TIMELINESS OF MICROBIOLOGY TEST RESULT REPORTING AND ASSOCIATION WITH OUTCOMES OF ADULTS HOSPITALISED WITH PNEUMONIA: A DATA LINKAGE STUDY

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DECLARATION

I hereby declare that this submission is my own work and to the best of my knowledge it contains no materials previously published or written by another person, or substantial proportions of material which have been accepted for the award of any other degree or diploma at Macquarie University or any other educational institution, except where due acknowledgment is made in this thesis. Any contribution made to the research by others, with whom I have worked at Macquarie University or elsewhere, is explicitly acknowledged in the thesis.

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ABSTRACT

Background: Pneumonia is one of the major causes of morbidity and mortality among young and elderly people across the globe. Microbiology tests play a critical role in the diagnosis of pneumonia. To date, the relationship between the time to first microbiology test result reporting and patient outcomes has not been reported in the existing literature.

Objective: The objectives of this study are to determine: (1) microbiological test ordering patterns, (2) the timeliness of microbiological test reporting (e.g. the time from hospital admission to the first test result) and (3) associations of time to first microbiology test result reporting with patient outcomes (e.g. in-hospital mortality) among adult patients (aged ≥ 18 years) hospitalised with unspecified pneumonia.

Method: A 3-year (2016-2018) retrospective cohort (data linkage) study in six hospitals in NSW, Australia. Study data were obtained by linking hospital and laboratory system databases. We used the International Classification of Diseases version 10-Australian Modification (ICD-10-AM) code J18.9 to identify patients hospitalised with unspecified pneumonia. Timeliness of result reporting indicators including the time from admission to the first and the last microbiology tests were determined. The outcome measures were hospital length of stay (LOS) and in-hospital mortality. We fit median and logistic regression to evaluate the association of timeto first microbiology test result reporting with hospital LOS and in-hospital mortality respectively.

Results: A total of 6,298 patients met the inclusion criteria. Of these, 85.3% (n=5,375) ordered at least one microbiology test. The top 5 microbiology tests were blood culture, urine culture, respiratory PCR, urine antigen and sputum culture. The median time to the first test result was 26 hrs (IQR, 13-58) while the median time to the last test was 144 hrs (IQR, 128-211). The rate of in-hospital mortality was 5.9% (n=371). After adjusting for confounders, every 5 hrs increase in the time-to first microbiology test was associated with an increase of 3.9 hrs in the median hospital LOS (95% CI, 3.5 to 4.3; P<0.001). There was no association between time to the first microbiology result and in-hospital mortality (OR 1.01; 95% CI 1.00-1.02; P=0.122).

Conclusion: Time to first microbiology test result reporting was significantly associated with hospital LOS but not with in-hospital mortality. Further study should be conducted to understand if shortening time to first microbiology test result reporting can reduce the length of hospital stay of patients.

Key words: Microbiology diagnositics; Test result reporting; Pneumonia; Diagnostic informatics

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TAT	Turnaround time
LOS	Length of stay
CAP	Community acquired pneumonia
HCAP	Healthcare-associated pneumonia
HAP	Hospital acquired pneumonia
ED	Emergency Department
MCS	Microscopy, culture and sensitivity
PCR	Polymerase chain reaction
CCI	Charlson comorbidity index
DRG	Diagnosis-related group
ICU	Intensive care unit
CDC	Centre for Disease Control and Prevention
MDR	Multidrug resistance

Chapter 1
Introduction

1.1 Pneumonia

1.1.1 Overview and definition

Lower respiratory tract infection, including pneumonia, is the fifth-highest cause of death in the world, accounting for 2.5 million deaths in 2016 (1). Pneumonia is one of the major causes of morbidity and mortality among elderly people in developed countries (2). In developing countries, however, pneumonia is a major cause of morbidity and mortality among children under the age of 5 years, accounting for 15% of total deaths (3).

Pneumonia is a type of acute lower respiratory tract infection that inflames the air sacs of the lungs, which become filled with pus and other liquids (4). The presence of fluid or pus in the alveoli, instead of air, reduces the oxygen level in the body and makes the lungs painful during breathing (5). Pneumonia is caused by various species of microorganisms, including bacteria, viruses and fungi (2, 4). However, the causative agents of pneumonia are unidentified in about 30–50% of cases (2, 4). Such cases are called *unspecified pneumonia* (2, 4).

The common clinical manifestations of pneumonia include respiratory symptoms (sputum, cough, chest pain, dyspnoea), infection symptoms (flu-like symptoms, fever, malaise, hypothermia, circulatory symptoms), and related physical findings (focal auscultatory abnormality, arterial hypotension, tachycardia) (6). Some of the other common symptoms are fatigue, low appetite, nausea, and vomiting in children (7, 8) . Although clinical manifestations are used in the diagnosis of pneumonia, microbiological diagnostic testing and medical imaging may also be useful for confirming the infection (6).

1.1.2 Types of pneumonia

Pneumonia can be classified in different ways based on the microorganism causing the disease, the severity of the disease and the source of the infection.

Based on the microorganism causing it, pneumonia can be classified as bacterial, viral and fungal (9-11). Pneumonia caused by bacterial infection is known as *bacterial pneumonia* (9), with the most common bacteria being *Streptococcus pneumoniae* and *Staphylococcus aureus* (12). Similarly, pneumonia caused by viral infection is known as *viral pneumonia* and pneumonia

caused by fungal infection is known as *fungal pneumonia* (10, 11). The main risk factors for viral pneumonia are age, chemotherapy, human immune deficiency virus (HIV) infection and organ transplantation (13). The most common viruses causing pneumonia are respiratory syncytial viruses, influenza viruses and coronaviruses (2, 14). Fungal pneumonia is not very common; however, the common fungi causing pneumonia are *Aspergillus* species, *Coccidiodes immitis*, *Histoplasma capsulatum*, *Crytococcus neoformans*, and *Chrysosporium* species (15, 16).

Based on the severity of pneumonia, community-acquired pneumonia (CAP) can be classified as mild, moderate and severe (17). Pneumonia is considered mild in patients younger than 65 years who have a normal pulse rate and blood pressure, 30 breaths per minute, sufficient oxygen in their blood, are conscious, and are free from other severe medical conditions (18). Moderate pneumonia signs include worsening shortness of breath, low blood pressure, drowsiness and confusion (19). Moderate pneumonia is treated at a hospital (19). The risk factors for moderate pneumonia are age and comorbidities (19). Severe pneumonia is defined as the presence of CURB-65 factors (confusion, urea > 7 mmol/ lit, respiratory rate > 30/ minute, blood pressure < 90 mm Hg systolic <60 mm Hg diastolic, age > 65 years) or a pneumonia severity index of IV-V (20, 21).

Based on the source of infection, pneumonia can also be classified as community-acquired pneumonia (CAP) and healthcare-associated pneumonia (HCAP) (22, 23).

I. Community-acquired pneumonia:

Community-acquired pneumonia is acquired by an immune-competent individual from the community without direct contact with a hospital or healthcare setting (22). CAP is a life threatening disease in elder adults and patients with comorbidities (24). In developed countries, CAP is a major cause of hospital admission and mortality (25). CAP is responsible for excessive consumption of healthcare resources (25). CAP can be caused mostly by one pathogen but infection by multiple bacteria is also reported and is increasing in number (25). In the pre-antibiotic era, 95% of CAP was caused by the bacterium *Streptococcus pneumoniae* (22). After the introduction of the pneumococcal polysaccharide vaccine for adults and pneumococcal conjugate vaccine for children, the incidence of CAP by *S. pneumoniae* decreased and now detected only among 10-15% of inpatients in the United States (22). However, the predominant bacteria causing CAP is still *S. pneumoniae*, followed by *Haemophilus influenzae*, *Staphylococcus aureus*, and *Mycoplasma pneumoniae* (26). The common viruses responsible for

CAP are rhinoviruses, respiratory syncytial viruses, influenza viruses, adenoviruses, parainfluenza viruses and bocavirus (27, 28). The strongest risk factor for CAP among adults is cigarette smoking (24).

CAP can be classified into typical and atypical pneumonia (29). Typical CAP is caused by common bacteria such as *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Klebsiella pneumoniae* (29, 30). The symptoms of typical pneumonia are sudden onset of fever, productive cough, pleuritic chest pain and chills (29). Atypical pneumonia is caused by atypical bacteria (*Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, *Legionella pneumophila*) and viruses that do not commonly cause pneumonia (29, 30). The symptoms of atypical pneumonia are fever without chills, unproductive cough, myalgia and headache (29). The prevalence of atypical bacteria in CAP in Latin America has been reported to be 3.4–6.1 % for *Chlamydophila pneumoniae*, 1.7–15.7 % for *Mycoplasma pneumoniae*, and 1.1–4 % for *Legionella pneumophila* (31). Similarly, the prevalence of atypical pneumonia in CAP in Australia from 2004 to 2006 has been reported to be 1.2 % for *Chlamydophila pneumoniae*, 8.8 % for *Mycoplasma pneumoniae*, and 3.4 % for *Legionella pneumophila* (32). Furthermore, the prevalence of atypical pneumonia in CAP in the world from 2001 to 2006 has been reported to be 7 % for *Chlamydophila pneumoniae*, 12 % for *Mycoplasma pneumoniae*, and 5 % for *Legionella pneumophila* (32).

II. Healthcare-associated pneumonia:

Healthcare-associated pneumonia is acquired within a hospital or long-term care facility (33). Most of the healthcare-associated pneumonia are caused by bacteria that are resistant to the majority of antibiotics (33). According to American thoracic society (ATS) guidelines, patients who have a clinical presentation of pneumonia within 90 days after hospitalization or hospital discharge are considered to have HCAP (33) Depending on the study type and population analysed, the incidence of HCAP has been reported to range from 17.3% to 67.4% (34). A retrospective study done in the United States in 2005 found HAP of 21.7% and the observational study done in Spain in 2007 found HAP of 17.3% (34). The risk factors for HCAP are old age, comorbidities, length of stay at a hospital, immunosuppression, frequent visitors to healthcare, invasive procedures, ventilatory support and intensive care unit (ICU) admission (35). It can be further classified as hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP; (23, 35).

HAP is an infection of the lungs acquired at least 48–72 hours after hospital admission (35). The common causes of HAP are *Enterobacter* spp., *Staphylococcus aureus*, and *Pseudomonas aeruginosa* (36). About 50% of cases of HAP are due to polymicrobial infection (36). VAP is hospital-acquired pneumonia which occurs after tracheal intubation and mechanical ventilation (37, 38). VAP can be classified into early-onset pneumonia and late-onset pneumonia (38). Early-onset pneumonia occurs within four days of mechanical ventilation and tracheal intubation (38). Early-onset pneumonia is caused by bacteria that are susceptible to antibiotics (38). The antibiotic susceptible bacteria for causing early-onset VAP are *Streptococcus pneumoniae, Haemophilus* spp., and methicillin sensitive *Staphylococcus aureus* (38). Late-onset pneumonia occurs after four days of mechanical ventilation and tracheal intubation (38). Late-onset pneumonia is caused by multidrug resistant bacteria (38). The multidrug resistance bacteria for causing late-onset VAP are *Acinetobacter* spp., *Pseudomonas aeruginosa*, and methicillin resistant *Staphylococcus aureus* (38).

VAP is a major economical and clinical problem in patients because it is associated with prolonged ventilation requirements, ICU length of stay, increased resistance to antibiotics, morbidity and mortality (37, 39, 40). The global prevalence of VAP is 15.6% and the global incidence is 5–20 cases per 1000 mechanical ventilation per day (37). The estimated attributable mortality of VAP is 9% (38).

According to a report published by the Centre for Disease Control and Prevention (CDC), about 4% of patients admitted to hospital have at least one healthcare-acquired infection, among which HAP is dominant (35).

1.1.3 Etiological agents for pneumonia

The aetiology of pneumonia is complicated because there are numerous and extremely diverse microorganisms that can cause it (41). The common causes of pneumonia are bacteria, viruses and fungi (42). Although the most common causative agents are viruses, bacterial pneumonia is a major public health issue because of the severity of its clinical symptoms and its increasing antibiotic resistance (42).

I. Bacteria:

The distribution of bacteria that cause CAP differs according to place and time (24). The factors that cause these differences may include the extent of environmental pollution, life expectancy, people's awareness of pneumonia preventive measures and the use of antibiotics (24). The most common causative agent of CAP is *Streptococcus pneumoniae*, which occurs in 50% of cases (24). Infection by *S. pneumoniae* can be fatal in up to 20% of patients (24). *Streptococcus pneumonia* has become a global threat due to its increasing antimicrobial resistance (43).

Another bacterium, *Mycoplasma pneumoniae*, is responsible for 10-40% or more of CAP cases in children globally (44). *Mycoplasma pneumoniae* infection is usually associated with co-infection by other bacteria (44). A prospective cross sectional study found that prevalence of CAP caused by *M. pneumoniae* was 35% (44). Similarly, *Pseudomonas aeruginosa* is another major pathogen in VAP, with a prevalence of 4% and a mortality rate of approximately 13.5% (37). The mortality rate can even rise to 35.8% in multidrug-resistant *P. aeruginosa* (37). Other etiological agents responsible for causing pneumonia are *Staphylococcus aureus*, *Mycobacterium tuberculosis*, *Haemophilus influenza*, *Bordetella pertussis*, *Moraxella catarrhalis* and *Klebsiella pneumonia* (24).

It has been challenging to prescribe antimicrobial agents for pneumonia patients due to the emergence and spread of multidrug-resistant bacteria (43). K. pneumonia is one of the major cause of pneumonia and this bacteria plasmid may contain a carbapenem-resistant gene and can be transferred among other strain of *K. pneumoniae* and other pneumonia-causing bacteria (41). Also, there has been a recent emergence of other bacteria with plasmid-mediated colistin-resistant genes that show resistance to all licensed antibiotics (41). The emergence of plasmid-mediated carbapenem- and colistin-resistant genes in pneumonia-causing bacteria has resulted in treatment failure, increase in patients length of stay at hospital and increase in treatment cost (41, 45). Treatment option for penumonia has been use by combined antibiotics such as Imipenam/ Cilastation/ Relebactam and Piperacillin/ Tazobactam (46). A recent study suggests Imipenam/ Cilastation/ Relebactam as an effective antibiotic combination for adults of high risk pneumonia (46).

