDM Probability>0.3,ED Discharge Time,Actual AB Time)),Actual AB Time)	If either EDM or ED primary diagnosis is positive and the patient was treated after transfer to a ward, change the treatment time to that of ED discharge
8) ED primary diagnosis or CXR positive, treat by ED discharge	If(treat by EDDC if ED dx AB time<Treat by ED DC if CXR positive AB Time,treat by EDDC if ED dx AB time,Treat by ED DC if CXR positive AB Time)	If the ED primary diagnosis or the CXR is positive and the patient was treated after transfer to a ward, change the treatment time to that of ED discharge
9) Treat all by ED discharge	If(Actual AB time>ED Discharge time,ED discharge Time,Actual AB time)	If the patient was treated after transfer to a ward, change the treatment time to that of ED discharge
10) EDM-positive, treat after physician assessment	If((Actual AB Time>(Physician Assess Time+0.5)),If(EDM Probability>0.3,(Physician Assess Time+0.5),Actual AB Time),Actual AB Time)	If the EDM is positive and the treatment time is not less than physician assessment time plus 30 minutes, change the treatment time to physician assessment time plus 30 minutes
11) EDM-positive, treat following triage	If(Actual AB Time>0.5,If(EDM Probability>0.3,0.5,Actual AB Time),Actual AB Time)	If the EDM is positive and treatment occurred later than 30 minutes after triage, change the treatment time to 30 minutes after triage
12) EDM-positive, treat as triage 2	If(Actual AB Time>2.16,If(EDM Probability>0.3,2.16,Actual AB Time),Actual AB Time)	If the is EDM positive and the treatment time was not less than the median treatment time for those in triage group 2, then change the treatment time to the median for those in triage group 2
13) EDM-positive, treat following triage, ED primary diagnosis positive, treat by ED discharge	If(treat by EDDC if ED dx AB time< treat by triage assess if EDM-positive AB Time,treat by EDDC if ED dx AB time, treat by triage assess if EDM-positive AB Time)	If the EDM is positive and treatment occurred later than 30 minutes after triage, then change the treatment time to 30 minutes after triage; alternatively, if the ED primary diagnosis is positive and the patient was treated after transfer to a ward, change the treatment time to that of ED discharge
14) EDM-positive, treat following triage, ED primary diagnosis positive or CXR report positive, treat by ED discharge	If(If(treat by EDDC if ED dx AB time<Treat by ED DC if CXR positive AB Time,treat by EDDC if ED dx AB time,Treat by ED DC if CXR positive AB Time))< (If(treat by EDDC if ED dx AB time<Treat by ED DC if CXR positive AB Time,treat by EDDC if ED dx AB time,Treat by ED DC if CXR positive AB Time)), (If(treat by EDDC if ED dx AB time<Treat by ED DC if CXR positive AB Time,treat by EDDC if ED dx AB time,Treat by ED DC if CXR positive AB Time)), (If(treat by EDDC if ED dx AB time<Treat by ED DC if CXR positive AB Time,treat by EDDC if ED dx AB time,Treat by ED DC if CXR positive AB Time)))	If the EDM is positive and treatment occurred later than 30 minutes after triage, then change the treatment time to 30 minutes after triage; alternatively, if the ED primary diagnosis or CXR is positive and the patient was treated after transfer to a ward, change the treatment time to that of ED discharge

Table 6.6: CRB-65 based triage scoring

CRB-65 score	ATS
1	3
2	2
3	2
4	1

7 Results

7.1 Overview

Figure 7.1 shows a simple model of predictors of process performance. Using workflow assessment I identified key factors associated with delay to the antibiotic treatment of community-acquired pneumonia (CAP) from each these areas. I constructed a qualitative CAP workflow model using sequence diagrams, and formulated a simplified deterministic quantitative workflow model, using timing data obtained during workflow assessment. I assessed the impact of uncertainty in decision-making by calculating the accuracy of emergency department (ED) physician diagnosis, chest x-ray (CXR) and Australasian Triage Score (ATS). I assessed the impact of these decisions on key processes in treatment.

In order to construct an alerting system, designed to reduce the delay to antibiotic treatment for CAP, I built a Bayesian early diagnostic model (EDM) based on variables available in the clinical history and examination. I also assessed the accuracy of published CAP-specific mortality risk models, in comparison to the Australasian Triage Score (ATS), in order to identify the best available early mortality risk model. I performed workflow simulations of an alerting system based on the EDM and the CRB-65 risk model by combining them with the deterministic process flow model.

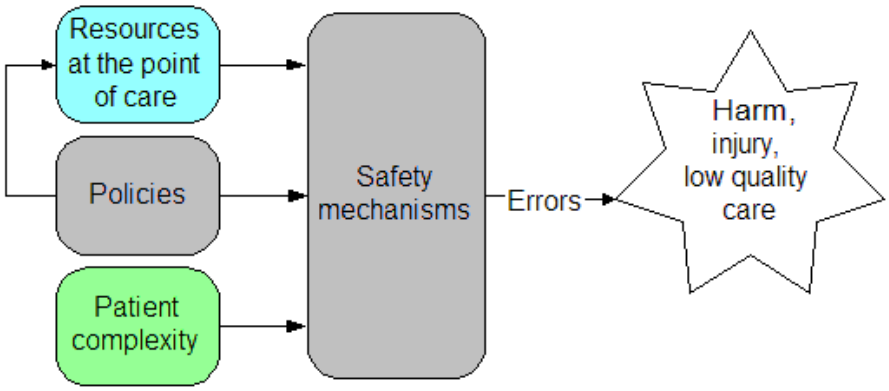

Figure 7.1: Simple model of predictors of process performance/error

7.2 Qualitative process flow assessment

7.2.1 Common pathways in CAP treatment

CAP patients moved through the ED via two major paths. Those with severe CAP, assessed as ATS level 1 upon arrival, were seen immediately by an ED physician and transferred to a specialised resuscitation room if available. Urgent blood tests were taken and sent to the laboratory via a pneumatic tube system where they received priority. Blood testing generally included a full blood count, serum electrolytes, renal and liver function tests. Arterial blood gas assessment was also performed if acidosis, hypoxia or carbon dioxide retention were suspected. A local analyser was available for more immediate blood gas and electrolyte assessment. CXRs were performed in the resuscitation room rather than in radiology, and were viewed rapidly, often without radiologist input. Unstable patients were sometimes reviewed by an intensive care physician, who then made a decision on the need for intubation, ventilation and transfer to the intensive care unit (ICU). When CAP was strongly suspected, patients were occasionally treated with antibiotics prior to the return of a CXR result. This contradicted the local guideline recommendation that antibiotic treatment for CAP should not proceed until a CXR result is obtained (see appendix figure 9.1). In contrast, patients of low to moderate severity illness experienced longer delays to most processes. Figure 7.2 shows a sequence diagram of the workflow around these patients. Actors involved in CAP care are listed across the top of the diagram. These include clinical staff, support staff, medical records, and IT systems. Each vertical column represents the time that an actor is involved in CAP care. Solid blue arrows represent actions or provision of information. Dashed red arrows represent requests for information. Decisions in CAP diagnosis and care are represented by red dots. These are summarised in table 7.1.

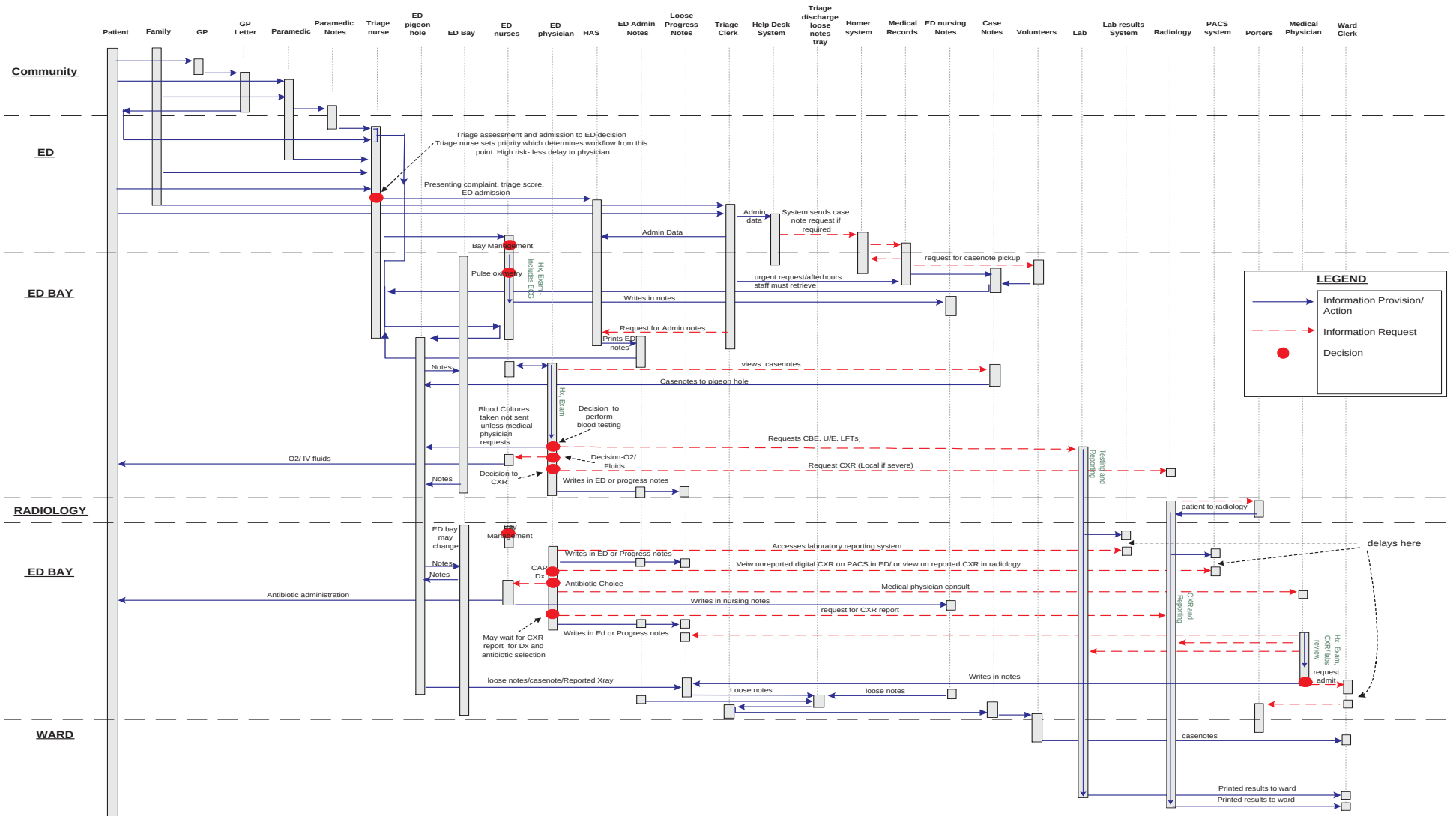

Figure 7.2: Sequence diagram of workflow around patients with low to moderate severity CAP presenting to the ED

Table 7.1: Emergency department decisions in CAP care

Decision	Actor	Key information
Decision to admit to ED and triage score	Triage nurse	History, signs and symptoms on presentation
ED bay management	ED nurse	Bed availability, triage category
Pulse oximetry	ED nurse	ED nurse history and physical examination
Supportive care (Oxygen, IV fluids)	ED physician	ED physician history and examination
CXR	ED physician	ED physician history and examination
Blood testing	ED physician	ED physician history and examination
Diagnosis of CAP	ED physician	ED physician history and examination and CXR result
Antibiotic selection	ED physician/medical physician	ED/Medical physician history and examination, blood test results, CXR result, risk assessment
Admission to ward/ICU	Medical physician/ ICU physician	Medical physician history and examination, blood test results, CXR result, risk assessment, bed availability

In Figure 7.2 long vertical columns for the radiology department and the laboratory illustrate that there were long delays to CXR and blood test result return, for low to moderate severity CAP patients. Long vertical columns indicate long delays between information request and delivery. This is associated with delays in decision-making and with increased risk for information to be overlooked. Low to moderate severity CAP patients were initially assessed by a triage nurse and then admitted to the ED. An assessment by an ED Nurse followed, depending on staff availability. This process included basic observations, pulse oximetry, and an electrocardiograph. In some cases more experienced nurses also took blood samples. ED physician assessment occurred at a time dependent on triage score - lower scores, indicating higher urgency, were seen sooner. Following examination the ED physician ordered a similar set of investigations to those previously listed for ATS 1 patients. Once a CXR was ordered, nursing staff contacted an orderly to move the patient to the radiology department. There were delays to the contact of orderlies, in the arrival of orderlies, in preparing the patient for movement, and long delays in radiology waiting for CXR. CXRs were usually available for viewing by ED physicians before they were formally reported by radiologists. Consequently, the decision to give antibiotics was often based on the ED physician's interpretation of the CXR. This was more common outside normal working hours when a radiologist was not available or at times of peak

demand on radiology services. The decision to admit to hospital was made in conjunction with a medical ward physician. There were often significant delays to medical physician review. If no antibiotics had been given up to this point the medical physician usually prescribed them as part of the admission process. Patients then often waited for long periods in the ED prior to transfer to the ward. Table 7.2 summarises estimates of the timing of key processes in CAP care derived from observation and expert opinion.

Table 7.2: Estimation of key process timings

Process	Triage 1 timings	Triage 2-4 timings	Notes
Nursing assessment	Immediate/physician may review first	Within 10 minutes	
Casenote retrieval	5-15minutes	5-30 minutes	After hours treating staff may have to locate notes from medical records
ED physician attendance	Immediate	10-60 minutes	
Blood test order	Immediate (following/during resuscitation)	20-145 minutes	
Blood test result	Urgent test, can phone for result in around 30 minutes depending on the test	60 minutes	
CXR order	Immediate (following/during resuscitation)	20-145 minutes	
Time in radiology	Done in resuscitation room	40-45 minutes	High severity patients may have local CXR
CXR result	View in 15 minutes, report in 60 minutes	View in 30 minutes, report in 60 minutes	Reports not available after hours
Ward admission	Variable delay to medical or ICU physician review, 15 minutes for assessment, admission may be delayed if unstable in ED and resuscitation required (variable)	Variable delay to medical physician review, 30 minutes for assessment, 1 hour to admission if bed is available (variable)	Patients will remain in ED until bed is available on ward

Figure 7.2 also indicates that the transfer of information was inefficient. There was low redundancy around important test results. For example, an abnormal CXR or laboratory result was reported via the same non-urgent channels (i.e. the radiology or laboratory information systems) as a normal result. Only when results were severely abnormal were the treating physicians contacted by radiology or laboratory staff. ED physicians were required to repeatedly check existing computer systems for the return of results, having to “log on” to the IT system on each

occasion. Consequently, there were delays to the assessment of abnormal results. Much of the information gathered in the ED existed as loose progress notes which were moved between ED treatment bays and pigeon holes. These notes were assembled prior to transfer to the ward. Therefore transfer of patient information often lagged behind the transfer of the patient. At this site digital x-rays were available only in the ED. The transfer of hard copy CXR films to the ward was commonly delayed. Printed reports for blood test results were directed to the emergency department from the laboratory, however, these arrived some time after the patient had been discharged from the ED to the ward. The courier system for the laboratory was deemed to be superior to that of the hospital and therefore printed results were sent back to the laboratory and then on to the ward. During this time results were available electronically.

Elderly volunteers were responsible for the transport of case notes, as well as some test orders and results. This reliance on volunteers increased with increasing workload in the ED. The redirection of information and the use of untrained volunteers may increase the likelihood of delayed or misplaced information. Multiple transfers of individual pieces of information were common, such as the passage of letters from general practitioners, via patients to triage staff, or from lab testing site via volunteer staff to pigeon hole, to ED physician. These multiple transfers increase the risk of misplaced information. There were 3 overlapping changes of shift at the study site (8:00 to 5:00 hours, 14:00 to 24:00 hours and 20:00 to 8:00 hours). Prior to the end of each shift a hand-over of patients occurred that involved the transfer of information and responsibility for care from an ED physician from the previous shift to another from the commencing shift. There was no evidence of failure to communicate CAP patient information at hand-over in this small sample, however the process of hand over itself is a source of delay in care.

In summary, the major factors determining delay to antibiotic treatment, based on my initial workflow and stakeholder assessment, were delays in diagnosis and low perceived urgency for treatment as indicated by triage score. Delays in diagnosis were associated with delay to review of CXR and blood test results. The time to CXR result review consisted of a number of components including time to CXR order, time to patient arrival in radiology, time spent waiting in radiology, time to process CXR, and time to ED physician assessment of CXR result. Patients with low urgency triage scores experienced longer delays to assessment, test ordering, test result review and antibiotic administration. There were likely to be long delays to initial antibiotic when the dose was left until after ward admission. This was due to delay in transfer to the ward,

delay in the transfer of information to the ward (e.g. CXRs) and the availability of medical physicians on the ward to assess and prescribe antibiotics for the patient. All delays were increased by heavier workload in the ED.

The workflow around the treatment of low to moderate severity CAP in the ED at the study site was complex. It involved multiple staff, multiple patient transfers, and multiple sources of information from different departments. Much of the information collected in history taking and physical examination is highly redundant. This process may be performed by the triage nurse, the ED nurse, the ED physician and the medical physician. The coordinator of the process is usually the treating ED physician who is responsible for many patients at one time. There was no system to integrate the multiple sources of information or to alert busy ED and medical physicians of the return of important information in a timely fashion.

7.3 Quantitative workflow assessment

7.3.1 Local CAP database

Data was integrated from 7 local systems. These included the patient management index (PMI), the ED management system, the radiology system, a number of laboratory result systems (at this site there were 3 redundant systems in operation for the return of the same laboratory results) and the administration system. The PMI held information on patient demographics, past ward admissions, and ward admission and discharge timings. The ED management system database contained ED admission and discharge times, demographic data, triage scores, presenting complaints, physician assessment times, primary diagnoses, and discharge destinations. Radiology and laboratory results and test timings were available from the respective information systems. I was not able to access order times or physician access times for CXR or laboratory data. Outcome data including diagnosis codes, costs, and mortality was available via the administration system. Medical record review was required to assess time to antibiotic, and the timing and result of point of care tests (e.g. oxygen saturation and arterial blood gases).

7.3.2 Key process timings

Figures 7.3 and 7.4 show box plots of the distributions of time to time to CXR, time to first antibiotic, and time to ED discharge, for the 1998 and 2000 CAP-positive data sets. CXRs and antibiotic doses delayed by more than 10 days were excluded from the analysis. In these figures the median time value is represented by a brown dot with a horizontal line inside a blue box. The ends of the blue box surrounding this dot represent the 1st to 3rd quartiles of the sample (the inter-quartile range). The “whiskers” or square brackets above and below the box are placed at the furthest data point within 1.5 times the inter-quartile range, and give some indication of the spread of data beyond this range. Outliers are usually shown as a black dot with a horizontal line (not present in figures 7.3 and 7.4; see appendix figures 9.2 and 9.3). These are values greater than 1.5 times the inter-quartile range. Box plots enable a rough visual estimation and comparison of data distributions [353]. Figures 7.3 and 7.4 show that the process timing data for both the 1998 and 2000 data sets is similarly distributed. The inter-quartile range for timing of initial antibiotic treatment is large indicating high variability. Both the CXR and antibiotic timing distributions are positively skewed as indicated by the presence of the median in the lower half of the inter-quartile range. The progression of median process timings from left to right supports the process flow model (i.e. ED physician assessment followed by CXR followed by antibiotic and ED discharge). The range of timings for CXR and initial antibiotic extends well beyond that of time to ED discharge. This indicates that in a number of cases these processes did not take place in the ED. Box plots complete with outliers (see appendix figures 9.2 and 9.3) showed many more outliers in the 1998 versus the 2000 dataset, for both CXR and antibiotic delivery. The longest delay to CXR or antibiotic treatment was also greater for the 1998 data set. In both data sets a number of CXR outliers occurred later than any antibiotic dose, supporting that some patients are treated prior to CXR.

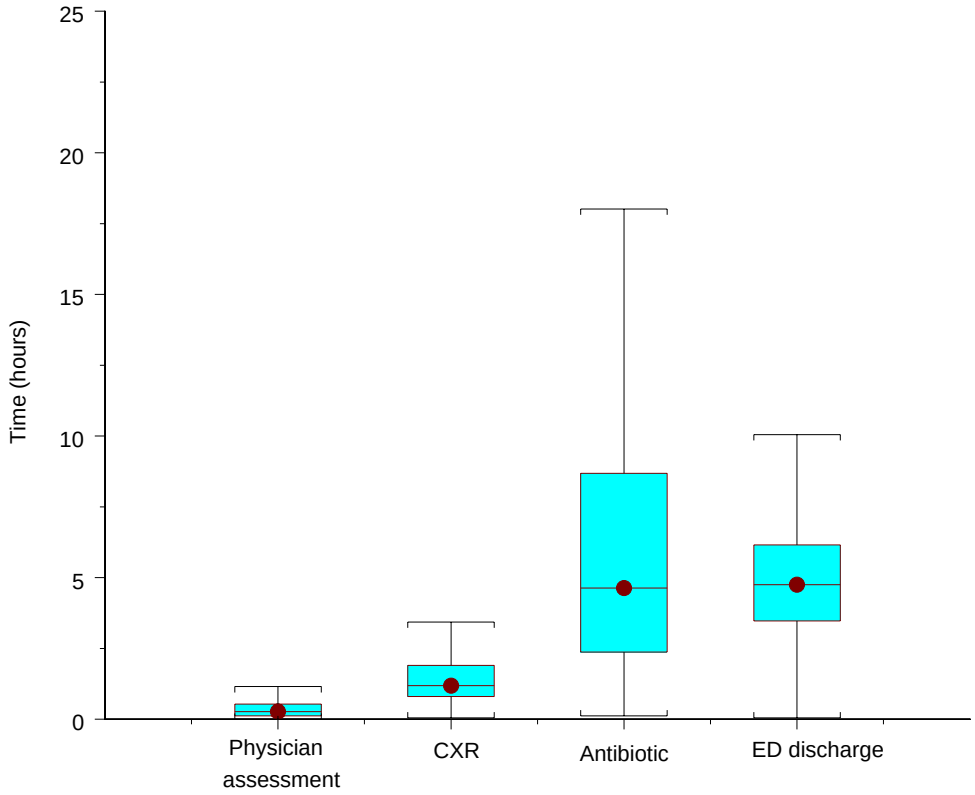

Figure 7.3: Distribution of key process timings - 1998 sample

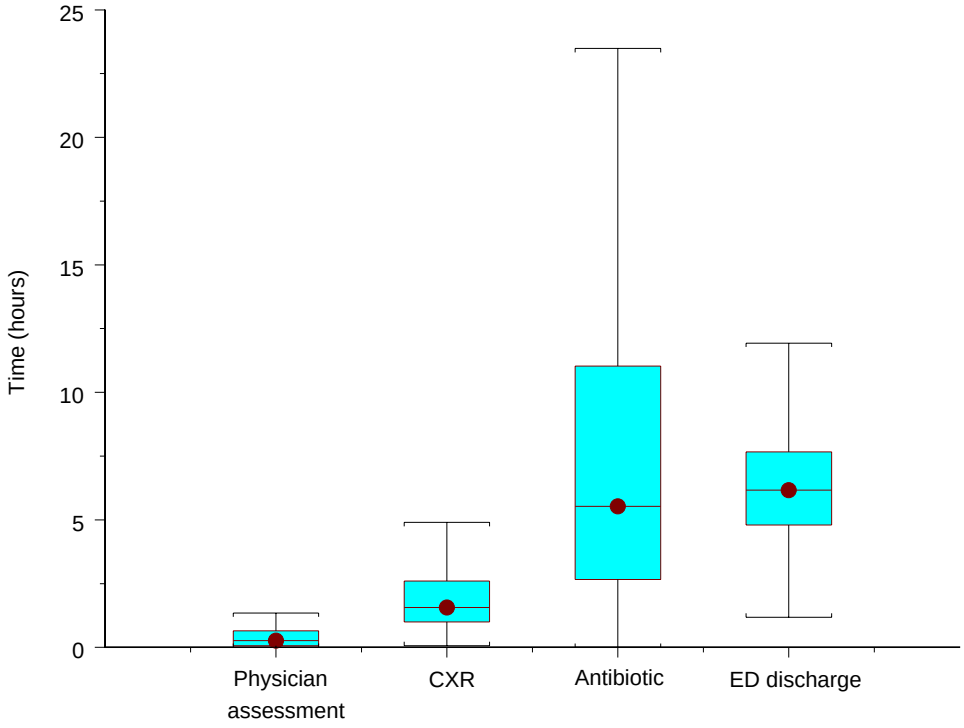

Figure 7.4: Distribution of key process timings - 2000 sample

Table 7.3 shows that in both samples patients were seen by an ED physician at a median time of around 16 minutes. Median delay from assessment to CXR was 0.91 to 1.3 hours, and from CXR to antibiotic was approximately 3.45 to 3.96 hours. This equates to roughly a 4-5 hour delay surrounding the CXR process and subsequent decision-making. Patients spent a median difference of 1.42 hours longer in the ED in the 2000 sample. Median antibiotic delivery time was between 7 to 40 minutes prior to discharge from the ED. Median process timings beyond ED physician assessment were more delayed in the 2000 sample, indicating the local guideline intervention did not impact on these values. Table 7.4 shows that around 60% of patients had delayed antibiotic treatment. There was a small increase in those treated later than both 4 and 8 hours between the 1998 and 2000 samples.

Table 7.3: Descriptive statistics for time to key process performance

	n		Mean (hours)		Standard deviation		Range (hours)		Median (hours)	
Process	**1998**	**2000**	**1998**	**2000**	**1998**	**2000**	**1998**	**2000**	**1998**	**2000**
ED Physician assessment	246	137	0.42	0.5	0.5	0.6	0 - 3.48	0 - 3.88	0.27	0.27
CXR	225	137	9.17	4.43	31.6	16.2	0.05 -204.5	0.07 -151	1.18	1.57
Antibiotic	223	125	9.07	8.48	13.8	7.9	0.12-124.3	0 -33.43	4.63	5.53
ED discharge	246	134	4.9	6.38	2	2.3	0.05 -13.5	1.2 -14.2	4.75	6.17

Table 7.4: Comparison of 1998 and 2000 samples: percentage treated by 4 and 8 hours

	1998	2000
% treatment delayed > 4 hours	57.8	62.6
% treatment delayed > 8 hours	27.5	35.8

7.3.3 Correlations between process timing

Correlations between processes were low, indicating poor linkage between processes (see Table 7.5). The largest correlation in both complete samples was between the timing of physician assessment and discharge (r = 0.36 to 0.41). For the subset treated within the ED the correlation between physician assessment time and antibiotic time was higher (r = 0.48 to 0.59) (see table 7.6). In the 1998 sample antibiotic dosing was closely associated to ED discharge for those treated in the ED (r = 0.72). There was no clear relationship between the timing of CXR and any

other variable. There was little difference in process correlations for those treated in the ED, and those both diagnosed with CAP and treated in the ED.

Table 7.5: Comparison of 1998 and 2000 samples: process timing correlations

	CXR		Antibiotic		ED discharge	
	1998	**2000**	**1998**	**2000**	**1998**	**2000**
ED physician assessment	0.18	0.02	-0.07	0.22	0.41	0.36
CXR			0.12	- 0.02	- 0.04	- 0.04
Antibiotic					0.01	0.16

Table 7.6: Comparison of 1998 and 2000 samples: process timing correlations for those treated in ED

	CXR		Antibiotic		ED discharge	
	1998	**2000**	**1998**	**2000**	**1998**	**2000**
ED physician assessment	0.18	0.07	0.48	0.59	0.42	0.37
CXR			0.07	-0.03	0.01	0.04
Antibiotic					0.72	0.17

Table 7.7: Comparison of 1998 and 2000 samples: process timing correlations for those with a primary diagnosis of CAP that were treated in ED

	CXR		Antibiotic		ED discharge	
	1998	**2000**	**1998**	**2000**	**1998**	**2000**
ED physician assessment	0.32	0.09	0.55	0.26	0.5	0.33
CXR			0.17	-0.05	0.09	0.04
Antibiotic					0.75	0.11

7.3.4 Association of primary diagnosis with process times

Only just over half of all patients discharged with a diagnosis of CAP after admission to hospital were given a primary diagnosis of CAP (1998 data set = 54.1%; 2000 dataset = 56.9%). Table 7.8 lists key process timings and antibiotic treatment targets by ED diagnosis. There was no relationship between primary diagnosis and ED physician assessment timing, CXR timing or ED discharge timing. Patients without a primary diagnosis of CAP had longer median times to antibiotic treatment (by 0.95 hours in the 1998 sample and 5.47 hours in the 2000 sample). The box plots displayed in figures 7.5 and 7.6 illustrate that those with alternative primary diagnoses were more likely to have a delay beyond 4 hours. Outliers for these plots are shown in appendix figures 9.4 and 9.5. The median time to treatment was close to the 4 hour target when patients received a primary diagnosis of CAP. Patients were more likely to experience delays in treatment greater than 4 and 8 hours if they did not receive a diagnosis of CAP in the ED. This difference was significant in the 2000 sample for both thresholds, however in the 1998 sample only the percentage treated later than 8 hours was significantly larger (p = 0.017).

Table 7.8: Process timing by primary diagnosis (hours)

	Primary diagnosis CAP		Primary diagnosis other	
Process	**1998**	**2000**	**1998**	**2000**
ED physician assessment	0.28	0.33	0.2	0.23
CXR	1.1	1.51	1.32	1.6
Antibiotic	4.33	3.65	5.28	9.12
ED discharge	4.73	6.34	4.77	6.13
% treatment delayed > 4 hours	54.2	45.5	62.7	86**
% treatment delayed > 8 hours	21.7	20.8	36.2*	56.1**

* chi-square p = 0.017
** chi-square p<<0.0001

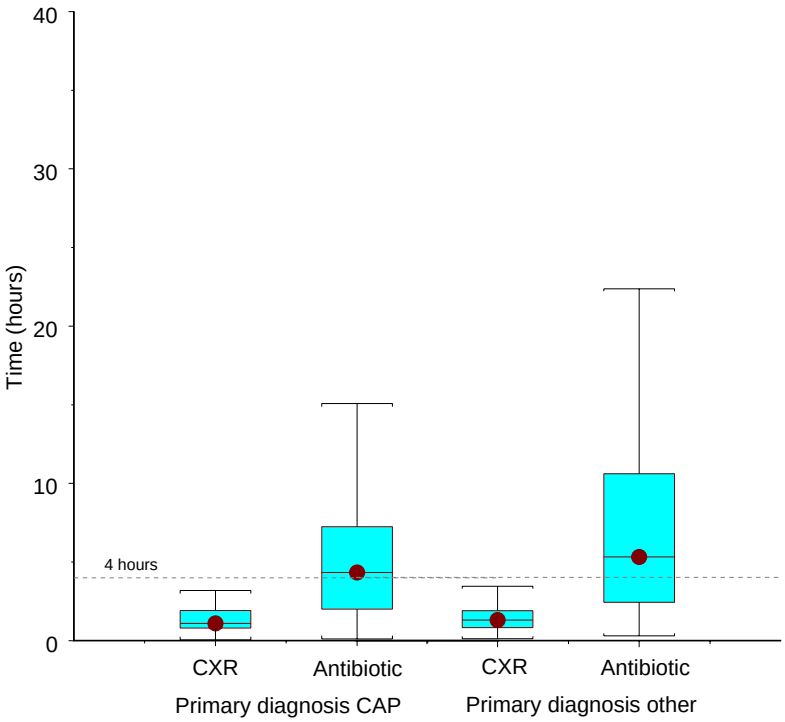

Figure 7.5: Distribution of CXR and antibiotic timings by primary diagnosis - 1998 sample

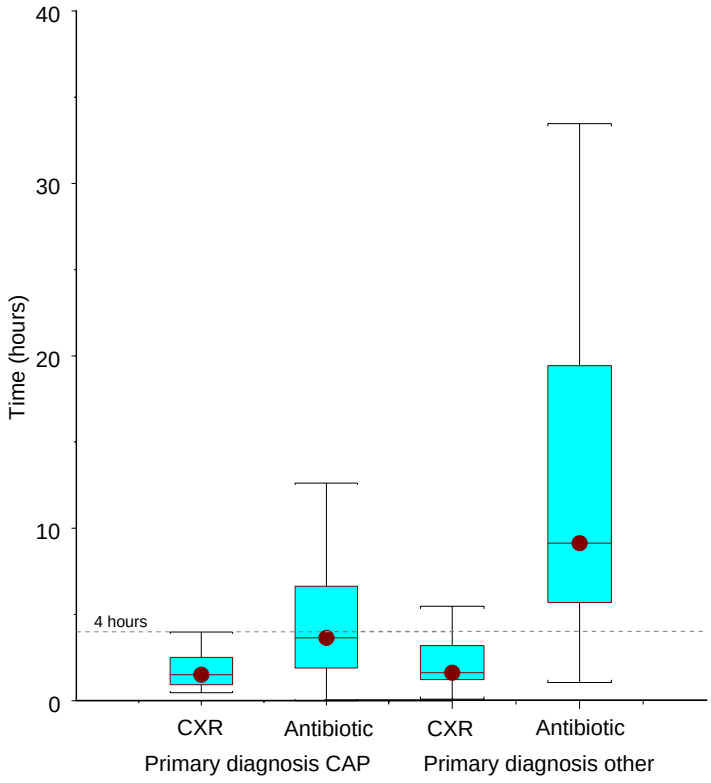

Figure 7.6: Distribution of CXR and antibiotic timings by primary diagnosis - 2000 sample

7.3.5 Association of site of antibiotic delivery with process times

Only half of all CAP patients were treated in the ED (1998 data set = 53.1%; 2000 dataset = 52.3%). Table 7.9 shows the distribution of process timing by antibiotic delivery site. There were no substantial differences in time to ED physician assessment, CXR, and discharge from ED, by site of antibiotic treatment. Patients treated on the ward had much longer median delays to antibiotic dose in comparison to those treated in the ED (6.75 hours greater for the 1998 sample and 7.4 hours greater for the 2000 sample). The median treatment time for those treated in the ED was well within the 4 hour goal, while for those treated on the wards it was beyond 8 hours. Figures 7.7 and 7.8 show that most of the patients treated within the ED were treated in 4 hours, while the vast majority of those treated on the ward did not receive antibiotics in this time. Appendix figure 9.6 illustrates that outliers were more common for both CXR and antibiotic timing in those treated on the ward in the 1998 sample, however this was not apparent in the 2000 sample (see Appendix figure 9.7). Table 7.9 shows that around a quarter of patients treated in the ED had delays longer than 4 hours and less than 10% had delays longer than 8 hours. Nearly all cases treated on the ward had delays longer than 4 hours and around 60% had delays longer than 8 hours. These differences were significant in both samples.