II. Viruses:

The introduction of the pneumococcal conjugate vaccine and *Haemophilus influenza* type b vaccine has decreased bacterial pneumonia rates but there has been an increase in viral pneumonia cases (2). Studies on etiological agents have reported an increased rate of mixed bacterial/viral infection among pneumonia patients (47). A study done in Finland found both viruses and bacteria in 66% of sputum specimens of children suffering from pneumonia (47). In the past decade, coronaviruses HKU1 and NL63, human metapneumovirus and human bocavirus have been discovered to cause pneumonia (2).

In recent years, avian influenza A (H5N1) virus, influenza A (H1N1), severe acute respiratory syndrome (SARS) and novel coronavirus (SARS-CoV-2) have also been found to be causative agents of pneumonia (2, 14). Furthermore, respiratory syncytial virus, adenovirus, rhinovirus, parainfluenza virus, enterovirus, varicella-zoster virus, cytomegalovirus, herpes simplex virus and human parechoviruses have been detected as causative agents of pneumonia (2, 48).

The novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in December 2019 in Wuhan, China (49). This virus is highly transmittable and was declared a pandemic on 11 March 2020 (50). The disease caused by this virus is called COVID-19 (50). Recently, this virus has become a major threat as it can increase the risk of pneumonia. Pneumonia due to SARS-CoV2 is the most common reason for patients with COVID-19 to be hospitalised (50).

III. Fungi:

Fungal pneumonia is caused by an infection of the respiratory tract by fungi, and represents a smaller proportion of cases than bacterial and viral pneumonia (15). Pneumonia due to fungal infection is most prevalent among immune-compromised people (15). Fungal spores are inhaled and remain in the upper and lower respiratory tract (51). The inhaled fungal spores can cause pneumonia in people with low immunity (51). Common fungi causing pneumonia are *Aspergillus* species, *Chrysosporium* species, *Candida* species, *Cryptococcus* species and *Curvularia* species (15, 52). *Aspergillus* species are the predominant fungus causing pneumonia in hospitalised

patients (51). Poor air filtration systems in hospitals and contamination of hospital ventilation systems with *Aspergillus* species are the major sources of pneumonia in hospitalised patients (51).

1.1.4 Risk factors for pneumonia

Pneumonia is a serious condition that can affect people of any age; however, people aged above 65, young children and infants are most affected (53). The incidence of pneumonia in adults is 2.5 per 1000 people per year in the United States (54). From the 65–79 year age group to the 80+ age group, the incidence of pneumonia increases from 6.3 to 16.4 per 1000 people per year (54). This increase in mortality in elderly people may be because of a potential increase in co-morbidities in elderly people, which makes them more susceptible to infection (54). Patients with comorbidities such as chronic cardiovascular disease, splenic dysfunction, chronic renal failure, chronic pulmonary disease, cochlear implants, chronic renal failure, HIV, epilepsy, Parkinson's disease, dementia, dysphagia, liver disease, asthma and diabetes are at greater risk of pneumonia (53, 55-57).

In 2015, among all infectious diseases, pneumonia was the leading cause of mortality among children aged below 5 years (58). In children, certain environmental factors are associated with an increased risk of pneumonia (58). These include indoor air pollution due to cooking with biomass fuels, crowding, second-hand smoke from parents, poor ventilation while using a gas stove, dampness, chemicals such as paints, and sudden changes in temperature in the working environment (58).

Lifestyle factors such as alcohol consumption, smoking, poor dental hygiene, low body weight, low body mass index, malnutrition, lack of exclusive breastfeeding, low birth weight, absence of measles immunization, and regular contact with young children or pet animals have also been associated with increased risk of pneumonia (55, 56, 59, 60).

People with low immunity, such as those with HIV, the elderly, and people with underdeveloped immune systems such as young children and infants, are more likely to contract pneumonia (53, 57). People with previous pneumonia, previous respiratory tract infection, or previous immunosuppressive therapy are also at increased risk of pneumonia (56). Other risk factor pneumonia include initial antibiotic treatment and bacteraemia (61). Prolonged hospitalization of patients with pre-existing health conditions such as cardiac surgery is also associated with the risk

of HCAP (62). Pneumonia and its complications, such as sepsis and respiratory failure, are the major cause of death among infection-related diseases in the United States (54).

1.1.5 Epidemiology of pneumonia

Although progress in science and technology has lead to better preventive strategies, laboratory diagnoses and antimicrobial therapy, pneumonia remains an important global public health issue due to its high morbidity and mortality (43). In 2015, 3.2 million deaths out of the 56.4 million total deaths in the world were caused by lower respiratory tract infection, which includes pneumonia (63). The global burden of disease in 2015 estimated that 2 million adults died due to pneumonia (54). Between 2010 and 2011 globally, more than 120 million cases of pneumonia were estimated to have occurred among children aged under 5 years, with about 10% having severe cases (64). In 2015, pneumonia was the leading global cause of mortality among all infectious diseases in children aged below 5 years (58). Globally, pneumonia has taken the lives of 808,000 children aged under 5 years, which accounts for 15% of all child deaths in 2017 (65).

The incidence of pneumonia in developing countries is estimated to be 20–30%; while in developed countries, it is 3–4% (66). Also, an estimated 40% of the world's acute respiratory infections occur in four countries: India, Indonesia, Nepal and Bangladesh (67). Moreover, the incidence rate of pneumonia is higher in Asia than in Europe (63). The incidence of pneumonia in Asia is 16.9 cases per 1000 persons per year, while in Europe it is 1.07–1.2 cases per 1000 persons per year (63).

Pneumonia is the main cause of child death and adult hospitalisation in developing countries (67). In developed countries, 70% of deaths due to pneumonia occurred in people aged 70 years and above (54). However, in developing countries, the majority of deaths due to pneumonia are among people below 70 years of age (54). The early childhood mortality of pneumonia in India was 369,000 in the year 2014 and the incidence was 0.37 episodes per child per year (60). In Maharastra, a state of India, the prevalence of pneumonia among children below 5 years of age was 2.4–8.9% in 2014 (60). In Nepal, the incidence of pneumonia in children under the age of 5 years was 14.7 percent in 2015/2016, while the incidence of pneumonia in adults was not available (67). In 2002, the annual incidence of pneumonia in elderly people in Spain was reported to be 1.04 percent (68). Similarly, in Finland, the incidence of pneumonia among people aged 60–74 years was reported to be 15 percent and for people above 75 years, it was 3.4 percent (68). In

Germany, 20,000 patients died because of pneumonia and influenza, out of which 18,000 patients were aged 65 years and above in 2011 (69). The incidence of CAP in Germany ranges from 400,000 to 680,000 cases annually (69).

The hospitalisation rates due to pneumonia are increasing in the United States and European countries (66). The increase in hospitalisation among these developed countries is due to the large elderly proportion of the population, the presence of co-morbidities, and risk behaviors such as hypertension, diabetes mellitus, heart disease, asthma, diabetes, excessive weight, immunosuppressive treatment, alcoholism, smoking and chronic obstructive pulmonary disease (65, 66, 70). Pneumonia in elderly patients with comorbidities has a poor prognosis and the mortality rate among this group of patients ranges from 5% to 35% (66). The National Hospital Discharge Survey for 2007 reported 1,056,000 patients with pneumonia, of which 610,000 were aged 65 and above (71). The incidence of hospitalized older adults with CAP ranges from 1150 to 1830 per 100,000 people (71). The number of pneumonia patients visiting the emergency departments of hospitals in the United States was 1.3 million in 2018 (72). The number of deaths due to pneumonia in the United States was 47,956 in 2018 (72). A study done in the United States by Stroms *et al.* (2017) found that 19% of hospitalized adult patients were admitted to an ICU. The rate of pneumonia patients that required ICU admission 76 per 100,000 people/year (73).

Hospitalized pneumonia cases cause the greatest healthcare cost burden (68). Each year, an estimated 77,000 patients with pneumonia are admitted to hospitals in Australia (74). The severity of the disease is also expected to increase in Australia due to its high population of aged people (68). In Australia, one study reported that 4% of the total admitted patients aged above 65 years had some form of pneumonia (68). The total number of deaths due to pneumonia in Australia was 4,269 in 2017 (75). In Australia, the 30-day mortality rate is 11.1% among patients aged over 65 years that were hospitalized patients with CAP (70). The rate is even higher in the USA at 12.5% (70). In New South Wales (NSW), 911 deaths from pneumonia were reported in 2018 (76), a mortality rate of 7.7 deaths per 100,000 people (76). Due to pneumonia, the mortality rate was greater in people aged above 65 years, at 55.1 deaths per 100,000 people (76).

The recent outbreak of COVID-19 disease is also responsible for causing viral pneumonia (77). A study found that about 80% of the patients hospitalized with COVID-19-related pneumonia were admitted to a general ward, while a smaller percentage of patients were required ventilator and

ICU (77). A study found that the rate of in-hospital mortality due to COVID-19-related pneumonia was 4.3% in China (78). Older age and number of comorbidities are associated with the severity of disease and death from COVID-19-related pneumonia (77).

1.2 Microbiological laboratory tests for pneumonia

Many microbiological laboratory tests can be performed to detect the etiological agents causing pneumonia (79). These may include culture-based tests such as blood and sputum cultures, gram staining, serology tests and molecular tests using polymerase chain reaction (PCR) (79).

Serological tests for the detection of pathogens have been available for many years, but are rarely used for laboratory diagnosis because many are less reliable (80). Molecular PCR-based tests offer rapid detection of pathogens compared to culture-based tests but may have technical difficulties (80, 81). The specimens used for the detection of respiratory tract infections can be nasopharyngeal swabs, blood, sputum, nasal washes, oropharyngeal swabs or throat swabs, depending on the likely causative agent (79).

Some commonly ordered microbiological tests for patients suspected of having pneumonia are presented below (80).

1.2.1 Blood microscopy, culture and sensitivity (MCS):

Blood MCS (or simply blood culture) is one of the commonly requested tests for diagnosing pneumonia (82). It is done to detect pathogenic bacteria and their antibiotic susceptibility pattern for prescribing antibiotics (82).

The first step is the aseptic transfer of blood to brain heart infusion (BHI) broth or Hartley broth (82). Then, the BHI broth is incubated at 37 °C for 12–24 hours and subcultured in soild media; preferably on MacConkey agar or blood agar (82, 83). The solid media is then incubated for 18–24 hours (82), the presence of bacterial colonies indicates blood infection (83). If no bacterial colonies are obtained it is said to be no growth, and repeated subcultures are done on the fourth and seventh days (82). The isolated bacteria are further identified by gram staining techniques and biochemical reactions and an antibiotic susceptibility test is performed (82). All these steps consume time; as a result, the turnaround time from sample collection to result dissemination may take minimum of 96 hours (82).

Another blood culture technique is automated blood culture systems which uses the BacT/ALERT 3D system (82). This system can detect the growth of bacteria from a minimum of 6 hours to a maximum of 48 days (82). The use of the BacT/ALERT 3D system can reduce turnaround times to 30–72 hours (82).

1.2.2 Molecular PCR-based methods:

PCR is a commonly used molecular technique for the detection of microorganisms (84). The first step in PCR is the extraction of deoxyribonucleic acid (DNA), either from a microbiological (bacteria, virus, fungi) culture or from a sample of patients (84). The targeted genes of the extracted nucleic acids are then amplified by the use of primers (84). Primers are a short segment of a gene that is complementary to the sequence of the target gene (84). The amplification process involves denaturation of DNA, annealing of the primer to the target gene of the DNA, amplification of hybridized DNA, and denaturation of amplified DNA (84). These steps are repeated and exponential amplification of target DNA is obtained. (84) The amplified DNA is detected by use of specific probes and gel electrophoresis (84). In conventional PCR, one primer is used, which can detect one microorganism in one reaction (84).

Nested PCR is a molecular test that can detect even a small amount of target DNA (84). Nested PCR uses two different pairs of primers and two PCR reactions (85). Primers are designed in such a way that the first primer is used to anneal the DNA sequence and initiate the PCR reaction (85). The amplified DNA is used as a templated DNA by the second set of primers (85). The use of two pairs of primers increases the sensitivity and specificity of the reaction (85). Another PCR technique—Multiplex PCR uses multiple sets of primers and can identify up to 100 different species of microorganisms in a reaction using Luminex technology (84).

For the detection of RNA viruses, reverse transcriptase (RT) PCR was developed (84). The RT-PCR has a reverse transcriptase enzyme that converts the RNA of the virus to complementary DNA (84). Then, the complementary DNA is amplified by the PCR method (84). RT-PCR has an advantage over other PCR techniques in the differentiation of living and dead microorganisms (84). This is because, after the death of a cell, the RNA degrades rapidly (84).

Real-time PCR is widely accepted because of its rapid detection, high sensitivity, high specificity, and low risk of contamination (86). A real-time PCR test takes less than 1 hour to detect pathogens

(86). Real-time PCR combines PCR with a fluorescent probe that detects amplified DNA products within the same reaction vessel (86). Research suggests that, compared to conventional PCR, real-time PCR is faster and has higher sensitivity and specificity for the detection of *Pneumocystis*, one of the causative agents of pneumonia (87).

Multiplex real-time PCR was developed for the rapid screening of a wide range of viruses and atypical bacteria in a small number of PCR reactions (88). Multiplex real-time PCR has not been accepted for use with typical pathogenic bacteria because of difficulties in the interpretation of the results, which cannot distinguish between pathogens and contamination in a nonsterile sample (88). For example, a non-sterile sample such as sputum may be contaminated with the normal flora of the oropharynx (88).

Apart from the detection of microorganisms, PCR techniques can also be useful for investigating antibiotic resistance and its sources (84). The antibiotic resistance genes responsible for the production of extended-spectrum beta-lactamase, AmpC beta-lactamase, can be detected by PCR methods (84, 89). At first, the DNA with the antibiotic resistance gene is isolated from the bacteria (84). Then, antibiotic resistance genes such as bla CTX-M, bla TEM, bla SHV and bla AmpC are amplified using a specific primer in a thermocycler (84, 89). The amplified gene is then detected by gel electrophoresis and a specific DNA probes (84).

1.2.3 Sputum MCS (culture):

Sputum is a thick fluid present usually present in patients with lower respiratory tract infection (90). Sputum contains pathogenic bacteria responsible for the infection (90). The bacteria commonly isolated from sputum are *E. coli*, *Streptococcus* sp., *Moraxella* sp., *Acinetobacter* sp., *P. aeruginosa*, *Klebsiella* spp. and *H. influenza* (90). For the microbiological detection of pneumonia in adults, the gram staining and culture of sputum is a routine test (91, 92).

Sputum culture is a routine diagnostic test for identifying the pathogens causing pneumonia (92). Sputum from the suspected patient is inoculated into a culture medium that is incubated for 18–24 hours at 37 °C (92). The media used for sputum culture are blood agar, chocolate agar, MacConkey agar and buffered charcoal yeast agar (93). After growth in the culture medium, the bacteria are identified by biochemical tests and microscopy (92). This is the most widely used test by clinicians for the diagnosis of pneumonia and to determine the correct antibiotics for treatment (92). In

children, a sputum culture is not considered the test of choice due to their low volume of sputum production (91). Based on the bacteria involved, the growth time in the sputum culture medium varies from 24 hours to 10 days (93).

Bacteria that can resist the inhibitory effect of three or more antibiotic groups are considered *multi-drug-resistant* (MDR) *bacteria* (94). The majority of upper respiratory tract infections are caused by viruses (95). Viruses invade the epithelial layers of the respiratory tract and may be a predisposing factor for secondary bacterial infection (95). *Staphylococcus aureus*, *Haemophilus influenzae*, *Streptococcus pyogens*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae* are responsible for causing upper respiratory tract infections that can be MDR (95). Other bacteria that may be MDR and responsible for respiratory tract infection include *Klebsiella pneumoniae*, *Stenotrophomonas maltophilia*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and other species of Enterobacteriaceae (96). The laboratory turnaround time for an antibiotic sensitivity test is 18–24 hours (97). However, MDR bacteria may need two or more antibiotic sensitivity tests (97). Therefore, a greater laboratory turnaround time may be needed for an antibiotic prescription for MDR bacteria than for non-MDR bacteria (97).

1.2.4 Serological test for pneumonia:

Serological tests play a critical role in the diagnosis of atypical CAP (31). In CAP, infection by atypical bacteria *Legionella pneumophila*, *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae* are common among children and adults (31).

M. pneumoniae requires up to 5 weeks for growth in culture medium (98). Also, sensitivity is lower in culture as compared to serological test (98). The common serological test for detection of *M. pneumoniae* is complement fixation test (98). *Coxiella burnetti*, *Chlamydophila* spp., parainfluenza virus, influenza virus, adenovirus and respiratory syncytial virus antibodies can be detected by complement fixation test (98). This test uses blood serum as a sample (98). The sensitivity of this test depends whether the sample is collected during early onset of disease or late onset of disease (98).

Another serological test, indirect immunofluorescence is used for the detection of antibodies of *Legionella pneumophila* (25). For detection of *Chlamydophila psittaci* and *Chlamydophila pneumoniae*, microimmunofluorescence test is used (25).

1.2.5 Urine MCS (culture):

Urine culture is done to detect the presence of pathogens in urine (99). Urine is sterile fluid but when it comes out from the body, it encounters muscles that contaminate it (99). So, mid-stream urine is the sample of choice for urine culture (99). The presence of more than 10^5 microorganisms in mid-stream urine indicates significant growth and is considered a urinary tract infection (99). A semi-quantitative test is performed to estimate the number of microorganisms in the urine (99). In the semi-quantitative method, urine is cultured in MacConkey agar and nutrient agar (99). After significant growth, the bacterial colonies are sub-cultured in nutrient agar, then biochemical and antibiotic susceptibility tests are performed (99). The overall time taken to obtain the final laboratory result is a minimum of 72 hours (99). In cases of multidrug resistant isolates, antibiotic susceptibility tests may need to be performed again, which can take another 24 hours (99).

1.2.6 Pneumococcal urine antigen test:

Although blood culture test is considered as gold standard test for detection of bacteria, in majority of pneumonia patients the blood culture is negative (100). Similarly, molecular techniques less commonly available (100). Pneumococcal urine antigen test is a simple, non-invasive and culture independent (100). This test has excellent specificity greater than 90%, but moderate sensitivity of range 50-80% (100).

S. pneumoniae is one the predominant bacteria causing pneumonia (100). *S. pneumoniae* have C-polysaccharide antigen which is the basis for detection of bacteria in the urine sample (100). One advantage of the test is relatively easy to collect the sample (100). Another advantage of this test is shorter laboratory result time of approximately 15 minutes (100). Even the test can detect pneumococcal antigen of patients administered with antibiotics (100).

1.3 Laboratory test turnaround time (TAT) and its impact on patient outcomes

Lundberg was a pioneer in discussing the issues of test turnaround time (TAT) and was later referenced by many national and international organizations (101). Lundberg outlined the steps required for laboratory tests (102), which include ordering the test, collecting a sample, identification, transportation within or between laboratories, preparation, analysis, reporting, interpretation and action (103). These activities are factors influencing the TAT of laboratory tests

(103). However, the definition of laboratory test TAT differs between laboratory personnel and clinicians (101). For laboratory personnel, TAT is defined as the interval between sample receipt in the laboratory and test report generation; while for clinicians, TAT is defined as the interval between test ordering and receipt of laboratory results (101). The time interval between test ordering and the clinician's awareness of the result is called the *therapeutic TAT* (103).

Most laboratories limit the definition of TAT as an intra-laboratory activity because steps such as the ordering of tests, interpretation and actions are not under the direct control of laboratory personnel (103). Also, data on the timing of extra-laboratory activities are not readily available (103). Such a perspective may underestimate TAT because extra-laboratory activities can comprise up to 96% of the total TAT (103). One of the major factors delaying TAT is the capacity of clinicians to make a clinical decision regarding the laboratory result (103, 104). Therefore, the time from patient's admission to laboratory reporting to a physician would be a suitable measure of patient outcomes.

Laboratory TAT can impact patient outcomes in many ways (105). Nearly 80% of the complaints to laboratories are associated with turnaround times (103). It is a universally accepted fact that the faster the diagnosis, the more effective and efficient the treatment (103). In one study, delays in laboratory test results in the emergency department (ED) resulted in treatment delays of 43% and length of stay (LOS) increases of 61% (106). Furthermore, delays in TAT can increase the duplication of testing (increasing the likelihood of repeating the original tests) (106). This may increase the cost of healthcare treatment and laboratory workload (106). Shorter TATs are desirable for reducing treatment times and costs and for the effective management of patients (106). Thus, it is important to monitor the TAT of laboratory tests as a quality of care indicator (101).

Quantitative data regarding the timelines of microbiology culture and reporting of laboratory results are scarce (107). For more than 100 years, the pace of microbiology testing has been similar because the identification of bacteria is done after its growth, which requires 24 hours of incubation (108). Furthermore, the emergence of multidrug-resistant bacteria, such as methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Staphylococcus aureus* and the extended-spectrum of beta-lactamase and Metallo beta-lactamase-producing bacteria have increased the TATs for microbiology culture and antibiotic susceptibility testing (108). Laboratory processing times are

lower for modern microbiological tests, such as PCR for antigen detection, but the TAT of PCR is usually long due to the laboratory reporting time (107). A long TAT for microbiological test results may lead to a longer LOS in a hospital, which can harm the health of the patient (109). Conversely, a shorter test TAT can reduce hospital LOS and improve the patient's outcome (109). Furthermore, the International Organization for Standardization has made guidelines for TAT, suggesting that laboratories establish a TAT for each test considering clinical needs and examine whether the tests are meeting the established TAT (106).

In evaluating the impact of laboratory testing on patient outcomes in the hospital inpatient setting, a TAT calculated as the interval between hospital admission and test result availability may provide a more relevant predictor of patient outcomes. This project will use this approach to define the timeliness of microbiological test reporting and its potential association with patient outcomes.

1.4 Rationale of the study

Globally, pneumonia is one of the major infectious diseases causing high rates of hospitalisation, morbidity and mortality (110, 111). In Australia, it is estimated that 77,000 people are hospitalised each year due to pneumonia (74). According to the Australian Bureau of Statistics (ABS), there were 4,269 deaths due to pneumonia in Australia in 2017 alone (75). Since late 2019, the world has faced new challenges with the emergence of novel SARS-CoV-2 (COVID-19), which can cause pneumonia and has the potential to greatly increase its incidence (112). Thus, the risk of people becoming infected with pneumonia is increasing worldwide.

Hospitals can become overcrowded due to increases in admissions as well as increases in LOS (113). According to the ABS, the incidence of vaccine-preventable influenza and pneumonia cases increased by 46.5% between 2016/17 and 2017/18 (114). Similarly, a study done in Australia found a mean LOS of pneumonia patients of 7 days (median = 5 days, IQR = 1–54 days) (115).

Various factors influence increases in the LOS of patients at hospital (116). Some studies have suggested that laboratory TAT is a factor leading to longer LOSs and subsequent overcrowding in hospitals (109, 117). Several laboratory tests, such as microbiological, biochemical and haematology tests, are ordered for pneumonia patients (80). In comparison with biochemical tests, microbiological tests usually take more time for laboratory processing and to detect the actual causative agents (80, 105, 107). Commonly ordered microbiological tests for pneumonia patients are blood MCS, sputum MCS, respiratory PCR and urine antigen tests (43). Previous studies have

evaluated the associations between biochemical test TAT, LOS and in-hospital mortality (118, 119). To the best of our knowledge, there has been no research on the relationships between microbiological test reporting timeliness and patient outcomes, such as hospital LOS and in-hospital mortality, among pneumonia patients.

It is important to determine these relationships in relation to the different types of microbiological tests ordered for pneumonia patients. Indeed, understanding these relationships will help to determine which microbiological tests are effective for pneumonia patients. Similarly, determining the relationships between test timeliness, LOS and in-hospital mortality will highlight the importance of TAT.

This study uses the interval between hospital admission to the time of the first microbiological test result as an indicator of laboratory TAT. It aims to evaluate the associations between this TAT indicator and hospital LOS and in-hospital mortality while adjusting for potential confounding factors.

1.5 Thesis aims and objectives

The aim of the thesis is to determine timelines of microbiological test result reporting and their association with hospital LOS and in-hospital mortality among adult patients admitted to hospitals with unspecified pneumonia.

The objectives of the study are three-fold:

1. To determine microbiological test ordering patterns for adult patients (aged ≥ 18 years) hospitalised with unspecified pneumonia across six hospitals in NSW, Australia.
2. To evaluate the timeliness of microbiological test result reporting, including the time from hospital admission to the first and last microbiological test results, and turnaround times for selected tests.
3. To determine the associations between the timelines of microbiological test reporting (e.g. the time from hospital admission to the first test result) with hospital LOS and in-hospital mortality.

1.6 Research questions

1. What are the patterns of microbiological test ordering among adult patients (aged ≥ 18 years) hospitalised with unspecified pneumonia across six hospitals in NSW, Australia?
2. What are the timelines of microbiological test result reporting, including the time from hospital admission to the first microbiological test result, and the TATs of common microbiological tests for unspecified pneumonia?
3. Are there any associations between the time from hospital admission to the first microbiological test result and 1) hospital LOS and 2) in-hospital mortality?

Chapter 2

Methodology

2.1 Study setting

The project was conducted across six public hospitals in New South Wales (NSW), Australia. The hospitals included in the project are listed in Table 1. Three of the hospitals (Hospitals A-C) are located within the South Eastern Sydney Local Health District (SESLHD) and the other three (Hospitals D-F) are located within the Illawarra Shoalhaven Local Health District (ISLHD).

Hospital peer grouping is used to classify similar hospitals based on their shared characteristics and the level of services they deliver. (120) According to the Australian Institute of Health and Welfare's hospital peer groupings, three of the study hospitals are classified as *principal referral*, two hospitals as a*cute group A* and one hospital as *acute group B*. Principal referral hospitals are among the largest hospitals in the Australian health system and provide a very broad range of services, including 24-hour emergency department (ED), intensive care unit (ICU) and several other highly specialised units. Public acute group A and B hospitals are relatively large but do not provide the same range of services as principal referral hospitals. (120)

Table 1: Characteristics of the study hospitals.

Hospital	LHD or Network	Hospital peer group	Annual ED visits	Annual hospital admissions
A	SESLHD	Principal referral	79,894	65,582
B	SESLHD	Principal referral	58,602	48,118
C	SESLHD	Acute group A	53,645	32,159
D	ISLHD	Principal referral	68,985	54,373
E	ISLHD	Acute group B	30,764	13,309
F	ISLHD	Acute group A	40,096	20,231

ED, Emergency Department; SESLHD, South Eastern Sydney Local Health Districts; ISLHD, Illawarra Shoalhaven Local Health Districts; SCHN, Sydney Children's Hospital Network. Data on ED visits and hospital admissions are for 2018 and were obtained from the Bureau of Health Information (121).

2.2 Study design

The study is a retrospective observational (data linkage) study. The duration of the study was 3 years. The study used data collected from 2016 to 2018 across six hospitals in NSW, Australia.

2.3 Participants

The study period was 1 January 2016–31 December 2018. The patient inclusion criteria were: 1) aged 18 years or greater and 2) admitted with unspecified pneumonia as a principal diagnosis..

Unspecified pneumonia was identified according to the *International Classification of Disease Version 10 Australian Modification* (ICD-10-AM) J18.9. Unspecified pneumonia involves acute inflammation of the bronchiole walls and is purulent and septic with the causative microorganism being unidentified. Patients with unspecified pneumonia who were not admitted to the hospital and patients with diseases other than unspecified pneumonia were excluded from the study.

2.4 Data sources and linkage

2.4.1 Data source

The study utilized existing administrative hospital databases and did not collect any additional data. Comprehensive data on patient demographics, clinical aspects and test utilisation were obtained by linking two hospital databases: the Laboratory Information System (LIS) and the Admitted Patient Data Collection (APDC). The LIS contains data on laboratory test utilisation (e.g. blood culture orders, dates and times of test ordering). The APDC contains data on hospital admissions (e.g. diagnosis codes, mode of separation). Detailed information regarding key variables from each of these datasets is presented in Table 2.

Table 2: Selected study variables from each database.