Table 7.9: Process timing by antibiotic delivery site (hours)

	Antibiotic in ED		**Antibiotic on ward**	
Process	**1998**	**2000**	**1998**	**2000**
ED physician assessment	0.2	0.17	0.29	0.32
CXR	1.11	1.51	1.25	1.66
Antibiotic	2.45	2.7	9.2	10.1
ED discharge	5.1	6.38	4.36	6.13
% Treatment delayed > 4 hours	25.8	29.4	95.1*	98.4*
% Treatment delayed > 8 hours	2.5	7.4	57.3*	67.2*

*chi-square p<<0.0001

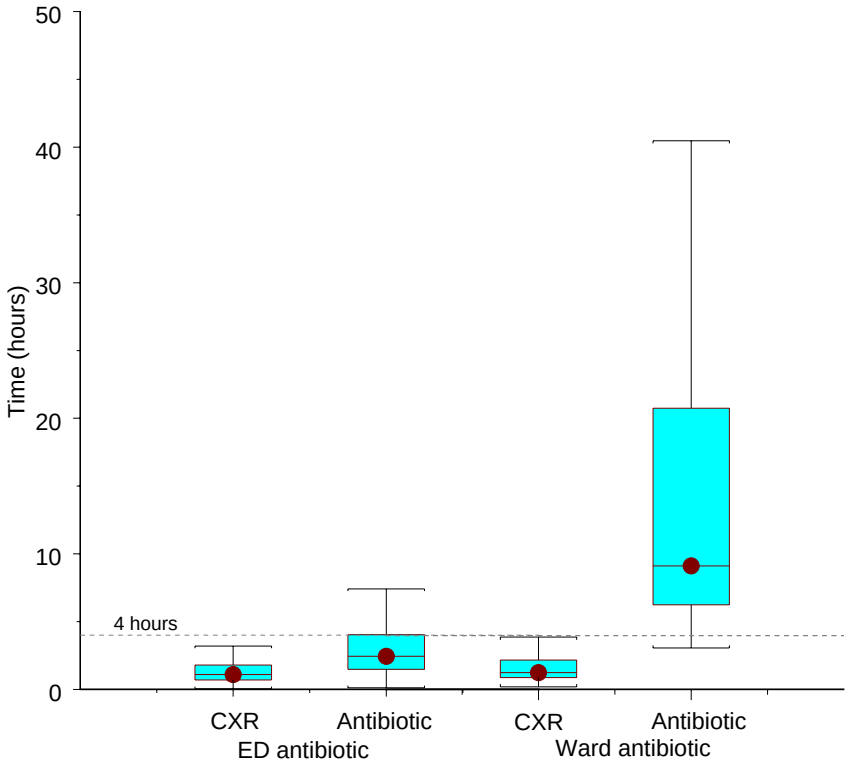

Figure 7.7: Distribution of CXR and antibiotic timings by antibiotic site - 1998 sample

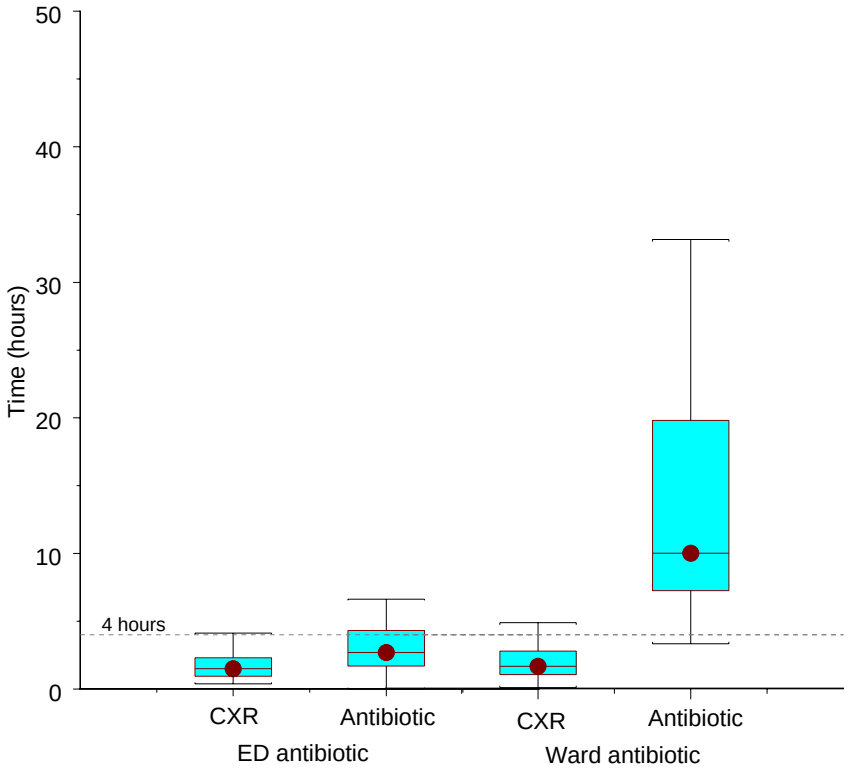

Figure 7.8: Distribution of CXR and antibiotic timings by antibiotic site - 2000 sample

7.3.6 Association of primary diagnosis and antibiotic treatment site

Table 7.10 shows the relationship between primary diagnosis and treatment site. Those with a primary diagnosis of CAP were more likely to receive antibiotics in the ED in comparison to those with alternative diagnoses. This finding was statistically significant for the 2000 sample and approached significance in the 1998 sample.

Table 7.10: Association between primary diagnosis and treatment site

	% antibiotic in ED		% antibiotic on ward	
Primary diagnosis	**1998**	**2000**	**1998**	**2000**
CAP	63.3	79.7	50.9*	34.9**
Other	36.7	20.3	49.1*	65.1**

*chi-square p = 0.06
**chi-square p << 0.0001

7.3.7 Effect of Australasian Triage Score (ATS) on process timing

I used only the 1998 sample to assess the effect of ATS on time to process completion.

7.3.7.1 Time to ED physician assessment by ATS

Both figure 7.9 and table 7.11 indicate that median time to ED physician assessment in the 1998 sample was within ATS guidelines for each triage group, however, there were a number of outliers in ATS 2-4. Consequently, the percentage of patients who were assessed within the recommended time did not meet ATS performance indicators for these groups.

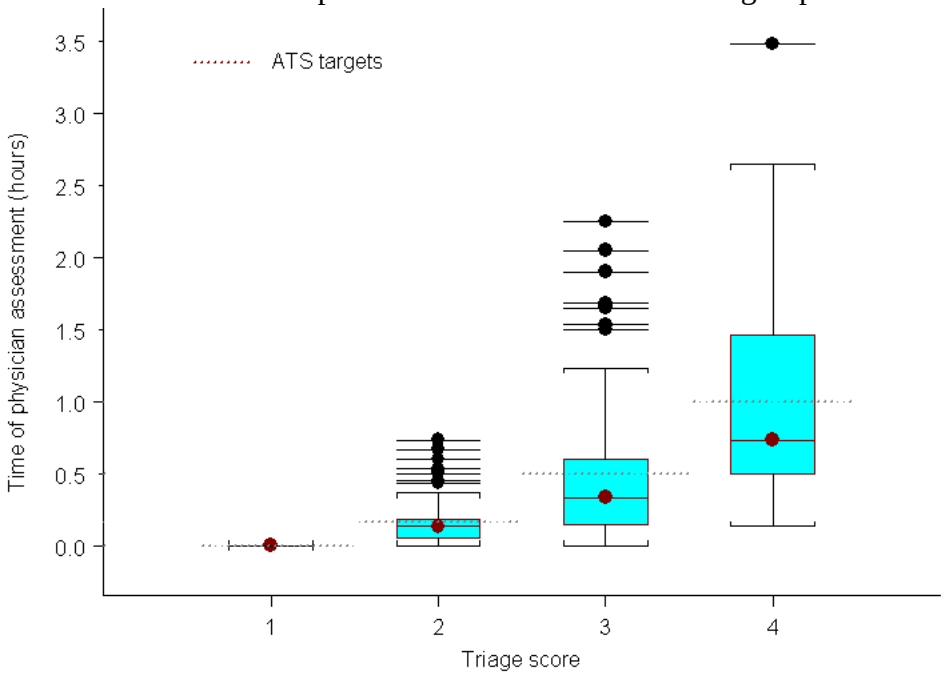

Figure 7.9: Distribution of time to physician assessment in the ED by ATS - 1998 sample

Table 7.11: ED Physician assessment timing by ATS

Triage score	Recommended time to assessment (hours) [354])	Actual median time to assessment (hours)	Performance indicator (Percentage assessed in recommended time) [164]	Actual percentage assessed in recommended time
1	0	0	100	100
2	0.17	0.13	80	69
3	0.5	0.33	75	72
4	1.0	0.73	70	59
5	2.0	-	70	-

7.3.7.2 Time to first CXR by ATS

Figure 7.10 indicates that the median time to CXR increased with lower urgency ATS (higher score). The median time to CXR for all admissions was 1.18 hours. The median times to CXR for patients with ATS 1-4 were 0.26, 1.08, 1.26, and 1.87 hours, respectively. Appendix figure 9.8 shows that a number of patients with an ATS of 3 had very long times to CXR (outliers).

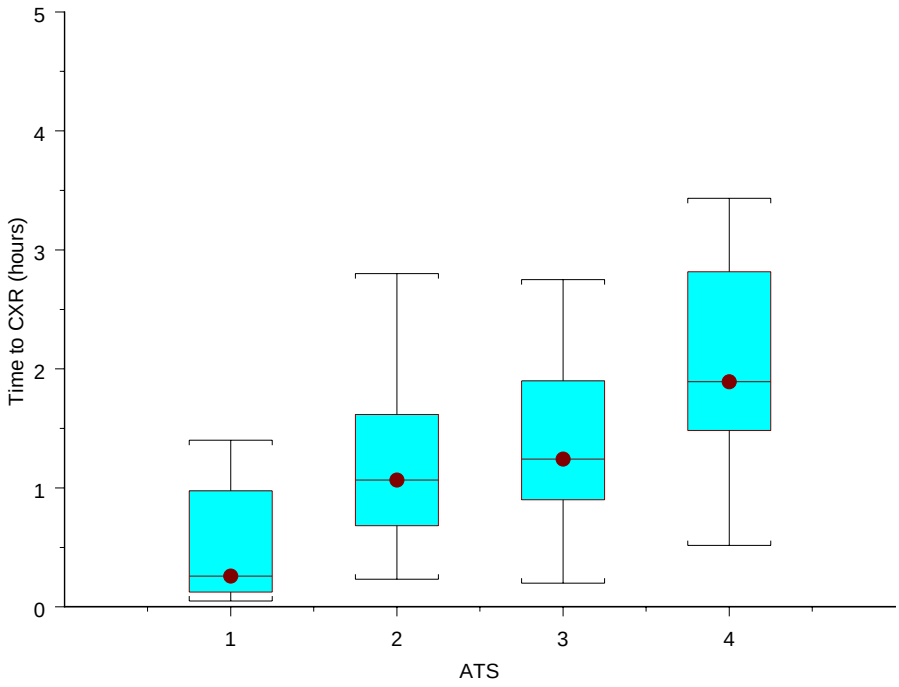

Figure 7.10: Distribution of CXR timings by ATS - 1998 sample

7.3.7.3 Time to antibiotic by ATS

Appendix figure 9.9 shows that a number of patients with ATS 2 and 3 had long delays to antibiotic treatment (outliers). Figure 7.11 indicates that the median time to first antibiotic increased with lower urgency ATS. The median times to first antibiotic for ATS 1-4 were 0.975, 2.87, 5.13 and 5.03 respectively. Figure 7.11 also indicates that median time to antibiotic was within the 4 hour guideline recommendation for ATS 1 and 2 but not for scores of 3 or 4.

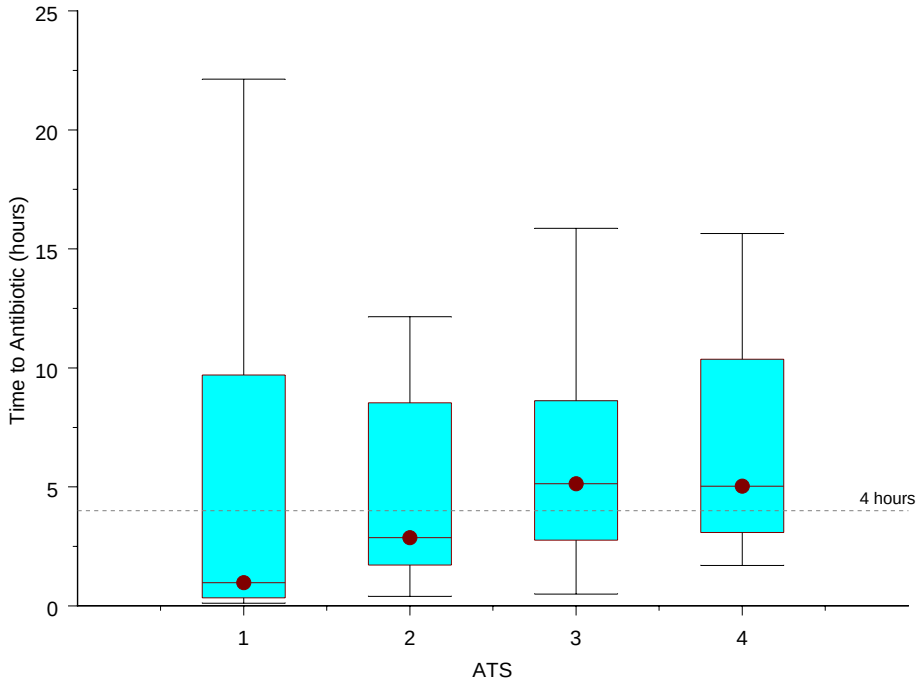

Figure 7.11: Distribution of antibiotic timing by ATS - 1998 sample

Figure 7.12 shows that the percentage of patients receiving antibiotics later than 4 hours increased with lower urgency ATS (higher score) (ATS 1 = 25%, 2 = 43%, 3 = 65%, 4 = 63%; chi-square p = 0.01). The percentage of patients receiving antibiotics with a delay in excess of 8 hours was similar across all ATS (Triage 1 = 25%, 2 = 27%, 3 = 28%, 4 = 36%; chi-square p > 0.05). The majority of CAP patients were discharged to the wards within 8 hours of admission (see figure 7.3). Therefore ATS only has an effect on the timing of antibiotic delivery in the ED.

.

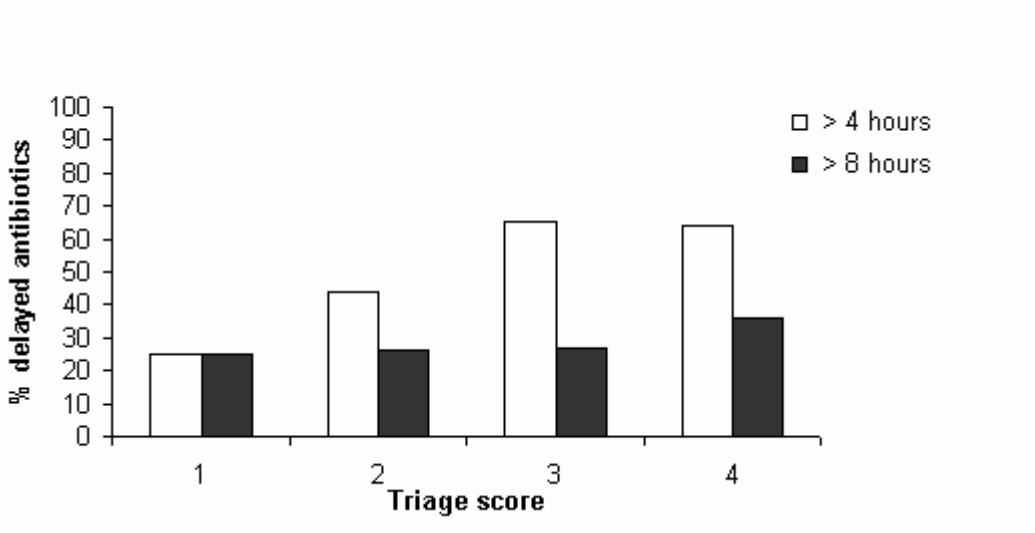

Figure 7.12: Percentage delayed antibiotics by ATS - 1998 sample

Figure 7.13 shows that median time to first antibiotic, when given in the ED increased with lower urgency triage score. Median time to first antibiotic equalled 0.37, 1.78, 2.76 and 3.93 hours, for triage groups 1-4 respectively. Median values were all below the recommended 4 hour limit. In comparison, median time to antibiotic for patients who were not treated until after ward admission was higher for all triage groups, without a consistent pattern (see figure 7.14). Median values equalled 15.61,10.17, 8.62 and 10.42 hours, for triage groups 1-4 respectively. Triage score was not associated with the site of antibiotic administration (chi-square p=0.57).

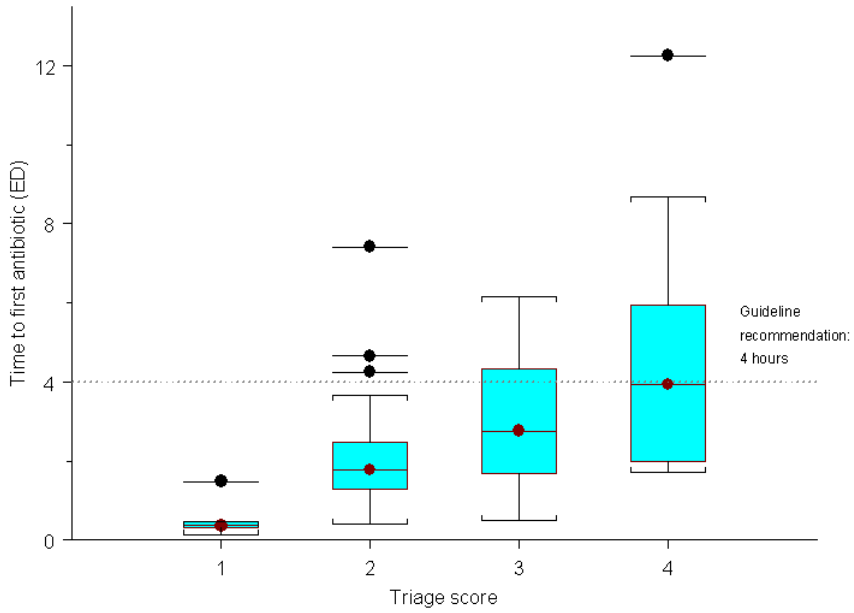

Figure 7.13: Distribution of time to first antibiotic by ATS - 1998 sample: antibiotic given in the ED

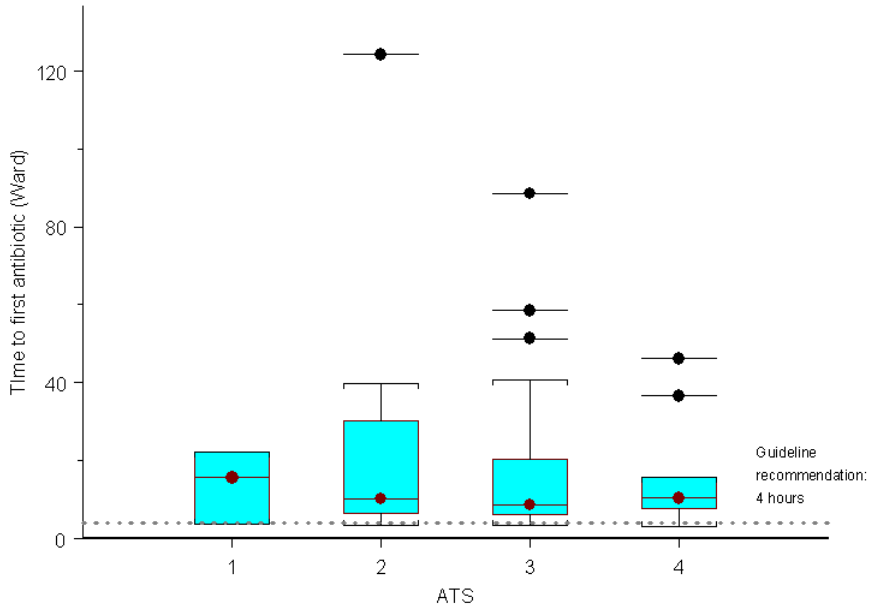

Figure 7.14: Distribution of time to first antibiotic by ATS - 1998 sample: antibiotic given on the ward

Figure 7.15 shows that the percentage of antibiotics given in the ED delayed beyond 4 hours increased with lower urgency ATS (higher score). This effect approached significance (chi-square p = 0.09). Only 20% of the patients given an ATS of 4 received antibiotics after 8 hours, when treated in the ED. In comparison figure 7.16 indicates that the majority of patients who were treated on the ward had a delay in excess of 4 hours. Only for patients in triage group 1 were rates of 8 hour delay less than 50%.

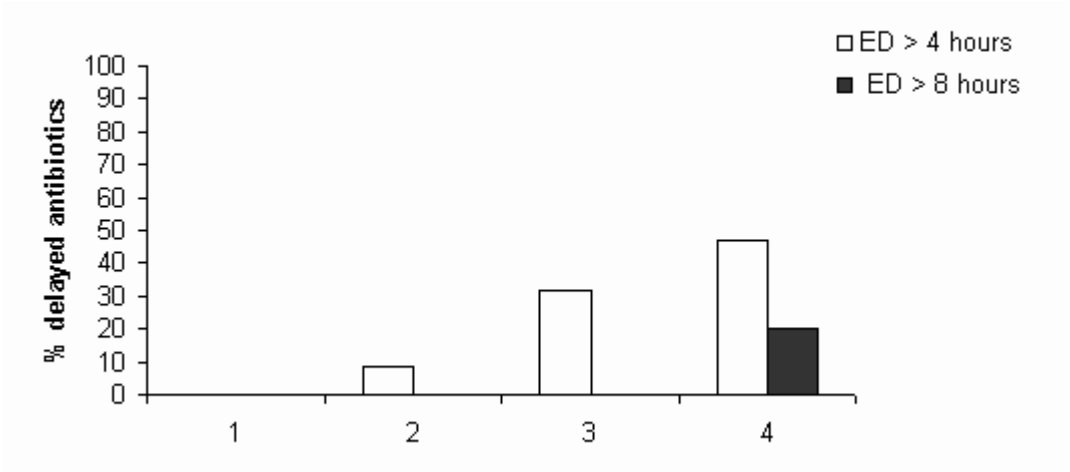

Figure 7.15: Percentage of delayed antibiotics by site of administration by ATS - 1998 sample: antibiotic given in the ED

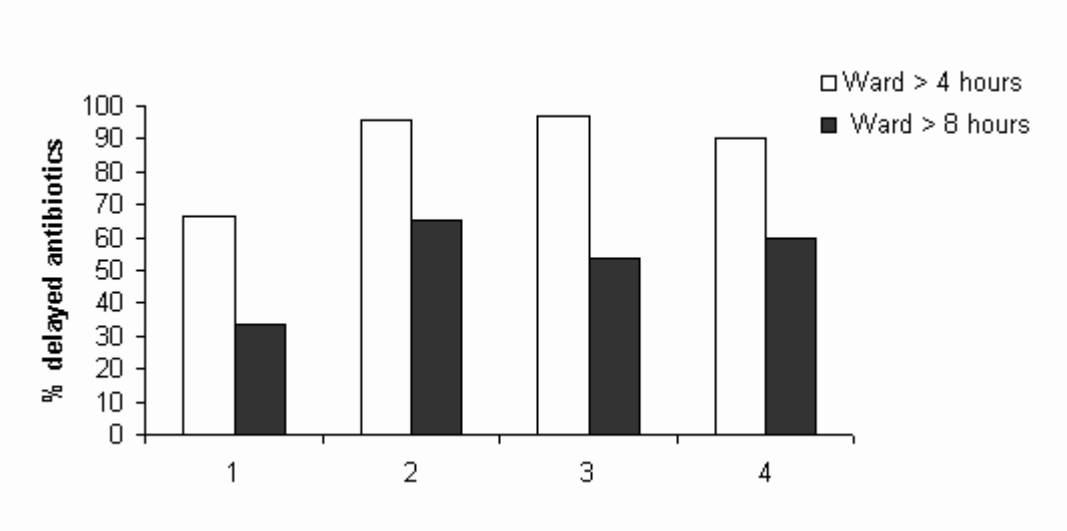

Figure 7.16: Percentage of delayed antibiotics by site of administration by ATS - 1998 sample: antibiotic given on the ward

7.3.7.4 The effect of ATS beyond time to ED physician assessment

Figure 7.17 shows the median times to CXR and first antibiotic, adjusted for time to ED physician assessment. These processes appear to be independently influenced by ATS as delay to their completion increases with lower urgency score (higher score), even when times are adjusted for delay in initial assessment. Median time to CXR from assessment appears shorter for ATS 1 patients treated in the ED. This was not the case for those with treatment delayed until the ward. Median time from initial assessment to antibiotic treatment in the ED increased with lower urgency ATS (higher score). Median time from CXR performance to antibiotic increased dramatically when the antibiotic was given on the ward. There appeared to be no linear relationship between ATS and time to antibiotic for this group.

.

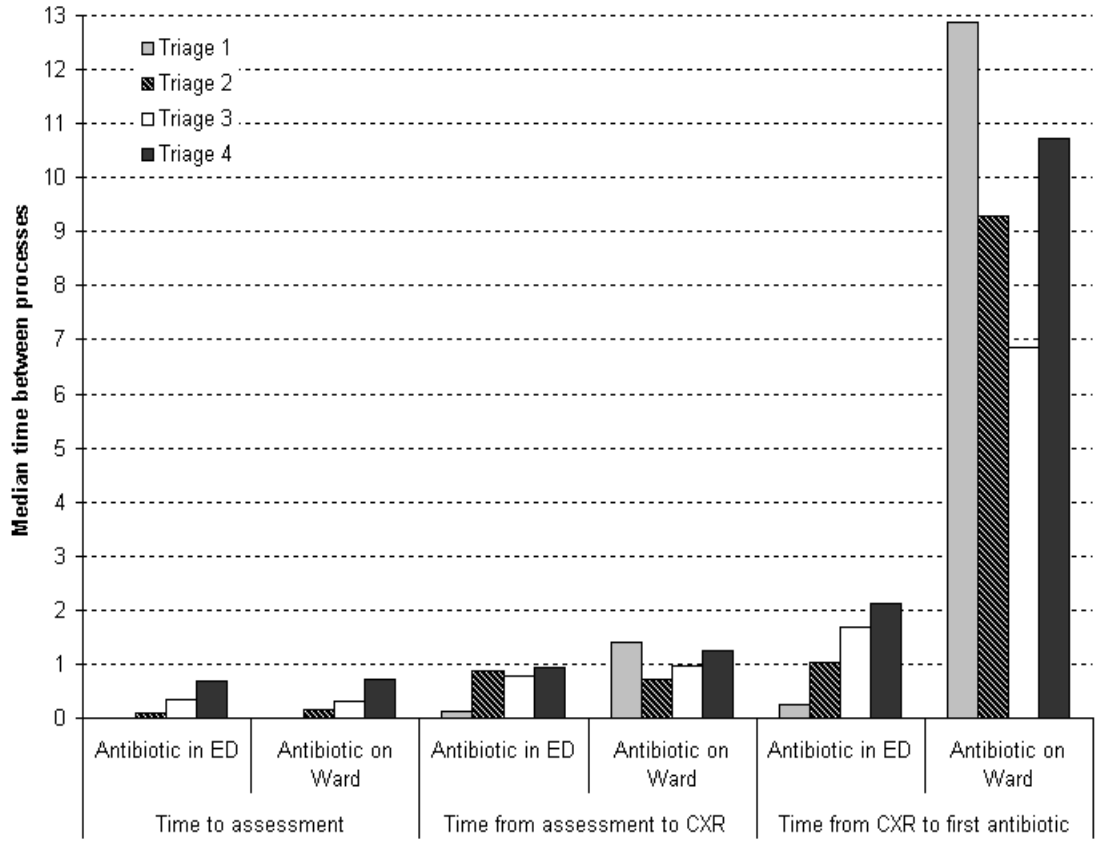

Figure 7.17: Time between processes by site of administration by ATS - 1998 sample

7.4 Accuracy of CXR and its association with primary diagnosis, site of care and antibiotic timing

Assessment of CXR accuracy and its relationship to primary diagnosis, and discharge diagnosis was performed using the year 2000 CAP sample, and the year 2003 non-CAP sample.

7.4.1 Accuracy of CXR in comparison to primary and discharge diagnoses

Tables 7.12 and 7.13 are two by two tables for association between CAP-positive CXRs and discharge diagnosis. Using the broad CXR criteria (pneumonia, consolidation, infection, opacity, and shadowing) the sensitivity of CXR for predicting discharge diagnosis was 66.7%, and the specificity was 70.4%. More conservative criteria (pneumonia and consolidation) produced a lower sensitivity (47%) and a higher specificity (85.9%). Up to a half (33.3 to 53%) of those with a diagnosis of CAP at discharge did not have CXR evidence in the initial radiology report. A number of cases (14.1 to 29.6%) given a non-CAP diagnosis at discharge had CXR evidence for CAP on initial CXR. These differences were significant in chi-square testing ($p<<0.0001$) for both tables.

Table 7.12: The association between broad CXR criteria and discharge diagnosis

	CAP-positive [b]	CAP-negative	Total
CXR-positive [a]	88 (66.7%)	21 (29.6%)	109
CXR-negative	44 (33.3%)	50 (70.4%)	94
Total	132	71	203

a: CXR-positive if report indicates “pneumonia”, “consolidation”, “infection”, “opacity”, “shadowing”
b: CAP-positive based on ward discharge diagnosis.

Table 7.13: The association between conservative CXR criteria and discharge diagnosis

	CAP-positive [b]	CAP-negative	Total
CXR-positive [a]	62 (47%)	10 (14.1%)	72
CXR-negative	70 (53%)	61(85.9%)	131
Total	132	71	203

a: CXR-positive if report indicates “pneumonia” or “consolidation”
b: CAP-positive based on ward discharge diagnosis

7.4.2 Relationship between CXR and ED primary diagnosis

Tables 7.14 and 7.15 show the relationship between CXR report and ED primary diagnosis for broad and conservative CAP-positive CXR criteria. Again, broad criteria had a higher sensitivity (79.5% vs. 60.3%) and a lower specificity (62.1% vs. 79.8%) in comparison to conservative criteria. These tables indicate that 20.2 to 37.9% of CAP cases given a non-CAP diagnosis in the ED had CXR evidence for CAP, while 20.5 to 39.7% of those with a CAP diagnosis in the ED did not have CXR evidence in the radiology report. These differences were significant in chi-square testing ($p<<0.0001$) for both criteria. CXR was a more sensitive but less specific for the prediction of ED primary diagnosis, in comparison to ward discharge diagnosis (see tables 7.12 and 7.13).

Table 7.14: The association between broad CXR criteria and primary diagnosis

	CAP-positive [b]	CAP-negative	Total
CXR-positive [a]	58 (79.5%)	47(37.9%)	105
CXR-negative	15 (20.5%)	77(62.1%)	92
Total	73	124	197

a: CXR-positive if report indicates “pneumonia”, “consolidation”, “infection”, “opacity”, “shadowing”
b: CAP-positive based on ED primary diagnosis

Table 7.15: The association between conservative CXR criteria and primary diagnosis

	CAP-positive [b]	CAP-negative	Total
CXR-positive [a]	44 (60.3%)	25 (20.2%)	69
CXR-negative	29 (39.7%)	99 (79.8%)	128
Total	73	124	197

a: CXR-positive if report indicates “pneumonia” or “consolidation”
b: CAP-positive based on ED primary diagnosis

7.4.3 Relationship between CXR result and time to antibiotic

Figure 7.18 shows that patients with positive CXR evidence for pneumonia had a lower median time to antibiotic treatment (broad criteria: 4.79 vs. 8.31; conservative criteria: 4.79 vs. 6.63), however, all median times were above 4 hours.

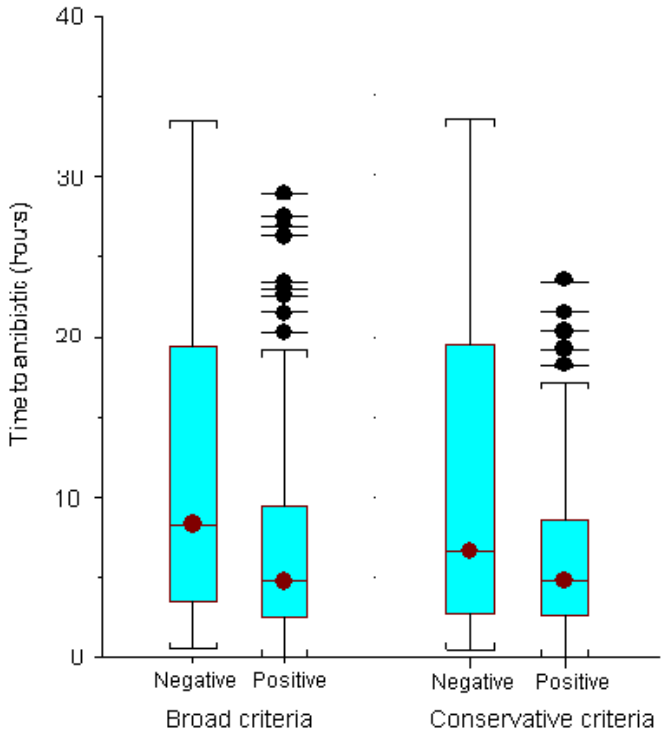

Figure 7.18: Time to antibiotic by CXR result

Table 7.16 shows that the percentage of patients receiving antibiotics later than 4 and 8 hours was significantly greater for those with no CXR evidence of CAP using broad CXR report criteria. This was also true using conservative CXR criteria, however, the differences were not significant at alpha level 0.05.

Table 7.16: Percentage with delayed antibiotics by CXR result

CXR model	CXR result	n (% total)	% > 4 hours	% > 8hours
Broad	CXR positive	82 (67)	56	28
	CXR negative	40 (33)	75*	50**
Conservative	CXR positive	57 (47)	60	26
	CXR negative	65 (53)	65***	43****

* Significantly greater percentage of antibiotic delay > 4 hours (chi-square p = 0.043)
** Significantly greater percentage of antibiotic delay > 8 hours (chi-square p = 0.017)
*** Greater percentage of antibiotic delay > 4 hours (chi-square p = 0.057)
**** Greater percentage of antibiotic delay > 8 hours (chi-square p = 0.053)

Table 7.17 Shows that patients with CXR evidence of CAP were significantly more likely to receive antibiotics in the ED, however a large proportion of patients who were CXR-negative (39.44 to 53.03%) also received antibiotics in the ED.

.

Table 7.17: Pneumonia patients given antibiotics in ED by CXR result

CXR model	CXR result	n (% total)	% Antibiotic in ED
Broad	CXR positive	83 (66)	63*
	CXR negative	42 (34)	33
Conservative	CXR positive	58 (46)	66**
	CXR negative	67 (54)	42

*Significantly greater percentage of antibiotics given in the ED (chi-square p = 0.002)
**Significantly greater percentage of antibiotics given in the ED (chi-square p = 0.008)

7.5 Early diagnosis model (EDM) validation and predicted impact on processes and outcomes

7.5.1 EDM data

To validate the EDM I compared the literature-populated EDM to a similar EDM, based on local data. Table 7.18 shows the some variability in likelihood ratios (LRs) between studies in the literature and local data. For the literature model I used average values across studies. The positive LRs of cough, dyspnoea, dementia, respiratory rate, heart rate, temperature, decreased breath sounds, crackles and rhonchi were all lower in the local data set. The positive LRs for sputum, fever and chills were larger in the local data set, indicating they were better predictors

of CAP. Negative LRs were lower for dementia, asthma, decreased breath sounds and crackles in the local sample. Negative LRs were higher for the remaining variables, excluding fever and respiratory rate which were approximately the same value. Rates of dyspnoea, increased heart rate, and rhonchi were actually higher in non-CAP patients in the local sample.

Table 7.18: A comparison of literature-derived and local LRs for CAP diagnosis

	Positive LR						Negative LR					
Findings	**1**	**2**	**3**	**4**	**Average**	**Local data**	**1**	**2**	**3**	**4**	**Average**	**Local data**
Cough	ns	ns		1.8	1.8	1.34	ns	ns		0.31	0.31	0.47
Dyspnoea	1.4	ns		ns	1.4	0.83	0.67	ns		ns	0.67	2.87
Sputum	ns	ns	1.3		1.3	1.47	ns	ns	0.55		0.55	0.72
Fever	ns	1.7	2.1		1.9	2.94	ns	0.59	0.71		0.65	0.70
Chills	1.3	1.7	1.6		1.53	2.43	0.72	0.7	0.85		0.76	0.90
Dementia		3.4			3.4	2.94		0.94			0.94	0.70
Asthma		0.1			0.1	0.14		3.8			3.8	1.34
Respiratory rate > 25		1.5	3.4	ns	2.45	1.66		0.82	0.78	ns	0.8	0.78
Heart rate > 100	1.6	2.3	ns	ns	1.95	0.95	0.73	0.49	ns	ns	0.61	1.03
Tempera-ture > 37.8	1.4	2.4	4.4	2.4	2.65	2.15	0.63	0.58	0.78	0.68	0.67	0.83
Decreased breath sounds	2.3	2.5	ns		2.4	2.19	0.78	0.64	ns		0.71	0.39
Crackles	1.6	2.6	2.7	1.7	2.15	1.38	0.83	0.62	0.87	0.78	0.78	0.51
Rhonchi	1.5	1.4	ns		1.45	0.12	0.85	0.76	ns		0.81	1.06

1) Gennis et. al. [255], 2) Heckerling et. al. [256], 3) Diehr et. al. [252], 4) Singal et. al. [253], ns = non-significant

7.5.2 Comparison of receiver operating characteristic (ROC) curves

I then plotted ROC curves for the 2 models and determined the area under these curves. Figure 7.19 shows the ROC curves for the literature and local data model. The use of local data improved the area under the ROC curve (literature model = 0.8, local data model = 0.85). This 0.05 difference was statistically significant (DeLong, Delong, Clarke-Pearson ROC curve comparison method; 95% confidence interval (CI) = 0.01-0.09, standard error (SE) = 0.019, z = 2.58, p = 0.01).