Variable	Definition	Variable type	Data source
Age (years)	Age of the patient at presentation or admission	Continuous	APDC/LIS
Sex	Patient gender	Binary	APDC/LIS
Hospital	Name of the hospital where the service was provided	Categorical	APDC/LIS
Marital status	Marital status of the patient upon admission	Categorical	APDC
Hospital separation	Method or mode of separation from the hospital	Categorical	APDC
Admission urgency	Urgency of admission in the opinion of the treating clinician	Categorical	APDC
Source of referral	Source from which the patient was referred for care	Categorical	APDC
Admission DRG	Description of the AR-DRG at hospital admission	Categorical	APDC
Procedure	Whether a procedure has been conducted or not	Binary	APDC
No. of procedures	Number of procedures performed during a hospital stay	Binary	APDC
No. of comorbidities	Number of comorbidities of a patient during a hospital stay	Continuous	APDC
Charlson CI	Comorbidity index calculated using patient comorbidities based on ICD10 diagnosis codes	Continuous	APDC

Test type	Type of tests ordered (e.g. haematology, microbiology)	Categorical	LIS
Add-on	Whether the ordered test was an add-on or not	Binary	LIS
Test location	Location where the test was ordered (ED/ICU)	Categorical	LIS
No. of tests ordered	Overall no. of tests ordered during a given episode of care	Continuous	LIS
Test order episodes	No. of test ordering episodes during an episode of care	Continuous	LIS

APDC, Admitted Patient Data Collection; LIS, Laboratory Information System; AR-DRG, Australian Refined Diagnosis Related Group; CI, Comorbidity Index; ICD, International Classification of Diseases.

2.4.2 Data linkage

Data linkage was carried out using a validated *deterministic linkage method*, which has previously been successfully used by researchers at Macquarie University (119, 122-124). Data were linked in two steps. Firstly, all datasets were linked using patient identifiers including medical record numbers (scrambled, non-identifiable), date of birth, gender and admission date/times. The records were said to be 'matched' if there was an exact match of all identifiers. In the second step, all records matched in the first step were assessed if the service date/time occurred between the arrival and departure times of the patient at a given site. Because a given patient could have multiple visits at the same or different sites over time, the second step confirmed that the services provided were matched to the correct patient.

2.5 Variables

2.5.1 Outcome measures:

The study outcome measures were *hospital LOS* and *in-hospital mortality*. *Hospital LOS* is defined as the total duration of a patient's stay in hospital, which is the interval between hospital admission and discharge. The modes of discharge were: "discharged by the hospital", "transferred to another setting", "died in hospital", and "left at own risk". *In-hospital mortality* is defined as the death of the patient within the hospital during an episode of admission.

2.5.2 Microbiological test result reporting times:

The indicator for microbiological test result reporting is the *time to the first microbiological test result*, the *time to the last microbiology result*, and the *TAT of the test*. The *time to the first test result* is defined as the duration from the patient's admission to the hospital to their first microbiological test result becoming available. For example, if the first microbiological test result

received was for a blood culture test, then the time from hospital admission to the availability of the blood culture results was chosen as the 'time to the first test result'. Similarly, the *time to the last microbiological test* is defined as the duration from a patient's admission to the hospital to the last microbiological test result becoming available. For example, if the last microbiological test result received was for a sputum culture test, then the time from hospital admission to the availability of sputum culture results was chosen as the *time to the last microbiology test*.

The *TAT* for a given test was calculated as the duration between the receipt of a sample in the laboratory and the availability of the final test report. For example, the turnaround time for a blood culture test is the duration from sample receipt at the laboratory to the final report of blood culture becoming available.

In our study, the time to the first microbiological test was used as a key predictor variable in the statistical modelling (see 'statistical analysis' section). The time to the last microbiological test result was not used because most patients were either discharged, had left the hospital, transferred to another setting, or were deceased before the last test result was available. Similarly, most patients had ordered more than one test; therefore, it would not be practical to find an association between each test TAT with LOS and in-hospital mortality.

2.5.3 Confounders:

The key predictor variable in this study was the time to the first microbiological test, as outlined above. The potential confounders were age, gender, Charlson comorbidity index, DRG complexity, number of tests ordered, source of referral, urgency of admission, repeated microbiological tests ordered, types of microbiological tests ordered and the hospital of admission. The updated version of the Charlson comorbidity index was calculated based on the ICD-10-AM codes. (125)

2.6 Microbiological tests

The microbiological tests included in our study were blood MCS (culture), urine MCS, respiratory PCR, urine antigen (legionella, pneumococcus) and sputum MCS. These tests are common microbiological tests used for the detection of the etiological agent of pneumonia. The microbiology blood culture, urine MCS and sputum MCS tests are used for the detection of bacteria in blood, urine and sputum samples, respectively. Blood culture, urine MCS and sputum

MCS are conventional microbiological tests and follow the steps of isolation of bacteria, identification of bacteria by microscopic examination and biochemical testing, and antibiotic susceptibility testing. So, these three tests guide the correct use of antibiotics for treatment but have longer TATs. Respiratory PCR is a molecular test that requires the isolation and amplification of DNA and detection of a target gene by gene electrophoresis or gene sequencing. PCR testing is an advanced and relatively rapid test method compared to culture-based tests. PCR can be used for the detection of resistance genes in bacteria. Respiratory PCR is commonly used for the detection of viruses in samples. Similarly, urine antigen tests are serological tests that require the detection of antigens in urine. These tests are rapid and have short TATs but do not provide information that can guide antibiotic treatment.

2.7 Statistical analysis

The Stata software package was used for data analysis. GraphPad Prism was used to construct figures. Descriptive analysis of baseline characteristics was conducted by calculating their frequencies as percentages for categorical variables and as medians with interquartile ranges (IQRs) for continuous variables. These characteristics included age, gender, number of microbiological tests, number of laboratory tests, urgency of admission, source of referral, Charlson comorbidity index, year of admission and hospital. Determination of the microbiological test ordering pattern was analysed by calculating their frequencies across the study hospitals.

The times to the first and last microbiological tests are presented using boxplots. Similarly, the TATs of the top five microbiological tests (blood culture, urine MCS, respiratory PCR, urine antigen, and sputum MCS) were compared using boxplots. Boxplots are a standardised method of representing the spread of a dataset and show its range, IQR (25th–75th percentile) and median (50th percentile).

The times from hospital admission to the first and last microbiological tests were used as indicators of the timeliness of microbiological test reporting. Time from admission to the last microbiological test result is a good indicator; however, most patients were either discharged, died or were transferred to other settings before the test results arrived. Therefore, in the modelling methods described below, the time from admission to the first microbiological test was used as a key independent variable. It was also highly correlated with the time from admission to the last microbiological test and, thus, was not useful for later use in modelling.

The type of statistical modelling methods used in the evaluation of associations between an independent variable (i.e. the time from admission to the first microbiological test report) and outcome variables (i.e. hospital LOS and in-hospital mortality) depends on the nature of the outcome variable (i.e. whether it is continuous or categorical). For continuous variables, other assumptions were also checked, such as whether the residuals were normally distributed or not. As a result, to model the association between the independent variable and hospital LOS, median regression was used. Binary logistic regression was used to model the association between the independent variable and in-hospital mortality.

2.7.1 Median regression

Linear regression is often used to determine the association between a continuous dependent variable and an independent variable. For linear regression, the dependent variable's data should have a normal distribution. However, in laboratory studies, dependent variables can be highly skewed or have non-normal distributions. In such cases, the mean is not the preferred measure of central tendency because it is sensitive to outliers. Linear regression uses the mean as the measure of central tendency, so cannot be used with such data. One approach for improving the normality and symmetry of highly skewed data for linear regression is transformation. However, the transformation of data makes it difficult to interpret the results and, often, normalisation of the data fails. So, for highly skewed data, the median is often used as the measure of central tendency. Therefore, median regression can be used for highly skewed continuous data.

Likewise, in our study, the dependent variable was LOS, which is continuous. However, the LOS in hospital was highly skewed with a non-normal distribution. Therefore, linear regression was not the preferred analysis method. Therefore, the association between the time of the first microbiological result and hospital LOS was determined by median regression. Univariate and multivariate analyses were conducted to find the association between LOS and the time of the first microbiological result. In this analysis, the association between *time to first microbiological test result* and *LOS* was analysed at a resolution of 5 hours for interpretation purposes.

The relationships between *LOS* and baseline characteristics were also determined using median regression. One baseline characteristic, *age*, was analysed for every 10-year increase in patient age. At first, univariate analysis was conducted to find the associations between baseline characteristics and *LOS.*

Similarly, the relationship between *LOS* and microbiological test ordering characteristics was also predicted using median regression. One microbiological test order characteristic, *the number of tests ordered* was analysed for every five tests ordered. At first, univariate analysis was used to find the associations between microbiological test order characteristics and *LOS*. Multivariate analysis was then conducted for variables found to be associated according to univariate analysis.

2.7.2 Binary logistic regression

Like linear regression, binary logistic regression is a predictive analysis technique. Linear regression cannot be used when dependent variables are binary (dichotomous). Binary logistic regression is an extension of linear regression used to predict the relationships between a binary dependent variable and independent variables. The independent variables can be nominal, ordinal or interval. In binary logistic regression, the baseline odds with the outcome versus baseline odds without the outcome is calculated which gives a constant known as intercept. Then, the Regression coefficient and P-value are calculated by entering the independent variable into the model.

Another dependent variable evaluated in this study was *in-hospital mortality*. In-hospital mortality data contain information on whether the patient died in the hospital or not. Thus, this is binary data. If the dependent variable is binary, then binary logistic regression is one of the most commonly used methods for determining relationships with independent variables.

In this study, we predicted the relationship between *in-hospital mortality* and *time to the first microbiological test result* using binary logistic regression. At first, univariate analysis was conducted to find an association between *in-hospital mortality* and *time to the first microbiology test result*, then multivariate analysis was done to adjust for any confounding factors. Like the median regression analysis, the *time to the first microbiology test result* was analysed for every 5 hours increase in time.

The relationships between *in-hospital mortality* and baseline characteristics were also predicted using binary logistic regression. One baseline characteristic, *age*, was analysed for every 10 years increase in the patient's age. At first, univariate analysis was done to find the associations between baseline characteristics and *in-hospital mortality*. Multivariate analysis was conducted with the baseline characteristics associated with *in-hospital mortality*.

Similarly, the relationship between *in-hospital mortality* and microbiological test ordering characteristics was predicted using binary logistic regression. One microbiological test order characteristic, *the number of tests ordered*, was analysed for every 5 numbers of tests ordered. At first, univariate analysis was done to find the association of microbiological test ordering characteristics and *in-hospital mortality*. Multivariate analysis was conducted with the microbiological test order characteristics associated with *in-hospital mortality*.

2.7 Ethical approval

This study received ethical approval from the Human Research Ethics Committee of the South Eastern Sydney Local Health District (reference number HREC/16/POWH/412) and was ratified by Macquarie University.

Chapter 3

Results

3.1 Participants

This study included 6,298 patients with unspecified pneumonia admitted to six different hospitals across NSW over three years (2016–2018). Among the 6,298 patients, 85.35% (*n* = 5,375) had at least one microbiological test ordered for them. A total of 48.8% (*n* = 3,076) patients were female and 51.16% (n = 3,222) were male. The median age of patients was 79 years (IQR 68-86). In our study, 22.4% of patients were aged below 65 years, 18.1% were 66-75 years, 31% were 76-85 years and 28.5% were aged above 86 years. The referral source was the ED in the majority of cases (*n* = 5,931; 94.2% of patients) while 367 patients were referred from 'other sources'. These included community health centres, outpatients departments, other hospitals, day procedure care, nursing homes, residential aged care, medical practitioners and other agencies.

In our study, 6,076 patients admitted to the hospital were considered 'urgent admissions'. Among them, 5,228 (86.07%) patients had at least one microbiological test ordered for them. Accordingly, 224 patients were admitted as non-urgent and, among them, 147 (65.62%) had at least one microbiological test ordered. According to the Australian refined diagnosis-related group (AR-DRG), about 94.17% of patients had major complexity and 5.83% had minor or intermediate complexity. A total of 5170 patients had procedures conducted and, among them, 4,557 (88.14%) had at least one microbiological test ordered (Table 3).

The median number of total laboratory tests ordered (including non-microbiological tests) was 10 (IQR 7-13). The median number of microbiological tests ordered was 3 (IQR 1-4). Our study had a greater number of patients with a Charlson comorbidity index (CCI) greater than 2. The median of comorbidities among all patients with unspecified pneumonia was 7 (IQR 4-11). The median of patients with a CCI > 2 was 2126 (33.76%). The numbers of patients with CCIs of 1 and 2 were 1,428 (22.67%) and 1,172 (18.61%), respectively.

Over the study period, the numbers of patients admitted to the six hospitals with unspecified pneumonia were 1,972 (31.31%) in 2016, 2,121 (33.68%) in 2017, and 2,205 (35.01%) in 2018. Hospital A had the highest number of patient admissions, with 1,901 (30.18%) cases. The number of patients admitted to each hospital ranged from 403 (6.40%) at Hospital F to 1,901 (30.18%) at

Hospital A. The microbiological test ordering rates ranged from 80.51% to 90.07% across the six hospitals for the study sample (Table 3).

Table 3: Comparison of patient characteristics by microbiological test order status, 2016-2018.

Variable	Total	Microbiological test ordered?	
		No	Yes
All patients: *n* (%)	6,298 (100)	923	5,375
Male	3,222 (51.16)	423 (13.13)	2799 (86.87)
Female	3,076 (48.84)	500 (16.25)	2576 (83.75)
Age in years: median (IQR)	79 (68-86)	80 (68-87)	79 (67-86)
Age group in years: *n* (%)			
≤ 65	1,412 (22.42)	193 (13.67)	1219 (86.33)
66-75	1,141 (18.12)	144 (12.62)	997 (87.38)
76-85	1,951 (30.98)	290 (14.86)	1,661 (85.14)
≥ 86	1,794 (28.48)	296 (16.50)	1,498 (83.50)
Source of referral: *n* (%)			
ED	5,931 (94.17)	810 (13.66)	5,121 (86.34)
Other	367 (5.83)	113 (30.79)	254 (69.21)
Urgency on admission: *n* (%)			
Urgent	6,074 (96.44)	846 (13.93)	5,228 (86.07)
Non-urgent	224 (3.56)	77 (34.38)	147 (65.62)
Total number of laboratory tests ordered: median (IQR)	10 (7-13)	4 (2-6)	10 (8-13)
Number of microbiological tests ordered: median (IQR)	3 (1-4)	-	3 (1-4)
AR-DRG complexity: *n* (%)			
Minor/intermediate	2,064 (32.77)	413 (20.01)	1,651 (79.99)
Major	4,234 (67.23)	510 (12.05)	3,724 (87.95)
Procedure conducted? *n* (%)			
No	1,128 (17.91)	310 (27.48)	818 (72.52)
Yes	5,170 (82.09)	613 (11.86)	4,557 (88.14)
Number of comorbidities: median (IQR)	7 (4-11)	5 (3-9)	7 (4-11)
Charlson comorbidity index: *n* (%)			
0	1,572 (24.96)	265 (16.86)	1,307 (83.14)
1	1,428 (22.67)	217 (15.20)	1,211 (84.80)

2	1,172 (18.61)	159 (13.57)	1,013 (86.43)
>2	2,126 (33.76)	282 (13.26)	1,844 (86.74)
Year of admission: *n* (%)			
2016	1,972 (31.31)	291 (14.76)	1,681 (85.24)
2017	2,121 (33.68)	311 (14.66)	1,810 (85.34)
2018	2,205 (35.01)	321 (14.56)	1,884 (85.44)
Hospital: *n* (%)			
A	1,901 (30.18)	285 (14.99)	1,616 (85.01)
B	1,221 (19.39)	238 (19.49)	983 (80.51)
C	1,219 (19.36)	157 (12.88)	1,062 (87.12)
D	1,083 (17.20)	133 (12.28)	950 (87.72)
E	471 (7.47)	70 (14.86)	401 (85.14)
F	403 (6.40)	40 (9.93)	363 (90.07)

3.2 Microbiological test ordering patterns

3.2.1 Number of microbiological tests ordered:

The total number of microbiological tests performed across the six hospitals during the three year study period was 18,608. Figure 1 presents a boxplot showing the overall and hospital-specific median numbers of microbiological test orders. The overall median number of microbiological tests (all hospitals combined) was 3 (IQR 1-4). Hospitals A, B, C, D, E and F had microbiological test medians of 3 (IQR 1-5), 2 (IQR 1-4), 2 (IQR 1-4), 3 (IQR 1-4), 2 (IQR 1-4) and 3 (1-4), respectively.

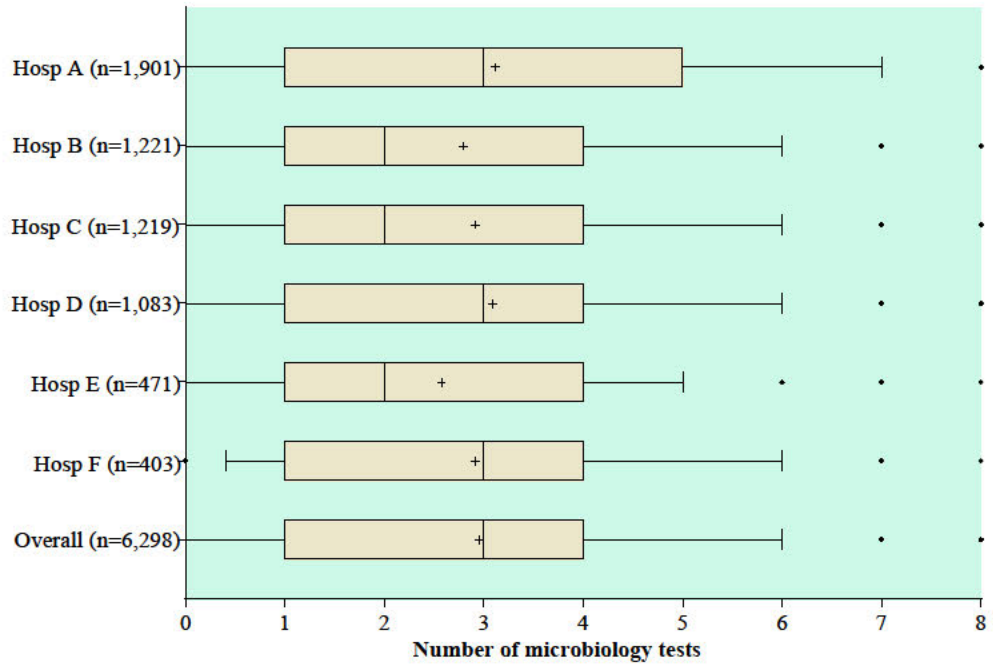


Figure 1: Numbers of microbiological tests ordered across the hospitals. Boxes represent the IQR (25th–75th percentiles). The middle lines within the boxes indicate median values (50th percentile), '+' shows the mean, and the whiskers represent the 10th and 90th percentiles.

3.2.2 Types of microbiological tests ordered:

Of the 18,608 microbiology tests, blood culture was the predominant one, with 4,012 (63.7%) patients receiving one. This was followed by urine MCS (*n* = 2,786, 44.2%), respiratory PCR (*n* = 2,196, 34.9%), urine antigen (*n* = 2,176, 34.6%), sputum MCS (*n* = 1,939, 30.8%) and respiratory serology (*n* = 1,254, 19.9%).

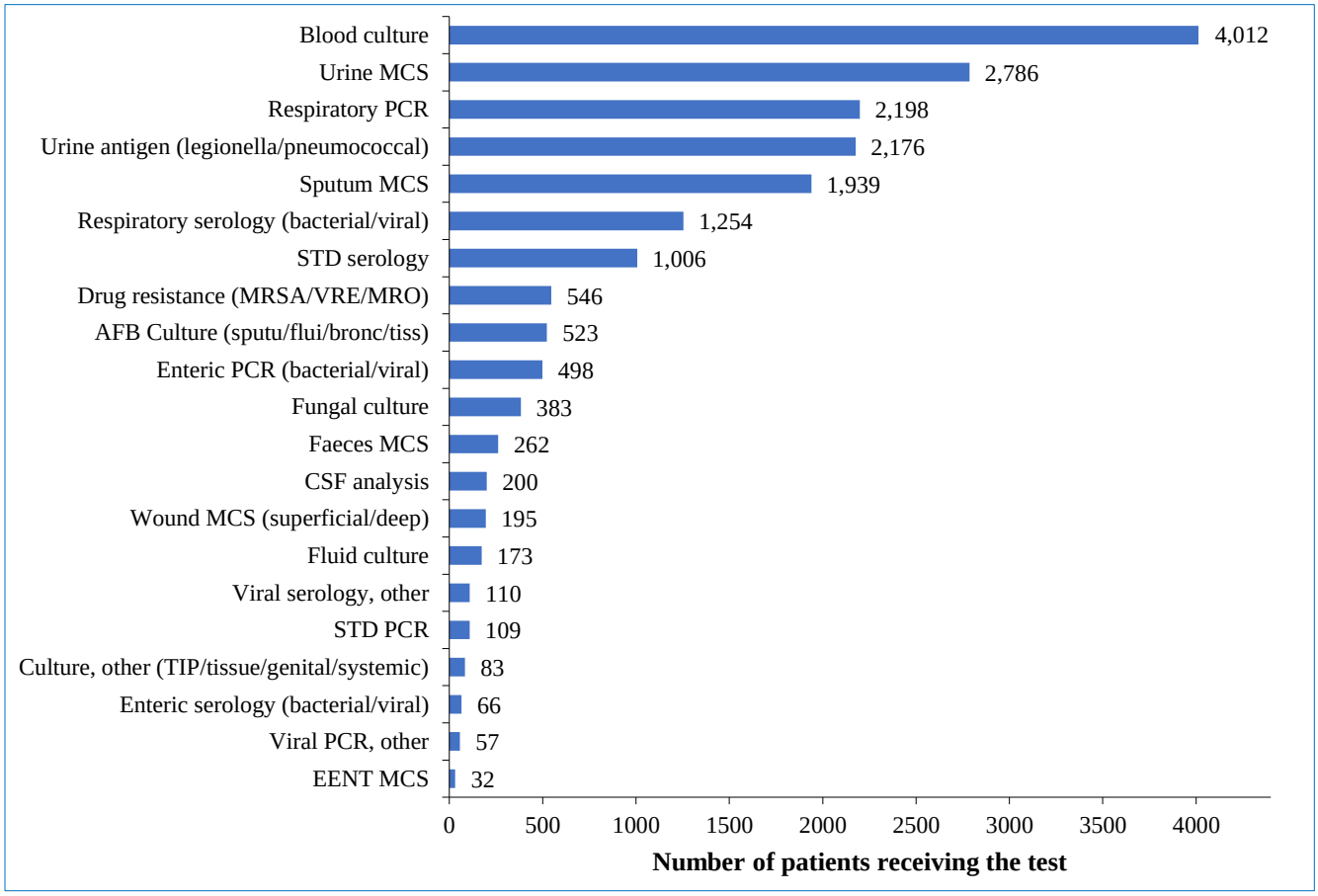


Figure 2: Microbiological test ordering frequencies for patients hospitalized with unspecified pneumonia across the six study hospitals, 2016-2018.

3.2.3 Top five microbiological test ordering rates across hospitals:

Table 2 compares the ordering rates for the top five microbiological tests across the six study hospitals. As indicated in Figure 2, the top five microbiological tests were blood culture, urine MCS, respiratory PCR, urine antigen, and sputum MCS. The rate of ordering blood culture tests

ranged from 57.6% (n = 703) at Hospital B to 68.5% (n = 835) at Hospital C. The rate of ordering of urine MCS ranged from 36.9% (n = 702) at Hospital A to 52.6% (n = 570) at Hospital D. The rate of ordering respiratory PCR ranged from 30.1% (n = 367) to 40.1% (n = 434). The rate of the ordering urine antigen tests ranged from 28.5% (n = 348) at Hospital B to 40.4% (n = 437) at Hospital D. The rate of ordering sputum MCS ranged from 26.9% (n = 328) at Hospital C to 36% (n = 390) at Hospital D.

Table 4: Comparison of the top five microbiological test ordering rates across hospitals.

Hospital	No. of patients (*n*)	Blood MCS	Urine MCS	Respiratory PCR	Urine antigen*	Sputum MCS
A	1,901	1261 (66.3)	702 (36.9)	667 (35.1)	690 (36.3)	587 (30.9)
B	1,221	703 (57.6)	537 (44.0)	442 (36.2)	348 (28.5)	357 (29.2)
C	1,219	835 (68.5)	569 (46.7)	367 (30.1)	402 (33.0)	328 (26.9)
D	1,083	653 (60.3)	570 (52.6)	434 (40.1)	437 (40.4)	390 (36.0)
E	471	298 (63.3)	230 (48.8)	155 (32.9)	152 (32.3)	141 (29.9)
F	403	262 (65.0)	178 (44.2)	133 (33.0)	147 (36.5)	136 (33.7)
Overall	6,298	4012 (63.7)	2,786 (44.2)	2,198 (34.9)	2,176 (34.6)	1,939 (30.8)

*legionella/pneumococcal; MCS, microscopy culture and sensitivity; PCR, polymerase chain reaction.

3.3 Timeliness of test result reporting

Of the 5,375 patients who received at least one microbiological test, 86.3% (n = 4,641) of patients the first test results before hospital disposition. However, the proportion of patients for whom the last test results were available before disposition was only 35.5% (n = 1,908).

3.3.1 Time from admission to the first microbiological test result:

The overall median time from admission to the first microbiological test result was 26 hours (IQR, 13-58 hours). There was some variation in the time from admission to the first microbiological test result across the study hospitals. Hospital C took longer, with a median of 30 hours (IQR, 17-59 hours). On the other hand, Hospital D was quicker, with a median of 24 hours (IQR, 12-47 hours; Figure 3A).

3.3.2 Time from admission to the last microbiological test result:

The overall median time from admission to the last microbiological test result was 144 hours (IQR, 128-211 hours). Hospital A took a relatively long time, with a median of 147 hours (IQR, 133-216 hours), while Hospital E took a relatively short time, with a median of 139 hours (IQR, 126-181 hours).

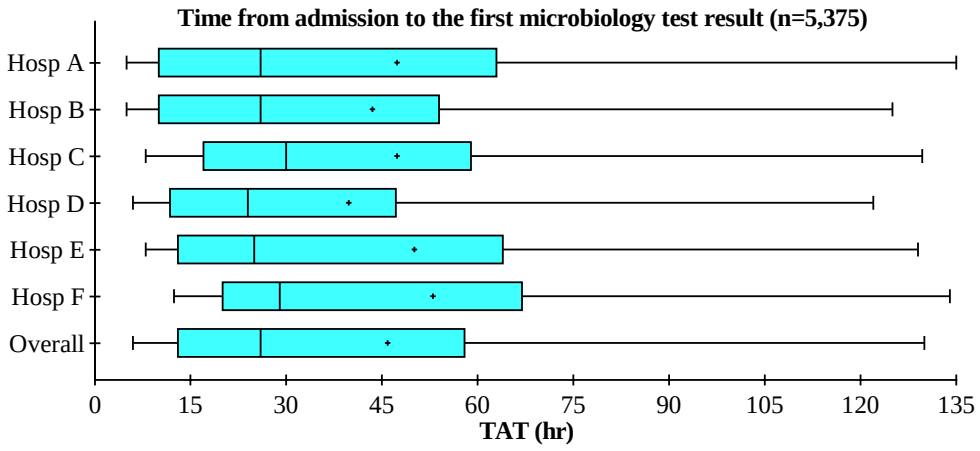
3.3.3 TATs for the top five microbiology tests:

Figures 3G-H presents the test TATs (i.e. time from sample receipt at the lab to the result being available) for the top five microbiology tests. Of the five tests, blood culture had the longest TAT, with a median of 135.8 hours (IQR, 127.9-141 hours). As expected, the test with the shortest TAT was the urine antigen test (legionella/pneumococcal antigen test), with a median of 3.1 hours (IQR 1.8-7.1 hours). There was a high range of median TATs for urine antigen tests (legionella/pneumococcal antigen test) across the hospitals, from 2.3 hours (IQR, 1.3-4.1 hours) to 11.1 hours (IQR, 6.1-16.3 hours).