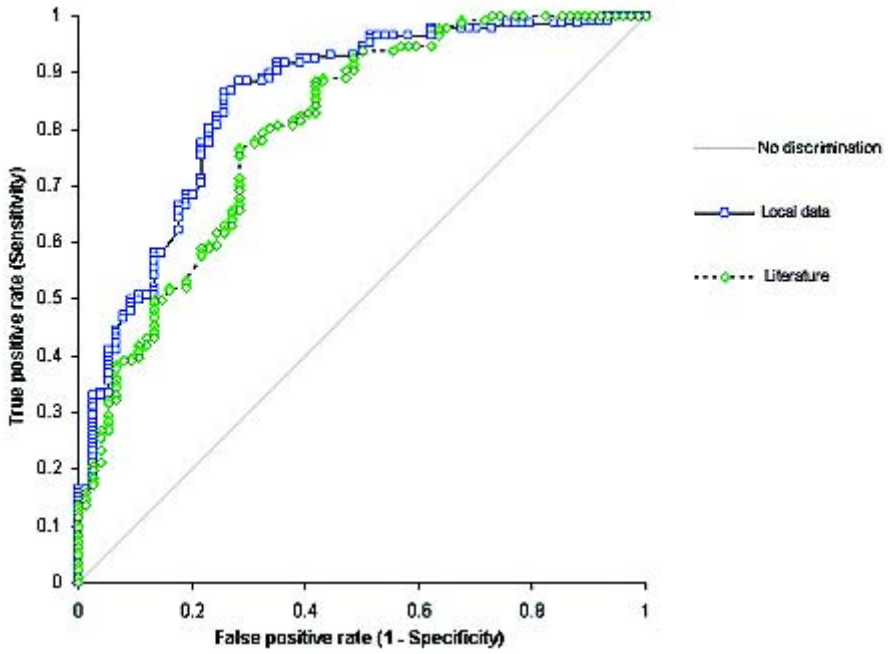

Figure 7.19: Comparison of literature-based and local data-based EDMs - ROC

7.5.3 EDM calibration

Both models were found to have poor calibration (see figure 7.19). A perfect model would produce a linear increase in the fraction of total CAP-positive patients with an increase in the post-test probability of CAP [342]. The vast majority of CAP-positive patients in this sample have a very low probability of CAP (p[CAP]) based on symptoms and signs alone. The calibration of the literature model was superior to that of the local data model. Using the local data model, over 60% of patients had a probability of 0.1 or less at initial examination.

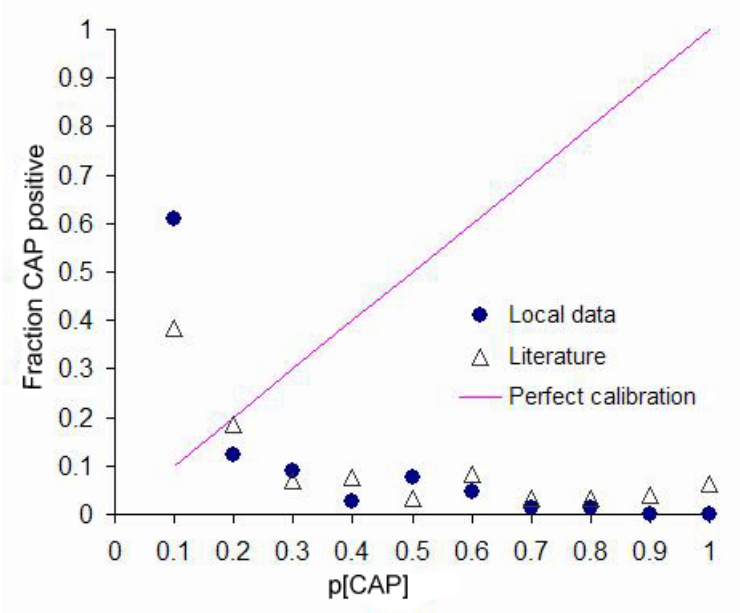

Figure 7.20: Comparison of literature-based and local data-based EDMs - calibration

7.5.4 EDM model and threshold selection

Figure 7.21 shows a plot of the sensitivity and specificity of the literature-based and local data-based EDMs. A diagnostic threshold probability of 0.3 using the literature EDM was selected to balance the need for high specificity with maximum sensitivity. The local data model was less sensitive (27% vs. 36%) but more specific (97% vs. 93%) at a diagnostic threshold of CAP post-test probability = 0.3.

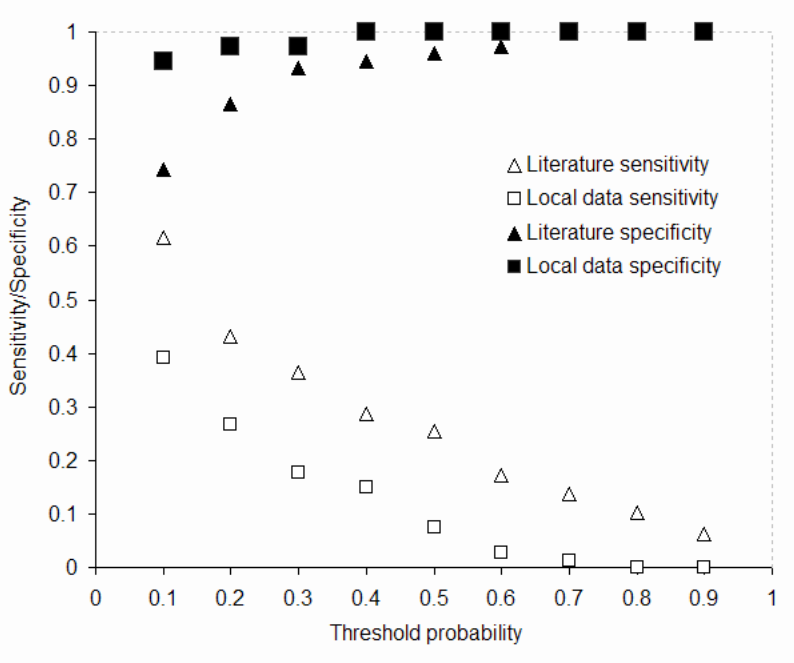

Figure 7.21: Plot of sensitivity and specificity for the literature and local data EDMs

7.5.5 Effect of dependency between predictor variables

Table 7.19 lists the commonly co-occurring variables selected to test the effect of dependence on model accuracy. All variable pairs chosen occurred together in greater than 50% of CAP-positive patients.

Table 7.19: Commonly co-occurring CAP predictor variables

Co-occurring variables	% Co-occurring in CAP-positive patients	% Co-occurring in all patients
Cough + shortness of breath	66.4	63.2
Cough + sputum	54.8	49.1
Cough + decreased breath sounds	61.6	48.2
Cough + crackles	63.0	53.2
Shortness of breath + decreased breath sounds	58.2	48.6
Shortness of breath + crackles	61	58.2

Using the literature-based EDM at a threshold probability of 0.3, I compared the post-test probability of joint LRs for pairs of commonly co-occurring variables, to that calculated from combined single LRs for the same variables. Post-test probability was calculated using the odds ratio (OR) form of Bayes' Theorem. Pre-test odds (0.014) were calculated from local CAP incidence. Table 7.20 illustrates that there is only a small difference between calculated joint and combined post-test probabilities, calculated from and therefore minimal effect of dependence amongst variables in this model.

Table 7.20: Joint LRs versus combined LRs: post-test probability of CAP

	Positive LR			Negative LR		
Paired variables	**Joint LR**	**Post-test probability for joint LR**	**Post-test probability for combined LRs**	**Joint LR**	**Post-test probability given joint LR**	**Post-test probability combined LRs**
Cough + shortness of breath	1.2	0.02	0.02	0.78	0.01	0.02
Cough + sputum	1.45	0.02	0.03	0.73	0.01	0.01
Cough + decreased breath sounds	2.85	0.04	0.05	0.49	0.01	0.01
Cough + crackles	1.87	0.03	0.03	0.56	0.01	0.003
Dyspnoea + decreased breath sounds	1.96	0.03	0.03	0.6	0.01	0.02
Dyspnoea + crackles	1.16	0.02	0.02	0.83	0.01	0.02

7.5.6 Theoretical effect of EDM on mortality and processes

Using the literature-based EDM at a threshold probability of 0.3, I estimated the possible impact of the EDM on CAP treatment by calculating the percentage of EDM-positive patients that died, had delayed CXR, or had delayed antibiotic treatment. The literature-based model identified 24% of those who died, 26% of patients with delayed CXR, and 38% of those with a delay to antibiotic treatment greater than 4 hours.

7.5.7 Correlations between process timings in patients identified by the EDM

Table 7.21 shows that correlations between ED physician assessment and CXR timing in the 2000 data set were larger in those CAP-positive on the literature-based EDM at a threshold probability of 0.3 (r = 0.79 vs. 0.02 in the complete sample - see table 7.5). Patients that were EDM-positive had a slightly shorter median time to CXR (1.45 vs. 1.75 hours), but had a much shorter maximum time to CXR (17.23 vs. 151.9 hours). This indicates that the majority of CXR outlier times occurred in patients with a non-specific presentation.

Table 7.21: Correlations between process timings in CAP-positive patients identified by the EDM

	CXR	Antibiotic	ED discharge
Physician assessment	0.79	0.36	0.22
CXR		0.1	0.12
Antibiotic			0.08

7.6 Risk model assessment

7.6.1 Accuracy of the ATS for the prediction of CAP complications

Figure 7.22 shows that triage scores predicted outcomes of heart failure, respiratory failure, ICU/HDU admission, vasopressor use, mechanical ventilation, and death in the 1998 CAP-positive sample. There was no significant association of triage score with atrial fibrillation (AF), hypotension, sepsis, renal failure, lung abscess, empyema or pleural effusion. There were substantial rates of complications in triage groups 2 and 3, particularly AF, heart failure, renal failure, respiratory failure and mortality. Although those with a high urgency triage score more often had complications, figure 7.23 shows that patients with a triage score of 1 accounted for less than 1/3 of any given CAP complication. Triage groups 2 and 3 experienced the most complications in terms of total percentage, and triage group 3 had over 40% of the total number of deaths.

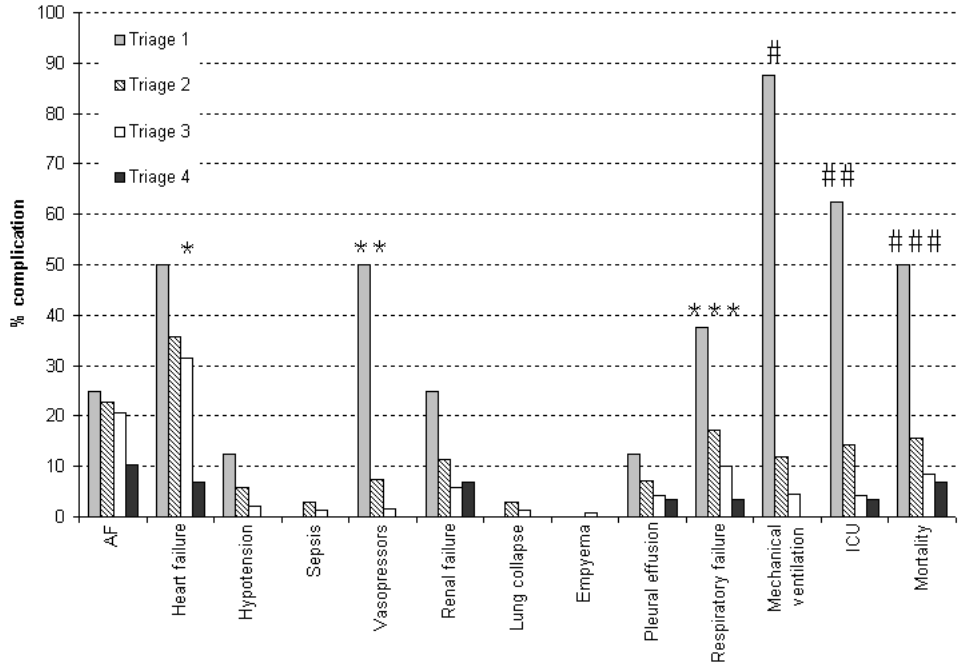

Figure 7.22: Percentage of complications by ATS

Significant difference between triage groups (chi-square): * p=0.02, ** p<0.0001, *** p=0.035, # p< 0.0001, ## p<0.001, ### p=0.003

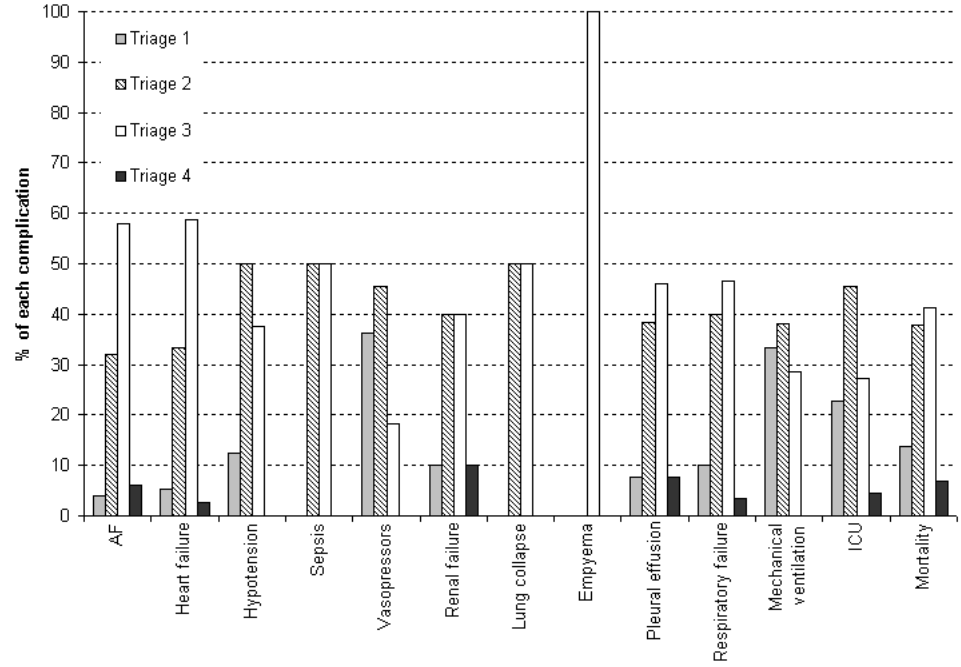

Figure 7.23: Percentage of the total occurrence of each complication for each ATS

7.6.2 Comparison of CAP-specific risk models and the ATS

Figure 7.24 shows ROC curves for each of the risk models. Table 7.22 lists values for the area under these curves, and Table 7.23 details the results of DeLong, Delong, Clarke-Pearson comparisons between each of the curves. Given that all patients were over 65, there were no patients in Pneumonia Severity Index (PSI) group 1, no CURB-65 model scores less than 1, or low risk patients in the local guideline risk model (see appendix figure 9.1). There were no patients with an ATS lower urgency than 4. Table 7.22 shows that the PSI had the largest area under the ROC curve at 0.71. The CURB-65 model had a lower area under the ROC curve at 0.67, but this difference did not reach significance at the 0.05 level (see table 7.23). The CRB-65RF model provided slightly superior mortality risk prediction in comparison to the CRB-65 (0.64 vs. 0.60, respectively), but this difference was not significant. The CRB-65 model performed significantly worse than the PSI. In contrast, the difference between CRB-65RF and the PSI was not significant. The local guideline model performed significantly worse than both the PSI and the CURB-65 at 0.54. Despite its lower value (0.56), the area under the ROC curve for the ATS was not significantly different to the ATS.

Table 7.22: Area under the ROC curve for risk models

Test	Area under ROC curve	95% Confidence interval	Standard error
PSI	0.71	0.60 to 0.81	0.05
CURB -65	0.67	0.56 to 0.78	0.06
CRB-65RF	0.64	0.51 to 0.77	0.07
CRB-65	0.60	0.49 to 0.72	0.06
ATS	0.56	0.41 to 0.71	0.08
Local guideline	0.54	0.48 to 0.59	0.03

Table 7.23: Difference in area under the ROC curve between risk models

Contrast	Difference in area under ROC curve	95% confidence interval	Standard error	Z score	p value
CURB-65 vs. CRB-65	0.07	0.00 - 0.14	0.04	1.96	0.049*
CURB-65 vs. CRB-65RF	0.03	-0.06 - 0.12	0.05	0.66	0.51
CURB-65 vs. Local guideline	0.13	0.02 - 0.25	0.06	2.29	0.02*
CURB-65 vs. PSI	-0.04	-0.16 - 0.08	0.06	-0.64	0.52
CURB-65 vs. ATS	0.11	-0.10 - 0.32	0.11	1.04	0.3
CRB-65 vs. CRB-65RF	-0.04	-0.11 - 0.03	0.04	-1.02	0.3
CRB-65 vs. Local guideline	0.06	-0.04 - 0.17	0.06	1.16	0.25
CRB-65 vs. PSI	-0.11	-0.21 - -0.00	0.06	-1.97	0.049*
CRB-65 vs. ATS	0.04	-0.16 - 0.25	0.1	0.42	0.68
CRB-65RF vs. Local guideline	0.10	-0.02 - 0.23	0.06	1.60	0.11
CRB-65RF vs. PSI	-0.07	-0.19 - 0.05	0.06	-1.18	0.24
CRB-65RF vs. ATS	0.08	-0.13 - 0.29	0.11	0.75	0.45
Local guideline vs. PSI	-0.17	-0.28 - -0.06	0.06	-3.11	0.002*
Local guideline vs. ATS	-0.02	-0.18 - 0.14	0.08	-0.26	0.79
PSI v ATS	0.15	-0.04 - 0.35	0.1	1.51	0.13

* $p < 0.05$

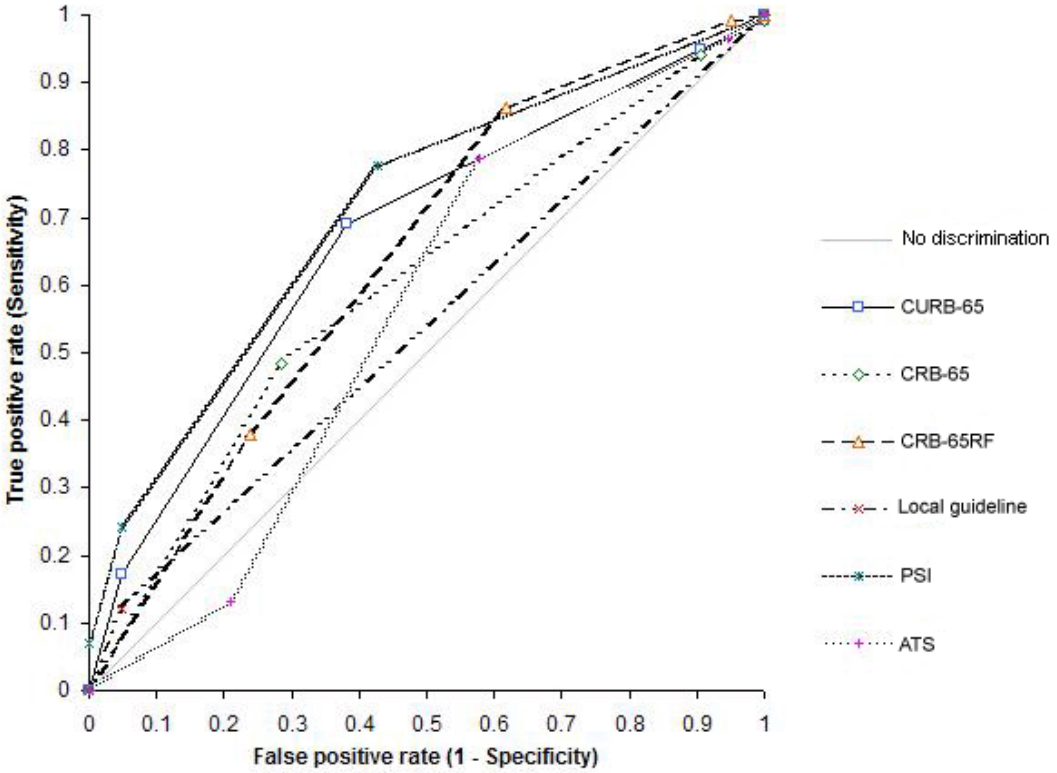

Figure 7.24: ROC curves of the prediction of CAP mortality by risk models

7.7 Antibiotic alerting simulations

Figure 7.25 illustrates box plots of the distributions of antibiotic timing for each of the simulations. Table 7.24 shows the descriptive statistics for each simulation. Figures 7.26 and 7.27 show the percentage of patients with over 4 and 8 hours delay to antibiotics, respectively. The actual median value for time to antibiotic treatment in the year 2000 CAP-positive sample was in excess of the goal of 4 hours (5.53 hours), with 62% treated after 4 hours, and 35% treated after 8 hours. The numbering of interventions remains constant for the following reporting and graphical representations of the simulations. Note that the numbering of interventions begins at 2 as the label 1 is used for the actual distribution of antibiotic timing in the year 2000 sample.

Intervention 2, the use of the CRB-65 model to triage patients that are EDM-positive, produced a minimal simulated reduction in the median time to antibiotic (0.08 hours), and in the percentage of antibiotics delayed more than 4 hours (0.73%), however it did reduce the percentage of antibiotics later than 8 hours by 8.76%.

Intervention 3, alerting for CAP if the EDM was positive and treating by ED discharge, reduced the median time to antibiotic by just over 30 minutes. This simulation produced small reductions in the percentage of antibiotics delayed greater than 4 hours (3.65%), and percentage of antibiotics delayed greater than 8 hours (7.3%).

Intervention 4, alerting for a positive ED primary diagnosis and treating by ED discharge, reduced the median time to antibiotic by 0.73 hours. This simulation produced a 4.38% reduction in the percentage of antibiotics delayed greater than 4 hours and a 7.3% reduction in those treated after 8 hours.

Intervention 5, alerting for a positive CXR report and treating by ED discharge, reduced the time to initial antibiotic by 0.84 hours. The simulated percentage of antibiotics delayed greater than 4 hours was reduced by 3.65%, and the percentage of antibiotics delayed greater than 8 hours by 8.03%.

Intervention 6, if EDM-positive, alert for investigations at triage and treat by ED discharge, decreased the median time to antibiotic by the same amount as intervention 5 (0.84 hours). The reduction in simulated percentage of antibiotics delayed greater than 4 hours was 4.38%, and that delayed more than 8 hours was 7.3%.

Intervention 7, alert if EDM-positive or ED primary diagnosis positive and treat by ED discharge, also reduced the simulated median time to antibiotic by 0.84 hours. The percentage of antibiotics delayed longer than 4 hours was decreased by 5.11%, and that delayed by greater than 8 hours by 12.41%.

Intervention 8, alert if the ED primary diagnosis was CAP, or the CXR report was positive for CAP, and treat by ED discharge, reduced the simulated median time to antibiotic by 0.92 hours. The percentage of antibiotics delayed longer than 4 hours was decreased by 5.84%, and that delayed by greater than 8 hours by 10.95%.

Intervention 9, simulating the treatment of all CAP patients in the ED (i.e an alerting system with a 100% sensitivity), reduced the median time to antibiotic by an hour (0.99), the percentage of antibiotics delayed longer than 4 hours by 6.57%, and the percentage delayed by greater than 8 hours by 23.36%.

Intervention 10, alert if EDM-positive and treat by 30 minutes after ED physician assessment, reduced the simulated median time to antibiotic by 2.78 hours. This is the first of the interventions listed to reduce the median time to antibiotic below the 4 hour goal. Simulations of interventions 11, 12, 13, and 14 also bettered this mark. The percentage of antibiotic treatment delayed greater than 4 hours was reduced by 19.71%, and that delayed greater than 8 hours by 9.49%.

Intervention 11, alert if EDM-positive and treat following triage, reduced the simulated median time to antibiotic by 2.93 hours, the percentage of patients treated later than 4 hours by 20.44%, and percentage treated later than 8 hours by 9.49%.

Intervention 12, alert if EDM-positive and triage at level 2, had similar simulated effects to intervention 11 on antibiotic timing. This finding highlights the effect that risk assessment has on subsequent workflow in the treatment of CAP.

Intervention 13, alert if EDM-positive and treat following triage, and alert if ED primary diagnosis positive and treat by ED discharge, reduced the simulated median time to antibiotic by over 3 hours (3.12). The percentage of patients with antibiotics delayed greater than 4 hours was reduced by 21.9%, and those delayed greater than 8 hours was reduced by 14.6%.

Intervention 14, alert if EDM-positive and treat following triage, and alert if ED primary diagnosis was positive or CXR report was positive and treat by ED discharge, reduced the simulated median time to antibiotic by 3.26 hours. The percentage of patients with antibiotics delayed greater than 4 hours was reduced by 22.63%, and those delayed greater than 8 hours was reduced by 17.52%. In comparison to intervention 13 the addition of CXR report to the simulation had only a small effect on antibiotic timing. The use of CXR reports to alert for CAP would increase the rate of false positives, given that the specificity of CXR was between 70-86% at the study site, and that of the EDM was 93%.

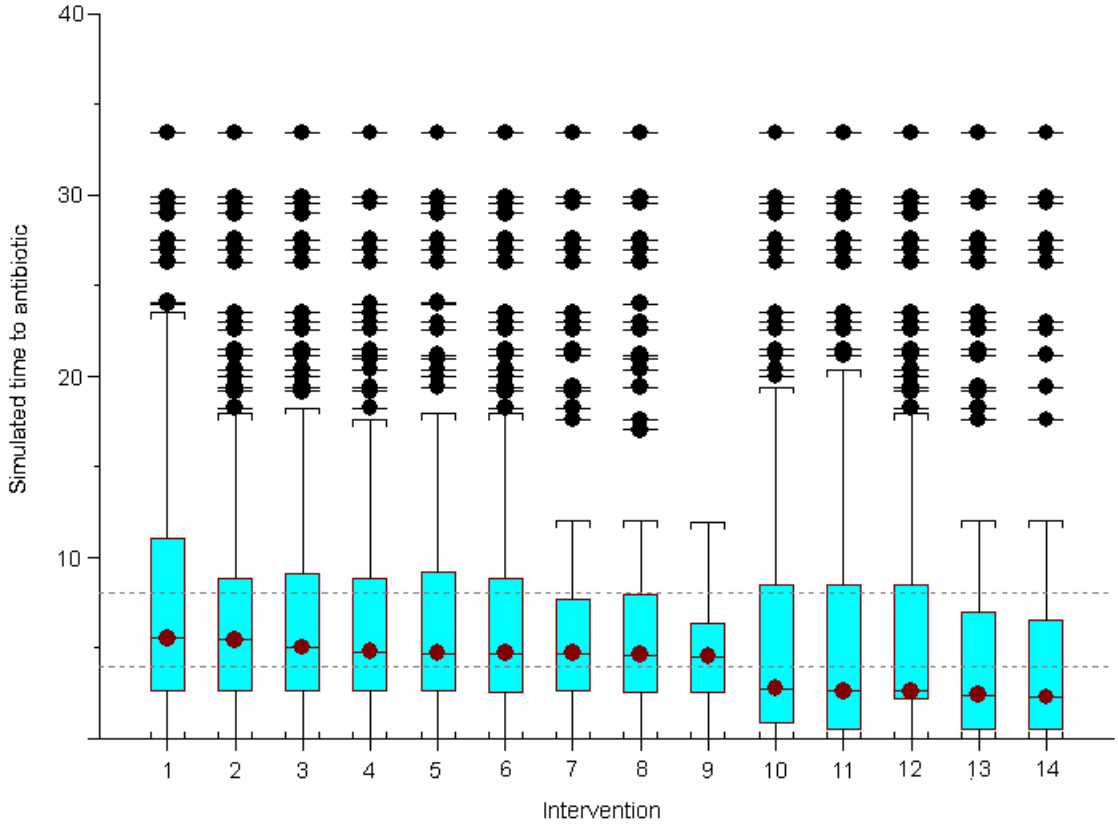

Figure 7.25: Box plots of the distribution of simulated antibiotic timing

Legend: 1) Actual data; 2) EDM-positive, triage with CRB-65; 3) EDM-positive, treat by ED discharge; 4) ED primary diagnosis positive, treat by ED discharge; 5) CXR-positive, treat by ED discharge; 6) EDM-positive, investigations ordered at triage, treat by ED discharge; 7) EDM-positive or ED primary diagnosis positive, treat by ED discharge; 8) ED primary diagnosis or CXR-positive, treat by ED discharge; 9) Treat all by ED discharge; 10) EDM-positive, treat after ED physician assessment; 11) EDM-positive, treat following triage; 12) EDM-positive, treat as triage 2; 13) EDM-positive, treat following triage, ED primary diagnosis positive, treat by ED discharge; 14) EDM-positive, treat following triage, ED primary diagnosis positive or CXR-positive, treat by ED discharge.

Table 7.24: Descriptive statistics for simulated antibiotic timing

Intervention	Simulated median time to antibiotic (hours)	Simulated change in median antibiotic time (hours)	Simulated inter-quartile range in antibiotic time (hours)	Simulated percentage treated after 4 hours (% reduction from actual data)	Simulated percentage treated after 8 hours (% reduction from actual data)
2) EDM-positive, triage with CRB-65	5.45	0.08	2.63 - 8.72	60.58 (0.73)	26.28 (8.76)
3) EDM-positive, treat by ED discharge	5.03	0.51	2.63 - 9.04	57.66 (3.65)	27.74 (7.3)
4) ED primary diagnosis positive, treat by ED discharge	4.80	0.73	2.6 - 8.79	56.93 (4.38)	27.74 (7.3)
5) CXR report positive, treat by ED discharge	4.69	0.84	2.6 - 9.18	57.66 (3.65)	27.01 (8.03)
6) EDM-positive, investigations ordered at triage, treat by ED discharge	4.69	0.84	2.56 - 8.72	56.93 (4.38)	27.74 (7.3)
7) EDM-positive or ED primary diagnosis positive, treat by ED discharge	4.69	0.84	2.6 - 7.66	56.2 (5.11)	22.63 (12.41)
8) ED primary diagnosis positive or CXR-positive, treat by ED discharge	4.62	0.92	2.56 - 7.89	55.47 (5.84)	24.09 (10.95)
9) Treat all by ED discharge	4.54	0.99	2.56 - 6.35	54.74 (6.57)	11.86 (23.36)
10) EDM-positive, treat after ED physician assessment	2.75	2.78	0.93 - 8.44	41.61 (19.71)	25.55 (9.49)
11) EDM-positive, treat following triage	2.61	2.93	0.5 - 8.44	40.88 (20.44)	25.55 (9.49)
12) EDM-positive, treat as triage 2	2.61	2.93	2.16 - 8.44	40.88 (20.44)	25.55 (9.49)
13) EDM-positive, treat following triage, ED primary diagnosis positive, treat by ED discharge	2.42	3.12	0.50 - 6.88	39.42 (21.9)	20.44 (14.6)
14) EDM-positive, treat following triage, ED primary diagnosis positive or CXR-positive, treat by ED discharge	2.28	3.26	0.50 - 6.48	38.69 (22.63)	17.52 (17.52)

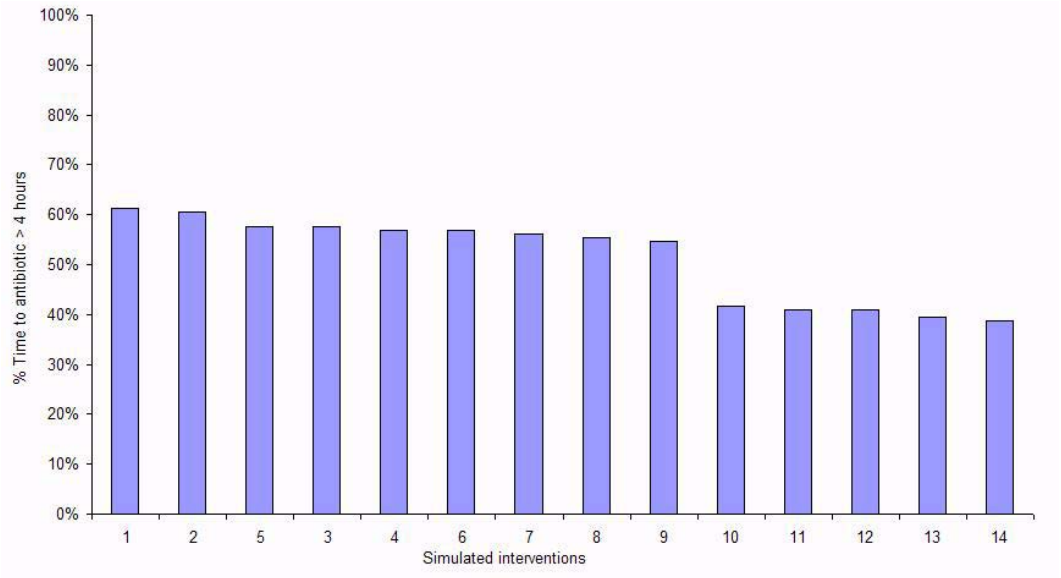

Figure 7.26: Simulated percentage of patients with antibiotic time greater than 4

Legend (numbering matches figure 7.25): 1) Actual data; 2) EDM-positive, triage with CRB-65; 3) EDM-positive, treat by ED discharge; 4) ED primary diagnosis positive, treat by ED discharge; 5) CXR-positive, treat by ED discharge; 6) EDM-positive, investigations ordered at triage, treat by ED discharge; 7) EDM-positive or ED primary diagnosis positive, treat by ED discharge; 8) ED primary diagnosis or CXR-positive, treat by ED discharge; 9) Treat all by ED discharge; 10) EDM-positive, treat after ED physician assessment; 11) EDM-positive, treat following triage; 12) EDM-positive, treat as triage 2; 13) EDM-positive, treat following triage, ED primary diagnosis positive, treat by ED discharge; 14) EDM-positive, treat following triage, ED primary diagnosis positive or CXR-positive, treat by ED discharge

.

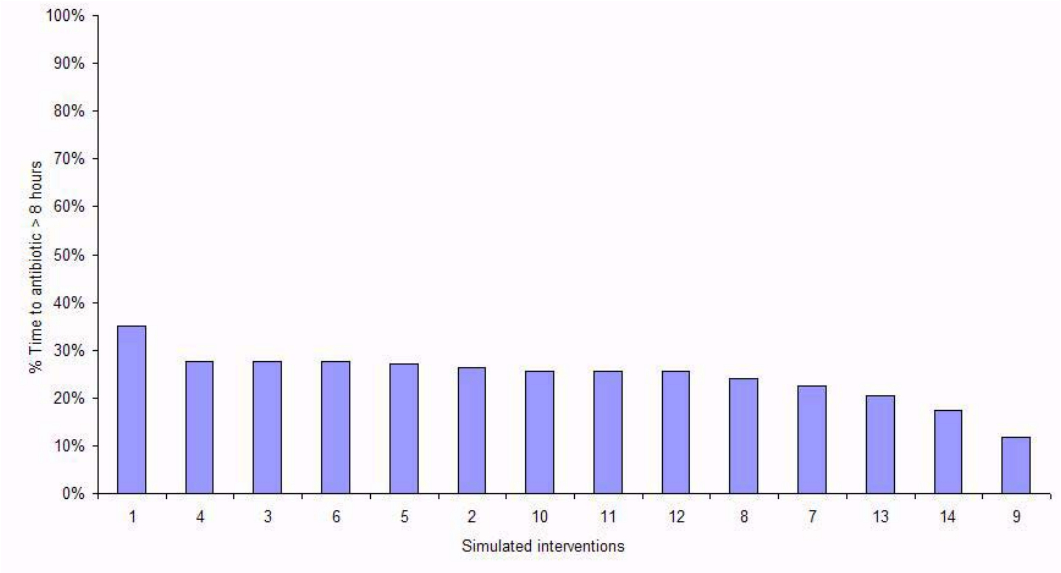

Figure 7.27: Simulated percentage of patients with antibiotic time greater than 8 hours

Legend (numbering matches figure 7.25: 1) Actual data; 2) EDM-positive, triage with CRB-65; 3) EDM-positive, treat by ED discharge; 4) ED primary diagnosis positive, treat by ED discharge; 5) CXR-positive, treat by ED discharge; 6) EDM-positive, investigations ordered at triage, treat by ED discharge; 7) EDM-positive or ED primary diagnosis positive, treat by ED discharge; 8) ED primary diagnosis or CXR-positive, treat by ED discharge; 9) Treat all by ED discharge; 10) EDM-positive, treat after ED physician assessment; 11) EDM-positive, treat following triage; 12) EDM-positive, treat as triage 2; 13) EDM-positive, treat following triage, ED primary diagnosis positive, treat by ED discharge; 14) EDM-positive, treat following triage, ED primary diagnosis positive or CXR-positive, treat by ED discharge.