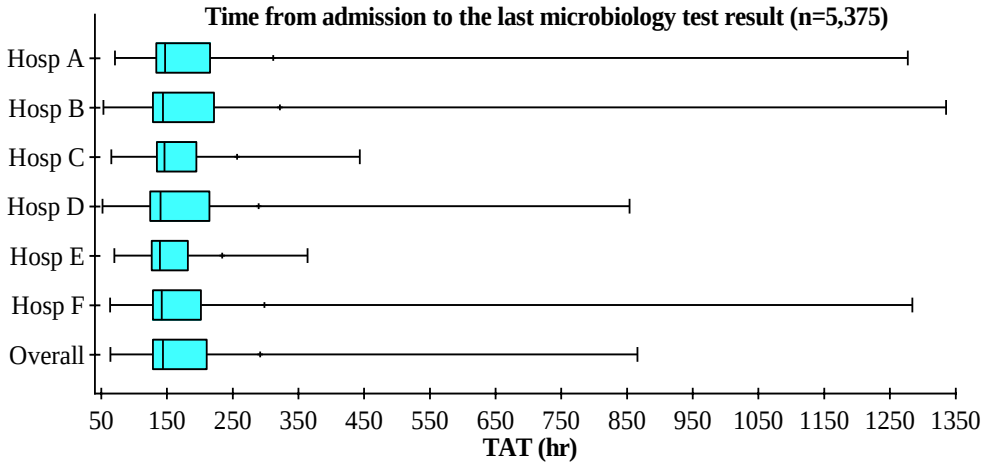
The urine MCS had an overall median TAT of 25.5 hours (IQR, 192.8-36.3 hours). The median TAT of urine MCS ranged from 22.7 hours (IQR, 18.3-31.0 hours) to 37.3 hours (IQR, 28.5-42 hours) across the hospitals.

The sputum MCS test had an overall median TAT of 42.3 hours (IQR, 26.1-61.7 hours). This TAT ranged from 34.9 hours (IQR, 24.6-43 hours) at Hospital A to 57.5 hours (IQR, 36-68 hours) at Hospital F. Another microbiology test, respiratory PCR, had an overall median TAT of 14.1 hours (IQR 3-27.9 hours), which ranged from 3.23 hours (IQR 1.8-9.8 hours) at Hospital D to 23.6 hours (IQR 2.6-31.8 hours) at Hospital A.

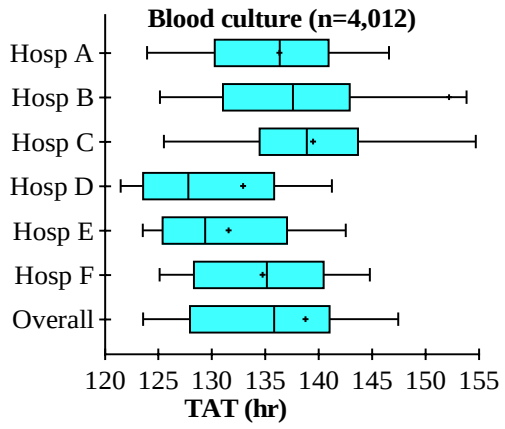
A


Time from admission to the first microbiology test result (n=5,375)
Hosp A
Hosp B
Hosp C
Hosp D
Hosp E
Hosp F
Overall
0
15
30
45
60
75
90
105
120
135
TAT (hr)

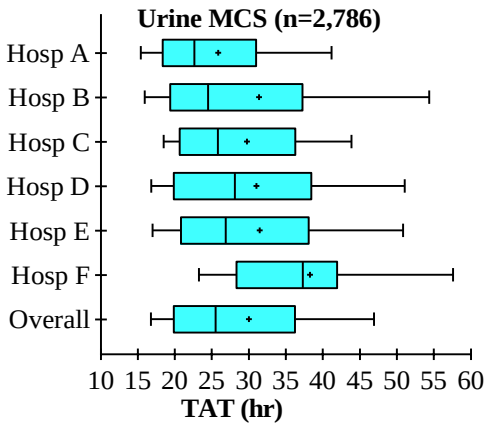
B


Time from admission to the last microbiology test result (n=5,375)
Hosp A
Hosp B
Hosp C
Hosp D
Hosp E
Hosp F
Overall
50
150
250
350
450
550
650
750
850
950
1050
1150
1250
1350
TAT (hr)

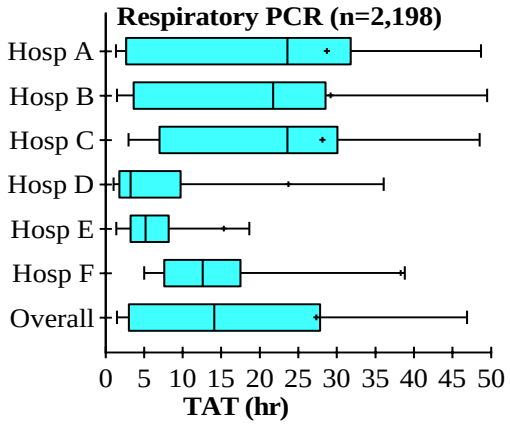
C


Blood culture (n=4,012)
Hosp A
Hosp B
Hosp C
Hosp D
Hosp E
Hosp F
Overall
120 125 130 135 140 145 150 155
TAT (hr)

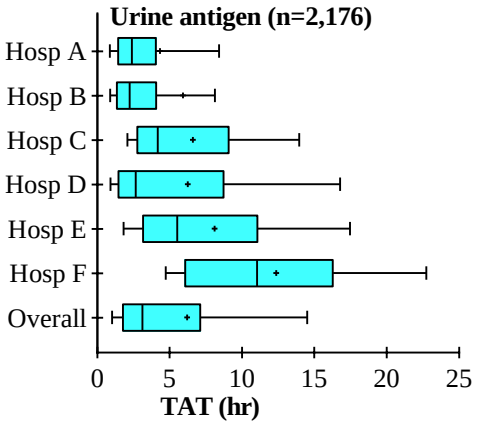
D


Urine MCS (n=2,786)
Hosp A
Hosp B
Hosp C
Hosp D
Hosp E
Hosp F
Overall
10 15 20 25 30 35 40 45 50 55 60
TAT (hr)

E


Respiratory PCR (n=2,198)
Hosp A
Hosp B
Hosp C
Hosp D
Hosp E
Hosp F
Overall
0 5 10 15 20 25 30 35 40 45 50
TAT (hr)

F


Urine antigen (n=2,176)
Hosp A
Hosp B
Hosp C
Hosp D
Hosp E
Hosp F
Overall
0 5 10 15 20 25
TAT (hr)

G

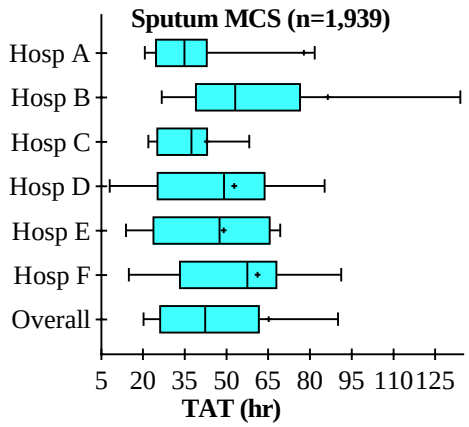


Figure 3: Time from admission to the first (A) and the last (B) microbiological test results, and turnaround times (B-G) of the top five microbiology tests. TAT, turnaround time; MCS, microscopy culture and sensitivity; PCR, polymerase chain reaction.

3.4 Patient outcomes

3.4.1 Hospital LOS:

Of the 5,375 pneumonia patients who had at least one microbiological test, 734 were discharged and 4,641 were still at hospital when they received their first test result.

The overall median LOS of patients who had at least one microbiological test ordered and were discharged before the first microbiological test result was available was 47 hours (IQR, 20-79 hours). The overall median LOS of patients who had at least one microbiological test and were not discharged from the hospital when the first test result was received was 133 hours (IQR, 84-218 hours). There was a wide variation in the median LOS of patients across hospitals. Hospital B had the lowest median LOS among patients who were not discharged when the first test result became available. The median LOS at Hospital B was 123 hours (IQR, 76-197 hours). Hospital F had the highest median LOS among patients who were not discharged when the first test result was available, at 145 hours (IQR, 97-246 hours).

3.4.2 In-hospital mortality:

The in-hospital mortality rate was 7.4% among patients who did not receive any microbiology tests. There was variation in the rates across hospitals, with Hospital F having the highest percentage at 12.5% (n = 12.5), whereas Hospital F had the lowest in-hospital mortality rate of 5% (n = 12).

Of patients who received at least one microbiological test, 46 (6.3%) patients died before receiving the first test result, while 257 (5.5%) patients died afterwards. Furthermore, those who had not received the first test result had a slightly higher rate of mortality (6.3%) than those who had received the first test result (5.5%).

Table 5: Patient outcomes.

	Hospital length of stay (h): median (IQR)			**In-hospital mortality: *n* (%)**		
	Microbiological test ordered?			Microbiological test ordered?		
	No	Yes		No	Yes	
Hospital	(n = 923)	**X** (n = 734)	**Y** (n = 4,641)	(n = 923)	**X** (n = 734)	**Y** (n = 4,641)
A	65 (20-132)	41 (20-76)	124 (77-213)	19 (6.7)	11 (4.0)	79 (5.9)
B	60 (11-112)	23 (12-57)	123 (76-197)	12 (5.0)	10 (6.2)	42 (5.1)
C	71 (27-126)	56 (23-77)	141 (84-219)	17 (10.8)	11 (8.0)	53 (5.7)
D	95 (72-148)	72 (42-100)	145 (97-246)	11 (8.3)	8 (12.1)	53 (6.0)
E	120 (74-170)	65 (36-99)	124 (88-197)	4 (5.7)	3 (7.3)	10 (2.8)

F	97 (59-150)	73 (48-105)	139 (91-238)	5(12.5)	3 (5.6)	20 (6.5)
Overall	75 (27-136)	47 (20-79)	133 (84-218)	68 (7.4)	46 (6.3)	257 (5.5)

X = Patient disposition occurred before the first test result was available; **Y** = patient disposition occurred after the first test result was available.

3.5 Associations between the timeliness of test result reporting and patient outcomes

The time to the last test result is a good indicator for timeliness of microbiology test; however, most patients were either discharged/deceased/transferred to other settings before the test results arrived. In this study, only 35.5% (n = 1,908) of the 5,375 patients who had a microbiological test received their results before hospital disposition (i.e. were discharged, died, or transferred to other settings). Therefore, we used the time-to-first test result as an indicator of the timeliness of test reporting.

Accordingly, this analysis was conducted among patients for whom the first test results were available before hospital disposition (n = 4,641) to evaluate the associations of time to the first test result with hospital LOS and in-hospital mortality while adjusting for known demographic and clinical characteristics.

3.5.1 Associations with hospital LOS

Hospital LOS data were highly skewed (Figure 4). Therefore, traditional linear regression was unsuitable for its analysis. In this study, median regression was used, which is a type of quantile regression suitable for highly skewed data.

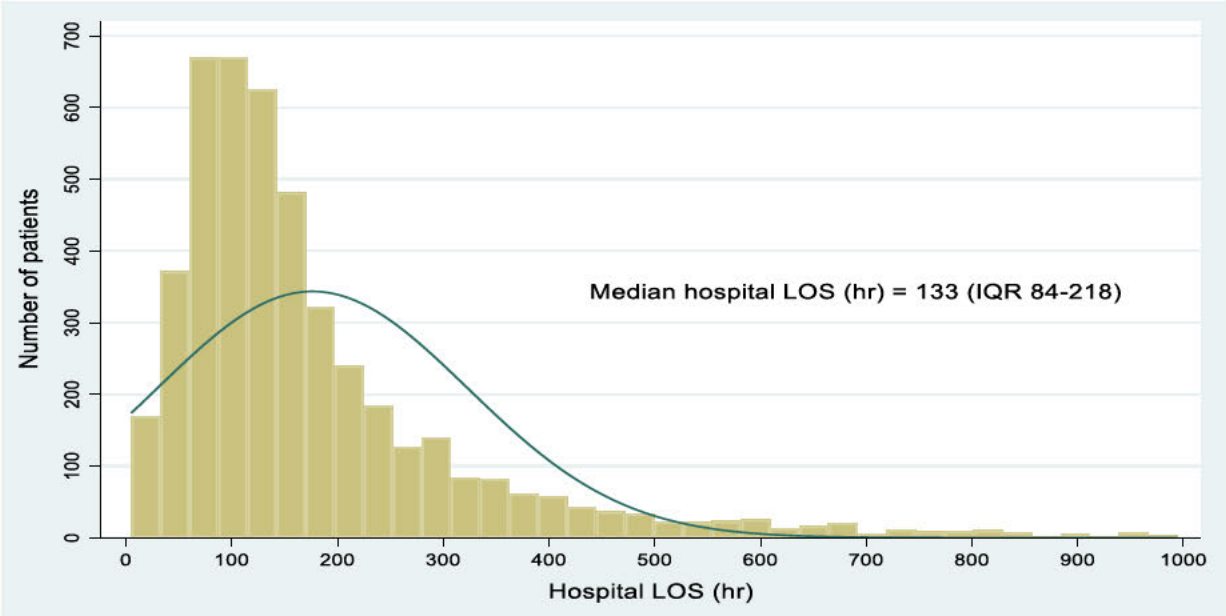


Fig 4. Histogram of hospital LOS in patients for whom the first microbiology results were available before hospital disposition (*n* = 4,641).

I. Univariate analysis:

Table 6 presents the results of the univariate analysis of the associations between 16 baseline characteristics, microbiological test ordering characteristics, and hospital LOS. Most baseline and test ordering characteristics were associated with hospital LOS. The *time-to-first test result* was strongly associated with hospital *LOS*. The univariate analysis results showed that every 5-hour increase in the time-to-first test was associated with an increase of 4.8 hours in median hospital LOS (95% CI, 4.4-5.2; $P < 0.001$). Similarly, for every 10-year increase in patient age, LOS increased by 11.4 hours (95% CI, 9.4-13.3; $P = 0.000$). The univariate analysis also shows that those patients who were referred from ED were more likely to have shorter LOSs, by a median of 57 hours (95% CI, −72–−42); $P = 0.000$) than with other sources of referral such as community health centres, outpatients departments, other hospitals, day procedure care, nursing homes, residential aged care, medical practitioners and other agencies. In this study, patients who had procedures conducted had longer LOSs than those who did not, by 71 hours (95% CI, 60.2–81.8, $P = 0.000$).

Compared with a patient with a CCI of 0, patients with CCIs of 1, 2 and > 2 had hospital LOSs that were greater, by 18 hours (95% CI, 8-28, $P = 0.000$), 35 hours (95% CI, 24.6-45.4, $P = 0.000$), and 70 hours (95% CI, 61-79, $P = 0.000$), respectively. For every five microbiological tests ordered, the hospital LOS increased by 59.2 hours (95% CI, 55.5-62.8, $P = 0.000$).