7.8 Association between process and mortality

7.8.1 Association between antibiotic timing and mortality

The rate of mortality in the 1998 sample was 11.9%, and in the 2000 sample was 14.4%. Table 7.25 and figure 7.28 show that median treatment time for patients that died in the 1998 sample was less than those who lived (2.6 vs. 4.7 hours). The majority of outlier treatment times occurred in those alive at discharge. Table 7.25 and figure 7.29 indicate the timing distribution and the median treatment time was similar between outcomes in the 2000 data set (5 vs. 5.5 hours).

Table 7.25: Median antibiotic timing by mortality (hours)

	Antibiotic time (hours)	
	1998	**2000**
Lived	4.7	5.5
Died	2.6	5

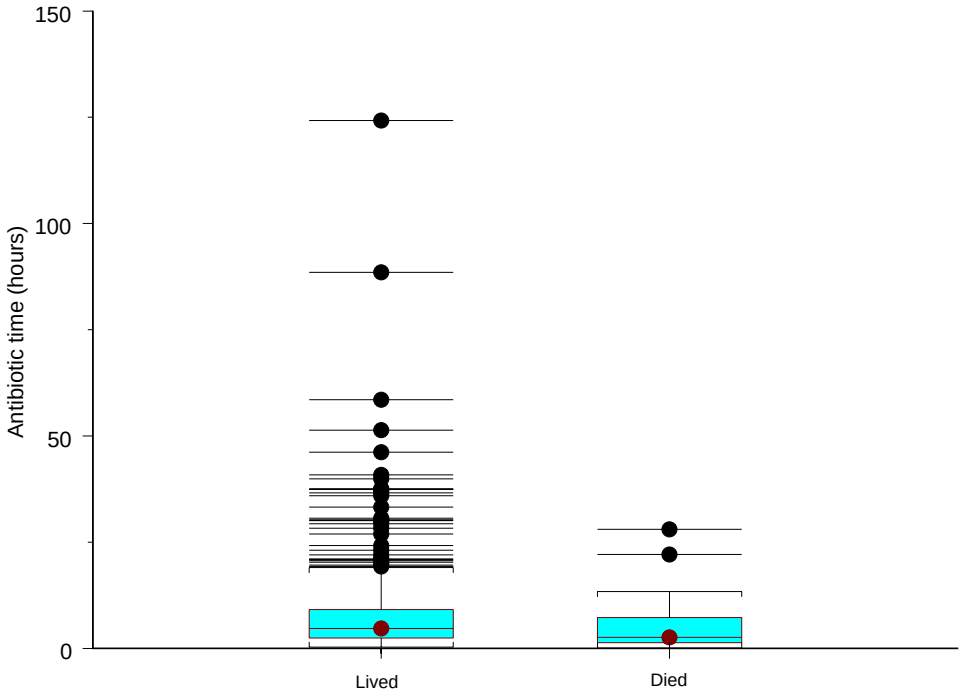

Figure 7.28: Antibiotic timing by mortality - 1998 sample

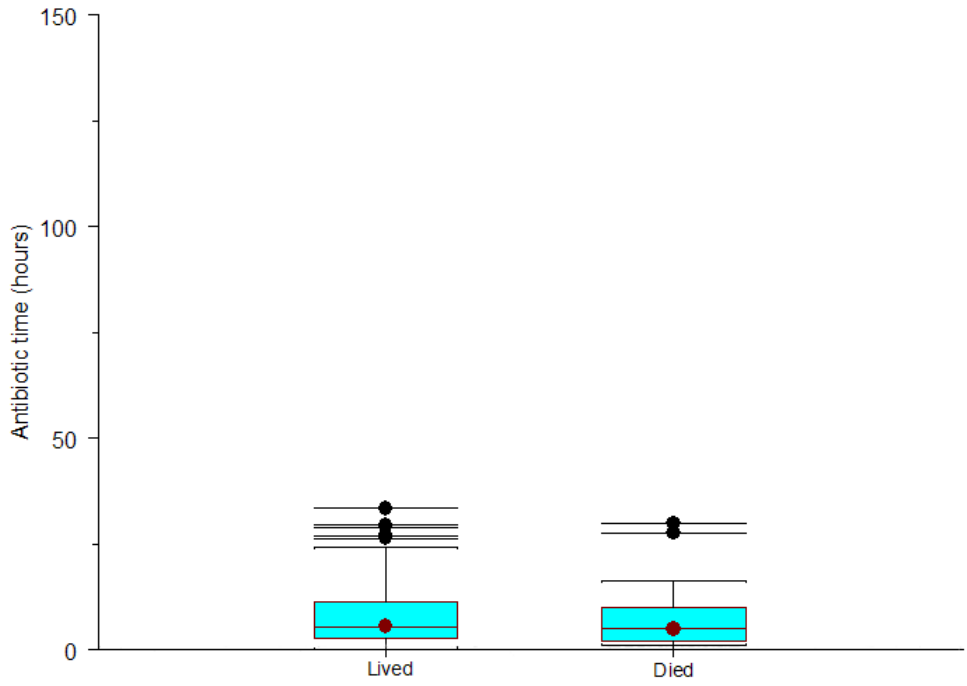

Figure 7.29: Antibiotic timing by mortality - 2000 sample

Table 7.26 shows that mortality was significantly higher in those patients that received antibiotics within 4 hours in comparison to those that had delayed antibiotics (18 vs. 7.8%). There was a similar trend for those with delay greater than 8 hours, however this was not significant (13 vs. 9.7%). In the 2000 sample (Table 7.27) patients with delayed antibiotics had a 1% higher rate of mortality for delays greater than 4 and 8 hours, but this was not significant.

Table 7.26: Association between antibiotic delay and mortality - 1998 sample

	% Mortality	
	Delayed	**Not Delayed**
Delay > 4 hours	7.8	18*
Delay > 8 hours	9.7	13

* chi-square p = 0.02

Table 7.27: Association between antibiotic delay and mortality - 2000 sample

	% Mortality	
	Delayed	**Not Delayed**
Delay > 4 hours	15	14
Delay > 8 hours	16	13

7.8.2 Effect of primary diagnosis and CXR result on outcome

Table 7.28 shows that the rate of mortality was similar, regardless of whether patients had a primary diagnosis of CAP in the ED, in both the 1998 and 2000 samples. Table 7.29 shows that in the 2000 CAP-positive sample there was a trend for mortality to be higher in patients with a positive CXR. This difference was significant in those with a positive CXR result using the conservative model.

Table 7.28: Association between primary diagnosis and mortality - 1998 and 2000 samples

	% Mortality	
	1998	**2000**
CAP	11	14
Non-CAP	12	15

Table 7.29: Association between CXR result and mortality - 2000 sample

	% Mortality	
	CXR Positive	**CXR Negative**
CXR conservative model	20	5*
CXR broad model	15	5

* chi-square p = 0.01

8 Discussion

8.1 Overview

Community-acquired pneumonia (CAP) is a common disease with high morbidity, mortality, and high variability in treatment practices. This variability occurs in the context of complexity in diagnosis, risk assessment, treatment selection, and in process flow (see chapter 1). Paper-based guidelines, feedback of performance, and financial incentive programs, have thus far failed to adequately improve the percentage of patients appropriately treated within 4-8 hours of presentation to hospital emergency departments (EDs) (see chapters 2 and 3). Delay in initiating antibiotic treatment has been linked to an increased risk of poor outcomes (see chapter 3). Evidence suggests that recent attempts to use financial incentives to reach antibiotic timing targets have resulted in inappropriate CAP diagnosis and treatment (see chapter 3).

I used a workflow analysis approach to determine the factors that influenced the timing of antibiotic delivery for patients diagnosed with CAP at a large Australian teaching hospital. The impact of uncertainty in decision-making (patient complexity) was assessed by looking at the association of ED physician diagnosis, and chest x-ray (CXR) with key processes of treatment. The impact of local policies on care was demonstrated by the assessment of the impact of the Australasian Triage Score (ATS) on process timing. I constructed qualitative and quantitative models of workflow, and used a bayesian early diagnosis model (EDM), and a specific CAP risk model (the CRB-65) to simulate the possible impact of an alerting system, sensitive to individual patient complexity. The impact of resources at the point of care was subsumed in the deterministic workflow model. Thus all elements of my simple process model (see figure 8.1) formed part of the final simulation model (see figure 8.2).

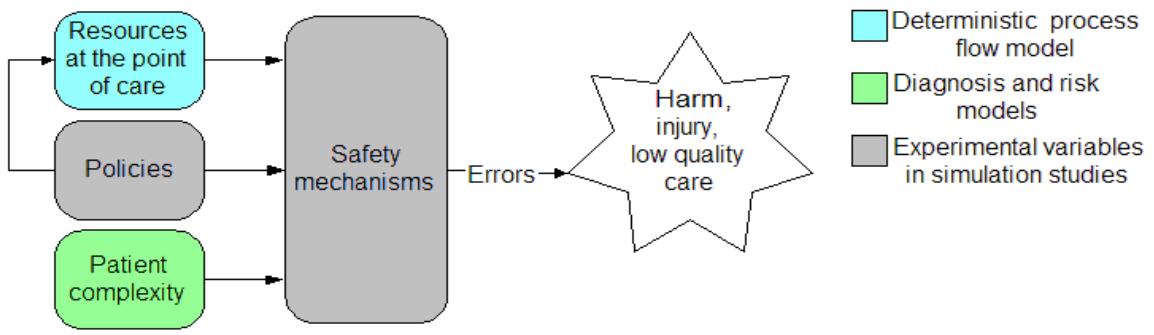

Figure 8.1: Simple model of predictors of process performance/error

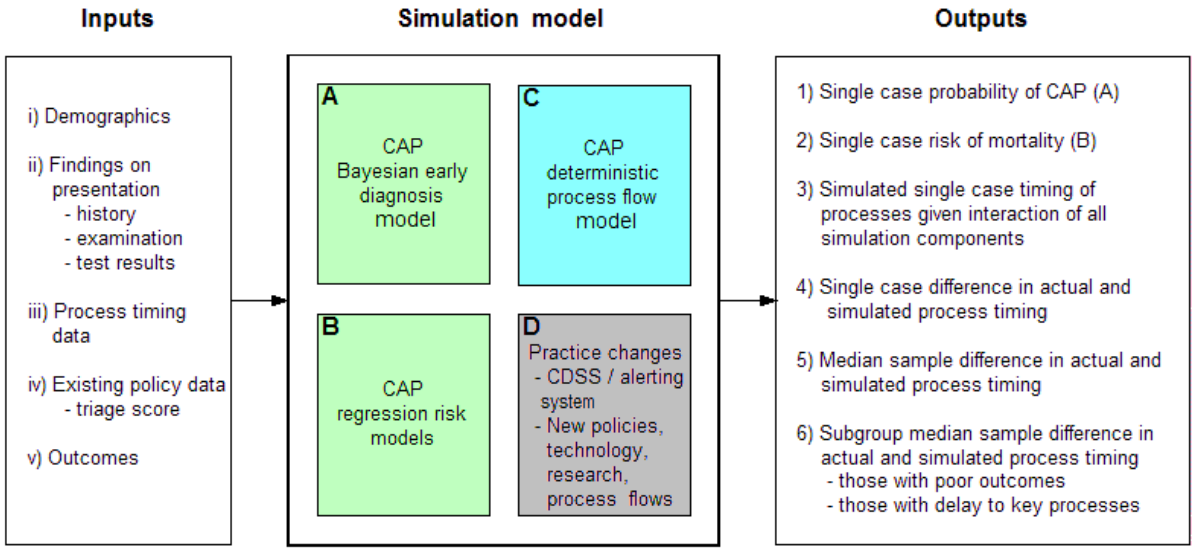

Figure 8.2: CAP alerting system simulation model

In simulation I investigated the effect of the site of computer-based decision support system (CDSS) implementation (triage vs. ED bay), the processes alerted for (investigations, treatment, or modification of triage score), and the timing of treatment (within 30 minutes of an alert or ED physician assessment, or by the time of ED discharge). I argue that the use of workflow assessment and simulation to derive practical policy produces decision support that provides a flexible care plan, sensitive to overall workflow. Such systems developed to suit local conditions are more likely to be successfully implemented.

8.2 Summary of findings in terms of hypotheses

My major hypothesis that such a system would identify enough CAP patients to reduce the simulated percentage of patients with delay to antibiotic greater than 4 hours, was supported. The percentage with treatment delay greater than 4 hours was reduced by 20%, from 61 to 41%, by

using the EDM to alert for treatment at triage. Table 8.1 summarises the findings for all hypotheses. This table is colour coded to match variables in my simple model of the predictors of process performance (see figure 8.1). Interestingly, triaging all EDM-positive patients at ATS 2, produced a similar effect to treating these patients at triage. This supported my hypothesis that increasing the urgency of triage would reduce treatment delay in simulation. A hybrid alerting system using the EDM, ED primary diagnosis, and CXR report produced the greatest reduction in antibiotic timing, as predicted. This increased sensitivity is likely to be associated with reduced specificity, given the higher false positive rates for ED diagnosis and CXR report. Site of diagnosis, site of treatment, and triage score were all significant univariate predictors of antibiotic delay, as hypothesised. A lack of evidence of CAP on initial CXR was associated with a non-CAP diagnosis in the ED, and with antibiotic delay, as predicted. The literature-based EDM approached the accuracy of a similar model generated from local data (area under the ROC curve = 0.8 vs. 0.85, respectively, difference significant at $p < 0.05$), indicating that it was a valid predictor of CAP in the local sample. Contrary to my hypothesis CAP early diagnostic variables were independent, and the model was therefore not overconfident. The sensitivity of the EDM at 36% was not equivalent to that of CXR (47% using the conservative model) as hypothesised, however the model's specificity of 93% surpassed that of CXR (85.9% using the conservative model). Mortality prediction using the ATS was less accurate than all but the local guideline CAP-specific risk model (see appendix figure 9.1), however these differences were not significant as hypothesised. The addition of a "history of renal failure" improved the performance of the CRB-65 model to be statistically equivalent to the CURB-65 model, supporting my hypothesis. The CRB-65RF was not significantly more accurate than the CRB-65.

Table 8.1: Hypotheses and findings

Shaded by predictor group: green = patient complexity, blue = resources at the point of care, grey = policy		
	Hypotheses	**Findings**
Major hypothesis	An alerting system, triggered by a CAP-specific Bayesian EDM, will reduce the simulated percentage of CAP patients with a treatment delay of greater than 4 hours.	**Supported:** an alerting system triggered by the CAP-specific EDM reduced the simulated percentage of patients treated in greater than 4 hours by 20.44% (from 61.31 to 40.87%), assuming treatment occurred within 30 minutes of an alert at triage.
Alerting simulation studies	Increasing the urgency of triage score for CAP patients identified by a Bayesian EDM will reduce the simulated percentage of patients with delay to antibiotic greater than 4 hours.	**Supported:** in workflow simulation increasing the urgency of CAP patients identified by the EDM to level 2, reduced the percentage of patients treated later than 4 hours by 20.44%, and was equivalent to treating these patients at triage.
	A hybrid alerting system combining a Bayesian EDM, ED primary diagnosis and CXR report, will provide a larger simulated decrease in the percentage of patients with delay to antibiotic greater than 4 hours, than any of these triggers alone.	**Supported:** in workflow simulation the hybrid model reduced the percentage of patients with antibiotics delayed greater than 4 hours by 22.63%. This was greater than the reduction produced by treating those identified by the EDM at triage (20.44%) or by treating those with a CAP primary diagnosis (7.3%) or a positive CXR report (3.65%) by ED discharge.
Process flow assessment	Failure to diagnose CAP in the ED will be associated with a significantly increased percentage of patients with delay to antibiotic greater than 4 hours.	**Supported:** significantly more CAP patients without a primary diagnosis of CAP had a delay to antibiotic treatment greater that 4 hours in the 2000 sample (86 vs. 45.5%, chi-square $p<<0.001$). This trend was apparent in the 1998 sample, but the difference was not significant (62.7 vs. 54.2%, chi-square $p>0.05$).
	Failure to treat CAP in the ED will be associated with a significantly increased percentage of patients with delay to antibiotic greater than 4 hours.	**Supported:** nearly all patients whose treatment occurred after ward admission had delay to treatment greater than 4 hours (1998 sample - 95.1 vs. 25.8, $p<<0.0001$; 2000 sample - 98.4 vs. 29.4%, chi-square $p<<0.0001$).
	Low urgency triage score will be associated with a significantly increased percentage of patients with delay to antibiotic greater than 4 hours.	**Supported:** the percentage of patients receiving antibiotics later than 4 hours increased with lower urgency triage score (1998 sample - Triage 1 = 25%, 2 = 43%, 3 = 65%, 4 = 63%; chi-square $p = 0.01$).

Table 8.1: Hypotheses and findings

Shaded by predictor group: green = patient complexity, blue = resources at the point of care, grey = policy		
	Hypotheses	**Findings**
Diagnostic decision studies	The absence of evidence of CAP on initial CXR will be significantly associated with a non-CAP primary diagnosis.	**Supported:** CAP diagnosis in ED was less common when there was a lack of evidence on initial CXR (2000 sample - broad radiological diagnostic criteria: sensitivity for primary diagnosis = 79.5%, specificity for primary diagnosis = 62.1%; conservative criteria: sensitivity for primary diagnosis = 60.3%, specificity for primary diagnosis = 79.8%). These differences were statistically significant at chi-square p<<0.0001.
	The absence of evidence of CAP on initial CXR will be significantly associated with antibiotic treatment delay greater than 4 hours.	**Supported:** CXR negative patients were more likely to have antibiotics delayed greater than 4 hours, significant under the broad criteria for CAP on CXR (75 vs. 56%, chi-square p = 0.043) and approaching significance under conservative criteria (65 vs. 60%, chi-square p = 0.057).
Construction and validation of the EDM	A Bayesian EDM for CAP populated with LRs from literature review will have an equivalent accuracy to one using locally derived LRs, as indicated by area under the ROC curve.	**Supported:** the area under the ROC curve was slightly greater for the local data model (0.85 vs. 0.8). This difference was statistically significant (DeLong, Delong, Clarke-Pearson ROC curve comparison method; 95% confidence interval (CI) = 0.01-0.09, standard error (SE) = 0.019, z = 2.58, p = 0.01).
	Due to dependence amongst commonly co-occurring variables, post-test probability calculated using joint LRs for CAP will be significantly less than that for combined LRs.	**Not supported:** the post-test probability calculated with joint likelihood ratios (LRs) was similar to combined LRs for these variables, thus indicating that they were independent, and that the model was not overconfident (see results table 7.20).
	A Bayesian early diagnostic model will have an equivalent or higher sensitivity for CAP than CXR.	**Not supported:** at the 0.3 threshold, the model's sensitivity of 36% approached that of local CXR report (47% using the conservative model) and ED physician judgement as indicated by primary diagnosis (54.1-56.9%). The model's specificity of 93% surpassed that of CXR (85.9% using the conservative model).
Risk decision studies	CAP-specific risk models will display higher accuracy for the prediction of CAP mortality in comparison to the ATS as indicated by a significantly larger area under the ROC curve.	**Not supported:** the ATS produced the second lowest area under the ROC curve (PSI = 0.71, CURB-65 = 0.67, CRB-65RF = 0.64, CRB-65 = 0.60, ATS = 0.56, local guideline = 0.54), however, this difference was not statistically significant using the DeLong, Delong, Clarke-Pearson ROC curve comparison method (see results table 7.23).
	Adding a historical measure of renal impairment to the CRB-65 will improve its performance closer to that of the CURB-65 model as indicated by area under the ROC curve.	**Supported:** there was no significant difference between the area under the ROC curve for CURB-65 (0.67) and the CRB-65RF (0.64) using the DeLong, Delong, Clarke-Pearson ROC curve comparison method (see results table 7.23). The CURB-65 was significantly superior to the CRB-65 (p = 0.0499). The CRB-65RF produced a larger area under the ROC curve than the CRB-65 (0.64 vs. 0.60), however this difference was not significant.

8.3 Contributions to current knowledge

Workflow in the emergency department (ED) was particularly sensitive to ATS. Cases with less urgency for treatment based on the triage scale had a longer delay to initial assessment and therefore treatment. Current triage practices, embodied mainly by the disease-independent, sign and symptom based ATS are too coarse to deal with individual, difficult to diagnose, conditions such as CAP, where diagnostic and treatment delays are critical determinants of outcomes. Better outcomes may be achieved with quicker diagnostic and treatment workflows via:

a Analysis of current diagnosis and treatment workflows.
b Analysis and correlation of a comprehensive set of patient symptoms, signs and risk factors for the specific condition.
c Improving triaging and subsequent workflow through a process alerting system driven by a disease-specific, computer-based decision support system (CDSS) based on early diagnostic models (EDMs) derived from a) and b).

The development of these techniques is the major contribution of this thesis.

These techniques have wide ranging clinical applications. Similar problems with the complexity of decision and workflow uncertainty are likely to exist in the treatment of other life threatening diseases with time critical treatment processes (e.g. percutaneous intervention for myocardial infarction without ECG changes [1]).

It is important here to note that EDMs do not have to be highly sensitive to improve workflow, given the uncertainty around CAP diagnosis and risk assessment. In simulation my system had a significant impact with a sensitivity of less than 40% for CAP diagnosis.

Using my workflow modelling methods I was able to make a number of other contributions to the understanding of CAP treatment. These include the study of CAP workflow and the predictors of antibiotic timing in an Australian hospital setting, the comparison of the ATS to CAP-specific mortality prediction models, and the assessment of the CRB-65RF, an extension of the CRB-65 CAP-specific risk model with the added variable of “history of renal failure”.

I will now discuss findings for each component of this study.

8.4 Process flow analysis

I performed qualitative workflow analysis on 1 small sample of patients with probable CAP presenting to the study site ED during October 2001, and quantitative analysis on 2 samples of CAP patients admitted to a large Australian teaching hospital in the years 1998 and 2000. The median time to antibiotic ranged between 4.6 to 5.5 hours, respectively. Over half of the patients presenting to the ED with CAP experienced delays to treatment longer than 4 hours. Time to antibiotic was greater than 4 hours in 58 to 62%, and greater than 8 hours in 21 to 36% of all patients (respectively). This supports a significant problem for quality of CAP care at this site, and places this hospital in the lowest 1-2% of performance in comparison to JCAHO/CMS hospitals in the U.S (see chapter 1). The local CAP guideline implemented prior to the 2000 sample collection did not successful reduce the number of patients with a delay to treatment greater than 4 or 8 hours.

The construction of sequence diagrams based on observation and stakeholder interview proved useful for identifying the site and context of decisions, the actors involved in processes, the ordering of processes, and the risks in information flow. Information in the ED existed mainly as loose paper-based items, which were transferred between a number of sites. Part of this transfer was carried out by untrained volunteers. These factors increase the risk that treatment could be delayed by missing information, however there was no evidence of this during observation. A recent study of information gaps in the ED showed that missing information does delay decision-making, treatment and increases time spent in the ED [355].

The responsibility for seeking out test results in the ED lay with the treating clinician, who was responsible for many patients at once. There was low redundancy around the return of important results. For example, an abnormal CXR result was returned via the same channels as a normal CXR result (either electronically or via hard copy film), with no alerting to result return. During workflow observation I noted that there were delays to radiology and laboratory result access. Unfortunately, neither time to test order or result return was readily available from either the radiology or laboratory clinical information systems (CIS). Other investigators have found significant delays in accessing test results in the ED, that impact on the timeliness of treatment. Alerting systems have been used successfully to improve result access times and are likely to have a similar impact at the study site [160, 211].

In the 1998 and 2000 CAP-positive samples correlations between care processes were low. The strongest association being between physician assessment time and ED discharge time (r = 0.36-0.41). Two factors may contribute to this relationship. Firstly, delay in assessment and discharge may reflect overall workload in the ED. When there is high workload it is likely that both time to ED physician assessment and time to discharge will be delayed. Secondly, those with low urgency triage scores may have both delayed assessment and delayed discharge due to low perceived need to treat quickly. This is consistent with my finding of an impact of triage score on all ED processes beyond the initial ED physician assessment. These hypotheses also explain the stronger positive association between ED physician assessment time and antibiotic time for those treated in the ED. This relationship is more apparent in the ED due to the long delays experienced if treatment is not commenced until after ward admission. An assessment of the association between ED workload and process performance would further clarify these findings.

There are a number of explanations for low correlations between ED physician assessment and CXR timing in the 1998 and 2000 samples. Firstly, not all CXRs were ordered while the patient was in the ED. This is supported by outlier values in the CXR timing box plots (see appendix figures 9.2 and 9.3). Secondly, there may have been delays between CXR order and CXR performance due to delays in radiology. Finally, cases with non-specific presentations are more likely to have delays to CXR order, as the differential diagnosis of chest pathology may not have been considered. The correlation between physician assessment and CXR timing in the 2000 data set was larger in those with high probability of CAP based on presenting history and examination (i.e. EDM-positive on presentation, r = 0.79 vs. 0.02 in the complete sample). Patients that were EDM-positive, and therefore had a more typical presentation, had a slightly shorter median time to CXR (1.5 vs. 1.8 hours), and a much smaller maximum time to CXR (17 vs. 152 hours). This indicates that the majority of CXR outlier times occurred in patients with a non-specific presentation. Together, these findings support that cases presenting in a non-specific manner are more likely to have long delays to CXR. This is consistent with other studies [287] [289]. An analysis of CXR order timing data would clarify this relationship.

Even when patients had a primary diagnosis of CAP and were treated in the ED there was no association between CXR time and antibiotic dose. Not all CXRs were performed whilst patients were in the ED. There were variable delays in both the assessment of CXR result and in the delivery of antibiotics. Observation and stakeholder review found at least 30 minutes delay to film availability, and 60 minutes to CXR reports for those triaged lower than 1. These timings

were sensitive to workload and shift. In quantitative process studies, median delay from ED physician assessment to CXR was 0.9 to 1.3 hours and delay from CXR to antibiotic was approximately 3.5 to 4 hours. This equates to roughly 4-5 hours delay surrounding the CXR process and subsequent decision-making. Pines et. al. [94] found the median process timing values across 2 hospital sites were as follows: ED physician assessment to CXR order - 38 minutes, CXR order to CXR performance - 66 minutes, CXR performance to CXR assessment - 61 minutes, CXR assessment to antibiotic order - 40 minutes, antibiotic order to antibiotic administration - 69 minutes. The total median delay associated with CXR was 3.4 hours, with greater than 1 hour delay from the decision to treat to antibiotic delivery. These times are roughly equivalent to my findings. An alerting system is likely to reduce the delays from CXR performance to CXR assessment, CXR assessment to antibiotic order, and antibiotic order to antibiotic treatment, if adequate resources are available.

8.4.1 CAP primary diagnosis, site of treatment and delay to treatment

ED physicians were only able to identify 54-57% of those discharged with a diagnosis of CAP. Those with a primary diagnosis of CAP had much shorter median delay to initial antibiotic (3.7-4.3 hours vs. 5.3-9.1 hours). The majority of those with a primary diagnosis of CAP were treated in the ED (63-80%). The median time to antibiotic was approximately 2.5 hours if dosing occurred in the ED, in contrast to 10 hours if given on the ward. Under 30% of those treated in ED waited longer than 4 hours, and less than 8% waited longer than 8 hours, for antibiotic treatment.

Those without a primary diagnosis of CAP were more likely to have a significant delay to treatment (> 4 hours 63-86% vs. 46-54%; > 8 hours 36 -56% vs. 21-22%). Nearly all patients whose treatment occurred after ward admission had delay to treatment greater than 4 hours (95-98%), and over half (57-67%) waited longer than 8 hours. Some cases with an alternative primary diagnosis still received antibiotics in the ED (20-37%).

Together these results suggest that, as I hypothesised, those without a diagnosis of CAP in the ED and those not treated in the ED are more likely to receive significantly delayed treatment. Observational workflow assessment and stakeholder interview supported long delays in ED waiting for a ward bed, and then further delays to assessment once on the ward. There was an exchange of responsibility from ED staff to ward staff at the point where the decision to admit to hospital was made. Following this decision the patient remained in the ED for some time,

physically removed from those responsible for their care. For those with a diagnosis of CAP in the ED, inaccurate or incomplete exchange of information at this juncture may have resulted in an oversight of the need for antibiotics by ward staff. Impediments to drug administration such as work load and antibiotic availability may have also influenced the delay to treatment at this point. Further study of the workflow between the diagnostic, treatment, and admission decisions, and the administration of antibiotic is required to assess these hypotheses.

The role for diagnostic decision-support is compelling given that nearly half of those discharged with CAP were not identified in the ED, and that those without a primary CAP diagnosis were significantly more likely to be treated late. It is interesting to note that a substantial proportion of cases with a non-CAP primary diagnosis still received antibiotics in the ED. Some of these patients are likely to have alternative infectious diagnoses such as non-pneumonic respiratory infection. An alternative possibility is that some patients may have had more than 1 illness on presentation. In these cases pneumonia may have been recognised in the ED, but another co-morbid illness listed as the primary diagnosis (e.g. the primary diagnosis atrial fibrillation may be secondary to CAP). Case note review of the treating doctors differential diagnoses and plan would help to clarify this.

8.4.2 Triage score and delay to treatment

Consistent with my hypothesis, the percentage of patients treated later than 4 hours from admission increased significantly with lower urgency triage score, from 25% for triage score 1 to above 60% in scores 3 and 4. Low urgency triage scores were associated with an increased median delay to antibiotic treatment, such that those with scores greater than 2 exceeded a median value of 4 hours. Triage 1 patients were treated in a median of 1 hour and triage 2, 2.9 hours. The median treatment time for scores 3 and 4 was approximately 5 hours. There was no consistent relationship between triage score and delay greater than 8 hours to treatment. This can be explained by the fact that the majority of patients were discharged from the ED within 8 hours. The long delays to treatment encountered after ward admission had a dilutional effect on the impact of triage score.

The ATS is designed to balance the management of risk and workload in the ED by setting targets for ED physician assessment times based on urgency of treatment. Some delay in the treatment of CAP patients at this site was associated with delay in ED physician assessment beyond ATS targets. These were only met for the triage score 1. I was able to map 2 major pathways of

care for the treatment of CAP based on triage score. Patients triaged at level 1 saw a physician immediately and received a prioritised CXR. If the patient was not stable enough for transfer to radiology, the CXR was been carried out locally in the ED. CIS data indicated that the time from ED physician assessment to CXR for triage score 1 was shorter than for triage scores 2-4, who had a similar delay to CXR time. This finding is consistent with a prioritised CXR for triage 1 patients. Increased delay to CXR and antibiotic administration with lower urgency triage score was still apparent when times were adjusted for delay to physician assessment, indicating that low urgency triage score has a delaying effect on all treatment processes in the ED, independent to the timing of initial assessment.

Together, these findings indicate that existing triage policy prevents some CAP patients from being treated within 4 hours, by delaying all treatment processes for those initially triaged as low urgency. Even though the ATS had similar mortality prediction accuracy to CAP-specific risk models, most deaths occurred in those with low urgency triage scores. This inadvertently places a large proportion of CAP patients at increased risk of mortality. A better approach would be to identify CAP earlier using an EDM, and triage individual patients based on diagnosis, or fast track their investigations and treatment. In my workflow simulation studies these methods were able to increase the percentage of patients treated within 4 hours by around 20%.

8.5 Analysis of CXR accuracy and its impact on CAP diagnosis and treatment

I investigated the accuracy of CXR based on radiology reports and determined the association between CXR result, primary diagnosis and antibiotic delivery. I hypothesised that the absence of evidence of CAP on initial CXR would be significantly associated with both a non-CAP primary diagnosis, and antibiotic treatment delay > 4 hours. Both of these hypotheses were supported.

Two models were used to identify CXR report findings consistent with pneumonia. A conservative model, using only the terms “pneumonia” and “consolidation”, and a broad model using the terms “pneumonia”, “consolidation”, “infection”, “opacity” and “shadowing”. The broad model was more sensitive (67 vs. 47%) but less specific (70 vs. 86%) for a discharge diagnosis of CAP. These results agree with current literature that despite its gold standard status, there is little evidence for high sensitivity and specificity of CXR for CAP (see chapter 1).

The broad model was less specific as it contained a number of terms which are present in both pneumonia and other respiratory diseases. Radiological evidence of infection may be present in non-pneumonic lung infection such as bronchitis, however the term consolidation is reserved for pneumonic processes. Opacity is a general term for radio-opaque areas in the lung that may be caused by fluid, masses, consolidation or a foreign body. Similarly, shadowing is a term used to indicate areas of decreased lucency. The broad model's increased sensitivity is likely to be due to the inclusion of these terms in reports that did not specifically indicate pneumonia or consolidation.

CAP diagnosis in ED was less common when there was a lack of evidence on initial CXR (broad model: sensitivity for primary diagnosis = 80%, specificity for primary diagnosis = 62%; conservative model: sensitivity for primary diagnosis = 60%, specificity for primary diagnosis = 80%). Of the 43% of CAP patients not identified in the ED in the year 2000 sample, 28 to 48% had evidence of pneumonia on initial CXR report, depending on criteria. Therefore, a significant proportion of non-CAP primary diagnoses may be associated with missed radiological evidence of CAP. I did not establish how many of these CXRs occurred whilst the patient was still in the ED. It is possible that the treating ED doctor missed the possibility of chest pathology in their differential diagnosis and therefore did not order a CXR. Another possibility is that the patient was admitted to the ward prior to the performance of CXR, even though it had already been ordered. A study of the relationship between differential diagnoses, CXR ordering and ward admission is required to answer these questions.

Many of those diagnosed with CAP in the ED lacked radiological evidence of CAP based on radiology report (21 to 40%). These patients may have been identified based either on clinical grounds alone or secondary to CXR misinterpretation. Disagreements between ED physicians and radiologists in the diagnosis of CAP are common [95, 356]. Together these results underline the difficulty in determining adequate criteria for monitoring hospital performance of antibiotic timing in CAP as outlined in chapter 3, and support a role for diagnostic decision support.

CAP patients with positive initial CXR had a lower median time to antibiotic (broad criteria: 4.8 vs. 8.3 hours; conservative criteria: 4.8 vs. 6.6 hours) and were more likely to receive antibiotics in the ED (broad criteria: 79 vs. 53%; conservative criteria: 62 vs. 39%). CXR negative patients were more likely to have antibiotics delayed greater than 4 and 8 hours, significant under the broad criteria for CAP on CXR (75 vs. 56% and 50 vs. 28%, respectively). This differ-

ence was also present under the conservative criteria (65 vs. 60% and 43 vs. 26% respectively), however, p values were slightly above 0.05. These results support a relationship between a positive CXR result and a CAP primary diagnosis; if it is not possible to identify CAP on initial CXR then it is unlikely to be diagnosed and treated in the ED.

Given CXR's low sensitivity and specificity, what is the utility of waiting for a CXR prior to treating with antibiotics in those who clearly have a lung infection based on clinical history and examination findings alone? I have previously discussed the substantial delays associated with waiting for a CXR prior to treatment. My studies are consistent with current evidence that the sensitivity and specificity of CXR are poor, and that some ED physicians do not accurately use CXR information (see chapter 1). Basi et. al. [96] have shown that patients with serious respiratory tract infections are at the same risk for mortality as those with pneumonia, regardless of evidence of consolidation on CXR. If initial CXR is inaccurate and positive radiological evidence of CAP on initial CXR has little impact on outcome, then it is potentially valid to treat those with strong clinical evidence of CAP prior to CXR. It is possible that this approach may increase the rate of antibiotic side effects such as gastrointestinal disturbances, phlebitis, reversible deafness, reversible hair loss, and urticaria [146], however the health cost of these effects must be weighed against the 15% increase in mortality associated with delayed antibiotics (see chapter 3). At many sites in the US there is evidence that patients are already being treated prior to CXR result return in an attempt to meet managed care "pay for performance" targets, with no clear formal approach to limit false positive treatment (see chapter 3). Diagnostic decision support, as developed in this thesis, offers a formally designed method to address both the sensitivity and specificity of early CAP diagnosis, thereby minimising adverse effects of false positive treatment.

8.5.1 Patient complexity and workflow pathways

Considering my findings, there are likely to be 4 major types of workflow pathway through the ED (see Table 8.2). Patients with severe illness are usually assessed, investigated, diagnosed and treated early. Those with a typical presentation usually receive the correct diagnosis early and are usually given the correct treatment. Those with low severity are more likely to experience delays in assessment, investigation, diagnosis and treatment. Low severity patients with typical presentations are less likely to have delayed diagnosis and are more likely to have correct initial treatment than low severity patients that present in an atypical fashion. These groups are important to differentiate in the process of re-engineering care. Clearly, severe presentations

that are easy to diagnose should be treated in a timely fashion. Many serious conditions present in a non-specific fashion and it is more difficult to achieve timing targets for these patients. Improving process flow is likely to have less impact on the care of this group as diagnosis is the rate-limiting factor for correct treatment. The new exclusion criteria for JCAHO/CMS CAP antibiotic timing performance measurement effectively excludes atypical presentations [66], which for my study was half of all those discharged with CAP. While this is a more achievable target it takes focus away from the need to improve CAP diagnostic processes, which is arguably more important than addressing issues with process flow.

Table 8.2: CAP treatment pathways: interaction of diagnostic and risk uncertainty

Severity	Presentation	Diagnosis time	Treatment time	Initial treatment type
High	Typical	Early	Early	Correct
	Atypical	Delayed	Early	Incorrect/ non-specific
Low	Typical	Early/ delayed	Early/ delayed	Correct
	Atypical	Delayed	Delayed	Incorrect/ non-specific

8.6 EDM construction and validation

The final version of the naive Bayesian EDM used in this study represented a compromise between predictor variables identified in the literature and those available in the local CAP database (see figure 8.3). I hypothesised that common co-occurrence of some of these variables secondary to similar underlying mechanisms would result in over confidence in the model. I found however, that the post-test probability calculated with joint likelihood ratios (LRs) was similar to combined LRs for these variables, thus indicating that they were independent, and that the model was not overconfident. I validated the literature model by comparing it to one derived from local data. At a diagnostic threshold of 0.3, the sensitivity of the literature model was superior to that of the local model (36% vs. 27%) with slightly lower specificity (93% vs. 97%). Area under the receiver operating characteristic (ROC) curve was slightly greater for the local data model (0.85 vs. 0.8, $p < 0.05$). Despite this difference reaching statistical significance, the literature model is a reasonable approximation of an optimal model for local conditions and therefore valid in this population. This supported my hypothesis that the literature model would have an equivalent area under the ROC curve.

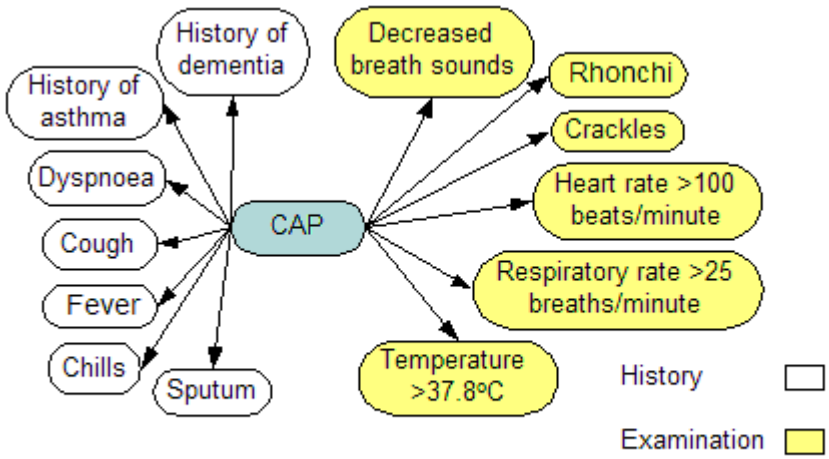

Figure 8.3: Influence diagram of early CAP diagnosis model

I selected a threshold probability of 0.3 for CAP diagnosis as this maximised the sensitivity at a high specificity. The model was poorly calibrated, with the majority of patients not exceeding a probability of 0.2. This reflects how difficult CAP is to diagnose at initial presentation. At the 0.3 threshold, the model's sensitivity of 36% approached that of local CXR report (47% using the conservative model) and ED physician judgement (including review of CXR) as indicated by primary diagnosis (54-57%). The model's specificity of 93% surpassed that of CXR (86% using the conservative model). While this does not directly support the hypothesis that the EDM would have equivalent accuracy to CXR, the literature-based EDM was able to identify 38% of those with antibiotic times greater than 4 hours and 26% of those with CXR delayed longer than 4 hours. The model also identified a close to a quarter of those who died in hospital (24%). These results indicate that EDMs can be used to target a substantial proportion of CAP patients with delayed care processes or poor outcomes. Such models could supplement rather than replace traditional diagnostic methods.

National consensus statements published in recent years have not supported CAP diagnostic modelling due to the poor sensitivity and specificity of predictors (see chapter 2). Given that diagnostic performance is currently so poor, a model with low sensitivity and high specificity is likely to provide a significant impact. Consensus groups have focused on the short comings of CAP diagnostic models at the expense of practical benefits. This is in contrast to the effort that has gone into the development of CAP-specific risk models, which are now widely implemented.

A diagnostic model need not be as sensitive as a physician to drive workflow if it is specific (i.e. it may miss cases but it does not initiate errors in treatment). Less accurate models could be used to improve workflow planning prior and supplementary to physician input, but should not replace physician review. In this way a flexible care plan could be promoted by a clinical decision support system (CDSS).

The sensitivity of my EDM is low in comparison to previously published simple CAP diagnostic models, which range from 74 to 97%. All previous studies of simple CAP diagnosis models use some form of respiratory presentation as selection criteria, and some include the performance of a CXR. Whilst these criteria may reflect the likely use of such models (i.e. they will only be used in presentations that are likely to have respiratory illness), it does not accurately indicate the possible impact on CAP care, as it excludes the proportion of patients who present in an atypical fashion (see figure 8.6 and the associated discussion). The operating characteristics for these models are therefore inflated. To avoid this bias, studies of the accuracy of CAP models in hospital should give an equal chance for all patients presenting to be included in sampling (see further discussion in section 8.9). In an attempt to do this, I included all those with an eventual discharge diagnosis of CAP in my study sample, and compared it to a control group of patients with a respiratory presentation, stratified by primary diagnosis.

I selected to optimise the specificity of the EDM to avoid false positives, given current concerns over inappropriate antibiotic use (see Chapter 3). The specificity of the CAP EDM was superior to that of other published simple models (93 Vs. 38 to 92%, see table 2.13). In past studies of simple CAP diagnostic models, high sensitivity has been generally associated with low specificity. This is due the fact that CAP shares many symptoms and signs with other respiratory diseases. The sensitivity of my CAP EDM could be improved by 7%, at a threshold probability of 0.2, if a specificity of 86% could be tolerated (see figure 7.21). This would close the gap between the sensitivity of the EDM and CXR (43 vs. 47%) and ED physician judgement (54-57%). The sensitivity of the EDM may be further improved by the inclusion of other predictor variables identified in the literature (see table 6.3), that were not available in the local CAP database. It is also possible that the EDM may be more sensitive for CAP in patients aged less than 65 years, given that elderly CAP patients are more likely to present in a non-specific fashion [81]. My estimates of the impact of a CAP EDM are thus conservative.

Large CAP diagnostic models have exceeded 90% in both sensitivity and specificity [250 264]. These models require more data input, and their output is delayed until the return of test results. This delay in decision-making, may translate to an increased risk of mortality if the total time to treatment exceeds 4-8 hours [22, 61, 63, 357]. In contrast, EDMs maximise the use of information to make earlier, evidence-based decisions. The use of such models does not preclude the gathering of further evidence for inclusion in more complex CAP diagnostic or risk models. It is conceivable that simple Bayesian EDMs could form a subset of a more comprehensive diagnostic model. Such a multi-tiered system, tailored to local workflow, could optimise the timely use of diagnostic information across the whole population of CAP patients. It is also possible that higher level models could encompass CAP and other respiratory diseases, such that low probability of one diagnosis could alert for specific investigation of other differentials, and ultimately to alerting for disease specific treatment.

There are a number of “point of care” tests, easily implemented at triage, that could be used to improve the accuracy of the EDM (e.g. pulse oximetry and urinary antigen testing, see chapter 1 for a review). The simple structure of the naive Bayesian model, using the odds ratio form of Bayes’ theorem, allows the easy addition of new variables to the diagnostic model, once data is available for LR calculation. The impact of the addition of new tests could then be calculated using my workflow simulation method.

In summary, the CAP-specific EDM was not over-confident, but was poorly calibrated, with low sensitivity at high specificity. Even at low sensitivity the model was able to accurately identify a substantial proportion of patients with delayed processes and poor outcomes. Therefore, EDMs do not need to be more sensitive than physician judgement to have the potential to impact on treatment processes. The sensitivity of the EDM may be improved by the sacrifice of some specificity, and the addition of other predictor variables.

8.7 Risk decision studies

The goal of this section of my studies was to compare the performance of the ATS to that of CAP-specific risk models, in order to select a simple model for implementation prior to investigation result return that accurately identified risk of CAP mortality. This risk model could then be used to adjust triage for those likely to have CAP. I have already discussed the delaying effect of low urgency ATS on time to all processes in CAP care. Higher urgency ATS significantly differentiated between outcomes related to cardiorespiratory failure, such as mortality, ICU ad-

mission, mechanical ventilation, respiratory failure, use of vasopressors, and heart failure. While this supports that the ATS algorithm is valid for CAP risk prediction, there were substantial rates of all complications for CAP patients in ATS 2 and 3. ATS 3 had the highest incidence of death, respiratory failure, pleural effusion, empyema and heart failure. The majority of CAP patients were coded as ATS 3. Surprisingly, there are few studies relating formal triage scores to in-hospital mortality [182]. Similar to my results, both Doherty et. al. [182], and Dent et. al. [358] found that majority of all deaths occur with lower urgency ATS.

Together these results support that ATS is not accurate at identifying emergent mortality, and that this constitutes the bulk of patients that die in hospital. The ATS has been designed with urgency or acuity of treatment across all conditions in mind [164]. Acuity of treatment is a concept different to mortality risk in that distressing conditions such as severe pain and mental illness receive high ratings on humanitarian grounds, even though they may not be directly related to death in the short term (see ATS criteria - appendix table 9.1). Serious illness such as CAP often presents with low acuity as defined in the ATS. Given that I found that delay to antibiotic treatment was associated with lower urgency ATS, it is possible that poor outcomes in these patients are associated with increased delay to antibiotic treatment.

Contrary to my hypothesis, CAP-specific risk models did not offer a statistically significant improvement over the ATS in predicting CAP mortality. Of the currently published models, the PSI had the largest area under the ROC curve at 0.71, and the CRB-65 the lowest at 0.60. The local CAP guideline model (see appendix figure 9.1) showed the worst performance at 0.54. The CRB-65RF model provided slightly superior mortality risk prediction, in comparison to the CRB-65 (0.64 vs. 0.60, respectively), but this difference was not significant. The CRB-65, but not the CRB-65RF model performed significantly worse than the PSI and the CURB-65. In contrast, the difference between CRB-65RF and the PSI or the CURB-65 was not significant. This supported my hypothesis that the addition of renal failure history to the CRB-65 would improve its performance, closer to that of the CURB-65.

The calculated area under the ROC curve for recognised CAP-specific risk models was less than that in previously published studies (0.6-0.71 vs. 0.73-0.89, see tables 7.22 and 2.8, respectively). These models were originally derived to predict 30 day mortality [128, 135], however I was only able to assess in-hospital deaths. The relationship between these risk models and mortality

may be stronger at 30 days, and there is some evidence of different causes for early and late CAP deaths [290].

In summary, triage performance at the study site gave the majority of CAP patients who developed a significant complication a lower urgency ATS, with an associated delay to treatment. Published CAP-specific risk models were not significantly superior to the ATS for mortality prediction. The addition of a history of renal failure to the CRB-65 model, improved its performance, closer to that of the CURB-65 and the PSI.

8.8 Alerting simulations

I investigated the impact of various alerting triggers and policies via simulation using the model depicted in figure 8.4, composed of a Bayesian EDM, either the local ATS score or the calculated CRB-65 score as a risk assessment, and a simple deterministic process flow model.

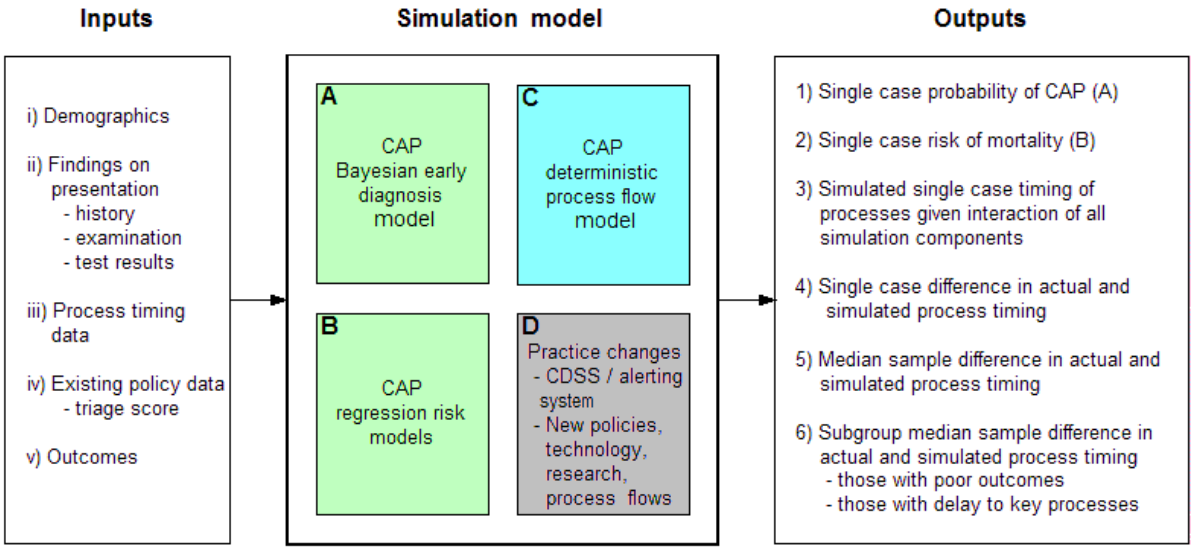

Figure 8.4: CAP alerting system simulation model

8.8.1 Simulated impact of an alerting system on antibiotic timing

In alerting simulation, the use of the EDM to trigger the CRB-65 risk model to triage patients had a minimal effect on the median time to antibiotic (0.1 hours). It also had little effect on the percentage of antibiotics given later than 4 hours (0.7%), and that given later than 8 hours (9%). This is not surprising given that there was little difference between the accuracy of the ATS and the CRB-65. Increasing the risk/urgency rating of all CAP patients appears to be a more effective method. Triaging all patients identified by the EDM at level 2 or above reduced the median time to antibiotic by 2.9 hours, the percentage of patients treated later than 4 hours by around

20%, and those treated later than 8 hours by 10% (a similar result to treating all EDM-positive patients at triage).

Treating CAP by ED discharge triggered by ED diagnosis, EDM, or CXR produced small simulated improvements in antibiotic delivery time, less than 1 hour in terms of median value. This translated to around a 4% decrease in antibiotic delay greater than 4 hours, and an 8% decrease in antibiotic delay greater than 8 hours. This is a conservative estimate of the impact of an alerting system as antibiotic treatment may occur well before ED discharge. It sets the lower bounds of what can be achieved with an alerting system given the available diagnostic techniques. If all CAP patients were able to be diagnosed in the ED and treated by the time of discharge to the ward, the median time to antibiotic would reduce by 1 hour, resulting in a reduction of delay greater than 4 hours by around 7% and greater than 8 hours by 23%. This represents the impact of an optimal diagnostic model (but not an optimal implementation as some may be treated earlier than ED discharge), not achievable with current diagnostic techniques.

Combining diagnostic trigger sources improved the simulated sensitivity of the alerting system. Treating by ED discharge if EDM-positive or ED primary diagnosis positive reduced the median time to antibiotic by 0.8 hours. The percentage of antibiotics delayed longer than 4 hours was decreased by 5%, and that delayed by greater than 8 hours by 12%. Treating by ED discharge if the ED primary diagnosis or the CXR report was positive reduced the median time to antibiotic by 0.9 hours. The percentage of antibiotics delayed longer than 4 hours was decreased by 6% and that delayed by greater than 8 hours by 11%. Given that the specificity of primary diagnosis and CXR is lower than that of the EDM, it is likely that the increased specificity comes at the price of some specificity.

Ordering CAP-specific investigations at triage for those identified by the EDM, is likely to save some delay in the timing of these processes. Combining this with alerting for treatment by ED discharge (assuming this time is shortened by the same amount) only marginally improved the simulated impact of the system over treating by ED discharge alone. Alerting for antibiotic following physician assessment in those EDM positive, assuming that patients were treated within 30 minutes of this alert, halved the median time to antibiotic to 2.8 hours. The percentage of antibiotics delayed greater then 4 hours was reduced by 20% and those greater than 8 hours delay by 10%. Alerting for antibiotics based on the EDM implemented at triage reduced simulated median time to antibiotic by 2.9 hours, the percentage of patients treated later than 4 hours ap-

proached 21%, and those treated later than 8 hours by 10%. Surprisingly, this had the same simulated effect as triaging all patients at level 2.

Combining alerting for treatment at triage based on the EDM with treatment by ED discharge for those with ED primary diagnoses improved the simulated median antibiotic delay reduction to 3.1 hours. There was an associated reduction in patients treated later than 4 hours after presentation of 22%, and in those treated 8 hours after presentation of 15%. Adding treatment by ED discharge if the CXR was positive to this model reduced the simulated median time to antibiotic by 3.3 hours. The percentage of patients with antibiotics delayed greater than 4 hours was reduced by 23% and those delayed greater than 8 hours was reduced by 18%. The use of CXR report and ED diagnosis as a trigger for the alerting system would likely reduce the specificity of the model, increasing the rate of false positives, given both these sources of information have an inferior specificity in comparison to the EDM. It is important to note that CXR reports were often not available while he patient was in the ED. Simulations using them as a trigger assume that radiology workflow could be altered to enable this.

8.8.2 Theoretical impact of an alerting system on CAP mortality

Figure 8.5 shows a plot of the hypothesised decrease in loss associated with early diagnostic and risk modelling. Treatment of CAP delayed by more than 4 hours has been associated with a 15% increased risk of mortality (see chapter 3). If the year 2000 mortality rate of 14.4% is considered to be a result of best current management, and the number of patients treated later than 4 hours is 63%, then total mortality contains 15% excess mortality associated with delayed treatment for 63% of the sample (14.4 x0.63 x 0.15 = 1.4%). Treating all patients within 4 hours would hypothetically reduce the total mortality to 13%. Given that it is desirable to minimise mortality associated with treatment delay this value can be considered as “minimum acceptable management”. I calculated that the reduction in delayed treatment achieved by using a high specificity EDM and an early risk model was around 20%. Hypothetically this equates to a reduction of total mortality of 0.43% (14.4 x 0.2 x 0.15 = 0.43%), to around 14%. This figure represents the “best management practical” given the introduction of an alerting system. The 0.43% improvement in mortality with the EDM represents the “manageability” of the CAP treatment process, given evidence-based early diagnostic alerting and risk assessment. There are over a million hospital admissions per year for CAP in the United States alone [34]. At a conservative estimate of an incidence of one million, a 0.43% reduction in mortality would result in 4300 fewer deaths in the US alone.

Interestingly, the EDM identified 24% of those who died. Further prospective study is required to determine if the specific sub-set of patients identified by the EDM are at higher risk of mortality from delayed treatment.

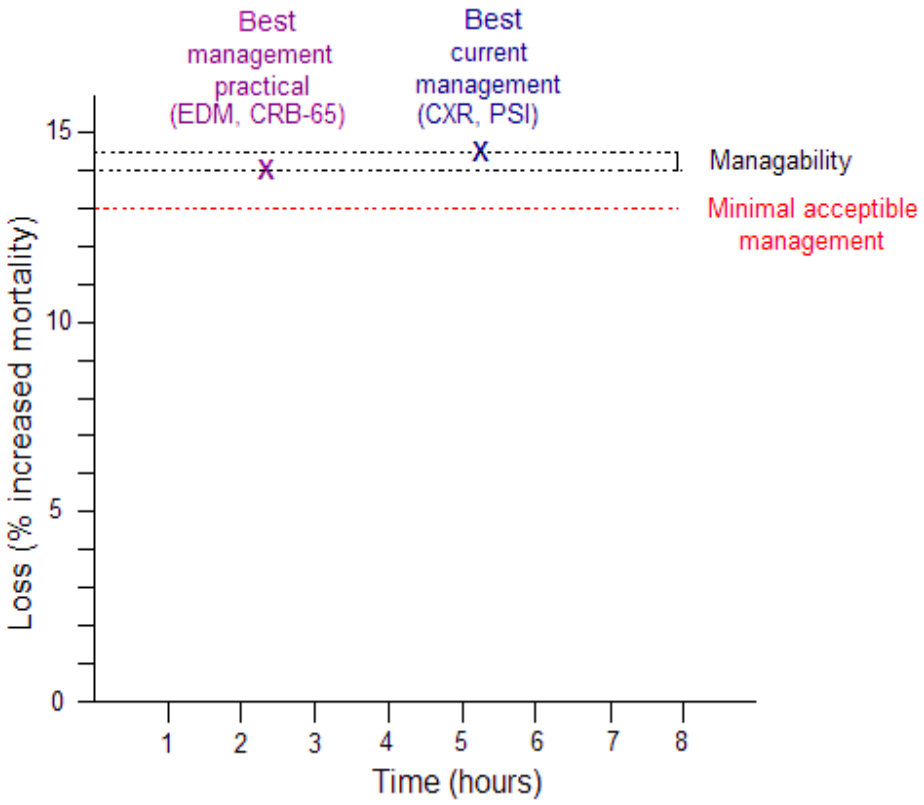

Figure 8.5: Loss model: hypothesised percentage decrease in 30 day mortality using early diagnostic and risk models

8.9 Study design limitations

This study is of a retrospective design and therefore vulnerable to confounding factors.

8.9.1 Inclusion and exclusion criteria

Restricted availability of data from the ED information system forced the selection of a CAP-negative sample from the year 2003. During this time the emergency and radiology departments at the study site were shifted into a new building and therefore the workflow was significantly modified. CAP-negative data was used only to assess the accuracy of the EDM, primary diagnosis, and CXR. It is unlikely that the change in geographical location significantly affected the process of history taking, physical examination and documentation. It is possible that changes in radiology equipment or processes altered the accuracy of radiological diagnosis in the 2003 sample, in comparison to the year 2000 sample. Bias may also exist if some systematic variation in the quality of ED and radiology staff occurred between the two time points. The 2003 CAP-

negative sample was randomly selected, stratified by primary diagnosis, from non-CAP patients aged 65 and over, presenting with respiratory symptoms listed as presenting complaints. The sample had similar illness severity to the year 2000 cohort, as indicated by triage score. I believe the sampling process limited selection bias, whilst controlling the representativeness of the sample in terms of presenting non-CAP diagnoses. The sample stratification was not, however, matched exactly to the proportion of each diagnosis in the total sample. A significant amount of time has elapsed since the study data was collected. It is possible that practice changes over this period have caused some alteration in process timing at the study site. It is likely these would only make relative and not absolute changes to the results, and therefore this delay to publication is unlikely to affect the study conclusions. The diagnostic process remains unchanged.

Subjects in the local CAP database were admitted to a ward and were identified using their principle ICD-9 discharge diagnosis code. CAP is generally differentiated from pneumonia in the immunosuppressed, if aspiration is suspected, or if pneumonia was likely acquired in hospital. These definitions are made based on likely aetiology, outcomes and empirical treatment (see chapter 1). There are no ICD codes that differentiate between these types of pneumonia, and therefore CAP is usually separated on the basis of exclusion criteria [359]. ICD codes do not identify all likely cases of CAP. Errors in discharge diagnosis coding may occur in the diagnostic process, medical record keeping, filling the discharge abstract form by the treating physician, and interpretation by the coding clerk [360]. Cases with a high number of comorbidities or longer admissions with multiple complications are more likely to receive false-negative codes [359, 360]. In these presentations the admission may be attributed to a confounding comorbidity or complication.

Approaches that combine principle and secondary ICD-9 discharge diagnosis codes, and those that also include clinical diagnosis algorithms are more accurate than relying on principle diagnosis code alone [359-361]. For example, Whittle et. al. [359] found that in comparison to chart review, principle ICD discharge diagnosis was 84% sensitive and 86% specific. Sensitivity was improved to 89%, and specificity reduced to 80%, with the use of an algorithm consisting of multiple discharge codes and clinical findings. Aronsky et. al. [361] point out that medical record review is able to exclude false positives but not false negatives, if discharge codes alone are used to select cases. This “verification bias” is present if the whole population of subjects (i.e. ED presentations) doesn’t have an equal chance of CAP diagnosis. These authors performed a

large prospective study of all presentations to a large ED over a 6 month period (n=10828). They used a comprehensive approach to identify CAP cases including presenting complaint, a diagnosis model consisting of findings from the history, examination signs, blood tests, and CXR results, and case note review. They found that sensitivity (54.8-69.8%) was lower and specificity higher (98.9-99.1) for 3 ICD-9 pneumonia code groups, in comparison to other studies. These findings support a significant rate of false negatives when CAP is identified on the basis of ICD codes alone, and are similar to the lower sensitivity values for ICD-9 codes found in comparisons of CAP patients identified for drug trials using clinical criteria (57-72%) [360, 362].

Figure 8.6 graphically summarises the problems in defining pneumonia presentations to the ED. My study has highlighted that there are a number of pathways to CAP diagnosis and treatment. In this diagram I have differentiated between atypical and typical presentations. Typical presentations being those that present with clinical history and signs consistent with pneumonia, and are positive on initial CXR in ED. Atypical presentations may still receive a primary or discharge diagnosis of CAP if they present without typical clinical findings, and receive a CXR for another reason (e.g. a septic screen in a febrile patient with altered consciousness), or if they develop typical clinical findings later in the admission. It is important to note that there are both false-positives and false-negatives for physician interpretation of the history, examination, and CXR. CAP study inclusion criteria are variable and including administrative codes such as primary and discharge diagnosis, specific CAP-associated clinical criteria (e.g. consolidation, fever, etc.), broad clinical criteria (e.g. “respiratory illness”), and CXR result (current “gold standard”). Study designs that include only patients that are admitted to hospital are likely to exclude less severe cases and those misdiagnosed in the ED. Studies that select on the basis of primary diagnosis are likely to miss around half the cases that present given my findings. These are most likely those that present in an atypical fashion.

In using ICD-9 codes it is likely that my study has excluded some atypical presentations of CAP. My study was also restricted to patients that were admitted to a hospital ward. Cases in the CAP database were reviewed by the hospital’s Quality and Safety Unit staff to exclude false positives. Unlike many studies of antibiotic delay I included cases with long delays to CXR and to antibiotic treatment, and cases without initial CXR evidence. In doing so I hoped to include the majority of atypical presentations. This partially explains the low sensitivity of the CAP-specific EDM. Despite verification bias and coding errors, ICD codes are easily available and

will probably remain the mainstay of this type of research given the cost of implementing detailed prospective trials.

Most studies of CAP outcome have used 30 day mortality as a major outcome. Studies that use 30 day mortality rather than in-hospital mortality are more likely to include a higher proportion of mortality that is not related to the pneumonia itself. Mortensen et. al. [290] were able to divide the cause of death into CAP-related and CAP-unrelated groups. These authors found that mortality not related to CAP increased as a proportion of total mortality with time, up to 90 days after presentation. They found that older patients (i.e. those over 65 years) were more at risk of common causes of CAP unrelated mortality such as malignancy and cardiac disease at 30 days and beyond. This complicates any inferences made about the association between CAP treatment and mortality. Only in-hospital mortality was measured in this study.

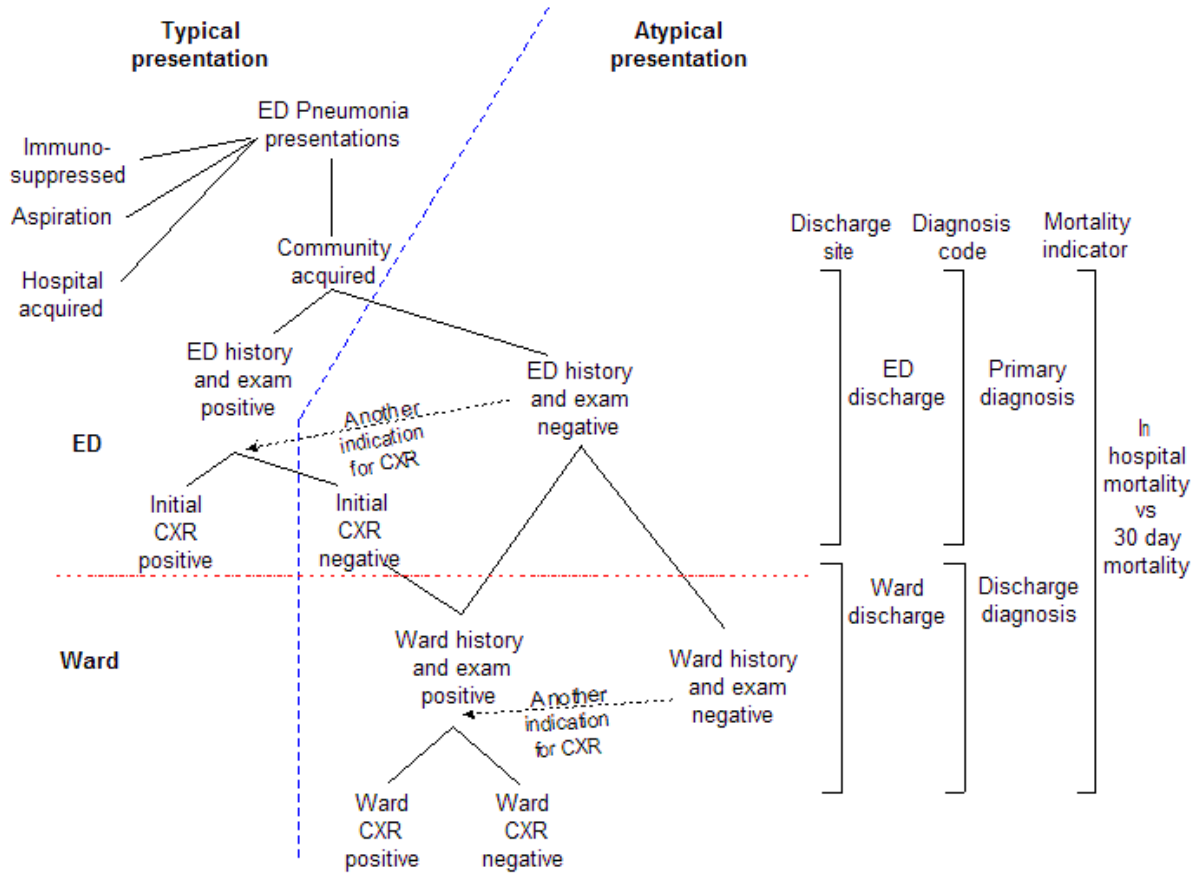

Figure 8.6: Sample selection bias map

8.9.2 Study data availability and reliability

The majority of coding of clinical data was performed by members of the study hospital's Quality and Safety Unit with the goal of assessing the performance of a local CAP guideline (see

appendix figure 9.1). I was not able to assess the inter-rater reliability of this coding as has been performed in similar studies of CAP processes. One study has shown that the adjusted Kappa value for antibiotic timing is moderate (0.74 for treatment within 8 hours) [363]. This is not surprising given that most treatment processes are logged manually on loose drug charts and in case notes, and are therefore subject to human error, or may be lost from the case notes.

The completeness of both risk and diagnosis modelling was limited by the variables in the database. The data available was extensive, however there were 2 variables missing from calculations of both the PSI ("nursing home resident" and "haematocrit") and the local guideline risk model ("nursing home resident" and "mechanical ventilation required") see appendix figure 9.1). These risk scores were calculated assuming missing variables were normal as is common practice in previous studies [232]. Diagnostic modelling was also limited to the variables available.

8.9.3 Simulation design

Workflow simulation in this study was deterministic in nature and did not consider the effects of all factors likely to affect process timing distributions. I assumed that treatment within 30 minutes of an alert was a reasonable delay. Factors such as staff availability and experience, and the interaction between different departments are likely to impact on the minimum time to processes. The representativeness of median values for each process time could be assessed in more detailed modelling studies that consider the impact of other predictors of resource availability at the point of care. My approach represents a method to handle the complexity of the interaction between these process flow factors and patient uncertainty, and therefore complex process flow modelling was not performed. A comparison of my methods to a more detailed discrete event model (see chapter 4) of CAP care would clarify this.

8.9.4 The association between antibiotic timing and mortality

I did not find increased rates of mortality with delay to initial antibiotic treatment for CAP. Instead those who died were more likely to be treated earlier than other patients. This indicates that patients of high severity CAP, that were at greater risk of dying, were identified and treated early at this site. The majority of studies linking antibiotic delay to outcomes have been much larger studies, measuring the association between antibiotic timing and 30 day mortality (see chapter 3). This study is likely not powered to assess this relationship and used in-hospital mortality as the outcome measure.

8.9.5 Conclusions on study design

All of the above mentioned design issues with this simulation study could be addressed in a prospectively designed case-control study including the required variable set, adequately powered to find a 15% increased risk of mortality in those presenting to an ED with CAP. The sample should include a cohort of all patients presenting to ED, and CAP patients should be identified by a multifactorial model including ICD codes and clinical findings. Obviously, a clinical trial of an alerting system using the EDM, would provide the best evidence of its utility. These issues aside, my study shows the power of linking data available in local CIS, and clinical findings and process performance indicators gleaned from casenote review. At most sites this data remains isolated in separate repositories, with little value added.

8.10 Future work

I have identified a number of areas for further research of workflow in CAP care. One of the major problems is the lack of a true gold standard for diagnosis. This leads to difficulties in the identification of cases and therefore study design. A greater understanding and acknowledgement of the operating characteristics of the CXR is essential to the understanding of delays in processes - it is not possible to treat CAP without identifying it.

Despite claims that it is not possible to accurately identify CAP aetiology based on history and non-microbiological findings, multivariate models may assist in targeting subsets of patients with high probability of specific pathogens based on these findings. Models have been derived to differentiate between specific CAP aetiology, such as typical bacterial, atypical bacterial, and viral pathogens [11, 364-368]. My workflow simulation technique provides the ability to explore the utility of these models for the diagnosis of CAP aetiology. The combination of aetiology models with new diagnostic investigations, such as antigen and PCR testing, may provide more accurate early antibiotic selection. Evidence for the selection of empirical antibiotics is largely based on in-vitro studies, inferred to local aetiology. Adequate clinical trials that provide data to differentiate between antibiotic groups are long overdue, but are unlikely to be conducted without public funding.

More attention needs to be paid to the outcome measures for CAP treatment. The relationship between delayed treatment and cause of mortality is not currently clear, and there are significant CAP outcomes other than mortality. Risk modelling that considers these factors may be of more

use than those focused on 30 day mortality, particularly for predicting load on other services such as intensive care [136].

It is clear from my study that current triage mechanisms inhibit the ability to treat CAP in a timely fashion. Further simulation of triage systems is required to assess the best way to balance resources. The majority of CAP mortality and complications occur in the middle urgency triage scores. This indicates that treatment is not deemed as urgent at presentation and poor outcomes are emergent. A worthy target for further modelling would be to identify predictors of patients with poor emergent outcomes that present as less severe.

My process flow model could be improved by the inclusion of test order, availability and review times, and treatment order times. Analysis of these process times should give a more detailed understanding of how alerting may impact on treatment time.

A trial implementation of an alerting system based on the my model would help answer questions around the validity of the use of median values in simulation studies, and the overall impact of the system.