Table 6 shows that the hospital LOS of patients who had a blood culture test was 11 hours greater than those who did not (95% CI, 4.2-17.8, $P = 0.001$). Sputum MCS-tested patients had a 27 hour longer LOS (95% CI, 20.3-33.7, $P = 0.000$). Table 6 shows that the hospital LOS of patients who had a urine antigen test was 9 hours less than those who did not, while for respiratory PCR tests, it was 18 hours less.

Table 6: Factors associated with hospital LOS (univariate analysis).

Variable	Change in median LOS (h)	
	Coefficient (95% CI)	*P*-value
Time-to-first test result (for every 5 hours increase)	4.8 (4.4–5.2)	0.000
Gender		
Female *vs* male	1 (−4.9–6.9)	0.741
Age (for every 10 years increase)	11.4 (9.4–13.3)	0.000

Source of referral		
ED *vs* Other	−57 (−72–−42)	0.000
ICU/HDU admission		
Yes *vs* No	99 (86.9–111.1)	0.000
Procedure conducted		
Yes *vs* No	71 (60.2–81.8)	0.000
Charlson comorbidity index		
0	*Reference*	
1	18 (8–28)	0.000
2	35 (24.6–45.4)	0.000
>2	70 (61–79)	0.000
DRG complexity		
Major *vs* Minor/intermediate	69 (62.2–75.8)	0.000
No. of tests ordered (for every 5 tests)	59.2 (55.5–62.8)	0.000
Repeat microbiological test requested?		
Yes *vs* No	44 (37.5–50.5)	0.000
Blood culture ordered?		
Yes *vs* No	11 (4.2–17.8)	0.001
Respiratory PCR ordered?		
Yes *vs* No	−9 (−15.2–−2.8)	0.004
Urine MCS ordered?		
Yes *vs* No	27 (20.3–33.7)	0.000
Urine antigen test ordered?*		
Yes *vs* No	−18 (−24.3–11.7)	0.000
Sputum culture ordered?		
Yes *vs* No	5 (−1.1–11.1)	0.109
Hospital		
A	*Reference*	
B	−1 (−10.6–8.6)	0.838
C	17 (7.7–26.3)	0.000
D	21 (11.6–30.4)	0.879
E	1 (−11.9–13.9)	0.879
F	15 (1.3–28.7)	0.032

- *legionella/pneumococcal.

II. Multivariate analysis:

Table 7 presents the results of multivariate analysis after placing all 16 baseline variables into the model. In the multivariate analysis, the time to first test result, age, source of referral,

ICU/HDU admission, procedure conducted, CCI, DRG complexity, number of tests ordered, repeated microbiology test, and blood culture order were associated with hospital LOS.

The study showed that for every 5 hours' increase in the time from admission to the first test result, the median hospital LOS increased by 3.9 hours (95% CI, 3.5–4.3; $P = 0.000$). For every 10 years' increase in age, the median hospital LOS increased by 6.1 hours. There was also an increase in the LOS of patients admitted to ICU/HDU of 26 hours (95% CI, IQR 13.3–38.7; $P = 0.000$) compared to those in general inpatient wards. Similarly, there was an increase in the hospital LOS of patients who had repeat microbiological tests, by 20.8 (95% CI, 13.6–28; $P = 0.000$) compared to those who did not receive repeated microbiology tests. There was an increase in the hospital LOS of patients for every five more microbiological tests ordered, by 48.3 hours (95% CI, IQR 43.8–52.8; $P = 0.000$). Furthermore, the multivariate analysis showed that there was a decrease in the hospital LOS of patients who had a blood culture test, by 15.4 hours (95% CI, IQR −23–−7.8 hours, $P = 0.000$), compared to those who did not.

Table 7: Factors associated with hospital LOS (multivariate analysis).

Variable	Change in median LOS (hr)	
	Coefficient (95% CI)	*P*-value
Time-to-first test results (for every 5 hours increase)	3.9 (3.5–4.3)	0.000
Age (for every 10 years increase)	6.1 (3.8–8.3)	0.000
Source of referral		
ED vs Other	−24.1 (−39.5–−8.7)	0.002
ICU/HDU admission		
Yes *vs* No	26 (13.3–38.7)	0.000
Procedure conducted		
Yes *vs* No	29 (18.1–40.1)	0.000
Charlson comorbidity index		
0	*Reference*	
1	−3.7 (−13.4–5.9)	0.445
2	2.1 (−8.1–12.3)	0.683
>2	21.9 (12.5–31.3)	0.000
DRG complexity		
Major *vs* Minor/intermediate	22.2 (14.1–30.4)	0.000
No. of tests ordered (for every 5 more tests)	48.3 (43.8–52.8)	0.000
Repeat microbiological test requested?		
Yes *vs* No	20.8 (13.6–28)	0.000

Blood culture ordered?		
Yes *vs* No	−15.4 (−23–−7.8)	0.000
Respiratory PCR ordered?		
Yes *vs* No	4.2 (2.7–11.1)	0.235
Urine MCS ordered?		
Yes *vs* No	2.7(−4.3–9.8)	0.445
Urine antigen test ordered?*		
Yes *vs* No	−5.8 (−13.1–1.5)	0.120
Hospital		
A	*Reference*	
B	−5.2 (−14.8–4.4)	0.290
C	1.2 (−8.1–10.4)	0.806
D	−9.2 (−18.9–0.6)	0.066
E	−28.3 (−41.4–−15.2)	0.000
F	−28.9 (−42.8–−15)	0.000

- *legionella/pneumococcal.

3.5.2 Associations with in-hospital mortality

The dependent variable *in-hospital mortality* is binary. Therefore, binary logistic regression was used to determine the association of baseline and test-related characteristics with in-hospital mortality.

I. Univariate analysis:

Table 8 represents the univariate analysis of 16 baseline and microbiology test-related characteristics associated with in-hospital mortality. The baseline characteristics of gender, CCI = 1, and respiratory PCR and sputum culture test ordering were not associated with in-hospital mortality.

There was a 1.02-fold increase in in-hospital mortality for every 5-hour increase in time from hospital admission to the first test result (equivalent to 2%; OR = 1.02; 95% CI = 1.01-1.03; P = 0.003). The effect was too small but still significant. For every 10 year increase in patient age, there was a 1.56-fold increase in in-hospital mortality (OR = 1.56; 95% CI = 1.39-1.75; P = 0.000). The likelihood (odds) of in-hospital mortality was higher by a factor of 4.30 (OR = 4.30; 95% CI = 3.17-5.82; P = 0.003) for patients admitted to ICU/HDU versus those who were not.

For every five tests ordered, patients had a 1.51-fold (OR = 1.51, 95% CI = 1.35-1.69; *P* = 0.000). Similarly, patients who had repeated tests had a 1.46-fold greater chance of in-hospital mortality (OR = 1.46, 95% CI = 1.13-1.88, *P* = 0.003).

Patients who had a blood culture test had a 1.70-fold greater chance of in-hospital mortality than those who did not (OR = 1.70, 95% CI = 1.22-2.36, *P* = 0.002). Similarly, patients who had a urine MCS test had a 1.90-fold greater chance of in-hospital mortality than those who did not (OR = 1.90, 95% CI = 1.44-2.51, *P* = 0.000).

Table 8: Factors associated with in-hospital mortality (univariate analysis).

Variable	In-hospital mortality	
	OR (95% CI)	*P*-value
Time-to-first test results (for every 5 hours increase)	1.02 (1.01–1.03)	0.003
Gender		
Female *vs* male	0.89 (0.69–1.15)	0.374
Age (every 10 years increase)	1.56 (1.39–1.75)	0.000
Source of referral		
ED vs Other	0.61 (0.38–1)	0.048
ICU/HDU admission		
Yes *vs* No	4.30 (3.17–5.82)	0.000
Procedure conducted		
Yes *vs* No	1.84 (1.12–3.04)	0.017
Charlson comorbidity index		
0	*Reference*	
1	1.42 (0.79–2.55)	0.236
2	2.76 (1.61–4.72)	0.000
>2	5.97 (3.73–9.56)	0.000
DRG complexity		
Major *vs* Minor/intermediate	2.99 (2.03–4.40)	0.000
No. of tests ordered (for every 5 more tests)	1.51 (1.35–1.69)	0.000
Repeat microbiological test requested?		
Yes *vs* No	1.46 (1.13–1.88)	0.003
Blood culture ordered?		
Yes *vs* No	1.70 (1.22–2.36)	0.002
Respiratory PCR ordered?		
Yes *vs* No	0.97 (0.75–1.24)	0.785
Urine MCS ordered?		
Yes *vs* No	1.90 (1.44–2.51)	0.000

Urine antigen test ordered?*		
Yes *vs* No	0.77 (0.60–0.99)	0.044
Sputum culture ordered?		
Yes *vs* No	0.83 (0.64–1.08)	0.162
Hospital		
A	*Reference*	
B	0.86 (0.59–1.26)	0.443
C	0.97 (0.68–1.39)	0.872
D	1.02 (0.71–1.46)	0.919
E	0.46 (0.23–0.89)	0.021
F	1.11 (0.67–1.84)	0.698

- *legionella/pneumococcal.

II. Multivariate analysis:

The multivariate analysis showed that there was no association between *time to the first microbiological test result* and *in-hospital mortality*. However, age, ICU admission, CCI>2 and number of tests ordered were significantly associated with the outcome. For every 10 years increase in patient age, the in-hospital mortality rate increased by 68% (OR = 1.68, 95% CI = 1.46-1.94; P = 0.000). Patients who were admitted to the ICU/HDU were 4.16 times more likely to die in hospital (OR = 4.16; 95% CI = 2.83-6.12; P = 0.000). For every 5 microbiology tests, the likelihood of in-hospital mortality increased by a factor of 1.25 (OR = 1.25; 95% CI = 1.06-1.46, P = 0.007). Similarly, there was a 1.54-fold greater chance of in-hospital mortality for patients who had a blood culture test (OR = 1.54; 95% CI = 1.08-2.19, P = 0.017).

Table 9: Factors associated with in-hospital mortality (multivariate analysis).

Variable	In-hospital mortality	
	OR (95% CI)	*P*-value
Time-to-first test results (for every 5 hours increase)	1.01 (1–1.02)	0.122
Age (for every 10 years increase)	1.68 (1.46–1.94)	0.000
Source of referral		
ED vs Other	0.57 (0.33–0.98)	0.043
ICU/HDU admission		
Yes *vs* No	4.16 (2.83–6.12)	0.000
Procedure conducted		
Yes *vs* No	0.68 (0.39–1.17)	0.166
Charlson comorbidity index		
0	*Reference*	

1	1.21 (0.67–2.20)	0.529
2	1.76 (1.01–3.06)	0.045
>2	3.61 (2.20–5.92)	0.000
DRG complexity		
Major *vs* Minor/intermediate	1.60 (1.05–2.45)	0.029
No. of tests ordered (for every 5 more tests)	1.25 (1.06–1.46)	0.007
Repeat microbiological test requested?		
Yes *vs* No	1.08 (0.79–1.46)	0.637
Blood culture ordered?		
Yes *vs* No	1.54 (1.08–2.19)	0.017
Respiratory PCR ordered?	-	-
Yes *vs* No	-	-
Urine MCS ordered?		
Yes *vs* No	1.36 (0.99–1.85)	0.055
Urine antigen test ordered?*		
Yes *vs* No	0.79 (0.58–1.07)	0.129
Hospital		
A	*Reference*	
B	0.90 (0.60–1.35)	0.607
C	0.85 (0.58–1.24)	0.393
D	0.85 (0.58–1.26)	0.417
E	0.38 (0.19–0.76)	0.006
F	0.65 (0.38–1.12)	0.118

- *legionella/pneumococcal.

Chapter 4
Discussion

4.1 Key findings

This study found that the overall median time between a patient's admission to hospital and obtaining their first microbiological test result was 26 hours (IQR, 13-58 hours). The overall median LOS of patients who had at least one microbiological test and were not discharged from the hospital until the first test result was obtained was 133 hours (IQR, 84-218 hours).

Mortality was lower among patients who received at least one microbiological test and were not discharged from the hospital until the first result was received than in patients who did not have a test or receive a result. The mortality rate among patients who received a test and stayed until the result was received was 5.5%.

The key finding of this study is that there was a significant association between time to the first microbiological test result and hospital LOS. Every 5 hours increase in time from admission to the first test result was associated with an increase in median hospital LOS of 3.9 hours, after adjusting for confounding variables. However, there was no association between the time to the first test and in-hospital mortality. Furthermore, every 10-year increase in the age of unspecified pneumonia patients was associated with a 6.1-hour increase in LOS and a 68% increase in in-hospital mortality.

4.2 Interpretation and comparison with existing literature

In our study, blood culture tests had the longest median TAT of 135.8 hours (IQR 127.9-141). A study of 13 hospitals in the United States by Tabak *et al.* (2017) found a median blood culture TAT of 65 hours (2.71 days) (107). That study also found a median TAT for blood culture of *Streptococcus* species (the predominant bacteria causing pneumonia) of 34.8 hours (1.45 days) (107). The difference in blood culture TAT compared with the present study may be because our study only included unspecified pneumonia patients, while Tabek *et al.* (2017) included blood cultures for patients with all diseases (107). Furthermore, Tabek *et al.* (2017) considered rapid identification methods such as matrix-assisted laser desorption/ionization mass spectrometry, spot biochemical tests, Vitek system, and rapid antibiotic susceptibility tests (107).

Our study showed that the urine antigen test had the shortest median TAT, which was 3.1 hours. Our study is consistent with a study conducted at Concord Hospital in Sydney by Weatherall

et al. (2007), who found a median urine antigen test TAT of 2 hours 39 minutes (126). A retrospective study in the United States by Banks *et al*. (2020) found a TAT for pneumococcal antigen testing of urine of approximately 5.04 hours [0.21 days (0.17-1.17 days)], which higher than our result (127). The difference may be because our study included a larger number of urine antigen tests (n = 2176; Table 4, compared with n = 72) (127).

As expected, there was a range of TATs among microbiological tests, from a median TAT of 3.1 minutes for urine antigen tests to a median TAT of 135.8 minutes for blood culture tests. The microbiological tests with shorter TATs involve immunological (urine antigen tests) and molecular methods (respiratory PCR) of bacteria detection. Such test results can be quickly generated in a laboratory, while microbiological culture tests require 24–72 hours of incubation for microbial growth (128, 129). However, a microbiology culture test is necessary for the selection of antibiotics for treatment when the causative agent is multidrug-resistant bacteria.