There are a number of significant issues in CDSS implementation and integration into existing legacy systems (discussed in chapter 4). Given that EDMs and early risk models only require the entry of limited data, a stand alone CDSS connected to an alerting device may be sufficient. To automatically monitor the downstream effect on processes however, requires a higher level of integration of legacy systems (e.g. patient management, radiology and laboratory information systems). In this case using web services with extensible mark-up language (XML) messaging could allow data integration. A combination of bayesian models with event-condition-action (ECA) rules could be used to represent the decision support component. Process monitoring could be assisted by a capacity for order entry and monitoring of antibiotic delivery using bar codes, radio frequency identification tags, or menu driven interfaces [331].

8.11 Conclusions

My major hypothesis that an alerting system, based on a CDSS, composed of a CAP-specific early diagnostic model (EDM) and a simple risk model, would reduce the simulated percentage of CAP patients with a treatment delay of greater than 4 hours was supported. The alerting system was designed taking into account the major aspects of workflow: patient complexity, re-

sources at the point of care and local policy. It thus represents an implementable flexible care plan for CAP treatment, that has a higher likelihood of local success than a previously implemented paper-based guideline, which failed to improve the timing of antibiotic delivery.

The minor hypotheses of an effect of triage score, site of administration, and primary diagnosis on timing to initial antibiotic were all supported. My prediction that an EDM for CAP would be as accurate as CXR was not upheld, however, its accuracy approached that of CXR and simulation studies indicated that an alerting system based on this model would still have an impact on antibiotic timing in patients with delayed antibiotics and poor outcomes. Against my predictions, CAP-specific risk models showed no advantage over the ATS in predicting mortality. Increasing the triage score to 2 for EDM-positive patients produced simulated reductions in antibiotic timing equivalent to treating all those EDM-positive at triage. This indicates that changing the way staff respond to CAP, rather than improved risk assessment would reduce antibiotic delays.

Current triage practices, embodied mainly by the disease-independent, sign and symptom based ATS are too coarse to deal with individual, difficult to diagnose, conditions such as CAP, where diagnostic and treatment delays are critical determinants of outcomes. Better outcomes may be achieved with quicker diagnostic and treatment workflows via:

a Analysis of current diagnosis and treatment workflows.
b Analysis and correlation of a comprehensive set of patient symptoms, signs and risk factors for the specific condition.
c Improving triaging and subsequent workflow through a process alerting system driven by a disease-specific, computer-based decision support system (CDSS) based on early diagnostic models (EDMs) derived from a) and b).

These techniques have wide ranging clinical applications. Similar complexity in the interaction of decision and workflow uncertainty is likely exist in the treatment of other life threatening diseases with time critical treatment processes.

My modular method of workflow simulation combining simple targeted models to account for aspects of workflow provides a unique, flexible approach to designing practical health care interventions. Initial qualitative workflow modelling, using sequence diagrams, allowed the rep-

resentation of the complexity of process flow, and identified redundant and inefficient information transfer. Qualitative process flow modelling then allowed the use of simulation to assess the impact of interventions designed to reduce the uncertainty around decisions.

The cost of implementing change in clinical practice is significant, in terms of health dollars, time and also the unintended effects of interventions. The recent, well documented, problems encountered in the implementation of a 4 hour treatment rule for CAP by JCAHO/CMS in the United States, provides clear evidence of the cost of implementing untested policies. This policy has effectively reduced the specificity of antibiotic treatment in the ED by setting a target beyond the reach of current diagnostic sensitivity and workflow. Policy development may have taken a different track if studies similar to those conducted in this thesis were performed prior to roll-out. Simple analyses of process quality indicators is inadequate for practice intervention design, as workflow within the ED is highly complex.

9 Appendix

Table 9.1: Australasian Triage Score (ATS) rules

ATS category	Response	Description of Category	Clinical Descriptors (indicative only)
1	Immediate: simultaneous assessment and treatment	Immediately life-threatening (conditions that are threats to life, or imminent risk of deterioration and require immediate aggressive intervention)	Cardiac arrest
			Respiratory arrest
			Immediate risk to airway - impending arrest
			Respiratory rate <10/min
			Extreme respiratory distress
			Blood pressure < 80 systolic (adult) or severely shocked child/infant
			Unresponsive or responds to pain only (GCS < 9)
			Ongoing/prolonged seizure
			IV overdose and unresponsive or hypoventilating
			Severe behavioural disorder with immediate threat of dangerous violence

Table 9.1: Australasian Triage Score (ATS) rules

ATS category	Response	Description of Category	Clinical Descriptors (indicative only)
2	Assessment and treatment within 10 minutes	Imminently life-threatening (the patient's condition is serious enough or deteriorating so rapidly that there is the potential of threat to life, or organ system failure, if not treated within ten minutes of arrival), or potential for time-critical treatment to make a significant effect on clinical outcome depends on treatment commencing within a few minutes of the patient's arrival in the ED, or very severe pain (humane practice mandates the relief of very severe pain or distress within 10 minutes)	Airway risk - severe stridor or drooling with distress
			Severe respiratory distress
			Circulatory compromise: clammy/mottled skin, poor perfusion, heart rate < 50 or > 150, hypotension with haemodynamic effects, severe blood loss
			Very severe pain - any cause
			BSL < 2 mmol/l
			Drowsy, decreased responsiveness - any cause (GCS< 13)
			Acute hemiparesis/dysphasia
			Fever with signs of lethargy
			Acid or alkali splash to eye requiring irrigation
			Major multi trauma requiring rapid organised team response
			Severe localised trauma - major fracture, amputation
			High-risk history: significant sedative or other toxic ingestion, significant/dangerous envenomation; severe pain suggesting pulmonary embolism, abdominal aortic aneurysm, or ectopic pregnancy
			Behavioural/psychiatric: violent or aggressive, immediate threat to self or others, requires or has required restraint, severe agitation or aggression

Table 9.1: Australasian Triage Score (ATS) rules

ATS category	Response	Description of Category	Clinical Descriptors (indicative only)
3	Assessment and treatment start within 30 minutes	Potentially life-threatening (the patient's condition may progress to life or limb threatening, or may lead to significant morbidity if assessment and treatment are not commenced within thirty minutes of arrival), or situational urgency (there is potential for adverse outcome if time-critical treatment is not commenced within thirty minutes), or humane practice mandates the relief of severe discomfort or distress within thirty minutes	Severe hypertension
			Moderately severe blood loss - any cause
			Moderate shortness of breath
			SAO2 90 - 95%
			BSL >16 mmol/l
			Seizure (now alert)
			Any fever if immunosuppressed e.g. oncology patient, steroid treatment
			Persistent vomiting
			Dehydration
			Head injury with short loss of consciousness - now alert
			Moderately severe pain - any cause, requiring analgesia
			Chest pain likely non-cardiac and of moderate severity
			Abdominal pain with high risk features - moderate to severe, patient age > 65 years
			Moderate limb injury - deformity, severe laceration, crush
			Limb - altered sensation, acutely absent pulse
			Trauma - high-risk history with no other high-risk features
			Stable neonate
			Child at risk
			Behavioural/psychiatric: very distressed, risk of self-harm, acutely psychotic or thought disordered, or situational crisis, deliberate self harm, agitated / withdrawn, potentially aggressive

Table 9.1: Australasian Triage Score (ATS) rules

ATS category	Response	Description of Category	Clinical Descriptors (indicative only)
4	Assessment and treatment start within 60 minutes	Potentially serious (the patient's condition may deteriorate, or adverse outcome may result, if assessment and treatment is not commenced within one hour of arrival in ED), or symptoms moderate/ prolonged, or situational urgency (there is potential for adverse outcome if time-critical treatment is not commenced within hour), or significant complexity/severity (likely to require complex work-up and consultation and/or inpatient management), or humane practice mandates the relief of discomfort or distress within one hour	Mild haemorrhage
			Foreign body aspiration, no respiratory distress
			Chest injury without rib pain or respiratory distress
			Difficulty swallowing, no respiratory distress
			Minor head injury, no loss of consciousness
			Moderate pain, some risk features
			Vomiting or diarrhoea without dehydration
			Eye inflammation or foreign body - normal vision
			Minor limb trauma - sprained ankle, possible fracture, uncomplicated laceration requiring investigation or intervention, normal vital signs, low/ moderate pain
			Tight cast, no neurovascular impairment
			Swollen “hot” joint
			Non-specific abdominal pain
			Behavioural/psychiatric: semi-urgent mental health problem, under observation and no immediate risk to self or others
5	Assessment and treatment start within 120 minutes	Less urgent (the patient's condition is chronic or minor enough that symptoms or clinical outcome will not be significantly affected if assessment and treatment are delayed up to two hours from arrival), or clinico-administrative problems (result review, medical certificates, prescriptions only)	Minimal pain with no high risk features
			Low-risk history and now asymptomatic
			Minor symptoms of existing stable illness
			Minor symptoms of low-risk conditions
			Minor wounds - small abrasions, minor lacerations (not requiring sutures)
			Scheduled revisit e.g. wound review, complex dressings
			Immunisation only
			Behavioural/psychiatric - known patient with chronic symptoms, social crisis, clinically well patient

NOTE:
This guideline is included on page 222 of the print copy of the thesis held in the University of Adelaide Library.

Figure 9.1: Local CAP guideline

Table 9.2: Principle ICD-9 CAP discharge diagnoses

Principle Diagnosis (ICD-9)	CAP-positive patients: June to December 1998 (% total)	CAP-positive patients: May to December 2000 (% total)	CAP-negative patients: 2003 (% total)
Pneumonia organism unspecified	219 (81.7)	102 (69.9)	0
Lobar pneumonia organism unspecified	0	37 (25.3)	0
Bronchopneumonia organism unspecified	7 (2.6)	3 (2.1)	0
Pneumonia due to *Streptococcus pneumoniae*	10 (3.7)	0	0
Pneumonia due to *Mycoplasma pneumoniae*	7 (2.6)	0	0
Pneumonia due to other aerobic gram negative bacteria	7 (2.6)	0	0
Pneumonia due to *Haemophilus influenzae*	7 (2.6)	0	0
Pneumonia due to Pseudomonas	4 (1.5)	1 (0.7)	0
Pneumonia due to *Klebsiella pneumoniae*	2 (0.7)	1 (0.7)	0
Viral pneumonia unspecified	2 (0.7)	0	0
Adenoviral pneumonia	1 (0.4)	0	0
Pneumonia due to other streptococci	1 (0.4)	1 (0.7)	0
Pneumonia due to staphylococcus	1 (0.4)	1 (0.7)	0
Chronic obstructive airways disease	0	0	23 (31.1)
Respiratory tract infection (non pneumonic)	0	0	12 (16.2)
Atrial fibrillation	0	0	8 (10.8)
Asthma	0	0	8 (10.8)
Heart failure	0	0	7 (9.5)
Pulmonary embolism	0	0	5 (6.8)
Chest pain	0	0	2 (2.7)
Dyspnoea	0	0	2 (2.7)
Bronchiectasis	0	0	1 (1.4)
Cellulitis	0	0	1 (1.4)
Ischaemic heart disease	0	0	1 (1.4)
Musculoskeletal	0	0	1 (1.4)
Pulmonary hypertension	0	0	1 (1.4)
Pericarditis	0	0	1 (1.4)
Urinary tract infection	0	0	1 (1.4)
Total	268 (100)	146 (100)	74 (100)

Table 9.3: Primary diagnoses made in the Emergency Department

ED diagnosis	CAP-positive patients: June to December 1998 (% total)	CAP-positive patients: May to December 2000 (% total)	CAP-negative patients: 2003 (% total)
Pneumonia	133 (54.1)	78 (54.2)	0
Respiratory tract infection	29 (11.7)	16 (11.1)	10 (13.5)
Viral infection / common cold / influenza	2 (0.8)	1 (0.7)	5 (6.8)
Bronchiectasis	0	1 (0.7)	0
Chronic obstructive airways disease	8 (3.3)	7 (4.9)	11 (14.9)
Asthma / wheezing	3(1.2)	1 (0.7)	11 (14.9)
Pulmonary embolism	1 (0.4)	3 (2.1)	9 (12.2)
Respiratory failure	2 (0.8)	1 (0.7)	7 (9.5)
Lung mass / cancer	2 (0.8)	1 (0.7)	0
Pleural effusion	5 (2)	1 (0.7)	0
Dyspnoea	3 (1.2)	1 (0.7)	0
Chest pain	9 (3.6)	2 (1.4)	0
Fever	1 (0.4)	2 (1.4)	0
Sore throat	0	1 (0.7)	0
Cardiac failure	9 (3.6)	4 (2.8)	9 (12.2)
Arrythmia / atrial fibrillation	2 (0.8)	4 (2.8)	12 (16.2)
Myocardial infarction	1 (0.4)	2 (1.5)	0
Angina	6 (2.4)	1 (0.7)	0
Cerebrovascular accident	0	3 (2.1)	0
Central nervous system disorder / multiple sclerosis	1 (0.4)	1 (0.7)	0
Gastrointestinal: haematemasis / abdominal pain / constipation / hepatitis	4 (1.6)	1 (0.7)	0
Social / acopia	1 (0.4)	2 (1.5)	0
Peripheral oedema	0	1 (0.7)	0
Fracture	1 (0.4)	1 (0.7)	0
Dehydration	3(1.2)	1 (0.7)	0
Missing	20 (8.1)	7 (4.9)	0
Total	246	144	74

Table 9.4: Presenting complaints of 2003 CAP-negative sample

Presenting complaint	n (% total)
Dyspnoea alone	39 (52.7)
Chest pain alone	10 (13.5)
Chest pain and dyspnoea	6 (8.1)
Dyspnoea and cough	3 (4.1)
Chest pain and atrial fibrillation	2 (2.7)
Dyspnoea and fever	1 (1.4)
Dyspnoea and abdominal pain	1 (1.4)
Dyspnoea and wheeze	1 (1.4)
Dyspnoea and atrial fibrillation	1 (1.4)
Dyspnoea and asthma	1 (1.4)
Dyspnoea and COAD	1 (1.4)
Chest pain and abdominal pain	1 (1.4)
Dyspnoea and pulmonary embolism	1 (1.4)
Cough and fever	1 (1.4)
Pulmonary embolism	1 (1.4)
Dyspnoea and fall	1 (1.4)
Dyspnoea and pneumonia	1 (1.4)
Chest pain and pulmonary embolism	1 (1.4)
Chest pain and cough	1 (1.4)
Total	74 (100)

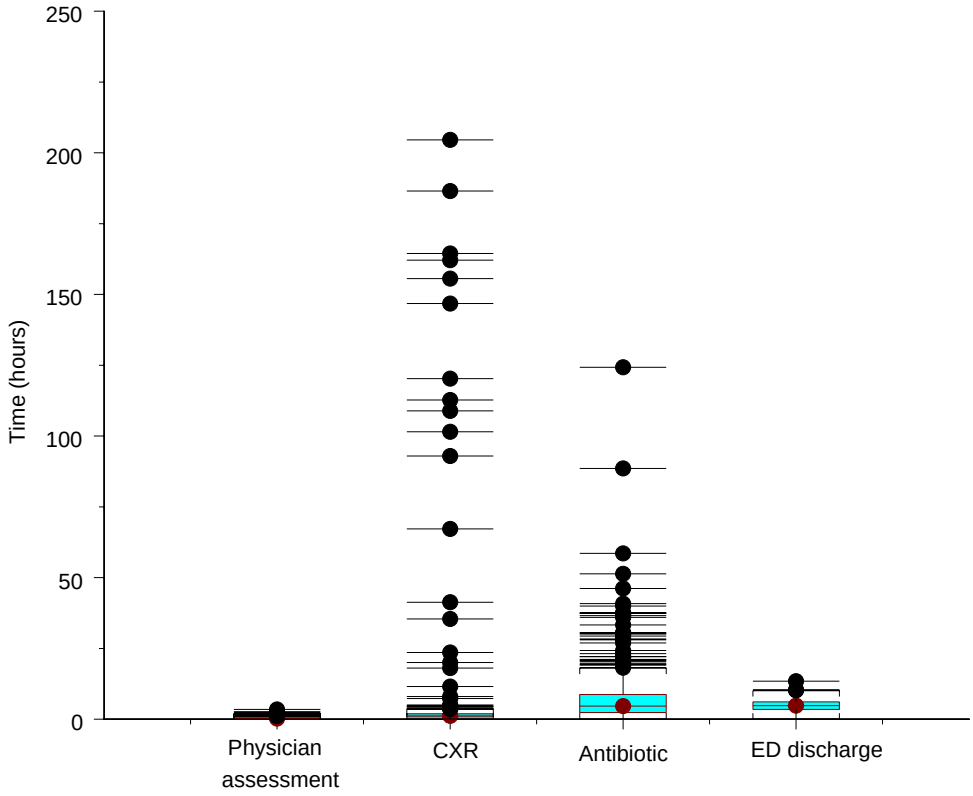

Figure 9.2: Distribution of key process timings with outliers - 1998 sample

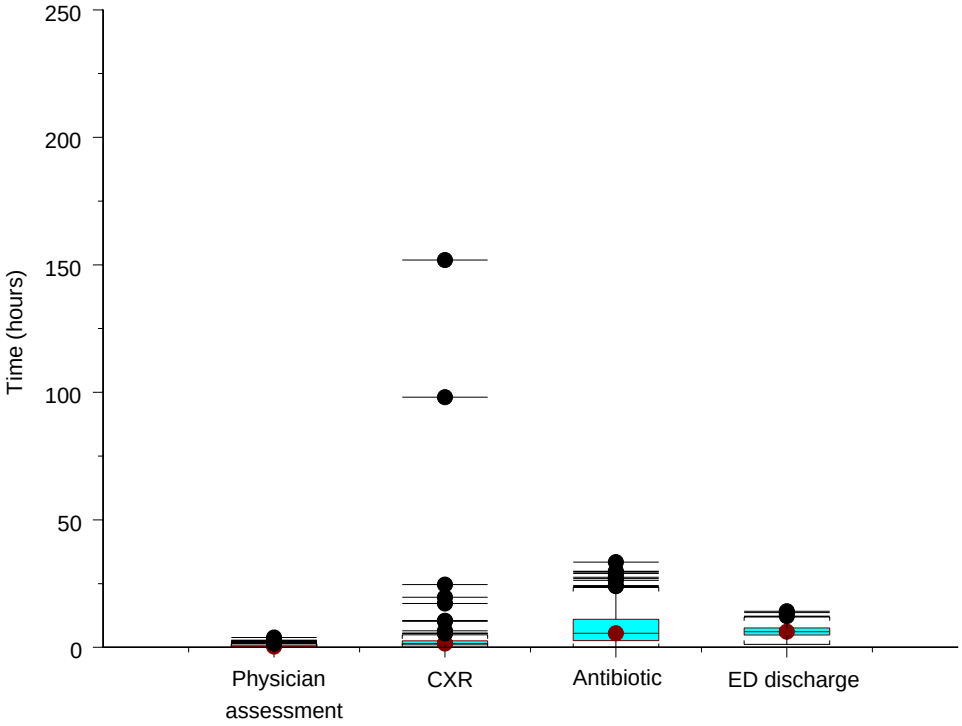

Figure 9.3: Distribution of key process timings with outliers - 2000 sample

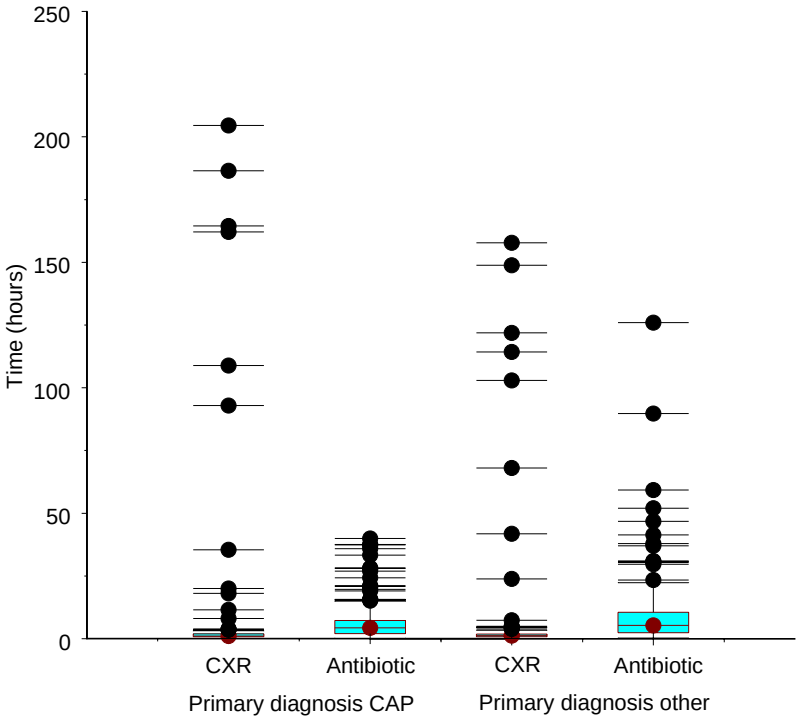

Figure 9.4: Distribution of timings by primary diagnosis with outliers - 1998 sample

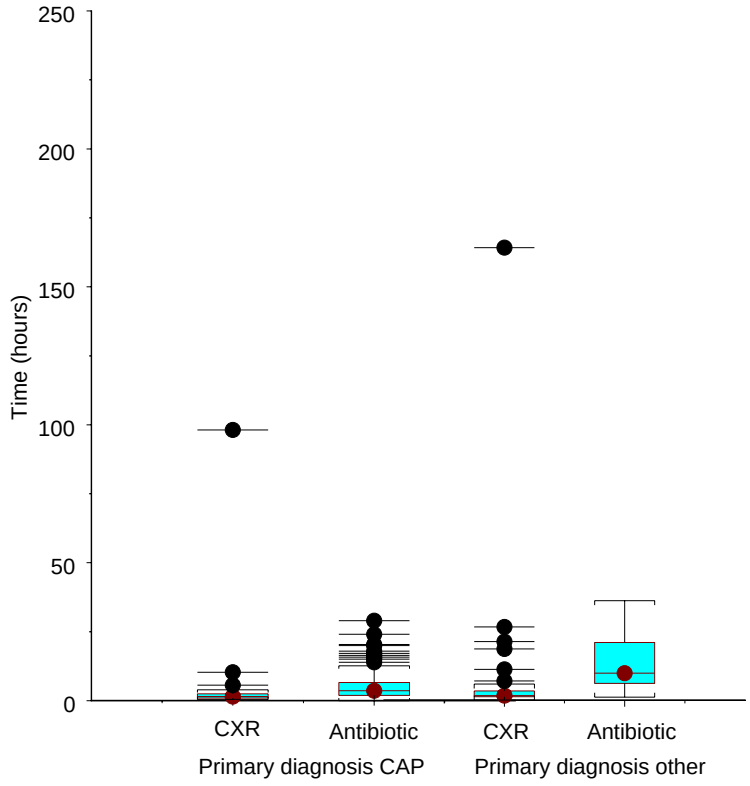

Figure 9.5: Distribution of timings by primary diagnosis with outliers - 2000 sample

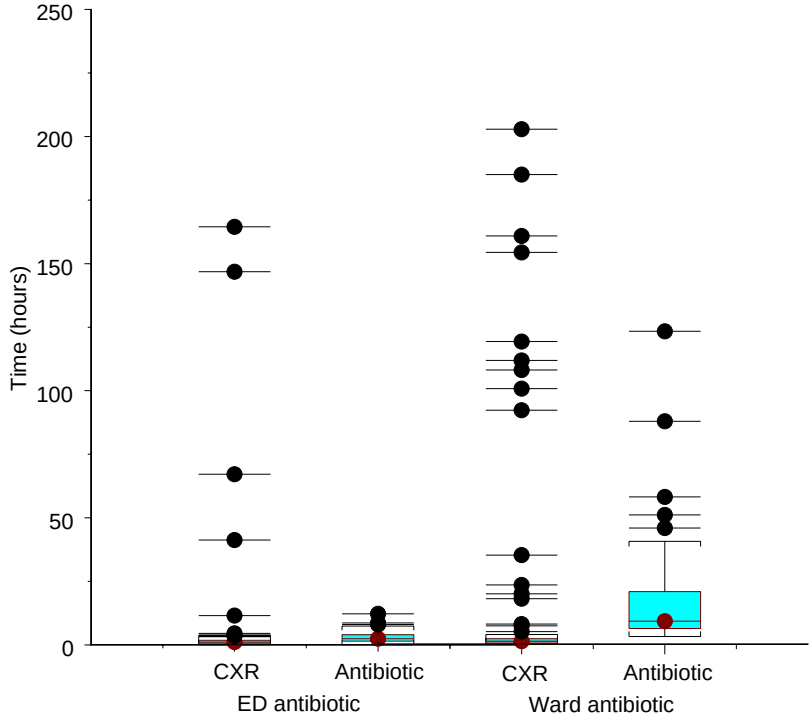

Figure 9.6: Distribution of process timings by antibiotic site with outliers - 1998 sample

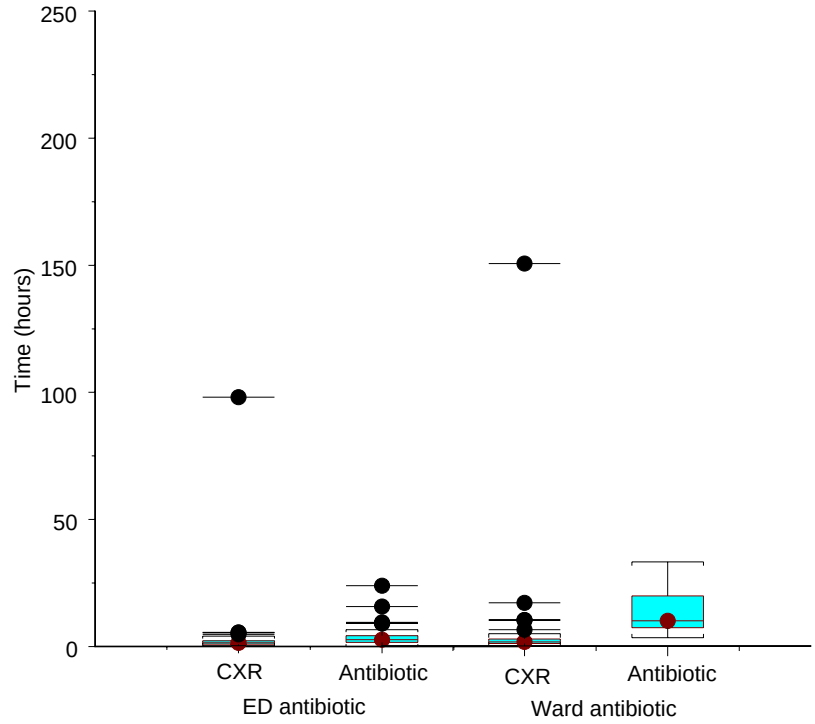

Figure 9.7: Distribution of process timings by antibiotic site with outliers - 2000 sample

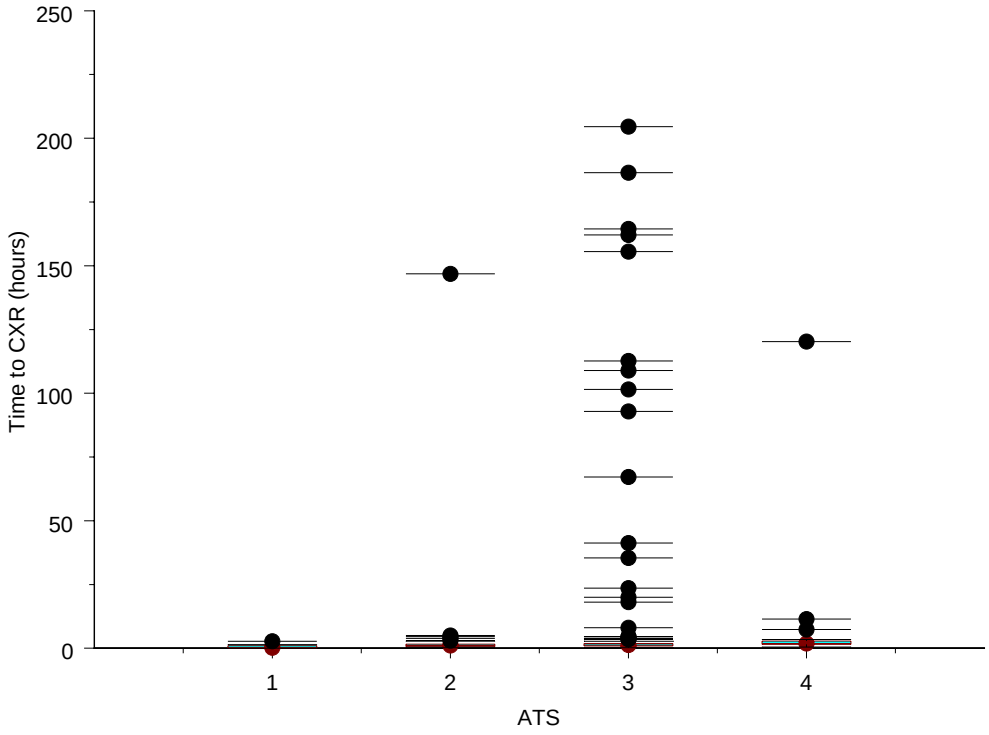

Figure 9.8: Distribution of CXR timings by ATS with outliers - 1998 sample

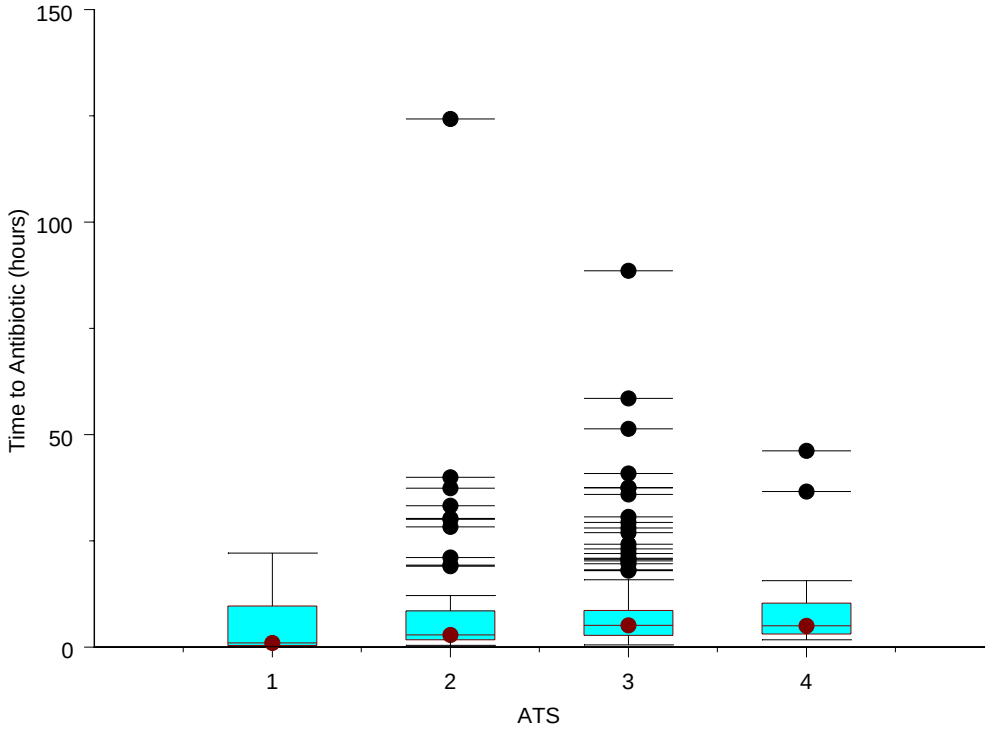

Figure 9.9: Distribution of antibiotic timing by ATS with outliers - 1998 sample

10 Bibliography

1. Pines J, Hollander J, Localio A, Metlay J. The Association between Emergency Department Crowding and Hospital Performance on Antibiotic Timing for Pneumonia and Percutaneous Intervention for Myocardial Infarction. *Acad Emerg Med* 2006;13(8):873-8.

2. Garg AX, Adhikari NK, McDonald H, Rosas-Arellano MP, Devereaux PJ, Beyene J, et al. Effects of computerized clinical decision support systems on practitioner performance and patient outcomes: a systematic review. *Jama* 2005;293(10):1223-38.

2a. Kumar A, Smith B, Novotny, D.D. Biomedical informatics and granularity. *Comparative and Functional Genomics* 2004;5: 501–508.

2b. Bleeker SE, Derksen-Lubsen, G. Ginneken A,et al. Structured data entry for narrative data in a broad specialty: patient history and physical examination in pediatrics. *BMC Medical Informatics and Decision Making* 2006;6:29.

3. Bartlett JG, Breiman RF, Mandell LA, File TM, Jr. Community-acquired pneumonia in adults: guidelines for management. The Infectious Diseases Society of America. *Clin Infect Dis* 1998;26(4):811-38.

4. Metlay JP, Kapoor WN, Fine MJ. Does this patient have community-acquired pneumonia? Diagnosing pneumonia by history and physical examination. *Jama* 1997;278(17):1440-5.

5. BTS Guidelines for the Management of Community Acquired Pneumonia in Adults. *Thorax* 2001;56 Suppl 4:IV1-64.

6. Smith PR. What diagnostic tests are needed for community-acquired pneumonia? *Med Clin North Am* 2001;85(6):1381-96.

7. Collin BA, Ramphal R. Pneumonia in the compromised host including cancer patients and transplant patients. *Infect Dis Clin North Am* 1998;12(3):781-805, xi.
8. Belleza WG, Browne B. Pulmonary considerations in the immunocompromised patient. *Emerg Med Clin North Am* 2003;21(2):499-531, x-xi.

9. Cunha BA. Pneumonias in the compromised host. *Infect Dis Clin North Am* 2001;15(2):591-612.

10. Tsirgiotis E, Ruffin R. Community acquired pneumonia. A perspective for general practice. *Aust Fam Physician* 2000;29(7):639-45.

11. Niederman MS, Mandell LA, Anzueto A, Bass JB, Broughton WA, Campbell GD, et. al. Guidelines for the management of adults with community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy, and prevention. *Am J Respir Crit Care Med* 2001;163(7):1730-54.

12. Jin Y, Marrie TJ, Carriere KC, Predy G, Houston C, Ness K, et al. Variation in management of community-acquired pneumonia requiring admission to Alberta, Canada hospitals. *Epidemiol Infect* 2003;130(1):41-51.

13. Fine MJ, Singer DE, Phelps AL, Hanusa BH, Kapoor WN. Differences in length of hospital stay in patients with community-acquired pneumonia: a prospective four-hospital study. *Med Care* 1993;31(4):371-80.

14. Gilbert K, Gleason PP, Singer DE, Marrie TJ, Coley CM, Obrosky DS, et al. Variations in antimicrobial use and cost in more than 2,000 patients with community-acquired pneumonia. *Am J Med* 1998;104(1):17-27.

15. Gleason PP, Kapoor WN, Stone RA, Lave JR, Obrosky DS, Schulz R, et al. Medical outcomes and antimicrobial costs with the use of the American Thoracic Society guidelines for outpatients with community-acquired pneumonia. *Jama* 1997;278(1):32-9.

16. Feagan BG, Marrie TJ, Lau CY, Wheeler SL, Wong CJ, Vandervoort MK. Treatment and outcomes of community-acquired pneumonia at Canadian hospitals. *Cmaj* 2000;162(10):1415-20.

17. Fine MJ, Stone RA, Singer DE, Coley CM, Marrie TJ, Lave JR, et al. Processes and outcomes of care for patients with community-acquired pneumonia: results from the Pneumonia Patient Outcomes Research Team (PORT) cohort study. *Arch Intern Med* 1999;159(9):970-80.

18. Fine MJ, Smith MA, Carson CA, Mutha SS, Sankey SS, Weissfeld LA, et al. Prognosis and outcomes of patients with community-acquired pneumonia. A meta-analysis. *Jama* 1996;275(2):134-41.

19. Lave JR, Fine MJ, Sankey SS, Hanusa BH, Weissfeld LA, Kapoor WN. Hospitalized pneumonia. Outcomes, treatment patterns, and costs in urban and rural areas. *J Gen Intern Med* 1996;11(7):415-21.

20. McCormick D, Fine MJ, Coley CM, Marrie TJ, Lave JR, Obrosky DS, et al. Variation in length of hospital stay in patients with community-acquired pneumonia: are shorter stays associated with worse medical outcomes? *Am J Med* 1999;107(1):5-12.

21. Meehan TP, Chua-Reyes JM, Tate J, Prestwood KM, Scinto JD, Petrillo MK, et al. Process of care performance, patient characteristics, and outcomes in elderly patients hospitalized with community-acquired or nursing home-acquired pneumonia. *Chest* 2000;117(5):1378-85.

22. Meehan TP, Fine MJ, Krumholz HM, Scinto JD, Galusha DH, Mockalis JT, et al. Quality of care, process, and outcomes in elderly patients with pneumonia. *Jama* 1997;278(23):2080-4.

23. Menendez R, Cremades MJ, Martinez-Moragon E, Soler JJ, Reyes S, Perpina M. Duration of length of stay in pneumonia: influence of clinical factors and hospital type. *Eur Respir J* 2003;22(4):643-8.

24. Menendez R, Ferrando D, Valles JM, Martinez E, Perpina M. Initial risk class and length of hospital stay in community-acquired pneumonia. *Eur Respir J* 2001;18(1):151-6.

25. Rifkin WD, Conner D, Silver A, Eichorn A. Comparison of processes and outcomes of pneumonia care between hospitalists and community-based primary care physicians. *Mayo Clin Proc* 2002;77(10):1053-8.

26. Rosenthal GE, Harper DL, Quinn LM, Cooper GS. Severity-adjusted mortality and length of stay in teaching and nonteaching hospitals. Results of a regional study. *Jama* 1997;278(6):485-90.

27. Stein MD, Hanson S, Tammaro D, Hanna L, Most AS. Economic effects of community versus hospital-based faculty pneumonia care. *J Gen Intern Med* 1998;13(11):774-7.

28. Whittle J, Lin CJ, Lave JR, Fine MJ, Delaney KM, Joyce DZ, et al. Relationship of provider characteristics to outcomes, process, and costs of care for community-acquired pneumonia. *Med Care* 1998;36(7):977-87.

29. Minogue MF, Coley CM, Fine MJ, Marrie TJ, Kapoor WN, Singer DE. Patients hospitalized after initial outpatient treatment for community-acquired pneumonia. *Ann Emerg Med* 1998;31(3):376-80.

30. Metlay JP, Fine MJ, Schulz R, Marrie TJ, Coley CM, Kapoor WN, et al. Measuring symptomatic and functional recovery in patients with community-acquired pneumonia. *J Gen Intern Med* 1997;12(7):423-30.

31. Metlay JP, Atlas SJ, Borowsky LH, Singer DE. Time course of symptom resolution in patients with community-acquired pneumonia. *Respir Med* 1998;92(9):1137-42.

32. Birnbaum HG, Morley M, Greenberg PE, Cifaldi M, Colice GL. Economic burden of pneumonia in an employed population. *Arch Intern Med* 2001;161(22):2725-31.

33. Niederman MS, McCombs JS, Unger AN, Kumar A, Popovian R. The cost of treating community-acquired pneumonia. *Clin Ther* 1998;20(4):820-37.

34. Fine MJ, Pratt HM, Obrosky DS, Lave JR, McIntosh LJ, Singer DE, et al. Relation between length of hospital stay and costs of care for patients with community-acquired pneumonia. *Am J Med* 2000;109(5):378-85.

35. Guest JF, Morris A. Community-acquired pneumonia: the annual cost to the National Health Service in the UK. *Eur Respir J* 1997;10(7):1530-4.

36. Fine MJ, Hough LJ, Medsger AR, Li YH, Ricci EM, Singer DE, et al. The hospital admission decision for patients with community-acquired pneumonia. Results from the pneumonia Patient Outcomes Research Team cohort study. *Arch Intern Med* 1997;157(1):36-44.

37. Marrie TJ. Risks and outcomes in community acquired pneumonia. *Can Respir J* 1999;6 Suppl A:6A-9A.

38. Auble TE, Yealy DM, Fine MJ. Assessing prognosis and selecting an initial site of care for adults with community-acquired pneumonia. *Infect Dis Clin North Am* 1998;12(3):741-59, x.

39. Dean NC. Use of prognostic scoring and outcome assessment tools in the admission decision for community-acquired pneumonia. *Clin Chest Med* 1999;20(3):521-9, viii.

40. Halm EA, Atlas SJ, Borowsky LH, Benzer TI, Metlay JP, Chang YC, et al. Understanding physician adherence with a pneumonia practice guideline: effects of patient, system, and physician factors. *Arch Intern Med* 2000;160(1):98-104.

41. Marras TK, Gutierrez C, Chan CK. Applying a prediction rule To identify low-risk patients with community-acquired pneumonia. *Chest* 2000;118(5):1339-43.

42. Leber MJ, Hubahib H, Callahan M, Brenner B. Computer-assisted decision making for patients with pneumonia. *Acad Emerg Med* 2001;8(5):477.

43. Stauble SP, Reichlin S, Dieterle T, Leimenstoll B, Schoenenberger R, Martina B. Community-acquired pneumonia--which patients are hospitalised? *Swiss Med Wkly* 2001;131(13-14):188-92.

44. Goss CH, Rubenfeld GD, Park DR, Sherbin VL, Goodman MS, Root RK. Cost and incidence of social comorbidities in low-risk patients with community-acquired pneumonia admitted to a public hospital. *Chest* 2003;124(6):2148-55.

45. Runciman WB, Edmonds MJ, Pradhan M. Setting priorities for patient safety. *Qual Saf Health Care* 2002;11(3):224-9.

46. Halm EA, Switzer GE, Mittman BS, Walsh MB, Chang CC, Fine MJ. What factors influence physicians' decisions to switch from intravenous to oral antibiotics for community-acquired pneumonia? *J Gen Intern Med* 2001;16(9):599-605.

47. Rhew DC, Tu GS, Ofman J, Henning JM, Richards MS, Weingarten SR. Early switch and early discharge strategies in patients with community-acquired pneumonia: a meta-analysis. *Arch Intern Med* 2001;161(5):722-7.

48. Lee RW, Lindstrom ST. Early switch to oral antibiotics and early discharge guidelines in the management of community-acquired pneumonia. *Respirology* 2007;12(1):111-6.

49. Oosterheert JJ, Bonten MJ, Schneider MM, Buskens E, Lammers JW, Hustinx WM, et al. Effectiveness of early switch from intravenous to oral antibiotics in severe community acquired pneumonia: multicentre randomised trial. *Bmj* 2006;333(7580):1193.

50. Nathan RV, Rhew DC, Murray C, Bratzler DW, Houck PM, Weingarten SR. In-hospital observation after antibiotic switch in pneumonia: a national evaluation. *Am J Med* 2006;119(6):512 e1-7.

51. Santos-Eggimann B, Chavaz N, Larequi T, Lamy O, Yersin B. Heart failure and community-acquired pneumonia: cases for home hospital? *Int J Qual Health Care* 2001;13(4):301-7.

52. Williams DN. Reducing costs and hospital stay for pneumonia with home intravenous cefotaxime treatment: results with a computerized ambulatory drug delivery system. *Am J Med* 1994;97(2A):50-5.

53. Richards DA, Toop LJ, Epton MJ, McGeoch GR, Town GI, Wynn-Thomas SM, et al. Home management of mild to moderately severe community-acquired pneumonia: a randomised controlled trial. *Med J Aust* 2005;183(5):235-8.

54. Barlow GD, Lamping DL, Davey PG, Nathwani D. Evaluation of outcomes in community-acquired pneumonia: a guide for patients, physicians, and policy-makers. *Lancet Infect Dis* 2003;3(8):476-88.

55. Collopy BT, Williams J, Rodgers L, Campbell J, Jenner N, Andrews N. The ACHS Care Evaluation Program: a decade of achievement. Australian Council on Healthcare Standards. *J Qual Clin Pract* 2000;20(1):36-41.

56. McGlynn EA, Asch SM, Adams J, Keesey J, Hicks J, DeCristofaro A, et al. The quality of health care delivered to adults in the United States. *N Engl J Med* 2003;348(26):2635-45.

57. Jencks SF, Cuerdon T, Burwen DR, Fleming B, Houck PM, Kussmaul AE, et al. Quality of medical care delivered to Medicare beneficiaries: A profile at state and national levels. *Jama* 2000;284(13):1670-6.

58. Graff L, Stevens C, Spaite D, Foody J. Measuring and improving quality in emergency medicine. *Acad Emerg Med* 2002;9(11):1091-107.

59. Rubin HR, Pronovost P, Diette GB. From a process of care to a measure: the development and testing of a quality indicator. *Int J Qual Health Care* 2001;13(6):489-96.

60. Rubin HR, Pronovost P, Diette GB. The advantages and disadvantages of process-based measures of health care quality. *Int J Qual Health Care* 2001;13(6):469-74.

61. Houck PM, Bratzler DW, Nsa W, Ma A, Bartlett JG. Timing of antibiotic administration and outcomes for Medicare patients hospitalized with community-acquired pneumonia. *Arch Intern Med* 2004;164(6):637-44.

62. Gleason PP, Meehan TP, Fine JM, Galusha DH, Fine MJ. Associations between initial antimicrobial therapy and medical outcomes for hospitalized elderly patients with pneumonia. *Arch Intern Med* 1999;159(21):2562-72.

63. Battleman DS, Callahan M, Thaler HT. Rapid antibiotic delivery and appropriate antibiotic selection reduce length of hospital stay of patients with community-acquired pneumonia: link between quality of care and resource utilization. *Arch Intern Med* 2002;162(6):682-8.

64. Frei CR, Restrepo MI, Mortensen EM, Burgess DS. Impact of guideline-concordant empiric antibiotic therapy in community-acquired pneumonia. *Am J Med* 2006;119(10):865-71.

65. Landon BE, Normand SL, Lessler A, O'Malley AJ, Schmaltz S, Loeb JM, et al. Quality of care for the treatment of acute medical conditions in US hospitals. *Arch Intern Med* 2006;166(22):2511-7.

66. Mitka M. JCAHO tweaks emergency departments' pneumonia treatment standards. *Jama* 2007;297(16):1758-9.

67. Rosenthal MB, Dudley RA. Pay-for-performance: will the latest payment trend improve care? *Jama* 2007;297(7):740-4.

68. Fee C, Weber E, Sharpe BA, Nguy M, Quon T, Bookwalter T. JCAHO/CMS core measures for community-acquired pneumonia. *Ann Emerg Med* 2006;47(5):505; author reply 506.

69. Schwartz DN, Furumoto-Dawson A, Itokazu GS, Chinikamwala M, Levasseur S, Weinstein RA. Preventing mismanagement of community-acquired pneumonia at an urban public hospital: implications for institution-specific practice guidelines. *Chest* 1998;113(3 Suppl):194S-198S.

70. United States Department of Health and Human Services. Hospital Compare Database: 2007. http://www.hospitalcompare.hhs.gov/Hospital/Static/Resources-Download-DB.asp?dest=NAV|Home|Resources|DownloadDB; accessed 10-5-07.

71. Grol R, Grimshaw G. From best evidence to best practice: effective implementation of change in patient's care. *Lancet* 2003;362:1225-30.

72. Mason J, Freemantle N, Nazareth I, Eccles M, Haines A, Drummond M. When is it cost-effective to change the behavior of health professionals? *Jama* 2001;286(23):2988-92.

73. Baldwin LP, Eldabi T, R.J P. Simulation in healthcare management: a soft approach (MAPIU). *Simulation Modelling Practice and Theory* 2004;12:541–557.

74. Pradhan M, Edmonds M, Runciman W. Quality in Healthcare: Process. *Best Practice & Research Clinical Anaesthesiology* 2001;15(4):555-571.

75. Clemens RT. *Making hard decisions: An introduction to decision analysis*. 2nd ed. Belmont: Duxbury Press, 1996.

76. Vincent C, Taylor-Adams S, Stanhope N. Framework for analysing risk and safety in clinical medicine. *Bmj* 1998;316(7138):1154-7.

77. Reason J. The contribution of latent human failures to the breakdown of complex systems. *Philos Trans R Soc Lond B Biol Sci* 1990;327(1241):475-84.

78. Nathwani D, Rubinstein E, Barlow G, Davey P. Do guidelines for community-acquired pneumonia improve the cost-effectiveness of hospital care? *Clin Infect Dis* 2001;32(5):728-41.

79. Wipf JE, Lipsky BA, Hirschmann JV, Boyko EJ, Takasugi J, Peugeot RL, et al. Diagnosing pneumonia by physical examination: relevant or relic? *Arch Intern Med* 1999;159(10):1082-7.

80. Feldman C. Pneumonia in the elderly. *Med Clin North Am* 2001;85(6):1441-59.

81. Metlay JP, Schulz R, Li YH, Singer DE, Marrie TJ, Coley CM, et al. Influence of age on symptoms at presentation in patients with community-acquired pneumonia. *Arch Intern Med* 1997;157(13):1453-9.

82. Gupta SK, Sarosi GA. The role of atypical pathogens in community-acquired pneumonia. *Med Clin North Am* 2001;85(6):1349-65, vii.

83. Bartlett JG, Dowell SF, Mandell LA, File Jr TM, Musher DM, Fine MJ. Practice guidelines for the management of community-acquired pneumonia in adults. Infectious Diseases Society of America. *Clin Infect Dis* 2000;31(2):347-82.

84. Mandell LA, Marrie TJ, Grossman RF, Chow AW, Hyland RH. Canadian Guidelines for the Initial Management of Community-Acquired Pneumonia: An Evidence-Based Update by the Canadian Infectious Diseases Society and the Canadian Thoracic Society. *Clin Infect Dis* 2000;31(2):383-421.

85. Syrjala H, Broas M, Suramo I, Ojala A, Lahde S. High-resolution computed tomography for the diagnosis of community-acquired pneumonia. *Clinical Infectious Diseases* 1998;27:358-63.

86. Metlay JP, Fine MJ. Testing strategies in the initial management of patients with community-acquired pneumonia. *Ann Intern Med* 2003;138(2):109-18.

87. Winer-Muram HT, Rubin SA, Ellis JV, Jennings SG, Arheart KL, Wunderink RG, et al. Pneumonia and ARDS in patients receiving mechanical ventilation: diagnostic accuracy of chest radiography. *Radiology* 1993;188(2):479-85.

88. Lefcoe MS, Fox GA, Leasa DJ, Sparrow RK, McCormack DG. Accuracy of portable chest radiography in the critical care setting. Diagnosis of pneumonia based on quantitative cultures obtained from protected brush catheter. *Chest* 1994;105(3):885-7.

89. Young M, Marrie TJ. Interobserver variability in the interpretation of chest roentgenograms of patients with possible pneumonia. *Arch Intern Med* 1994;154(23):2729-32.

90. Herman PG, Hessel SJ. Accuracy and its relationship to experience in the interpretation of chest radiographs. *Invest Radiol* 1975;10(1):62-7.

91. Melbye H, Dale K. Interobserver variability in the radiographic diagnosis of adult outpatient pneumonia. *Acta Radiol* 1992;33(1):79-81.

92. Albaum MN, Hill LC, Murphy M, Li YH, Fuhrman CR, Britton CA, et al. Interobserver reliability of the chest radiograph in community-acquired pneumonia. PORT Investigators. *Chest* 1996;110(2):343-50.

93. O'Leary MR, Smith M, Olmsted WW, Curtis DJ. Physician assessments of practice patterns in emergency department radiograph interpretation. *Ann Emerg Med* 1988;17(10):1019-23.

94. Pines JM, Morton MJ, Datner EM, Hollander JE. Systematic delays in antibiotic administration in the emergency department for adult patients admitted with pneumonia. *Acad Emerg Med* 2006;13(9):939-45.

95. Campbell SG, Murray DD, Hawass A, Urquhart D, Ackroyd-Stolarz S, Maxwell D. Agreement between emergency physician diagnosis and radiologist reports in patients discharged from an emergency department with community-acquired pneumonia. *Emerg Radiol* 2005;11(4):242-6.

96. Basi SK, Marrie TJ, Huang JQ, Majumdar SR. Patients admitted to hospital with suspected pneumonia and normal chest radiographs: epidemiology, microbiology, and outcomes. *Am J Med* 2004;117(5):305-11.

97. Fee C, Weber EJ. Identification of 90% of patients ultimately diagnosed with community-acquired pneumonia within four hours of emergency department arrival may not be feasible. *Ann Emerg Med* 2007;49(5):553-9.

98. Lieberman D, Schlaeffer F, Boldur I, Horowitz S, Friedman MG, Leiononen M, et al. Multiple pathogens in adult patients admitted with community-acquired pneumonia: a one year prospective study of 346 consecutive patients. *Thorax* 1996;51(2):179-84.

99. Lieberman D, Porath A. Seasonal variation in community-acquired pneumonia. *Eur Respir J* 1996;9(12):2630-4.

100. Houck PM, MacLehose RF, Niederman MS, Lowery JK. Empiric antibiotic therapy and mortality among medicare pneumonia inpatients in 10 western states: 1993, 1995, and 1997. *Chest* 2001;119(5):1420-6.

101. Cunha BA, Shea KW. Emergence of antimicrobial resistance in community-acquired pulmonary pathogens. *Semin Respir Infect* 1998;13(1):43-53.

102. Metlay JP, Singer DE. Outcomes in lower respiratory tract infections and the impact of antimicrobial drug resistance. *Clin Microbiol Infect* 2002;8 Suppl 2:1-11.

103. Cunha BA. Clinical relevance of penicillin-resistant Streptococcus pneumoniae. *Semin Respir Infect* 2002;17(3):204-14.

104. Metlay JP, Shea JA, Crossette LB, Asch DA. Tensions in antibiotic prescribing: pitting social concerns against the interests of individual patients. *J Gen Intern Med* 2002;17(2):87-94.

105. Arancibia F, Ewig S, Martinez JA, Ruiz M, Bauer T, Marcos MA, et al. Antimicrobial treatment failures in patients with community-acquired pneumonia: causes and prognostic implications. *Am J Respir Crit Care Med* 2000;162(1):154-60.

106. Lim I, Shaw DR, Stanley DP, Lumb R, McLennan G. A prospective hospital study of the aetiology of community-acquired pneumonia. *Med J Aust* 1989;151(2):87-91.

107. Wunderink RG, Waterer GW. Appropriate microbiological testing in community-acquired pneumonia. *Chest* 2001;119(1):5-7.

108. Lidman C, Burman LG, Lagergren A, Ortqvist A. Limited value of routine microbiological diagnostics in patients hospitalized for community-acquired pneumonia. *Scand J Infect Dis* 2002;34(12):873-9.

109. Ewig S, Schlochtermeier M, Goke N, Niederman MS. Applying sputum as a diagnostic tool in pneumonia: limited yield, minimal impact on treatment decisions. *Chest* 2002;121(5):1486-92.

110. Woodhead MA, Arrowsmith J, Chamberlain-Webber R, Wooding S, Williams I. The value of routine microbial investigation in community-acquired pneumonia. *Respir Med* 1991;85(4):313-7.

111. Sanyal S, Smith PR, Saha AC, Gupta S, Berkowitz L, Homel P. Initial microbiologic studies did not affect outcome in adults hospitalized with community-acquired pneumonia. *Am J Respir Crit Care Med* 1999;160(1):346-8.

112. Rello J, Bodi M, Mariscal D, Navarro M, Diaz E, Gallego M, et al. Microbiological testing and outcome of patients with severe community-acquired pneumonia. *Chest* 2003;123(1):174-80.

113. Ewig S, Torres A, Angeles Marcos M, Angrill J, Rano A, de Roux A, et al. Factors associated with unknown aetiology in patients with community-acquired pneumonia. *Eur Respir J* 2002;20(5):1254-62.

114. Theerthakarai R, El-Halees W, Ismail M, Solis RA, Khan MA. Nonvalue of the initial microbiological studies in the management of nonsevere community-acquired pneumonia. *Chest* 2001;119(1):181-4.

115. Metersky ML, Ma A, Bratzler DW, Houck PM. Predicting bacteremia in patients with community-acquired pneumonia. *Am J Respir Crit Care Med* 2004;169(3):342-7.

116. Campbell SG, Marrie TJ, Anstey R, Dickinson G, Ackroyd-Stolarz S. The contribution of blood cultures to the clinical management of adult patients admitted to the hospital with community-acquired pneumonia: a prospective observational study. *Chest* 2003;123(4):1142-50.

117. Campbell SG, Marrie TJ, Anstey R, Ackroyd-Stolarz S, Dickinson G. Utility of blood cultures in the management of adults with community acquired pneumonia discharged from the emergency department. *Emerg Med J* 2003;20(6):521-523.

118. Craven DE. Blood cultures for community-acquired pneumonia: piecing together a mosaic for doing less. *Am J Respir Crit Care Med* 2004;169(3):327-8.

119. Chalasani NP, Valdecanas MA, Gopal AK, McGowan JE, Jr., Jurado RL. Clinical utility of blood cultures in adult patients with community-acquired pneumonia without defined underlying risks. *Chest* 1995;108(4):932-6.

120. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2007;44 Suppl 2:S27-72.

121. British Thoracic Society Pneumonia Guideline Committee. BTS guidelines for the management of communty acquired pneumonia in adults - 2004 update: British Thoracic Society, 2004. http://www.brit-thoracic.org.uk/c2/uploads/MACAPrevisedApr04.pdf. Accessed 1-9-05.

122. File TM, Jr., Kozlov RS. Rapid detection of Streptococcus pneumoniae in community-acquired pneumonia. *Clin Microbiol Infect* 2006;12 Suppl 9:27-33.

123. Andreo F, Dominguez J, Ruiz J, Blanco S, Arellano E, Prat C, et al. Impact of rapid urine antigen tests to determine the etiology of community-acquired pneumonia in adults. *Respir Med* 2006;100(5):884-91.

124. Guchev IA, Yu VL, Sinopalnikov A, Klochkov OI, Kozlov RS, Stratchounski LS. Management of nonsevere pneumonia in military trainees with the urinary antigen test for Streptococcus pneumoniae: an innovative approach to targeted therapy. *Clin Infect Dis* 2005;40(11):1608-16.

125. Templeton KE, Scheltinga SA, van den Eeden WC, Graffelman AW, van den Broek PJ, Claas EC. Improved diagnosis of the etiology of community-acquired pneumonia with real-time polymerase chain reaction. *Clin Infect Dis* 2005;41(3):345-51.

126. Morozumi M, Nakayama E, Iwata S, Aoki Y, Hasegawa K, Kobayashi R, et al. Simultaneous detection of pathogens in clinical samples from patients with community-acquired pneumonia by real-time PCR with pathogen-specific molecular beacon probes. *J Clin Microbiol* 2006;44(4):1440-6.

127. Oosterheert JJ, van Loon AM, Schuurman R, Hoepelman AI, Hak E, Thijsen S, et al. Impact of rapid detection of viral and atypical bacterial pathogens by real-time polymerase chain reaction for patients with lower respiratory tract infection. *Clin Infect Dis* 2005;41(10):1438-44.

128. Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med* 1997;336(4):243-50.

129. Roson B, Carratala J, Dorca J, Casanova A, Manresa F, Gudiol F. Etiology, reasons for hospitalization, risk classes, and outcomes of community-acquired pneumonia in patients hospitalized on the basis of conventional admission criteria. *Clin Infect Dis* 2001;33(2):158-65.

130. Etzion O, Novack V, Avnon L, Porath A, Dagan E, Riesenberg K, et al. Characteristics of low-risk patients hospitalized with community-acquired pneumonia. *Eur J Intern Med* 2007;18(3):209-14.

131. van der Eerden MM, de Graaff CS, Bronsveld W, Jansen HM, Boersma WG. Prospective evaluation of pneumonia severity index in hospitalised patients with community-acquired pneumonia. *Respir Med* 2004;98(9):872-8.

132. Hedlund J, Stralin K, Ortqvist A, Holmberg H. Swedish guidelines for the management of community-acquired pneumonia in immunocompetent adults. *Scand J Infect Dis* 2005;37(11-12):791-805.

133. Niederman MS, Bass JB, Jr., Campbell GD, Fein AM, Grossman RF, Mandell LA, et al. Guidelines for the initial management of adults with community-acquired pneumonia: diagnosis, assessment of severity, and initial antimicrobial therapy. American Thoracic Society. Medical Section of the American Lung Association. *Am Rev Respir Dis* 1993;148(5):1418-26.

134. Guidelines for the management of community-acquired pneumonia in adults admitted to hospital. The British Thoracic Society. *Br J Hosp Med* 1993;49(5):346-50.

135. Lim WS, van der Eerden MM, Laing R, Boersma WG, Karalus N, Town GI, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax* 2003;58(5):377-82.

136. Buising KL, Thursky KA, Black JF, MacGregor L, Street AC, Kennedy MP, et al. A prospective comparison of severity scores for identifying patients with severe community acquired pneumonia: reconsidering what is meant by severe pneumonia. *Thorax* 2006;61(5):419-24.

137. Read RC. Evidence-based medicine: empiric antibiotic therapy in community-acquired pneumonia. *J Infect* 1999;39(3):171-8.

138. Oosterheert JJ, Bonten MJ, Hak E, Schneider MM, Hoepelman IM. How good is the evidence for the recommended empirical antimicrobial treatment of patients hospitalized because of community-acquired pneumonia? A systematic review. *J Antimicrob Chemother* 2003;52(4):555-63.

139. Guidelines AT. Australian Therapeutic Guidelines. 2006 ed: Australian Therapeutic Guidelines, 2006.

140. Shefet D, Robenshtok E, Paul M, Leibovici L. Empirical atypical coverage for inpatients with community-acquired pneumonia: systematic review of randomized controlled trials. *Arch Intern Med* 2005;165(17):1992-2000

.

141. Shefet D, Robenshtock E, Paul M, Leibovici L. Empiric antibiotic coverage of atypical pathogens for community acquired pneumonia in hospitalized adults. *Cochrane Database Syst Rev* 2005(2):CD004418.

142. Mills GD, Oehley MR, Arrol B. Effectiveness of beta lactam antibiotics compared with antibiotics active against atypical pathogens in non-severe community acquired pneumonia: meta-analysis. *Bmj* 2005;330(7489):456.

143. Dudas V, Hopefl A, Jacobs R, Guglielmo BJ. Antimicrobial selection for hospitalized patients with presumed community-acquired pneumonia: a survey of nonteaching US community hospitals. *Ann Pharmacother* 2000;34(4):446-52.

144. Brown RB, Iannini P, Gross P, Kunkel M. Impact of initial antibiotic choice on clinical outcomes in community-acquired pneumonia: analysis of a hospital claims-made database. *Chest* 2003;123(5):1503-11.

145. Weiss K, Tillotson GS. The controversy of combination vs monotherapy in the treatment of hospitalized community-acquired pneumonia. *Chest* 2005;128(2):940-6.

146. van der Eerden MM, Vlaspolder F, de Graaff CS, Groot T, Bronsveld W, Jansen HM, et al. Comparison between pathogen directed antibiotic treatment and empirical broad spectrum antibiotic treatment in patients with community acquired pneumonia: a prospective randomised study. *Thorax* 2005;60(8):672-8.

147. Hagaman JT, Yurkowski P, Trott A, Rouan GW. Getting physicians to make "the switch": the role of clinical guidelines in the management of community-acquired pneumonia. *Am J Med Qual* 2005;20(1):15-21.

148. Fine MJ, Stone RA, Lave JR, Hough LJ, Obrosky DS, Mor MK, et al. Implementation of an evidence-based guideline to reduce duration of intravenous antibiotic therapy and length of stay for patients hospitalized with community-acquired pneumonia: a randomized controlled trial. *Am J Med* 2003;115(5):343-51.

149. Tan JS. Nonresponses and treatment failures with conventional empiric regimens in patients with community-acquired pneumonia. *Infect Dis Clin North Am* 2004;18(4):883-97.

150. Roson B, Carratala J, Fernandez-Sabe N, Tubau F, Manresa F, Gudiol F. Causes and factors associated with early failure in hospitalized patients with community-acquired pneumonia. *Arch Intern Med* 2004;164(5):502-8.

151. Menendez R, Torres A, Zalacain R, Aspa J, Martin Villasclaras JJ, Borderias L, et al. Risk factors of treatment failure in community acquired pneumonia: implications for disease outcome. *Thorax* 2004;59(11):960-5.

152. Hoogewerf M, Oosterheert JJ, Hak E, Hoepelman IM, Bonten MJ. Prognostic factors for early clinical failure in patients with severe community-acquired pneumonia. *Clin Microbiol Infect* 2006;12(11):1097-104.

153. Genne D, Sommer R, Kaiser L, Saaidia A, Pasche A, Unger PF, et al. Analysis of factors that contribute to treatment failure in patients with community-acquired pneumonia. *Eur J Clin Microbiol Infect Dis* 2006;25(3):159-66.

154. Fine MJ, Medsger AR, Stone RA, Marrie TJ, Coley CM, Singer DE, et al. The hospital discharge decision for patients with community-acquired pneumonia. Results from the Pneumonia Patient Outcomes Research Team cohort study. *Arch Intern Med* 1997;157(1):47-56.

155. Halm EA, Fine MJ, Kapoor WN, Singer DE, Marrie TJ, Siu AL. Instability on hospital discharge and the risk of adverse outcomes in patients with pneumonia. *Arch Intern Med* 2002;162(11):1278-84.

156. Halm EA, Fine MJ, Marrie TJ, Coley CM, Kapoor WN, Obrosky DS, et al. Time to clinical stability in patients hospitalized with community-acquired pneumonia: implications for practice guidelines. *Jama* 1998;279(18):1452-7.

157. Coiera EW, Jayasuriya RA, Hardy J, Bannan A, Thorpe ME. Communication loads on clinical staff in the emergency department. *Med J Aust* 2002;176(9):415-8.

158. Chisholm CD, Collison EK, Nelson DR, Cordell WH. Emergency department workplace interruptions: are emergency physicians "interrupt-driven" and "multi-tasking"? *Acad Emerg Med* 2000;7(11):1239-43.

159. Spencer R, Coiera E, Logan P. Variation in communication loads on clinical staff in the emergency department. *Ann Emerg Med* 2004;44(3):268-73.

160. Kilpatrick ES, Holding S. Use of computer terminals on wards to access emergency test results: a retrospective audit. *Bmj* 2001;322(7294):1101-3.

161. Kyriacou DN, Ricketts V, Dyne PL, McCollough MD, Talan DA. A 5-year time study analysis of emergency department patient care efficiency. *Ann Emerg Med* 1999;34(3):326-35.

162. Docimo AB, Pronovost PJ, Davis RO, Concordia EB, Gabrish CM, Adessa MS, et al. Using the online and offline change model to improve efficiency for fast-track patients in an emergency department. *Jt Comm J Qual Improv* 2000;26(9):503-14.

163. Spaite DW, Bartholomeaux F, Guisto J, Lindberg E, Hull B, Eyherabide A, et al. Rapid process redesign in a university-based emergency department: decreasing waiting time intervals and improving patient satisfaction. *Ann Emerg Med* 2002;39(2):168-77.

164. ACEM. The Australasian Triage Scale. *Emergency Medicine* 2002;14:335-336.

165. Goransson K, Ehrenberg A, Marklund B, Ehnfors M. Accuracy and concordance of nurses in emergency department triage. *Scand J Caring Sci* 2005;19(4):432-8.

166. Goransson KE, Ehrenberg A, Ehnfors M. Triage in emergency departments: national survey. *J Clin Nurs* 2005;14(9):1067-74.

167. Goransson KE, Ehrenberg A, Marklund B, Ehnfors M. Emergency department triage: is there a link between nurses' personal characteristics and accuracy in triage decisions? *Accid Emerg Nurs* 2006;14(2):83-8.

168. Vance J, Sprivulis P. Triage nurses validly and reliably estimate emergency department patient complexity. *Emerg Med Australas* 2005;17(4):382-6.

169. Cooper RJ, Schriger DL, Flaherty HL, Lin EJ, Hubbell KA. Effect of vital signs on triage decisions. *Ann Emerg Med* 2002;39(3):223-32.

170. Salk ED, Schriger DL, Hubbell KA, Schwartz BL. Effect of visual cues, vital signs, and protocols on triage: a prospective randomized crossover trial. *Ann Emerg Med* 1998;32(6):655-64.

171. Considine J, LeVasseur SA, Villanueva E. The Australasian Triage Scale: examining emergency department nurses' performance using computer and paper scenarios. *Ann Emerg Med* 2004;44(5):516-23.

172. Considine J, Ung L, Thomas S. Clinical decisions using the National Triage Scale: how important is postgraduate education? *Accid Emerg Nurs* 2001;9(2):101-8.

173. Bergeron S, Gouin S, Bailey B, Patel H. Comparison of triage assessments among pediatric registered nurses and pediatric emergency physicians. *Acad Emerg Med* 2002;9(12):1397-401.

174. Beveridge R, Ducharme J, Janes L, Beaulieu S, Walter S. Reliability of the Canadian emergency department triage and acuity scale: interrater agreement. *Ann Emerg Med* 1999;34(2):155-9.

175. Hay E, Bekerman L, Rosenberg G, Peled R. Quality assurance of nurse triage: consistency of results over three years. *Am J Emerg Med* 2001;19(2):113-7.

176. Gill JM, Reese CL, Diamond JJ. Disagreement among health care professionals about the urgent care needs of emergency department patients. *Ann Emerg Med* 1996;28(5):474-9.

177. Wuerz R, Fernandes CM, Alarcon J. Inconsistency of emergency department triage. Emergency Department Operations Research Working Group. *Ann Emerg Med* 1998;32(4):431-5.

178. Worster A, Gilboy N, Fernandes CM, Eitel D, Eva K, Geisler R, et al. Assessment of inter-observer reliability of two five-level triage and acuity scales: a randomized controlled trial. *Cjem* 2004;6(4):240-5.

179. Fernandes CM, Wuerz R, Clark S, Djurdjev O. How reliable is emergency department triage? *Ann Emerg Med* 1999;34(2):141-7.

180. Brillman JC, Doezema D, Tandberg D, Sklar DP, Davis KD, Simms S, et al. Triage: limitations in predicting need for emergent care and hospital admission. *Ann Emerg Med* 1996;27(4):493-500.

181. Gerdtz MF, Bucknall TK. Triage nurses' clinical decision making. An observational study of urgency assessment. *Journal of Advanced Nursing* 2001;35(4):550-561.

182. Doherty SR, Hore CT, Curran SW. Inpatient mortality as related to triage category in three New South Wales regional base hospitals. *Emerg Med (Fremantle)* 2003;15(4):334-40.

183. Institute of Medicine. Crossing the Quality Chasm: A New Health System for the 21st Century, 2001.

184. Grol R. Improving the quality of medical care: building bridges among professional pride, payer profit, and patient satisfaction. *Jama* 2001;286(20):2578-85.

185. Tversky A, Kahneman D. Judgement Under Uncertainty: Heuristics and Biases. *Science* 1974;185:1124-1132.

186. Bornstein BH, Emler AC. Rationality in medical decision making: a review of the literature on doctors' decision-making biases. *J Eval Clin Pract* 2001;7(2):97-107.

187. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. *Bmj* 1996;312(7023):71-2.

188. Craig JC, Irwig LM, Stockler MR. Evidence-based medicine: useful tools for decision making. *Med J Aust* 2001;174(5):248-53.

189. National Library of Medicine. Pubmed, 2004. http://www.ncbi.nlm.nih.gov/sites/entrez

190. Hunt DL, Haynes RB, Hanna SE, Smith K. Effects of computer-based clinical decision support systems on physician performance and patient outcomes: a systematic review. *JAMA* 1998;280(15):1339-46.

191. Shiffman RN, Liaw Y, Brandt CA, Corb GJ. Computer-based guideline implementation systems: a systematic review of functionality and effectiveness. *J Am Med Inform Assoc* 1999;6(2):104-14.

192. Kaplan B. Evaluating informatics applications--clinical decision support systems literature review. *Int J Med Inf* 2001;64(1):15-37.

193. Stevenson KB, Barbera J, Moore JW, Samore MH, Houck P. Understanding keys to successful implementation of electronic decision support in rural hospitals: analysis of a pilot study for antimicrobial prescribing. *Am J Med Qual* 2005;20(6):313-8.

194. Wright AA, Maydom BW. Improving the implementation of community-acquired pneumonia guidelines. *Intern Med J* 2004;34(8):507-9.

195. Aronsky D, Haug PJ. An integrated decision support system for diagnosing and managing patients with community-acquired pneumonia. *Proc AMIA Symp* 1999:197-201.

196. Branson RD, Johannigman JA, Campbell RS, Davis K, Jr. Closed-loop mechanical ventilation. *Respir Care* 2002;47(4):427-51; discussion 451-3.