The multivariate analysis in our study found a 3.9-hour increase in the LOS of patients for every 5 hours increase in time to the first microbiological test. Several studies have reported associations between laboratory TATs and hospital LOS (109, 122). A retrospective study of four hospitals in Sydney from 2008–2011 by Li *et al.* (2015) found that for every 60 minutes increase in laboratory TAT, there was an increase in ED LOS of 35 minutes (122). A similar study by Kaushik *et al.* (2018) in the United States also found a significant association between ED LOS and TAT (109). They found that for every 1-minute decrease in laboratory TAT, there was a 0.50-minute decrease in ED LOS (109). However, the differences in the increase in time may be because our study focused on unspecified pneumonia, and we used the time to the first microbiological test as an indicator of laboratory time. Also, the studies of Li *et al.* (2015) and Kaushik *et al.* (2018) examined ED patients, whereas we examined general patients admitted to the hospital. Furthermore, the research by Li *et al.* (2015) used data from two months (August and September) of each year from 2008 to 2011, while our study used three years of data (122). Overall, the studies by Li *et al*. (2015) and Kaushik *et al*. (2018) support our finding of a significant association between the timing of laboratory test results and hospital LOS (109, 122).

Our study found a significant association between patient age and hospital LOS. We also found that for every 10-year increase in patient age, the LOS increased by 6.1 hours (Table 7). This finding is consistent with previous studies; for instance, Kayser *et al*. (2008) studied 200 pneumonia patients discharged from a Singapore hospital and found shorter LOSs among

younger patients (< 65 years) than older ones (> 65 years) (130). Another study by Richard *et al*. (2003) of a large population of 44,814 CAP patients in the USA also found shorter LOSs among patients aged < 65 years old than in those aged > 65 years (131). From these studies, we can conclude that older age is one of the key factors increasing the LOS of pneumonia patients (130, 131). However, unlike our study, these studies stratified patients into two age groups (> and < 65 years) and did not include information on actual increases in LOS with increases in age (130, 131).

The findings of the study showed a significant association between the patient age and in-hospital mortality. The multivariate binary logistic regression model showed that for every 10 years increase in age, there was an increase in mortality of 68% (Table 9). A prospective observational study by Marrie *et al*. (2005) in six different hospitals in Canada in 2000–2002 also found a significant association between age and in-hospital mortality among CAP patients (132). The study found that every 1-year increase in patient age was associated with a 1.03-fold increase in in-hospital mortality. In Marrie *et al*. (2005), the mean ± SD age of the CAP patients was 69.6 ± 17.7, while in our study, the median age was 79 years (IQR, 68-86; Table 3) (132). An observational cohort study done in the United States by Kaplan *et al* (2002) among hospitalized elderly CAP patients older than 65 years found an association between age and in-hospital mortality (133). The age groups of 70-74 years, 75-79 years, 80-84 years, 85-89 years and 90+ years had 4%, 16%, 32%, 46%, and 75% higher in-hospital mortality, respectively, in comparison to the reference age group (65-69 years) (133). Similarly, a retrospective cohort study by Micek *et al.* (2015) in 12 hospitals across 5 countries (the United States, France, Germany, Italy, and Spain) also found a significant association between the age of patients and in-hospital mortality in ventilator-associated pneumonia (134). Micek *et al.* (2015) studied 339 VAP patients with a mean age of 59.7 years (134). They found that for every 1-year increase in age, the risk of in-hospital mortality increased by 2% (134). However, a retrospective study in Zurich by Franzen *et al*. (2016) found no significant association of age and in-hospital mortality (135). This may be because it had a small sample size of only 108 patients, while our study analysed 6298 patients (135). Furthermore, the non-significant association between age and in-hospital mortality may be due to a high difference in the median ages of the two studies. In the study by Franzen *et al*. (2016), the median age of patients was 59 years (IQR 43-69) while our study had older patients with a median of 79 years (IQR 68-86; Table 3) (135).

In our study, there was also a significant association between in-hospital mortality and ICU admission patients (Table 9). The in-hospital mortality of ICU patients was 4.16 times greater

than that of patients who were not admitted to an ICU (Table 9). A retrospective study by Garau *et al*. (2008) in ten Spanish university-based tertiary-care hospitals between 2001 and 2002 found a significant association between ICU admission and in-hospital mortality. The study found that ICU-admitted patients had a 7.7-fold greater risk of in-hospital mortality than non-ICU admitted patients (136). This may be because the ICU-admitted patients had pneumonia severity indexes (PSIs) of IV or V and, therefore, were of higher risk than the non-ICU admitted patients (136). However, our study lacks information on PSI.

Our study also found a significant association between the Charlson comorbidity index (CCI) and in-hospital mortality. Similarly, a retrospective cohort study of pneumonia patients in Japan by Nguyen *et al*. (2019) found that an increase in CCI of one point increased the risk of in-hospital mortality 1.28-fold (137). In contrast, a retrospective study by Franzen *et al*. (2016) found an insignificant association of CCI with in-hospital mortality (135). This might be because the study of Franzen *et al*. (2016) had a smaller sample population (n = 108) and lower median CCI (CCI = 4; IQR = 1-8) than our study (sample population n = 6298; median CCI = 7; IQR = 4-11) (135). A retrospective study by Wessemann *et al*. (2015) of hospitalised CAP patients in Germany from 2005 and 2009 found higher mortality in patients with an immediate and high risk of CCI within one year of discharge (69). Overall, it can be concluded that higher CCIs are associated with death due to pneumonia.

Our study also found a significant association between CCI and hospital LOS. Our study found that patients with CCIs > 2 had a 21.9-hour longer hospital LOS than patients with a CCI of 0 (Table 7). A similar association was observed in a study Skull *et al*. (2009) of elderly hospitalized pneumonia patients in Australia. That study found an increased LOS for patients with more than two comorbidities (68).

Our study also found that for every five microbiological tests ordered, the hospital LOS of pneumonia patients increased by 48.3 hours (IQR 43.8-52.8; Table 7). A study by Li *et al*. (2015) also found a significant association between the number of additional tests ordered and ED LOS (122). They found that for every five additional microbiological tests, the LOS increased by 10 minutes (122). However, there were very high differences in the LOS vs additional test relationships reported in our study and that of Li *et al*. (2015) (122). This may be because, in our study, we used microbiological tests that take longer than those considered by Li *et al.* (2015), who considered laboratory tests such as clinical chemistry, molecular genetics, immunology, haematology, anatomical pathology, blood bank and endocrinology,

which have relatively short laboratory TATs (122). Furthermore, Li *et al.* (2015) recruited ED patients, whereas our study only considered general hospital admissions (122). Patients in an ED usually have shorter LOSs than hospital-admitted patients. Therefore, differences in study setting and laboratory tests might be responsible for the great differences in the LOS vs additional test relationships reported by our study and that of Li *et al*. (2015) (122).

Similarly, our study found a significant association between LOS and blood culture ordering status. Pneumonia patients who had a blood culture test had 15.4-hour shorter LOSs than patients who did not (Table 7). In our study, blood culture tests had a median TAT of 135.83 hours, which is very high compared to the median TAT of other microbiological culture tests, such as urine MCS (25.49 hours) and sputum culture (42.3 hours). However, in the multivariate analysis, we obtained an interesting result whereby patients who had a blood culture test (high median TAT) had a shorter hospital LOS (Table 7). This result contradicts the univariate analysis, which showed a difference in hospital LOS of 11 hours (IQR 4.2–17.8) between patients who had blood culture test and those who did not (Table 4). No study has reported an association between blood culture ordering status and hospital LOS. Garau *et al.* (2008) found that patients with positive bacterial growth results in their blood culture tests had a 1.22-fold greater LOS than patients with a negative growth result (136). Our study did not differentiate between the positive and negative results of blood culture tests. However, the finding of Garau *et al.* (2008) partially support our finding of an association between LOS and the number of blood culture tests ordered.

The top-five microbiological tests ordered in our study were blood culture, respiratory PCR, urine MCS, urine antigen and sputum culture. Among these, only one test—blood culture—was significantly associated with in-hospital mortality and hospital LOS. In our study, a total of 63.7% of subjects had a blood culture test (Table 4). Our study found that mortality was 1.54-fold greater among patients who had a blood culture test than among those who did not. A study by Kim *et al*. (2010) found a risk factor of 2.57 (range = 1.02-6.48) between time to blood culture positivity of greater than 48 hours with mortality. Our study lacked information on the distribution of mortality between patients with positive and negative cases. The median TAT for blood culture tests in our study was 135.83 hours, which may be an important factor in the association between blood culture ordering and mortality. Furthermore, the significant association between mortality and blood culture testing may be due to our study having an older population (median age = 79) than others. Blood culture tests may have been prescribed

to more severely ill patients, as 67.22% of our patients had a major degree of complexity, and the median CCI was seven (Table 3).

Our study found no significant association between the time to first microbiological test and in-hospital mortality (Table 9).

4.3 Implications for practice and policy

The main objective of this research was to determine the association between the LOS of patients at hospital and the time from admission to the first microbiological test result. This research has provided evidence that an increase in time from admission to the first test result increases hospital LOS. The time from admission to the first microbiological test includes time taken for a physician to examine the patients, prescribe a microbiological test and collect a sample, and for the laboratory to process the sample and disseminate the results. This research has found that if the time from physician check-up to laboratory result dissemination of the first microbiological test result can be minimized, then the LOS of pneumonia patients at hospital can be decreased.

Similarly, blood culture order decreased the LOS of pneumonia patients; hence, prescription of blood cultures may reduce the LOS of pneumonia patients. This information may assist physicians in ordering microbiological tests and thus reduce overcrowding at hospitals. Thus, these research findings may assist in decreasing the LOS of unspecified pneumonia patients across hospitals in NSW, Australia.

This research is probably the first research to use the “time from hospital admission to first microbiological test result” as an indicator of the timeliness of microbiological tests in pneumonia patients. Therefore, these research findings can be used in the future and will be a milestone for future research on the timeliness of microbiology tests. The research findings provide evidence of interest to policymakers to help decrease the LOS of patients at hospital. The implementation of these research findings can also decrease hospital costs by reducing the LOS of patients at hospital. The research findings also provide laboratories impetus for change in practices, analytical method and equipment upgrades to aid our clinical colleagues deliver improved outcomes for patients, being more effective and efficient.

4.4 Strengths and limitations of the study

To our best knowledge, this is the first study to find an association between the first microbiological test result and LOS and in-hospital mortality in pneumonia patients. The study included a large sample from six hospitals in NSW. Due to the large sample being from principal referral hospitals, major hospitals and district hospitals, the information provided by the study can be applied as general information for all hospitals regarding unspecified pneumonia patients aged 18 years and above.

The main limitation of this study is that this is an observational study, so unmeasured factors can be a potential confounder of its outcomes. For example, this study did not have data on the pneumonia severity index (PSI) and types of comorbidities of patients. Secondly, the study considered unspecified pneumonia and did not distinguish between community-acquired (CAP) and healthcare-associated pneumonia (HCAP). The majority of HCAP is caused by multi-drug-resistant bacteria, which may increase LOS and mortality. Information on CAP and HCAP would have given more precise information on the association of LOS and in-hospital mortality with the time to the first microbiological test result and other factors. Furthermore, our study considered microbiological tests such as bacteriological tests, virological tests and serological tests. The turnaround times for those tests differ. Therefore, more precise information would be obtained if test timeliness and patient outcomes were examined for each specific type of microbiological test.

Chapter 5
Conclusions

This study found a signifcant association between the time to the first microbiological test result and hospital LOS in adult patients admitted with unspecified pneumonia. This implies that improving the time to the first microbiological test result may help to shorten the LOS of pneumonia patients in hospitals. However, this study did not find statistically significant association between the time to the first microbiology test result and in-hospital mortality. Similarly, the research findings also provides evidence to change in laboratory practice, analytical methods and equipment upgrades to improve patients outcome.

Furthermore, the study also found significant association between an increase in age, comorbidity index, and major diagnosis related group complexity with hospital LOS and in-hospital mortality. The study also found the significant association of microbiological test repeat ordering and number of microbiology tests ordered with hospital LOS.

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ETHICAL APPROVAL LETTER

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22 May 2018

A/Prof Georgiou
Att: Dr Mary Dahm
Macquarie University
Centre for Health Systems and Safety Research
Level 6, 75 Talavera Road
NORTH RYDE NSW 2109

Dear A/Prof Georgiou and Dr Dahm,

HREC ref no: 16/041 (HREC/16/POWH/412)
Project title: Delivering safe and effective test result communication, management and follow-up

Thank you for your correspondence dated **30 April 2018** to the Human Research Ethics Committee (HREC) requesting an amendment to the above stated ethics approval. Your amendment request was reviewed at the Executive Committee meeting on 22 May 2018.

I am pleased to advise that the following documentation has been approved:

- Amendment Form, dated 30 April 2018
- MASTER PIS&CF for Patient focus group V1.4 dated 30 April 2018

Ethics approval is valid for the following site(s):

- Prince of Wales Hospital
- Shellharbour Hospital
- Shoalhaven Hospital
- St George Hospital
- Sutherland Hospital
- Sydney Children's Hospital
- Wollongong Hospital
- Royal Hospital for Women

This amendment has also been reviewed by the Research Governance Officer at SESLHD. Further authorisation of the above approved documents is not required for any site that has the Research Governance conducted by the SESLHD Research Support Office. Implementation of this amendment can now proceed.

Prince of Wales Hospital
Community Health Services
Barker Street
Randwick NSW 2031

For multi-site projects reviewed by the HREC after 1 January 2011 a copy of this letter must be forwarded to all Principal Investigators at every site approved by the SESLHD HREC for submission to the relevant Research Governance Officer along with a copy of the approved documents.

Should you have any queries, please contact the Research Support Office on (02) 9382 3587. The HREC Terms of Reference, Standard Operating Procedures, membership and standard forms are available from the Research Support Office website: www.seslhd.health.nsw.gov.au/POWH/researchsupport/.

Please quote **HREC ref no 16/041** in all correspondence.

We wish you every success in your research.

Yours sincerely

Andrew Bohlken
Executive Officer, Human Research Ethics Committee

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's (NHMRC) *National Statement on Ethical Conduct in Human Research (2007)*, NHMRC and Universities Australia *Australian Code for the Responsible Conduct of Research (2007)* and the *CPMP/ICH Note for Guidance on Good Clinical Practice*.