197. Cook DJ, Greengold NL, Ellrodt AG, Weingarten SR. The relation between systematic reviews and practice guidelines. *Ann Intern Med* 1997;127(3):210-6.

198. Woolf SH. Do clinical practice guidelines define good medical care? The need for good science and the disclosure of uncertainty when defining 'best practices'. *Chest* 1998;113(3 Suppl):166S-171S.

199. Hackner D, Tu G, Weingarten S, Mohsenifar Z. Guidelines in pulmonary medicine: a 25-year profile. *Chest* 1999;116(4):1046-62.

200. Woodhead M, Macfarlane J. Local antibiotic guidelines for adult community-acquired pneumonia (CAP): a survey of UK hospital practice in 1999. *J Antimicrob Chemother* 2000;46(1):141-3.

201. Protheroe J, Fahey T, Montgomery AA, Peters TJ. The impact of patients' preferences on the treatment of atrial fibrillation: observational study of patient based decision analysis. *Bmj* 2000;320(7246):1380-4.

202. Owens DK, Nease RF, Jr. A normative analytic framework for development of practice guidelines for specific clinical populations. *Med Decis Making* 1997;17(4):409-26.

203. National Library of Medicine. Pubmed, 2000. http://www.ncbi.nlm.nih.gov/sites/entrez

204. Eccles M, Mason J. How to develop cost-conscious guidelines. *Health Technol Assess* 2001;5(16):1-69.

205. Grilli R, Lomas J. Evaluating the message: the relationship between compliance rate and the subject of a practice guideline. *Med Care* 1994;32(3):202-13.

206. Goldfarb S. The utility of decision support, clinical guidelines, and financial incentives as tools to achieve improved clinical performance. *Jt Comm J Qual Improv* 1999;25(3):137-44.

207. Patel VL, Arocha JF, Diermeier M, How J, Mottur-Pilson C. Cognitive psychological studies of representation and use of clinical practice guidelines. *Int J Med Inf* 2001;63(3):147-67.

208. Cabana MD, Rand CS, Powe NR, Wu AW, Wilson MH, Abboud PA, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA* 1999;282(15):1458-65.

209. Switzer GE, Halm EA, Chang CC, Mittman BS, Walsh MB, Fine MJ. Physician Awareness and Self-reported Use of Local and National Guidelines for Community-acquired Pneumonia. *J Gen Intern Med* 2003;18(10):816-23.

210. Schiff GD, Klass D, Peterson J, Shah G, Bates DW. Linking laboratory and pharmacy: opportunities for reducing errors and improving care. *Arch Intern Med* 2003;163(8):893-900.

211. Kuperman GJ, Teich JM, Tanasijevic MJ, Ma'Luf N, Rittenberg E, Jha A, et al. Improving response to critical laboratory results with automation: results of a randomized controlled trial. *J Am Med Inform Assoc* 1999;6(6):512-22.

212. Kaushal R, Shojania KG, Bates DW. Effects of computerized physician order entry and clinical decision support systems on medication safety: a systematic review. *Arch Intern Med* 2003;163(12):1409-16.

213. Bates DW, Cohen M, Leape LL, Overhage JM, Shabot MM, Sheridan T. Reducing the frequency of errors in medicine using information technology. *J Am Med Inform Assoc* 2001;8(4):299-308.

214. Bates DW, Teich JM, Lee J, Seger D, Kuperman GJ, Ma'Luf N, et al. The impact of computerized physician order entry on medication error prevention. *J Am Med Inform Assoc* 1999;6(4):313-21.

215. Metzger J, Turisco F. Computerized Physician Order Entry: A look at the market place: First Consulting Group, 2001.

216. Hsia DC. Medicare quality improvement: bad apples or bad systems? *Jama* 2003;289(3):354-6.

217. Miller RA. Medical diagnostic decision support systems--past, present, and future: a threaded bibliography and brief commentary. *J Am Med Inform Assoc* 1994;1(1):8-27.

218. Kawamoto K, Houlihan CA, Balas EA, Lobach DF. Improving clinical practice using clinical decision support systems: a systematic review of trials to identify features critical to success. *Bmj* 2005;330(7494):765.

219. Bates DW, Kuperman GJ, Wang S, Gandhi T, Kittler A, Volk L, et al. Ten commandments for effective clinical decision support: making the practice of evidence-based medicine a reality. *J Am Med Inform Assoc* 2003;10(6):523-30.

220. Finch RG, Low DE. A critical assessment of published guidelines and other decision-support systems for the antibiotic treatment of community-acquired respiratory tract infections. *Clin Microbiol Infect* 2002;8 Suppl 2:69-91.

221. Woodhead M. Community-acquired pneumonia guidelines: much guidance, but not much evidence. *Eur Respir J* 2002;20(1):1-3.

222. Mandell LA, Bartlett JG, Dowell SF, File TM, Jr., Musher DM, Whitney C. Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. *Clin Infect Dis* 2003;37(11):1405-33.

223. AMH. *Australian Medicines Handbook 2007*. January 2007 ed. Adelaide: Australian Medicines Handbook, 2007.

224. Medical Algorithms Project, 2007. http://www.medal.org.

225. British Thoracic Society. Community-acquired pneumonia in adults in British hospitals in 1982-1983: a survey of aetiology, mortality, prognostic factors and outcome. The British Thoracic Society and the Public Health Laboratory Service. *Q J Med* 1987;62(239):195-220.

226. Neill AM, Martin IR, Weir R, Anderson R, Chereshsky A, Epton MJ, et al. Community acquired pneumonia: aetiology and usefulness of severity criteria on admission. *Thorax* 1996;51(10):1010-6.

227. Renaud B, Coma E, Labarere J, Hayon J, Roy PM, Boureaux H, et al. Routine use of the Pneumonia Severity Index for guiding the site-of-treatment decision of patients with pneumonia in the emergency department: a multicenter, prospective, observational, controlled cohort study. *Clin Infect Dis* 2007;44(1):41-9.

228. Atlas SJ, Benzer TI, Borowsky LH, Chang Y, Burnham DC, Metlay JP, et al. Safely increasing the proportion of patients with community-acquired pneumonia treated as outpatients: an interventional trial. *Arch Intern Med* 1998;158(12):1350-6.

229. Yealy DM, Auble TE, Stone RA, Lave JR, Meehan TP, Graff LG, et al. Effect of increasing the intensity of implementing pneumonia guidelines: a randomized, controlled trial. *Ann Intern Med* 2005;143(12):881-94.

230. Marrie TJ, Lau CY, Wheeler SL, Wong CJ, Vandervoort MK, Feagan BG. A controlled trial of a critical pathway for treatment of community-acquired pneumonia. CAPITAL Study Investigators. Community-Acquired Pneumonia Intervention Trial Assessing Levofloxacin. *Jama* 2000;283(6):749-55.

231. Ewig S, Ruiz M, Mensa J, Marcos MA, Martinez JA, Arancibia F, et al. Severe community-acquired pneumonia. Assessment of severity criteria. *Am J Respir Crit Care Med* 1998;158(4):1102-8.

232. Aujesky D, Auble TE, Yealy DM, Stone RA, Obrosky DS, Meehan TP, et al. Prospective comparison of three validated prediction rules for prognosis in community-acquired pneumonia. *Am J Med* 2005;118(4):384-92.

233. Spindler C, Ortqvist A. Prognostic score systems and community-acquired bacteraemic pneumococcal pneumonia. *Eur Respir J* 2006;28(4):816-23.

234. Capelastegui A, Espana PP, Quintana JM, Areitio I, Gorordo I, Egurrola M, et al. Validation of a predictive rule for the management of community-acquired pneumonia. *Eur Respir J* 2006;27(1):151-7.

235. Barlow G, Nathwani D, Davey P. The CURB65 pneumonia severity score outperforms generic sepsis and early warning scores in predicting mortality in community-acquired pneumonia. *Thorax* 2007;62(3):253-9.

236. Bauer TT, Ewig S, Marre R, Suttorp N, Welte T. CRB-65 predicts death from community-acquired pneumonia. *J Intern Med* 2006;260(1):93-101.

237. Buising KL, Thursky KA, Black JF, Brown GV. Are the Australian guidelines asking too much of the Pneumonia Severity Index (PSI)? *Med J Aust* 2004;180(9):486-7.
238. Marras TK, Chan CK. Use of guidelines in treating community-acquired pneumonia. *Chest* 1998;113(6):1689-94.

239. Menendez R, Ferrando D, Valles JM, Vallterra J. Influence of deviation from guidelines on the outcome of community-acquired pneumonia. *Chest* 2002;122(2):612-7.

240. Menendez R, Reyes S, Martinez R, de la Cuadra P, Manuel Valles J, Vallterra J. Economic evaluation of adherence to treatment guidelines in nonintensive care pneumonia. *Eur Respir J* 2007;29(4):751-6.

241. Clark S, Pradhan M, Faunt J, Swart R. A comparison of a paper-based clinical guideline and a decision support system for the management of community acquired pneumonia. *Health Informatics Society of Australia Conference Proceedings* 2000.

242. Royal Adelaide Hospital Comminity-Acquired Pneumonia Working Group. Royal Adelaide Hospital Community-Acquired Pneumonia Guideline, 2000.

243. Dean NC, Silver MP, Bateman KA, James B, Hadlock CJ, Hale D. Decreased mortality after implementation of a treatment guideline for community-acquired pneumonia. *Am J Med* 2001;110(6):451-7.

244. Dean NC, Suchyta MR, Bateman KA, Aronsky D, Hadlock CJ. Implementation of admission decision support for community-acquired pneumonia. *Chest* 2000;117(5):1368-77.

245. Estrada CA, Unterborn JN, Price J, Thompson D, Gibson L. Judging the effectiveness of clinical pathways for pneumonia: the role of risk adjustment. *Eff Clin Pract* 2000;3(5):221-8.

246. Weingarten SR, Riedinger MS, Hobson P, Noah MS, Johnson B, Giugliano G, et al. Evaluation of a pneumonia practice guideline in an interventional trial. *Am J Respir Crit Care Med* 1996;153(3):1110-5.

247. Benenson R, Magalski A, Cavanaugh S, Williams E. Effects of a pneumonia clinical pathway on time to antibiotic treatment, length of stay, and mortality. *Acad Emerg Med* 1999;6(12):1243-8.

248. Meehan TP, Weingarten SR, Holmboe ES, Mathur D, Wang Y, Petrillo MK, et al. A statewide initiative to improve the care of hospitalized pneumonia patients: The Connecticut Pneumonia Pathway Project. *Am J Med* 2001;111(3):203-10.

249. Rhew DC, Riedinger MS, Sandhu M, Bowers C, Greengold N, Weingarten SR. A prospective, multicenter study of a pneumonia practice guideline. *Chest* 1998;114(1):115-9.

250. Aronsky D, Haug PJ. Diagnosing community-acquired pneumonia with a Bayesian network. *Proc AMIA Symp* 1998:632-6.

251. Khalil A, Kelen G, Rothman RE. A simple screening tool for identification of community-acquired pneumonia in an inner city emergency department. *Emerg Med J* 2007;24(5):336-8.

252. Diehr P, Wood RW, Bushyhead J, Krueger L, Wolcott B, Tompkins RK. Prediction of pneumonia in outpatients with acute cough--a statistical approach. *J Chronic Dis* 1984;37(3):215-25.

253. Singal BM, Hedges JR, Radack KL. Decision rules and clinical prediction of pneumonia: evaluation of low-yield criteria. *Ann Emerg Med* 1989;18(1):13-20.

254. Heckerling PS. The need for chest roentgenograms in adults with acute respiratory illness. Clinical predictors. *Arch Intern Med* 1986;146(7):1321-4.

255. Gennis P, Gallagher J, Falvo C, Baker S, Than W. Clinical criteria for the detection of pneumonia in adults: guidelines for ordering chest roentgenograms in the emergency department. *J Emerg Med* 1989;7(3):263-8.

256. Heckerling PS, Tape TG, Wigton RS, Hissong KK, Leikin JB, Ornato JP, et al. Clinical prediction rule for pulmonary infiltrates. *Ann Intern Med* 1990;113(9):664-70.

257. Okimoto N, Yamato K, Kurihara T, Honda Y, Osaki K, Asaoka N, et al. Clinical predictors for the detection of community-acquired pneumonia in adults as a guide to ordering chest radiographs. *Respirology* 2006;11(3):322-4.

258. Kyriacou D, Yarnold P, Soltysik R, Wunderink R, Schmitt B, Parada J, et al. Triage Algorithm for Chest Radiography of Community-acquired Pneumonia in the Emergency Department. *Acad Emerg Med* 2007;14(5 Suppl 1):S88.

259. Emerman CL, Dawson N, Speroff T, Siciliano C, Effron D, Rashad F, et al. Comparison of physician judgment and decision aids for ordering chest radiographs for pneumonia in outpatients. *Ann Emerg Med* 1991;20(11):1215-9.

260. Aronsky D, Haug PJ. Automatic identification of patients eligible for a pneumonia guideline. *Proc AMIA Symp* 2000:12-6.

261. Heckerling PS, Gerber BS, Tape TG, Wigton RS. Selection of predictor variables for pneumonia using neural networks and genetic algorithms. *Methods Inf Med* 2005;44(1):89-97.

262. Heckerling PS, Gerber BS, Tape TG, Wigton RS. Use of genetic algorithms for neural networks to predict community-acquired pneumonia. *Artif Intell Med* 2004;30(1):71-84.

263. Heckerling PS, Gerber BS, Tape TG, Wigton RS. Prediction of community-acquired pneumonia using artificial neural networks. *Med Decis Making* 2003;23(2):112-21.

264. Lagor C, Aronsky D, Fiszman M, Haug PJ. Automatic identification of patients eligible for a pneumonia guideline: comparing the diagnostic accuracy of two decision support models. *Medinfo* 2001;10(Pt 1):493-7.

265. Schouten JA, Hulscher ME, Kullberg BJ, Cox A, Gyssens IC, van der Meer JW, et al. Understanding variation in quality of antibiotic use for community-acquired pneumonia: effect of patient, professional and hospital factors. *J Antimicrob Chemother* 2005.

266. Joint Commission on Accreditation of Healthcare Organizations. Specifications Manual for National Hospital Quality Measures, version 2.2b. 2.2b ed: Joint Commission on Accreditation of Healthcare Organizations, 2007.

267. Houck PM. Antibiotics and pneumonia: is timing everything or just a cause of more problems? *Chest* 2006;130(1):1-3.

268. Rollow W, Lied TR, McGann P, Poyer J, LaVoie L, Kambic RT, et al. Assessment of the Medicare quality improvement organization program. *Ann Intern Med* 2006;145(5):342-53.

269. Frohna W, King K, Photowala H. Improving Time to Antibiotics in Pneumonia- Does it Save Lives? *Acad Emerg Med* 2007;14(5 Suppl 1):S161.

270. Kelen GD, Rothman RE. Community pneumonia practice standard mandates: can't see the forest for the trees. *Acad Emerg Med* 2006;13(9):986-8.

271. Pines J. Profiles in Patient Safety: Antibiotic Timing in Pneumonia and Pay-for-performance. *Acad Emerg Med* 2006;13(7):787-90.

272. Metersky ML, Sweeney TA, Getzow MB, Siddiqui F, Nsa W, Bratzler DW. Antibiotic timing and diagnostic uncertainty in Medicare patients with pneumonia: is it reasonable to expect all patients to receive antibiotics within 4 hours? *Chest* 2006;130(1):16-21.

273. Kanwar M, Brar N, Khatib R, Fakih MG. Misdiagnosis of Community Acquired Pneumonia and Inappropriate Utilization of Antibiotics: Side Effects of the 4-Hour Antibiotic Administration Rule. *Chest* 2007;131:1865-1869.

274. Thompson D. The pneumonia controversy: hospitals grapple with 4 hour benchmark. *Ann Emerg Med* 2006;47(3):259-61.

275. American Medical Association. Guidelines for pay for performance programs: AMA, 2005.

276. Fee C, Weber EJ, Sharpe BA, Quon T. When is a scarlet letter really a red badge of courage?: the paradox of percentage of pneumonia patients receiving antibiotics within 4 hours in accordance with JCAHO and CMS core measures. *Ann Emerg Med* 2007;50(2):205-6.

277. Maroun V, Cochrane D, Allegra J. Delays in antibiotic administration associated with chest X-ray negative and computed tomographic scan positive for pneumonia. *Am J Emerg Med* 2006;24(3):390-1.

278. Pines JM, Hollander JE, Lee H, Everett WW, Uscher-Pines L, Metlay JP. Emergency Department Operational Changes in Response to Pay-for-performance and Antibiotic Timing in Pneumonia. *Acad Emerg Med* 2007; 14(6):545-8.

279. Kahn KL, Rogers WH, Rubenstein LV, Sherwood MJ, Reinisch EJ, Keeler EB, et al. Measuring quality of care with explicit process criteria before and after implementation of the DRG-based prospective payment system. *Jama* 1990;264(15):1969-73.

280. Werner RM, Bradlow ET. Relationship between Medicare's hospital compare performance measures and mortality rates. *Jama* 2006;296(22):2694-702.

281. Dedier J, Singer DE, Chang Y, Moore M, Atlas SJ. Processes of care, illness severity, and outcomes in the management of community-acquired pneumonia at academic hospitals. *Arch Intern Med* 2001;161(17):2099-104.

282. Marrie TJ, Wu L. Factors influencing in-hospital mortality in community-acquired pneumonia: a prospective study of patients not initially admitted to the ICU. *Chest* 2005;127(4):1260-70.

283. Wilson PA, Ferguson J. Severe community-acquired pneumonia: an Australian perspective. *Intern Med J* 2005;35(12):699-705.

284. Silber SH, Garrett C, Singh R, Sweeney A, Rosenberg C, Parachiv D, et al. Early administration of antibiotics does not shorten time to clinical stability in patients with moderate-to-severe community-acquired pneumonia. *Chest* 2003;124(5):1798-804.

285. Ziss DR, Stowers A, Feild C. Community-acquired pneumonia: compliance with centers for Medicare and Medicaid services, national guidelines, and factors associated with outcome. *South Med J* 2003;96(10):949-59.

286. Irvin CB, Bishop D, Southall A. What are the effects of timing of antibiotic administration less than and greater than 4 hours in pneumonia patients. *Acad Emerg Med* 2004;11(5):555.

287. Waterer GW, Kessler LA, Wunderink RG. Delayed administration of antibiotics and atypical presentation in community-acquired pneumonia. *Chest* 2006;130(1):11-5.

288. Low R, Elie M, Jacobs C, Acanfara R, Meehan S, Dunn V, et al. Early antibiotic therapy does not improve mortality of community acquired pneumonia. *Acad Emerg Med* 2007;14(5 Suppl 1):S161.

289. Pines JM. Measuring antibiotic timing for pneumonia in the emergency department: another nail in the coffin. *Ann Emerg Med* 2007;49(5):561-3.

290. Mortensen EM, Coley CM, Singer DE, Marrie TJ, Obrosky DS, Kapoor WN, et al. Causes of death for patients with community-acquired pneumonia: results from the Pneumonia Patient Outcomes Research Team cohort study. *Arch Intern Med* 2002;162(9):1059-64.

291. Walls RM, Resnick J. The Joint Commission on Accreditation of Healthcare Organizations and Center for Medicare and Medicaid Services community-acquired pneumonia initiative: what went wrong? *Ann Emerg Med* 2005;46(5):409-11.

292. Houck PM, Bratzler DW, Nsa W, Ma A, Bartlett JG. Antibiotic administration in community-acquired pneumonia. *Chest* 2004;126(1):320-1.

293. Shah MN, Croley WC, Jin L, Meltzer D. Predictors of delay to antibiotic dosing in patients with community acquired pneumonia. *Acad Emerg Med* 2001;8(5):487.

294. Fine JM, Fine MJ, Galusha D, Petrillo M, Meehan TP. Patient and hospital characteristics associated with recommended processes of care for elderly patients hospitalized with pneumonia: results from the medicare quality indicator system pneumonia module. *Arch Intern Med* 2002;162(7):827-33.

295. Nathwani D, Williams F, Winter J, Ogston S, Davey P. Use of indicators to evaluate the quality of community-acquired pneumonia management. *Clin Infect Dis* 2002;34(3):318-23.

296. Mortensen EM, Cornell J, Whittle J. Racial variations in processes of care for patients with community-acquired pneumonia. *BMC Health Serv Res* 2004;4(1):20.

297. McGarvey RN, Harper JJ. Pneumonia mortality reduction and quality improvement in a community hospital. *QRB Qual Rev Bull* 1993;19(4):124-30.

298. Fee C. Impact of Emergency Department Crowding on Door to Antibiotic Timing in Admitted Patients with Community-acquired Pneumonia. *Acad Emerg Med* 2006;13(5, supp1):S59-S60.

299. Pines J, Hollander J, Localio R, Baxt W, Lee H, Phillips C, et al. The Association Between ED Crowding and Time To Antibiotics For Pneumonia. *Acad Emerg Med* 2007;14(5 Suppl 1):S160-1.

300. Richardson DB. The access-block effect: relationship between delay to reaching an inpatient bed and inpatient length of stay. *Med J Aust* 2002;177(9):492-5.

301. Dempsey CL, Shillington AC, Jewell MA, Farely PA, Goliak MK. Optimising management of hospitalised patients with community acquired pneumonia. *Infection Medicine* 1999;16(10):670-680.

302. Lindenauer PK, Behal R, Murray CK, Nsa W, Houck PM, Bratzler DW. Volume, quality of care, and outcome in pneumonia. *Ann Intern Med* 2006;144(4):262-9.

303. Schouten JA, Hulscher ME, Natsch S, Kullberg BJ, van der Meer JW, Grol RP. Barriers to optimal antibiotic use for community-acquired pneumonia at hospitals: a qualitative study. *Qual Saf Health Care* 2007;16(2):143-9.

304. Cregin R, Segal-Maurer S, Weinbaum F, Rahal J, Kabrowitz S, Sixsmith D, et al. Multidisciplinary approach to improving treatment of community-acquired pneumonia. *Am J Health Syst Pharm* 2002;59(4):364-8.

305. Barlow G, Nathwani D, Williams F, Ogston S, Winter J, Jones M, et al. Reducing door-to-antibiotic time in community-acquired pneumonia: Controlled before-and-after evaluation and cost-effectiveness analysis. *Thorax* 2007;62(1):67-74.

306. Chu LA, Bratzler DW, Lewis RJ, Murray C, Moore L, Shook C, et al. Improving the quality of care for patients with pneumonia in very small hospitals. *Arch Intern Med* 2003;163(3):326-32.

307. Halm EA, Horowitz C, Silver A, Fein A, Dlugacz YD, Hirsch B, et al. Limited impact of a multicenter intervention to improve the quality and efficiency of pneumonia care. *Chest* 2004;126(1):100-7.

308. Vanhoy SN, Laskowski-Jones L. Early intervention for the pneumonia patient: an emergency department triage protocol. *J Emerg Nurs* 2006;32(2):154-8.

309. Katz B, Burton J, Lin C, McErlean M. Effect on time to antibiotic administration of a comprehensive program for emergency department patients with community acquired pneumonia. *Acad Emerg Med* 2007;14(5 Suppl 1):S55.

310. Metersky ML, Galusha DH, Meehan TP. Improving the care of patients with community-acquired pneumonia: a multihospital collaborative QI project. *Conn Med* 1999;63(7):425-31.

311. Lawrence SJ, Shadel BN, Leet TL, Hall JB, Mundy LM. An intervention to improve antibiotic delivery and sputum procurement in patients hospitalized with community-acquired pneumonia. *Chest* 2002;122(3):913-9.

312. Cooper J, Datner E, Pines J. The Effect of a Chest X-ray at Triage Protocol on Time to Antibiotics for Admitted Patients with Pneumonia. *Acad Emerg Med* 2007;14(5 Suppl 1):S162.

313. Covington D, Hill J, Martinez F, Bennett A, Muehlberg K. Antibiotic timeliness for pneumonia performance improvement. *J Emerg Nurs* 2007;33(4):361-6.

314. Stemper-Bartkus C, Stewart C, Mandell M, Richman PB. An Algorithm to Complement Triage Nurse Clinical Judgment of Risk for Community acquired Pneumonia Improves the Time from Emergency Department Arrival to Administration of Antibiotics. 2006 SAEM Annual Meeting; 2006; S58.

315. Capelastegui A, Espana PP, Quintana JM, Gorordo I, Ortega M, Idoiaga I, et al. Improvement of process-of-care and outcomes after implementing a guideline for the management of community-acquired pneumonia: a controlled before-and-after design study. *Clin Infect Dis* 2004;39(7):955-63.

316. Stone RA, Mor MK, Lave JR, Hough LJ, Fine MJ. Implementation of an inpatient management and discharge strategy for patients with community-acquired pneumonia. *Am J Manag Care* 2005;11(8):491-9.

317. Capelastegui A, Espana PP, Quintana JM, Gorordo I, Sanudo C, Bilbao A. Evaluation of clinical practice in patients admitted with community-acquired pneumonia over a 4-year period. *Arch Bronconeumol* 2006;42(6):283-9.

318. National Library of Medicine. Pubmed, 2005. http://www.ncbi.nlm.nih.gov/sites/entrez

319. Ammenwerth E, Ehlers F, Eichstadter R, Haux R, Kruppa B, Parzer P, et al. Analysis and modeling of the treatment process characterizing the cooperation within multi-professional treatment teams. *Stud Health Technol Inform* 2000;77:57-61.

320. Ammenwerth E, Ehlers F, Eichstadter R, Haux R, Pohl U, Resch F. Systems analysis in health care: framework and example. *Methods Inf Med* 2002;41(2):134-40.

321. Poulymenopoulou M, Malamateniou F, Vassilacopoulos G. Specifying workflow process requirements for an emergency medical service. *J Med Syst* 2003;27(4):325-35.

322. Vassilacopoulos G, Paraskevopoulou E. A process model basis for evolving hospital information systems. *J Med Syst* 1997;21(3):141-53.

323. Fridsma DB. Error analysis using organizational simulation. *Proc AMIA Symp* 2000:260-4.

324. Cain C. Representing and reasoning about contextually changing organisational behaviour using simulation models of medical work. Stanford, 2004.

325. Fischer L. *The Workflow Handbook 2001*. Florida: Future Strategies Inc, 2000.

326. Coalition WM. Workflow Management Coalition Terminology & Glossary: Workflow Management Coalition, 1999. http://www.wfmc.org/standards/docs/TC-1011_term_glossary_v3.pdf

327. Hollinsworth D. Workflow Management Coalition: The Workflow Reference Model: Workflow Management Coalition, 1995. http://www.wfmc.org/standards/docs/tc003v11.pdf

328. Allen R. Workflow: An introduction: Workflow Managment Coalition, 2001. http://www.wfmc.org/standards/docs/Workflow_An_Introduction.pdf

329. Aggarwal V. The Application of the Unified Modeling Language in Object-Oriented Analysis of Healthcare Information Systems. *Journal of Medical Systems* 2002;26(5):383-397.

330. Maij E, Toussaint PJ, Kalshoven M, Poerschke M, Zwetsloot-Schonk JHM. Use cases and DEMO: aligning functional features of ICT-infrastructure to business processes. *International Journal of Medical Informatics* 2002;65:179–191.

331. Ashar BS, Ferriter A. Radiofrequency identification technology in health care: benefits and potential risks. *Jama* 2007;298(19):2305-7.

332. Augusto JC. Temporal reasoning for decision support in medicine. *Artif Intell Med* 2005;33(1):1-24.

333. Mansour E, Wu B, Dube K, Li JX. An Event-Driven Approach to Computerizing Clinical Guidelines Using XML. Proceedings of the IEEE Services Computing Workshops (SCW'06); 2006.

334. Peleg M, Tu S, Bury J, Ciccarese P, Fox J, Greenes RA, et al. Comparing computer-interpretable guideline models: a case-study approach. *J Am Med Inform Assoc* 2003;10(1):52-68.

335. Wright A, Sittig DF. A four-phase model of the evolution of clinical decision support architectures. *Int J Med Inform* 2008;77(10):641-9.

336. Mykkanen J, Riekkinen A, Sormunen M, Karhunen H, Laitinen P. Designing web services in health information systems: from process to application level. *Int J Med Inform* 2007;76(2-3):89-95.

337. Laleci GB, Dogac A. A semantically enriched clinical guideline model enabling deployment in heterogeneous healthcare environments. *IEEE Trans Inf Technol Biomed* 2009;13(2):263-73.

338. Sox HC, Blatt MA, Higgins MC, Marton KI. *Medical Decision Making*. 1st ed. Stoneham: Butterworth, 1988.

339. Varvasovszky Z, Brugha R. A stakeholder analysis. *Health Policy Plan* 2000;15(3):338-45.

340. Brugha R, Varvasovszky Z. Stakeholder analysis: a review. *Health Policy Plan* 2000;15(3):239-46.

341. Sutton AJ, Jones DR, Abrams KR, Sheldon TA, Song F. Systematic reviews and meta-analysis: a structured review of the methodological literature. *J Health Serv Res Policy* 1999;4(1):49-55.

342. Monti S, Cooper GF. The impact of modeling the dependencies among patient findings on classification accuracy and calibration. *Proc AMIA Symp* 1998:592-6.

343. Maria A. Introduction to modeling and simulation. *Proceedings of the 1997 Winter Simulation Conference* 1997; Atlanta, Georgia. Institute for Operations Research and Management Sciences.

344. Davies HTO, Davies R. Simulating health systems: modelling problems and software solutions. *European Journal of Operational Research* 1995;87(1):35-44.

345. Jun JB, Jacobson SH, Swisher JR. Application of discrete-event simulation in health care clinics: A survey. *Journal of the Operational Research Society* 1999;50(2):109-123.

346. Zimmermann A. *Stochastic Discrete Event Systems Modeling, Evaluation, Applications*. Heidelberg: Springer Berlin, 2008.

347. Banks J, Carson JS. Introduction to discrete event simulation. *Proceedings of the 1986 Winter Simulation Conference*. 1986.

348. Mackay M, Pradhan M. Use of simulation modelling to overcome operational and structural inefficiencies. *Health Informatics Society of Australia Conference Proceedings* 2000; Adelaide. Health Informatics Society of Australia.

349. Harper P, Shahani A. Modelling for the planning and management of bed capacities in hospitals. *Journal of Operational Research Society* 2002(53):11–18.

350. Kelton, W. Tutorial on design and analysis of simulation experiments. *Winter Simulation Conference Proceedings* 1995;24-31.

351. Kaye KS, Stalam M, Shershen WE, Kaye D. Utility of pulse oximetry in diagnosing pneumonia in nursing home residents. *Am J Med Sci* 2002;324(5):237-42.

352. Aujesky D, Stone RA, Obrosky DS, Yealy DM, Auble TE, Meehan TP, et al. Using randomized controlled trial data, the agreement between retrospectively and prospectively collected data comprising the pneumonia severity index was substantial. *J Clin Epidemiol* 2005;58(4):357-63.

353. Corporation I. S-PLUS 6 for Windows User's Guide: Insightful Corporation, 2001.

354. Australasian College of Emergency Medicine. Policy document - the Australiasian Triage Scale: ACEM, 2000.

355. Stiell A, Forster AJ, Stiell IG, van Walraven C. Prevalence of information gaps in the emergency department and the effect on patient outcomes. *Cmaj* 2003;169(10):1023-8.

356. Espinosa JA, Nolan TW. Reducing errors made by emergency physicians in interpreting radiographs: longitudinal study. *Bmj* 2000;320(7237):737-40.

357. Houck PM, Bratzler DW, Niederman M, Bartlett JG. Pneumonia treatment process and quality. *Arch Intern Med* 2002;162(7):843-4.

358. Dent A, Rofe G, Sansom G. Which triage category patients die in hospital after being admitted through emergency departments? A study in one teaching hospital. *Emergency Medicine* 1999;11:68–71.

359. Whittle J, Fine MJ, Joyce DZ, Lave JR, Young WW, Hough LJ, et al. Community-acquired pneumonia: can it be defined with claims data? *Am J Med Qual* 1997;12(4):187-93.

360. van de Garde EM, Oosterheert JJ, Bonten M, Kaplan RC, Leufkens HG. International classification of diseases codes showed modest sensitivity for detecting community-acquired pneumonia. *J Clin Epidemiol* 2007;60(8):834-8.

361. Aronsky D, Haug PJ, Lagor C, Dean NC. Accuracy of administrative data for identifying patients with pneumonia. *Am J Med Qual* 2005;20(6):319-28.

362. Marrie TJ, Durant H, Sealy E. Pneumonia--the quality of medical records data. *Med Care* 1987;25(1):20-4.

363. Scinto JD, Galusha DH, Krumholz HM, Meehan TP. The case for comprehensive quality indicator reliability assessment. *J Clin Epidemiol* 2001;54(11):1103-11.

364. Ishida T, Miyashita N, Nakahama C. Clinical differentiation of atypical pneumonia using Japanese guidelines. *Respirology* 2007;12(1):104-10.

365. Masia M, Gutierrez F, Padilla S, Soldan B, Mirete C, Shum C, et al. Clinical characterisation of pneumonia caused by atypical pathogens combining classic and novel predictors. *Clin Microbiol Infect* 2007;13(2):153-61.

366. Miyashita N, Fukano H, Yoshida K, Niki Y, Matsushima T. Is it possible to distinguish between atypical pneumonia and bacterial pneumonia?: evaluation of the guidelines for community-acquired pneumonia in Japan. *Respir Med* 2004;98(10):952-60.

367. Moolenaar RL, Dalton C, Lipman HB, Umland ET, Gallaher M, Duchin JS, et al. Clinical features that differentiate hantavirus pulmonary syndrome from three other acute respiratory illnesses. *Clin Infect Dis* 1995;21(3):643-9.

368. Ruiz-Gonzalez A, Falguera M, Vives M, Nogues A, Porcel JM, Rubio-Caballero M. Community-acquired pneumonia: development of a bedside predictive model and scoring system to identify the aetiology. *Respir Med* 2000;94(5):505-10.

11 Glossary

AF- atrial fibrillation

AMH- Australian Medicines Handbook

ARRR- absolute relative risk reduction

ATG- Australian Therapeutic Guidelines

ATS- Australasian Triage Score

AmTS- American Thoracic Society

BPR- business process re-engineering

BTS- British Thoracic Society

CAP- community-acquired pneumonia

CAVHAT- Context Aware Virtual Health Administration Team

CDSS- computer-based decision support system(s)

CIDS- Canadian Infectious Disease Society

CIS- clinical information system(s)

CMS- Centres for Medicare and Medicaid Services

COAD- chronic obstructive airways disease

CRB-65- variant of CURB-65 (see below)

CRB-65RF- variant of CURB-65 (see below) where RF stands for Renal Failure

CT- computer tomography

CURB- variant of CURB-65 (see below)

CURB-65- community-acquired pneumonia mortality risk prediction rule consisting of Confusion, Urea 7 mmol/l, respiratory rate >30, blood pressure < 90 systolic, diastolic < 60, and age 65 years and over

CXR- chest x-ray

DNA- deoxyribonucleic acid

EBM- evidence-based medicine

ECA- event-condition-action rules

ECG- electrocardiogram

ED- emergency department

EDM- early diagnostic model

EHR- electronic health record

FIO2- fraction of inspired oxygen

HAP- hospital-acquired pneumonia

HDU- high dependency unit

HIV- Human Immunodeficiency Virus

ICD- International Classification of Disease

ICU- intensive care unit

IDSA- Infectious Disease Society of America

IT- information technology

IV- intravenous

JCAHO- Joint Commission on Accreditation of Health care Organizations

LOS- length of stay

LR- likelihood ratio(s)

LVF- left ventricular failure

mBTS- modified British Thoracic Society community-acquired pneumonia mortality risk prediction rule

mmHg - pressure in millimetres of mercury

MI- myocardial infarction

OR- odds ratio(s)

pO2 - partial pressure of oxygen

pCAP - probability that a patient has community-acquired pneumonia

PCR- polymerase chain reaction

pH - acidity

PMI- patient management index

PSI- Pneumonia Severity Index

ROC- receiver operating characteristic

SaO2 - blood oxygen saturation

SARS- severe acute respiratory syndrome

SOA - service oriented architecture

SQL - Structured Query Language

UK- United Kingdom

UML- Unified Modelling Language

US- United States

VDT- Virtual Design Team

WBC - white cell count

XML - extensible mark-up language